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A Study Of The Bromine Fluoride And Bromine Additions To Bicyclo (221) Heptene

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A STUDY OF THE BROMINE FLUORIDE AND BROMINE ADDITIONS TO BICYCLO[2.2.1]HEPTENE

by

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ABSTRACT

The structures of the major products from the reaction of bromine fluoride with bicyclo [2.2.1] heptene (norbornylene) have been elucidated. The results of this work led to the reinvestigation of the reaction of bromine with norbornylene. Three new dibromides, 7-anti-2-exo-,2-exo-5-endo- and 2-exo-5-exo-dibromonorbornane, were isolated as well as those reported previously (7-syn-2-exo- and 2-exo-3-endo-dibromonorbornane). All structures were convincingly assigned on the basis of nuclear magnetic resonance spectroscopy, dipole moments and chemical data. A study of the factors controlling the product ratios was carried out and the probable mechanisms leading to the products discussed in the light of this work and previous reports concerning similar systems. The effects of tertiary amines on the addition of bromine to norbornylene were studied.

A degradation of 2-exo-3-endo-dibromonorbornane formed in the addition of bromine to 5,6-^{14}C-labelled norbornylene allowed an estimate of its formation via 6,1-hydride shift and bromonium ion pathways.

A brief study of the reaction of perchloryl fluoride with Grignard reagents and diazo compounds revealed that perchloryl fluoride has little preparative value with the former and none with the latter for preparation of fluoro compounds.

A reinvestigation of the reductive dehalogenation of

2α-bromocholestan-3-one showed that reductive debromination is unequivocally a significant product forming pathway when α-substituted pyridines are used.

ACKNOWLEDGMENTS

The author thanks Dr. E. W. Warnhoff for guidance, forbearance, and most of all for the readiness with which he passed on his own ideas, knowledge and experience. Thanks are also due to Dr. F. L. M. Pattison for advice during the perchloryl fluoride project. The author wishes to express his appreciation to Dr. W. A. Ayer of the University of Alberta for the double irradiation and 100 Mc/s nmr spectra, Dr. R. K. Chan of the University of Western Ontario for advice in determining the dipole moments, and Dr. J. A. Berson of the University of Wisconsin, Madison, for valuable discussions. Thanks are also due to Dr. J. R. Robinson of the Agricultural Research Institute, London, Ontario, for personally carrying out the counting of the ^{14}C samples and for the generous use of his facilities and advice for the degradation project.

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Finally the author wishes to thank his wife Ruth for her patience and moral support throughout the last four years.

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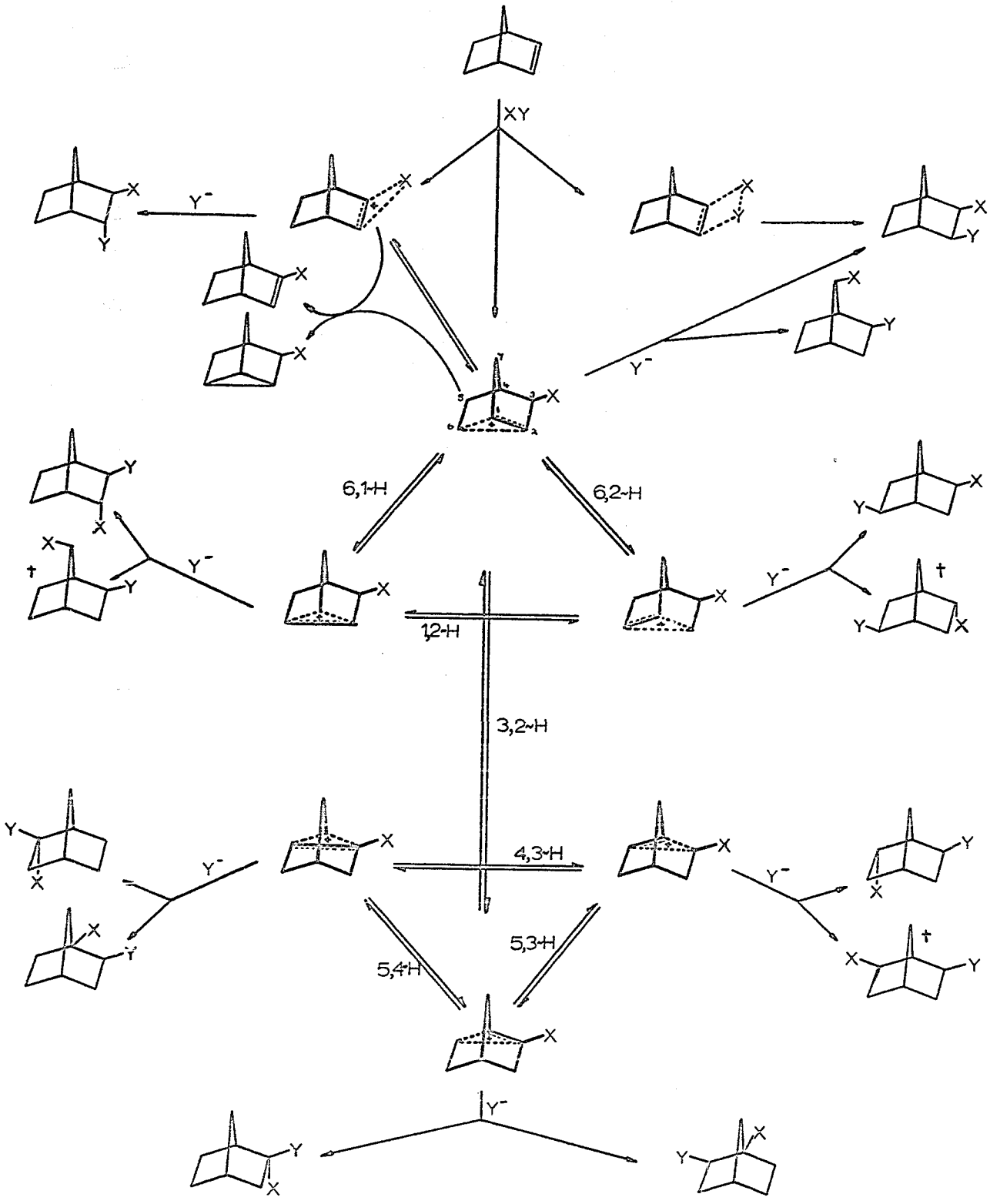
INTRODUCTION

It is doubtful whether Meerwein and van Empster(1) in 1922 and Nevell, de Salas and Wilson(2) in 1939 realised the contention and experimentation which would result from their hypotheses relating to cationic 'classical' carbon and mesomeric bridged carbon intermediates respectively. Thus, it was only seventeen years after the classical carbonium ions had gained respectability as discrete intermediates that a non-classical ion was first postulated and in the three decades since has developed from an esoteric concept into one pervading nearly all aspects of organic chemistry.

The situations in which Wagner-Meerwein rearrangements, hydride shifts and non-classical bridged bicyclic carbonium ions can occur may be initiated in a number of ways such as the reaction of an olefin with cationic species, solvolysis, deamination with nitrous acid or occasionally dissolution of a halide in a nonhydroxylic solvent. It will be the principal purpose of this Introduction to review only one route into these cationic species, this being the addition of cations to olefins, in particular, bicyclo[2.2.1]hept-2-ene (norbornene, norbornylene) and its derivatives. A schematic representation of the possible modes of addition is shown in Fig. 1.

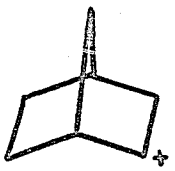
Before any discussion of these additions and subsequent reactions, it is important to clarify the position taken herein as regards non-classical versus classical carbonium ions in bicyclic compounds. It is the author's intention not to become involved in the controversial question of non-classical ion 1(3) vs. rapidly equilibrating classical ions 2, 3 and 4 in the subsequent review and discussion. The dotted

Fig. 1
Possible Modes of Addition to Norbornylene



†enantiomer

lines in 1 represent the overlap of two atomic orbitals each of which



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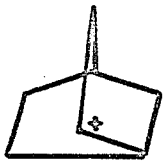

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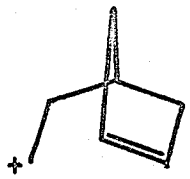

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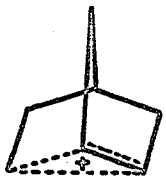
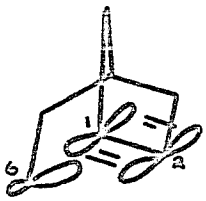


1

contributes to a multicentre orbital containing four electrons. A possible orbital structure for the non-classical carbon bridged 2-bicyclo[2.2.1]heptyl (norbornyl) cation is shown below (5) (4).



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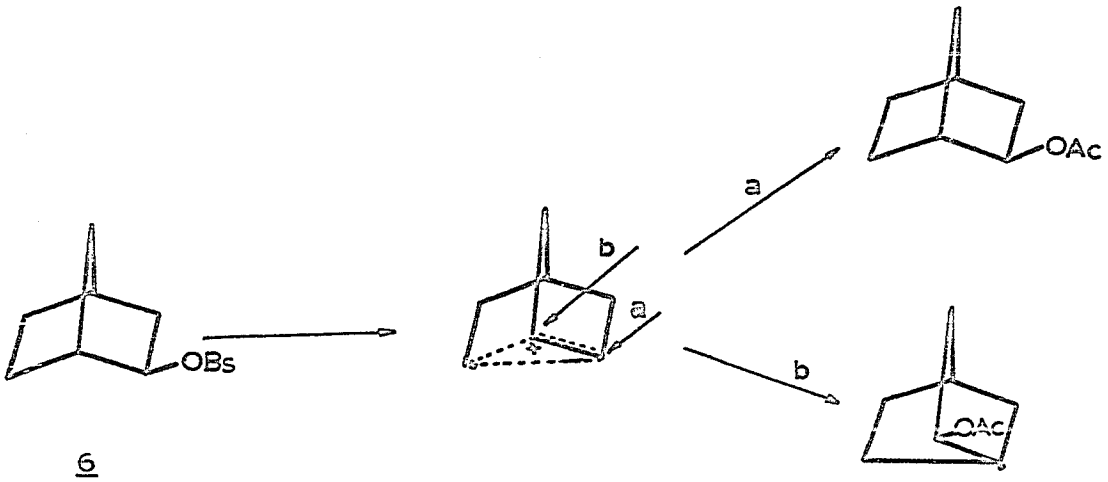
Treatment of this non-classical cation by simple Huckel molecular orbital theory gives the geometry for overlap corresponding to maximum delocalisation energy for minimum strain energy. In 5 there is considerable $\sigma\pi$ interaction between the sp^3 orbital at C-6 and the π type overlap of the p orbitals on C-1 and C-2. It is possible on this basis

to define a nonclassical ion as a positively charged species representing a 'total energy' minimum with respect to strain energy on the one hand, and delocalisation energy on the other, via a multicentre molecular orbital. For the sake of convenience the formulation 1 will be used in future, bearing in mind that both formulations can interpret the results presented with parity. There are several recent discussions on the norbornyl cation and its analogues in the literature which review the problem exhaustively (5,6,7,8).

Before the ionic additions to norbornylene, as reported in the literature, are reviewed it would be of value to discuss briefly the salient factors controlling product stereochemistry and formation, as dictated by the mechanisms of hydride shifts (vide infra) and Wagner-Meerwein rearrangements. An intrinsic property of these systems is the almost exclusive formation of exo products whenever a carbonium ion is created. Winstein, et al,(9) have shown that acetolysis of optically



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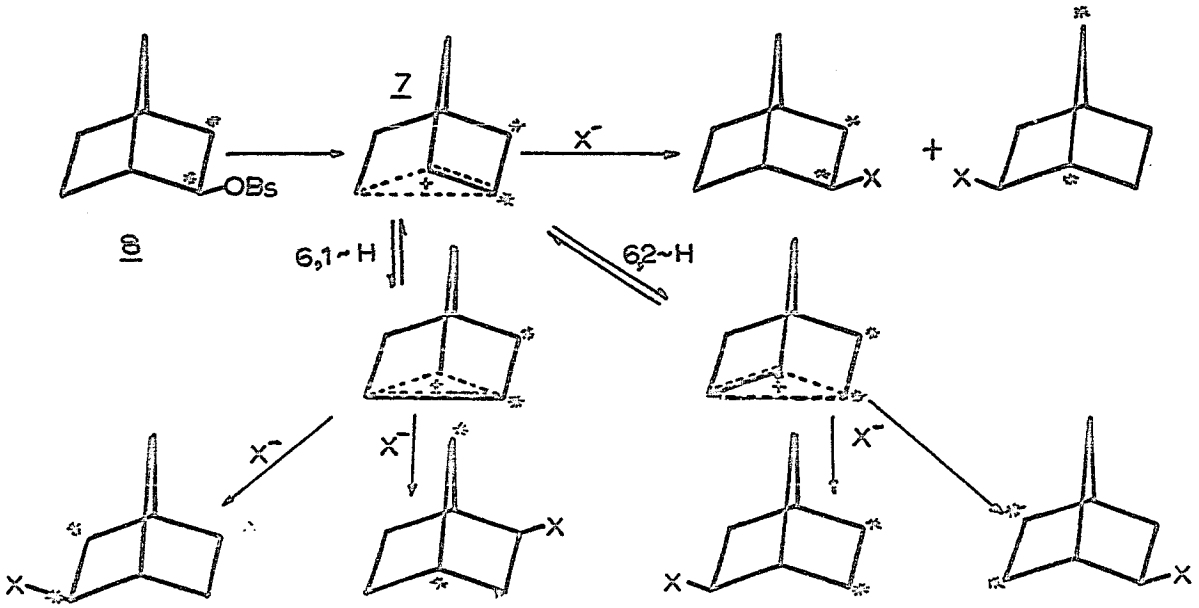
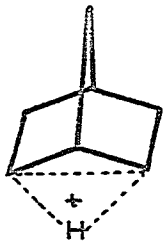
active 2-exo-norbornyl brosylate (6) gives completely racemic exo-acetate and less than 0.02 percent of the endo-acetate. In addition, the rate of racemisation was found to exceed the rate of solvolysis. The non-classical formulation readily explains this stereospecificity; however, propenents of H. C. Brown's rapidly equilibrating classical ions argue that endo attack is precluded by the unfavourable geometry of the C-5- and C-6-endo-protons. From a pragmatic standpoint either interpretation gives the same result. The racemic nature of the exo-acetate can be explained on the basis of a Wagner-Meerwein rearrangement or alternatively, by a 6,2-hydride shift. Roberts et al (10) were able, by solvolysis of ^{14}C-labelled 2-exo-and 2-endo-norbornyl derivatives, to demonstrate the occurrence of 6,2-, 6,1-, and 3,2-hydride shifts. It



can be seen that the symmetrical cation 7 would not give product with C-5 and C-6 labelled via Wagner-Meerwein rearrangement. Formolysis of 8

however, and subsequent degradation indicated that 28 percent of the total activity, was located in these positions.

Recently the mechanism of the 6,2-hydride shift has been questioned (11). Roberts has proposed a face-protonated model 9(10) while Winstein prefers an edge-protonated transition state 10(12). The essential difference between 9 and 10 lies in their symmetry



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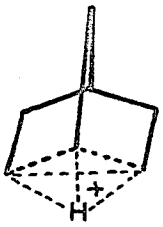
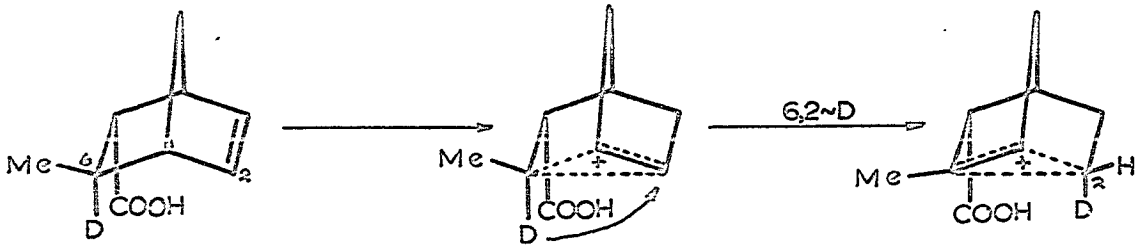


9

properties. When 9 collapses the hydrogen which lies on a three fold symmetry axis cannot show any preference for attachment to either side of C-1, C-2 or C-6 i.e. the distinction between exo and endo at the migration terminus has been lost. It has been shown (11) using 11 that exclusive endo-endo hydride shift occurs as the product 12 has no hydrogen at C-2. If an ion such as 9 had been involved the C-6-endo-deuterium could have migrated with equal probability to the two configurations at C-2.



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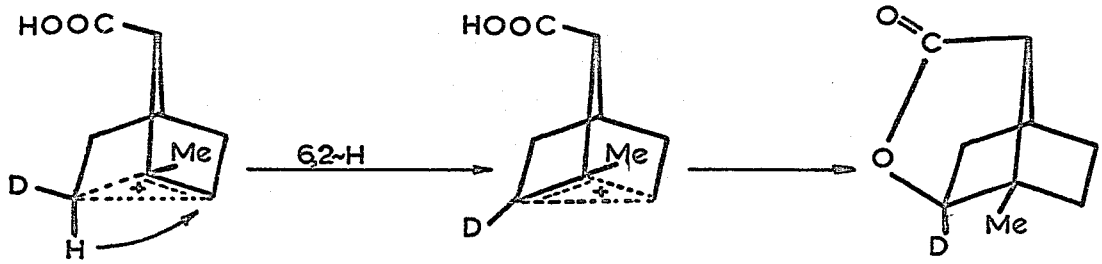

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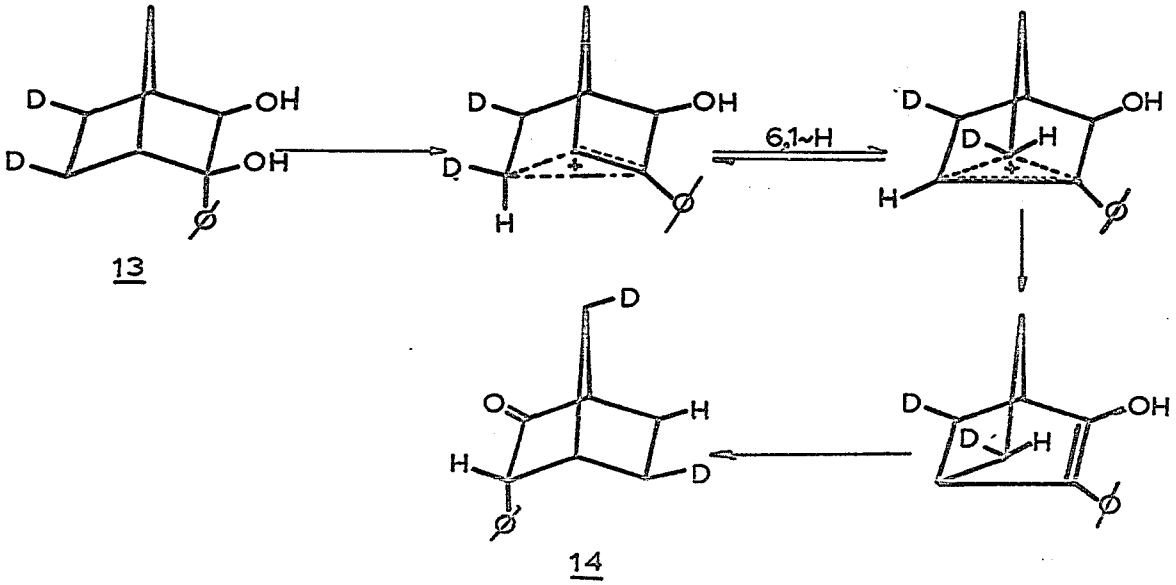
A stereospecific 6,1-hydride shift has been demonstrated by Collins, et al,(13) in the acid-catalysed rearrangement of 13 to 14.



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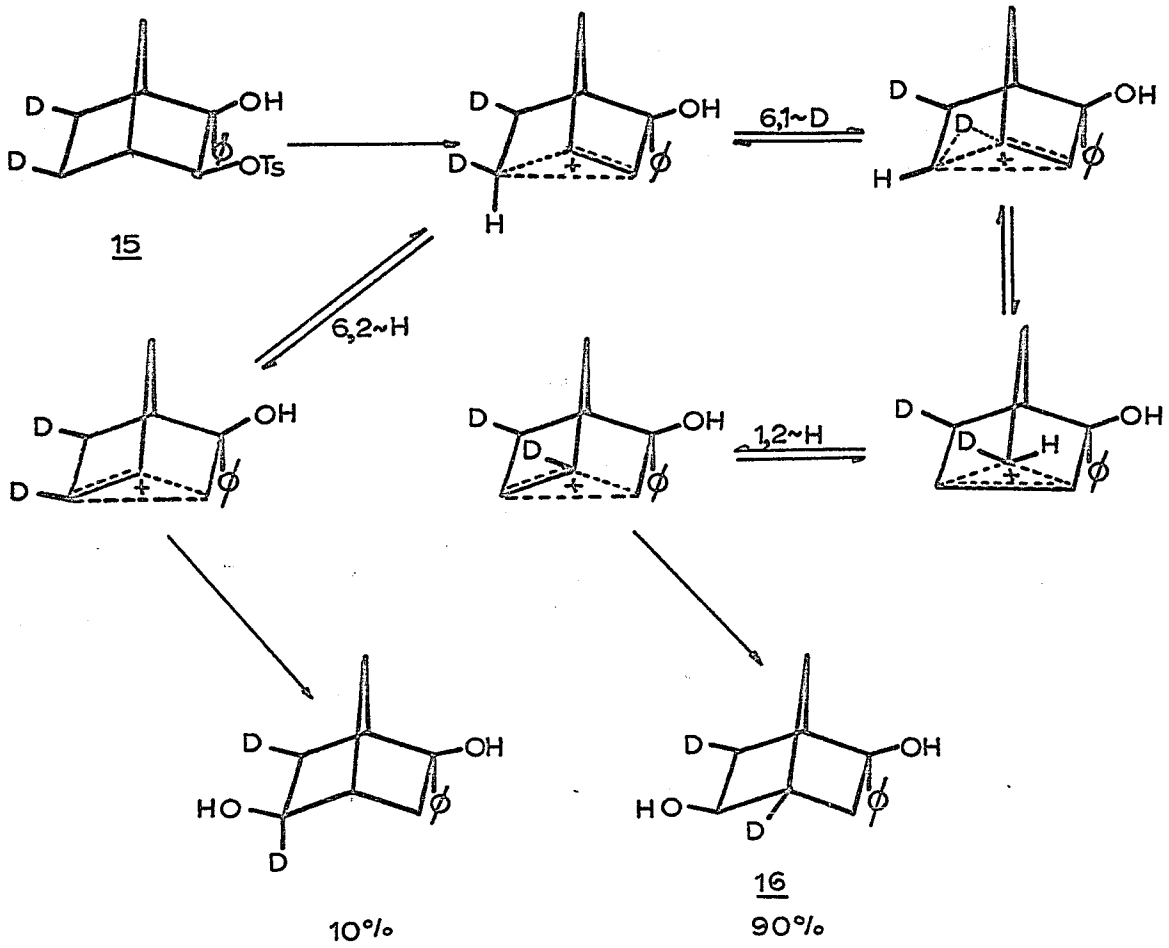
14

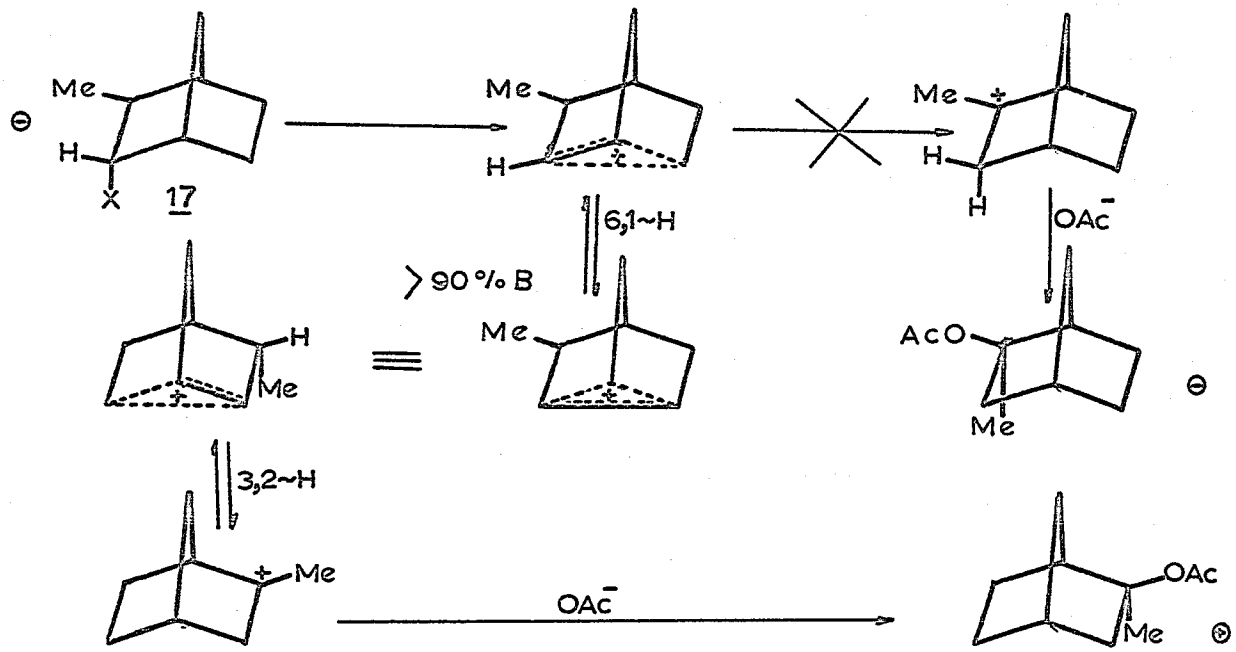
These workers have also presented evidence that 6,2-hydride shifts occur through pairs of sequential 1,2-hydride shifts (rather than 1, 3-shifts) (14). Hydrolysis of 2-exo-hydroxy-2-phenyl-3-exo-norbornyl tosylate (15) labelled at C-5 and C-6 with exo-deuterium gives product pairs differing only in their labelling pattern. The resultant pattern is indicative of the route.



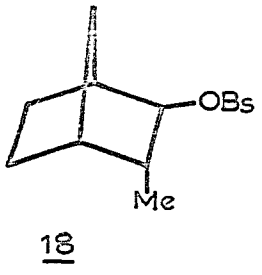
The preponderance of 16 in the abbreviated scheme above is evidence for discrete 1,2-hydride shifts.

A 3,2-hydride shift may also be observed in the formolysis of 2,3-^{14}C -2-exo-norbornyl brosylate (10) (8), but it is considerably slower. Indication that it does occur is shown by the argument that for 6,1-hydride shift only, the activity at C-7 should equal the sum of that at C-4 and C-1, but solvolysis in formic acid gives rise to product in which the C-7 activity is less than C-4 + C-1. Extensive data relating to 3,2-hydride shifts have been accumulated by examining the solvolytic demise of the 3-endo-(15) and 3-exo-methyl norbornyl (17) (16) cations. The necessity for the migrating hydrogen to be exo was demonstrated;

migration of the endo-proton occurred by the more circuitous route B outlined in the scheme below.



Solvolysis of 18 provided a measure of the rates of solvent capture versus 3,2-hydride shift (17); k_{t-s}/k_{s-s} was at least 14 and k solvent/



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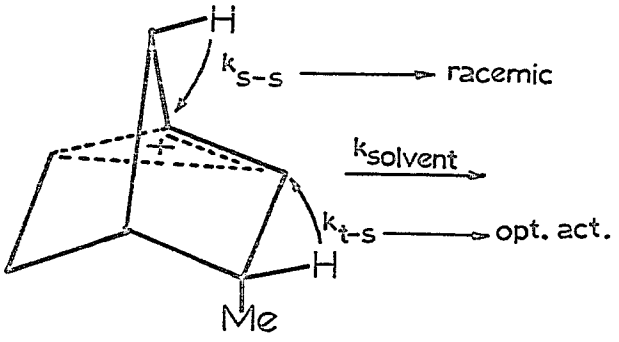
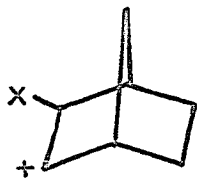


k_{s-s} at least 119. This latter large figure accounts for the failure to observe products from 3,2-hydride shift in solvolysis of norbornyl compounds.

Direct observation of the norbornyl cation by nmr spectroscopy (18, 19) has permitted an estimate of the relative rates of hydride shift and Wagner-Meerwein rearrangement. From the temperature dependence of the spectra it was calculated that at -120°C the rates of 6,2-H, 6,1-H and Wagner-Meerwein rearrangement were comparable but 3,2-H was $10^{8.8}$ slower. A rationale for this large difference is obscure at present.

The presence of a substituent group in the bicyclic cation may alter its behaviour relative to the unsubstituted analogue. Electron delocalisation may be influenced such that any one or a mixture of all three ions 19, 20 and 21, could be controlling product distribution.



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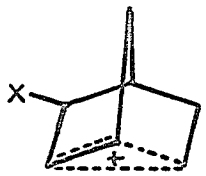

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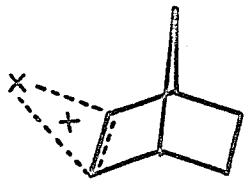

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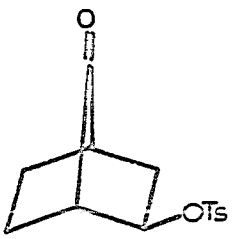
An example (20) of this is provided by the solvolysis of 7-oxo-2-exo- and 7-oxo-2-endo-norbornyl tosylates (22 and 23), in which the rate of



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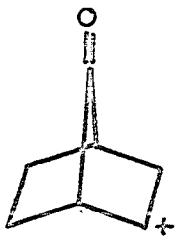

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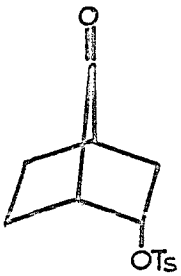


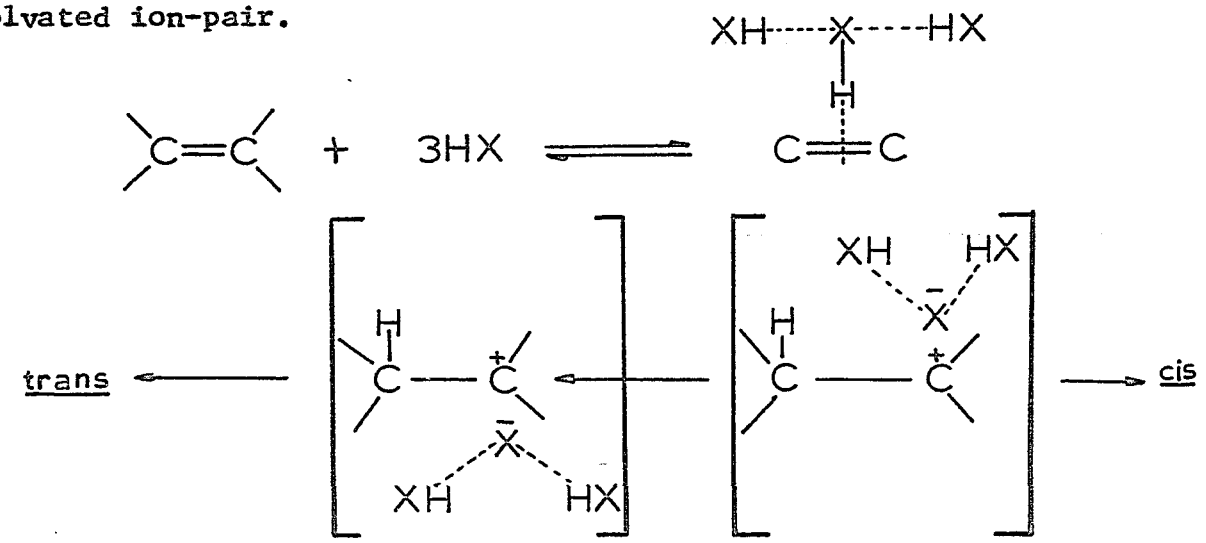
23

endo acetolyis is six times greater than that of the exo epimer, whereas in the unsubstituted tosylates, the ratio of exo to endo

solvolysis rate is about 3.5×10^{2}. These results are best interpreted on the basis of prior unassisted ionisation of 22 and 23 to give 24, a non-classical ion being precluded by the destabilizing inductive effect of the carbonyl group. Steric effects which tend to favour a particular rearrangement or hydride shift are also important. Insufficiently detailed results are available for rigorous general rules but observations have been made which serve as a useful framework. An outline of this work and its interpretation will occupy the remainder of this Introduction.

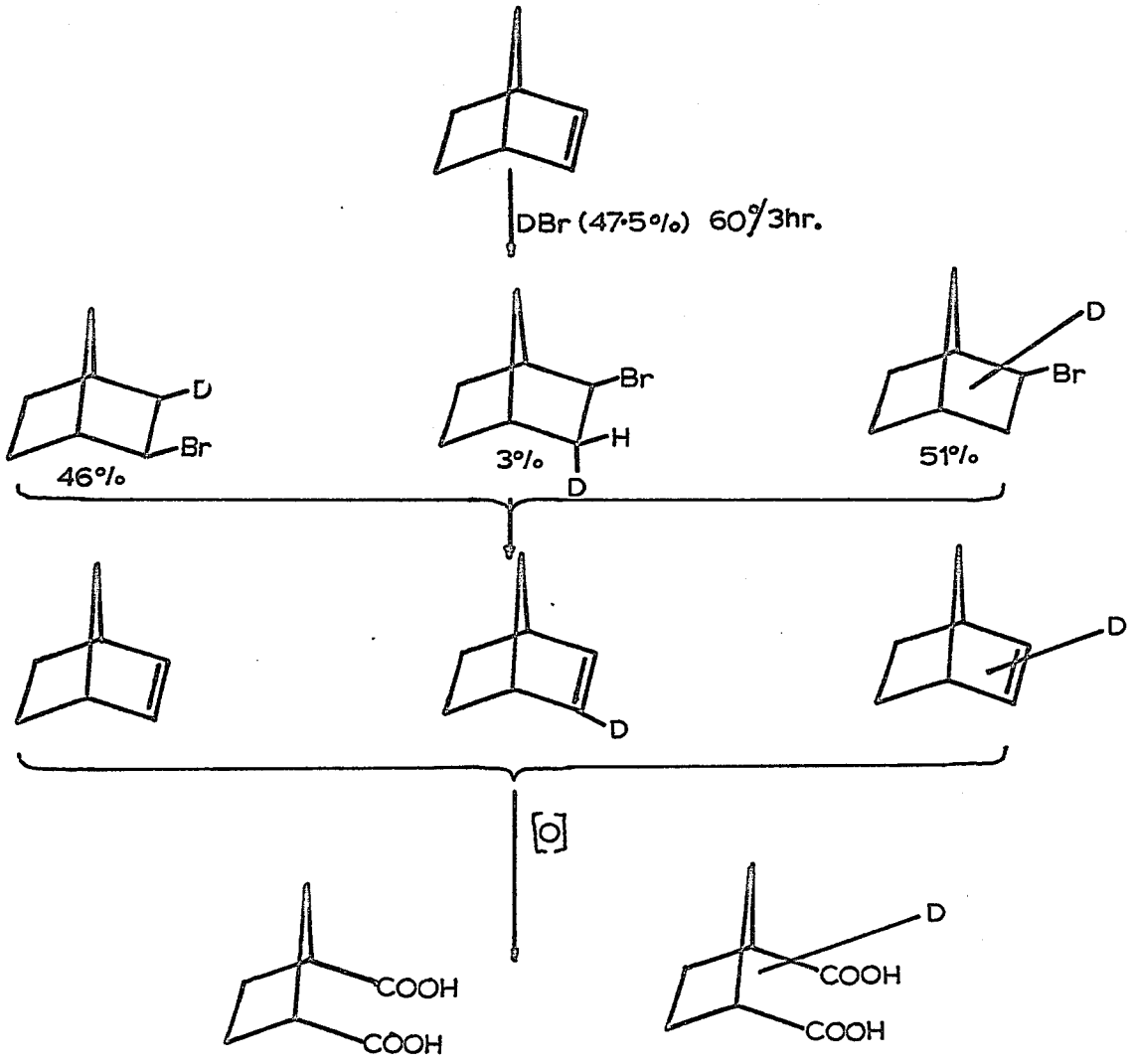
Addition of hydrogen chloride to norbornylene gave 75% of 2-*exo*-norbornyl chloride (21,22), however the nature of the reagent precluded determination of the stereochemistry of the addition, the presence of rearrangement, and hydride shifts. To circumvent this difficulty halogen addition was effected but this procedure suffered from the disadvantage that product formation could be influenced by the group that entered first and thereby becoming a substituent in the norbornyl cation. Hydrogen halide addition has long been tacitly assumed to be a *trans* addition. Recently, Dewar *et al* (23) have shown that in two cases at least, the addition is *cis*, these being the addition of deuterium bromide to acenaphthalene and indene. After initial attack by D^{+}, to give either a classical carbonium ion or a π-complex, approach of Br^{-} should exhibit no steric preference, there being a plane of symmetry through the two carbons to which addition is being made. The reaction was shown to be ionic and it was proven that the *trans* product formed in minor yields ($\sim$10%) was not a result of isomerisation of the *cis* adduct under the reaction conditions. With

deuterium bromide in pentane-methylene dichloride (at 0°C.), 90% cis addition resulted, the yield falling with concomitant increase in trans product, as solvent polarity was increased. The presence of trans product which was not formed via a radical or isomerisation process would seem to exclude a concerted four centre cyclic process. A π-complex is eliminated on the grounds of failure to give predominant trans product; however, as will be shown later cis products have been formed from postulated π-complexes. Dewar rationalises his results using a solvated ion-pair.

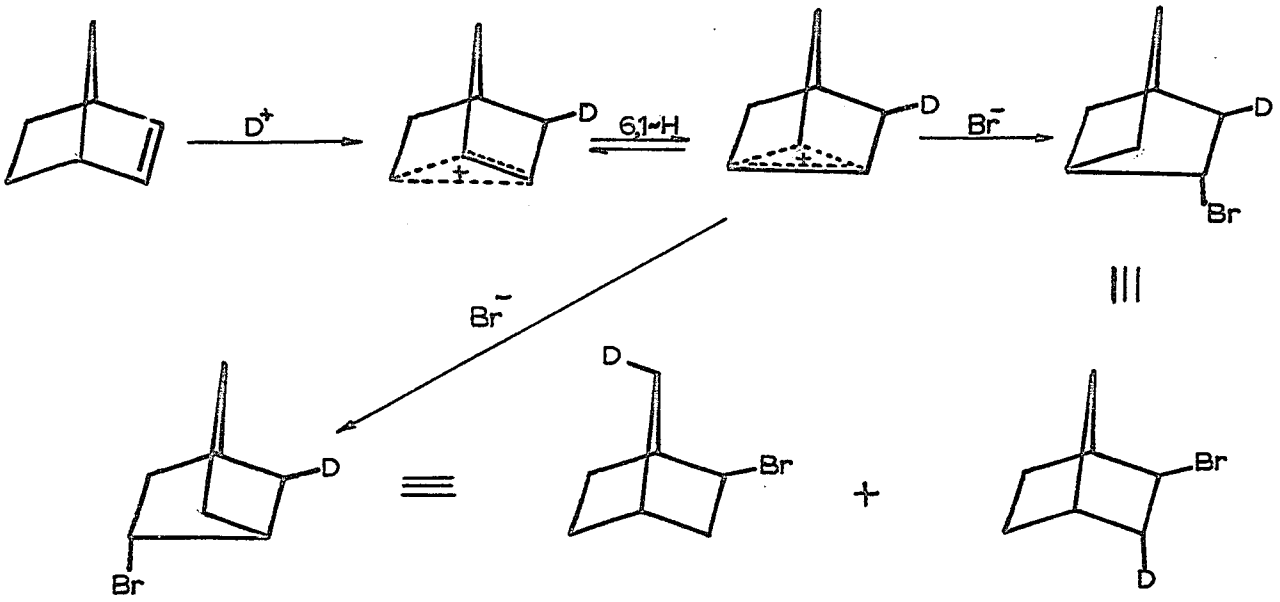


Any factor, such as stereochemistry or solvent polarity, which can decrease the rate of collapse of the ion-pair to cis product increases the probability of isomerisation to a trans ion-pair and subsequent collapse to trans product.

In the absence of any directing effects other than those intrinsic to the norbornyl system it was expected that norbornylene would add exo-cis. The products and degradation results are shown in the scheme below (24). From the scheme it should be noted that of the 49% bromide



in which deuterium was vicinal only 94% of this deuterium was lost on dehydrohalogenation. This would imply that either some trans elimination was taking place or else some trans product had been formed. An alternative explanation of this discrepancy would be the presence of some trans product arising via a 6,1-hydride shift. This would result in an increase in the percentage of non-vicinal deuterium and also explain the failure to remove all the deuterium in the



dehydrohalogenation of the vicinal deuterium bromide adduct. The results appear to confirm the postulate that, in the absence of any directing effect, the amounts of rearranged and cis-exo addition product are approximately equal.

The addition of hydrogen bromide and chloride to 2,3-dideuterio norbornyl-2-ene is reported to give results considerably different from those just discussed (25). Dehydrohalogenation of the adducts via a previously elucidated mechanism gave labelled norbornylenes whose relative quantities were estimated by nmr. The results were:-

	Cis Add $\pm$	W.-Meerwein	6.2-hydride shift
hydrogen chloride	50.1%	12.0%	37.9%
hydrogen bromide	40.6%	13.8%	45.6%

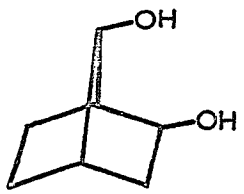
On the assumption that in this system the yield of cis addition should equal Wagner-Meerwein rearranged product the authors postulate that the

excess cis product is being formed by a concomitant four centre cyclic reaction. However, this latter mechanism, for which there has been no proven precedent in this reaction type, may not be required. The authors do not consider 6,1-hydride shifts, these leading to deuterium on the bridge and vicinal to the halide group. These are of particular importance as the amount of cis addition is based on the ratio of product with deuterium vicinal to the halide to that with hydrogen in this position, but 6,1-hydride shift would also give a product with deuterium vicinal to the halide substituent and therefore, the percentage reported for cis addition may easily be much lower. In addition, dehydrohalogenation will give products with one olefinic proton as well as those with two and none, resulting in complications for the analysis by nmr integration.

Recently, Brown et al (26) have added deuterium chloride to norbornylene in methylene chloride at -78° to yield 60% of exo-3-d-exo-norbornyl chloride, 34% of syn-7-d-2-exo-norbornyl chloride and 6% of hydride shift product. Clearly the excess of cis product over the Wagner-Meerwein product could be ascribed either to an additional four centre mechanism (25) or to a mechanism involving a pair of rapidly equilibrating classical carbonium ions which are trapped before they have fully equilibrated. However, once again the hydride shift product is reported to be the result of a 6,2-hydride shift which, as stated previously, is not in agreement with other additions to norbornylene. In the absence of more data it would be pointless to speculate further on the origin of the apparent excess of cis product.

The hydroxylation of norbornylene is not well documented.

Oxidation with peracid (27) gave a non-vicinal diol which could also be obtained in good yield (67%) from 2,3-exo-epoxynorbornane on treatment with formic acid (28). On the basis that (a) the epoxide can be reduced by lithium aluminium hydride to 2-exo alcohol, (b) the glycol is non-vicinal, and (c) the formation of a cyclic acetal is facile, the structure was considered to be the Wagner-Meerwein rearrangement product. The same product was also reported from the treatment of



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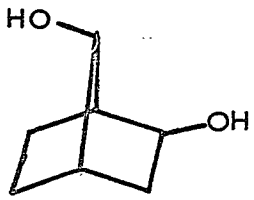

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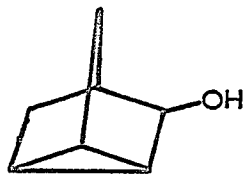
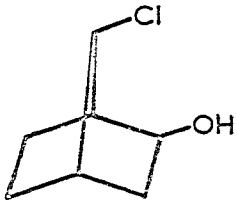


27

norbornylene with hydrogen peroxide and formic acid (28). More recently treatment of the 2,3-exo-epoxide with acid has been shown to give some 6,1-hydride shift product 26 and a minor amount of elimination product 27 as well as the major product 25 (29). The lack of vicinal diol (28) has been attributed to bridging by oxygen in the intermediate ion lowering the charge deficiency at C-3.

The addition of hypochlorous acid to norbornylene gave 51% of the Wagner-Meerwein product 28 and 30% of the elimination product 29 (30).



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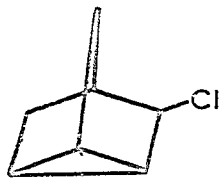
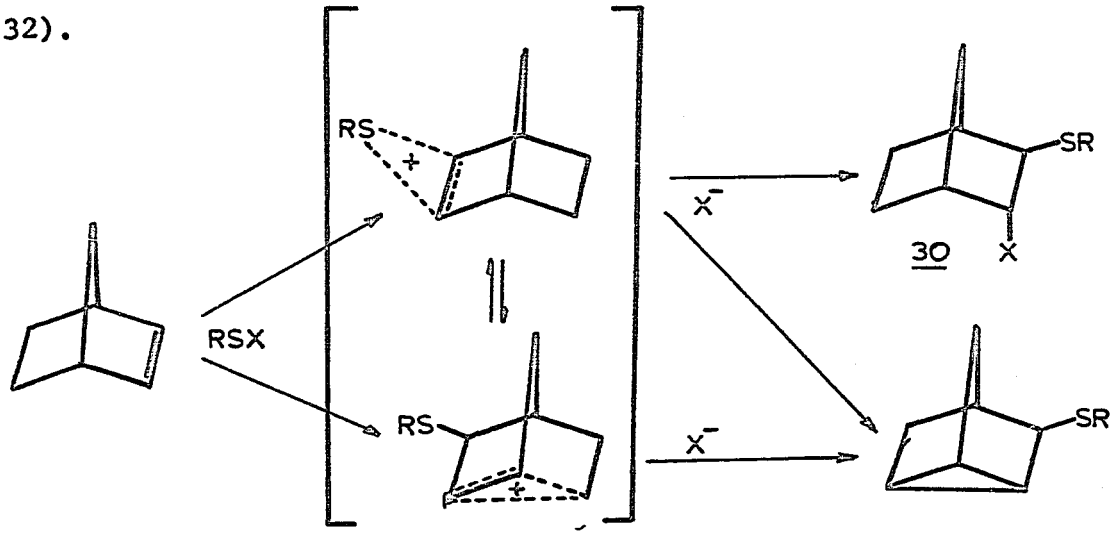


29

No Wagner-Meerwein rearrangement products were found in the addition of sulphur halides which gave only the normal trans adduct 30 (31,32).

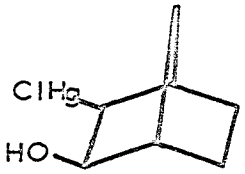


When R=2,4-dinitrophenyl, 5-10% yields of a tricyclic compound were detected, the amount increasing with increasing polarity of solvent. The failure to find rearranged products even when a tricyclic derivative is present, is attributed (31) to steric hindrance by the 2,4-dinitrophenyl group preventing attack at C-1. A rationalisation of the product distribution which does not necessitate an equilibrium between the two ions is based on their relative stabilities (32). Solvolysis rate enhancements are indicative of the relative efficiencies of β-carbon and β-sulphur as neighbouring groups and hence, of their ability to stabilise an adjacent positive charge. β-Sulphur, using unshared (non-bonding) electrons, produces a rate enhancement of 10^7 in the solvolysis of β-chlorosulphides, while carbon, using bonding electrons in the norbornyl series enhances rates of solvolysis by only 10^2-10^3. In the general case therefore, the cyclic sulphonium ion is more stable than the carbon bridged ion. When a powerful electron

abstractor such as 2,4-dinitrophenyl is present the stability of this ion will decrease.

The trans addition of nitrosyl chloride to Δ^9-octalin has been observed (33) and if the mechanism is considered to involve the equivalent of NO^+ and Cl^- (34), it might be expected that addition to norbornylene would give predominantly trans product in a similar manner to the sulphenyl halides. No rearrangement products were found when nitrosyl chloride was added to norbornylene and the product was the cis-exo adduct (33). Oxymercuration, as will be seen later, also gives predominantly cis-exo adduct. A four centre concerted cyclic transition state may be implicated though this can hardly be true with Δ^9-octalin. An alternative, as discussed in the oxymercuration addition, is the formation of a nitrosonium ion which opens in a cis manner due to unfavourable twist strain in the bicyclic system when going to a transition state for trans opening.

The addition of $Hg(OH)ClO_4$ to norbornylene (35) gave, after chloride exchange, an 86% yield of the 2,3-exo-cis-hydroxy mercury adduct 31. Addition to aliphatic olefins had previously been found to be trans, a mercurinium ion (32) intermediate being postulated. Traylor attributes this unusual addition to the presence of steric



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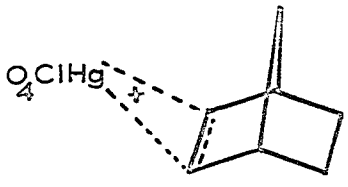

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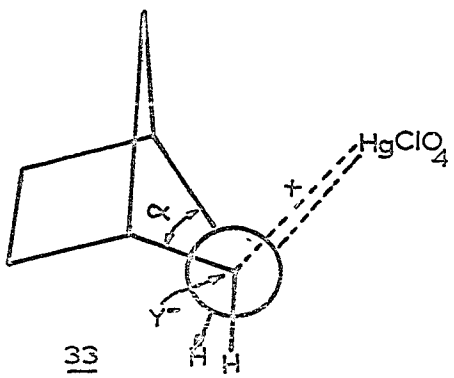
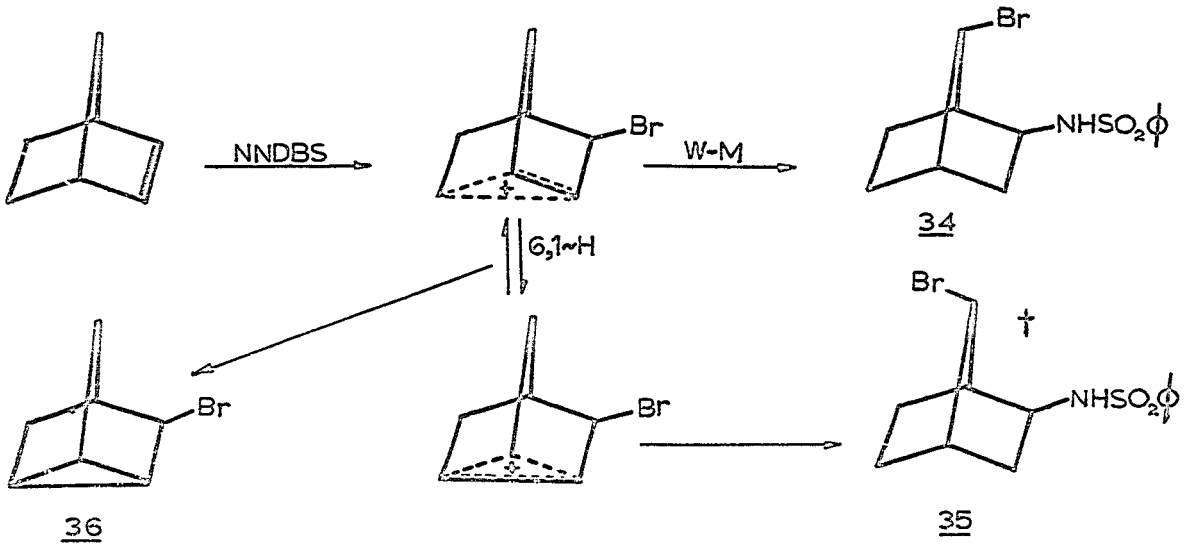


33

strain in the transition state which produces trans opening. It is argued that endo attack (32, 33) at C-2 tends to increase the dihedral angle α in an effort to invert C-2 which, the system being a rigid one, increases the energy of the transition state. Rearrangement does not take place for the same reasons put forward in the addition of sulphenyl halides. Traylor postulates that for electrophiles of low electronegativity cis or trans attack will depend on the ability of the electrophile to carry ligands. This capacity to carry other ligands decreases the activation energy for cis addition. The predominant trans opening of the bromonium ion is in agreement with this concept but the exclusive cis product from nitrosyl chloride addition is not so readily explicable.

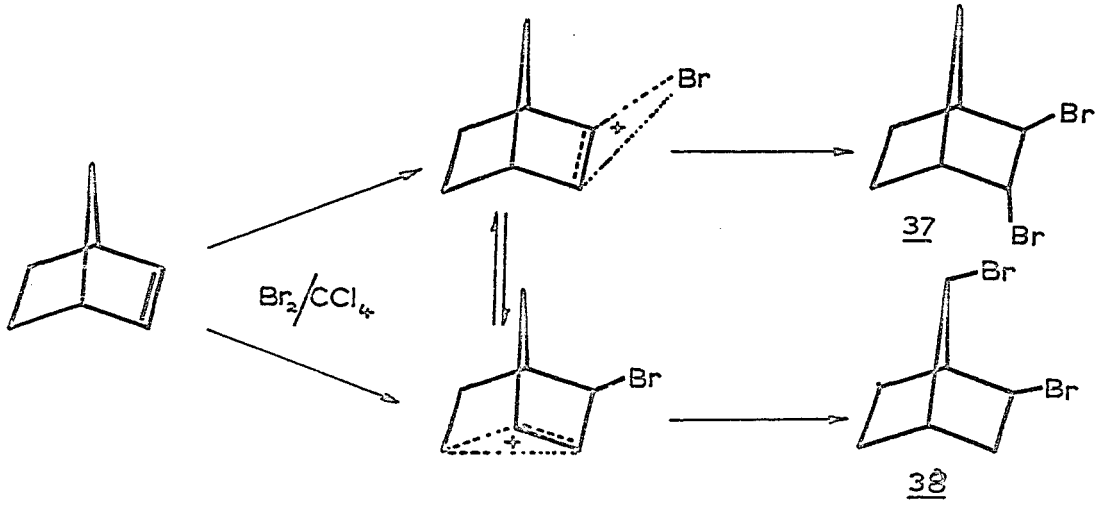
A parameter which has not been evaluated earlier is the strength of the nucleophile as a controlling factor in product distribution. Addition of N,N-dibromobenzenesulphonamide (36) to norbornylene resulted in the formation of three products 34, 35 and 36. No 2,3-exo-cis or 2,3-exo-endo trans products were found. This result is



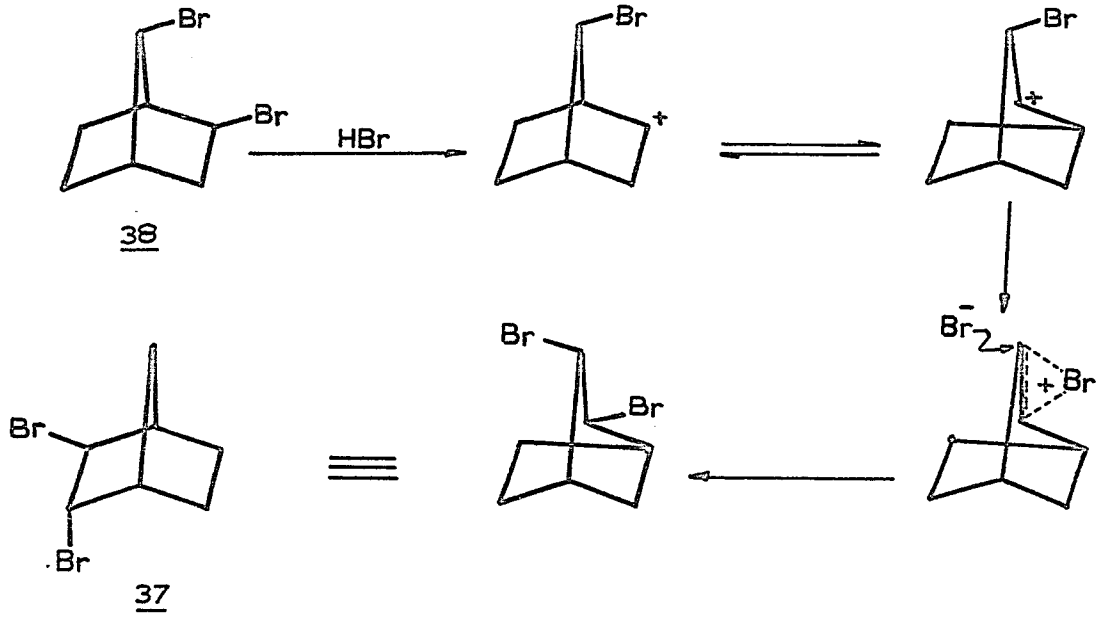
† enantiomer

apparently at variance with the addition of bromine (37) which has been claimed to give approximately 15% trans product and no 7-anti-2-exo-product (6,1-hydride shift). The explanation offered is based on the lower mucleophilicity of $^{-}NHSO_2C_6H_5$ versus $Br.^{-}$ If a bromonium ion is formed initially, collapse can occur in two ways; either to the bridged non-classical carbonium ion by participation of the C-1 — C-6 bond or via attack by nucleophile. It would appear that weaker nucleophiles such as $^{-}NHSO_2C_6H_5$ fail to capture the bromonium ion before it is converted to the non-classical ion. Some support for this concept has been acquired from the 'BrF' addition (38) to norbornylene reported later in this work. A bromoacetamido adduct, 7-syn-bromo-2-exo-acetamidonorbornane (from the N-bromoacetamide reagent) was obtained. This was the only such adduct found.

Earlier studies (39) on the bromination of norbornylene indicated the formation of 2-exo-norbornyl bromide, bromonortricyclene and a mixture of dibromides. Later (37), an attempt was made to resolve the dibromide mixture; two dibromides were isolated, 37 and 38. This product distribution is consistent with the concept that bromine is



less effective than sulphur as a neighbouring group. It was also found that 38 would isomerise to the trans product, the mechanistic rationale consisting of sequential bromonium ion and non-classical carbonium ion formation.



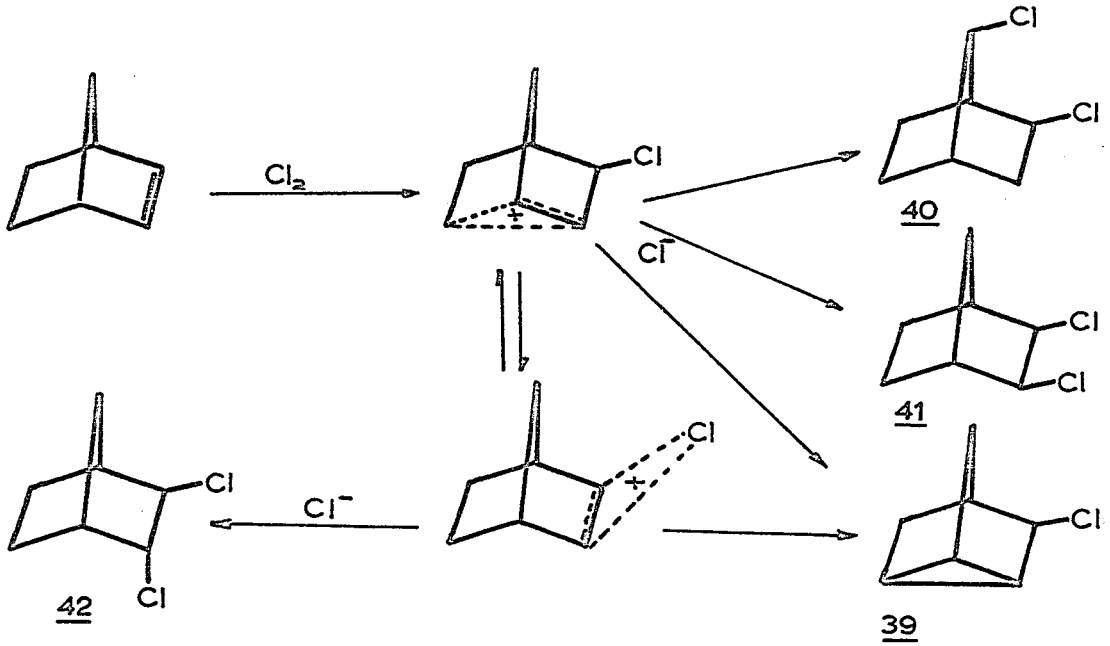
38

37

However, the trans product might also have been formed via a 6,1-hydride shift though in this case some of the 7-anti-2-exo-dibromide might have been expected. Although the work just mentioned was done prior to the introduction of gas-liquid chromatography (glc) techniques, there was no reason at the time to question the results or interpretation.

The very recently reinvestigated (40) ionic chlorination of norbornylene rests on a more secure footing. Early work (30) prior to the advent of glc showed that in pentane at -78°, chlorination gave 43% chloronortricyclene 39 and 37% 7-syn-2-exo-dichloronorbornane 40.

However, as olefin chlorinations in non-polar solvents had been shown to involve free radical as well as ionic mechanisms Poutsma (40) repeated the chlorination in the dark and in the presence of oxygen to inhibit radical processes. Four products were obtained which result from kinetic control. In this addition, two reaction modes are

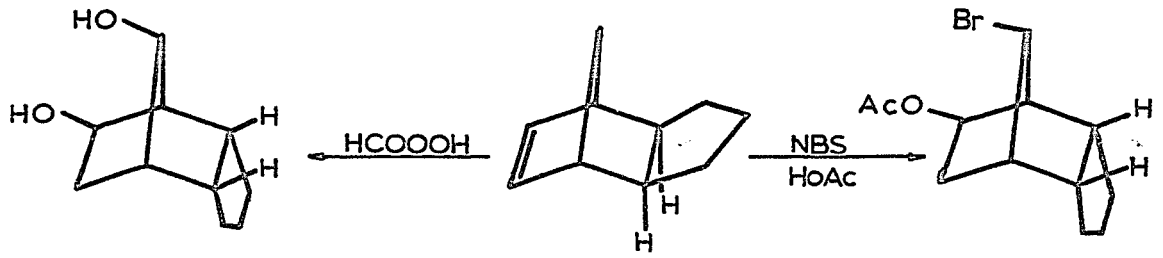


operative, these being trans addition and Wagner-Meerwein rearrangement. Examples have been given previously in which one of these modes can be exclusive in a particular reaction. The presence of trans product (6%) 42 in the absence of any hydride shift product indicates that some bridging is occurring. The minor amount is however, in agreement with theoretical requirements which predict chlorine to be a poorer bridging group than bromine. Similar products were obtained when iodobenzene dichloride was used as chlorinating agent under ionic conditions (41).

Examples have been given illustrating the course of reaction with variation in electrophile, nucleophile and solvent. It is of

interest to examine the effect of structural modifications to the olefin while keeping the norbornyl skeleton intact.

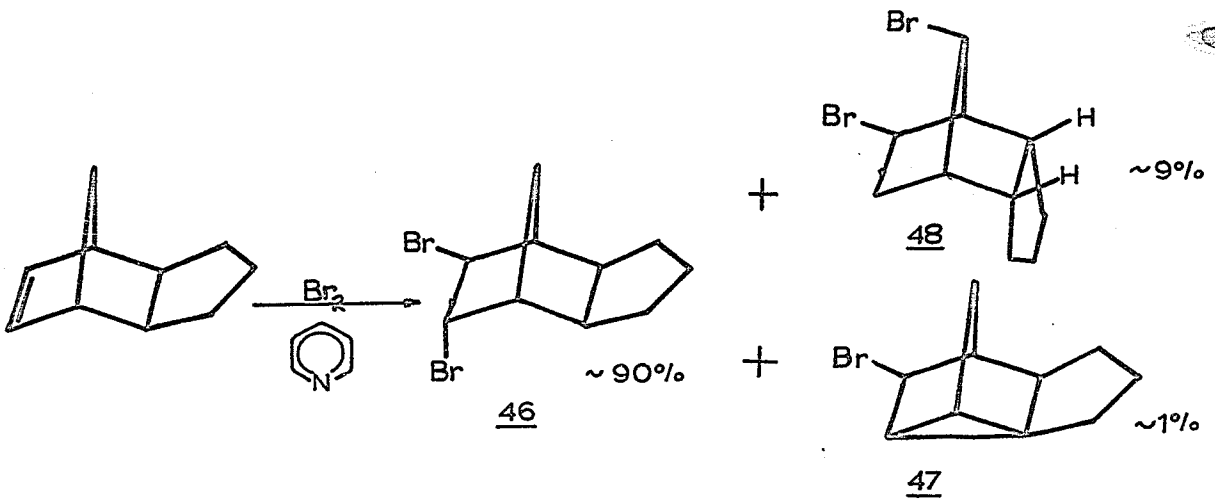
5,6-exo-Trimethylenenorbornyl-2-ene (43) gives 73% rearranged bromoacetate 45 when treated with N-bromo-succinimide in acetic acid (42); no other products were observed.



44 43 45

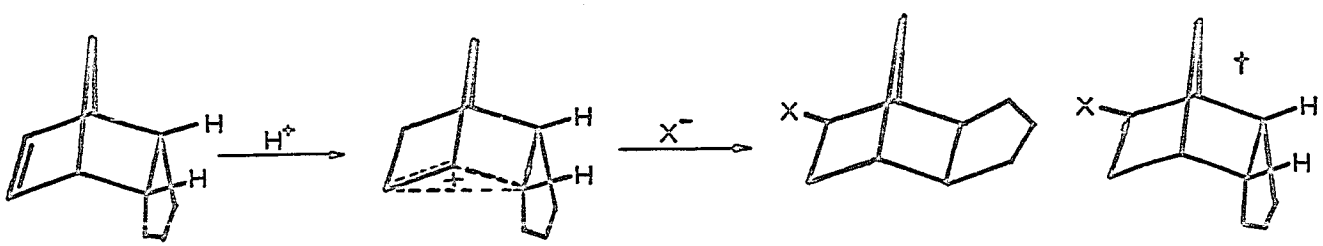
This behaviour may be compared with the addition of bromine (37) and 2,4-dinitrophenyl sulphenyl halides (31,32) to norbornylene where there was an increase in rearranged product on going from carbon tetrachloride to the more polar solvent pyridine. Performic acid oxidation (43) of 43 also gave only rearranged product 44. These exo to endo rearrangements have occurred despite the greater stability of the exo-trimethylene group with respect to the endo analogue.

In contrast to these two additions the bromination in carbon tetrachloride (43) gave 90% of normal trans addition product 46. The only explanation offered to the present is that the less polar solvent disfavours rearrangement. Evidence that this may at least be a contributing factor is the presence of a small yield of rearranged product when pyridine is used as solvent. However, the change from one extreme to another is surprising.



The failure to form tricyclic derivatives has been recorded earlier by Youngblood and Wilder (44) who found that 5,6-exo-trimethylene-norbornyl derivatives do not undergo internal displacement reactions readily, this being ascribed to the strain inherent in the 5,6-exo-trimethylene skeleton.

The additions of formic acid and methanol to norbornylene (49) have given rise to the interesting proposal that classical and non-classical carbonium ions may be involved in some of these reactions. Addition of formic acid, acetic acid and water to 5,6-endo-trimethylenenorbornyl-2-ene (49) gave greater than 90% yields of exo-trimethylene-exo-substituted product, as determined by glc (45).

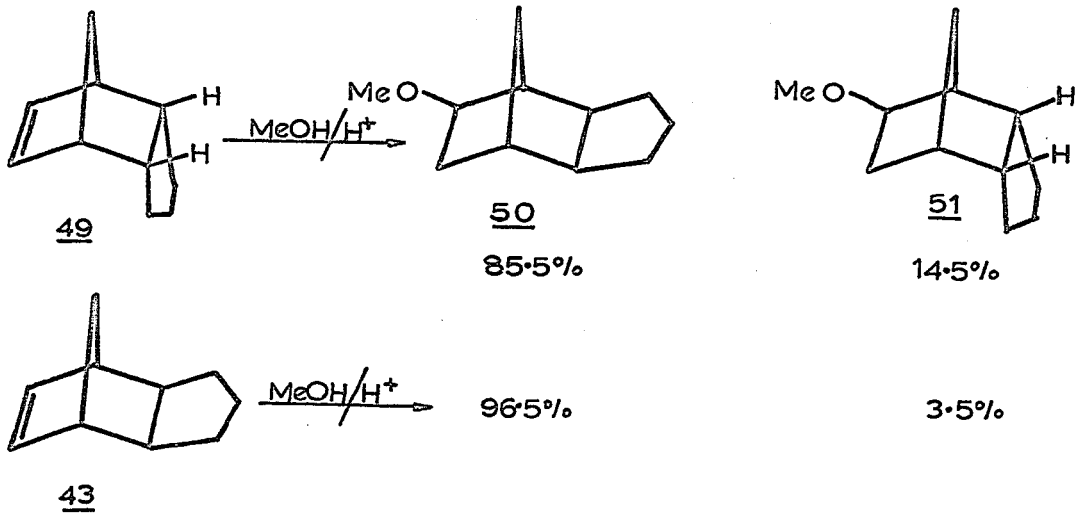


49

	exo	endo
X = HCOO⁻, -OAc	>90%	<10%
X = -OH	98%	2%

† enantiomer

The intermediate will account for these products. The addition of methanol provides interest in that the product distribution is inconsistent with those above.

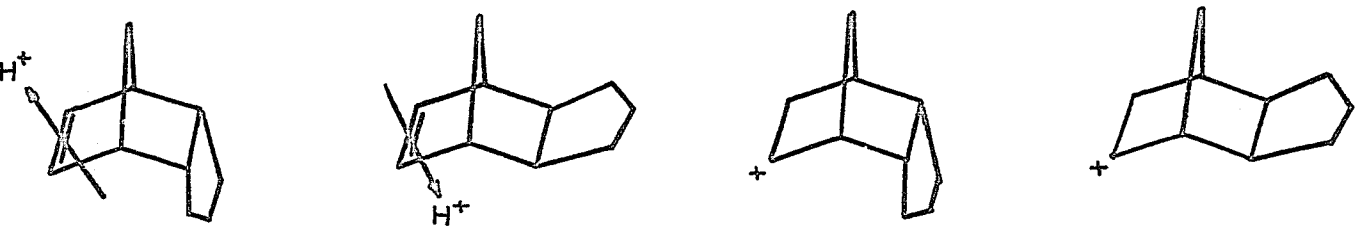


49 → 50 85·5% + 51 14·5%

43 → 96·5% + 3·5%

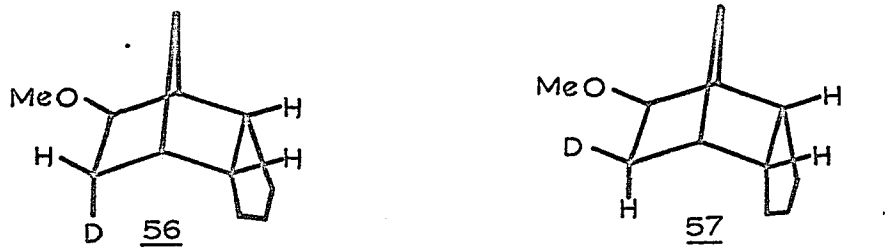
Solvolysis of the 2-exo- and endo-tosylates gave the same ratio of products as obtained in the addition of methanol to 5,6-exo-trimethylenenorbornyl-2-ene. Products were not significantly isomerised under the reaction conditions, nor were endo and exo olefins interconvertible. This result can be interpreted as indicating that methanol has succeeded in trapping an intermediate before it can rearrange to give another intermediate capable of partitioning itself to products in the high ratio found in acetic acid. This implies that two pathways are available for these additions. If one considers addition to the exo-trimethylene olefin to be 'normal' i.e. goes through a non-classical intermediate, then in the addition to the endo isomer at least 80% of 51 must arise via an alternative pathway. Cristol (45,46) has

considered intermediates 52, 53, 54 and 55.



52 53 54 55

The exo π-complex 52 may be rejected on the grounds that trans opening would lead to endo substitution and none was observed. Demonstration that an endo protonated π-complex 53 was also inadequate was achieved by addition of deuteriomethanol and subsequent product analysis by nmr spectroscopy (46). If the endo-protonated π-complex is involved the product will be labelled as in 56 otherwise as in 57.

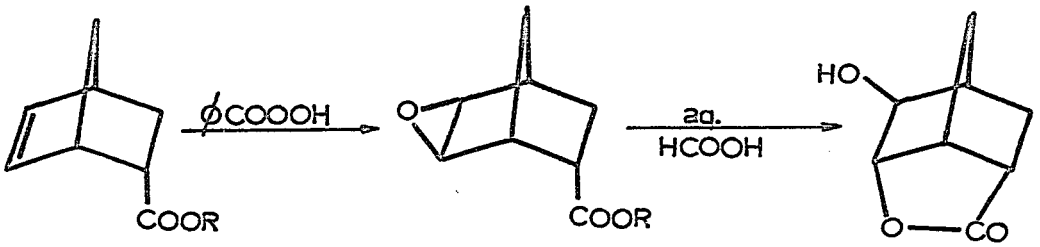


56 57

Nmr showed cis-exo addition was occurring. These results suggest that either a classical carbonium ion or a cyclic four-centre transition state controls product distribution in part.

The facility with which carbon bridging occurs will obviously depend on the groups attached to the carbon atoms involved. An example is provided by the solvolysis of 2-exo derivatives of norbornane and its 5,6-trimethylene analogue. The latter are 30-100 times slower (42); on the basis of inductive effects the opposite would be expected.

Introduction of a strong electron abstractor at C-6 might be expected to decrease participation of the C-1 - C-6 bond thus decreasing the degree of Wagner-Meerwein rearrangement. Observations on this point are scattered and product analysis frequently incomplete. When there is an endo substituent at C-6 the usual course is formation of a trans product arising via intramolecular anionic attack as shown in the following examples.



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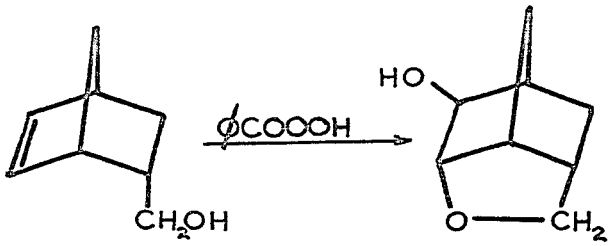

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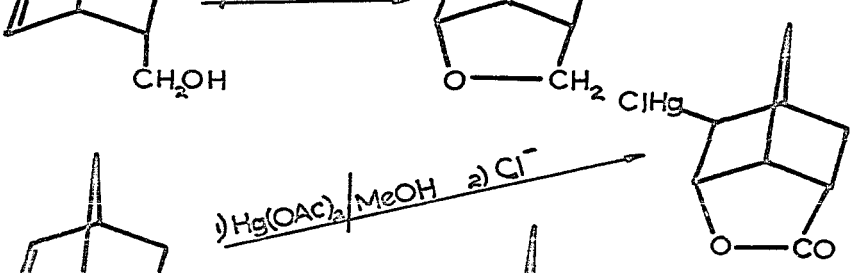

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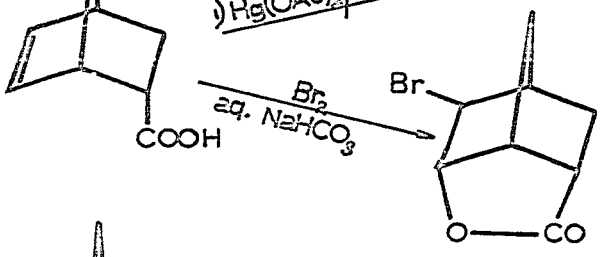

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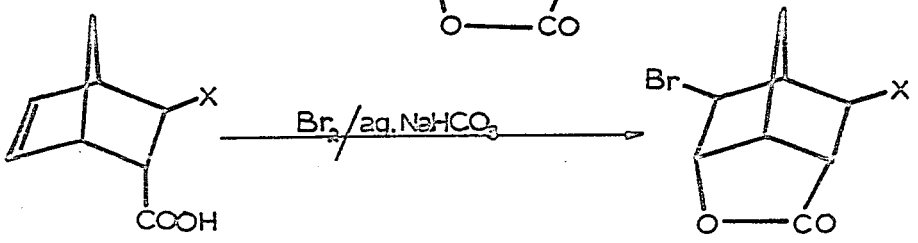
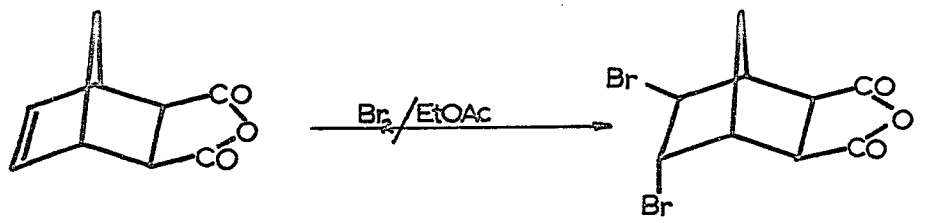


(51)

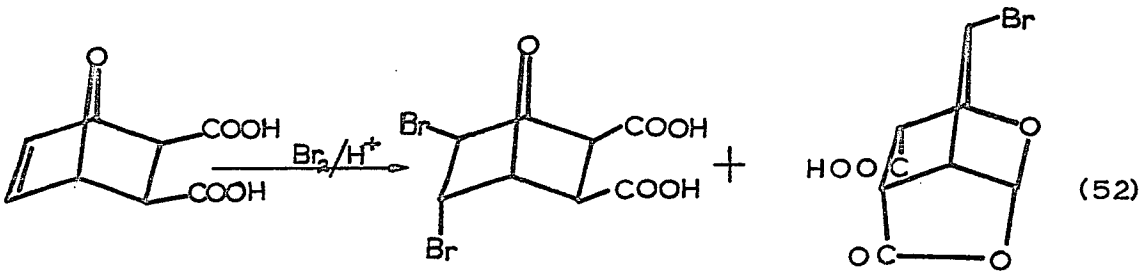
X = -CF_3

= p — subst. phenyl

When the C-6 substituent is exo, trans addition has been observed but, despite the theoretically less favourable circumstances for electron delocalisation, rearrangements are observed in some cases. The following examples serve as a somewhat inadequate qualitative guide.



92% (51)



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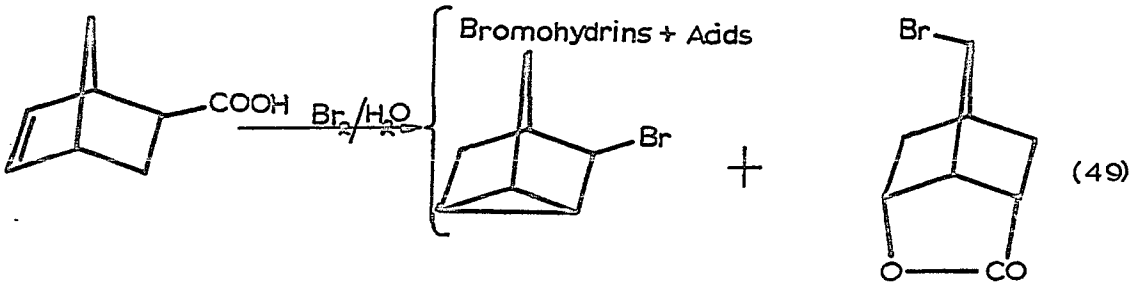

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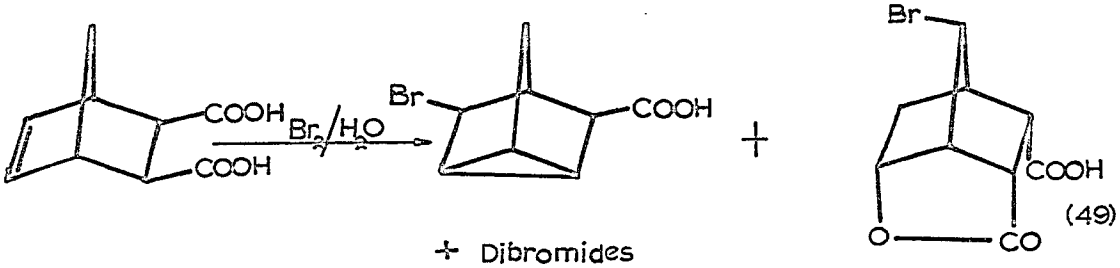


(49)

+ Dibromides

The possible modes of addition are summarized in Fig. 1. From this review of additions to norbornylene it becomes obvious that there are many factors controlling product formation and distribution. In general terms these appear to be:-

1. Substituent effects, both steric and electronic.
2. Ability of the incoming electrophile to stabilise positive charge once covalently bonded, relative to C-6 — C-1 participation.
3. Solvent effects.
4. Ease of elimination from the carbonium ion formed.
5. Nucleophilicity of incoming nucleophiles.
6. Temperature.
7. Stereoelectronic features of the carbonium ion toward incoming nucleophiles.

It is apparent that subtle changes in any one of these parameters can be sufficient to produce gross changes in the course of the reaction.

In most cases only the gross effects have been noted, as accurate quantitative and qualitative studies have not always been possible. This knowledge is a fundamental prerequisite to a full comprehension of the energy balance between all the pathways shown in the complete figure.

It would appear therefore, that many of these reactions could profitably be repeated in detail with rigorous, unambiguous control experiments. The result would be an understanding which would permit predictions to be made with some assurance of their validity.

DISCUSSION

A Reaction Details and Structural Proofs.

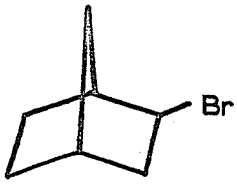
(a) Addition of Bromine fluoride to Bicyclo[2.2.1]heptene.

In a preliminary survey (53) the addition of bromine monofluoride to norbornylene in anhydrous ether at -78° was shown to give four major products; two of these, 7-syn-bromo-2-exo-fluoronorbornane and bromonortricyclene were identified, but the data for the remaining two components were inconclusive. As the reactions of bicyclic compounds currently continue to excite much interest, it seemed of value to repeat this reaction and to examine the products in more detail.

Addition of norbornylene and N-bromo-acetamide to a stirred solution of anhydrous hydrogen fluoride in ether at -78° gave a partially solid crude product which was fractionated on a spinning band distillation column after removal of the crystalline product by filtration; only partial separation of the three major liquid components was achieved in this way. The pure components were obtained by preparative glc.

Although losses due to pyrolysis on the hot metal surfaces of the detector were heavy no rearrangement of the crude reaction products occurred as indicated by an infrared spectral comparison of samples before and after injection. The three components were designated as A, B and C in the order of their elution on glc.

Compound A was shown to be a mono-bromide by elemental analysis, and comparison of its infrared spectrum and refractive index with those reported proved it to be bromonortricyclene (36) (39).



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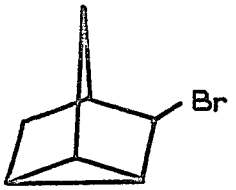

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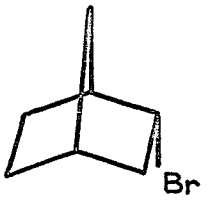

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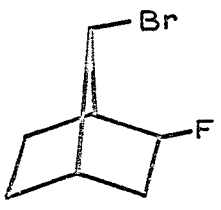
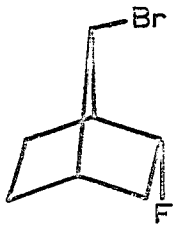
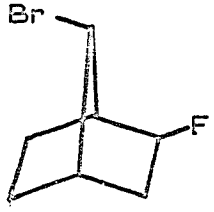
Compound B, isolated in a purity of 94% by fractional distillation, was further purified by glc and found to be a fluorobromonorbornane by elemental analysis. The proton nmr spectrum (Fig. 2) readily indicated the positions of substitution by the halogens; the stereochemistry was proven with the aid of dipole moment data. The appearance of the CHBr proton as a broad peak at δ4.20 (252 cps) (width at half height = 4 cps) without observable splitting locates the bromine atom at the C-7 position; formulae with bromine on any other methylene carbon would be expected to have much larger vicinal coupling constants (J = 2.1 to 9.5 cps) (54, 55, 56). The coupling constant J_{17} has been measured for C-7 substituted saturated (57) and unsaturated (55, 58) norbornylanes and found to be in the order of 0.0 to 0.5 cps. for the former and 1.5-2.0 cps. for the latter. Location of the bromine at C-7 unequivocally places the fluorine at C-2 with a J_{HF} value of ca. 52 cps. (59). There are four possible structures to be considered for compound B; 61, 62, 63 and 64. The observed dipole moment, 2.38 D, excludes structures 61 and 62 on the basis of their calculated dipole moments (Table 1), 3.86 D and 1.71 D respectively. The 7-anti-bromo-2-endo-fluoro (μ_{calc} = 2.09)



61



62



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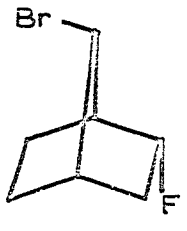
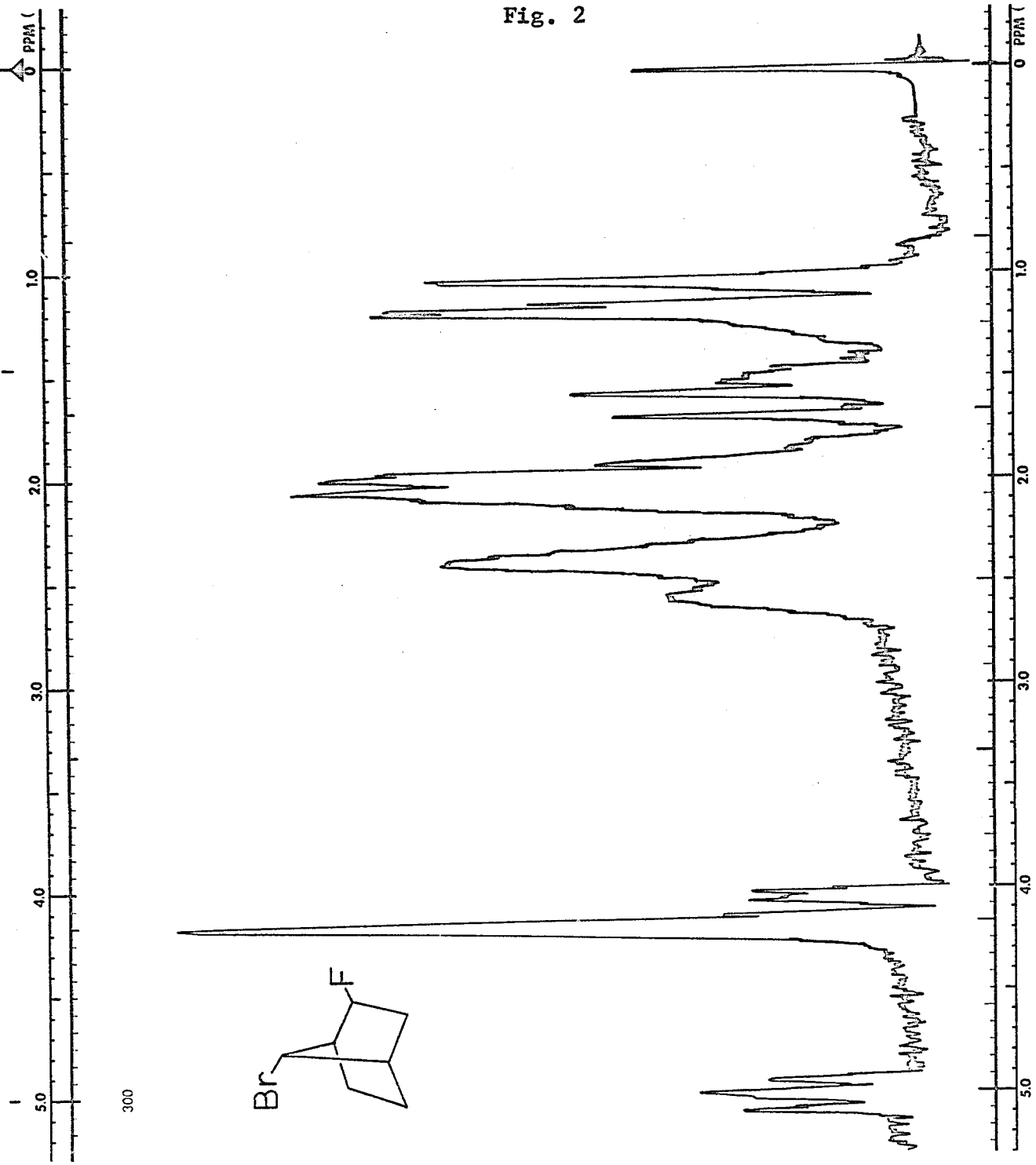


64

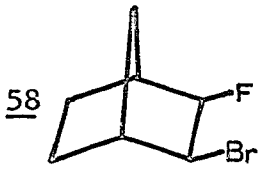
Fig. 2



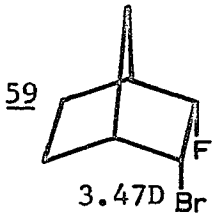
Nmr Spectrum of 7-anti-Bromo-2-exo-fluoronorbornane in CCl_4

Table 1

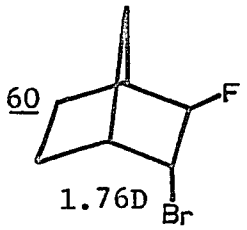
Calculated Dipole Moments of Bromofluoronorbornanes (64)



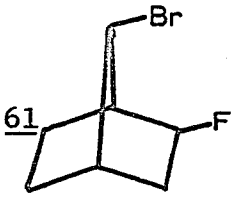
3.67D



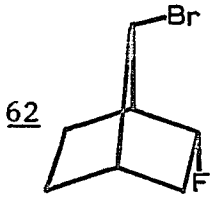
3.47D



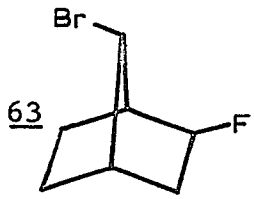
1.76D



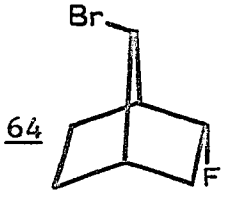
3.86D



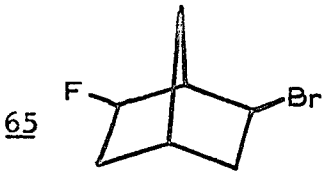
1.71D



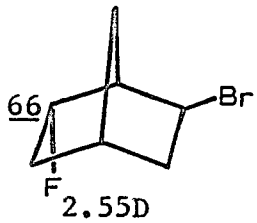
2.03D



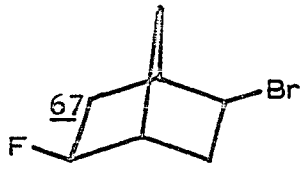
2.09D



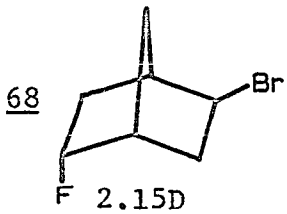
2.12D



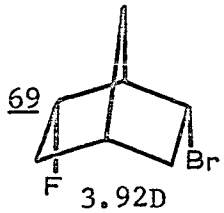
2.55D



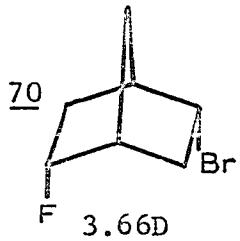
1.62D



2.15D

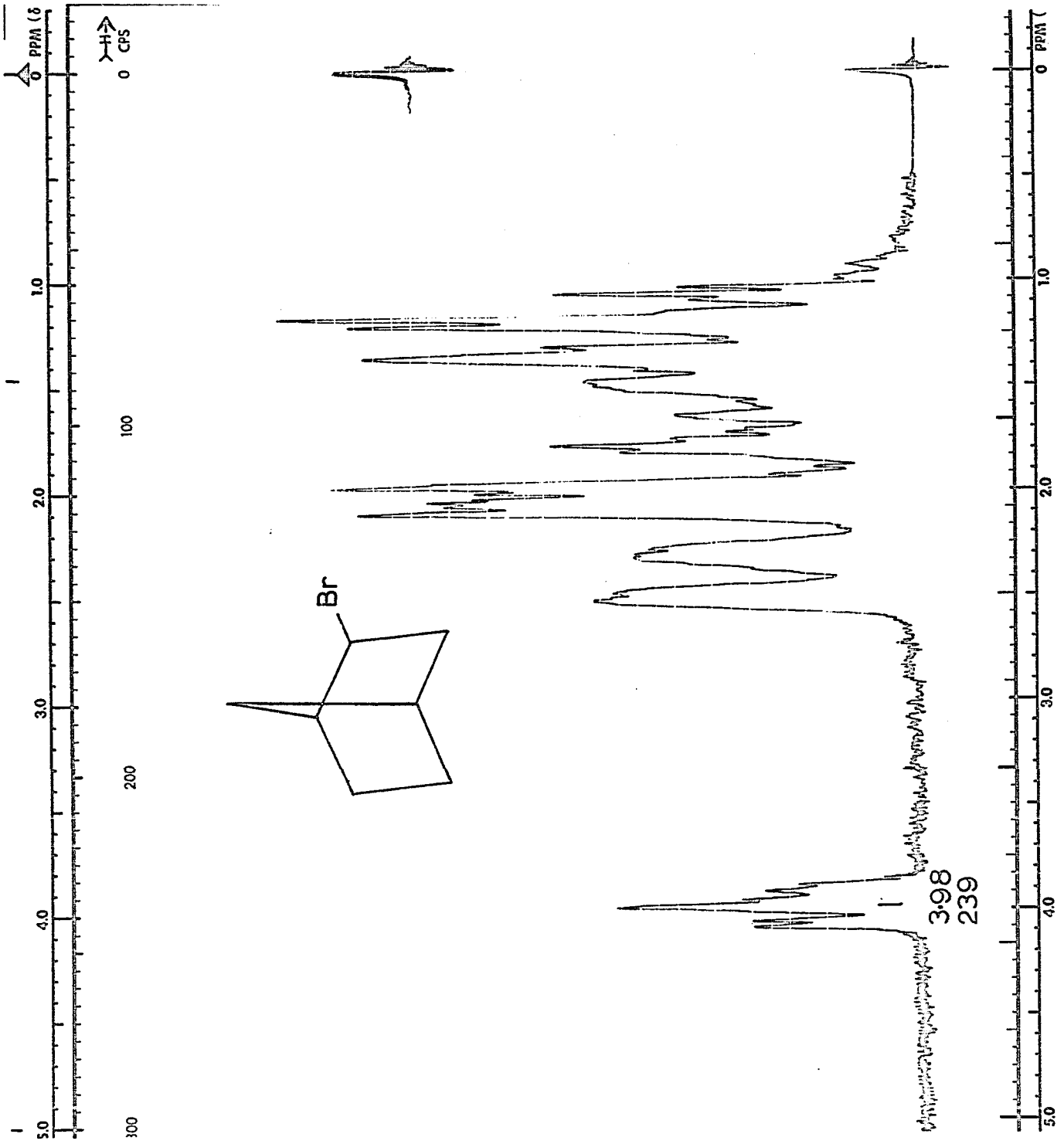


3.92D



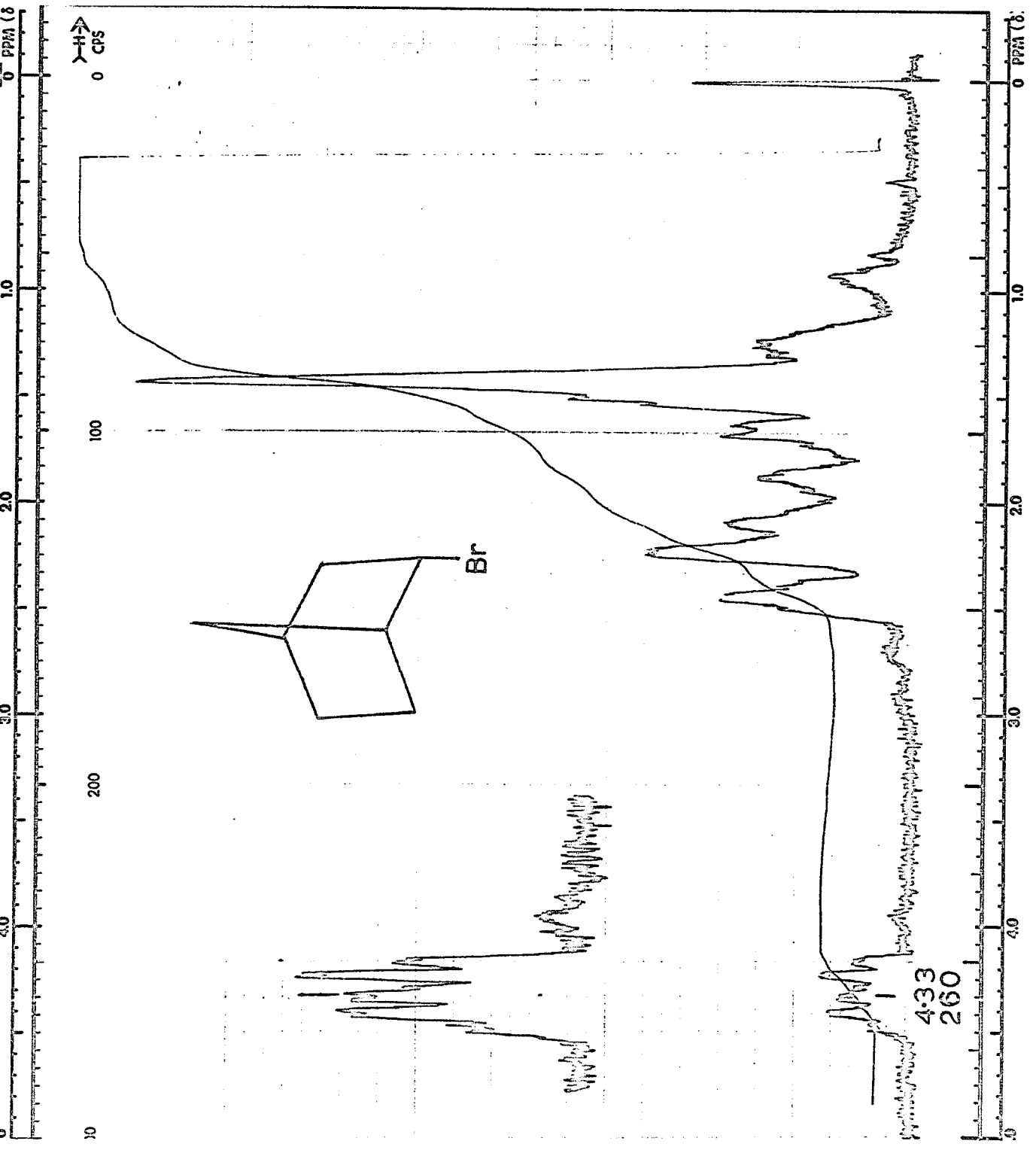
3.66D

Fig. 3



Nmr Spectrum of 2-exo-Bromonorbornane in $CDCl_3$

Fig. 4

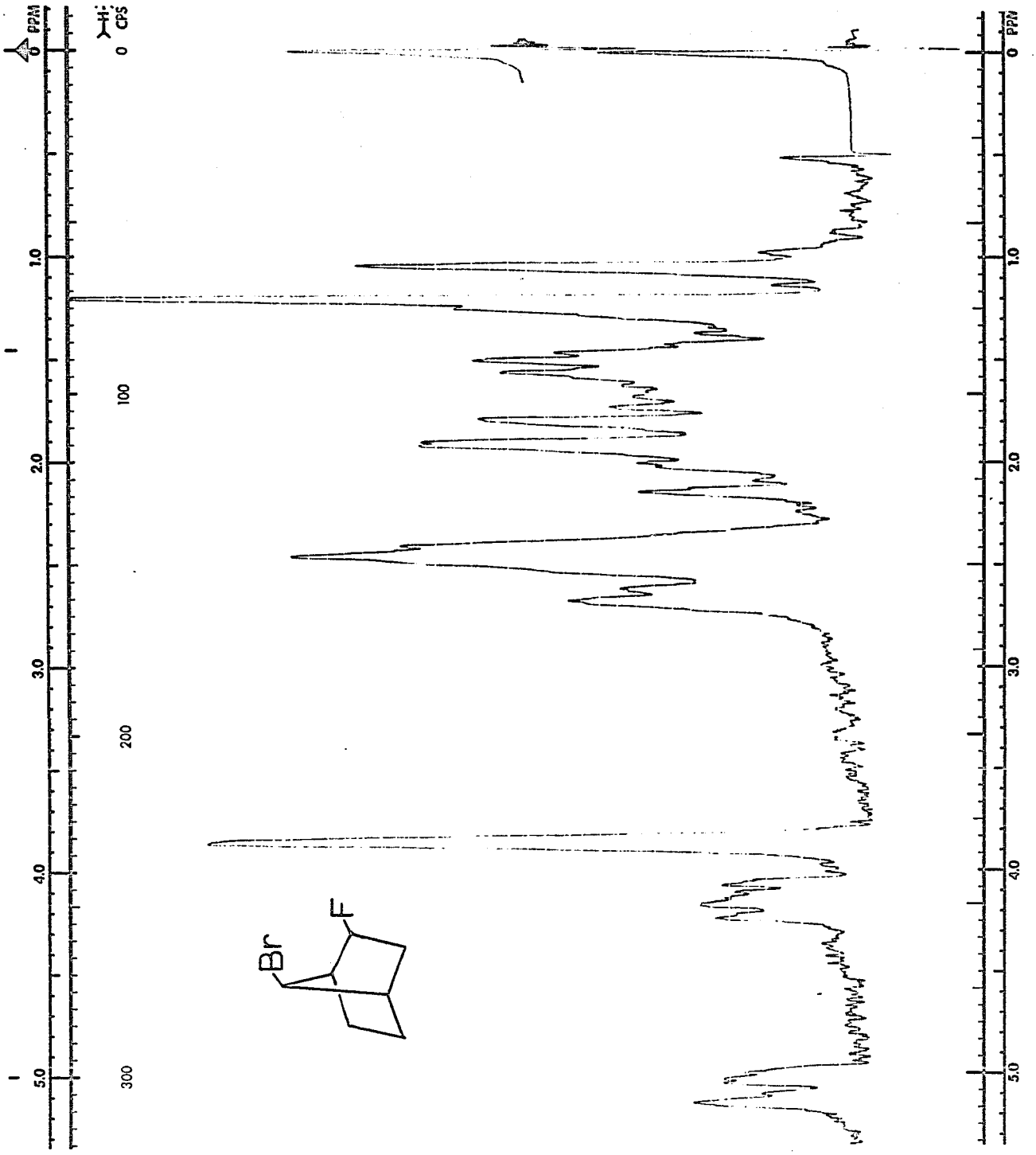


Nmr Spectrum of 2-endo-Bromonorbornane in $CDCl_3$

isomer 64 may be excluded on the basis of mechanistic and nmr evidence. The CHF absorption has the typical splitting pattern of an endo-hydrogen and in addition has almost the same chemical shift as Compound C which will be shown to be the 7-syn-bromo-2-exo-fluoro isomer. It has been observed that endo-α-proton resonance occurs at a higher field than that of exo-protons. For example the endo-2-proton of 71 occurs at 21 cps. higher field than the exo-2-proton of 72 (Figs. 3 and 4). In the 2,3-dihalonorbornanes this difference varies between 17 and 40 cps. (55). Moreover, as will be shown subsequently, an endo-fluoro isomer is mechanistically very unlikely and therefore Compound B may be assigned structure 63, 7-anti-bromo-2-exo-fluoronorbornane.

Compound C, isolated by preparative gas chromatography, was shown to be 7-syn-bromo-2-exo-fluoronorbornane (61). The elemental analysis, proton magnetic resonance spectrum (Fig. 5) and observed dipole moment of 3.54 D. are all consistent with this assignment. Thus, the CHBr (3.87 ppm, 232 cps.) peak in the nmr spectrum is again a broad singlet (width at half height = 4 cps.) permitting only structures with a C-7 bromine atom and hence placing the fluorine atom at C-2. Of the four possible compounds, 61, 62, 63, and 64, only 61 has a calculated dipole moment (3.86 D.) close to that observed, and therefore Compound C was confidently assigned structure 61. Confirmation of the position of the bromine atom in B and C came from a qualitative investigation of the reactivity of compounds 36, 61 and 63 toward silver nitrate. The expected order of reactivity is illustrated by the acetolysis of norbornyl tosylates relative to cyclohexyl tosylate (Table 2).

Fig. 5



Nmr Spectrum of 7-syn-Bromo-2-exo-fluoronorbornane in CCl_4

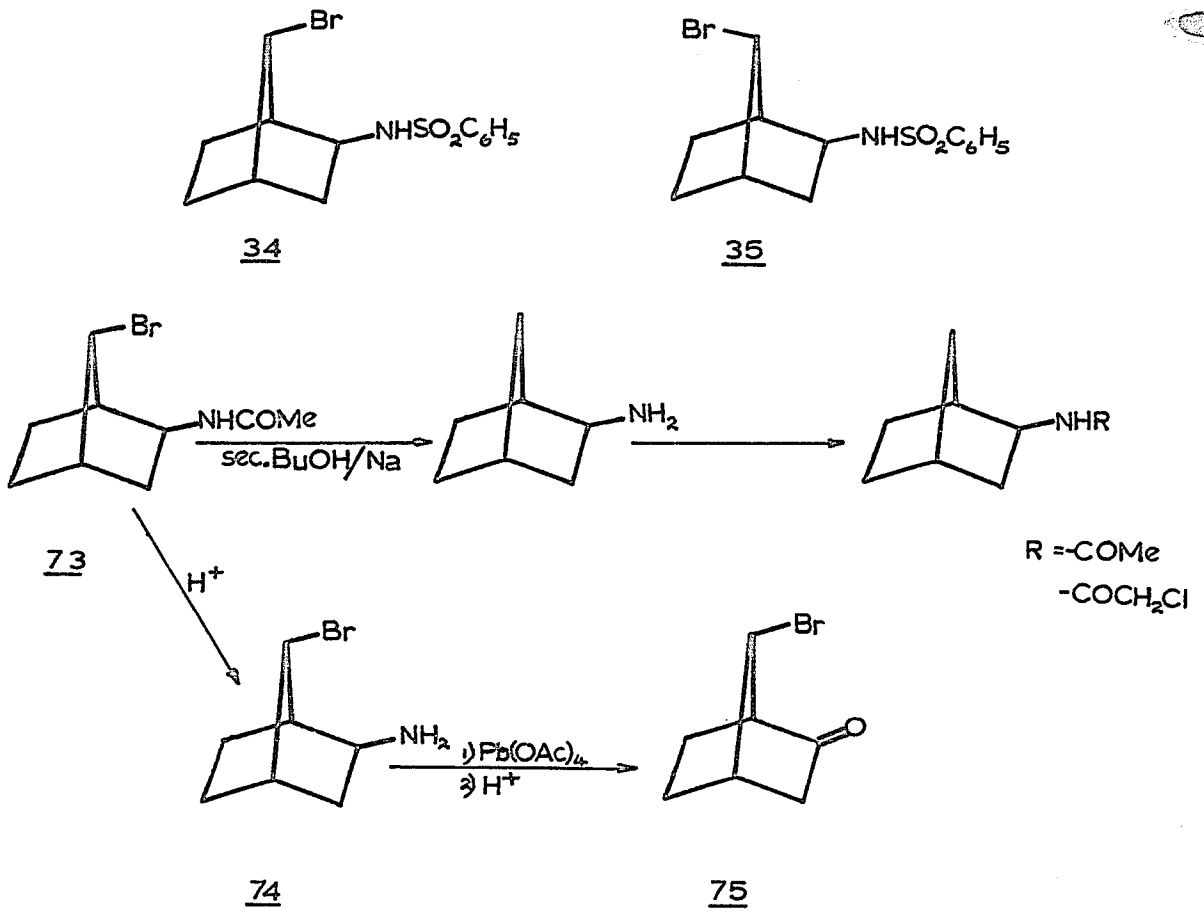
Table 2

Relative Acetolysis Rates, Norbornyl Tosylates (59)

	$\log. k_{rel}$
Cyclohexyl	0.00
2-exo-tosyloxy	2.71
2-endo-tosyloxy	0.18
3-tosyloxynortricyclene	1.82
7-tosyloxy	-7.00

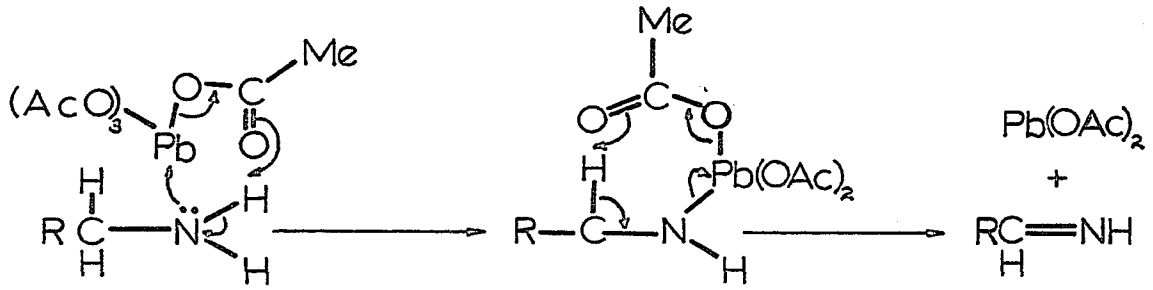
It was found that of the compounds 36, 61 and 63, only 36 gave a precipitate of silver bromide rapidly when treated with a solution of silver nitrate in acetonitrile, thus indicating that bromine in 61 and 63 was at the unreactive C-7 position.

The crystalline product was shown to be a bromoacetamido adduct of norbornylene by analysis and infrared data. A clue to its stereochemistry was provided by the reported addition of N,N-dibromobenzenesulphonamide to norbornylene in benzene at room temperature (36). Three products were isolated and their structures proven. These were bromonortricyclene (36), 7-syn-bromo-2-exo-benzenesulphonamido- (34) and 7-anti-bromo-2-exo-benzenesulphonamidonorbornane (35). It seemed probable, therefore, that the crystalline adduct was an analogue of 34 or 35. The adduct was shown to be 7-syn-bromo-2-exo-acetamidonorbornane (73) by conversion, using procedures similar to those reported for 34, into the known crystalline acetyl and chloroacetyl derivatives of 2-exo-aminonorbornane and the 2,4-dinitrophenylhydrazone of 7-syn-bromonorbornan-2-one (75) as outlined in the scheme below.



Two points are worthy of note in this degradation. Firstly, the liquid amine readily formed a solid amine-carbonate (60) on exposure to moist air which facilitated purification and subsequent derivative formation. Secondly, attempts to oxidise the bromoamine with sodium molybdate and hydrogen peroxide failed to give any substantial amount of ketone, in contrast to the results reported by Zalkow et al (36). The infrared spectrum of the crude product showed only a very weak band at 1750cm.$^{-1}$ indicative of a five-membered ring ketone; however very strong alcohol absorption bands were present. There exists

therefore, the possibility that any ketone formed may arise via a displacement of nitrogen by hydroxyl and subsequent oxidation, a contingency which should be avoided as there is now a possibility of rearrangement through an intermediate carbonium ion. To circumvent any ambiguity, an oxidising agent was sought which would afford the ketone with no possibility of rearrangement. Lead tetraacetate appeared the most promising as it had been reported to oxidise primary amines to nitriles in yields of 40-60% (61), the intermediate in this oxidation probably being an aldimine (76). With secondary amines the reaction would presumably stop at the ketimine stage as there are no further α-hydrogen atoms to be removed. Subsequent hydrolysis of the ketimine



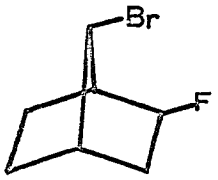
76

would afford the ketone. When the bromoamine was refluxed with 2.5 equivalents of lead tetraacetate in chloroform, a crude product was obtained which showed an imine absorption band at 1650cm.$^{-1}$ in the infrared; hydrolysis and subsequent treatment with acidic methanolic 2,4-dinitrophenylhydrazine gave the known derivative of 75 (36).

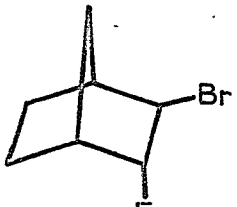
(b) Addition of Bromine to Norbornylene

By analogy with the reported reaction of bromine with norbornylene (37) it had been expected that the products from bromine fluoride

addition would be 61 and 77 rather than 61 and 63 as found. The detailed reasoning for expecting the analogy to hold will be evident



61



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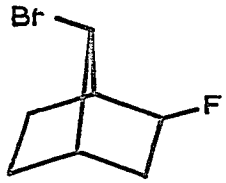


63

from the theoretical discussion (vide infra), but it is sufficient at present to point out that there appeared to be no reason to expect the change in products observed. Therefore, in view of this difference and also the unavailability, at the time of the original work (37), of the sensitive analytical techniques of nmr and glc it was considered advisable to repeat the addition of bromine to norbornylene.

As gas chromatography, both analytical and preparative, was of such extensive value in this work a brief digression will be made to discuss various aspects of the glc procedures used. It has been pointed out previously, that in the separation of the bromine fluoride adducts, losses of as much as 50% were incurred through pyrolysis in the column and hot wire detector. Similar effects were noted in the glc of the analogous dibromides, in particular when copper as opposed to stainless steel columns, were used. The problem was made more acute by the necessity of separating and purifying the relatively large quantities (0.5 g. to 1.0 g.) of each component required for dipole moment determinations. Use of a glass column and inlet port together with a steel detector block and hot wire detector, while improving the situation, did not eliminate all decomposition and concomitant loss. Finally a

satisfactory arrangement was achieved in the use of a glass injector, glass column and a stainless steel hydrogen flame ionisation detector.

For preparative gas chromatography a stainless steel 50:1 splitter working on the capillary tube principle was used in conjunction with a hydrogen flame detector. Calibration of the detector response to the different products of the bromine addition to norbornylene was achieved by chromatography of a series of mixtures containing known weight percentages of the compounds; comparison of the weight percentages as determined by the areas under the peaks with the known weight percentages, allowed proportionality factors to be determined. The results indicated that a correction factor of about 0.81 was required to convert the 'observed' area under the peak into the 'real' area for 2-exo-bromonorbornane; the areas under the individual peaks were proportional to the appropriate weight percent for all the other components. Recorder response linearity was also confirmed. It was found that reproducible results were readily obtainable if all analyses were made with the splitter absent; the splitter appeared to discriminate between components presumably by way of differential diffusion through the long capillary tube. The latter phenomenon may possibly account for the difficulty in obtaining two of the dibromide products, 5-endo-2-exo- and 5-exo-2-exo-dibromonorbornane, in a high state of purity without large losses, in that the response of the detector to a component from the splitter did not coincide exactly with its presence at the exit port. Column details and operating conditions are given in the Experimental section.

The addition of bromine to a stirred solution of norbornylene in carbon tetrachloride at $0^{\circ}C$ gave, after work up, a crude product

containing nine components (Fig. 6), two monobromides, five dibromides and two minor unidentified products (Table 3). Attempts at separation by distillation on a 23 plate spinning band column were successful only in separating the monobromides from the dibromides and in isolating the 7-syn-bromo-2-exo-bromonorbornane (38) from its isomers; refractionation of the dibromide mixtures gave no great improvement. The monobromides were shown to be 36 and 71 by glc comparison of their retention times with those of authentic samples. Separation and purification of the dibromide isomers was achieved by preparative glc using the glass apparatus described in the foregoing discussion on general glc techniques.

The identity of each dibromide was determined by elemental analysis, which showed that all five dibromides isolated were isomers of empirical formula $C_7H_{10}Br_2$, and by nmr spectroscopy, with confirmatory evidence from dipole moments, infrared spectra (Fig. 7) and chemical data.

Before proceeding to an elucidation of the stereochemistry it is essential to know that the five dibromide isomers have all retained the norbornane skeleton. The nmr data in themselves provide evidence for the retention of the skeleton by virtue of the complete absence of any absorption attributable to methyl, cyclopropyl or vinyl groups and the presence of characteristic exo, endo and bridge proton resonance patterns. The possibility of rearrangement of the norbornyl cation to a different type of skeleton is exemplified by the report that solutions of 2-exo-norbornanol in 100% sulphuric acid yield derivatives of cyclohexene when allowed to stand for several hours (62). Additional confirmation was sought in the conversion of at least one of the di-

* Retention times and conditions in Table 3.

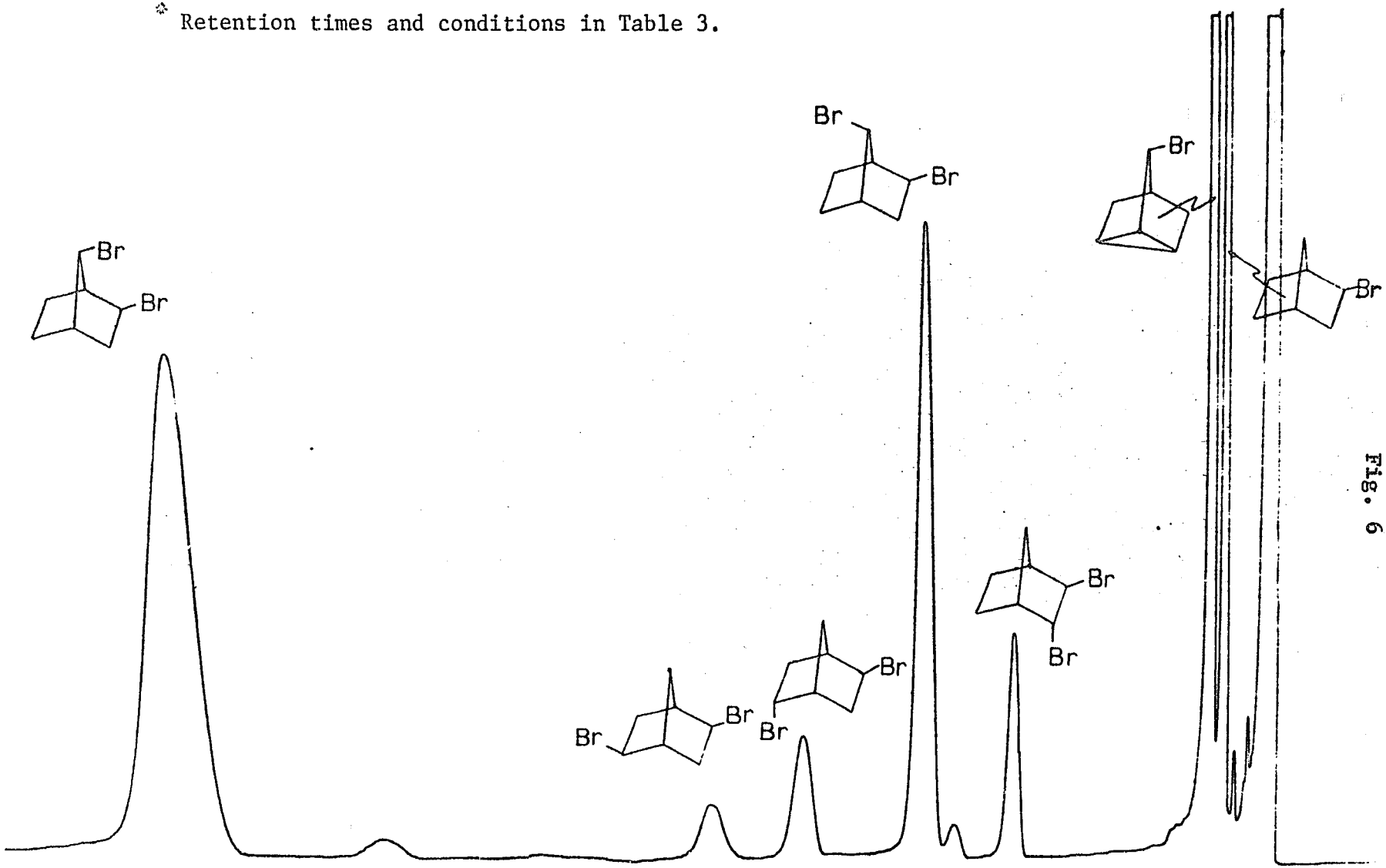


Fig. 6

Glc Trace* of Crude Product from Addition of Bromine to Norbornylene in CCl_4 at 0°

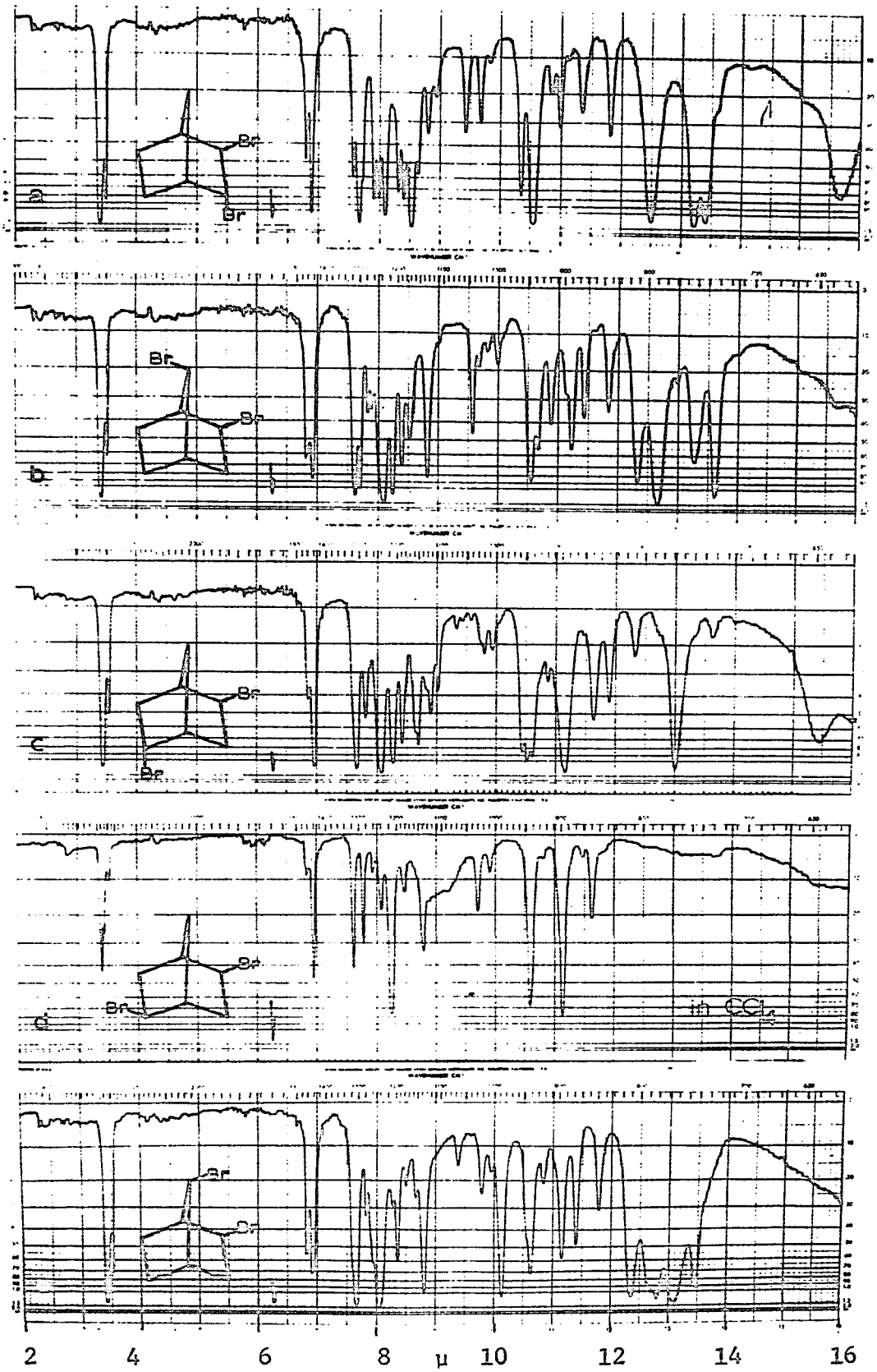
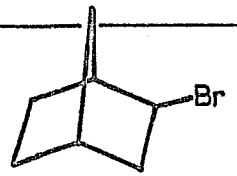
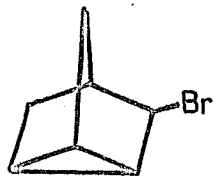
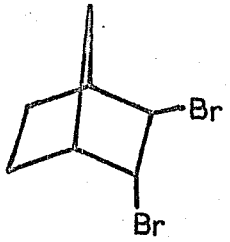
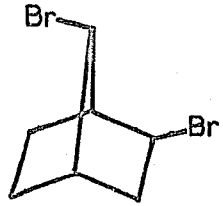
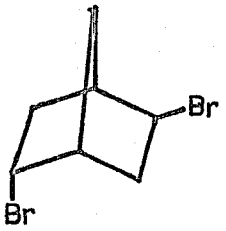
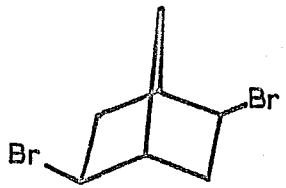
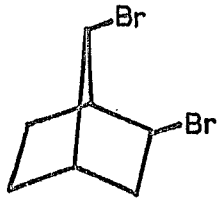


Fig. 7

Infrared Spectra of Dibromide Isomers: a,b,c and e as liq. film

Products: Reaction of Norbornylene with Bromine in CCl_4 at 0°

Compound	Form. No.	Structure	% by Wt.	Ret. Time * (min)
2-exo-bromonorbornane	71		28.2	1.6
bromonortricyclene	36		36.8	1.8
2-exo-3-endo-dibromo	37		5.1	5.4
7-anti-2-exo-dibromo	87		6.6	6.8
2-exo-5-endo-dibromo	83		2.1	8.6
2-exo-5-exo-dibromo	82		1.6	9.8
7-syn-2-exo-dibromo	38		18.4	17.0
Other			1.2	6.4 + 11.0

*Column [H] /120°/Helium flow, 45ml./min.

Table 3

bromides, via an unambiguous pathway, into a known derivative of norbornane. This was achieved by the reductive debromination of 7-syn-2-exo-dibromonorbornane by sodium in t-butyl alcohol and tetrahydrofuran (71) to give norbornane which was identical with a sample synthesized by hydrogenation of norbornylene over platinum oxide.

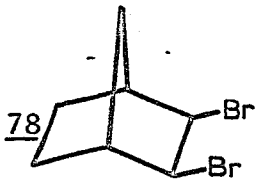
The structural assignments were simplified by unequivocal evidence excluding certain dibromide isomers; both the 2-exo-3-exo-, 78, and the 2-endo-3-endo-dibromo isomer 79 (Table 4) have been synthesized previously (65,66) and are crystalline compounds with melting points of 55.0 - 55.6° and 60.5 - 61.5° respectively. Only one of the dibromides isolated in the current work is crystalline with melting point 94-95.5°. This evidence together with failure to observe the expected nmr spectra, allows compounds 78 and 79 to be excluded from further consideration. The nmr spectra of all five dibromides show a proton α to each bromine atom and therefore any structure with a bromine atom geminal to another or at a bridgehead may be excluded; there remain eleven possible dibromide structures from among which the isolated dibromides were identified by nmr spectroscopy at 60 Mc/s, double irradiation experiments at 100 Mc/s and dipole moments (Tables 4 and 5). The isomers, except for the 2-exo-5-endo-dibromide, will be discussed in the order of their elution from the gas chromatogram.

2-exo-3-endo-dibromonorbornane (37)

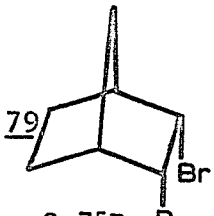
The compound of retention time 5.4 minutes was shown to be the 2-exo-3-endo-dibromide 37: the nmr spectrum corresponded to the literature description (55). The nmr spectrum obtained in carbon

Table 4

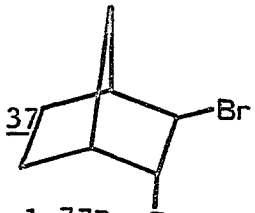
Calculated Dipole Moments of Dibromonorbornanes (64)



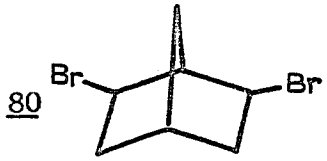
3.72D



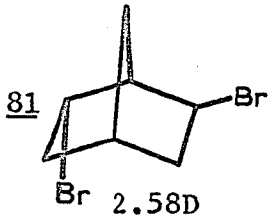
3.75D



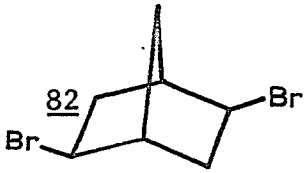
1.77D



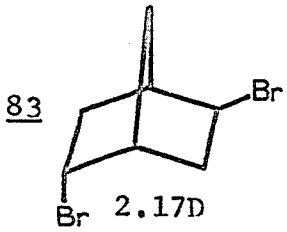
2.14D



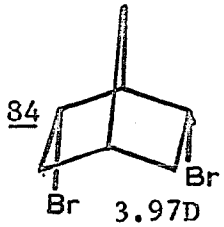
2.58D



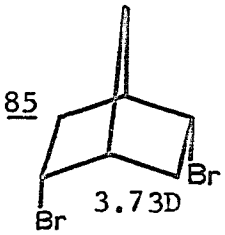
1.64D



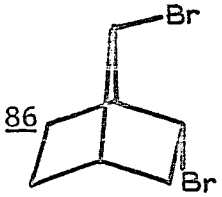
2.17D



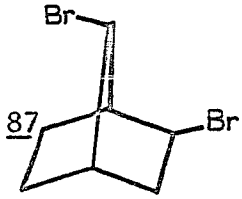
3.97D



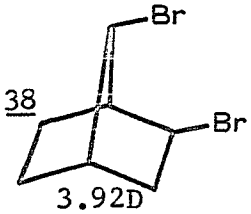
3.73D



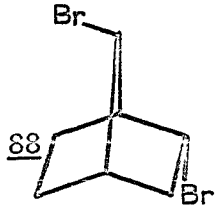
1.74D



2.07D



3.92D



2.12D

Table 5

Observed Dipole Moments of Disubstituted Norbornanes*

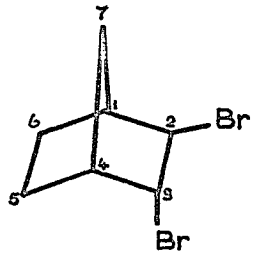
Compound	Solvent		Calculated (64)
	Benzene	Cyclohexane	
	Observed dipole moments		
7-anti-bromo-2-exo-fluoro	2.62	2.38	2.05
7-syn-bromo-2-exo-fluoro	3.76, (3.60)☆	3.54	3.88
2-exo-bromo-3-endo-bromo	-	2.60	1.77
7-anti-bromo-2-exo-bromo	-	2.42	2.07
2-exo-bromo-5-endo-bromo	-	1.10	2.17
2-exo-bromo-5-exo-bromo	-	0.66	1.64
7-syn-bromo-2-exo-bromo	3.45† (37)	3.30	3.92
		CCl_4	
2-fluoro-2 methylbutane	1.92	1.55	-
	(68)	(69)	
1-fluoropentane	1.85	1.31	-

☆Determined by F. H. Dean (53)

†Solvent 1,4-dioxane

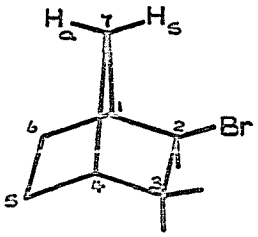
* Sample calculations showed that the calculated and observed dipole moments were in quite good agreement (within 0.1D) for molecules involving relatively small substituents, e.g. chloro-, but in the dibromides compounds non-bonded interractions may become significant, resulting in distortion of the molecule. The unsuitability of benzene in dipole moment measurements has been mentioned previously (70) on the grounds that the dielectric constants obtained were erratic in value with changing concentration; this behaviour has been ascribed to the hygroscopic nature of dried benzene. In the present case this erratic behaviour was not observed with benzene (distilled from calcium hydride before use) but the dipole moments so obtained were consistently higher than those in cyclohexane. This phenomenon has also been noted with fluoro compounds when measured in carbon tetrachloride versus benzene.

tetrachloride is shown in Fig. 8 and is consistent with the structure proposed. Any C-7 substituent may be excluded on the grounds of failure to observe the characteristic 'broad singlet' associated with a C-7-α-proton. It has been demonstrated (55) that in compounds with the

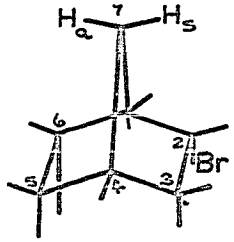


37

norbornane skeleton, an endo proton absorbs 17 to 40 cps upfield from its exo analogue. In addition an endo proton (H-2), as in 71, is frequently characterized by a three line pattern (an overlapping pair of doublets resulting from the couplings H-2 H-3exo and H-2 H-3endo) with



71



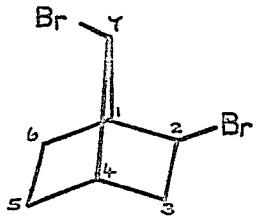
72

further fine splitting from coupling of H-2 with H-7a (Fig. 3). In 72 however, the C-2-exo-proton appears as a multiplet which results from the following couplings; H-2 H-3exo, H-2 H-3endo, H-2 H-1 and H-2 H-6exo (Fig. 4). The spectrum in Fig. 8 therefore, suggests the presence of an exo substituent (endo-proton absorption at 3.83 ppm (230 cps)) and an endo-substituent (exo-proton absorption at 4.42 ppm (265 cps)). The substituent bromine atoms are shown to be vicinal by the sharply resolved three line absorption ascribed to the C-2-endo-proton. As

mentioned previously two protons at C-3 would lead to a six line pattern as observed for 71 (Fig. 3). This structural assignment is amply confirmed by simultaneous irradiation of the compound at 2.46 ppm (H-1 and H-4) which results in collapse of the C-3-H absorption at 4.42 ppm to a slightly split doublet, the expected pattern from H-2 H-3 coupling (J-2.9 cps) with long range H-3 H-5 coupling (J 1.3-1.8 cps) (57) superimposed on it (Fig. 9).

Irradiation at 4.42 ppm induces collapse of the absorption ascribed to the C-2-endo-proton to a doublet (J~3 cps) which may be compared with the literature value of 2.9 cps for $J_{H-2\ H-7}$. This interdependence of H-2 and H-3 unambiguously demonstrates their attachment to vicinal carbons. Chemical evidence for the vicinal nature of the bromine atoms is provided by the observation that the rate of dehydrobromination with phenyllithium is much greater for this isomer than for the other isomers. This is to be expected on the basis of an increased acidity of the C-2 and C-3 protons due to the combined inductive effects of the vicinal bromine atoms.

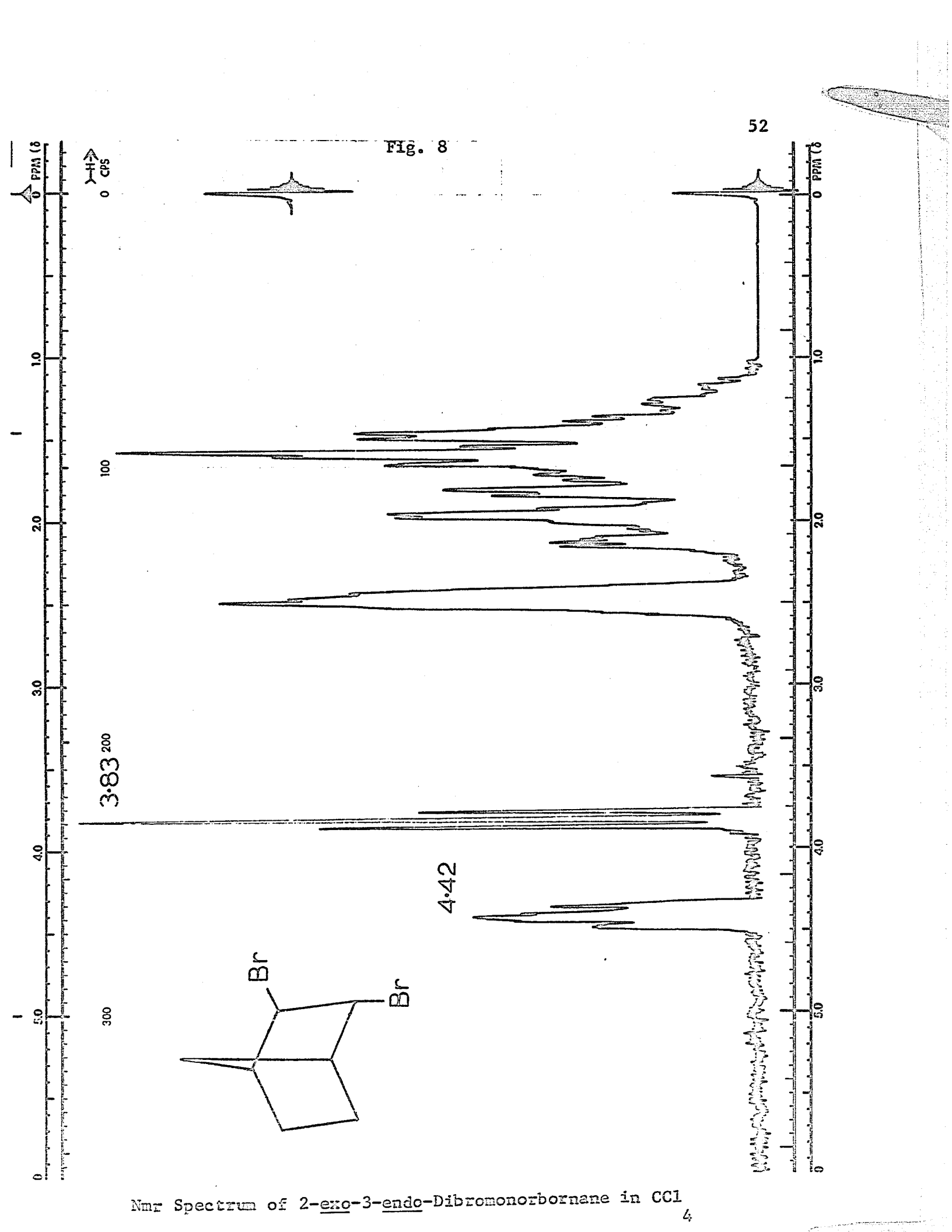
7-anti-2-exo-Dibromonorbornane (87)



87

The compound of retention time 6.8 min. was assigned the structure 7-anti-2-exo-dibromonorbornane (87) from nmr evidence (Fig. 10). The spectrum showed a three line absorption at 3.93 ppm (236 cps), which was ascribed to an endo-α-proton for the reasons discussed on page 50 , and

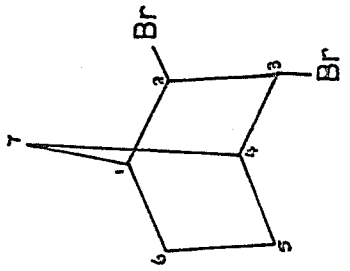
Fig. 8



Nmr Spectrum of 2-exo-3-endo-Dibromonorbornane in CCl_4

Fig. 9

Nmr Double Irradiation Spectra of 2-exo-3-endo-Dibromonorbornane (100Mc/s)



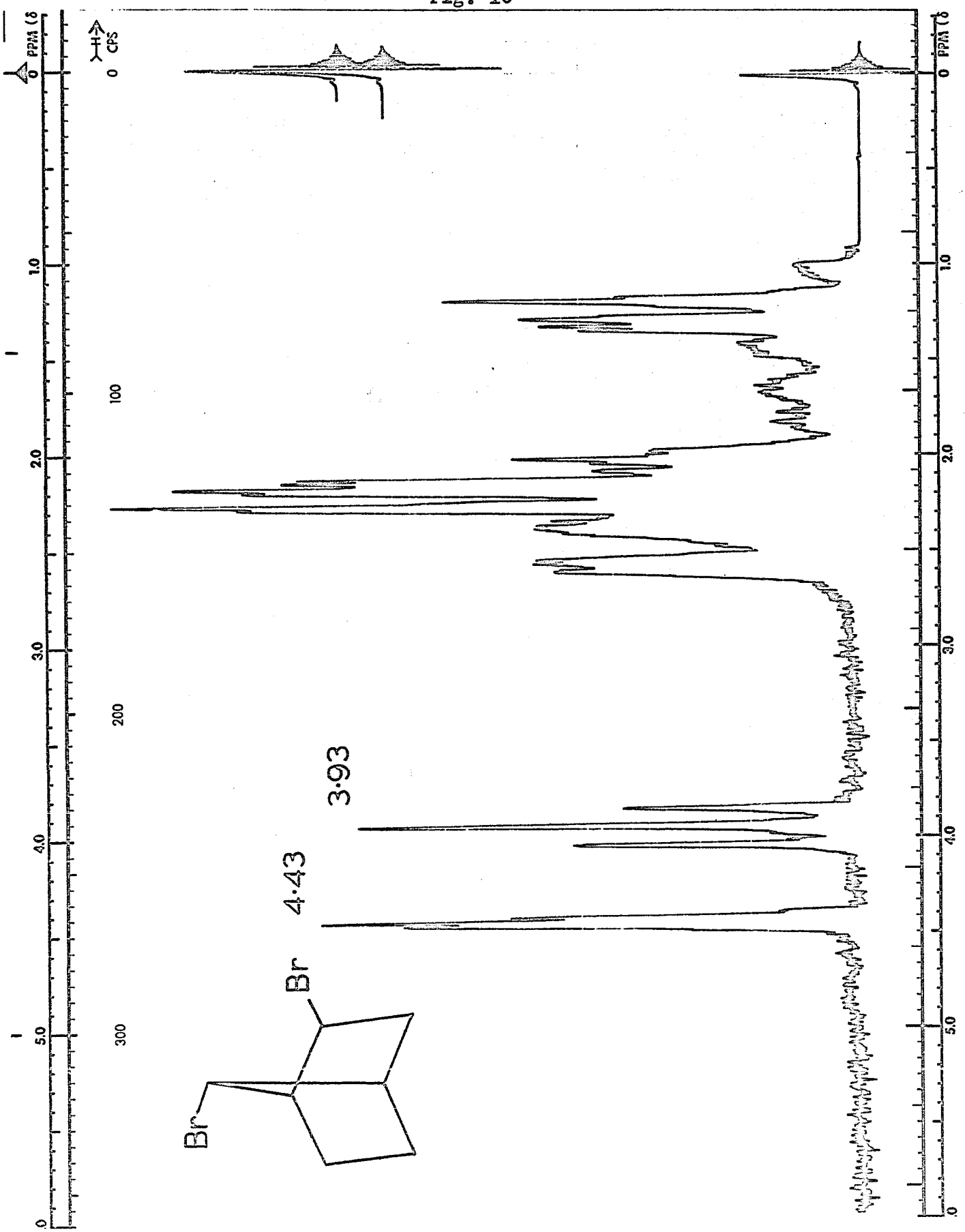
Note: figures in parentheses indicate the chemical shift of the absorption irradiated.

a broad absorption, (width at half height 4 cps) at 4.43 ppm (266 cps) with barely resolved fine splitting of approximately 0.5-1.0 cps. This absorption is consistent with substitution at the C-7 position, the fine splitting being derived from coupling of the C-7-syn-proton with the C-5 and C-6-endo-protons. The wide spacing of the absorption at 3.93 ppm (6 cps between peaks) is indicative of vicinal coupling and the absence of further splitting is consistent with the C-7-anti position being substituted.

The 2-exo-3-endo-dibromide has been reported to have $J_{endo\text{-}H\text{-}2,\ exo\text{-}H\text{-}3}$ equal to 2.9 cps (55) while the 2-exo-3-exo-bromochloro compound has $J_{endo\text{-}H\text{-}2,\ endo\text{-}H\text{-}3}$ equal to 6.8 cps. If this latter coupling constant is approximately the same in the 7-anti-2-exo-dibromide then $J_{endo\text{-}H\text{-}2,\ exo\text{-}H\text{-}3}$ for this isomer is about 5.2 cps. This increase in the trans coupling constant is explicable either on the basis of a difference in bond angles in the two dibromides or the decrease in the number of electronegative substituents α to the coupled protons (72).

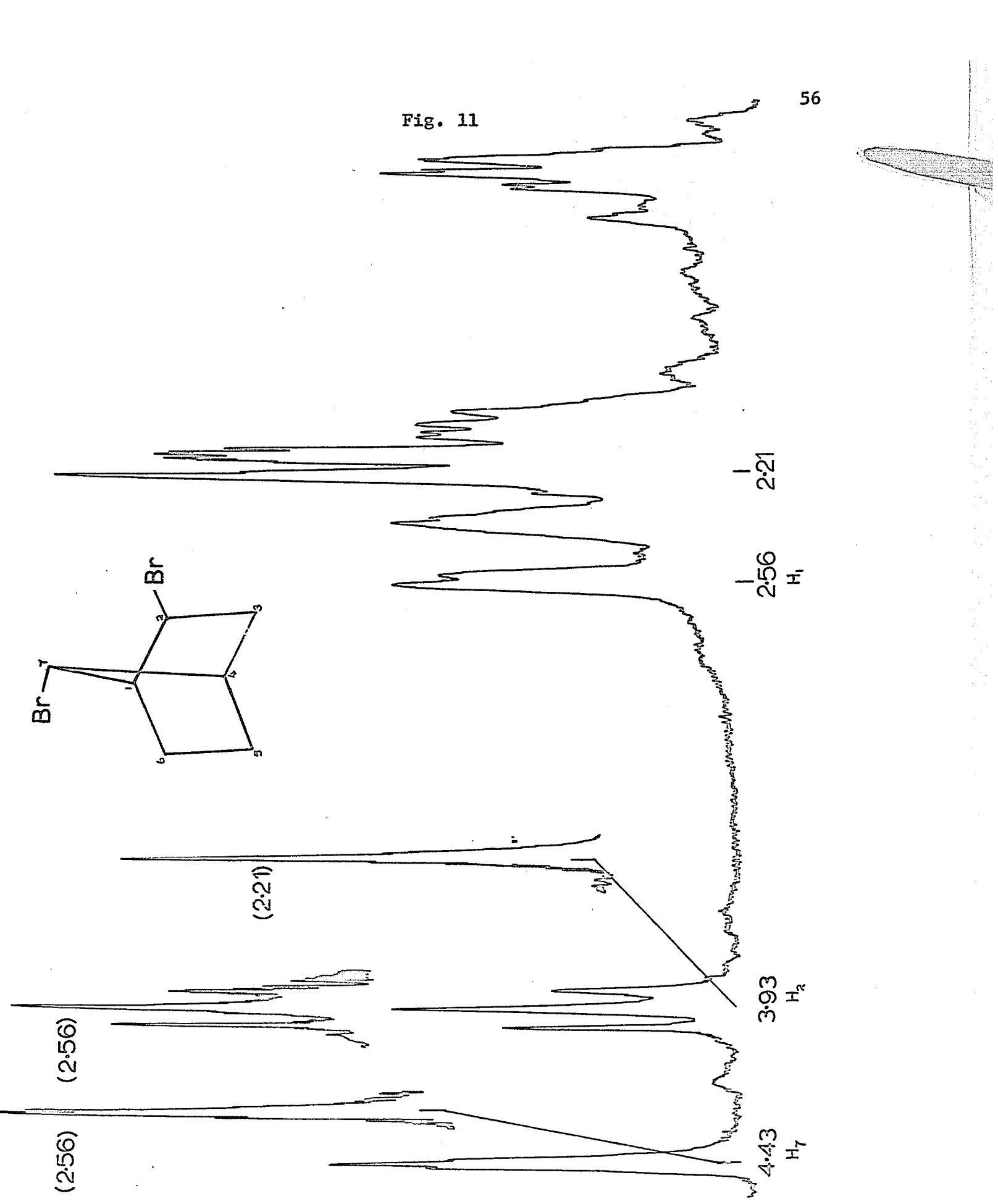
Double irradiation nmr confirms the substituent position (Fig. 11); irradiation at 2.56 ppm (H-1) has no effect on the absorption at 3.93 ppm (H-2) as expected, but it does appear to result in partial collapse of the absorption at 4.43 ppm (H=7) to a doublet split by less than 1 cps which indicates the presence of a very small coupling between H-7 and H-1. It has been shown that the analogous coupling constant in 89 is approximately 1.7 cps (55). Irradiation at 2.21 ppm (methylene absorption) results in collapse of the H-2 absorption to a singlet, a result consistent with the substituents being nonvicinal. The presence of the bromine atom in the C-7-anti position is confirmed by the dipole

Fig. 10



Nmr Spectrum of 7-anti-2-exo-Dibromonorbornane in CCl_4

Fig. 11



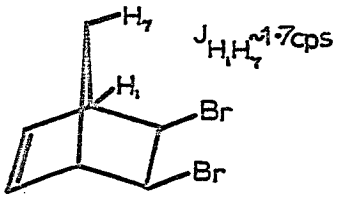
Nmr Double Irradiation Spectra of 7-anti-2-exo-Dibromonorbornane

(100Mc/s)

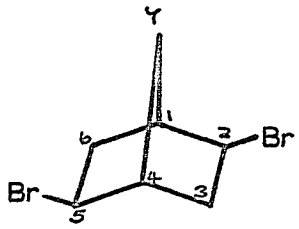
moment of 2.4 D in cyclohexane (calcd: 2.07D), a value much too small for the compound to be the syn isomer (calcd: 3.92D).

5-exo-2-exo-Dibromonorbornane (82)

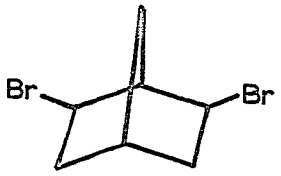
The compound of retention time 9.8 min. has been demonstrated to have properties consistent with structure 82. This isomer is crystalline, which together with the very simple infrared and nmr spectra (Fig. 12) plainly demonstrate the presence of a high degree of symmetry in the molecule. These properties are inherent in only six



89



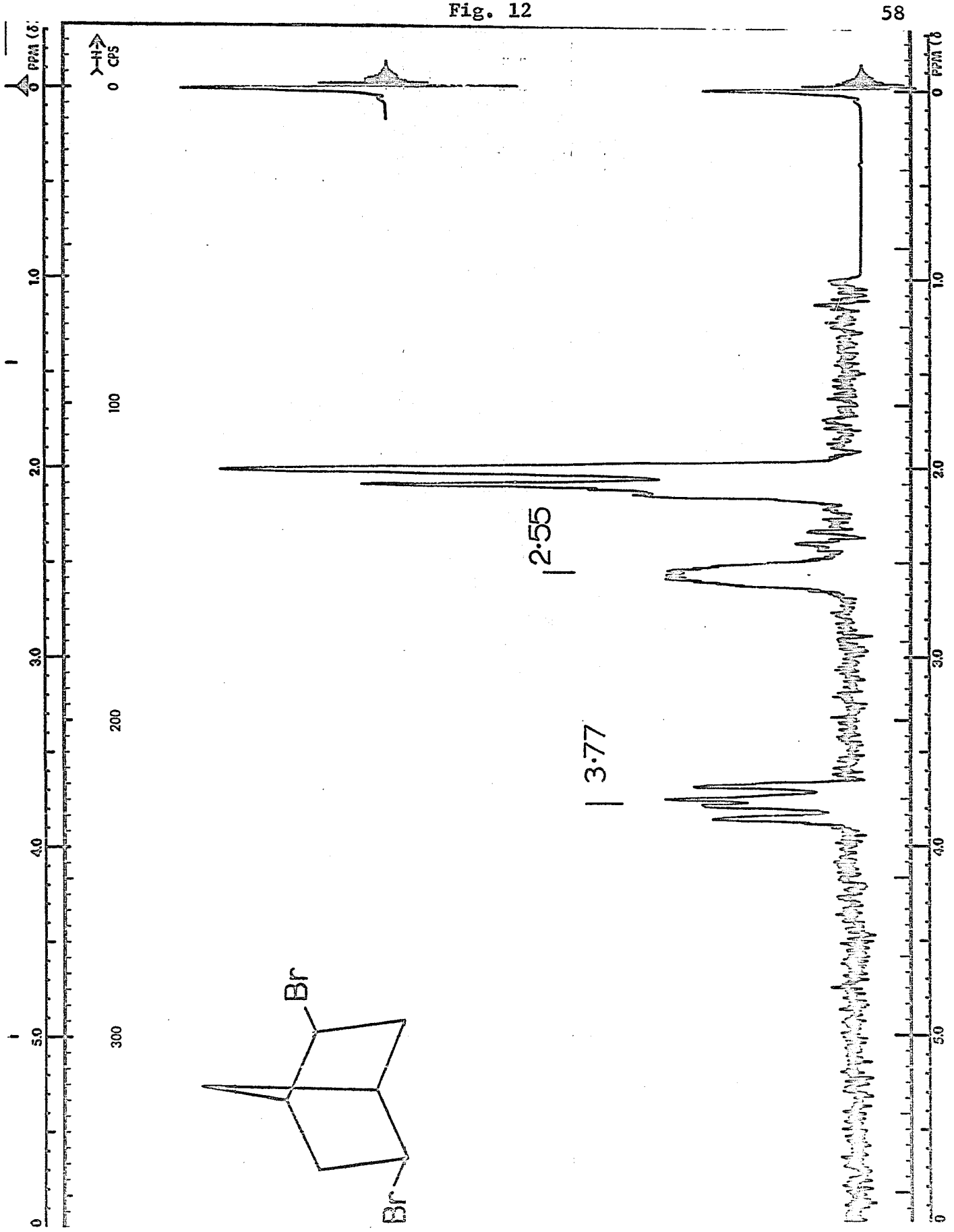
82



80

structures; 78, 79, 80, 82, 84 and 85. Compounds 78, 79, 84 and 85 may be immediately discarded on the grounds of melting point in the cases of 78 and 79, on the observed dipole moment (0.66D) being much too low for any of these four structures and on the absence of the characteristic 2-endo-proton splitting pattern which 79, 84 and 85 should exhibit. The doublet of doublets at 3.77 ppm, (226 cps) (H-2 + H-5) which shows further barely resolved splitting, is consistent with a structure in which the C-2-endo-proton (H-2) is coupled with two protons at C-3 and the C-7-anti-proton. The absorbance of the two methine protons, 2.55 ppm (153 cps), appears as a narrow symmetrical multiplet (width at half height 7 cps) which indicates that both methine protons are in an identical environment. Thus structure 80

Fig. 12



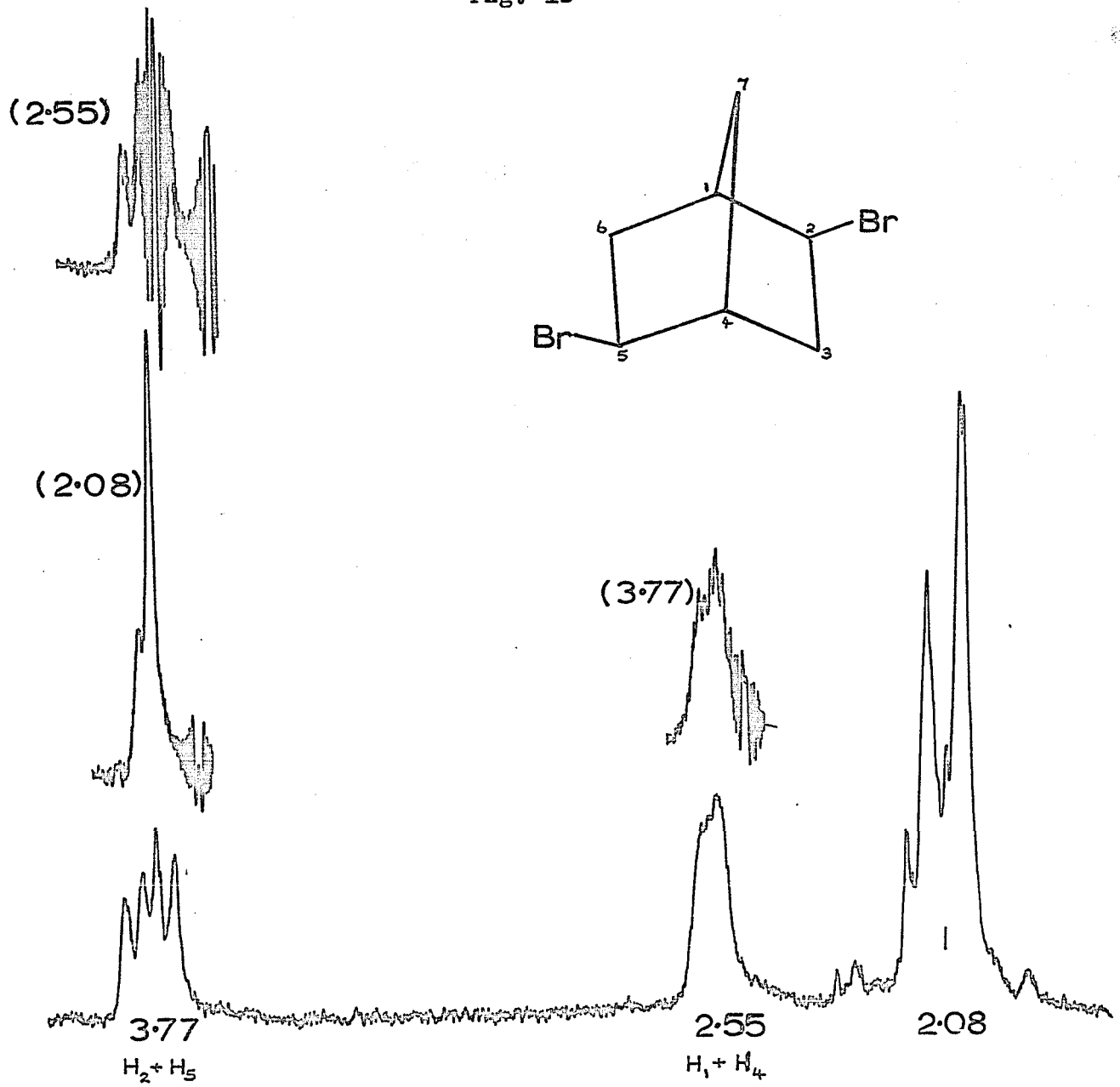
Nmr Spectrum of 2-exo-5-exo-Dibromonorbornane in CCl_4

may be excluded. Evidence to substantiate the assumption that the methine protons (H-1 and H-4) in structure 80 would have different chemical shifts is provided by the nmr spectrum of 7-anti-2-exo-dibromonorbornane (Fig. 10) in which the absorbance of H-1 and H-4 are clearly separated at 2.56 ppm (155 cps) and 2.39 ppm (143 cps) respectively. Confirmation for the assignment 82 was supplied by irradiation of the methylene protons at 2.08 ppm which brought about collapse of the doublet of doublets at 3.77 ppm to a singlet (Fig. 13) which is as expected. If the substituent had been endo, irradiation should have resulted in collapse to a well defined doublet due to the remaining coupling between H-1 and H-2-exo. The lack of coupling between H-1 and endo-H-2 also explains why irradiation at 2.55 ppm does not affect the 3.77 ppm absorption.

2-exo-5-endo-Dibromonorbornane (83)

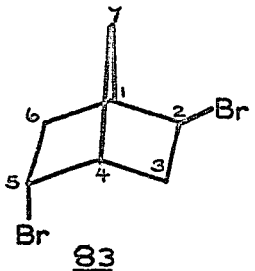
The dibromo isomer with retention time 8.6 minutes cannot be assigned a unique structure by nmr alone (Fig. 14); however, the number of possible structures may be limited to two and a choice made on the basis of mechanistic and dipole moment data. Structures with a substituent at C-7 may be excluded as the characteristic broad singlet associated with such a substitution is clearly absent. In addition, neither the broad multiplet between 4.37 and 3.67 ppm (262 and 220 cps), nor the general complexity of the spectrum is consistent with both substituents being exo or endo; a plane of symmetry would be an inherent property of such substitution and hence, as has been seen previously (Fig. 12), a greatly simplified spectrum would result. Only two

Fig. 13

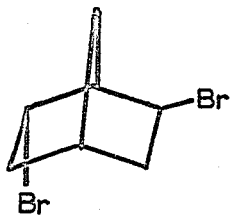


Nmr Double Irradiation Spectra of 2-exo-5-exo-Dibromonorbornane (100Mc/s)

structures remain, 83 and 81. On the basis of inductive and anisotropic effects it might be expected that H-1 in structure 81 would



83



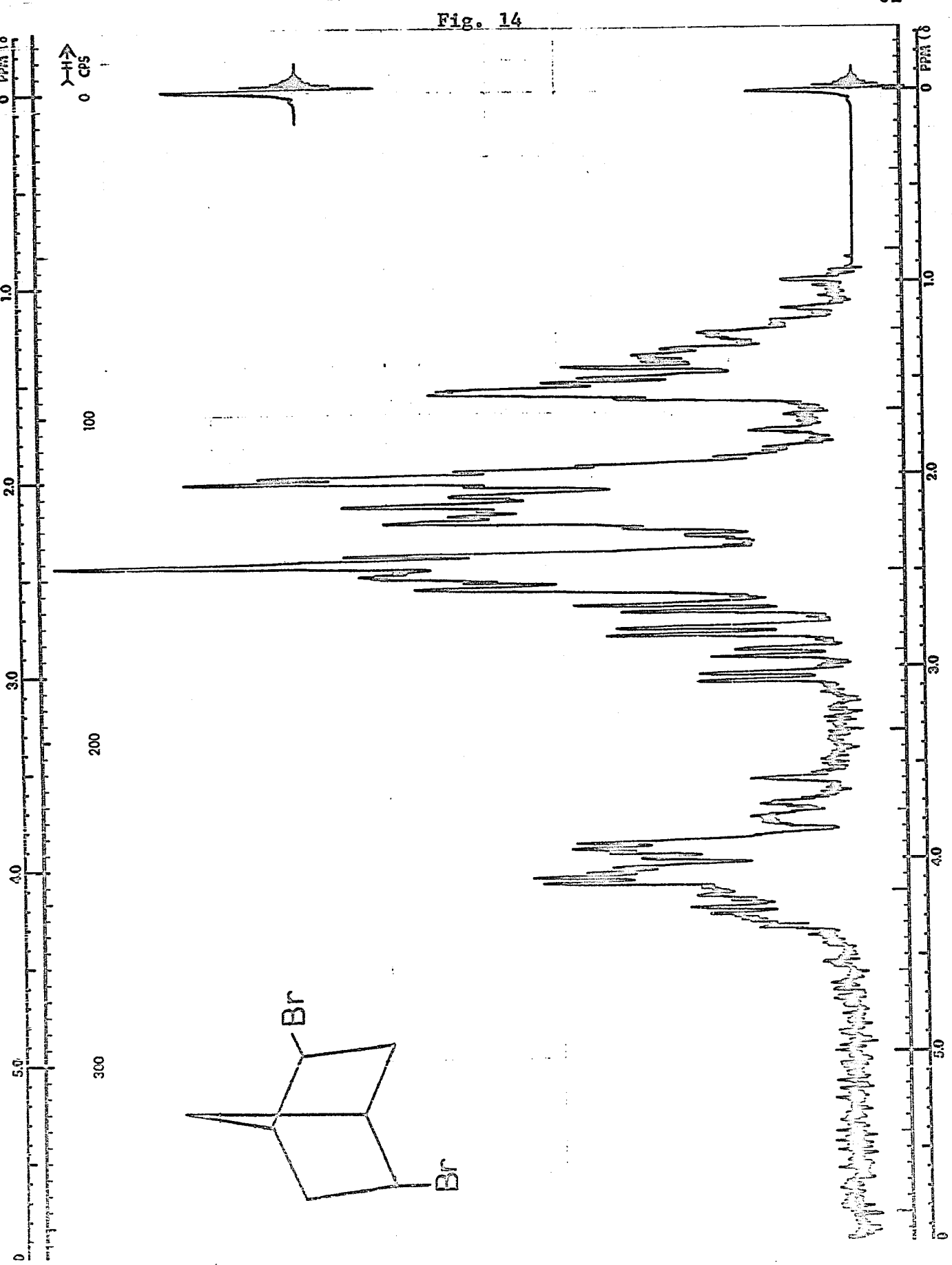
81

absorb downfield from H-4 as opposed to 83 in which H-1 and H-4 would show less separation. The observed dipole moment of 1.10D is closer to the calculated value for 83 (2.17D.) than that for 81 (2.58D), however, in view of the large discrepancy between the observed and calculated values this can only be considered significant in conjunction with some other less ambiguous evidence. This product was finally assigned the structure 2-exo-5-endo-dibromonorbornane (83), on the basis of its formation with 82 by attack on a non-classical ion formed by a 6,2-hydride shift. The grounds for this decision will be elucidated as a part of the theoretical discussion in the next section.

7-syn-2-exo-Dibromonorbornane (38)

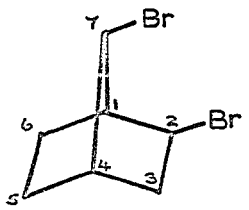
The stereostructure of the high boiling dibromide (retention time: 17 min.), which could be obtained pure by fractional distillation, was shown to be 7-syn-2-exo-dibromonorbornane (38) confirming the earlier assignment based on chemical evidence by Kwart and Kaplan (37). However, in the present work the structure has been conclusively demonstrated without recourse to chemical degradation, thus excluding any possibility

Fig. 14



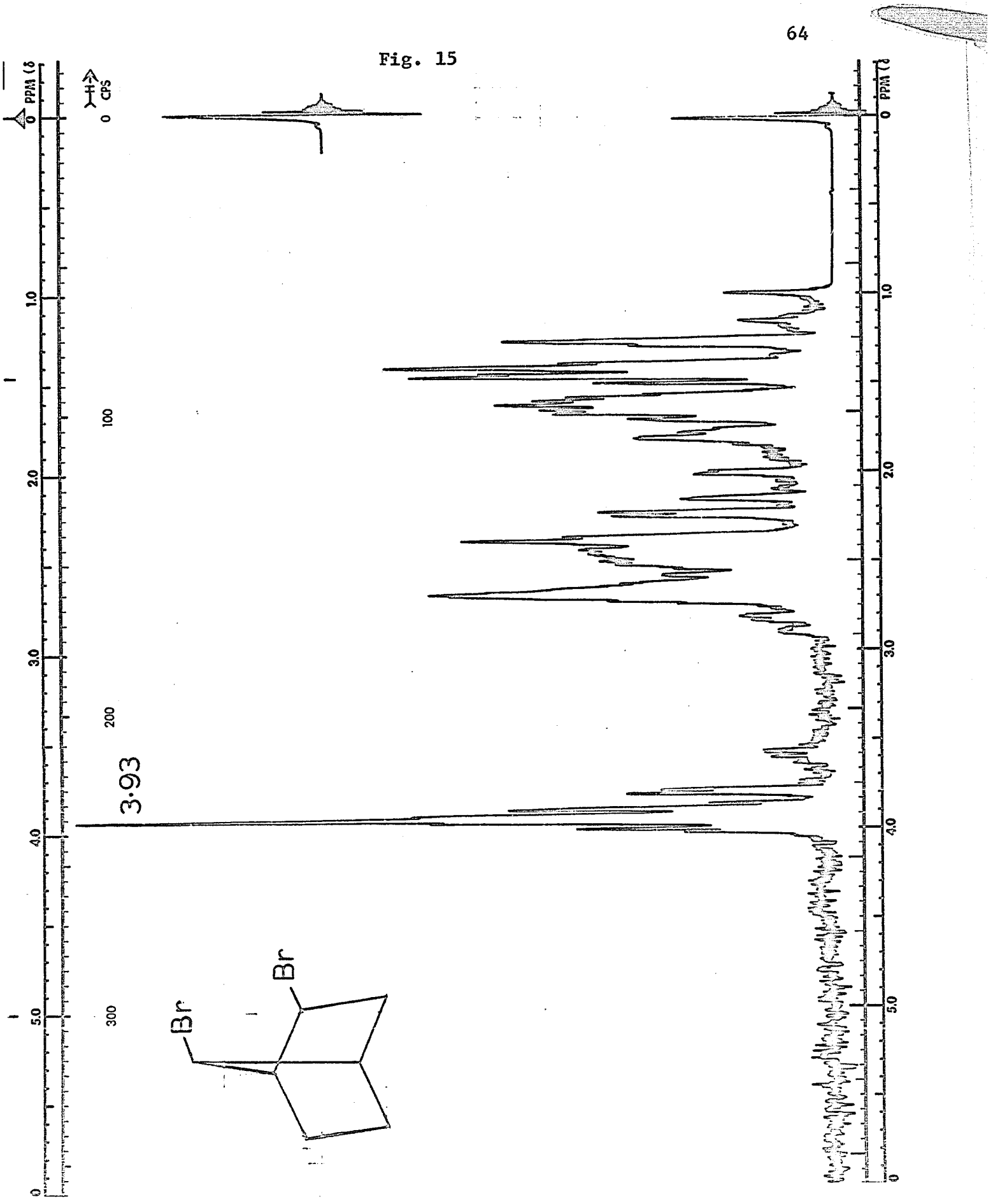
Nmr Spectrum of 2-exo-5-endo-Dibromonorbornane in CCl_4

of rearrangement. The nmr spectrum of this compound is shown in Fig. 15 (60 Mc/s) and Fig. 16 (100 Mc/s), the latter being of interest in view of the enhanced separation in the 2.0 to 3.0 ppm region. The α-protons appear as a two proton multiplet which is composed of a broad singlet at 3.93 ppm (236 cps) superimposed on a doublet of doublets (J~8 cps) which is slightly split again, centred at 3.90 ppm (234 cps). The absorption at 3.90 ppm may be assigned to an endo-proton not only on the basis of the characteristic sharpness of the resonance lines but also on its chemical shift. It can be seen from Table 6 that the α-endo-proton consistently absorbs at higher field than its α-exo counterpart; no exceptions have been found in the extensive series of 2,3-dihalonorbornanes studied by LeBel and co-workers (55). The broad singlet at 3.93 ppm has been assigned to absorption by a proton which is α to a substituent at C-7 for reasons discussed in the case of 7-anti-2-exo-dibromonorbornane. The syn configuration of the C-7 substituent is clearly evident by comparison of the spectra from the two C-7 substituted dibromo isomers (Figs. 10 and 15); the compound presently under discussion clearly shows the additional splitting of the doublet of doublets caused by coupling between endo-H-2 and anti-H-7 whereas the anti-bromo isomer, not having a C-7-anti-proton shows only a sharp doublet of doublets. Double

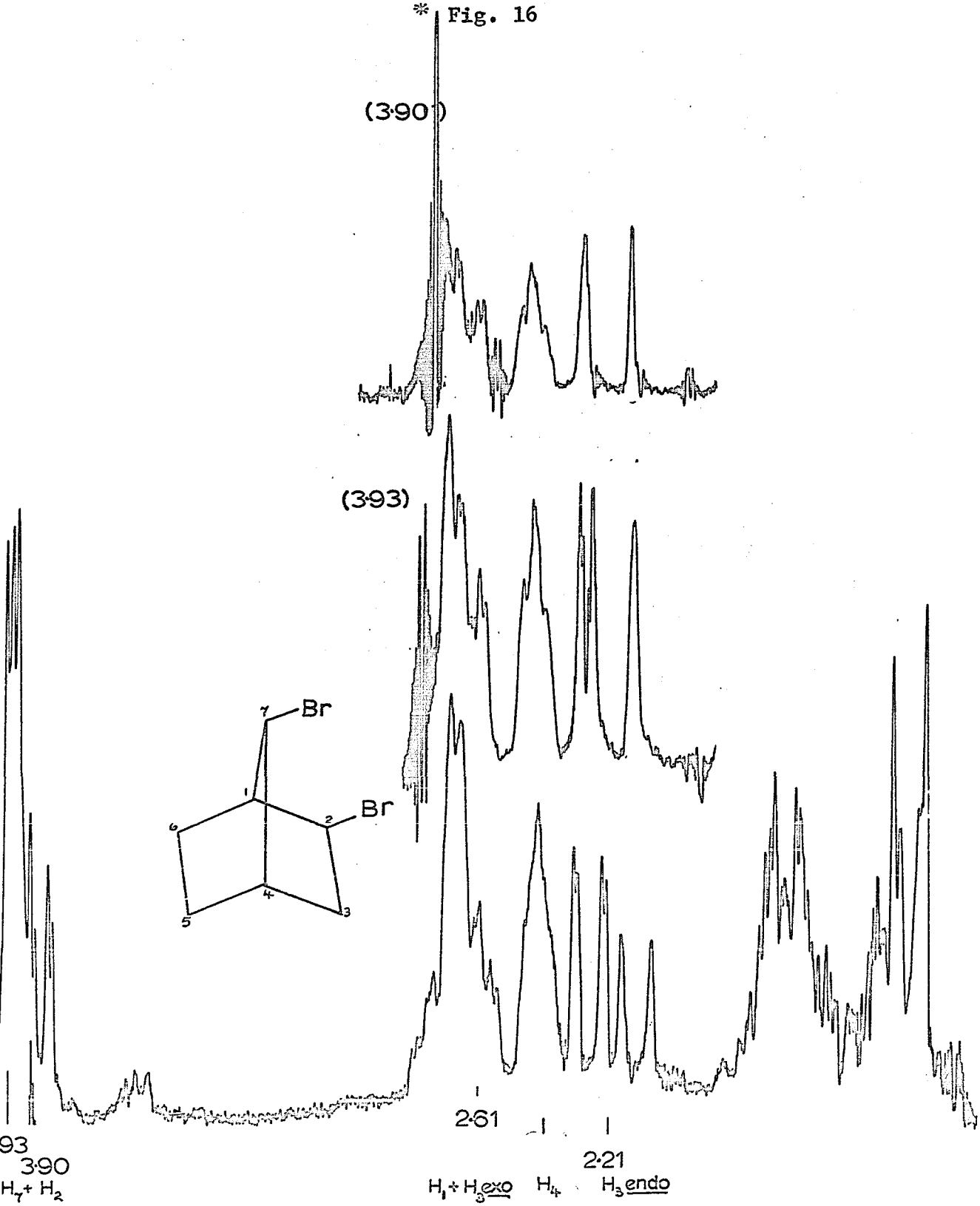


38

Fig. 15



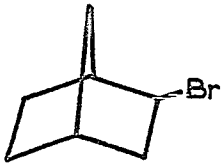
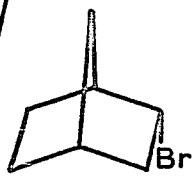
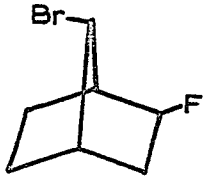
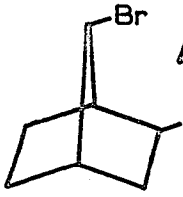
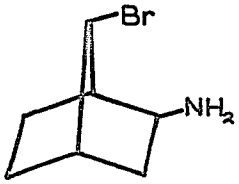
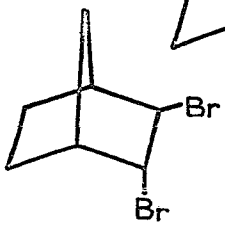
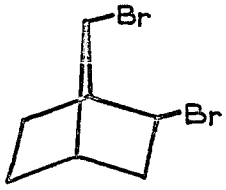
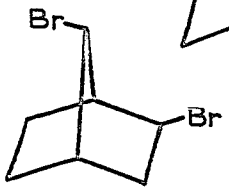
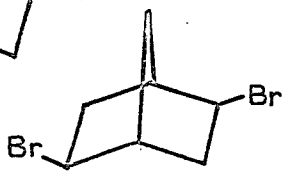
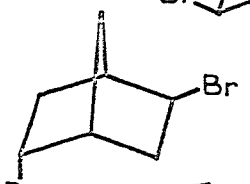
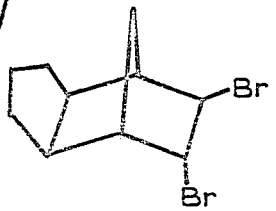
Nmr Spectrum of 7-syn-2-exo-Dibromonorbornane in CCl_4



*spurious signal
Nmr Double Irradiation Spectra of 7-syn-2-exo-Dibromonorbornane at 100Mc/s.

Table 6

Chemical Shifts and Multiplicity of Protons α to a Substituent

Compound	endo-H	exo-H	anti-H*	syn-H*
	239 3.97 (m)	-	-	-
	-	260 4.33 (m)	-	-
	271 4.61 (m)	-	232 3.87 (bs)	-
	273 4.55 (m)	-	-	252 4.20 (bs)
	242 4.03 (m)	-	238 3.96 (bs)	-
	172 2.86 (m)	-	232 3.87 (bs)	-
	230 3.83 (dd)	265 4.42 (m)	-	-
	234 3.90 (m)	-	236 3.93 (bs)	-
	236 3.93 (dd)	-	-	266 4.43 (bs)
	226 3.77 (m)	-	-	-
	~240 ~4.00 (m)	~242 ~4.03 (m)	-	-
	226 3.77 (dd)	264 4.40 (m)	-	-

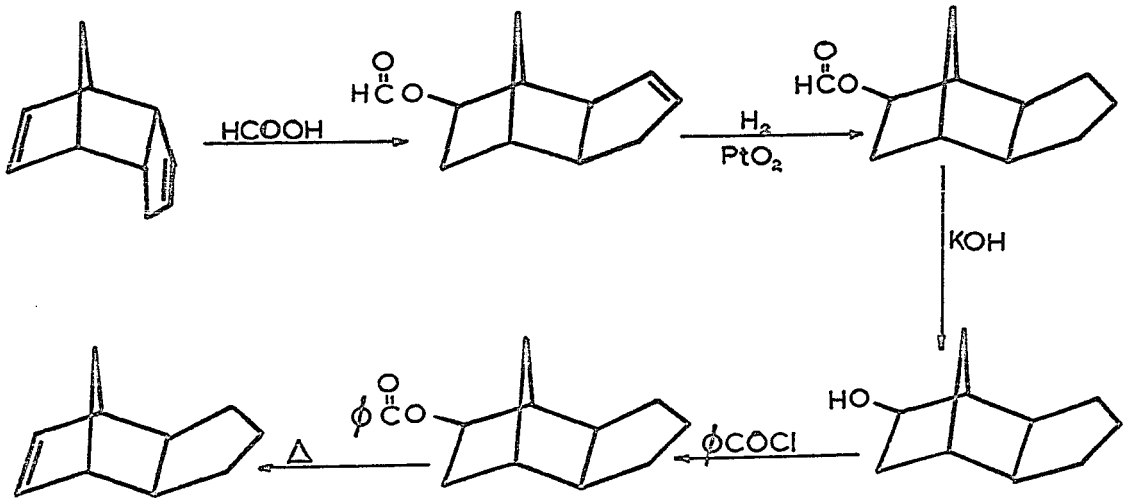
irradiation experiments (Fig. 16) with this compound, although exhibiting results expected for this structure, did not give further information conclusively defining the 7-syn-2-exo-structure because the C-7-anti- and the C-1-protons were fortuitously superimposed on the C-2-endo- and the C-3-protons respectively. Irradiation at 390 cps resulted in collapse of the four peaks centred at 221 cps to a doublet with a coupling constant of 13 cps, a value typical of geminal protons in these systems (63). The lack of further splitting identifies this latter absorption as that of the C-3-endo-proton. This irradiation also collapses the broad multiplet at 242 cps to a triplet pattern and hence this absorption may be ascribed to H-4 (the H-4 H-7 coupling has been lost), on the assumption that H-4 will absorb at higher field than H-1. The absorption at 261 cps may be ascribed to the C-1 and C-3-exo-protons and as expected it is perturbed by irradiation at ~390 cps. The large separation in chemical shift between exo-H-3 and endo-H-3 is presumably due to the deshielding effect of the 7-syn-bromo substituent, a conclusion substantiated by comparing the C-7-proton resonance in the 7-syn- and 7-anti-2-exo-dibromo isomers. The C-7-proton in the latter is at approximately 30 cps lower field than the former, presumably due to deshielding by the 2-exo-bromine. However, it has been shown that in the vicinal dibromides a β-CH eclipsed by a C-halogen is slightly shielded by the vicinal carbon-halogen bond (55), and therefore in the absence of further data it would be pointless to speculate on the factors contributing to the resultant exo-H-3 and endo-H-3 absorption separation.

Additional chemical evidence for assigning 7-syn-2-exo-stereo-

chemistry to this isomer is its facile isomerisation to a mixture of the other four isolated dibromide isomers when treated with aqueous hydrogen bromide. The instability of this isomer relative to the others is explicable in terms of repulsive non-bonded interaction between the two bromine atoms. The internuclear distance of the bromine atoms may be calculated to be 2.90 A^{o} (64) while the sum of the van der Waal's radii is 3.95 A^{o}, and therefore this isomer would be expected to show instability due to compression of the halogen atoms.

(c) Addition of Bromine to 5,6-exo-Trimethylenenorbornylene

Synthesis of the olefinic starting material was achieved by a previously reported procedure (42) shown schematically below.



43

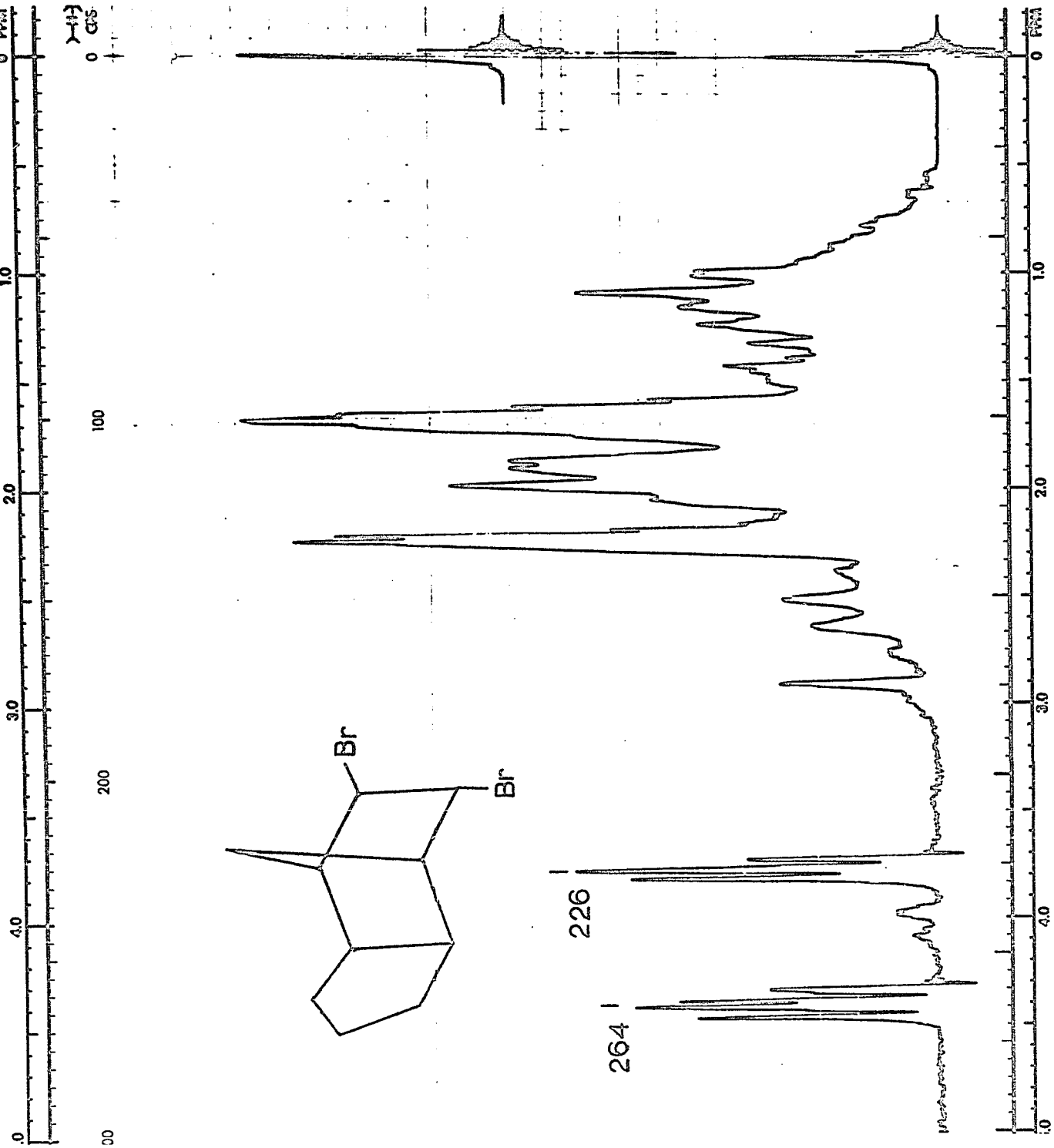
Purity was ascertained by nmr, glc (one peak), melting point of the crystalline phenylazide derivative and by the absence in the infrared spectrum of any band belonging to the endo isomer. The purity

is of importance in that any endo olefin present will complicate product analysis, particularly if minor amounts of hydride shift product are formed.

Addition of bromine, under conditions similar to those used previously (43), to the olefin in carbon tetrachloride at 0°C gave a crude product which was shown to contain one major (80%) and seven minor (0.5-8.5% each) components by glc.

Vacuum distillation gave a sample of the major component of purity greater than 95% (by glc); nmr spectroscopy confirmed the previous structural assignment of 2-exo-3-endo-dibromo-5,6-exo-trimethylenenorbornane (46) (Fig. 17). Comparison with the spectrum obtained from 2-exo-3-endo-dibromonorbornane (Fig. 8) is instructive; the 5,6-trimethylene analogue shows a three line pattern (H-2) at 3.80 ppm (226 cps) and a four line pattern (H-3) at 4.45 ppm (264 cps), whereas the parent compound shows a three line pattern at 3.83 ppm (230 cps) and a multiplet at 4.42 ppm (265 cps). The arguments advanced for the vicinal 2-exo-3-endo relationship between the bromine substituents are equally valid for the trimethylene case as for the parent compound, however, the spectrum obtained from the former exhibits an extra gratifying point of interest, this being the appearance of the C-3-exo-proton as a doublet of doublets and not as a multiplet, which clearly demonstrates the exo configuration for the trimethylene group; the coupling between the C-3-exo-proton and the C-5-exo-proton has been lost due to substitution in the latter position.

Fig. 17



Nmr Spectrum of

2-exo-3-endo-Dibromo-5,6-exo-trimethylenenorbornane in CCl_4

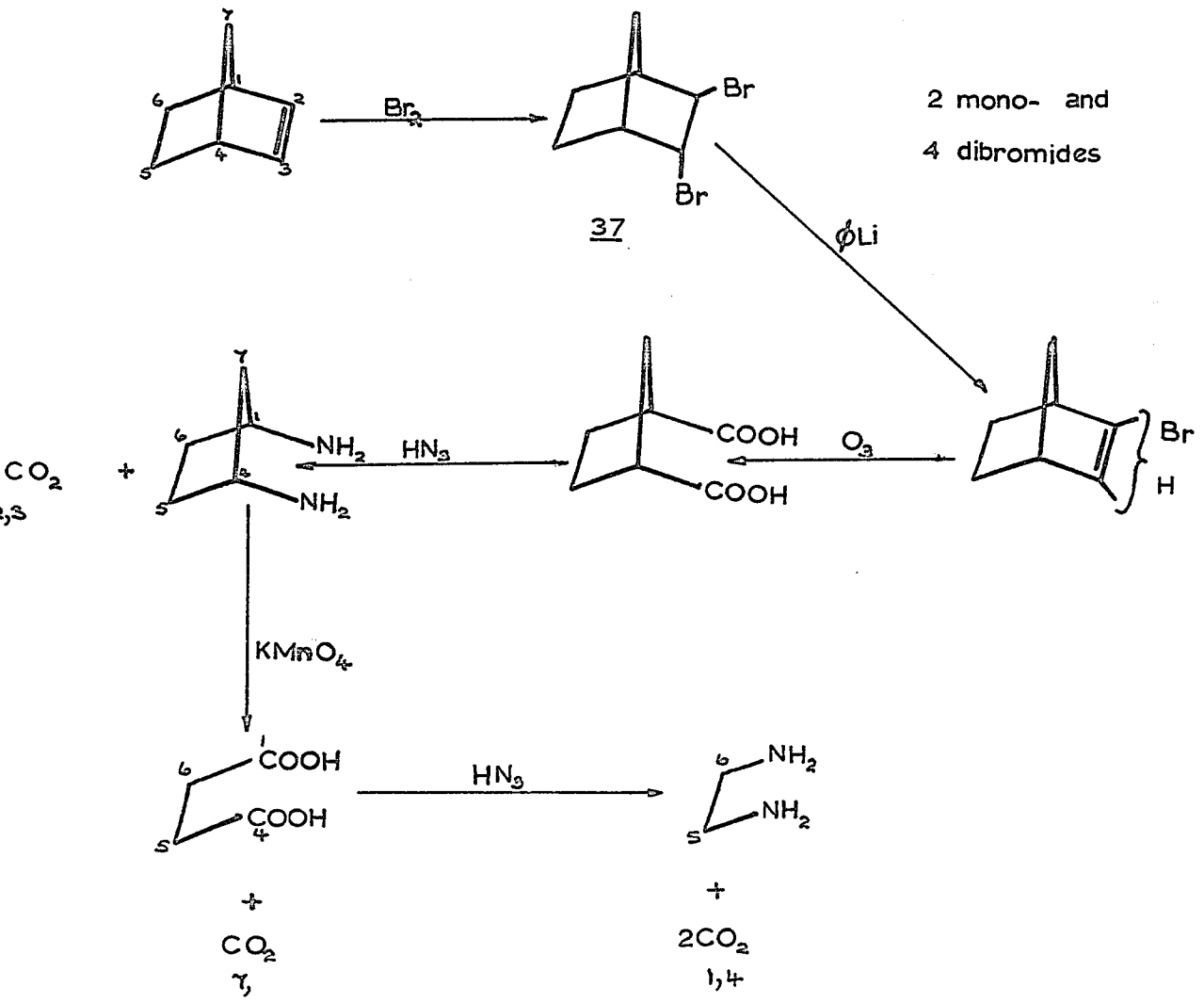
(d) Controlled Degradation of 2-exo-3-endo-Dibromonorbornane

One of the dibromide isomers, 2-exo-3-endo-dibromonorbornane (37) may be formed by two distinct pathways, the relative amounts of which may only be determined by isotopically labelling norbornylene and subsequently degrading the dibromide product in such a way that the activity at each carbon atom may be unambiguously assessed. Fortunately a much used scheme for degrading the norbornane system exists (10) and it was this route, with modifications to improve yields and shorten degradation time, which was used (Fig. 18).

The first problem facing any would-be user of this scheme is a method for converting the 2-exo-3-endodibromide into 1,3-cyclopentane dicarboxylic acid in good yield by a simple efficient method. The low yield of 2-exo-3-endo-dibromonorbornane and the tedium involved in separating it from its isomers by glc made it worthwhile to investigate methods which might lead to debromination of only the required isomer in the unseparated mixture to give an unsaturated compound which, on ozonisation and oxidation, would yield the required diacid.

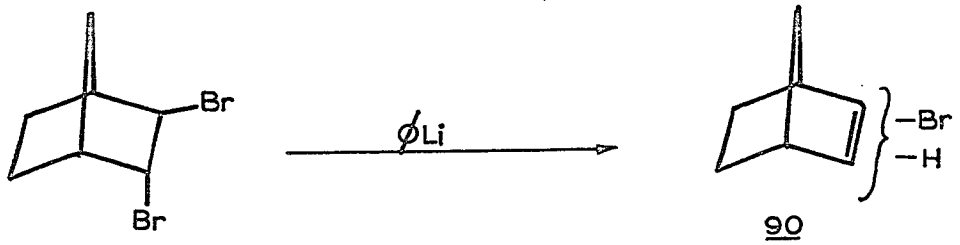
The obvious approach to this problem was to effect separation and degradation in one reaction by taking advantage of the vicinal nature of the dibromide, a feature unique to this isomer. However, as is frequently the case, the 'obvious' method, namely, zinc and acetic acid, failed. Debromination did occur to give acetate products but it was found that under the reaction conditions norbornylene reacted with glacial acetic acid so that even if the olefin was formed it was probably converted to an acetate. The use of other solvents such as ether and

Fig. 18



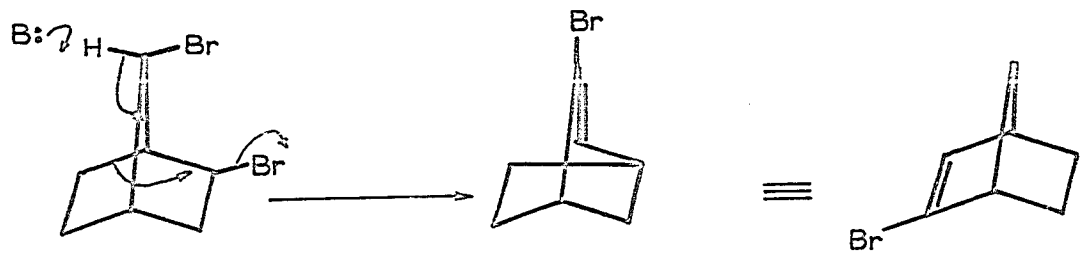
Degradation Scheme for 2-exo-3-endo-dibromonorbornane (37)

dimethoxyethane produced no reaction; reagents such as magnesium and triphenylphosphine were equally ineffective. The desired reaction was finally achieved using a solution of phenyllithium in benzene and ether at 0^{o} under nitrogen. By monitoring the reaction with glc it was found that the 2-exo-3-endo-dibromonorbornane was destroyed within a few minutes with the appearance in the nmr spectrum of vinyl proton absorption which was not coincident with the absorption of the vinyl protons in norbornylene. On the basis of previous work (65,43) in which 2,3-dihalonorbornanes have been reacted with strong base the product was considered to be the vinyl bromide 90 formed by dehydrohalogenation.



90

Control reactions with the other dibromides and monobromides revealed that these did not give any olefinic products under the reaction conditions. The 7-syn-2-exo-dibromo isomer in particular, was subjected to close scrutiny for the possible formation of a bromonorbornylene by an elimination-rearrangement mechanism. However, no vinyl absorption



was evident after treatment with phenyllithium, and in addition, quenching of the reaction mixture with deuterium oxide resulted in no exchange of the protons α to bromine.

Previous degradation procedures have involved the oxidation of the olefin (43) or saturated derivative (10) with potassium permanganate. However, ozonolysis offers the advantages of a simple rapid procedure with formation in 90-100% yields of the 1,3-cyclopentane dicarboxylic acid requiring little additional purification. A slight modification was made to the reported procedure (73) for ozonolysis of norbornylene in that ethyl acetate was used as solvent rather than methanol to avoid partial formation of the monomethylester which was noticed in methanol. Degradation of the diacid to 1,3-cyclopentanediamine was achieved using the Schmidt reaction as cited in the literature (10).

A weak step in this degradation scheme has always been the oxidation of 1,3-cyclopentanediamine hydrochloride to succinic acid; yields of only 15% have been realised (10). Efforts to increase this by use of chromic acid were unsuccessful, for although the yield was increased to 30% in one case this result was not reproducible.

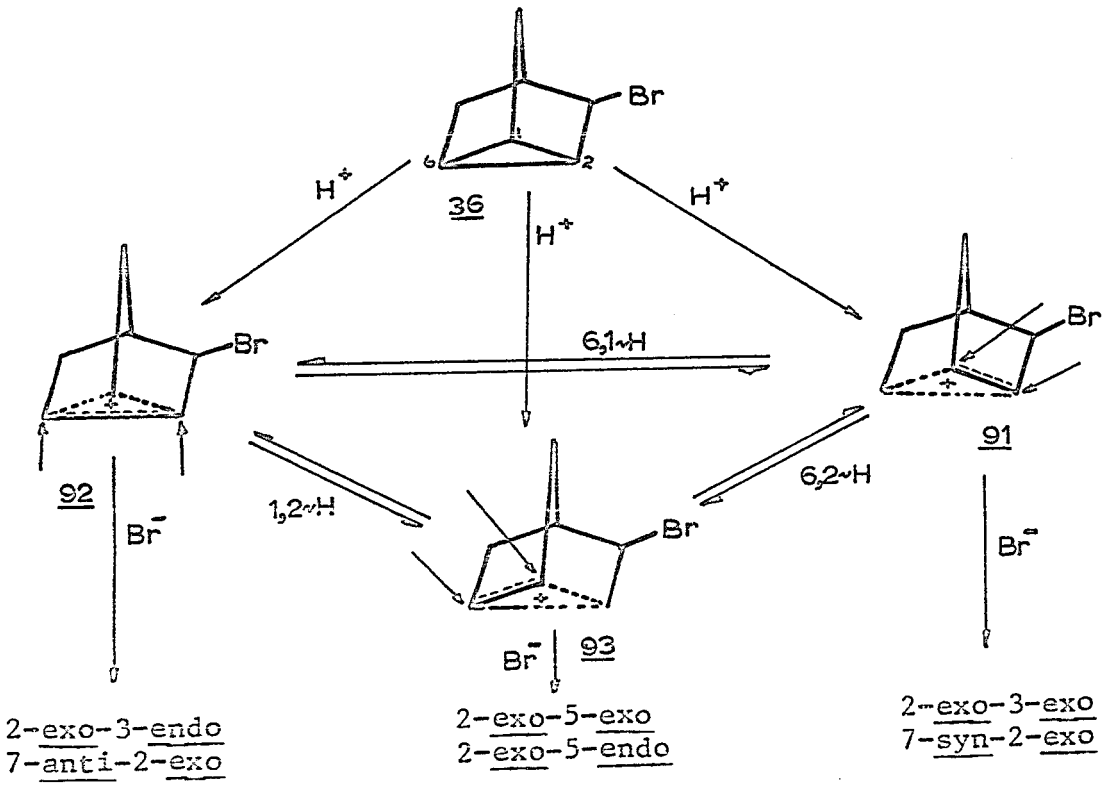
It has been reported that the Schmidt degradation of succinic acid to ethylenediamine goes in only 8% yield (74) and for this reason the alternative Curtius degradation *via* the azide and urethan (28) has been used in previous degradations. This procedure, although a vast improvement, is tedious and gives only 50% yield of the diamine. It has been reported (76) that the use of 20% oleum in the Schmidt degradation of aromatic acids bearing electronegative substituents increases the yield of amine dramatically over that obtained when 96%

sulphuric acid is used; in some cases from 8% to approximately 100%. When this procedure was applied in the present work to the degradation of succinic acid, yields of 67-83% of barium carbonate and 30-43% yields of the dibenzamide derivative of ethylenediamine were realised.

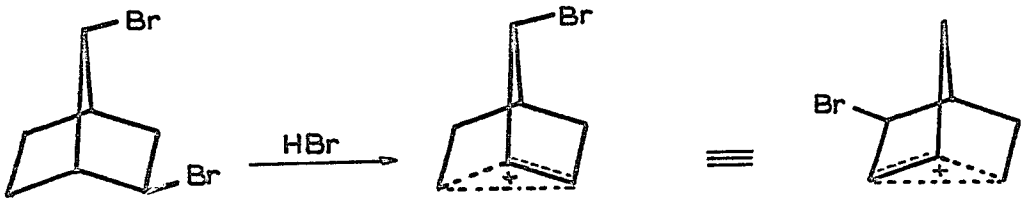
B Theoretical Implications and Results

(a) Reaction of Hydrogen Bromide with Bromonortricyclene and 7-syn-2-exo-Dibromonorbornane

The addition of bromine to norbornylene has been shown to give two monobromides, 2-exo-bromonorbornane and bromonortricyclene, five dibromide isomers namely, 2-exo-3-endo-, 7-anti-2-exo-, 2-exo-5-endo-, 2-exo-5-exo- and 7-syn-2-exo— dibromonorbornane, and traces of two other products not isolated. The relative proportions of these products, produced under a variety of reaction conditions, are shown in Table 14. Both bromonortricyclene and 7-syn-2-exo-dibromonorbornane react with hydrogen bromide to give other dibromide isomers. Protonation of 36 at C-1, C-2 and C-6, produces three parent non-classical ions (91, 92 and 93), which can



interconvert via 6,1- and 6,2-hydride shifts. Nucleophilic attack by bromide ion gives the same dibromide isomers as are observed in the bromination of norbornylene. The three parent non-classical ions may also be produced from the 7-syn-2-exo isomer by reaction with hydrogen bromide because of the inherent instability of this isomer resulting from steric compression of the bromine atoms. However, the absence of these two secondary paths under the conditions of the bromination was proven by control reactions of hydrogen bromide with both 36 and 38.



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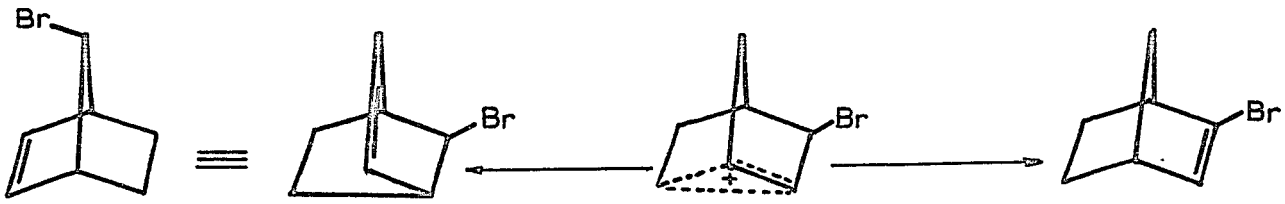
Earlier Kwart and Kaplan (37) had concluded that some of the dibromides were formed by the action of hydrogen bromide on 36. In the present work it was found that when the maximum hydrogen bromide concentration that could conceivably be realised i.e. that resulting from 100% conversion of the olefin to 36, was used, no change was observed. At least ten-fold increases in concentration of hydrogen bromide and reaction time were required before significant reaction of 7-syn-2-exo-dibromonorbornane and bromonortricyclene occurred. Similarly the other dibromide isomers were stable to hydrogen bromide under the reaction conditions and it may be concluded therefore that the product composition is that of kinetic control.

The stability of the products is further confirmed by the ob-

servation that the crude product composition was insensitive to the time that elapsed between reaction and glc analysis and there was no evidence of rearrangement when the same crude dibromide sample mixture was reinjected successively through the glass column gas chromatograph.

There is a further secondary route which can lead to dibromide formation via an elimination product. There is always a large amount of elimination product 36 formed, and it is not unreasonable to consider the possible formation of an olefin by elimination of a proton from the

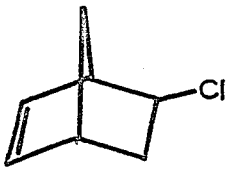


initially formed cation by attack of either hydrogen bromide or bromine. It has been shown in the acetolysis of 2-exo-norbornyl brosylate (9) that, of the 4% of elimination product, 2% is norbornylene and 98% the tricyclic derivative. Addition of less than one equivalent of bromine to norbornylene in pyridine gave a crude product which showed no vinyl absorption except that due to starting material, and glc analysis showed no new peaks which could be attributed to tribromides resulting from the addition of bromine to a bromo-olefin. The dibromide isomers are therefore primary products formed by attack of an electrophilic bromine species, possible rearrangement of the resulting cation and termination by attack of bromide anion.

(b) Evidence that the Addition of Bromine to Norbornylene Proceeds by a Polar rather than a Free Radical Mechanism.

In view of the recent work showing that chlorination of norbornylene involves both radical and ionic mechanisms in non-polar solvents (40) and that the addition of N-bromoacetamide to olefins in refluxing carbon tetrachloride in the presence of light involves a radical process (77) it is obviously essential that the ionic and/or radical nature of the 'BrF' and bromine additions be established before discussion of the mechanistic results. In this work the 'BrF' addition was conducted under conditions such as to disfavour a radical reaction, i.e. N-bromoacetamide and hydrogen fluoride in ether at -78° in an opaque reaction vessel. No products were observed which might be considered typical of a free radical process. The bromination of norbornylene was found to be relatively insensitive to both a radical scavenger (oxygen) and concentration differences. If some of the products had been partially or wholly formed by radical processes a change in product ratio would have been expected; however, these conditions do not exclude the remote, but conceivable, possibility that all of the dibromides are being formed by free radical processes. This may be excluded by two independent pieces of evidence. Firstly, no products were obtained which were typical of a free radical process; free radical chlorination of norbornylene (40) afforded two products, 94 and 95 which were not obtained under ionic reaction conditions. In addition the amount of cis addition to give 2-exo-3-exo-dichloro product 40 increased from 3 to 30% on changing from ionic to radical conditions. Although the analogous dibromide may be present in very small amounts in the bromination product, no significant changes in minor components were

observed when oxygen was present. A second argument against a totally



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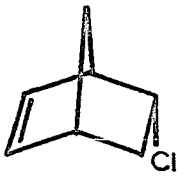

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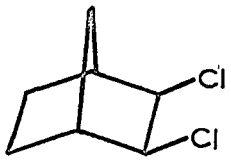

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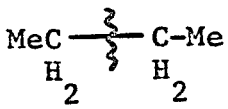
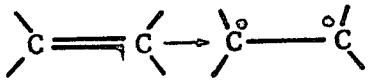
radical process rests on the energetic requirements of the postulated radical reaction. A crude estimate of the energy changes involved may be obtained from the dissociation energies of single and double carbon-carbon bonds.

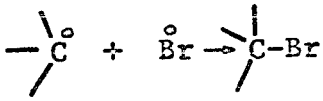
ΔH 145 kcal./mole. (78)



ΔH 78 kcal./mole.



ΔH -(145-78) = 67 kcal./mole.



ΔH -67 kcal./mole.

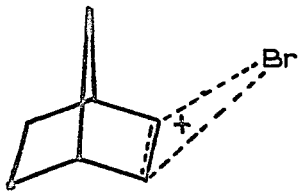
If one considers the difference in heat of hydrogenation between cyclohexene and norbornylene (79) (~6 kcal./mole.) to be a measure of the relief in strain achieved by the latter on breaking the double bond, then the addition of bromine to norbornylene by a free radical mechanism should by exothermic by approximately 6 kcal./mole. It has been shown that the rate of methyl hydrogen abstraction by bromine radicals from toluene is at least 10^3 greater than from ethane (80) and that it is exothermic to the extent of 10 kcal./mole. as calculated from bond

formation and dissociation energies. Thus, if bromine were to be added to norbornylene in the presence of toluene under conditions in which toluene was known to undergo bromination, one should observe formation of benzyl bromide, as this reaction is more favourable from a free radical standpoint. When slightly less than one equivalent of bromine, with respect to olefin, was added to a mixture of norbornylene and toluene in a ratio of about 1:5 no change in the ratios of dibromide products was observed and only a trace of benzyl bromide was found (less than 0.5% by glc). This result excludes a radical addition to norbornylene. It has been concluded therefore, that the addition of bromine to norbornylene under the conditions indicated in Table 14 is ionic.

(c) Possible Routes to Dibromide Products.

Now that the ionic nature of the addition and the formation of the products by primary reactions have been established it is possible to delineate the routes to these products and to compare their distribution with the reaction products from similar additions. Polar reactions with norbornylenes have been demonstrated to involve four general types of mechanism, the distribution of products from these mechanisms depending on a wide variety of subtle environmental and structural conditions, of the substrate and reagent. Briefly, these mechanisms may be classified as; (a) trans addition resulting from attack of nucleophile on a hetero atom bridged ion, (b) Wagner-Meerwein rearrangement, (c) hydride shift in the initially formed cation and subsequent attack by nucleophile, and finally (d) elimination from the initially formed cation to give

tricyclic and possibly olefinic products. A fifth mechanism leads to unrearranged cis products only, as in the oxymercuration (35) and addition of nitrosyl chloride (33) to norbornylene. However, the polar nature of these reactions is not beyond dispute; presumably the exclusive formation of cis product involves a different mechanism from that postulated when cis product is formed concomitantly with the Wagner-Meerwein rearrangement product i.e. 7-syn-2-exo-. It has been postulated that the equilibrium between the 'onium' ion 96 and the bridged ion 91 is the dominant factor in determining the products in the addition of bromine to norbornylene (43). Trans attack on 96 leads to

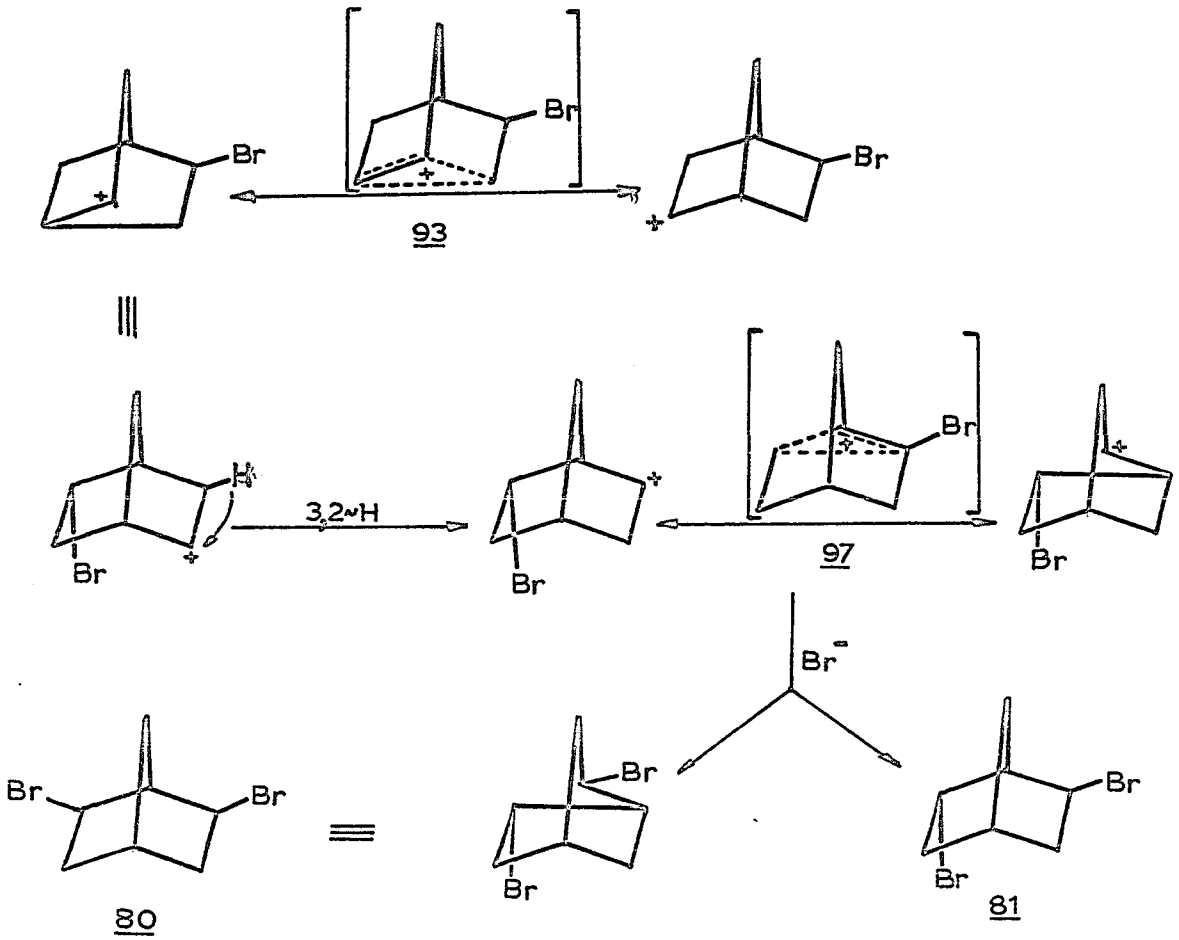


96

a 3-exo-2-endo- product while attack at C-1 and C-2 of the non-classical ion 91 leads to 78 (2-exo-3-exo-) and 38 (7-syn-2-exo-). As soon as the non-classical ion 91, (or the equivalent rapidly equilibrating classical ions) are formed there arises the possibility of hydride shifts of which there are copious examples in the solvolysis literature (see also the Introduction). The most facile of these, 6,1- and 6,2- hydride shifts, lead to two more non-classical ions and all three non-classical ions can be interconverted. Thus 91 may be in equilibrium with 92 and 93. Attack of nucleophile on 92 and 93 will lead to four different isomeric dibromides 87, 37, 83 and 82. In the present work all the isomeric dibromides except the cis product 78 were found.

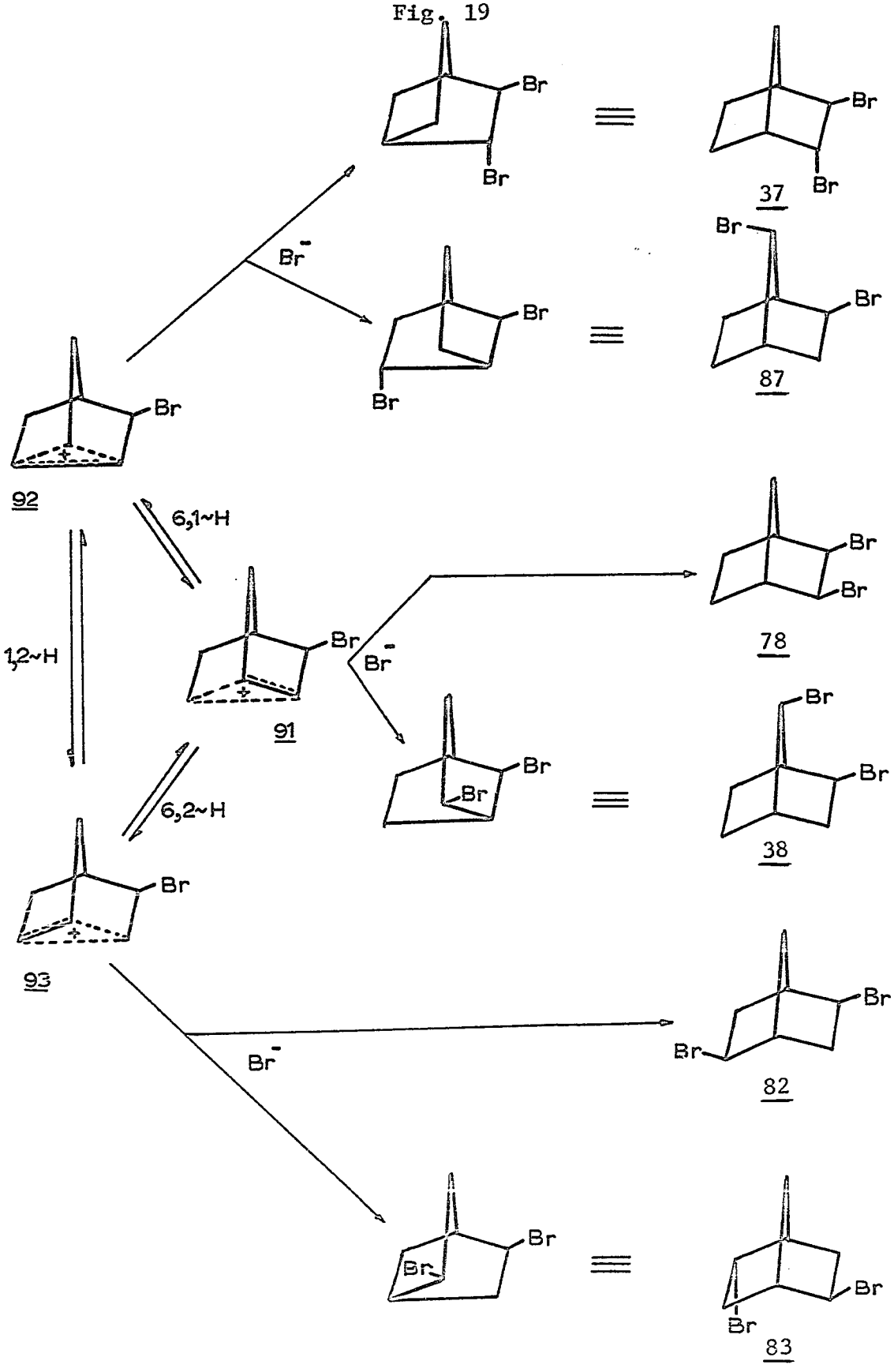
(d) Mechanistic Argument for the Structure 2-exo-5-endo-Dibromonorbornane.

As was mentioned in the discussion on the structures of the dibromides, one of them, 5-endo-2-exo-dibromonorbornane, can not be unambiguously identified without recourse to a mechanistic argument and it would be appropriate to discuss the basis for the structural assignment at this juncture. As can be seen from Fig. 19 the three parent non-classical ions give rise to three pairs of dibromide isomers



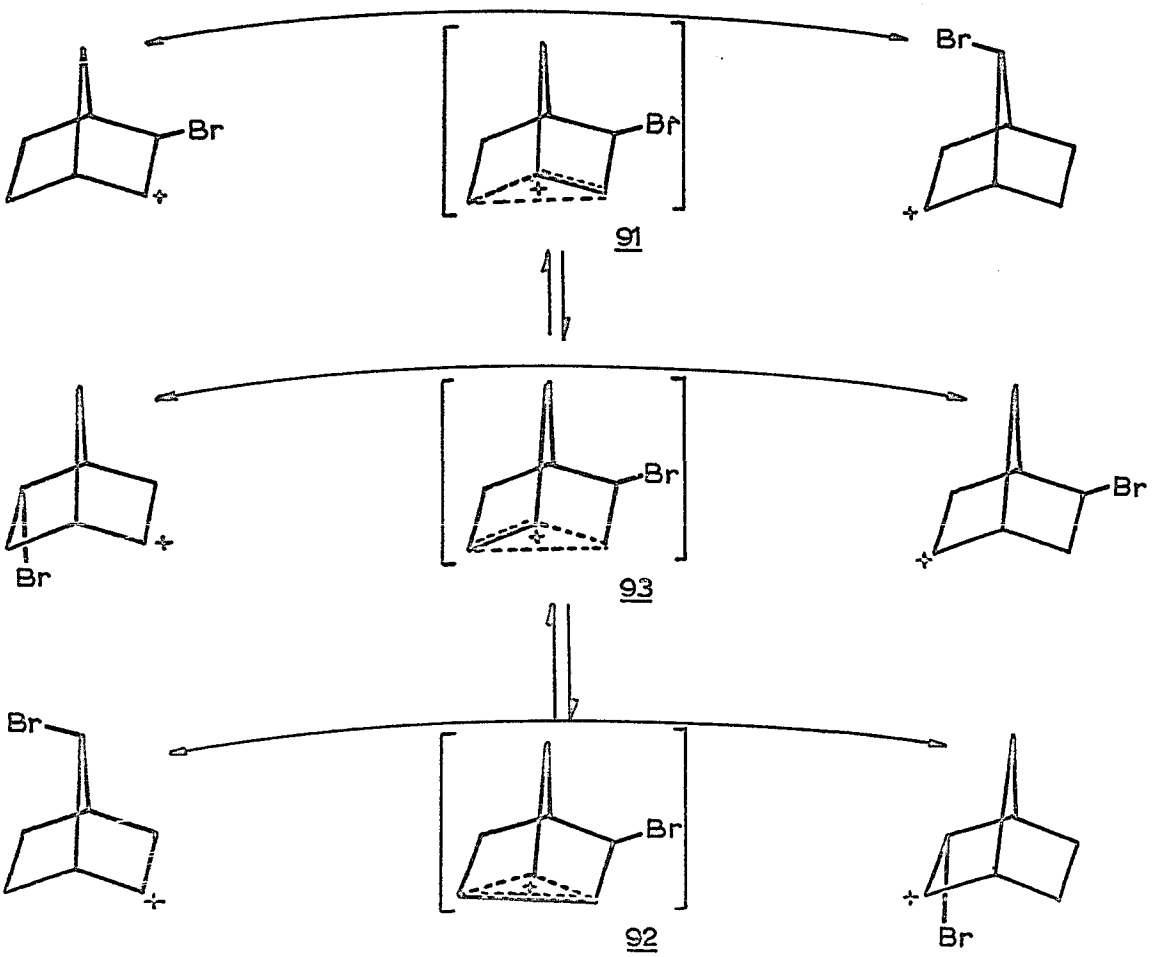
by nucleophilic attack of bromide ion. Four of the possible isomers 37, 87, 82 and 38, have been positively identified and the 2-exo-3-exo

Fig. 19



Pairs of Dibromide Isomers from Attack at Wagner-Meerwein Related Sites

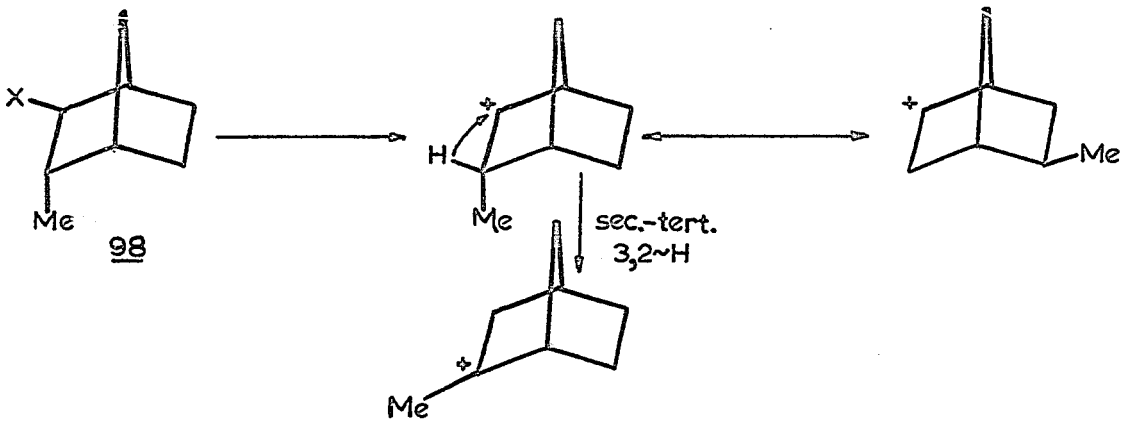
isomer has been definitely excluded both on melting point and spectral grounds; this leaves logically only 83 as a structure derived from one of the parent ions. However, though this 'structure by default' argument is strong it may be criticized on the grounds that a mechanistic scheme to give the other conceivable structure, 6-endo-2-exo-dibromide, from which it could not be distinguished by spectral means, is possible. However, this alternative structure may arise only via a 3,2-hydride shift from parent ion 93 as shown in the scheme on page 83. A 3,2-hydride shift in 93 gives a new non-classical ion 97 which may be



captured to give two new dibromides 80 and 81; the latter is the structure not readily distinguishable from the 5-endo-2-exo-dibromide by

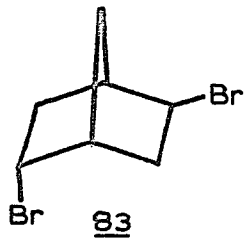
spectral considerations. Why, therefore, is this process unlikely in the reaction under discussion and furthermore, if this particular 3,2-hydride shift has occurred, why has no 3,2-hydride shift occurred in the other parent ions 91 and 93? A glance at the classical ion pairs represented by the non-classical parent ions 91, 92 and 93, indicates that only in the two cases where the positive charge is situated on carbon α to the bromine substituted carbon can an argument be made for failure to undergo secondary-secondary hydride shift relative to the other four cations (p85). (One of these is further prevented from 3,2-hydride shift by the presence of an exo-bromine as it has been shown that the 3-exo-methyl-2-norbornyl cation scrupulously avoids simple 3,2-endo-hydride shift but instead takes a more circuitous route; it has also been demonstrated that the rate of 3,2-exo-hydride shift is greater than 3,2-endo by at least a factor of 23 (81)). Some idea of the relative rates of solvent capture, 6,2-hydride shift and 3,2-hydride shift has been acquired by both nmr spectroscopy and solvolysis product analysis. In non-hydroxylic solvents nmr measurements indicated that 3,2-hydride shift was at least $10^{8.8}$ slower than 6,2-hydride shift (18,19) and product analysis in the solvolysis of 3-endo-methyl-2-exo-norbornyl brosylate indicated that the ratio of solvent capture rate to secondary-secondary 3,2-hydride shift rate was at least 122 in acetic acid (82). As 6,2-hydride shift and solvent capture are competitive and hence of the same order of magnitude in many norbornyl systems (83), it is valid to argue that the rate of 6,2-hydride shift is probably about 100 times greater than that of 3,2-hydride shift. Significant 3,2-hydride shift has been observed in the solvolysis of systems such as 98 where a 3,2-shift can give rise to a

more stable tertiary cation (83). However, the amount of product attributable to this route only becomes significant with equilibrating



conditions; under kinetic control very little vicinal hydride shift occurs. In the acetolysis of the 2-t-2-exo-norbornyl brosylate (84), about 7-10% of 3,2-hydride shift was observed indicating that 6,2- and 3,2-hydride shift rates do not differ by a great deal. It has also been reported that 3,2- and 6,2-hydride shift are both fast, and of comparable rate, by a study of the nmr spectra of 2-exo-hydroxynorbornane in trifluoroacetic acid-sulphuric acid mixtures at different temperatures (62). These results imply that the relative and absolute magnitudes of these rates can vary by several powers of ten as a function of solvent and at the same time emphasise the need for further data to resolve the discrepancies. In summary, 3,2-hydride shifts are only significant under non-kinetically controlled conditions; secondary-secondary 3,2-hydride shifts are much slower than secondary-tertiary, which in turn, are at least 100 times slower than 6,2-hydride shifts. Thus in considering the isomer to be 81, rather than 83, we are dealing with a third order improbability, and therefore, we may fairly conclude

that the identity of the unknown isomer is represented by 83, 5-endo-2-



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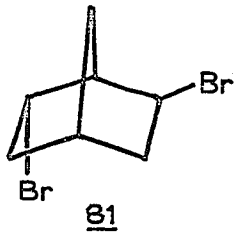
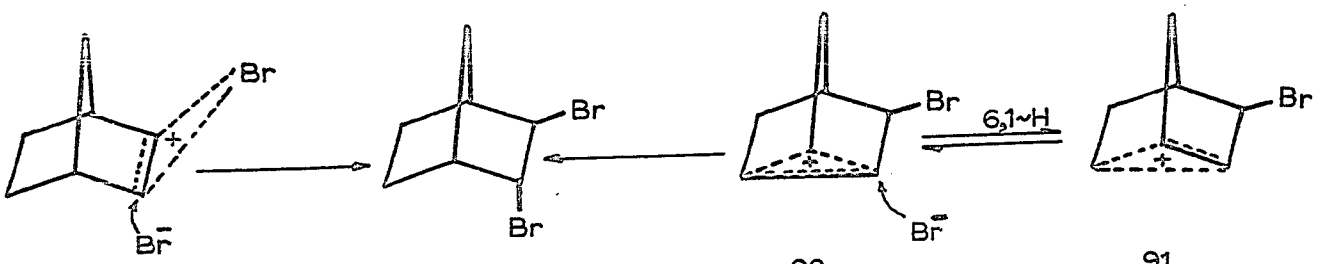


81

exo-dibromonorbornane.

(e) Evidence for Formation of 2-exo-3-endo-Dibromonorbornane by both a Bromonium Ion and a 6,1-Hydride Shift

The presence of 2-exo-3-endo-dibromonorbornane in the reaction product raises the vexatious problem of the bromonium ion. Has this product in fact been formed by trans addition of bromine to the olefin, ion 96 being an intermediate? If one considers the facility of 6,1- and 6,2-hydride shifts and the presence of products resulting from such shifts in this reaction it may well be thought that formation of the 2-exo-3-endo-dibromide can be rationalised by a simple 6,1-hydride shift



96 37 92 91

mechanism involving the two ions 91 and 92 without intervention of a bromonium ion (6). However, there is evidence to suggest that both mechanisms are operative in the formation of 37. Evidence for two

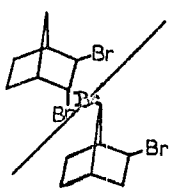
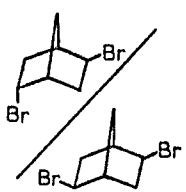
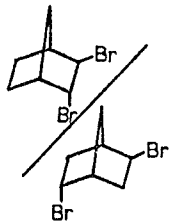
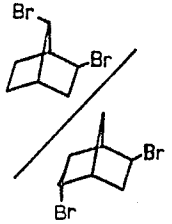
mechanisms leading to 37 of a permissive, rather than a compelling nature comes from the results of varying three reaction conditions; (a) temperature (b) solvent and (c) bromide anion concentration (Table 7). The results of these variations on the percentage of 2-exo-3-endo-dibromonorbornane and the changes in ratios of the four presumed hydride shift products are presented below (Table 7).

The evidence for bromonium ion formation leading to formation of 2-exo-3-endo-dibromide 37 as based on the effect of temperature is tenuous due to a further complication which will become evident in the following discussion. If the four dibromide isomers 37, 87, 83 and 82, are formed after hydride shift it would be reasonable to expect the temperature coefficients for nucleophilic attack at the two sites on each parent non-classical ion to be approximately the same, and therefore, even if decreasing temperatures lower the overall yield of hydride shift product by slowing down hydride shifts, (an unlikely event in that the 6,2-hydride shift rate constant is at least 3×10^6 sec.$^{-1}$ at -120° for the norbornyl cation in SbF_5-SO_2-SO_2F_2) (18) the cation collapse ratio $37/87$ and $83/82$ to give each pair of hydride shift products would not be expected to change. A marked temperature sensitivity of these ratios would imply that one of the dibromides, at least in part, is being formed by a different mechanism involving a different temperature coefficient.

The percentage yield of trans product 37 is decreased (2/3) when the temperature is lowered (0° to -78°) and at the same time both ratios 37/87 and 37/83 vary from 0.254 to 0.095 and 1.23 to 0.65 respectively. However, the ratio of 83/82 also varies with temperature change which

Table 7

Dibromide Ratios from Different Reaction Conditions

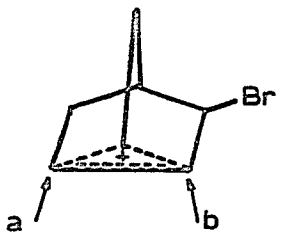
Rx. No.	Norborn -ylene mg./ml.	Solvent	Temp. °C	% of 37	 37/87	 83/82	 37/83	 87/83
1	498/100	CH_2Cl_2	0	3.0	0.243	1.63	0.97	4.00
2*	529/100	CH_2Cl_2	-3	-	0.254	1.66	-	-
3	481/2	CH_2Cl_2	0	2.7	0.248	1.47	1.23	4.95
4	510/100	CH_2Cl_2	-78	1.1	0.113	2.84	0.65	5.73
5*	531/100	CH_2Cl_2	-74	-	0.095	2.56	-	-
6	860/2	CCl_4	0	5.1	0.775	1.31	2.43	3.15
7	564/100	CH_3CN	0	4.65	0.294	1.31	1.11	3.75
8+	688/100	CH_2Cl_2	0	46.0	51.2	-	-	-

*Av. of 3 separate analyses

+Sat. $\bar{c}$ ~12.7g. $Et_4\overset{+}{N}\bar{B}r$

suggests that the assumption of constant capture ratio of each parent non-classical cation with temperature change is not strictly true, and therefore attribution of the change in the ratio of 37/87 to the participation of a second mechanism, i.e. bromonium ion as well as hydride shift, is little more than an intuitive one.

The ratios of the hydride shift products derived from attack at the four positions a,b,c and d in ions 92 and 93 will be determined in



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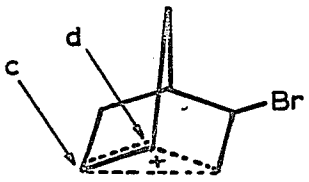


93

part by the solvent. If the mechanism of attack at the four positions is the same and the influence of solvent is regular, then a change in solvent should not alter the four product ratios; the only change expected might be a constant proportional increase or decrease in each of the four products. If, however, one of the isomers was being formed in part by another mechanism it might be expected that the influence of solvent would be different; the two mechanisms may be said to have different solvent coefficients.

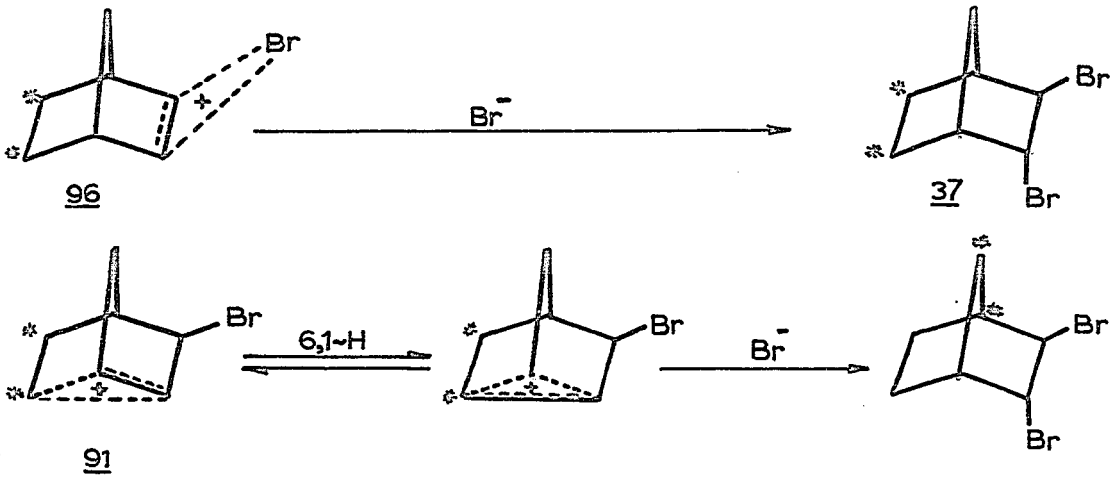
It has been shown in the capture of methylnorbornyl cations that the solvent has no effect on the ratio of capture by solvent at the two related Wagner-Meerwein sites (83). In the three solvents used in this work the ratio of 87/83 and 83/82 show little significant change, but the least polar solvent, carbon tetrachloride, definitely favours formation of the 2-exo-3-endo-dibromo isomer; the ratio of 37/87 in carbon

tetrachloride is approximately three times that in methylene chloride. This result strongly suggests either an alternative mechanism for formation of 37 or some special characteristic of the ions 92 and 93 which is peculiar to nucleophilic attack at position (b).

Increasing the bromide ion concentration (Rx. 8 Table 7) results in a dramatic increase in the yield of trans dibromide 37 to the detectable exclusion of two of the 6,2-hydride shift products 83 and 82 and a marked decrease in 87. This result can only be accommodated by a mechanism in which the increase in bromide ion concentration is allowing an intermediate to be captured before formation of a non-classical ion or 6,2-hydride shift takes place. Although this result does not prove that the trans product 37 arises at least in part from attack on bromonium ion in the reactions without added bromide ion, it does strongly favour it, and shows that the rate of attack by bromide ion, under the latter conditions, is slow enough to allow a significant amount of the competing hydride shift to occur before nucleophilic attack.

In an earlier report of the addition of bromine to norbornylene the trans vicinal product was considered to arise solely from attack on a bromonium ion (37) and likewise in the addition of bromine to 5,6-exo-trimethylenenorbornylene (43). On the other hand, addition of N-bromoamides (36,38) and bromine fluoride (38) gave little or no trans-2,3-product. Chlorination (40) gave 6% trans product but no other products necessarily derived from 6,2- or 6,1-hydride shift. The present results are therefore of particular interest in that the trans product may possibly be formed via both bromonium ion and 6,1-hydride shift processes. To determine definitively whether or not two mechanisms were involved,

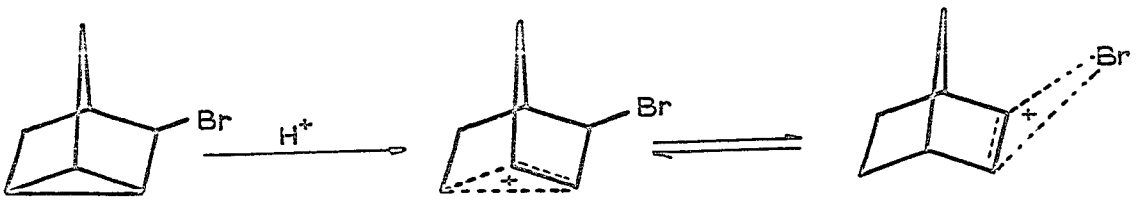
degradation of a sample of the 2-exo-3-endo isomer prepared from 5,6-^{14}C-norbornyl-2-ene was examined using the scheme outlined in Fig. 18. The positions of the label, as dictated by the 'bromonium ion' or 6,1-hydride shift mechanism, are shown below.



The counting results from two degradations are shown in Table 20 on page 171. Two sets of conditions were used for formation of the 2-exo-3-endo-dibromide; in the first (A) 5,6-^{14}C-labelled olefin was brominated in carbon tetrachloride at 0° and the resulting 2-exo-3-endo-dibromide degraded as described previously (Fig. 18); in the second (B) the mixture of mono- and dibromides, resulting from the addition at 0° in a mixture of methylene chloride and carbon tetrachloride (~1:1), was treated with anhydrous hydrogen bromide at 0° until all the bromonortricyclene had been converted to dibromides. The reasons for this latter procedure will become evident in the ensuing discussion. From the activity lost in degradation to succinic acid and to ethylenediamine the amount of trans product (37) arising from the 6,1-hydride route was calculated to be 23-27% in reaction A. Thus the ratio of attack at the two related Wagner-Meerwein sites in non-classical ion 92 to form the

2-exo-3-endo-(37) and 7-anti-2-exo-dibromide (87) is 0.11-0.14. The paucity of attack on non-classical ion 92 to give trans product (37) is in accord with the inductive effect of the bromo substituent as discussed on page 104.

It has been shown that dibromide products may also arise via attack of hydrogen bromide on bromonortricyclene. In view of the relatively small amount of 2-exo-3-endo-dibromide formed by 6,1-hydride shift it was considered worthwhile to try to increase the amount formed by this route relative to bromonium ion, in order to allow a more reliable estimation. This could be achieved by converting the bromonortricyclene, formed in the addition of bromine to norbornylene, to dibromides with hydrogen bromide, as the three non-classical ions 91, 92 and 93, are being formed directly in this case without prior intervention of a bromonium ion. At the same time the degree of reversibility, if any, of the non-classical ion 42 and bromonium ion (96) could be assessed. This latter process, though intuitively acceptable, has never been proved. It was shown (see page 170) that of 2-exo-3-endo-dibromide obtained via reaction of bromonortricyclene with hydrogen bromide ~40% was formed by attachment of a proton at C-6 and subsequent formation of a bromonium ion indicating that the formation of 91 from 96 is indeed reversible. It might be



36 91 96

argued that the trans product could be formed from a classical ion, endo attack being forced by the bulky bromine atom at the adjacent carbon; however there is no reason to suppose that ion 91 can give a classical ion while 92 and 93 do not. In addition, no loss in stereospecificity of the reaction was noted; thus the formation of a bromonium ion from 91 seems probable.

The large ratio of 7-anti-2-exo- to 2-exo-3-endo-isomer (~10) explains the failure to observe the latter in reactions such as the addition of 'BrF' and N,N-dibromobenzenesulphonamide to norbornylene in which conditions are unfavourable for nucleophilic attack on bromonium ion.

The small yield of transproduct in the polar chlorination of norbornylene (40) has been ascribed to the poorer bridging ability of chlorine relative to bromine, using the previously reported results of Kwart, et al, for comparison (37). However in the present work it has been shown that the yield of trans product arising from bromonium ion is less than that found in the analogous chlorination, even when carried out in the same solvent and at the same temperature. The high yield of trans product in the chlorination relative to the bromination reaction may be due to the intervention of a classical ion in which endo attack is forced by the chloro substituent in the cation.

(f) Comparison of the Results from the Various Polar Additions to Norbornylene.

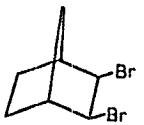
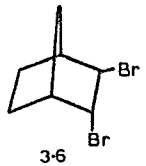
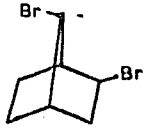
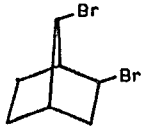
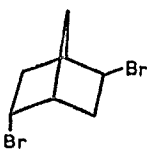
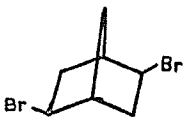
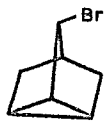
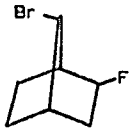
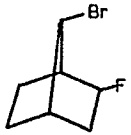
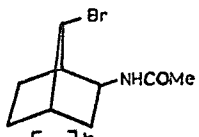
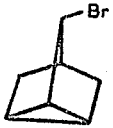
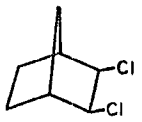
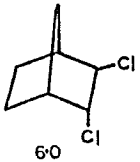
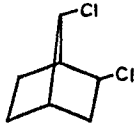
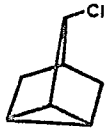
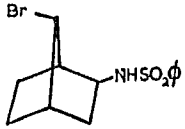
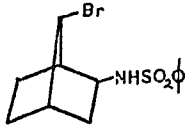
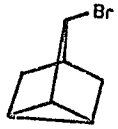
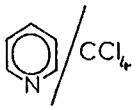
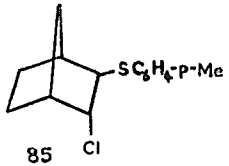
Now that the pathways to the bromide products have been elucidated, it would be fruitful to compare the results from other additions. The product compositions and reaction conditions for a number of additions

to norbornylene are tabulated in Table 8. Changes in product composition may be largely rationalised on the basis of the carbonium ion stability and the nucleophilicity of the anion; the influence of solvent will be discussed later. The addition of bromine to norbornylene exhibits products which may arise from the four modes of reaction previously postulated: (a) elimination, (b) trans addition, (c) Wagner-Meerwein rearrangement and (d) hydride shift. The postulated intermediates, and their rates of interconversion will be discussed with reference to Fig. 20.

(i) Formation of tricyclic product.

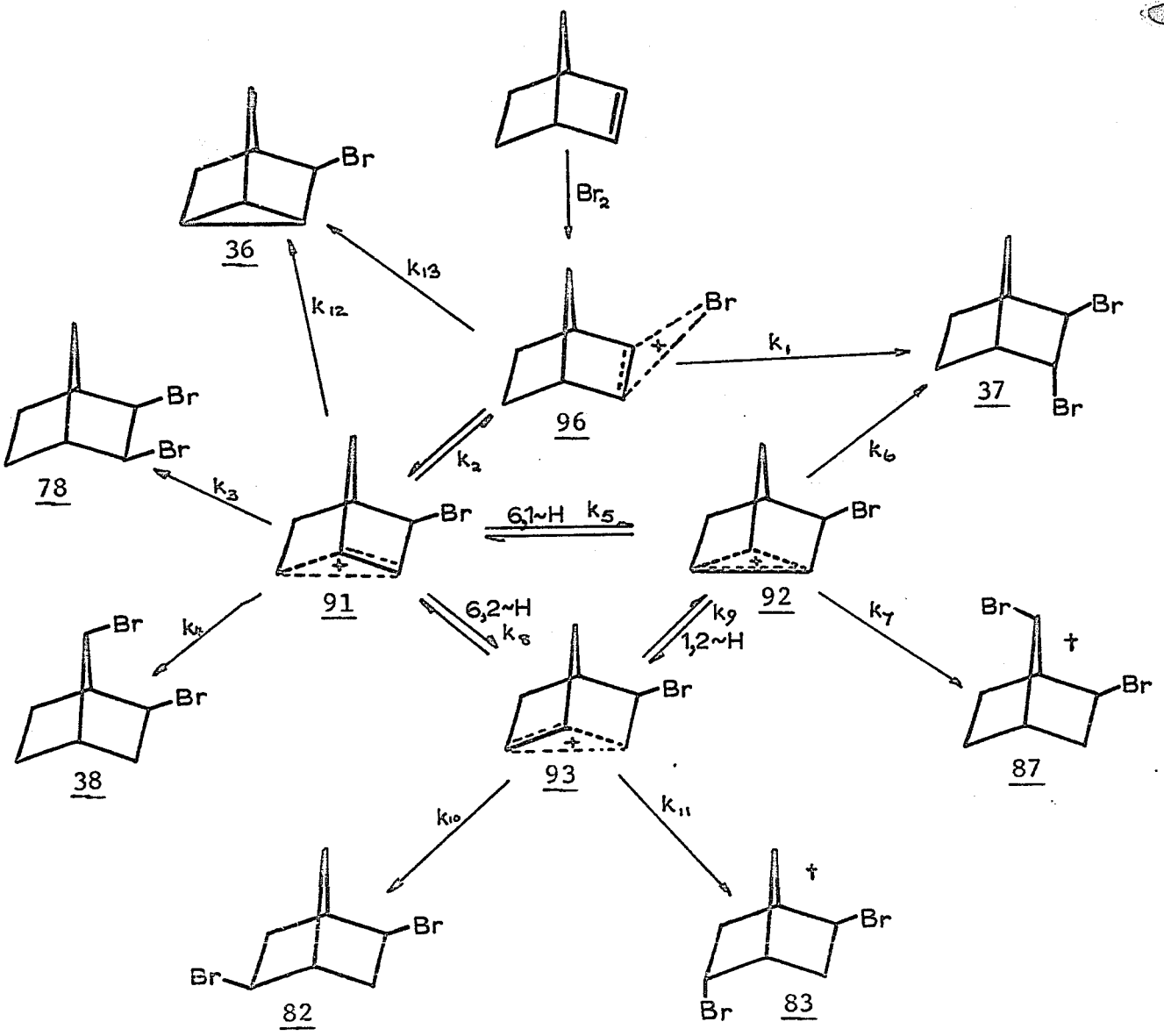
The tricyclic product is probably formed from one or all of the non-classical ions (91, 92 and 93), but may conceivably come from the bromonium ion (96) also. Evidence to support the formation of 96 before the non-classical ion 91 is provided by the observation that increasing bromide ion concentration by the addition of tetraethylammonium bromide increases the yield of trans-2,3-product dramatically i.e. the rate of bromide ion attack is increased to such an extent that it can capture ion 96 before it collapses to 91. What ever the origin of the tricyclic compounds, the greater yield from the chlorine addition is explicable either on the basis of chloride being a poorer nucleophile than bromide or that the chloro analogue of 96 and/or 91 is less stable than its bromo counterpart. The chloro substituent will destabilise the non-classical ion to a greater extent by its electron withdrawing inductive effect and at the same time it is less able to stabilise a neighbouring positive charge via a bridged 'onium' ion. The greater ability of bromine to stabilise neighbouring positive charge relative to that of

Comparison of Norbornylene Polar Addition Reactions

Reagent	Solvent	Temperature °C	Products and % Composition of Crude Product						
Br_2	CH_2Cl_2	0	 <0·5	 3·6	 14·9	 33·0	 3·7	 2·3	 41·5
BrNHCOMe HF	Et_2O/HF	−78	3 Unidentified Minor Products		 38·0	 22·0	 [11·0]†	—	 37·0
Cl_2	CCl_4	25	 3·5	 6·0	—	 25·5	—	—	 65·0
$Br_2NSO_2C_6H_5$		25	2 Unidentified Dibromides ~8		 ~13	 ~29	—	—	 ~46
p-MeC_6H_4SCl	 CCl_4	20—25	 85				No Other Products Reported		

† Isolated from separate run

Fig. 20



Reaction of Bromine with Norbornylene: Products and Reaction Rates

enantiomer

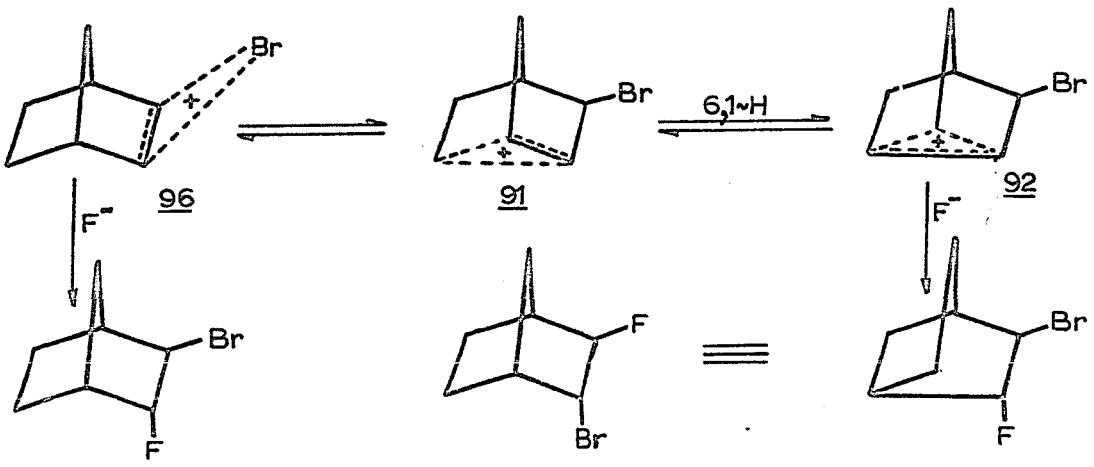
chlorine has been amply demonstrated by the acetolysis rate ratios for cis and trans 2-chloro and 2-bromocyclohexyl brosylates (87,88); intramolecular rearward attack is precluded in the cis isomer and, therefore, if it is assumed that the ratio of trans to cis solvolysis rates is approximately the same in the absence of participation, then any large increase in this ratio will be a rough measure of the extent of participation, i.e. the ability to stabilise positive charge, by the neighbouring halogen. It was found that k_{trans}/k_{cis} is equal to 3.8 and 810 for 2-chloro and 2-bromo substituents, respectively. As nucleophilic attack by chloride will be slower than bromide and the chloro analogues of 96 and 91 are both destabilised by the electronic effects mentioned previously, it seems reasonable that the rate of elimination to give a stable product will be faster than in the bromo case.

(ii) Wagner-Meerwein versus hydride shift products.

The relative amounts of hydride shift products in the various additions and their relation to the Wagner-Meerwein products are largely dependent on the stability of the non-classical ion 91, the nucleophilicity of the halide ion and the solvent. One might expect the Wagner-Meerwein products, 78 and 38, relative to the hydride shift products, to decrease with decreasing nucleophilicity of the anion. This appears to be the case in the BrF addition, in which the carbonium ions 96 and 91 are presumably the same as in the bromine addition. The total yield of hydride shift product 7-anti-bromo-2-exo-fluoro, is almost double the Wagner-Meerwein product, 7-syn-bromo-2-exo-fluoro;

this is probably because the nucleophile, fluoride ion or some associated hydrogen fluoride species, is a weaker nucleophile than bromide anion. A reduction in the yield of hydride shift products relative to Wagner-Meerwein products is also observed when the bromide ion concentration is increased, i.e. the rate of attack on non-classical ion 91 (k_4) and 96 (k_1) has been increased relative to k_8 and k_5.

The high yield of 7-anti-bromo-2-exo-fluoro isomer in the BrF addition is not the result of prior formation of a trans product followed by loss of bromide or fluoride anion to give a non-classical ion which could rearrange. The addition of an unsymmetrical reagent can give two trans-2,3-products as shown below. Any reaction involving removal of



bromide anion would lead to products substituted at C-7 with fluorine which are not observed. A control reaction in which 2-endo-bromo-norbornane was subjected to the 'BrF' reaction conditions showed no change in the substrate. Therefore, as the C-F bond energy is almost twice that of the C-Br bond it seems unlikely that an endo-fluoride anion would be removed under these reaction conditions. It has been observed in the addition of bromine to norbornylene that most (70-80%)

of the trans-product arises via a bromonium ion mechanism and not by 6,1-hydride shift and therefore, the possibility of 7-anti-bromo-2-exo-fluoro isomer formation occurring via removal of an exo-fluoride anion from the 2-exo-fluoro-3-endo-bromo isomer is remote.

The failure to obtain hydride shift products in the reaction of chlorine with norbornylene is explicable on the basis of the balance between the electrophilicity of the carbonium ion and the nucleophilicity of the anion. The chloro analogue of 91 is not stabilised by the chloro group as compared to the stabilising of 91 by the bromine substituent. As mentioned previously, chlorine destabilises the positive charge at C-3 via its inductive effect and at the same time fails to stabilise the positive charge via an 'onium' ion. Thus, although chloride ion is a poorer nucleophile than bromide ion, leading one to expect more hydride shift to have occurred before nucleophilic attack, the increased electrophilicity of the destabilised chloro non-classical ion offsets this to such a great extent that reaction with a nucleophile occurs before hydride shift.

The lower yield of hydride shift found in the addition of N,N-dibromobenzenesulphonamide to norbornylene is not readily interpretable in view of the change in solvent and the non-quantitative product analysis (small yields of other hydride shift products could have been missed using the reported isolation procedure). The absence of any trans-2,3-addition product is ascribed (36) in this work to the participation of the electrons of the C-1,6 bond before attack can occur on an initially formed bromonium ion by the benzenesulphonamido group. However, a trans-2,3-product is one of the pair of isomers that can be

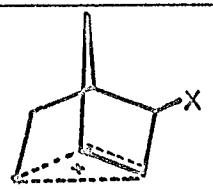
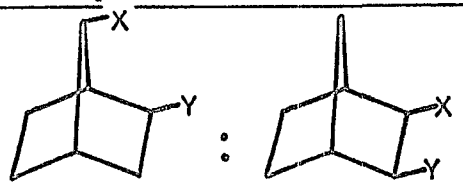
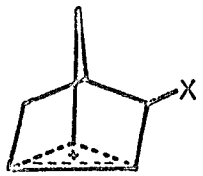
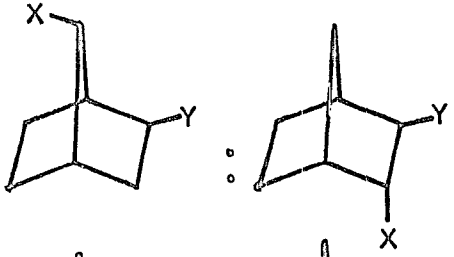
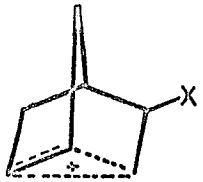
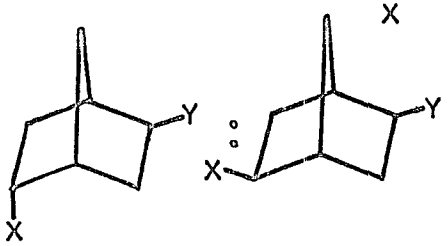
formed by attack on the non-classical ion resulting from 6,1-hydride shift. As one of the products, 7-anti-bromo-2-exo-benzenesulphonamido-norbornane, resulting from such a 6,1-hydride shift is found in this reaction, it would appear that the reported explanation for the absence of trans-2,3-product may be an oversimplification.

(iii) Relative rates of anion capture at Wagner-Meerwein related sites.

A comparison of the relative rates of anion capture at each of the related Wagner-Meerwein sites in ions 91, 92 and 93 is presented in Table 9 for additions to norbornylene, together with the ratios observed in the acetolysis of 2-exo-methyl-3-endo-norbornylbrosylate in acetic acid (83). The ratio of the 7-syn-2-exo- to the 2-exo-3-exo-dibromide probably depends on a combination of steric and electrostatic factors and will vary with solvent. The ratios obtained however, seem to indicate that the predominating factor in the chlorine and bromine addition arises from the spatial requirements of the 2-exo substituent; the electronegativities of C-Br, C-Cl are both very similar and yet there is much greater selectivity in the bromine addition than the chlorine addition. This is consistent with the stable conformation of 1,2-dibromo-4, 5-dichlorocyclohexane which has been shown by x-ray crystallographic means to exist in the axial-dibromo equatorial-dichloro conformation (89). The ratio obtained in the methylnorbornane system is of the order expected if both the Van der Waals radii of methyl and bromine, and the inductive effects of these two groups are considered. These two groups have approximately the same Van der Waals radii but the entry of acetate anion will be much less hindered than that of bromide

Table 9

Ratios of attack at Wagner-Meerwein Related Sites

Equivalent Non-Classical Ion	Wagner-Meerwein pair	Ratios of Products X=Y =Br	X=Br Y=F	X=Y =Cl	X=Br Y=NHSO$_2\phi$	X=Me Y=OAc
		$\geqslant$66:1[+]	$\geqslant$22:1[+]	7.3:1	$\geqslant$29:1[+]	5:1
		7-9:1[‡]	$\geqslant$38:1[b]	-	$\geqslant$13:1[b]	1.05:1
		1.6:1[ϟ]	-	-	-	1.13:1[ϟ]

+ 2,3-exo, exo was undetected

‡ Based on amount formed by hydride shift only

ϟ Insensitive to solvent

b no 2-exo-3-endo detected

because of the former's smaller radius (-O- = 1.4 A^{o}, -Br = 2.4A^{o}). The inductive effect of the methyl group also tends to increase positive charge at C-3, whereas bromide ion decreases it.

The non-classical cation 92 captures anions predominantly to yield 7-anti-2-exo products, a result in accord with electronic considerations. The bromine at C-2 will destablise positive charge at C-3 by virtue of an inductive effect and hence the lowest charge density will be at C-5. The differences in this ratio with the same bromo cation, but different nucleophiles, may be accounted for by both solvent effects and the nucleophilicity of the anion; again predictions are impossible without data for the same solvents.

Cation 93 which gives 5-exo-2-exo and 5-endo-2-exo products shows very little preference for attack at either position and change in solvent did not affect this ratio significantly. The bromide group is remote from the reaction site and therefore, can exert little effect on the approach of the nucleophile. However, there is a small bias in favour of the 5-endo-2-exo isomer which becomes more pronounced at lower temperatures, (2.6 at -75^{o}). This bias cannot be explained on the basis of pure inductive effects, both centres of attack being the same distance through bonds from the substituent, but the attack positions are not in the same spatial environment relative to the bromide group; it is possible that the bromine will have an electrostatic effect through space on the C-1 position in 93 which would tend to stabilise the positive charge more effectively at this position. That such a 'through space' electrostatic effect exists is given credence by the low field position of the 7-syn-proton in 87 relative to the 7-anti-proton

of 38. Another basis for this difference of capture rates may be a steric interaction of the bromo substituent with the syn-proton at C-7

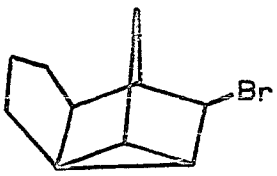
93

which may distort the non-classical ion, 93, such as to lengthen the partial bond between C-1 and C-2 and hence increase the positive charge at C-1. As the capture ratio is different for the two positions it is not improbable that the temperature coefficients for the rate constants may also differ slightly.

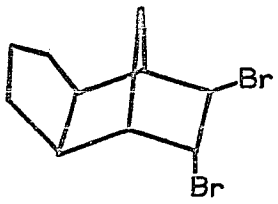
The absence of significant yields of 2-exo-fluoro-5-endo-bromo and 2-exofluoro-5-exo-bromo isomers by attack of fluoride ion on cation 93 is inexplicable in the absence of further data. If it is assumed that this cation arises via two discrete 6,1- and 1,2-hydride shifts from the initial non-classical ion 91 it can be postulated that capture of ion 92 occurs faster than the final 1,2-hydride shift. Alternatively, 6,2-hydride shift may be slower than 6,1-hydride shift in this medium. As fluoride ion is a weaker nucleophile than bromide ion one might expect capture of 92 to be faster with bromide ion than fluoride which is the opposite to the result observed. However, the relative stabilities of 91, 92 and 93 in the two solvents, methylene chloride and ether-hydrogen fluoride are not known which makes unambiguous analysis of this result impossible.

(iv) Solvent effects.

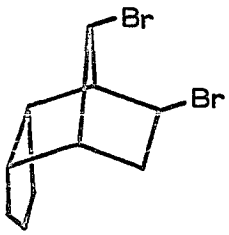
It is immediately apparent from Fig. 20 that the effect of solvent change is likely to be extremely difficult to interpret in view of the large number of rate constants. Little work has been reported on solvent effects in this system except the result of changing from carbon tetrachloride to pyridine (86,43). Previous reports of the addition of bromine to norbornylene in carbon tetrachloride with one equivalent of pyridine (37) claimed that the yield of 7-syn-2-exo-dibromide 38 is increased relative to the yield in carbon tetrachloride. In the present work, when pyridine was used as solvent, the dibromide 38 was reduced from a 33% to a 7.8% yield. Previously, it had been reported that addition of bromine to 5,6-exo-trimethylenenorbornylene in carbon tetrachloride (43) gave only 2-exo-3-endo-dibromide and that bromination in pyridine gave 47 (1.5%) 46 (90%) and 48 (8.5%).



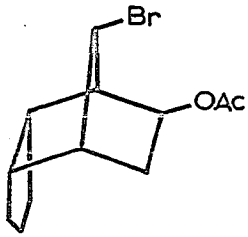
47



46



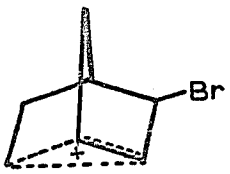
48



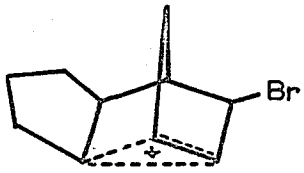
45

When this work was repeated using glc analysis, the result indicated no change in the yield of 46 when the solvent was changed from carbon tetrachloride to pyridine; the low boiling products increased from approximately 3 to 12 percent and there was a corresponding decrease in the high boiling products. Bromination of the same olefin by N-bromo succinimide in acetic acid (42) gave at least 73% of 45. These

results may be compared with those obtained when methylene chloride, carbon tetrachloride and acetonitrile were used as solvents in the bromination of norbornylene. The conclusion was drawn from the previously reported brominations in pyridine that its use promoted the formation of rearranged products 38 and 48 by "increasing the stability (43) and/or promotion of the equilibrium formation of the bridged ions 91 and 99". The present results demonstrate that the effect of



91



99

pyridine is more complex and, in view of the variety of results obtained with different pyridine analogues (vide infra), and the possibility of a different brominating agent being involved, there is no reason to consider the product distributions obtained in pyridine as merely a solvent effect. For this reason the brominations in the presence of amines will be excluded from further discussion.

Solvent polarity as measured by dielectric constant (Table 10) is not very important in determining the ratios of trans addition, hydride shift and simple Wagner-Meerwein rearrangement although the ratio of hydride shift product (excepting the trans isomer) to the primary Wagner-Meerwein product, 7-syn-2-exo-dibromide 38, slowly increases with increasing dielectric constant, indicating that the overall hydride shift rate is close to the nucleophile capture rate of the initial parent non-classical cation 91. This may be rationalised on the basis

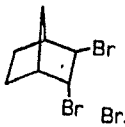
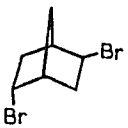
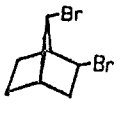
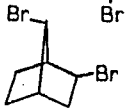
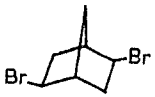
of increased stabilisation of the non-classical ion by the more polar solvent permitting more hydride shift to occur before capture by a nucleophile. The concomitant decrease in the 7-syn-2-exo-dibromide with increasing polarity is consistent with a decrease in nucleophilicity of bromide ion as it is more solvated in the more polar solvents. The least polar solvent, carbon tetrachloride, induces a small increase in the yield of trans product in agreement with the increased nucleophilicity of the bromide ion. All three of these aprotic solvents solvate anions poorly which makes the small changes in product distribution understandable (91,92).

Methylene dichloride (D=9.09) being more polar, will solvate the cations slightly better than its fully chlorinated analogue (D=2.24), however, acetonitrile (D=37.50) which might have been expected to solvate the cations much better has been shown not to do so (90,91) although one would still expect it to be better than the chlorinated hydrocarbons.

To add to the confusion, the usual Swain and Scott order of nucleophilicity (93) is only reliably applicable in protic solvents (94) making meaningful correlations between results in different solvents with different nucleophiles difficult. The two results obtained with the 5,6-trimethylene analogue are consistent with the non-classical bridged ion being favoured by a more polar solvent and by the lower nucleophilicity of acetate ion relative to bromide ion. The absence of hydride shift products in the 5,6-trimethylene analogue may be ascribed to the particular stereochemistry required for these shifts to take place; 6,1-shifts are precluded by the exo-trimethylene

Table 10

Influence of Solvent on the Addition of Bromine to Norbornylene and the exo-Trimethylene Analogue

Substrate	Solvent	Dielectric Constant	 37	 87	 83	  82	38
Norbornylene + Br_2	CCl_4	2.24	14.6	19.0	6.0	4.6	53.0
	CH_2Cl_2	9.08	5.9	24.4	6.1	3.8	54.0
	CH_3CN	37.50	10.4	35.2	9.4	7.1	37.3
			46†				
43 + Br_2	CCl_4	2.24	80				10‡
43 + NBS	HoAc	6.15	-				73#

† 5,6-exo-Trimethylene-2,3-dibromonorbornane
‡ 5,6-endo-Trimethylene-7-syn-2-exo-dibromonorbornane
# 5,6-endo-Trimethylene-7-syn-bromo-2-exo-acetoxynorbornane

bridge, even though the shift creates a tertiary carbonium ion centre, because it has been shown previously that it is the exo-proton at C-6 rather than the endo-proton which shifts to C-1. 6,2-Hydride shifts are not precluded but as observed in the addition of bromine to norbornylene the products from such a shift (or sequential 6,1- and 1,2-shifts) are in minor amount.

(v) Addition of Bromine to Norbornylene in the presence of Tertiary Amines.

When the previously reported reaction of bromine with norbornylene in pyridine (37) was repeated the yield of trans addition (37) and bromonortricyclene (36) formation were greatly increased at the expense of both hydride shift products and the 7-syn-2-exo-dibromo isomer 38. This result appeared inconsistent with the report (37) that bromination of norbornylene in carbon tetrachloride containing one equivalent of pyridine increased the yield of the 7-syn-2-exo-dibromide relative to the 2,3-trans isomer. However, it had been reported (85) that the bromination in pyridine gave a 2-exo-6-endo-dibromo isomer and the 7-syn-2-exo-dibromide in a ratio of approximately 2 to 1. A later report (86) showed by a chemical proof that the 2-exo-6-endo-dibromide structure for this isomer was erroneous and that this isomer was almost pure 2-exo-3-endo-dibromide. Unfortunately, no crude product composition data were given. As the exact details of the addition reaction in pyridine seemed uncertain a further, more detailed, study of the pyridine reaction (and subsequently other tertiary amines) was undertaken.

It seemed possible that the change in the reaction on using

pyridine might be the result of an intrinsic property of tertiary amines and not due to a general polarity effect. It has been reported that when bromine was mixed with pyridine in petroleum ether solution a red precipitate of pyridine perbromide was deposited (95). This was used to brominate bromomalonaldehydetetraethylacetal without destroying the acetal groups with the hydrogen bromide formed in the usual bromination procedure. Another similar reagent which has been used to brominate stereospecifically is pyridinium hydrobromide perbromide, a stable crystalline solid. This has been used to brominate steroid ketones (97) and to brominate stereospecifically cis- and trans-stilbene. Bromine in carbon disulphide adds to cis-stilbene to give dl-stilbene- and meso-stilbene dibromide in a ratio of 2:1 (98), whereas pyridinium hydrobromide perbromide in acetic acid gave exclusively the trans product (99), dl-stilbene dibromide. This reagent with trans-stilbene gave exclusively meso-dibromide (99). These results substantiate the assertion that brominations in pyridine should be considered as separate cases. From the reactions of pyridine hydrobromide perbromide it is reasonable to expect the stereochemistry of the tertiary amine to exert an influence on the product distribution both in its capacity to increase or decrease effectiveness of solvation by shielding the nitrogen and, as a bulky entering group it may exert a directional influence on the incoming nucleophile. In contrast to the reactions without amine present, there should be a greater availability of bromide ion which will depend on the pK_a of the amine. The most striking result obtained from the additions of bromine to olefin in the presence of pyridine (Table 11) is the change in product distribution between addition of bromine to olefin in pyridine and the addition of olefin to pyridine

Table 11

Effect of Variables on Reaction of Bromine with Norbornylene in the Presence of Pyridine

Conditions	Temp./Time °/min.	Dibromonorbornanes					
		36*	2-exo-3-endo- 37	7-anti-2-exo- 87	5-endo-2-exo- 83	5-exo-2-exo- 82	7-syn-2-exo- 38
Olefin in amine, Add Br_2	0°/20 min.	67.3	20.7	-	-	-	7.8
Olefin in amine Add Br_2	Reflux 20 min.	30.4	60.6	-	-	-	8.4
Add olefin to preformed pyridine perbromide in CCl_4	30 min./25° Reflux/60 min.	19.4	5.0	5.0	-	-	71.5
Add olefin to preformed pyridine perbromide in $CHCl_3$	0°	33.5	9.6	8.5	2.9		45.0

* bromonortricyclene.

perbromide in an inert solvent. The elimination to give tricyclic product is drastically reduced by raising the temperature, a surprising feature in that raising the temperature usually favours elimination; alternatively, the nucleophilic attack of bromide ion may be accelerated to a greater extent. The possibility that the increased yield of the trans dibromide 37 might arise via attack of pyridine on the tricyclic bromide 36 was disproven by the observation that 36 could be recovered unchanged from refluxing pyridine under the addition reaction conditions. The dibromide product distribution may be rationalised on the basis of the relative stabilities of an initially formed bromonium ion, of the non-classical carbonium ion 91 and of the bromide ion. When pyridine is used as solvent, it may stabilise the initially formed bromonium ion to such a degree that attack by nucleophilic bromide ion can be competitive with collapse to the non-classical ion 91. In the non-polar solvent, carbon tetrachloride, the stability of the bromonium ion relative to the non-classical ion appears to decrease to such an extent that even though nucleophilic attack by bromide ion may be faster it still prefers collapse to a more stable structure before attack.

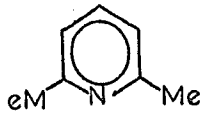
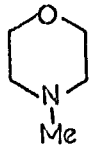
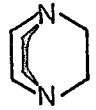
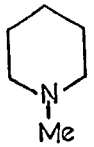
Chloroform stabilises the non-classical ion 91 such that hydride shift is now competitive with nucleophilic attack on non-classical ion 91. The stabilising influence of chloroform also results in an increase of product from attack on the bromonium ion. With these reaction conditions pyridine perbromide is acting in the same fashion as bromine.

The product distribution from addition of norbornylene to

preformed amine perbromide in chloroform is compared with base strength in Table 12. The increase in trans addition may be ascribed to the increased availability of bromide ion with increasing base strength hence the rate of nucleophilic attack is increased to the point at which the bromonium ion may be captured. Triethylamine is presumably a strong enough base that breakage of the nitrogen bromine bond becomes so slow that other processes such as oxidation of the amine occur faster than addition of positive bromine to the double bond.

Table 12

Reactions of Norbornylene with Amine Perbromides in $CHCl_3$

Base	pK_A	36*	Dibromonorbornanes				
			2-exo-3-endo-37	7-anti-2-exo-87	5-endo-2-exo-83	5-exo-2-exo-82	7-syn-2-exo-38
	5.23	33.5	9.6	8.5	2.9		45.0
	5.77	30.5	9.3	13.2	3.9		43.2
	7.41	44.3	27.1	8.3	8.3		20.7
	8.60	38.8	53.0	~zero	~zero	~zero	8.5
	10.08	21.5	54.0	2.0	+ other	14.5	7.8
Et_3N	10.72	-	No Dibromide Products				

Reaction temperature 0°C. throughout.

* bromonortricyclene

EXPERIMENTAL

General Equipment and Precautions.

Gas liquid chromatography (glc) was carried out on an F and M Model 700 and Aerograph Model A350 using 3.0 m. x 10 mm. copper columns and a hot wire detector for compounds insensitive to hot metal. A Glowall Model 400, fitted with a 1.8 m. x 3.4 mm. glass column and injection chamber for analysis and a 1.8 m. x 10 mm. column for preparative work, was used for metal sensitive compounds. Both hydrogen flame and argon ionisation detectors were used, the former in conjunction with a 50:1 stainless steel splitter. Collection losses were kept to a minimum by collecting the samples directly in weighed vials as follows: a short pyrex tube incorporating a rubber septum and packed with glass wool was fitted through the cap of a 1 dram vial and the latter immersed in a Dry Ice-acetone mixture. After collection, the collection unit was centrifuged to give a completely solvent free sample in the storage vial.

Infrared spectra were taken on a Beckman IR-5A spectrophotometer, with 0.1 mm. cells and sodium chloride optics, calibrated against polystyrene film. Ultraviolet spectra were obtained using a Cary Model 14 spectrophotometer. Nuclear magnetic resonance (nmr) spectra were recorded on a Varian A-60 and an HR-100 with field-sweep spin decoupling attachments.

The dipole moment measurements were obtained using a Wissenshaftlich-Technische Werkstatten Dipolemeter DM-01.

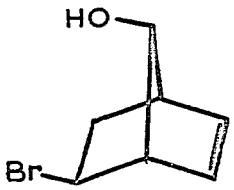
All melting points are uncorrected and were measured on a Kofler

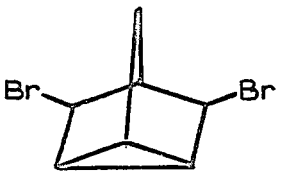
hot stage apparatus. Refractive Indices were measured on a thermostatically controlled Bausch and Lomb refractometer.

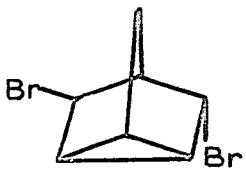
Microanalyses were performed by A. Bernhardt, Mülheim, Ruhr, W. Germany and by A. B. Gygli, Toronto.

While no accidents have occurred in this work in the use of perchloryl fluoride, explosions have been reported when the gas has been caused to liquefy in a cold trap, thus making it advisable to employ the safety precautions outlined in reference 14 (Appendix I).

In view of the fatalities which have occurred to workers using the two dibromides and bromohydrin (100) shown below all work with the dibromides including glc, was conducted in a well ventilated fume cupboard.







^{14}C Counting was carried out using a liquid scintillation spectrometer, Nuclear Chicago MKI. Samples were counted at balance point using a channels ratio method to ensure that counting efficiency did not change from sample to sample. As there was no variation in counting efficiency, counts per minute data were adequate for comparison.

The solvent (scintillation mixture) used for counting had the following composition: toluene containing 2,5-diphenyl oxazole (0.4%) and p-bis-(o-methylstyryl)-benzene(0.005%) was diluted with ethylene glycol monomethyl-ether in a ratio of 5:4 by volume.

Table 13

Gas Chromatographic Columns

Column	%	Substrate	Dimensions mm x m	Chromasorb Type	Mesh
F	10	SE30*	6.4 x 2.4	W	60-80
G	10	DEGS*	6.4 x 2.4	P	60-80
H	5	DEGS	3.4 x 1.8	P	60-80
I	10	DEGS	3.4 x 1.8	P	60-80
J	1	DEGS	3.4 x 1.8	P	60-80

* silicone oil

* Diethylene glycol succinate.

Addition of Bromine Fluoride to Norbornylene

Anhydrous hydrogen fluoride (50 g., 2.5 moles) was condensed into a 1 litre polythene bottle cooled in an acetone-Dry Ice bath and pre-cooled anhydrous ether (250 ml.) was added slowly with magnetic stirring. Norbornylene (20.05 g., 0.213 mole) and N-bromoacetamide (37.98 g., 0.275 mole) were added in alternate portions over 10 min. After being stirred for 1 hr. the reaction was allowed to stand overnight (~12 hr.) at -78°C. Moisture was excluded as far as possible throughout. The resulting solution was poured into a mixture of sodium bicarbonate (260 g.), ice, water (1 l.) and ether (150 ml.), stirred and separated. The aqueous layer was further extracted with

two 50-ml. portions of ether, and the combined ethereal solution dried over magnesium sulphate. Evaporation gave a crude semi-solid product (33.9 g.) which on filtration afforded a white solid (5.65 g.) (D) and a liquid fraction. Gas chromotography of the liquid fraction on column [F] at 150° indicated the presence of three main components (A, B & C) and traces of other products (53). Fractional distillation on a spinning band column effected only partial separation:-

Fract. No.	Wt. (g.)	B.P./press. (°C/mm.)	GLC analysis (cut & weigh) (Col.F) A%	B%	C%	other %
forerun	1.26	74-80/28				
4	2.97	80-82/28	86	9.5	-	4.5
5	3.45	82-83/28	77	19.0	-	4.0
6	1.87	83-85/28	60.3	36.4	-	3.3
7	1.45	85-87/28	36.5	62.0	-	1.5
8	1.36	87-89/28	16.4	83.0	-	0.6
9	1.54	89-93/28	5.7	94.3	-	-
10	0.73	93-98/28	-	87.0	12.0	1.0
11	1.15	98-108/28	-	58.0	42.0	-
12	4.32	108-114/28	-	-	70.0	30.0

Bromonortricyclene (Compound A, 36)

Compound A (200 mg., 99% pure) was isolated from fraction 4 by preparative gas chromatography on column [G] at 120°. (Rt:6.5 min.) The infrared and nmr spectra, and refractive index, n_D^{25} 1.5260 [lit: (2) n_D^{25} 1.5269], were in agreement with those reported for bromonortricyclene (39).

7-anti-Bromo-2-exo-fluoronorbornane (Compound B, 63)

Compound B (577 mg., > 99% pure) was obtained from fractions 7 and 8 by preparative gas chromatography on column [B] at 105°. This material gave a positive test for bromine (101) and fluorine (102) and had n_D^{25} 1.4981, $\mu^{25}_{benzene}$ 2.62D, $\mu^{25}_{cyclohexane}$ 2.38D. The nmr spectrum is shown in Fig. 2.

Anal. Calcd. for $C_7H_{10}BrF$ (193.06): C, 43.53; H, 5.22; Br, 42.35.
Found: C, 43.84; H, 5.34; Br, 42.03.

7-syn-Bromo-2-exo-fluoronorbornane (Compound C, 61)

Compound C (900 mg., 99% pure) was isolated from fraction 12 by preparative gas chromatography on column [G] at 155°. This material gave a positive test for bromine (101) and fluorine (102) and had n_D^{25} 1.5097, n_D^{30} 1.5084, $\mu^{25}_{benzene}$ 3.76D. $\mu^{25}_{cyclohexane}$ 3.54D.

Anal. Calcd. for $C_7H_{10}BrF$ (193.06): C, 43.53; H, 5.22; Br, 41.39.
Found: C, 43.73; H, 5.10; Br, 42.01.

Relative Reactivities of A, B & C.

Test-tubes containing silver nitrate (100 mg.) and acetonitrile (2 ml.) were treated with 2 drops of each compound, the resulting solution shaken for a few minutes and then allowed to stand. The solution of A showed turbidity within 3 min. while those of B and C showed only a trace of turbidity after 60 min.

7-syn-Bromo-2-exo-acetamidonorbornane (73)

The white solid D (5.65 g.) left after filtration of the crude

product from the 'BrF' addition was recrystallized twice from petroleum ether (b.p. 30-60°) to give colourless needles m.p. 125-127°, $\nu_{max.}^{CS_2}$ 3425 (NH) and 1675cm^{-1} (N-C=O), δ 1.94 (3H, s, CH_3C=O) and 3.8 - 4.25 (2H, m, C-2-H+C-7-H) ppm.

Anal. Calcd. for $C_9H_{14}NOBr$ (232.13):

C, 46.57; H, 6.08; N, 6.04; O, 6.89.

Found: C, 46.53; H, 6.35; N, 6.23; O, 6.99.

2-exo-Aminonorbornane

A solution of the acetamido derivative (586 mg., 2.46 mmoles.) in 10 ml. of sec-butyl alcohol was treated with 1.0 g. of sodium over a period of 10 min. at room temperature and was then heated at reflux for 6 hours (36). After cooling, the solution was acidified and extracted with two 25-ml. portions of ether. Neutralization of the aqueous solution, followed by ether extraction, drying and subsequent evaporation of the ethereal solution, afforded a basic oil (183 mg., 66%).

Treatment of the amine (62 mg.) in 2.5 ml. of pyridine, with excess acetyl chloride gave, after acidification, extraction and evaporation, a pale yellow oil (66 mg.). After decolourization, the oil slowly crystallized and had m.p. 125-129°. The crude N-acetyl derivative was sublimed at 95-100°/40 mm. to give fine needles, m.p. 137-138° [lit (36): 138-140°].

The crude amine, on standing in air, slowly formed a solid amine-carbonate (60) which could be readily collected by washing with a little ether followed by filtration.

The N-chloroacetyl derivative was prepared by treatment of the amine-carbonate (10 mg.) in chloroform with chloroacetyl chloride;

washing with 10% aqueous sodium bicarbonate and evaporation of the organic solution gave a solid which, after sublimation at 90°/40 mm., had m.p. 122-124° [lit (103): 120-121°] .

7-syn-Bromo-2-exo-aminonorbornane (74)

A suspension of 7-syn-bromo-2-exo-acetamidonorbornane (73) (640 mg., 2.77 mmoles.) in 10 ml. of 10% hydrochloric acid was heated at 165° in two sealed tubes for 24 hr. The resulting aqueous solution, containing a few black particles, was basified with 10% aqueous sodium hydroxide solution, extracted with three 25-ml. portions of ether and the extract dried over magnesium sulphate. Evaporation of the ether gave 7-syn-bromo-2-exo-aminonorbornane, (367 mg, 70%) δ_{CCl_4} 2.88 (1H, m, C_2-H), 3.88 ppm (1H, m, C_7-H).

7-syn-Bromonorbornan-2-one

(a) Attempted methods:

(i) 7-syn-Bromo-2-exo-aminonorbornane (105 mg., 0.45 mmole.) and sodium molybdate (10 mg.) were dissolved in 1 ml. of water and 3 ml. of methanol (36). After the addition of 1 ml. of 30% aqueous hydrogen peroxide, the solution was allowed to stand for 1 hr. at room temperature. Further sodium molybdate (5 mg.) and hydrogen peroxide (1 ml., 30%) were added and the solution allowed to stand at room temperature for 20 hr. Acidification and extraction, followed by drying and evaporation, gave an oil (60 mg.), $\nu_{max}^{CCl_4}$ 3080 (w), 3240 (b) (OH) and 1755 (vw) (C=O)cm^{-1}. This material did not give a 2, 4-dinitrophenylhydrazone.

(ii) 7-syn-Bromo-2-exo-aminonorbornane (74) (53 mg., 0.23 mmole.) and yellow mercuric oxide (216 mg., 1.0 mmole.) were stirred in 10 ml. of benzene for 36 hr. at room temperature followed by 24 hr. at reflux. After acid extraction no product was found in the organic layer.

(b) Successful method:

Recrystallized lead tetraacetate (570 mg., 1.30 mmoles.) was added to a stirred solution of bromoamine 74 (232 mg., 1.23 mmoles.) in 10 ml. of chloroform. After the solution had been refluxed for 90 min, 10 ml. of 10% sulphuric acid were added and the chloroform boiled off. The acidified mixture was refluxed for 5 hr, cooled and extracted with three 25-ml. portions of ether. Evaporation of the dried ethereal solution left 102 mg. of crude bromo ketone 75 which was treated with a methanolic solution of 2, 4-dinitrophenylhydrazine and hydrochloric acid. After heating this solution to reflux and allowing it to cool, a crystalline precipitate settled out over 2 hr. The crude derivative was chromatographed on Woelm acid-washed alumina and then on a preparative silica-gel plate developed in benzene. Extraction of the appropriate band gave the 2,4-dinitrophenylhydrazone of 7-syn-bromonorbornan-2-one (75) (42 mg., 9%) which after two recrystallizations from chloroform-petroleum ether (b.p. 80-100°) melted at 203-205° [lit (36): 203-203.5°] .

5,6-Dehydro-2-endo-bromonorbornane

Vinyl bromide supplied by City Chemical Corp. (18 g., 0.17 mole) and freshly distilled cyclopentadiene (7.5 g., 0.11 mole) were heated at 120° for 40 hr. in three sealed pyrex tubes. Distillation of the resulting

brown liquid gave 11.65 g. of crude product (88% based on cyclopentadiene), b.p. 60-61°/12 mm, n_D^{25} 1.5233 [lit (39): n_D^{25} 1.5231] . Glc on column [G] at 110° showed two components (Rt: 5.2 & 5.8 min.) in a ratio of two to one.

2-endo-Bromonorbornane (72)

Crude 2-endo-bromo-5,6-bicyclo [2.2.1] heptene (10 g.) in 30 ml. of ethyl acetate was hydrogenated in the presence of platinum oxide (110 mg.) at room temperature. Theoretical hydrogen uptake occurred in 15 min. Glc on column [G] at 110° indicated the presence of two components, one of which was identified as bromonortricyclene by it s glc retention time and nmr spectrum. Pure 2-endo-bromide was obtained by treating the mixture with silver nitrate with subsequent chromatography as follows. The crude hydrogenation product was treated with silver nitrate (5 g.) in 30 ml. of acetonitrile and stirred at room temperature for 20 min. After filtration, evaporation, addition of a little ether and further filtration, the crude oil, resulting from evaporation of the ether, was chromatographed on 300 g. of silica gel. Elution with 400 ml. of petroleum ether (b.p. 30-60°) gave pure 2-endo-bromonorbornane (2.70 g.) n_D^{25} 1.5119 [lit (104): n_D^{25} 1.5198] , nmr spectrum in carbon tetrachloride, δ 4.34 ppm (1H, m, C_2-H) (Fig. 4).

2-exo-Bromonorbornane (71)

Norbornylene (10 g., 110 mmoles.) and 47% aqueous hydrobromic acid (36 g.) were heated with stirring at 60° for 3 hr. The organic layer was separated and dried. Fractional distillation afforded one main

fraction (12.05 g, 64%) pure by glc on column [G] at 100°, b.p. 81-83°/28 mm, n_D^{25} 1.5136 [lit (39): 82°/29 mm, n_D^{25} 1.5126], nmr spectrum in carbon tetrachloride, δ 3.97 ppm (1H, m, C-2-H) (Fig. 3).

Reaction of 2-endo-Bromonorbornane with "BrF"

2-endo-Bromonorbornane (306 mg, 1.8 mmoles.) in 5 ml. of ether was added to a solution of anhydrous hydrogen fluoride in 50 ml. of ether at -78°. A little N-bromoacetamide was added and the mixture kept at -78° for 14 hr. Work up, as in the original addition of 'BrF' to norbornylene, afforded an oil (282 mg. 93% recovery) whose retention time on glc and nmr spectrum were identical with those of the starting material.

Determination of Dipole Moments.

The expression below was used in these calculations.

$$\mu^2 = \frac{27kT}{4\pi N} \cdot \frac{1}{d(\varepsilon_1+2)^2} \cdot (\alpha_\varepsilon - \alpha_\eta) \cdot M$$

Where
k = Boltzmann's constant
N = Avagadro's number
d = Density of solvent
ε_1 = Dielectric constant of the solvent
M = Molecular wt. of the solute
η_{12} = Refractive index of solution
η_1 = Refractive index of pure solvent

$(\varepsilon_{12}-\varepsilon_1)$ = [Dipole meter reading of soln. − Dipole meter reading for pure solvent] x cell constant

Cell constant 3.62×10^{-4}

$\alpha\varepsilon$ is the slope from a plot of wt. fraction against $(\varepsilon_{12}-\varepsilon_1)$
$\alpha\eta$ is the slope from a plot of wt. fraction against $(\eta_{12}^2-\eta_1^2)$

7-anti-Bromo-2-exo-fluoronorbornane

(a) Benzene as solvent.

Wt. fraction	$(\varepsilon_{12}-\varepsilon_1)$ x cell constant	$\eta_{12}^2 - \eta_1^2$
x10^{3}	x10^{-3}	x10^{3}
2.0800	5.1	-2.7
4.9442	15.4	-3.3
9.5984	31.5	-4.5
14.2260	46.4	-7.8

d^{25}_{benzene} 0.879 $\varepsilon^{25}_{\text{benzene}}$ 2.274 α_ε= 3.72 α_η= -0.24.

(b) Cyclohexane as solvent.

Wt. fraction	$(\varepsilon_{12}-\varepsilon_1)$ x cell constant	$\eta_{12}^2 - \eta_1^2$
x10^{3}	x10^{3}	x10^{3}
1.9127	4.9	0.0
3.3992	9.1	-0.3
7.0715	18.5	0.2
10.2749	26.7	1.0
15.6215	41.3	1.4

$d^{25}_{\text{Cyclohexane}}$ 0.779; $\varepsilon^{25}_{\text{Cyclohexane}}$ 2.015; α_ε=2.67; α_η= 0.086.

7-syn-Bromo-2-exo-fluoronorbornane

(a) Benzene as solvent. (Two determinations).

Wt. fraction		$(\varepsilon_{12}-\varepsilon_1)$ cell constant		$\eta\eta_{12}^2 - \eta_1^2$	
x10^{-3}		x10^{3}		x10^{3}	
(1)	(2)	(1)	(2)	(1)	(2)
1.4739	3.920	10.61	26.54	-0.6	-6.0
3.5536	6.790	25.78	48.62	-2.1	-7.5
5.4155	9.880	39.06	72.44	-2.4	-7.8
7.4468	13.380	54.56	102.67	-4.5	-7.8
9.3062	-	69.83	-	-1.8	-

d^{25} benzene 0.879 ε^{25} benzene 2.274 (1) α_ε 7.56; α_η -0.47.
α_ε 8.00; α_η -0.27.

(b) Cyclohexane as solvent

Wt. fraction	$(\varepsilon_{12}-\varepsilon_1)$ cell constant	$\eta_{12}^2 - \eta_1^2$
x10^{3}	x10^{3}	x10^{-3}
4.310	22.70	-1.1
8.426	44.70	-0.5
14.029	76.90	-1.1
17.716	98.80	1.5

d^{25} Cyclohexane 0.779 ε^{25} Cyclohexane 2.015 α_ε 5.65; α_η 0.000.

Calculated Dipole Moments (64) of fluorobromonorbornanes

Bond moments. C-Br 2.0D (105)

C-F 1.94D (106)

7-syn-bromo-2-exo-fluoro ≡ 7-syn-fluoro-2-exo-bromo;

$$\mu^2 = (2.0 \times 0.349 + 1.94 \times 0.000)^2 + (2.0 \times 0.842 + 1.94 \times 0.824)^2 + (2.0 \times 0.414 + 1.94 \times 0.566)^2$$

7-syn-bromo-2-endo-fluoro ≡ 7-syn-fluoro-2-endo-bromo;

$$\mu^2 = (2.0 \times 0.349 + 1.94 \times 0.000)^2 + (-2.0 \times 0.115 + 1.94 \times 0.824)^2 + (-2.0 \times 0.930 + 1.94 \times 0.566)^2$$

7-anti-bromo-2-exo-fluoro ≡ 7-anti-fluoro-2-exo-bromo;

$$\mu^2 = (2.0 \times 0.349 + 1.94 \times 0.000)^2 + (2.0 \times 0.842 - 1.94 \times 0.824)^2 + (2.0 \times 0.414 + 1.94 \times 0.566)^2$$

7-anti-bromo-2-endo-fluoro ≡ 7-anti-fluoro-2-endo-bromo;

$$\mu^2 = (2.0 \times 0.349 + 1.94 \times 0.000)^2 + (-2.0 \times 0.115 - 1.94 \times 0.824)^2 + (-2.0 \times 0.930 + 1.94 \times 0.566)^2$$

2-exo-fluoro-2-exo-bromo≡2-exo-bromo-2-exo-fluoro;

$$\mu^2 = (-2.0 \times 0.349 + 1.94 \times 0.349)^2 + (2.0 \times 0.842 + 1.94 \times 0.842)^2 + (2.0 \times 0.411 + 1.94 \times 0.414)^2$$

2-exo-fluoro-3-endo-bromo≡2-exo-bromo-2-endo-fluoro;

$$\mu^2 = (2.0 \times 0.349 - 1.94 \times 0.349)^2 + (2.0 \times 0.115 - 1.94 \times 0.842)^2 + (2.0 \times 0.930 - 1.94 \times 0.411)^2$$

2-exo-fluoro-5-exo-bromo≡2-exo-bromo-5-exo-fluoro;

$$\mu^2 = (-2.0 \times 0.349 + 1.94 \times 0.349)^2 + (2.0 \times 0.842 + 1.94 \times 0.842)^2 + (2.0 \times 0.411 + 1.94 \times 0.411)^2$$

2-exo-fluoro-5-endo-bromo≡2-exo-bromo-5-endo-fluoro;

$$\mu^2 = (+2.0 \times 0.349 - 1.94 \times 0.349)^2 + (2.0 \times 0.842 - 1.94 \times 0.115)^2 + (2.0 \times 0.411 + 1.94 \times 0.930)^2$$

2-endo-fluoro-5-endo-bromo≡2-endo-bromo-5-endo-fluoro;

$$\mu^2 = (-2.0 \times 0.349 + 1.94 \times 0.349)^2 + (2.0 \times 0.115 - 1.94 \times 0.115)^2 + (-2.0 \times 0.930 - 1.94 \times 0.930)^2$$

2-exo-fluoro-6-exo-bromo ≡ 2-exo-bromo-6-exo-fluoro;

$$\mu^2 = (2.0 \times 0.349 + 1.94 \times 0.349)^2 + (2.0 \times 0.842 - 1.94 \times 0.842)^2 + (2.0 \times 0.411 + 1.94 \times 0.411)^2$$

2-exo-fluoro-6-endo-bromo ≡ 2-exo-bromo-6-endo-fluoro;

$$\mu^2 = (2.0 \times 0.349 + 1.94 \times 0.349)^2 + (2.0 \times 0.842 + 1.94 \times 0.115)^2 + (2.0 \times 0.411 - 1.94 \times 0.930)^2$$

2-endo-fluoro-6-endo-bromo ≡ 2-endo-bromo-6-endo-fluoro;

$$\mu^2 = (2.0 \times 0.349 + 1.94 \times 0.349)^2 + (-2.0 \times 0.115 + 1.94 \times 0.115)^2 + (-2.0 \times 0.930 - 1.94 \times 0.930)^2$$

Gas Chromatograph Calibration.

This was carried out on a Glowall Model 400 using column [H] without the 50:1 splitter.

Weighed Mixtures	1 % by wt.	2 % by wt.	3 % by wt.	4 % by wt.
2-exo-bromo ✲	51.3	74.7	18.5	8.0
bromonortricyclene	48.7	25.3	81.5	-
2-exo-3-endo-dibromo ✲	-	-	-	25.2
7-anti-2-exo-dibromo ✲	-	-	-	27.2
2-exo-5-exo-dibromo ✲	-	-	-	13.6
7-syn-2-exo-dibromo ✲	-	-	-	26.4

At least two injections of each mixture were analysed by the cut and weigh method and the average taken. A proportionality constant for 2-exo-bromonorbornane was evaluated. No correcting proportionality constant was required for the dibromides in view of the calibration result obtained below.

Mixture No.	1			2			3	
	% by glc	% by wt./	% by glc	% by glc	% by wt./	% by glc	% by glc	% by wt./	% by glc
2-exo-bromo-norbornane	66.05		0.80	83.8		0.88	25.4		0.73
bromonor-tricyclene	33.95			16.2			74.6		

Average correction factor 0.81.

Comparison of analysis by wt. with analysis by glc on mixture 4.

	% by glc	% by wt.
2-exo-bromo- CORR	8.9	8.0
2-exo-3-endo-	24.8	25.2
7-anti-2-exo-	27.3	27.2
2-exo-5-exo-	13.1	13.6
7-syn-2-exo-	26.1	26.4

Addition of Bromine to Norbornylene

Norbornylene (20 g., 0.21 mole) in 40 ml. of carbon tetrachloride was cooled to -10°C with an ice-salt bath. Bromine (29 g., 0.182 mole) in 20 ml. of carbon tetrachloride was added with stirring at a rate

such that the temperature remained at or just below 0°C. After 30 ml. of the bromine solution had been added, the persistence of red colour and lack of exothermicity indicated that the norbornylene had been consumed. Evaporation of solvent gave 40.44 g of crude product. Glc of the crude product from a similar but smaller scale run, on column [H] at 130°C, helium flow 45 ml./min, indicated the presence of seven major components and two minor ones.

Attempts to separate the dibromo isomers by fractional distillation on a platinum spinning band column (23 theoretical plates) only succeeded in the separation of 7-syn-2-exo-dibromonorbornane. A reflux ratio of 1:30 was used throughout, the fractions being taken as shown below. A second fractionation of those fractions rich in the four lower boiling dibromides was equally unsuccessful, the constancy of the refractive index being misleading.

GLC Peak No.	Compound	Structure No.	% by wt.	Retention Time (min.)
	2-exo-bromonorbornane	71	28.2	1.6
	bromonortricyclene	36	36.8	1.8
1	2-exo-3-endo-dibromo-norbornane	37	5.1	5.4
2	7-anti-2-exo-	87	6.6	6.8
3	2-exo-5-endo-	83	2.1	8.6
4	2-exo-5-exo-	82	1.6	9.8
5	7-syn-2-exo-	38	18.4	17.0
Other			1.2	6.4 and 11.0

Spinning Band Fractionation of crude bromide product

First Fractionation:

Wt. (g.)	b.p./pressure (°/mm.)	Composition
19.55	60/11.0	2-exo-bromonorbornane bromonortricyclene
0.08	30-44/0.080	
1.85	49-50/0.060	
1.39	50-51/0.060	2-exo-3-endo- 7-anti-2-exo- dibromonorbornane
0.52	51-52/0.060	2-exo-5-endo- 2-exo-5-exo-
0.81	52-53/0.060	
0.21	53-54/0.060	
0.56	54-55/0.060	
0.64	55-56/0.060	
0.31	56-57/0.060	
0.19	57-59/0.060	
0.26	59-60/0.060	
0.21	60-61/0.060	
0.26	61-63/0.060	The above isomers +
0.24	63-65/0.060	7-syn-2-exo-dibromo
0.40	65-67/0.060	
0.43	67-69/0.060	
0.38	71-72/0.060	
0.30	72-74/0.060	
6.54	74-75/0.065	7-syn-2-exo-dibromonorbornane
Residue 3.13		> 98% pure by glc

Second Fractionation

Fractions 3-6 inclusive were combined and subjected to spinning band distillation:

Wt. (mg.)	B.P. (°)/press. (mm.)	n_D^{20}
248	70-75/2.0	1.5581
255	75-80/2.0	1.5584
267	65-70/1.0	1.5584
220	75-77/2.0	1.5585
362	77-78/2.0	1.5592
430	75-78/2.0	1.5598

Glc showed that all the above fractions contained two major (2-exo-3-endo- and 7-anti-2-exo-dibromonorbornane) and two minor components (5-endo-2-exo- and 5-exo-2-exo-dibromonorbornane).

Preparative Gas Chromatographic Separation.

A Glowall Model 400 unit equipped with a hydrogen flame detector and 50:1 stainless steel splitter incorporating a 1.8m. x 6.4 mm. all glass column and injection port was used. The column packing was 10% FFAP (Wilkens Aerograph "free fatty acid phase") on nonacid-washed 60-80 mesh Chromasorb P. Operating conditions were; injector temperature 270°, column temperature 170°; exit port temperature 200°; argon carrier gas with flow rate approximately 80 ml./ min; approximately 40-50 μl of dibromide mixture were injected each time.

Fractionation Data:

Peak No.	Fractionations Wt. (mg.)/Purity (%)			
	1st.	2nd.	3rd.	4th.
1	1204/97%	550/99%	-	-
2	2299/97%	703/97%	-	-
3	757/83%	439/90%	300/91%	151/91%
4	500/68%	Purified by Crystallization		
5	923/85%	489/98%		

Centrifuging the cooled impure peak 4 as obtained by glc separation gave 250 mg. of white solid (91% pure by glc). After washing this solid with a little cold ether, crystals (196 mg., 96% pure by glc) were obtained. Recrystallization from petroleum ether gave 2-exo-5-exo-dibromonorbornane, m.p. 94-95.5°C. Solvent free samples of the other four dibromides were prepared by bulb to bulb distillation at 0.04 mm.

Dibromonorbornanes - Physical data.

nmr spectra in CCl_4: see Figs. 8,10,12,14 and 15.

Infrared spectra (liquid film): see fig. 7.

2-exo-3-endo-dibromonorbornane (peak 1)

μ^{25} Cyclohexane 2.60D.

Anal. Calcd. for $C_7H_{10}Br_2$ (253.99):
C, 33.09; H, 3.97; Br, 62.89.

Found: C, 33.29; H, 3.91; Br, 62.76.

7-anti-2-exo-dibromonorbornane (peak 2)

μ^{25} Cyclohexane 2.42D.

Anal. Calcd. for $C_7H_{10}Br_2$ (253.99):
C, 33.09; H, 3.97; Br, 62.89.

Found: C, 32.89; H, 4.09; Br, 63.25.

2-exo-5-endo-dibromonorbornane (peak 3)

μ^{25} Cyclohexane 1.10D.

Anal. Calcd. for $C_7H_{10}Br_2$ (253.99):
C, 33.09; H, 3.97; Br, 62.89.

Found: C, 33.22; H, 4.05; Br, 62.72.

2-exo-5-exo-dibromonorbornane (peak 4)

μ^{25} Cyclohexane 0.66D. m.p. 94-95.5°C.

Anal. Calcd. for $C_7H_{10}Br_2$ (253.99):
C, 33.09; H, 3.97; Br, 62.89.

Found: C, 33.05; H, 3.94; Br, 62.60.

7-syn2-exo-dibromonorbornane (peak 5)

μ^{25} Cyclohexane 3.30D.

Anal. Calcd. for $C_7H_{10}Br_2$ (253.99):
C, 33.09; H, 3.97; Br, 62.89.

Found: C, 33.43; H, 4.03; Br, 62.65.

Determination of Dipole Moments for the Dibromonorbornanes

The procedure and calculations were the same as those for the bromofluoronorbornanes. Cyclohexane was the solvent throughout.

2-exo-3-endo-dibromonorbornane

Wt. fraction $\times 10^3$	$(\varepsilon_{12}-\varepsilon_1)$ cell constant $\times 10^3$	$\eta_{12}^2 - \eta_1^2$ $\times 10^3$
2.9080	7.2	2.8
5.6496	13.7	2.6
8.6930	21.3	2.8
12.2760	30.9	3.7

$\alpha_\varepsilon = 2.500.$ $\alpha_\eta = 0.18.$

7-anti-2-exo-dibromonorbornane

Wt. fraction $\times 10^3$	$\varepsilon_{12}-\varepsilon_1$) cell constant $\times 10^3$	$\eta_{12}^2 - \eta_1^2$ $\times 10^3$
2.0242	4.0	0.3
4.9160	9.8	0.3
8.6489	17.3	1.1
12.2341	24.5	2.3

$\alpha_\varepsilon = 2.18.$ $\alpha_\eta = 0.15.$

2-exo-5-endo-dibromonorbornane

Wt. fraction $x10^{3}$	$(\varepsilon_{12}-\varepsilon_{1})$ cell constant $x10^{3}$	$\eta_{12}^{2} - \eta_{1}^{2}$ $x10^{3}$
3.4740	4.4	0.9
6.0260	7.7	1.4
8.9860	11.4	2.3
10.0670	13.0	2.6

$\alpha_{\varepsilon} = 1.10.$ $\alpha_{\eta} = 0.25.$

2-exo-5-exo-dibromonorbornane

Wt. fraction $x10^{3}$	$(\varepsilon_{12}-\varepsilon_{1})$ cell constant $x10^{-3}$	$\eta_{12}^{2} - \eta_{1}^{2}$ $x10^{3}$
0.5905	0.33	0.00
1.3425	0.80	0.20
2.5466	1.59	2.80
3.9039	2.64	3.40
6.2056	4.27	3.70

$\alpha_{\varepsilon} = 0.75.$ $\alpha_{\eta} = 0.60.$

7-syn-2-exo-dibromonorbornane

Wt. fraction $x10^{3}$	$(\varepsilon_{12}-\varepsilon_{1})$ cell constant $x10^{3}$	$(\eta_{12}^{2} - \eta_{1}^{2}$ $x10^{3}$
2.1373	8.4	3.1
6.7795	28.2	4.3
9.0960	38.4	4.8
11.2875	48.2	4.8

$\alpha_{\varepsilon} = 4.30$ $\alpha_{\eta} = 0.55$

Calculated Dipole Moments for Dibromonorbornanes (64)

Bond moment C-Br = 2.0D (105). Structures in which the bromine atoms are geminal or at bridgehead positions have been omitted as these structures have been conclusively excluded by the nmr spectra which show that each isomer has a proton on each carbon bearing a bromine atom.

2-endo-3-endo-dibromo;

$$\mu^2 = (2.0 \times 0.349 - 2.0 \times 0.349)^2$$
$$+(-2.0 \times 0.115 - 2.0 \times 0.115)^2$$
$$+(-2.0 \times 0.930 - 2.0 \times 0.930)^2$$

2-exo-3-endo-dibromo;

$$\mu^2 = (-2.0 \times 0.349 + 2.0 \times 0.349)^2$$
$$+(2.0 \times 0.842 - 2.0 \times 0.115)^2$$
$$+(2.0 \times 0.411 - 2.0 \times 0.930)^2$$

2-exo-3-exo-dibromo;

$$\mu^2 = (2.0 \times 0.349 - 2.0 \times 0.349)^2$$
$$+(2.0 \times 0.842 - 2.0 \times 0.842)^2$$
$$+(2.0 \times 0.414 + 2.0 \times 0.411)^2$$

2-exo-6-endo-dibromo;

$$\mu^2 = (2.0 \times 0.349 + 2.0 \times 0.349)^2$$
$$+(2.0 \times 0.842 + 2.0 \times 0.115)^2$$
$$+(2.0 \times 0.411 - 2.0 \times 0.930)^2$$

2-exo-6-exo-dibromo;

$$\mu^2 = (2.0 \times 0.349 + 2.0 \times 0.349)^2 + (2.0 \times 0.842 - 2.0 \times 0.842)^2 + (2.0 \times 0.411 + 2.0 \times 0.411)^2$$

2-endo-6-endo-dibromo;

$$\mu^2 = (2.0 \times 0.349 + 2.0 \times 0.349)^2 + (-2.0 \times 0.115 + 2.0 \times 0.115)^2 + (-2.0 \times 0.930 - 2.0 \times 0.930)^2$$

2-exo-5-endo-dibromo;

$$\mu^2 = (+2.0 \times 0.349 - 2.0 \times 0.349)^2 + (2.0 \times 0.842 + 2.0 \times 0.115)^2 + (2.0 \times 0.411 - 2.0 \times 0.930)^2$$

2-exo-5-exo-dibromo;

$$\mu^2 = (+2.0 \times 0.349 - 2.0 \times 0.349)^2 + (2.0 \times 0.842 - 2.0 \times 0.842)^2 + (2.0 \times 0.411 + 2.0 \times 0.411)^2$$

2-endo-5-endo-dibromo;

$$\mu^2 = (+2.0 \times 0.349 - 2.0 \times 0.349)^2 + (-2.0 \times 0.115 + 2.0 \times 0.115)^2 + (-2.0 \times 0.930 - 2.0 \times 0.930)^2$$

7-syn-2-endo-dibromo;

$$\mu^2 = (2.0 \times 0.000 + 2.0 \times 0.349)^2 + (2.0 \times 0.824 - 2.0 \times 0.115)^2 + (2.0 \times 0.566 - 2.0 \times 0.930)^2$$

7-anti-2-endo-dibromo;

$$\mu^2 = (2.0 \times 0.000 + 2.0 \times 0.349)^2 + (2.0 \times 0.824 - 2.0 \times 0.115)^2 + (2.0 \times 0.566 - 2.0 \times 0.930)^2$$

7-syn-2-exo-dibromo;

$$\mu^2 = (2.0 \times 0.000 + 2.0 \times 0.349)^2 + (2.0 \times 0.824 + 2.0 \times 0.842)^2 + (2.0 \times 0.566 + 2.0 \times 0.414)^2$$

7-anti-2-exo-dibromo;

$$\mu^2 = (2.0 \times 0.000 + 2.0 \times 0.349)^2 + (-2.0 \times 0.824 + 2.0 \times 0.842)^2 + (2.0 \times 0.566 + 2.0 \times 0.414)^2$$

Relative Rates of Isomerisation

A solution of hydrogen bromide in methylene chloride was kept in a flask at 0°C. A bulb of 5 ml. capacity was incorporated into the stopper such that a constant volume could be withdrawn with minimum loss of hydrogen bromide. Concentration was estimated by transference, with vigorous mixing, of 5 ml. to a stoppered flask containing 5 ml. of

0.48N sodium hydroxide solution. Back titration against standard sulphuric acid using phenolphthalein as indicator gave the concentration of hydrogen bromide.

2-exo-3-endo-Dibromonorbornane (25 mg.) in a 10 ml. stoppered flask was cooled in an ice bath, 5 ml. of the hydrogen bromide solution added, the flask stoppered and the time noted. A second sample of hydrogen bromide solution was withdrawn at the same time for estimation. The reaction was quenched with 2 ml. of 10% aqueous sodium bicarbonate solution after the allotted time. After separation, drying and evaporation the crude product was analysed by glc on column [I].

All five dibromides were treated similarly:

Dibromide	Wt. (mg.)	Time/Temp (hr./°C.)	Wt. HBr per 5 ml.	glc result
2-exo-3-endo-	25.0	17/0	31.0	No isomerisation
7-anti-2-exo-	25.0	17/0	31.0	No isomerisation
2-exo-5-endo-	14.0	17/0	31.0	No isomerisation
2-exo-5-exo-	18.0	17/0	31.0	No isomerisation
7-syn-2-exo-	19.6	5/0	31.0	Trace (<4%)

Glc of dibromide shown to be free of 2-exo-3-endo-, 7-anti-2-exo-, 2-exo-5-endo- and 2-exo-5-exo-dibromonorbornane by nmr spectroscopy always shows a trace (~2%) of impurity possibly due to isomerisation in the injector port of the chromatogram.

Reaction of Bromonortricyclene with Hydrogen Bromide

The procedure was the same as that for the dibromides, the progress of reaction being monitored by glc.

Wt. or Vol. of Substrate	Time/Temp. (hr.)/°C.	Wt.HBr/Vol. solv. mg./ml. CH_2Cl_2	Result glc
76.4 mg.	73/0	43.5/25	No reaction
5 µl	0.33/25	6.6/1	No reaction
6.5 mg.	1.0/25	20.2/1	Slight attack
5 mg.	14.5/25	42/1	58.5% reaction
7-syn-2-exo-dibromo 7.4 mg.	14.5/25	42/1	No isomerisation

Glc analysis on column [I] showed five dibromide products from the 14.5 hr. reaction of hydrogen bromide with bromonortricyclene. (See Table immediately below.)

	Av. % of two runs	Ratio's
2-exo-3-endo- *	3.3	0.11
7-anti-2-exo- *	29.3	
2-exo-5-endo- *	33.1	1.81
2-exo-5-exo- *	18.4	
7-syn-2-exo- *	15.9	

* dibromonorbornane

Isomerisation of 7-syn-2-exo-Dibromonorbornane

A mixture of 7-syn-2-exo-dibromonorbornane (418 mg.) and 1 ml. of 47% aqueous hydrobromic acid was refluxed for 3.25 hr. The resulting dark coloured mixture was cooled and extracted with 10 ml. of ether. Analysis by glc on column [H] at 120° showed the presence of four dibromide isomers and three minor products one of which was found in the starting material.

Compound (dibromonorbornanes)	% by wt.	Ratios	Retention Time (min.)
2-exo-3-endo-	15.2	0.23	4.3
7-anti-2-exo-	34.5		6.1
5-endo-2-exo-	22.8	1.07	8.1
5-exo-2-exo-	21.3		10.0
7-syn-2-exo-	0.5		19.4
Other	6.0		5.6, 7.6, 14.2

Evidence for Lack of Elimination

Norbornylene (509 mg., 5.4 mmoles.) in 5 ml. of methylene chloride and 5 ml. of dry pyridine was cooled to 0°C and treated with bromine (750 mg., 4.8 mmoles.) The resulting solution was washed with four 25 ml. portions of water, dried (magnesium sulphate) and evaporated. The crude product was examined by nmr; no vinyl protons, other than those of starting material (~1%) were evident.

Hydrogenolysis of 7-syn-2-exo-Dibromonorbornane

Tetrahydrofuran (10 ml.), t-butyl alcohol (2.1 ml, 22 mmoles.) and finely chopped sodium (1.5 g., 63 mmoles.) were heated to reflux with stirring (107). 7-syn-2-exo-Dibromonorbornane (1.01 g., 4.0 mmoles.) was added over 5 min. and the resulting dark solution refluxed for 45 hr. After cooling and work-up, the resulting ethereal solution was very carefully distilled at atmospheric pressure until the distillation temperature reached 40°C. Analysis of the crude product remaining (1.005 g.) by glc on column [G] at 80° indicated a 30% yield of norbornane. The identity of the latter was established by comparison

of the retention time and infrared spectrum of a sample isolated by prepative glc with the retention time and infrared spectrum of an authentic sample prepared by hydrogenation of norbornylene.

Effect of Variables on the Addition of Bromine to Norbornylene

In a representative reaction bromine (1.0 g.) in 2 ml. of methylene chloride was added over 20 min. to a vigorously stirred solution of norbornylene (498 mg, 5.3 mmoles.) at 0°C. The resulting solution was quenched with 5 ml. of 10% aqueous sodium bicarbonate solution, separated, dried (magnesium sulphate) and evaporated to give crude product (1.12 g.). Analysis was carried out by glc on column [I]. The percentage compositions given are the average from two separate determinations (Table 14).

Addition of Bromine to Norbornylene in the Presence of Light

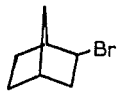
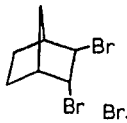
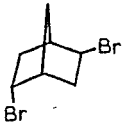
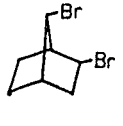
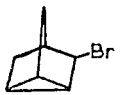
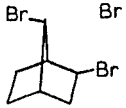
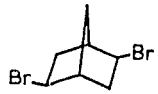
A solution of norbornylene (444 mg, 4.8 mmoles.) in 2 ml. of methylene chloride was added to 1.0 g. of bromine in 100 ml. of methylene chloride over five minutes at 26-28°C. Throughout the addition light from an incandescent lamp with reflector was shone directly on the reaction flask. The crude product was isolated and analysed in the manner previously described; no new products or changes in product ratios were observed in comparison to the runs without the light (Table 14).

Addition of Bromine to Norbornylene in the Presence of Toluene

A solution of bromine (350 ± 10 mg, 2.19 ± 0.006 mmoles.) in 2 ml. of methylene chloride was added over 20 min. to a stirred solution of norbornylene (526 mg, 5.6 mmoles.) and toluene (2.415 g, 26.2 mmoles.) in 100 ml. of methylene chloride at 0.5 - 1.5°C. The resulting mixture

Table 14

Effects of Variables on the Addition of Bromine to Norbornylene

Reaction Type	Solvent	Wt./Vol. mg./ml	Special Conditions	 *						
Dilution		498/100	-	16.7	34.4	3.0	12.4	3.1	1.9	27.3
Dilution		481/2	-	23.9	20.9	2.7	10.9	2.2	1.5	31.5
Temperature		510/100	-78°	10.2	45.5	1.1	9.75	1.7	0.6	30.7
Radical Scav.	CH_2Cl_2	518/100	-	11.4	36.0	3.1	12.1	3.0	1.3	31.8
$CaCO_3$		543/100	$CaCO_3$ (5g.)	7.2	41.8	3.2	12.2	3.0	1.6	30.6
$CaCO_3$		531/100	$CaCO_3$ (25g.)	2.4	42.2	3.6	13.5	3.2	1.5	33.8
Solvent	CCl_4	860/2	-	28.2	36.8	5.1	6.6	2.1	1.6	18.4
	CH_3CN	564/100	-	Not anal. for	Not anal. for	4.65	15.8	4.2	3.2	16.7
Variation	CH_2Cl_2	688/100	sat. with $Et_4\overset{+}{N}Br^-$ (1.27g.)	4.7	34.8	46.0	0.9	-	-	7.5

Footnote: Temperature (0°) and addition time of 20 min. were used unless otherwise stated. The $CaCO_3$ was in the form of a vigorously stirred suspension.

* Corrected values.

was evaporated to about 5 ml. in volume and analysed by glc on column [H]. The dibromide products were found in the same ratios as those in the absence of toluene and benzyl bromide was shown to be present only in a trace quantity (< 0.5%).

Reaction of Bromine with Norbornylene in the Presence of Benzoyl Peroxide

A solution of 20 mg. of benzoyl peroxide in 5 ml. of carbon tetrachloride was refluxed for 10 min., after which time bromine (0.8 g.) was added. A solution of norbornylene (470 mg, 5 mmoles.) was added to the refluxing solution. Glc on column [H] at 120° indicated no additional products when compared with a similar reaction in the absence of benzoyl peroxide.

Addition of Bromine to Norbornylene in the Presence of Tertiary Amines

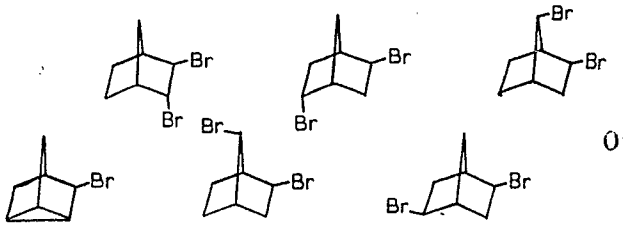
In a representative reaction bromine (1.0 g.) in 2 ml. of methylene dichloride was added to a solution of norbornylene in pyridine maintained at either 0°C. or reflux temperature throughout the 20 min. addition time. The solution (cooled if necessary) was washed with six 50 ml. portions of water, after addition of 50 ml. of methylene chloride. After drying and evaporation the crude product was analysed by glc on column [I]. The identities of the peaks were checked by injection of the crude product enriched with authentic samples and observation of the expected changes in appropriate peak ratio's. 2-exo-Bromonorbornane was not observed as a product in any of these reactions. The other reactions were carried out in the same general manner (Table 15).

Isolation of Unknown formed in Triethylenediamine Reaction

A solution of norbornylene (5.1 g , 54 mmoles.) and triethylene-

Table 15

Addition of Bromine to Norbornylene in the Presence of Tertiary Amines - Product Composition

Tertiary Base	Wt.(mg.)/Vol.(ml.) Solvent	Temp% Br_2 Addn						Other
100ml.	503/nil	0°C	67.3	20.7	nil	nil	nil	7.8	4.5
50ml.	287/nil	Reflux	30.4	60.6	nil	nil	nil	8.4	-0.5
25ml.	140/nil	Reflux	25.8	5.7	12.6	6.8	6.8	49.8	-
9g.	74/12.5 CH_2Cl_2	0°C	27.3	2.6	12.4	2.2	1.7	52.5	1.5
9g.	73/12.5 CCl_4	Reflux	One unknown component 90% purity						
2g.	649/12.5 CCl_4	Reflux	10.3	6.6	10.3	*	*	62.5	10.3

All addition times were 20 min.

* Included in "Other" percentage wt.

diamine (20 g., 180 mmoles.) in 62.5 ml. of carbon tetrachloride was refluxed while a solution of bromine (9.0 g., 56 mmoles.) in 2 ml. of carbon tetrachloride was added over 45 min. An extremely vigorous reaction occurred on addition of the bromine. After cooling, the solution was washed with 50 ml. portions of water six times, dried, filtered and evaporated to give 10.1 g. of crude product which analysed by gc for 35% of the unknown. Careful spinning band distillation failed to separate the unknown from 7-syn-2-exo-dibromonorbornane. A mixture of these two compounds containing 52.2% of the unknown was analysed. In view of the 1:1 adducts which may be formed from carbon tetrachloride and olefins on initiation with traces of peroxide (108), the unknown was considered to be 2-chloro, 3-trichloro-methylnorbornane. This compound has been observed (109) (stereochemistry undetermined) when a solution of norbornylene was refluxed in carbon tetrachloride in the presence of 0.2 mole % of benzoyl peroxide. The analysis of the mixture supported this conclusion.

For a mixture of $C_8H_{10}Cl_4$ (52.2%) and $C_7H_{10}Br_2$ (47.8%):

Calcd: C, 36.0; H, 4.0; Br*, 96.0

Found: C, 35.85; H, 4.08; Br*, 93.77

* The halogen was analysed and calculated as bromide.

Addition of Norbornylene to Preformed Tertiary Amine Perbromide

In a representative reaction a solution of 2,6-lutidine (1.0 g.) in 10 ml. of chloroform was cooled to 0°C. Bromine (0.5 g.) in 2 ml. of chloroform was added during 2 min. to give a pale yellow solution. Norbornylene (217 mg.) in 2 ml. of chloroform was immediately added over 1

min. Samples were withdrawn and tested with potassium iodide solution for the presence of positive bromine. The presence of dibromide products was monitored by glc. The reaction was terminated, either when the potassium iodide test became negative, or when the dibromide content had reached a maximum. The solution was washed with two 50-ml. portions of water, 50 ml. of 5% sulphuric acid, 50 ml. of water and after drying, evaporated to give crude product (398 mg.).

Reaction of 7-syn-2-exo-Dibromonorbornane with Pyridine

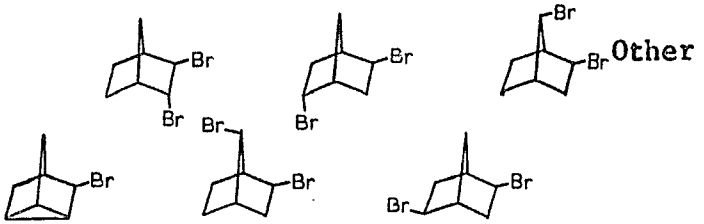
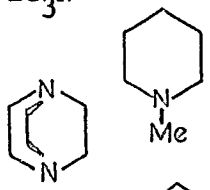
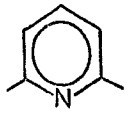
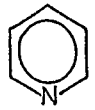
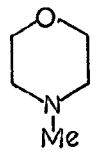
A solution of the dibromide (17.5 mg.) in 10 ml. of pyridine was refluxed for 20 min. Glc of the cooled solution indicated no change. Bromine (~ 100mg.) was added and the solution refluxed a further 20 min; glc of the cooled solution indicated no change.

Reaction of Bromonortricyclene with Pyridine

A mixture of 2-exo-bromonorbornane and bromonortricyclene (540 mg.), containing 59% of the latter, was refluxed in 25 ml. of pyridine with sufficient pyridine hydrobromide salt to saturate the solution at the reflux temperature and two drops of bromine. After 20 min. the solution was cooled, 25 ml. ether added, and the mixture extracted with six 25 ml. portions of water. Analysis, by glc at 60° and 110° on column [G], of the ethereal solution indicated that the ratio of the two bromides had remained constant and no new products had been formed.

Table 16

Reaction of Amine Perbromides with Norbornylene in $CHCl_3$ +

Tertiary Amine (1g./10ml.) $CHCl_3$	Wt./Vol. (mg./ml.)	$Br^{\oplus}$ Time (min.) conc. zero *		Other
Et_3N	218/2	30	No Bromide products	
	223/2	40	21.5 54.0 2.0 ✻ ✻ 7.8	14.5
	202/2	⊕ve at termination	38.8 53.0 nil nil nil 8.5	nil
	217/2	⊕ve at termination	30.5 9.3 13.2 3.9 3.9 43.2	nil
	230/2	⊕ve at termination	33.5 9.6 8.5 2.9 2.9 45.0	<1
	225/2 ϟ	60	44.3 27.1 ✻ ✻ ✻ 20.7	8.3

✻ : "Other" percentage includes any of these isomers formed.

* : This time is measured from the beginning of the bromine addition to the amine.

ϟ : The bromine addition was carried out in 10 ml. of carbon tetrachloride and the bicyclo [2.2.1] heptene added. As the amine perbromide was insoluble, chloroform (10 ml.) was added 10 min. after the first addition (the perbromide dissolved).

\+ : Yields of crude products were 45-70% based on dibromide.

Preparation of 5,6-exo-Trimethylenebicyclo [2.2.1] hept-2-ene (exo-Trimethylenenorbornylene, 43) (42)

(a) Preparation of hexahydro-exo-4,7-methanoinden-1-ene-exo-5-yl formate (110).

Dicyclopentadiene (264 g., 2 moles) and anhydrous formic acid were refluxed for 4.5 hr. The crude product was distilled at reduced pressure (117-120°/18 mm.) after excess formic acid had been removed. Yield 304 g., (86%), η_D^{28} 1.4996, [lit (110): η_D^{28} 1.4980], nmr (neat) δ 4.74 (1H, m.), 5.56 (2H, m.), 7.93 ppm (1H, s.).

(b) Preparation of Octahydro-exo-4,7-methanoinden-exo-5-yl Formate (42)

Unsaturated formate (151 g., 0.85 mole) and platinum oxide (400 mg.) were hydrogenated (5-20 psi.) in ethyl acetate. Theoretical uptake occurred in 3.5 hr. This procedure was repeated with 144 g. of unsaturated formate and the combined products from the two runs filtered and evaporated to give 284.4 g. (96%). This material was distilled under reduced pressure (116 / 15 mm.), $\eta_D^{22.5}$ 1.4905, [lit (42) η_D^{25} 1.4913] nmr (neat) δ 4.64 (1H, m.), 7.92 ppm (1H, s.).

(c) Preparation of 2-exo-Hydroxy-5,6-exotrimethylenebicyclo [2.2.1] heptane (42)

The saturated formate (280 g., 1.57 mole) and potassium hydroxide

(132 g., 2.35 moles) were dissolved in 500 ml. of ethanol and refluxed for 10 hr. The crude product (240 g., ~ 100%) was obtained by evaporation of the ethanol, addition of 100 ml. of water and subsequent ether extraction.

Nmr(CCl_4): δ 3.60 (1H, m.), 3.80 ppm (1H, s.); $\nu_{max}^{liq.\ film}$ 1055 (COH); 3300 (OH) $cm.^{-1}$.

Preparation of 2-exoBenzoxy-5,6-exotrimethylenebicyclo [2.2.1] heptane (42)

The crude alcohol (200 g., 1.33 moles) was added slowly with stirring to a solution of benzoyl chloride (225 g., 1.61 moles) in 300 ml. of dry pyridine and the resulting mixture heated on a steam bath for 17 hr. After pouring this mixture into water and extracting with two 250-ml. portions of ether, washing the ethereal extract with 10% aqueous sodium bicarbonate solution and drying, evaporation of solvent afforded a crude semi-solid product (298 g., 89%) which was recrystallized from petroleum-ether (b.p. 35-60°), m.p. 71-72°, [lit (42): m.p. 71.5-72°] ; nmr (CCl_4): δ 7.62 (5H, m.); 4.76 ppm (1H, m.); $\nu_{max}^{CCl_4}$ 1720 (C=O) and 712cm^{-1} (φ-).

Preparation of 5,6-exoTrimethylenebicyclo [2.2.1] hept-2-ene (43) (42)

The benzoate obtained above (10.0 g., 235 mmoles.) was heated under nitrogen with stirring (oil bath 325-330°C.). As pyrolysis occurred the olefin distilled out (2-3 hr.). Benzoic acid was removed by washing a solution of the distillate in petroleum ether (b.p. 30-60°) with 10% aqueous sodium bicarbonate solution. Drying and evaporation gave 10 g. (32%) of crude product: nmr (CCl_4): δ 6.0 (2H, dd); $\nu_{max.}^{liq.\ film}$ 3020cm^{-1} (C=C). The infrared spectrum showed no discernible peaks at 6.08, 7.42,

8.06 or 8.74cm^{-1} which indicates the absence of the endo isomer; glc on column [H] at 65° with helium flow of 45 ml./min. showed that the crude product was at least 98% pure. A further check on the purity was obtained from melting point analysis of the phenyltriazole derivative. Excess phenyl azide was added to the olefin (471 mgs.) and the solution cooled in an ice-salt bath for two hours. After the mother liquor had been removed by centrifuging; the crystals were washed with a little cold ethanol and dried at 70-80°/0.02 mm. for 2 hr, (477 mgs. 54%) m.p. 137-143°. On the basis of melting point data obtained for mixtures of the exo and endo isomers (42) this would indicate a composition of greater than 95% exo isomer.

Addition of Bromine to exo-Trimethylenenorbornylene (43)

A solution of the olefin (4.31 g., 32 mmoles.) in 50 ml. of carbon tetrachloride was cooled in an ice-salt bath, and bromine (5.0 g. in 10 ml. of carbon tetrachloride) added at such a rate that the temperature of the reaction mixture remained between -3° and 0° throughout (45 min.). Evaporation of the solvent gave a crude product which was analysed by glc on column [H] at 160° with a helium flow of 80 ml./min. The results and conditions are shown in Table 17. The addition procedure in the presence of pyridine was similar to that previously reported (43); the crude products were analysed by glc on column [H]. A pure sample of the 2,3-dibromide was obtained by vacuum distillation of the crude product from one of the pyridine reactions; a fraction of b.p. 85-100°/0.1-0.07 mm. was taken (>98% pure by glc); nmr spectrum Fig. 17.

Table 17

Addition of Bromine to exo-Trimethylenenorbornylene: Product Composition

		% of each component								
Prod. Retention time (min.)		1.56	2.20	1.80	2.40	4.4	13.30	14.10	17.6	21.0
Conc. of olefin mmole./C.	640									
Solvent	CH_2Cl_2									
Temp. during add.[n]	$-30 \rightarrow 0^0$									
Product. % by wt.	--			2.3#		80.0*		9.6#	8.5	—
Conc. of olefin mmole./C.	576					8.6	10.0			
Solvent	pyridine						0.8#			
Temp. during add.[n]	$-5^0 \rightarrow -1^0$									
Products. % by wt.	-	-	-	12.0#		80.0*		1.1#	3.4	2.5
Conc. of olefin g./l.	2331						0.8#			
Solvent	pyridine									
Temp. during add.[n]	$-5^0 \rightarrow 0^0$									
Products. % by wt.	-	-	-	9.9#		78.0*		3.7#	5.9	2.3

* 2-exo-3-endo-dibromo-5,6-exo-trimethylenenorbornane.

Total % of the components at the retention times cited.

Degradation of 2-exo-3-endo-Dibromonorbornane

Attempted Dehydrobromination of 2-exo-3-endo-Dibromonorbornane

(a) Sodium iodide in acetone:

A sample of the dibromide in a solution of the above reagent was kept at room temperature for 36 hr.; no iodine colour, as compared to a blank, appeared indicating no debromination.

(b) Zinc in various solvents. (Table 18)

In general, the crude dibromides were allowed to react with an excess of zinc dust in 5-10 ml. of solvent. Although reaction occurred, no unsaturated products were isolated and the products appeared to be acetates as indicated by the ester carbonyl band at 1735 cm^{-1} in the infrared. A control reaction of norbornylene with zinc and acetic acid was run. Norbornylene (50 mg., 0.53 mmole.), approximately 1.0 g. of zinc chloride and 200 mg. of zinc were stirred in 5 ml. of glacial acetic acid at room temperature for 15 min. and then 60° for a further 15 min. Work up gave a crude product which showed a strong ester carbonyl band in the infrared and which, after substraction of bands due to norbornylene, closely resembled that obtained for the crude product from the reaction of 2-exo-3-endo-dibromonorbornane with zinc and acetic acid. The control reaction indicated that even if norbornylene was formed by debromination of the 2-exo-3-endo-dibromide isomer, further reaction to give an acetate product would destroy the utility of the reaction.

(c) Triphenylphosphine.

Table 18

Reaction of 2-exo-3-endo-dibromide 37 with Zinc under Various Conditions

Wt. Zinc (g.)	Wt. substrate* (mg.)	Solvent	Temperature	Time	Result
0.133	107	Ether	Rm. temp.	15 hr.	No Reaction
0.233	96	HOAc	Rm. temp.	12.hr.	Slight loss of 2-exo-3-endo-dibromide
0.100	50	HOAc	60°	3.5 hr. 23 hr.	Some loss of 2-exo-3-endo- Change in all dibromides
1.0 g.	47	HOAc	Reflux	~10 min.	Low boiling product present; all dibromides reacted
1.0 g.	101	HOAc	Reflux	20 min.	No unsaturated product by nmr
1.0 g.	50	Ac_2O	100°	45 min.	Three low boiling products only
1.0 g.	159 (pk2)	HOAc	Rm. temp.	60 min.	Product shows medium >= 0 in IR (ester. no unsaturation
3.0 g.	893 (pk1)	HOAc	Rm. temp. Reflux	15 min. ~60 min.	IR showed strong ester >= 0 No unsaturation
1.0 g	36 (pk1)	DMOE	Reflux		No Rx. over several hr.

* Mixture of 2-exo-3-endo-, 7-anti-2-exo-, 5-endo-2-exo-, and 5-exo-2-exo-dibromonorbornane

Crude 2-exo-3-endo-dibromonorbornane (24 mg., 0.26 mmole.) and triphenylphosphine (200 mg.) in 2 ml. of methanol were stirred at room temperature for 1.25 hr. and at reflux for a further 3.5 hr; no reaction occurred as indicated by glc on column [J] at 110°.

(d) Magnesium.

Crude 2-exo-3-endo-dibromonorbornane (47 mg., 0.5 mmole.) and 500 mg. of clean, scraped magnesium turnings were stirred in 2 ml. of ether in a stoppered flask. An iodine crystal and a little ethylmagnesium bromide were added as initiators; no reaction had occurred after 12 hr.

Magnesium (1.0 g.) was washed with ether and dried in the reaction flask at 115°, after which, 3 ml. of n-butyl ether (previously dried over phosphorous pentoxide) was added and the mixture brought to reflux. Crude 2-exo-3-endo-dibromonorbornane (30µl.) was admitted through a septum into the mixture; glc indicated no change had occurred after 2 hr.

Successful Dehydrobromination of 2-exo-3-endo-Dibromonorbornane

Pure (97%) 2-exo-3-endo-dibromonorbornane (101 mg., 1.1 mmoles.) was treated with 0.75 ml. of phenyllithium (~ 1.5 M solution in benzene: ether) in a sealed flask, under nitrogen, cooled in an ice-bath. Samples which were withdrawn for glc showed complete reaction after 15 min. An nmr spectrum of the solution showed absorption attributed to vinyl proton(s) at 349 cps. (doublet). The non-identity of this absorption with that from the vinyl protons of norbornylene (doublet of doublets 355 cps.) was proven by addition of the latter and comparing the vinyl absorptions.

Controls for Debromination of 2-exo-3-endo-Dibromonorbornane by Phenyllithium

Phenyllithium and 7-syn-2-exo-dibromonorbornane

A solution of 7-syn-2-exo-dibromonorbornane (253 mg., 1.0 mmole.) in 0.5 ml. of benzene under nitrogen was treated with 0.55 ml. of fresh phenyllithium solution (~1.9 M) at 0°C. After 15 min. half of the reaction mixture was quenched with 0.5 ml. of deuterium oxide and the other half with water. Separation, drying and evaporation afforded 137 mg. and 126 mg. of crude product from the deuterium oxide and water quenched reactions respectively. The nmr spectra of the two crude products were identical; no deuterium exchange was evident. In addition the C-7-H and C-2-H absorptions were the same as in the starting material and no vinyl proton absorption was present. Comparison with the vinyl absorption from a known concentration of norbornylene indicated that < 1% of a compound containing a vinyl proton would have been clearly visible in the nmr spectrum. Analysis of the crude product by glc showed no new products.

7-syn-2-exo-Dibromonorbornane (625 mg., 2.5 mmoles.) was treated with 3 ml. of phenyllithium (~0.9 M) in benzene: ether at room temperature under nitrogen. Samples were withdrawn at timed intervals and analysed by glc which indicated little change had occurred over 75 min. At the end of this time the nmr spectrum clearly showed absorption in the vinylic region. A similar experiment, but run for only 30 min. at 0°C. showed no vinyl absorption in the nmr spectrum.

Phenyllithium and 7-anti-2-exo-Dibromonorbornane

A solution of phenyllithium (1.5 ml., ~0.9 M.) was added to 7-anti-

2-exo-dibromonorbornane (253 mg, 1.0 mmole.) at 0°C. under nitrogen; the mixture was allowed to stand for 2.5 hr. Nmr examination of the mixture showed the absence of vinyl protons.

Phenyllithium and a 7-anti-2-exo-, 5-endo-2-exo-, 5-exo-2-exo-Dibromonorbornane Mixture

A mixture (1.137 g, 4.5 mmoles.) of 2-exo-3-endo-, 7-anti-2-exo-, 5-endo-2-exo- and 5-exo-2-exo-dibromonorbornane was treated with 4 ml. of phenyllithium solution (~0.9 M.) at 0° under nitrogen for 30 min. Analysis by glc indicated that all the 2-exo-3-endo-dibromide isomer had been destroyed. The crude product mixture was distilled under vacuum until a boiling point of 60°/0.15 mm. was reached, at which time all the low boiling products including any vinylic bromide had been removed, (checked by nmr and glc). This mixture (335 mg.), containing no 2-exo-3-endo-dibromide isomer was treated with phenyllithium solution (4 ml, ~0.9 M.) at 0° under nitrogen for 30 min. The crude mixture was quenched with 2 ml. of 10% aqueous sodium hydroxide solution, separated and dried. The nmr spectrum of this crude product was compared with that obtained by treating 338 mg. of the same dibromide mixture with 4 ml. of phenyllithium solution that had previously been quenched with 2 ml. of 10% aqueous sodium hydroxide solution. This direct comparison indicated that no unsaturated material had been formed.

Reaction of 2-exo-Bromonorbornane and Bromonortricyclene with Phenyllithium

A mixture (570 mg.) of 2-exo-bromonorbornane (41%) and bromonortricyclene (59%) was treated with 5 ml. of phenyllithium solution (0.46 M.) at 0°C. in a sealed flask under nitrogen. After 2.75 hr. the solution,

still showing the purple colour of the phenyllithium, was quenched with 2 ml. of 10% aqueous sodium hydroxide solution, separated and dried over magnesium sulphate. Analysis by glc on column [H] at 65° revealed that no new components were in the product solution and that the ratio of the starting materials had remained constant. Analysis by nmr spectroscopy showed the absence of any absorption that could be ascribed to vinyl protons.

Analysis of Phenyllithium Solutions

The concentration of the phenyllithium solution was measured before use by titration under nitrogen against spectral grade acetone using triphenylmethane as indicator.

Reaction of Phenyllithium with a Mixture of the Five Isolated Dibromonorbornanes

A mixture (852 mg., 3.4 mmoles.) of 2-exo-3-endo-, 7-anti-2-exo-, 5-endo-2-exo-, 5-exo-2-exo- and 7-syn-2-exo-dibromonorbornane was treated with 3.5 ml. of phenyllithium solution (~0.6 M.) under nitrogen at 0°C. (The mixture contained 23.2% of the 2-exo-3-endo-dibromide isomer). Samples were withdrawn at known intervals and analysed by glc; the isomer ratios were plotted graphically against time of reaction to determine if any dibromide was being destroyed other than the 2-exo-3-endo-isomer. (Fig. 21 and Table 19)

Fig.21

Reaction of Dibromonorbornanes with Phenyllithium: Graph Plotting Ratio of Isomers against Reaction Time

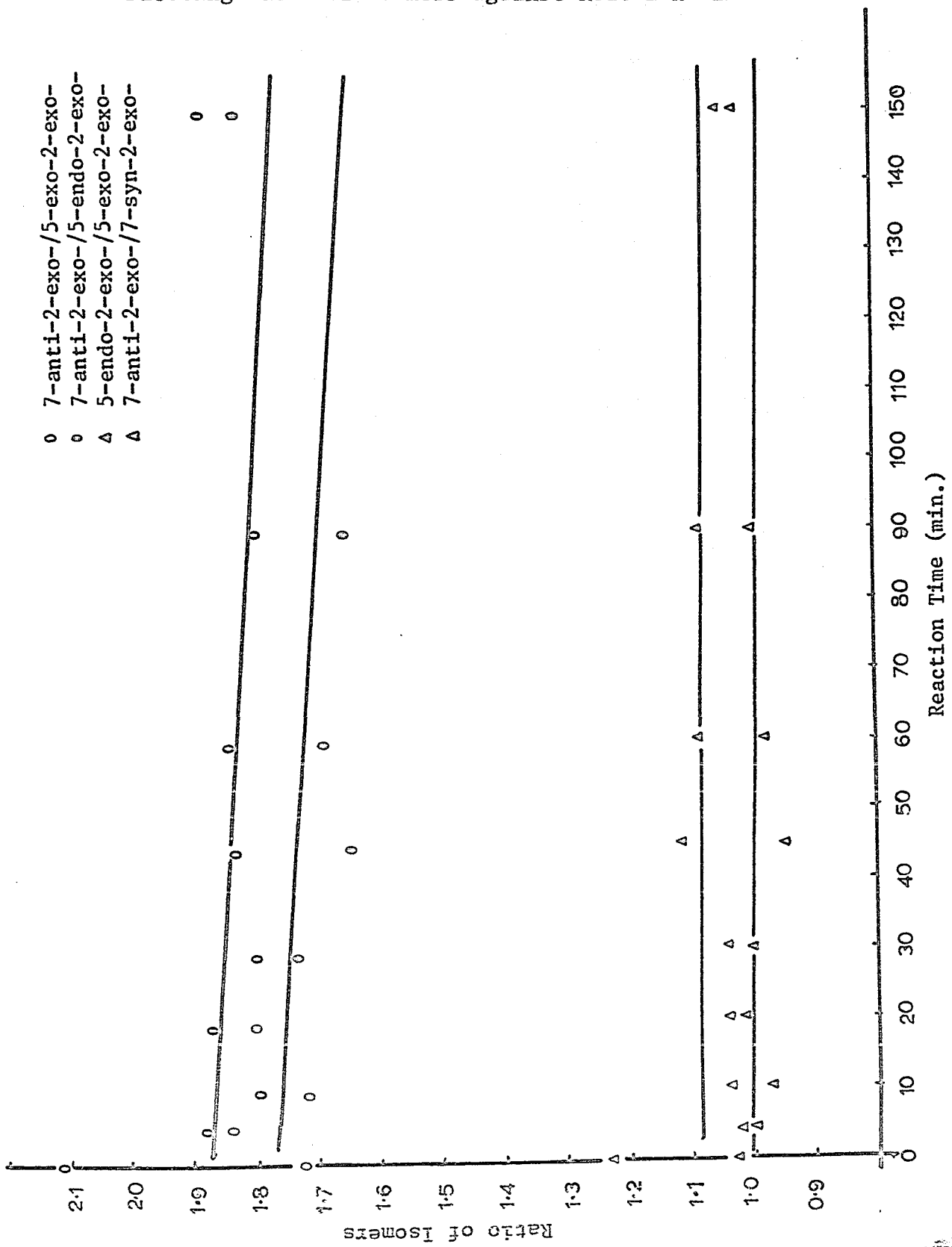


Table 19

Reaction of Phenyllithium with Dibromonorbornanes

Time (min.)	% by wt. Average isomer ratios 7-anti-2-exo- / 5-endo-2-exo-	7-anti-2-exo- / 5-exo-2-exo-	7-anti-2-exo- / 7-syn-2-exo-	5-endo-2-exo / 5-exo-2-exo-
0	1.725	2.114	1.029	1.225
5	1.845	1.885	1.012	1.023
10	1.722	1.795	0.966	1.043
20	1.807	1.879	1.022	1.041
30	1.732	1.802	1.008	1.043
45	1.644	1.831	0.945	1.120
60	1.697	1.845	0.979	1.087
90	1.653	1.797	1.008	1.088
150	1.820	1.881	1.019	1.035

From the slopes of the two upper curves it can be seen that a maximum of 1.4% reaction has occurred in 30 min. assuming that only one isomer is reacting much faster than the others.

cis-1,3-Cyclopentanedicarboxylic acid (73)

Norbornylene (5.86 g., 62 mmoles.) in 150 ml. of ethyl acetate was cooled to approximately -78°. Ozone was passed in until the solution was saturated as indicated by the persistence of a blue colour. The resulting solution was allowed to warm up to room temperature and then evaporated to give a viscous oil which was treated with 50 ml. of 98% formic acid and 30 ml. of 30% aqueous hydrogen peroxide solution. The resulting mixture was warmed to about 60° when a vigorous exothermic

reaction caused the solution to reflux; after maintaining reflux for one hour the solution was evaporated to give a viscous oil which slowly solidified, (9.53 g., 97%, m.p. 87-107°). Analysis by glc of the methyl ester (prepared by addition of an ethereal solution of diazomethane to a sample of the acid) showed this to be 92% cis diacid. Recrystallization four times from ether: petroleum ether (b.p. 30-60°) gave a white crystalline product of m.p. 118-120° [lit (111): 121.5-122.5°] . Yields of crude product were in the range 87-99%.

Isomerisation of cis-1,3-Cyclopentanedicarboxylic Acid

(a) With Base:

Crude cis diacid (86.5 mg., 0.55 mmole.) was dissolved in 5 ml. of ether and treated with excess diazomethane. The ether was evaporated and the resulting oil dissolved in 5 ml. of methanol containing sodium methoxide. After 12 hr. at room temperature the solution was acidified and extracted with ether. The ethereal extracts were treated with an excess of diazomethane before glc analysis on column [J] at 120°.

(b) With Acid:

Crude cis diacid (57 mg., 0.35 mmole.) in 22 ml. of 20% hydrochloric acid was heated at reflux for 118 hr. The solution was extracted with ether and the latter extracts treated with excess diazomethane.

Glc on column [J] at 120° showed three peaks: R_t 4.5 min, the impurity observed in the crude cis acid product from the ozonisation; R_t 6 min, trans diacid; R_t 7.5 min, cis diacid. These same peaks were observed in the base isomerisation reaction indicating that the impurity in the cis diacid was not the trans diacid.

Attempted Oxidations of 1,3-Cyclopentanediamine to Succinic Acid

(a) Chromic Acid.

An oxidizing solution was made up from chromium trioxide (33.6 g.), 50 ml. of concentrated sulphuric acid and 200 ml. of water (112).

Crude 1,3-cyclopentanediamine hydrochloride (379 mg, 2.2 mmoles.) and 25 ml. of the oxidizing solution were refluxed for 90 min. and, after subsequent cooling, continuously ether extracted for 41 hr. Drying and evaporation of the ethereal extract gave 70 mg. (27%) of crude succinic acid; m.p. 185-188°. However in another experiment under the same conditions, the yield of succinic acid was approximately zero. Increasing the reflux time and the volume of oxidizing agent was also detrimental. An attempt was made to oxidize the diamine to the diketone using chromic acid and acetone (Jones reagent) and completing the oxidation to succinic acid with aqueous chromic acid; this experiment also failed. In all the reactions the yield of carbon dioxide was much greater than the theoretical weight based on removal of one carbon atom.

Degradation of 2-exo-3-endo-Dibromonorbornane (A)

5,6-^{14}C-Norbornyl-2-ene supplied by Mallinckrodt Nuclear and synthesized by addition of 1,2-C^{14}- ethylene to cyclopentadiene (752 mg., 1mc.) was made up to 100 ml. with carbon tetrachloride.

Active 5,6-^{14}C-norbornyl-2-ene solution (20 ml., ~200μc.) was diluted with inactive norbornylene (20.24 g, 0.22 mole) in 20 ml. of carbon tetrachloride and cooled in an ice-salt bath. A solution of bromine (34g, 0.21 mole) in 23 ml. of carbon tetrachloride was added at such a rate to keep the temperature between -2° and +2°. (~1.25 hr). The

addition was stopped when the reaction solution retained the bromine colour. After removing the solvent at reduced pressure, the temperature was raised and some of the monobromides distilled out (72°/16mm.) leaving a residue (38.23 g.) of dibromides and some monobromides. Glc on column [H] at 80-130° showed the presence of 2-exo-3-endo-dibromonorbornane, 1.82 g. (calcd amt.) among the expected products. To this solution, which was cooled under nitrogen in an ice bath, was added 75 ml. of ~1.9 M phenyllithium solution through a rubber septum. After 30 min, the solution was cautiously quenched with 10 ml. of aqueous sodium hydroxide. Glc on column [H] at 120° indicated that the 2-exo-3-endo-dibromide had been completely destroyed. After separating the aqueous layer, the benzene and ether were removed under vacuum at room temperature. Decalin (20 ml.) was added and distillation, using a Bunsen burner to limit frothing, carried out until 80°/16mm was reached. The receiver was cooled in an ice bath. A further 20 ml. of decalin were added and distillation continued until approximately 30 ml. of distillate had been collected. Ethyl acetate (25 ml.) was added to the distillate and the solution cooled in a Dry-Ice-acetone bath. Ozone was passed into the stirred solution for 90 min. at which time the solution was pale green. After evaporation of the solvent, 98% formic acid (25 ml.) and 30% hydrogen peroxide (15 ml.) were added and the reaction mixture gently warmed until reaction, as indicated by gas evolution, was initiated. (Failure to warm carefully may result in a vigorous exothermic reaction accompanied by much frothing). When the exothermic reaction subsided, the mixture was heated on a steam bath for 30 min. After evaporation of most of the formic acid the solution was cooled and extracted with 10% aqueous sodium hydroxide solution. Acidification with 20% hydrochloric acid and

saturation with sodium chloride, followed by extraction with six 30-ml. portions of ether, drying over magnesium sulphate, filtration and evaporation, afforded 1,3-cyclopentanedicarboxylic acid as a pale brown oil which slowly solidified (865 mg., 77%). A sample was recrystallized from ethyl acetate, m.p. 121-122° [lit (19): 121.5-122.5°]. Yields of crude diacid ranged from 41-77%.

Degradation of 2-exo-3-endo-Dibromonorbornane (B)

Active 5,6-^{14}C-norbornyl-2-ene solution (40 ml., ~400μc) was added to inactive norbornylene (41.7 g., 0.45 mole) in 40 ml. of methylene dichloride. A solution of bromine (68.0 g., 0.43 mole) in 46 ml. of methylene chloride was added keeping the temperature between +2° and -5°. A sample was withdrawn for glc on column [J] at 120°. Anhydrous hydrogenbromide was passed into the solution (+2° to -5° throughout) until all the bromonortricyclene had reacted as indicated by glc. Isolation and degradation of the 2-exo-3-endo-dibromide was carried out using the same procedure described for (A).

1,3-Cyclopentanediamine Hydrochloride

1,3-Cyclopentanedicarboxylic acid (cis + trans, 1.32 g., 8.4 mmoles.) from the previous stage was dissolved in 15 ml. of 100% sulphuric acid. The flask was equipped with a side arm for addition of sodium azide and a nitrogen inlet which projected below the surface of the solution. A gas outlet was connected to two wash bottles, the first containing a dilute acidic solution of sodium dichromate and the second containing carbon dioxide free sodium hydroxide solution. After flushing the system with dry nitrogen (before attachment of the wash bottle containing the sodium

hydroxide solution) sodium azide (2.30 g, 35.5 mmoles.) was added slowly from the side arm as the solution was stirred and heated to 40-45°. After the addition (~1 hr.) a slow stream of nitrogen was passed through the system for a further 30 min. A final portion of sodium azide (~250 mg.) was added and nitrogen passed through for another 60 min. The carbon dioxide was precipitated as barium carbonate by washing the sodium hydroxide solution with 'boiled out' distilled water into 25 ml. of a solution of barium chloride and ammonium chloride (0.33 M in each). The yield of barium carbonate after filtration and drying at 120° for six hours was 2.366 g. (72%). The acidic solution was cooled and carefully neutralised with ~30 ml. of 50% aqueous sodium hydroxide and the resulting solution distilled to dryness into 20 ml. of 15% hydrochloric acid. Water (30 ml.) was added to the residue and the resulting mixture again distilled to dryness. This procedure was repeated six times. Failure to distil to almost complete dryness results in very low yields. The aqueous distillate, after evaporation, afforded 1,3-cyclopentanediamine hydrochloride as a buff powder, 1.02 g. (70%). Yields ranged between 40 and 80%.

The dibenzamide derivative used for counting, was obtained by treating a solution of 56 mg. of the diamine hydrochloride in 3 ml. of aqueous 10% sodium hydroxide with an excess of benzoyl chloride and shaking until the excess of the latter had been hydrolysed. The white precipitate was removed by filtration and washed with water (88 mg, 97%). Recrystallization twice from ethanol: ether gave colourless needles, m.p. 211.5-212.5° [lit (10); 213-215°] .

Succinic Acid

Potassium permanganate (6.21 g.) was added to a solution of 1,3-

cyclopentanediamine hydrochloride in 60 ml. of water. The reaction flask was immersed in an oil bath at 130-140° for 15 min. and then, after cooling, acidified with 5 ml. of 10% hydrochloric acid. Sulphur dioxide was passed in until the solution was colourless. Continuous ether extraction for 42 hr. followed by drying over sodium and magnesium sulphate and finally evaporation, afforded a pale yellow solid, 146.2 mg. (30%). Yields ranged from 10-30%. Glc of the dimethyl ester indicated the absence of other components. Recrystallization 5-6 times from ethyl acetate gave needles, m.p. 175-185°. [lit: 185-189°] .

Ethylenediamine (as the Dibenzamide Derivative)

Several variations in reaction procedure were investigated and it was found that failure to follow exactly the procedure described below frequently resulted in very low or no yield of the dibenzamide. A 50-ml. round bottom flask was fitted with a side arm, a nitrogen inlet projecting to the bottom of the flask and a gas outlet connected to two wash bottles containing a dilute solution of sodium dichromate and carbon dioxide free sodium hydroxide solution respectively. A solution of succinic acid (20 mg. 0.17 mmole.) in 1 ml. of 20% oleum was placed in the flask which was warmed to 40°: sodium azide (104 mg. 1.6 mmoles.) was weighed into the side arm. The apparatus was flushed with dry nitrogen before attachment of the wash bottle containing sodium hydroxide. The sodium azide was added rapidly (~1 min. addition time) to the stirred solution at 40°. The flow of nitrogen was maintained for 60 min. The carbon dioxide was precipitated as barium carbonateusing 10 ml. of ammonium chloride - barium chloride solution (0.33 M in each.) The yield of barium carbonate after filtration and drying was 27.3 mg. (41%). The

acidic solution was cooled and 6 ml. of water added. A rubber septum cap was attached to the flask outlet and 3 ml. of 50% sodium hydroxide slowly injected into the flask which was cooled throughout in an ice-bath; a small sample was withdrawn for verification of the alkalinity of the solution. The solution was allowed to warm to room temperature and water was injected to dissolve any salts which had precipitated. Benzoyl chloride (100µl) was injected into the flask which was then shaken vigorously until a white precipitate formed. The latter was filtered off, washed with water and taken up in hot ethanol. Evaporation afforded 23 mg. (51%) of crude dibenzamide; recrystallization from ethanol: water gave white needles, m.p. 253-254.5°. [lit: 249°] ; a mixed melting point with authentic material was undepressed. Yields of dibenzamide derivative ranged from 20-50% using this procedure.

Calculation of the Proportion of Hydride Shift in Reaction B

For 2-exo-3-endo-dibromide:

Let x equal amount of 6,1-hydride shift in addition of bromine to norbornylene.

Let y equal amount of 6,1-hydride shift in the reaction of hydrogen bromide with bromonortricyclene.

If it is assumed that the ratio of attack at the two Wagner-Meerwein related sites to give 2-exo-3-endo- and 7-anti-2-exo-dibromide is constant then:-

$$\frac{x}{12.4} = \frac{y}{21.0}$$

From ^{14}C results of degradation B, the total amount of 2-exo-3-endo-dibromide from 6,1-hydride shift is 43%[(5.67-3.21)/5.67].

Table 20

Degradation of ^{14}C-Labelled 2-exo-3-endo-Dibromonorbornane; Counting Results

	Wt. (mg.) counted		Counts/min. ✲ x10^{-3}		Counts/min/mmole x10^{-5}	
	A	B	A	B	A	B
1,3-Cyclopentane dicarboxylic Acid	5.72	3.62	20.0	12.3	5.53	5.37
1,3-Cyclopentanediamine ♄	3.21	3.45	5.93	6.3	5.70	5.67
Succinic Acid	2.30	1.53	9.59	6.18	4.93	4.75
Barium Carbonate #		10.67		3.27		0.57
Ethylenediamine ♄	2.38	2.49	3.91	2.98	4.39	3.21

♄ Counted as dibenzamide derivatives

✲ All samples counted to 10^5 counts

From degradation of the succinic acid

Table 21

Addition of Bromine to 5,6-^{14}C-norbornyl-2-ene Product: Composition

Compound	Product Composition %				
	A	B			
		before HBr	after HBr		
			Total +	addⁿ ♮	1*
bromonortricyclene	24.5	46.4	-	-	-
2-exo-3-endo-	8.3	6.0	9.3	5.0	4.3
7-anti-2-exo-	16.3	15.1	33.4	12.4	21.0
2-exo-5-endo-	5.1	5.5	12.9	4.6	8.3
2-exo-5-exo-	4.4	3.8	10.7	3.1	7.6
7-syn-2-exo-	40.6	22.8	33.5	18.9	14.6

\+ Total percentages of dibromides in crude product from the addition of bromine to norbornylene plus the reaction of hydrogen bromide with bromonortricyclene.

♮ The percentages of dibromides in the total which were formed in the addition of bromine to norbornylene.

* The percentages of dibromides in the total which were formed from the reaction of hydrogen bromide with bromonortricyclene.

$\therefore$ of the 9.3% total 4.0% comes from 6,1-hydride shift

$\therefore x + y = 4.0$ $\qquad\qquad$ $\therefore 4.0 - y = \frac{12.4y}{21.0}$

$\therefore y = 2.5$ $\qquad\qquad$ $\therefore x = 1.5$

$\therefore$ % of 2-<u>exo</u>-3-<u>endo</u>-dibromide formed via 6,1-hydride shift in the addition of bromine to norbornylene is <u>30%</u> (33† and 42‡%).

% of 2-<u>exo</u>-3-<u>endo</u>-dibromide formed via 6,1-hydride shift in the reaction of hydrogen bromide with bromonortricyclene is <u>47%</u> (44† and 36‡%).

† <u>Total</u> 6,1-Hydride shift = 40.2%((4 × 0.57)/5.67)

‡ <u>Total</u> 6,1-Hydride shift = 33% [2(5.67 - 4.75)/5.67]

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APPENDICES

APPENDIX I

Reactions of Perchloryl Fluoride with Grignard Reagents and Diazo Compounds

Introduction

Perchloryl fluoride is a stable derivative of perchloric acid (1) possessing C_{3v} tetrahedral symmetry (2) and a dipole moment of 0.023 ± 0.003 D.(3). In the presence of an aromatic compound and a strongly electrophilic reagent, such as aluminium chloride, heterolysis to give ClO_3^+ occurs, resulting in the formation of perchloryl aromatic derivatives depending on the nature of the aromatic compound present (4). Ammonolysis occurs readily to give the ammonium salt of perchlorylamide (1).

The most widely applicable reaction of perchloryl fluoride is nucleophilic displacement on fluorine by the sodium salts of active methylene compounds (5); the formation of α-fluoroketone derivatives by this route has been widely applied in the steroid field (6,7).

Attempts to form fluoro derivatives from the anions of oximes, nitroalkanes and hydroxamic acids by reaction with perchloryl fluoride have been largely unsuccessful (8,9); the best yields of fluoro-nitroalkanes (36-42%) are obtained from the salts of secondary nitroalkanes. Isolated double bonds do not appear to react with perchloryl fluoride unless substituted by nitrogen (10), oxygen (11) or phenyl groups (12). The enamines and enamides are much more reactive than the enol ethers and esters as might be expected from the greater ability of nitrogen to donate electrons to the double bond for interraction with the electrophilic fluorine.

Organolithium compounds, in which the organic moiety has carbanionic

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Organolithium compounds, in which the organic moiety has carbanionic

character, have been used as substrates but fluorine substituted products were only obtained when a group capable of stabilizing the carbanion was present (13).

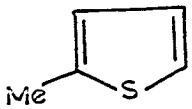
In all the reaction studies so far oxidation products may be formed, in many cases to the exclusion of any fluorine substituted product. Good yields of fluorine substituted products have only been obtained when a stabilized anion has been involved: e.g. diethyl malonate in the presence of excess ethoxide reacts with perchloryl fluoride to give an almost quantitative yield of diethyl α,α-difluoromalonate (5).

Any new synthetic procedure leading to the introduction of fluorine into an organic molecule is of interest considering the paucity of efficient methods currently available; it was therefore considered worthwhile to investigate the reactions of perchloryl fluoride with other species capable of anionic character.

Discussion

A. Reaction of Perchloryl Fluoride with Grignard Reagents.

The organic moiety of a Grignard reagent has considerable carbanionic character as the carbon-metal bond is not completely covalent. Evidence that perchloryl fluoride might yield organofluorine compounds when allowed to react with Grignard reagents was provided by the report (13) that some fluorine substituted products had been obtained by the reaction of perchloryl fluoride with several lithium-thiophene derivatives. Addition of perchloryl fluoride to the lithium derivatives of 1, 2, and 3 at 0° in ether resulted in 44, 49 and 70% yields respectively of the 2-fluoro derivative. When this procedure was applied to the lithium derivatives of benzene and naphthalene the yields of fluoro products were reported as negligible. In an exploratory reaction (6) of perchloryl fluoride with n-octylmagnesium bromide in ether at 10-18°, three main products were identified; octane, n-octyl fluoride and n-octyl alcohol. The yield of n-octyl fluoride based on isolated pure material was 16.5% with respect to n-octyl bromide. n-Octanol was reported as being formed in approximately 5% yield (glc analysis). The effects of change in reaction conditions and a more detailed product analysis were not attempted at that time. The work herein describes the reaction of



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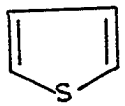

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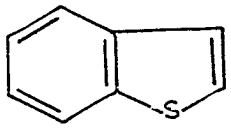

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perchloryl fluoride with Grignard reagents derived from n-octyl bromide, sec-octyl bromide and β-naphthyl bromide; the reaction conditions and

products are presented in Table 1. An apparatus was used such as to exclude air and as much moisture as possible; dry nitrogen was used to flush the Grignard reagent into the reaction flask. The Grignard reagent content was assayed, before addition of perchloryl fluoride, and in one case when the latter reaction had ceased to be exothermic (Rx. 3, Table 1); in general the reaction ceases to be exothermic when approximately one half the theoretical weight of perchloryl fluoride has been added which amply demonstrates the ambivalent role of perchloryl fluoride in this reaction. Addition of more than half the equivalent weight of perchloryl fluoride has no significant effect on product yields. The optimum temperature of addition appears to be around 0^{o}; lower temperatures may slightly decrease the yield of n-octyl fluoride but higher temperatures are quite definitely detrimental to the yield of alkyl fluoride. Temperature change has little effect on n-octane formation.

The complexities of this reaction arise out of the strong oxidizing capability of perchloryl fluoride (14) which is largely controlled by temperature, pH and concentration of reactants. Grignard reagents readily undergo oxidation, by oxygen to give peroxidic intermediates, and by transition metal halides to give predominantly coupled products possibly via a free radical mechanism. As perchloryl fluoride is a one electron oxidizing agent (14) the mechanism formally described by eq. 1 seems reasonable.

$$\bar{R}\,\overset{+}{M}gX \;+\; FClO_3 \longrightarrow R^{\bullet} \;+\; MgXF \;+\; ClO_3 \qquad \text{eq. 1}$$

The coupled product, hexadecane, may arise via dimerisation as well as by the conventional route described by eq. 2

Table 1

Rx. No.[♮]	RMgBr Yield %	RMgBr Conc.[n] mmoles./l.	RMgBr mmoles.	$FClO_3$ mmoles.	Temperature °C.	% Yd. w.r.t. R-MgBr (R=$C_8H_{17}^-$) R-H	R-F	R-OH	R-R
1	73	127	38.0	69	1→6°	14.0[+]	25.2[+]	-	-
2	79	350	81.5	115	-5→11°	3.4[‡]	21.5[‡]	15.7[+]	24[‡]
3[#]	76	338	78.5	48	-5→12°	6.3[‡]	20.6[‡]	15.7[+]	19[‡]
4	84	373	87.0	67	20→29°	10.6[‡]	11.3[‡]	14.5[+]	~29[‡]
5	74	327	76.5	67	22→31°	-	5.1[+]	-	-
6	88	375	91.5	>1eq.	-20→-32°	12.0[+]	20.0[+]	16[+]	-
7	85	2600	129.0	115	2-12°	6.5[+]	2.6[+]	19.0[+]	-
8[b]	88	1830	91.5	385	-2→0°	-	12.2[+]	14.5[+]	~31[‡]

[#] $FClO_3$ addition stopped when rx. no longer exothermic

[♮] Solvent: 1-6 and 8 ether; 7, $(CH_3)_2NC_6H_5$.

[+] by glc

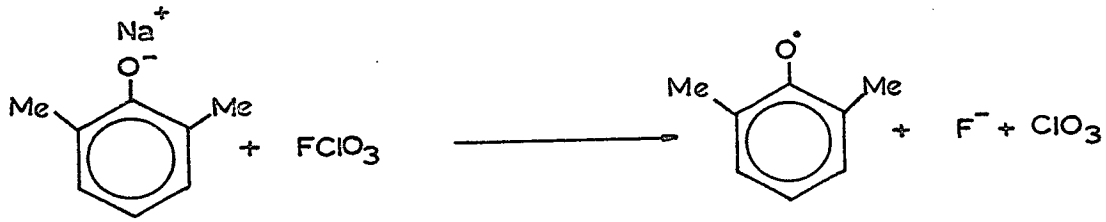
[‡] by wt.

[b] Inverse addition

Products and Conditions for Reaction of Perchloryl Fluoride with n-Octyl Magnesium Bromide

$$\overset{-+}{R}MgX + RX \longrightarrow R\text{-}R + MgX_2 \qquad \text{eq. 2}$$

This type of oxidation has been postulated previously to explain the formation of diphenoquinone 4 from the reaction of perchloryl fluoride with phenoxide 5 (15). It should be borne in mind that these reactions



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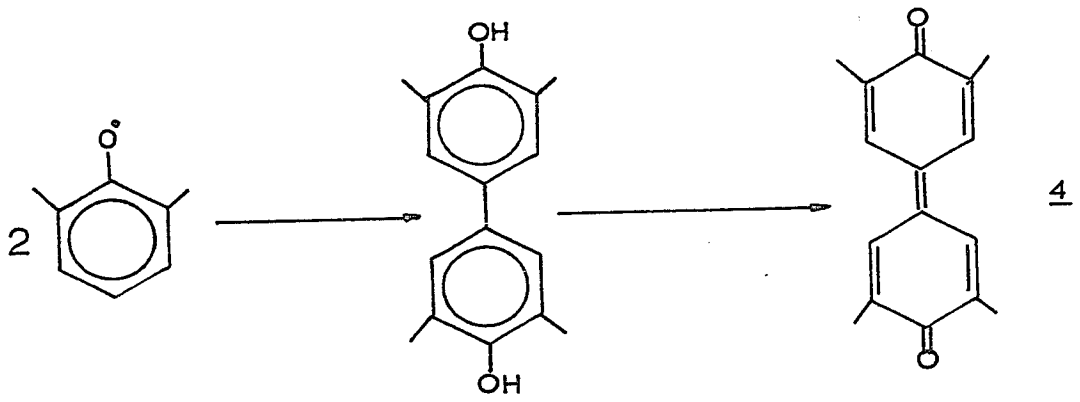

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were carried out under dry nitrogen and with every effort to exclude moisture, and any mechanisms proposed must take into account the significant yields of n-octane, coupled product and alcohol. Yields of coupled product can be reduced to less than 10% with little effort in normal reactions of Grignard reagents. The n-octane cannot have arisen from unchanged Grignard reagent remaining when water was added in the work-up, as carbon dioxide had been flushed through the reaction mixture beforehand; no acidic products were found in the basic wash and an assay for Grignard reagent after approximately one half an equivalent

of perchloryl fluoride had been added revealed that no Grignard reagent remained.

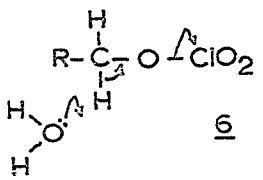
Chlorine trioxide decomposes even at 0°C to a mixture of other oxides of chlorine and ultimately to chlorine and oxygen. Thus oxygen is being formed *in situ* and conditions are now ideal to observe the direct reaction of the Grignard reagent with oxygen.

It has been postulated that this reaction takes place in two steps, the first being formation of a peroxide and the second being reduction of this peroxide to an intermediate which, on hydrolysis, yields an alcohol (16, 17). The first step has been amply demonstrated by the isolation of the hydroperoxide by treatment of oxygenated ether at -70° with alkyl Grignard reagents (18). The presence of *n*-octyl alcohol in the product is therefore readily understood on this basis. The Wurtz product, biphenyl, has been observed in abnormally large quantities in reactions of phenylmagnesium bromide with oxygen and while Wuyts (19) has considered that it arises in the fashion indicated by eq. 3. Kharasch and Reinmuth (20) consider that it could arise *via*

$$2\ \phi\ MgX \ + \ [O] \longrightarrow \phi\text{-}\phi \ + \ XMgOMgX \qquad \text{eq. 3}$$

decomposition or side reaction with solvent, of the peroxidised Grignard reagent. *n*-Octane may arise by abstraction of hydrogen by *n*-octyl radicals.

It is unlikely that an intermediate such as *6* is formed; *6* would probably decompose either during reaction or work up to give an aldehyde



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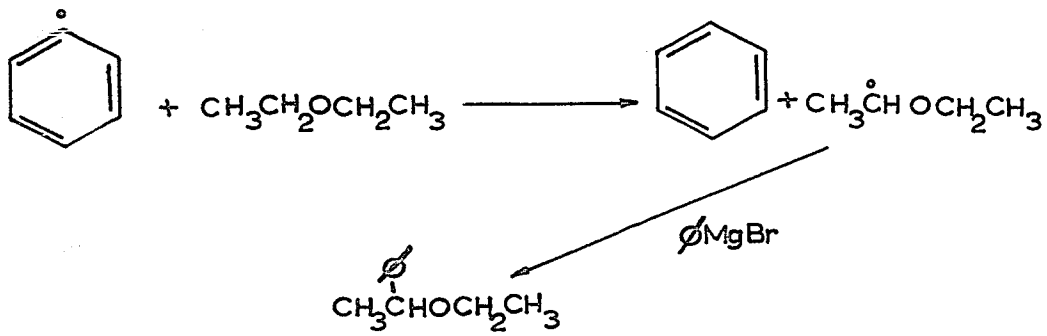
$$\longrightarrow \quad R - CHO \ + \ \bar{C}lO_2$$

(12), or possibly an acid depending on the oxidizing agent present when the intermediate decomposed; no aldehydes, acids or secondary alcohols were observed.

The formation of the perchlorylated derivative, $R\text{-}ClO_3$, and its subsequent hydrolysis to the alcohol is militated against on the grounds that the perchloryl benzenes have been found to be completely stable in neutral or strongly acidic solution.

Dean (6) has carried out an analysis of the products from the reaction of phenylmagnesium bromide with perchloryl fluoride and it is of interest to consider the products found, in the light of the mechanisms postulated above for the alkyl Grignard reagent. No phenol was found which is in agreement with the concept that phenyl magnesium bromide is a much inferior reducing agent toward the intermediate peroxide than the alkyl analogue. This result is in complete accord with those found for reaction of Grignard reagents with oxygen. A small amount of chlorobenzene was isolated from the phenyl Grignard reaction and this was ascribed to reduction of initially formed perchloryl benzene. Consideration of the latter's stability and the failure to isolate it from the reaction, would indicate that a more probable source of chlorobenzene is the reaction of chlorine, from decomposition of chlorine trioxide, with the Grignard reagent. One curious point remains however, and that is the formation of α-phenethyl ether and the non-formation of phenylethanol. The latter is a major product (20%) in the reaction of phenyl Grignard reagents with oxygen in ethereal solution (19). It is conceivable that the α-phenethyl ether is being formed via abstraction of hydrogen from the diethyl ether by phenyl radical (21).



Two other substrates were used in an effort to determine the scope of this reaction with non-primary Grignard reagents; these were 2-octyl- and β-naphthylmagnesium bromide. The former gave, after addition of excess perchloryl fluoride at 2-8° C, work-up and spinning band distillation, three fractions containing 2-octyl fluoride, which by glc analysis, amounted to a 11% yield with respect to Grignard reagent.

β-Naphthyl Grignard reagent afforded a trace of binaphthyl as the only isolable product from the tarry crude product. This result, if nothing else, is in agreement with the analogous reactions of phenyl- and α-naphthyllithium (13).

It is difficult to draw any meaningful conclusions on the mechanism of fluorination by perchloryl fluoride from the yields of fluoro product formed in these Grignard reactions when the yield is obviously influenced by the amount of a competing oxidation. It may only be coincidental that the yields of fluoro product in these reactions are in agreement with the previous observation that the greater the stability of the carbanion the greater the yield of fluorinated product (13, 15).

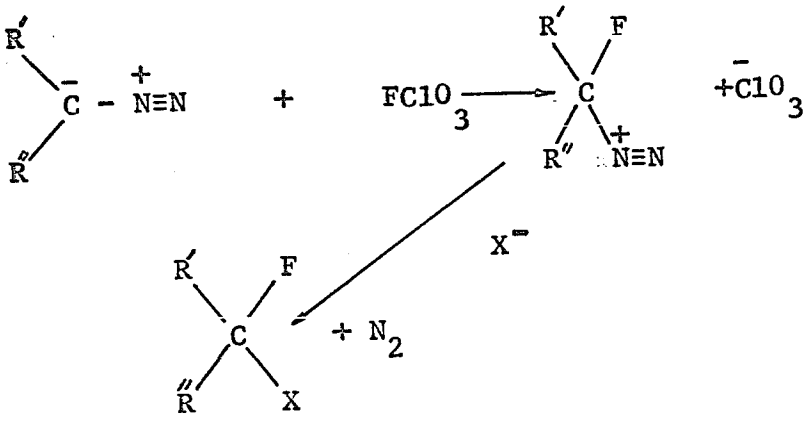
This work demonstrates that the reaction of perchloryl fluoride with Grignard reagents is unlikely to be of synthetic utility unless its oxidative rapacity toward these reagents is severely reduced.

B. Reaction of Perchloryl Fluoride with Diazo Compounds.

Diazoalkanes, ketones and esters frequently react via nucleophilic attack on an electrophile. The basis for this can be readily appreciated from a consideration of the principal mesomeric contributors for diazomethane.

$$\bar{C}H_2-\overset{+}{N}\equiv N \longleftrightarrow CH_2=\overset{+}{N}=\bar{N} \longleftrightarrow \bar{C}H_2-N=\overset{+}{N}$$

In an effort to extend the reactions of perchloryl fluoride it was felt worthwhile to examine its reaction with some diazo derivatives. The reaction scheme anticipated is shown below.



It seemed possible that if a nucleophile such as fluoride ion was available in high concentration, attack on the fluoro intermediate would result in a difluoro substituted product. Dimethylformamide was chosen as solvent as both perchloryl fluoride and potassium fluoride have an appreciable solubility in it. A less reactive diazo compound was chosen initially for two reasons: firstly most reactions with perchloryl fluoride are vigorously exothermic and secondly the latter property might promote explosive evolution of nitrogen. It was

slightly anticlimactic when it was found necessary to heat the reaction mixture to 40-45° before any visible sign of reaction occurred. At this temperature, a pale yellow saturated solution of potassium fluoride in dimethylformamide containing ethyl diazoacetate evolved nitrogen smoothly when perchloryl fluoride was passed into the solution. Evolution of nitrogen occurred until the solution decolourised quite sharply, at which point it was concluded that the diazoacetate had been consumed. It was shown that reaction occurred without the presence of potassium fluoride but no reaction occurred in the absence of perchloryl fluoride. Considerable difficulty was encountered in the isolation of pure components from the crude product; finally a combination of spinning band distillation at reduced pressure and column chromatography on silica gel was employed. Two products were identified from the same reaction mixture, these being ethyl chloroacetate and the formate ester of ethyl glycolate. The structure of the latter was verified by spectral data and analysis. The infrared spectrum showed two strong carbonyl bands at 1770 and 1742 $cm.^{-1}$. The former can be attributed to the acetyl ester carbonyl shifted to lower wavelength by the substitution at the α-carbon of the formyloxy group. The nmr spectrum was extremely simple exhibiting the characteristic quartet and doublet of doublets for the ethyl group centred at 4.23 and 1.25 ppm, respectively; a one proton singlet at 8.20 ppm is ascribed to the formyl hydrogen and may be compared to the formyl hydrogen absorption in methyl formate (8.08 ppm) and dimethyl formamide (8.02 ppm). The two proton singlet at 4.82 ppm is consistent with a methylene group carrying formyloxy and carboethoxy substituents. The

analogous protons in ethoxy-acetic acid absorb at 4.13 ppm.

In view of the mildness with which ethyl diazoacetate reacted with

Table 2

Reaction of Diazo Compounds with Perchloryl Fluoride

Substrate	Concentration mmoles./l.	Temperature	Products
Ethyl Diazoacetate	1.47	45-50°C	$CH_2ClCOOEt$ (11%) $HCOOCH_2COOEt$ (24%)
Phenacetyl diazomethane	970	60°C	$\phi COOH$ ϕCH_2COCH_2Cl
Phenacetyl diazomethane	840	40-45°C	$\phi CH_2COCOOH$ ϕCH_2COOH $\phi CHClCOOH$ ϕCH_2COCH_2Cl
Diphenyl diazomethane	144	2-4°C	$\phi CO\phi$ 61% (based on crude product)

Note: solvent Dimethylformamide

perchloryl fluoride, the obvious choice of a similarly reactive diazo compound was a diazo ketone. Reaction of phenacetyl diazomethane under the conditions used in the ethyl diazoacetate reaction afforded a steady evolution of nitrogen until the solution was decolourised. Work-up revealed the presence of both acidic and neutral products. Isolation and identification of the components in each fraction was complicated by instability of the major product, but fortuitously the

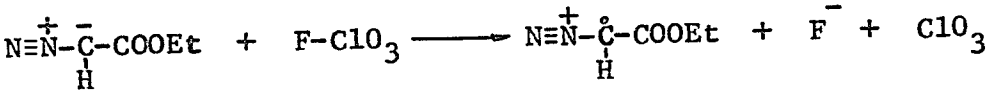
major acidic product slowly crystallized from the crude acidic mixture. Repeated recrystallization from chloroform gave phenylpyruvic acid showing one spot on tlc, providing the solution spotted was used immediately. The ultraviolet and nmr spectra were characteristic of an α-keto acid present as its keto or enol form according to solvent. The structure was finally confirmed by analysis and comparison of its infrared and nmr spectra with those of authentic phenylpyruvic acid. Thick layer chromatography of the liquid acidic mixture, after the crystalline acid had been removed, gave another acid slightly contaminated by a third acid. The major component was identified as phenylacetic acid by mixed melting point of its p-phenylazophenacyl derivative with that of an authentic specimen and by comparison of nmr and infrared spectra. The minor component was identified as α-chlorophenylacetic acid by comparison of the nmr spectrum of a synthetic mixture of the two acids with that mixture obtained by tlc of the liquid acidic fraction.

Thin layer chromatography of the neutral fraction in chloroform showed the presence of one major and three minor components. The major component was obtained in a fairly pure state by three successive thick layer chromatographic treatments. The resulting compound, which decomposed to a black oil within a few days, was identified by analysis and spectral comparison with an authentic sample as α-phenyl α'-chloroacetone.

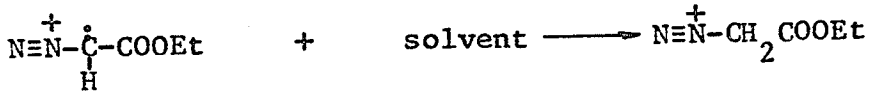
It is evident from the two reactions mentioned that the complexity of the products largely obscures the fundamental reaction of perchloryl fluoride with a diazo compound. It was hoped that the use of a diazoalkane would greatly simplify the reaction and indeed, this was completely

justified when it was found that only one major product was formed when diphenyl diazomethane was allowed to react with perchloryl fluoride in dioxane or dimethylformamide. After removal of solvent the pale yellow crude product crystallized completely and was shown by m.p. and infrared spectrum to be almost pure benzophenone.

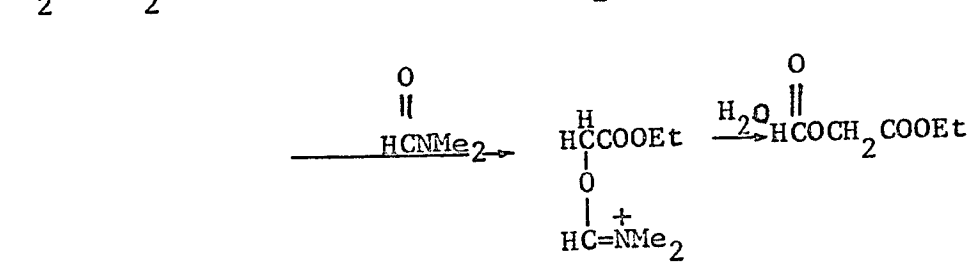
It is clear from the nature of the products that perchloryl fluoride is reacting with these diazo compounds in an oxidative capacity. The following rationale accounting for the products is perforce largely speculative. In all the reactions the first step is probably a one electron oxidation.



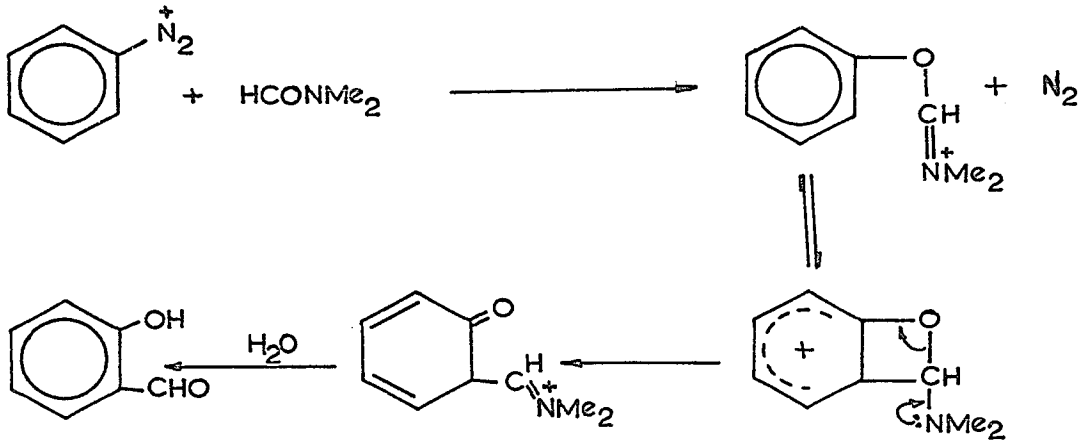
Hydrogen abstraction would then give a diazonium ion.



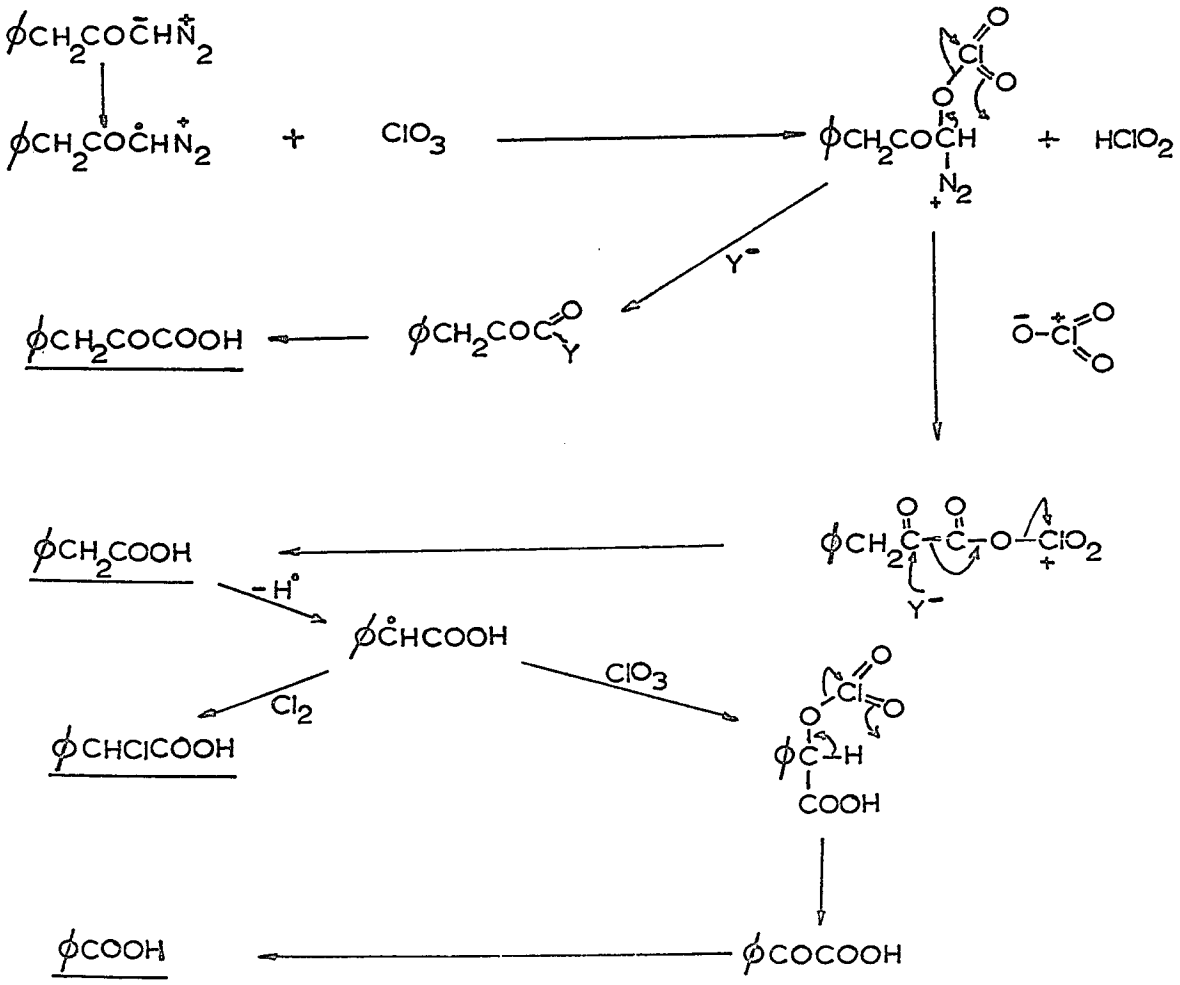
There should be a considerable concentration of chloride ion present from decomposition of the chlorine trioxide. Attack by chloride ion would give ethyl chloroacetate while attack by solvent gives an imonium ion intermediate which hydrolyses on work-up.



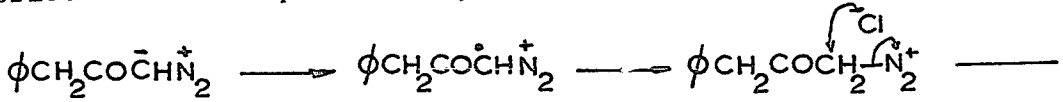
Precedent for the attack by dimethylformamide in this manner is to be found in the reaction of dimethyformamide with aryl diazonium ions (22) which has been postulated to take place as shown in the scheme on page 195.



When diazo ketones are used as substrates it would appear that attack by chlorine trioxide is a competing reaction with hydrogen abstraction.



The formation of the chloroketone may occur *via* attack on the diazoketone by hydrogen chloride, a known fast reaction, or alternatively from a competing hydrogen abstraction followed by nucleophilic attack of chloride ion. The possibility that the chloroketone was an impurity in



the starting material was excluded by a negative chlorine test on the recrystallized diazoketone.

The simplicity of the reaction with diphenyldiazomethane appears to depend on the lack of hydrogen at the α and β-positions to nitrogen. Once the α-carbon has been oxidized, oxidation ceases. What is perhaps surprising is the absence of any significant yield of formyloxy derivative in the reactions with diazoketones and diazoalkanes. However, the gross variations in product with small alterations in conditions and the complexity of the crude product mixtures make it difficult to draw any definite conclusions excepting the disappointingly obvious one: diazo compounds are not suitable substrates for fluorination by perchloryl fluoride.

EXPERIMENTAL

Reaction of Perchloryl Fluoride with Grignard Reagents

Assay of Grignard Reagent (23)

The ethereal solution (1 ml.) of Grignard reagent was transferred to a conical flask and 5 ml. of water, followed by 5 ml. of 0.25N sulphuric acid; the excess sulphuric acid was titrated against 0.095N sodium hydroxide using phenolphthalein as indicator.

Reaction of Perchloryl Fluoride with β-Naphthyl Magnesium Bromide

Small pieces of magnesium ribbon (600mg.) were dried in the Grignard flask at 120° for one hour. The three-necked flask was equipped with a condenser, nitrogen inlet, stirrer, dropping funnel and an outlet tube at the bottom of the flask containing a glass wool plug. This outlet tube was connected, via a stopcock, with another three-necked flask equipped with stirrer, sintered glass bubbler and gas exit; the bubbler was fitted with a two way stopcock allowing nitrogen and/or perchloryl fluoride to be admitted. The apparatus was all dried and assembled while warm and flushed with dry, oxygen free nitrogen. After sufficient ether (measured volume) was added to cover the magnesium, β-bromonaphthalene (0.5 g.) and a crystal of iodine were added and the solution brought to reflux. When the reaction had started β-bromonaphthalene (3.458 g., 17 mmoles.) in 60 ml. of ether was added, at reflux, over 3.5 hours. The Grignard reagent separates as a brown oil requiring the addition of 50 ml. of benzene to render the solution homogeneous; 1 ml. of this solution was withdrawn for assay of Grignard content (75%). The Grignard solution was blown over with nitrogen, any solid impurities such as magnesium bromide

being removed by the glass wool plug. An additional 200 ml. of benzene were used in washing the Grignard solution through. Perchloryl fluoride (115 mmoles.) was passed in over 60 min. at 18-22° throughout; during this time the solution turned from very pale yellow to a black opaque colour. After passing nitrogen through the solution for 1 hr. to remove all excess perchloryl fluoride, solid carbon dioxide (60 g.) followed by 50 ml. of 20% hydrochloric acid were carefully added. The crude product (2.5 g.) was obtained as a thick brown oil after the ethereal extract had been washed with 10% aqueous sodium hydroxide, dried and evaporated. The oil was tested for fluoride using both the dichromate (24) and complexometric (25) tests; both were negative. The crude product (0.5 g.) was chromatographed on a 20 x 2.5 cm. column of Alumina (Grade I). Elution with petroleum-ether (b.p. 30-60°) gave 107 mg. (43%) of naphthalene, m.p. 80-82°. Elution with benzene: petroleum-ether (b.p. 30-60°) (1:9) gave 59 mg. of solid with wide melting range. A solid (36 mg., m.p. 170-180°) believed to be β,β′-binaphthyl (m.p. 187°) was obtained on elution with benzene: carbon tetrachloride (1:1). No further material could be eluted from the column. Acid extraction of the sodium hydroxide wash gave only a thick black tar (600 mg.) which was not further investigated after a negative fluorine test was obtained.

Reaction of Perchloryl Fluoride with n-Octyl Magnesium Bromide

A representative reaction was carried out as follows.

n-Octyl bromide (20 g., 104 mmoles.) and magnesium (3.0 g.) were allowed to react together in 40 ml. of anhydrous ether to give a 78.5% yield of Grignard reagent. This, after addition of a further 150 ml. of ether, was treated with 12.0 g. (114 mmoles.) of perchloryl fluoride over 45 min. The addition of the first 5.5 g. (53 mmoles.) was strongly

exothermic and the temperature was maintained in the range -5° to +11°C throughout. At the end of the addition the solution (colourless with white precipitate) was thoroughly purged of excess perchloryl fluoride with nitrogen. Carbon dioxide gas was admitted over 20 mins. followed by 100 ml. of 20% hydrochloric acid which induced a vigorous exothermic reaction concomitant with bromine formation. Evaporation of the ethereal layer, after washing with two 50-ml. portions of 10% aqueous sodium hydroxide and drying with magnesium sulphate, left 13.23 g. of crude product which gave a positive test for fluorine. Glc on 10% DEGS on firebrick at 170° showed the presence of seven components. n-Octyl fluoride, n-octyl alcohol and n-octane were identified by comparison of retention times with those of authentic samples. The crude product (12.35 g.) from another reaction run under similar conditions was distilled on a 23 plate platinum spinning band column; individual fractions were analyzed by glc for identifiable components.

In one reaction the aqueous wash was acidified to pH 3 with hydrochloric acid and extracted with four 25-ml. portions of ether. After drying, evaporation afforded 40 mg. of acidic material. Grignard assay when the reaction ceased to be exothermic revealed that no Grignard reagent was present.

Spinning Band Distillation of Crude Product from Reaction of Perchloryl Fluoride with n-Octyl Magnesium Bromide.

Wt. of each fraction (mg.)	B.P./Pressure °C/mm.	Composition
400	43-50/35	
110	50-56/35	n-octane
50	56-57/35	
50	57-58/35	
1990	58-60/35	n-fluorooctane η_D^{25} 1.3945
200	59-60/35	(98%) [lit: (26) η_D^{25} 1.3927]
290	60-80/35	n-fluorooctane, n-octyl alcohol
180	80-100/35	+ three unidentified components
220	100-104/35	
100	103-104/35	
1770	104-111/35	n-octyl alcohol (80%)
230	110-111/35	n-octyl alcohol η_D^{20} 1.4307
1000	123-135/35	[lit: η_D^{20} 1.4304]
1770	140-170/35	hexadecane m.p. 16-17° [lit: m.p. 20°.]

Reaction of Perchloryl Fluoride with n-Octyl Magnesium Iodide - Inverse Addition

n-Octyl iodide (24.15 g., 100 mmoles.) gave an 88% yield of n-octyl magnesium iodide. Perchloryl fluoride, (4.0 g., 39 mmoles.) was passed into ether kept at 0° while the Grignard reagent in 50 ml. of ether was added from a dropping funnel through a subsurface capillary tube at such a rate that the perchloryl fluoride would always be in excess. It was essential that the solution be vigorously stirred and the addition be subsurface to avoid any possibility of contact between Grignard reagent and perchloryl fluorine at high concentrations. Work up as described in the n-octyl bromide reaction gave an oil (13.60 g.) which was

distilled on a 23 plate spinning band column under reduced pressure. Gas-liquid chromatography on a 1.8m. x 6.4mm. column of SE30 on Chromasorb W at 170° allowed calculation of the percentage yields of the three major products (see Table 1).

Reaction of Perchloryl Fluoride with 2-Octyl Magnesium Bromide

2-Bromooctane (25 g., 130 mmoles.) gave a 65.5% yield of Grignard reagent which was treated with perchloryl fluoride (6 g, 59 mmoles.) over 45 min. at 2-8°C. throughout. Work up as in previous examples gave 18.43 g. of crude product which was spinning band distilled under reduced pressure. The main fraction (1.48 g., b.p. 52-54°/31 mm.) containing 74% 2-fluorooctane by glc, was further purified by chromatography on silica gel (eluant, petroleum-ether b.p. 30-60°) to give an analysis sample of >99% purity by glc on a 1.8m. x 6.4mm. column of 10% DEGS. on firebrick. The pure product (n_D^{25} 1.3916) gave a strong positive fluorine test. $\nu_{max}^{CCl_4}$ 2945 (s), 1470 (m), 1388 (m) and 1136 (m) cm^{-1}.

Anal. Calcd. for $C_8H_{17}F$ (132.22): C, 72.63; H, 12.96.

Found: C, 72.64; H, 12.97.

Reaction of Perchloryl Fluoride with Diazo Compounds

Ethyl diazoacetate was prepared in the usual way:

	Yields obtained (%)
Methylene aminoacetonitrile (27)	67
Glycine ester hydrochloride (28)	83, 79, 96, 81
Ethyl diazoacetate (29)	16, 46, 57, 55

Reaction of Ethyl Diazoacetate with Perchloryl Fluoride in Dimethylformamide

A solution of ethyl diazoacetate (25 g., 220 mmoles.) and 150 ml. of dry dimethylformamide, in a three-necked flask equipped with a sintered glass bubbler, stirrer and gas outlet, was treated with perchloryl fluoride (14 g., 135 mmoles.) over 3.5 hr. at 45-50°C. The rate of addition and the temperature control were adjusted such that nitrogen evolution occurred smoothly. The exhaustion of the ethyl diazoacetate was marked by a definite change of colour from yellow to colourless over a few minutes. The reaction mixture was purged of excess perchloryl fluoride with nitrogen, poured into 200 ml. of water, and extracted with three 100-ml. portions of ether. Evaporation of the dry, filtered extract gave an oil (13.70 g) which gave a negative fluorine test. Spinning band distillation at reduced pressure gave two main fractions; the first (1.53 g., (~11%) b.p. 30-35°/6mm., n_D^{25} 1.4200) was identified as ethyl chloroacetate by the identity of its infrared spectrum with that of an authentic specimen [lit: n_D^{20} 1.4227] . The second fraction, (30) mainly α-formyloxy ethyl acetate (4.71 g., b.p. 41-46°/3mm, [lit: (30) 64-65°/12mm.] n_D^{25} 1.4120) was chromatographed on silica gel. Elution with carbon tetrachloride: ether (1:1) gave one main fraction (3.76 g., 24%) which was distilled (bulb to bulb) at 1 mm. to give an analysis sample, n_D^{25} 1.4086, $\nu_{max}^{CCl_4}$ 1770 and 1742 cm^{-1} (>C=O), δCCl_4 1.25 (3H, t, $-CH_3$), 4.23 (2H, q, $-CH_2-$), 4.73 (2H, s, $-OCH_2\overset{O}{C}-$), 8.20 ppm (1H, s, $H-\overset{O}{C}-O-$).

Anal. Calcd.for $C_5H_8O_4$ (132.114): C, 45.48; H, 6.10; O, 48.44.

Found: C, 44.79; H, 6.32; O, 48.76.

Control Reaction of Ethyl Diazoacetate with Dimethylformamide

Ethyl diazoacetate (2.5 g., 22 mmoles.) and potassium fluoride (1.4 g.) in 50 ml. of dry dimethylformamide were stirred at 50°C for 24 hr. No colour change or nitrogen evolution was observed. Ethereal extraction of the solution after filtration gave 1.5 g. of crude product on removal of the ether. This was shown to be a mixture of starting material and dimethylformamide by infrared comparison.

Preparation of phenacetyl diazomethane

Thionyl chloride (126 g., 1.06 moles) was added to phenyl-acetic acid (100 g., 740 mmoles.) and the mixture refluxed for 1 hr. followed by removal of excess thionyl chloride by distillation. Distillation under reduced pressure gave phenylacetyl chloride, 105 g. (92%), b.p. 94°/12 mm.

Phenylacetyl chloride (18 g, 118 mmoles.) in 50 ml. of anhydrous ether was added slowly to 9.7 g. (230 mmoles.) of diazomethane (assayed by titration against benzoic acid) dissolved in 700 ml. of ether. Evaporation gave a pale yellow solid which, after one recrystallization from petroleum ether: benzene had m.p. 47-48°. This material did not contain any chloride.

Reaction of Perchloryl Fluoride with Phenacetyl Diazomethane

Phenacetyl diazomethane (10.0 g., 63 mmoles.) dissolved in 75 ml. of redistilled dimethylformamide (51°/17mm.) was treated with perchloryl fluoride (9.5 g., 91 mmoles.) over 2.75 hr. at 40-45° throughout. After this time the smooth nitrogen evolution had ceased but the solution remained yellow in colour. The solution was poured into 250 ml. of water and extracted with five 50-ml. portions of ether. The acidic components

were removed by extraction with a 10% aqueous sodium bicarbonate solution, reacidification of the aqueous extract and further ether extraction.

(a) The acidic fraction of the crude product (3.30 g.) slowly crystallized over 48 hr. at 0°C. Filtration gave 168 mg. of white solid which, after three recrystallizations from chloroform had m.p. 150-152°C. The ultraviolet spectra exhibited properties expected of an α-keto-acid:-

Concentration and solvent	λ_{max} with respective extinction coeffs.				
1.1 mg./250 ml. 95% EtOH	220 mμ 14,200	228 mμ 10,900	275.5 mμ(s) 23,600	285 mμ 27,400	295 mμ(s) 19,400
1.15 mg./250 ml. 50% EtOH/H_2O	214.9 14,800	249 5,200	286 5,200		
1.04 mg./250 ml. 50% EtOH/$^N/_{10}$ NaOH	226 11,100	250 5,800	306 4,300		

This material gave negative tests for chlorine, fluorine and nitrogen. Tlc. of fresh solutions showed only one spot and some tailing in chloroform; solutions kept for a few hours always showed two spots:

$CHCl_3$ ν_{max} 1678 and 1695 cm.$^{-1}$(>C=O); nmr spectrum in deuterioacetone: δ 7.64 (5H, m.) and 6.61 ppm (1H, s.); also a broad peak (2H) of variable position. This latter peak dissappeared on addition of D_2O. These spectra were identical with those of an authentic specimen of phenylpyruvic acid.

Anal. Calcd. for $C_9H_8O_3$ (165.54): C, 65.85; H, 4.91; O, 29.14.

C, 66.46; H, 5.15; O, 28.16.

The liquid acid fraction was distilled to give two fractions (b.p. 110-120°/5 mm. and b.p. 120-130°/5 mm.) but these both deposited crystalline material on cooling. Filtration gave a liquid fraction which

was chromatographed on thick layer plates eluted with ethyl acetate. Removal of the main band gave 140 mg. of an oil which showed only one minor impurity on tlc and gave negative tests for nitrogen and fluorine, but warming with 10% sodium hydroxide and addition of acidic silver nitrate solution gave a slight precipitate of silver chloride indicating the presence of "labile" chlorine. Nmr spectrum in CCl_4: δ 7.42 (5H, m.); 11.42 (1H, s.); 3.56 (2H, s.) and 5.2 ppm(singlet corresponding to ~½ H). Comparison of this spectrum with those of phenylacetic acid and α-chlorophenylacetic acid indicated that both compounds were present in the mixture. Characterization of the main component was achieved by synthesis of its p-phenylazophenacyl derivative. A solution of the unknown acid (15 mg.) and p-phenylazophenacyl bromide (32) (30 mg.) in 1.5 ml. of 95% ethanol was refluxed for 2 hr. and cooled. The crude product crystallized from the ethanol: water mixture. Thick layer chromatography on silica gel in benzene: ether (95:5) gave 12 mg. (m.p. 75-83°) of crude product from the main band. After three recrystallizations from ethanol: water the material (m.p. 97-100°) did not depress the melting point of an authentic specimen of the phenylazophenacyl derivative of phenylacetic acid: [lit: 94-95° and 102-103°] .

(b) The neutral fraction (4 g.) contained 4 major and 2 minor components as shown by tlc eluted with chloroform. This material was chromatographed on thick layer plates, four bands being removed. The main band (1.42 g.) was chromatographed on thick layer plates in chloroform three times to remove persistent minor impurities. The final product (710 mg.) still showed an additional spot when run on tlc in petroleum ether: ethyl acetate (1:4). This material, which decomposed

to a black oil in a few days, gave a strong positive "labile chloride" test. Nmr spectrum in CCl_4: δ7.25 (5H, m.); 3.95 (2H, s.) and 3.76 ppm (2H, s.). The infrared and nmr spectra were identical with those of an authentic specimen of α-phenyl-α′-chloroacetone.

Anal. Calcd. for C_9H_9OCl (168.62): C, 64.14; H, 5.38; O, 9.49; Cl, 21.04.

Found: C, 64.36, H, 5.61: O, 12.42; Cl, 17.96.

In a similar reaction, except that the temperature of the reaction mixture was maintained at 60° for 3 hr., benzoic acid (identified by melting point and infrared spectrum) crystallized out from the crude acidic product.

Preparation of Authentic Specimens for Comparisons: α-Chlorophenylacetic Acid (31)

Phosphorous oxychloride was distilled out over a period of 3 hrs. from a mixture of mandelic acid (20 g, 130 mmoles.) and phosphorous pentachloride (50 g.). Distillation under reduced pressure (111-116°/16 mm.) gave the acid chloride (16.8 g, 70%). The acid chloride was poured into hot water and the resultant acid extracted with ether, m.p. 70-73° [lit (31): 70-71°].

α-Phenyl- α′-chloroacetone

A sample sufficient for nmr and infrared comparisons was synthesised by treatment of phenacetyl diazomethane with anhydrous hydrogen chloride in methanol and subsequent evaporation of the solvent.

p-Phenylazophenacyl Bromide (32)

Bromine (0.72 g.) was added to a stirred solution of p-phenylazoacetophenone (1.0 g.) and anhydrous aluminium chloride (10 mg.) in 4 ml. of chloroform at such a rate that the temperature remained below 20°. The crude product was purified by column chromatography on silica gel (25 g.) eluting with benzene-petroleum ether (b.p. 60-80°) (1:1): m.p. 100-104° [lit (32): 104-105] .

Preparation of Diphenyldiazomethane (33)

Benzophenone (25.2 g., 139 mmoles.) and 95% hydrazine (7.46 g., 223 mmoles.) were heated in a stainless steel bomb for 4 hrs. at 150°. The yield of crude crystalline hydrazone, m.p. 98-100°, was 27.2 g. (100%). Benzophenone hydrazone (19.6 g., 100 mmoles.) and yellow mercuric oxide (22 g.) in 100 ml. of petroleum ether (b.p. 60-80°) were shaken for 24 hrs. at room temperature in a glass pressure bottle. Work-up gave diphenyldiazomethane in 36-75% yields.

Reaction of Perchloryl Fluoride with Diphenyldiazomethane

A solution of diphenyldiazomethane (7.0 g., 36 mmoles.) in 210 ml. of dry dimethyformamide was treated with perchloryl fluoride (3.2 g., 30 mmoles.) over 45 min. The temperature of the reaction mixture was maintained at 2-4°C. throughout as the reaction was exothermic and accompanied by vigorous evolution of nitrogen. The end point was marked by cessation of nitrogen evolution and decolourization of the purple solution. After purging the solution of excess perchloryl fluoride the solution was poured into 300 ml. of water and extracted with five 100-ml. portions of ether. Work-up in the usual manner afforded 4.0 g. (61%) of a

pale yellow oil which slowly solidified. The crude material was distilled (b.p. 120°/1 mm.) to give 2.8 g. (42.7%) of pure benzophenone (m.p. 40-45°) whose infrared spectrum was identical with that of an authentic sample, $\nu_{max}^{CCl_4}$ 1670 cm^{-1} (>=0).

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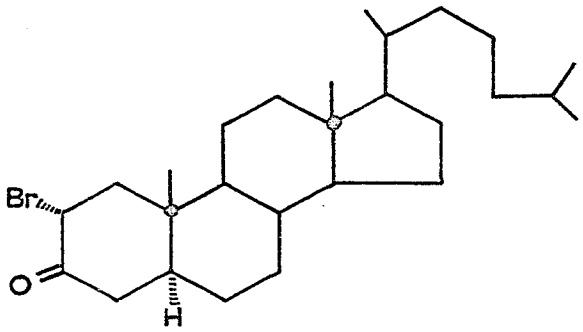
Appendix II

Reductive Dehalogenation of α-Halo Ketones by Substituted Pyridines

Introduction

Dehydrohalogenation of α-halo ketones with various pyridines has been widely used to introduce unsaturation into conjugation with carbonyl groups; for a number of references see (8). The ordinary course of this reaction, dehydrohalogenation and displacement, often occurs with concomitant reduction and double bond rearrangement. In many cases the presence and extent of double band migration and of reduction are questionable since the halo ketone was not always free of unhalogenated or isomeric ketone. This is particularly evident in the literature on the dehydrohalogenation of A/B-trans-3-keto steroid derivatives, in particular 2α-bromocholestan-3-one.

Refluxing a solution of 1 in pyridine has been reported to give only the pyridinium salt 2 (1)(2); analogous experiments using γ-collidine have been reported to afford, Δ^1-cholesten-3-one(3)(76%(3), Δ^1-cholesten-3-one(3)(74%) together with a small unspecified amount of cholestan-3-one(4)(4) and finally a mixture of Δ^1-cholesten-3-one(3)with Δ^4-cholesten-3-one only(6)(5). Djerassi isolated both the Δ^4- and Δ^1-ketones from the reaction of γ-collidine with the bicyclic analogue 5 of 2α-bromocholestan-3-one (6). In fairness to these authors it should be pointed out, that detection of the reduction product, cholestan-3-one, in the presence of the $^1\Delta$- and Δ^4-keto analogues would be very difficult in the absence of tlc or glc techniques, particularly as the maximum weight of cholestan-3-one found in the present work was only fifteen



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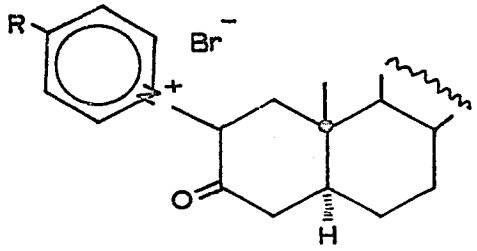

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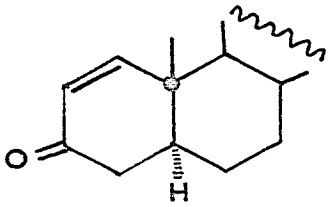

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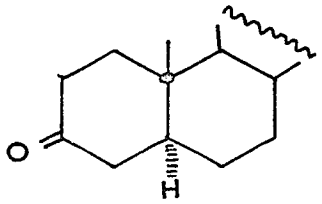

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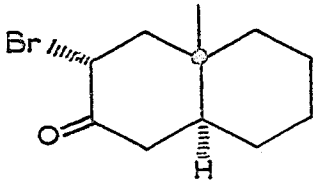

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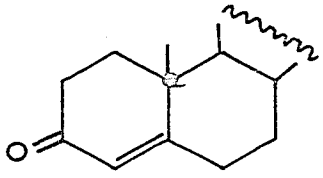

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percent of the total ether soluble crude product. Further discrepancies are evident in the literature when the reactions of 2,4-lutidine and 2,6-lutidine with 2α-bromocholestan-3-one (1) are compared. Inhoffen (7) has reported that the former dehydrohalogenates the bromoketone to Δ^1-cholesten-3-one while the latter gives a pyridinium salt in unspecified yield. These results are the opposite of expectation if the products from the γ-collidine reaction, as compared to those from pyridine, are considered to be a result of hindrance by the 2- and 6- methyl groups to approach of the nitrogen.

Warnhoff (8), using pure methyl substituted pyridines and tlc analysis, was able to resolve all these inconsistencies and to delineate possible pathways to the reduction, displacement and dehydrohalogenated products. It was shown that 2,6-lutidine, purified *via* its crystalline picrate gave, after 14 hr. reflux, a 94% yield of water soluble 2,6-lutidine hydrobromide whereas β-and γ-picoline under similar conditions, gave 82 and 88% yields respectively of water *insoluble* picolinium salt. 2,6-Lutidine, as obtained commercially, is nearly always contaminated with β-and γ-picoline; thus it seems probable that Inhoffen's compound was derived from these. The reaction of 2,4-lutidine with 2α-bromocholestan-3-one gave, as expected, pure water soluble 2,4-lutidine hydrobromide (95%).

Analysis of the ether soluble material showed that in each case it was a mixture of Δ^1-cholesten-3-one, Δ^4-cholesten-3-one and cholestan-3-one except that in the pyridine example no Δ^4-cholesten-3-one was detected. Previous reports (1-7) of the isolation of only one or two of these compounds may be ascribed to loss during

purification.

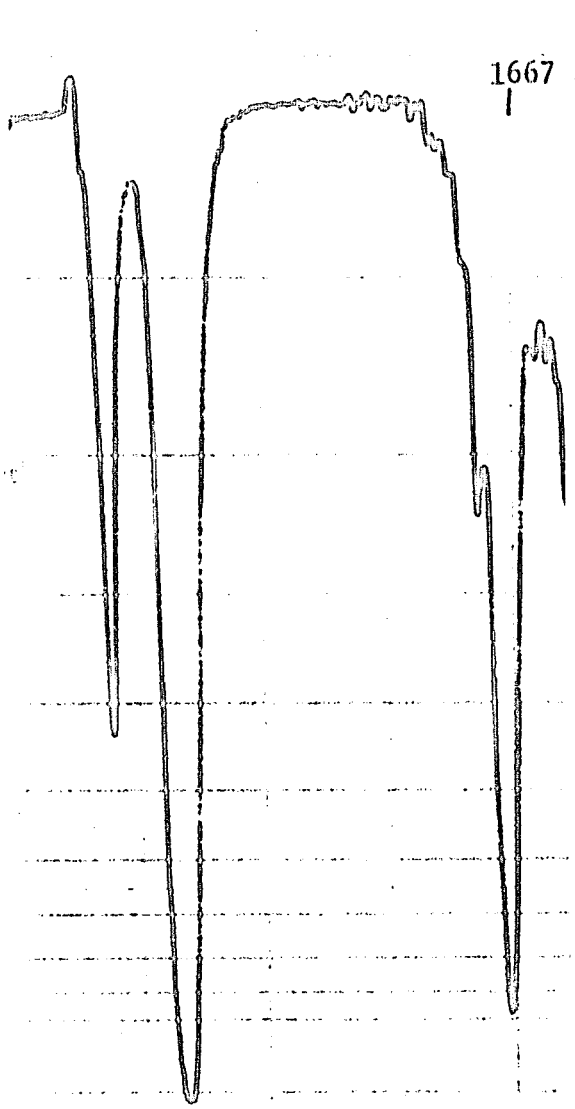
Quantitative analysis for the components in the ether soluble fraction was seriously hampered by two factors: cholestan-3-one cannot be fully resolved from Δ^1-cholestene-3-one by tlc on silica gel or alumina, and the 2α-bromocholestan-3-one, prepared and purified by the long used method (9) was discovered to contain about 12% of cholestan-3-one when the, then novel, technique of tlc was applied after most of the work had been completed. Recrystallization is ineffectual in removing the cholestan-3-one and in addition the capillary melting point of the impure bromo ketone is the same as that of pure 1 making sharpness of melting point an unreliable criterion of purity in this case. The presence of this necessarily introduces an area of uncertainty into the results, which were obtained from thin layer chromatography and ultraviolet spectroscopy as follows: the amount of Δ^4-cholesten-3-one was determined by comparing the intensity of the Δ^4-ketone spot with a set of spots of authentic known ketone content; taking the Δ^4-ketone concentration into account the Δ^1-cholesten-3-one content could be calculated from the ultraviolet spectrum knowing the extinction coefficients of the pure Δ^1- and Δ^4-ketones. The remainder of the product was taken to be cholestan-3-one after correcting for the amount in the starting material. Unfortunately, subsequent experience indicated that quantitative analysis of the Δ^4-cholesten-3-one based on tlc spot intensity is not very reliable, an error of as much as 10% occurring in several cases, as revealed by isolation procedures. The estimation of the cholestan-3-one content was therefore liable to cumulative error.

In a subsequent paper, Nace and Iacona (10) repeated one of the

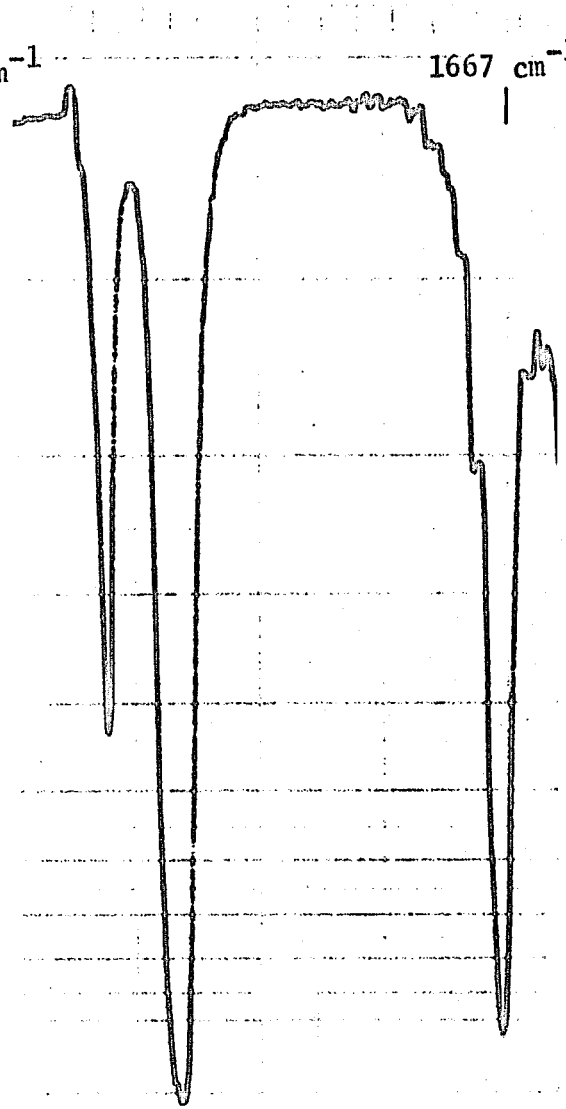
reactions of pyridines with 2α-bromocholestan-3-one, that involving γ-collidine. 2α-Bromocholestan-3-one,purified by chromatography on silica gel, and showing only one spot on tlc, was used for this experiment. It was reported that the ether soluble fraction, obtained in 80% yield, was a mixture of Δ^1-cholesten-3-one (65%), Δ^4-cholesten-3-one (15%) and less than 1.6% of cholestan-3-one. On the basis of these results they claimed that the reduction product amounted to less than 2% of the total and concluded that "the reduction reaction is not significant in the reaction of bromo ketones with γ-collidine."

However, these values were determined by a glc procedure in which the cholestan-3-one appeared as a shoulder at the base of the Δ^1-cholesten-3-one peak, and therefore, in the absence of precise calibration studies, the error in analysis of small quantities may be significant. Although the yields (20-46%) of cholestan-3-one reported in Warnhoff's (8) earlier work were admitted to be liable to cumulative error, it was felt certain that more than 1.6% of 6 was formed in the γ-collidine reaction. Support for this contention comes from a comparison of the carbonyl infrared absorption of the fraction containing Δ^1-cholesten-3-one and cholestan-3-one, obtained by tlc of the crude product, with the carbonyl infrared absorption of known synthetic mixtures. The saturated ketone gives rise to a carbonyl absorption band at 1720cm^{-1} which is clearly resolved from that of the unsaturated ketone at 1685cm^{-1} even at cholestan-3-one concentrations of 5%. Analysis by this method indicated that the crude product contained 5-10% of cholestan-3-one (Fig. 1). Therefore, to resolve this discrepancy and to put all the quantitative data on a more rigorous footing, it was decided to repeat the

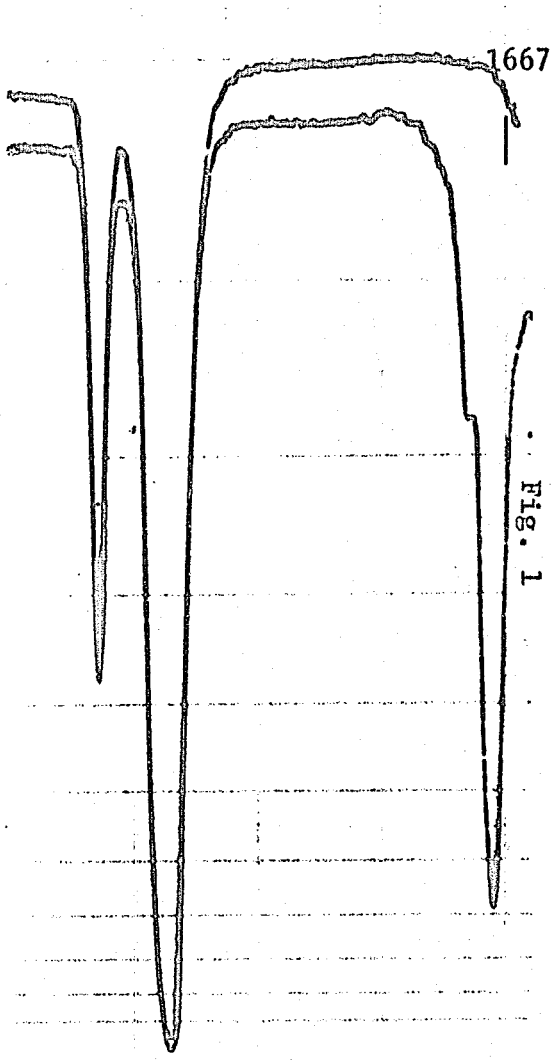
Infrared Spectra of Mixtures of Cholestan-3-one and Δ^1-Cholesten-3-one



Synthetic mixture of 10% Cholestan-3-one in Δ^1-Cholesten-3-one.



Synthetic mixture of 5% Cholestan-3-one in Δ^1-Cholesten-3-one.



Zone containing cholestan-3-one and Δ^1-cholesten-3-one as removed from the plate.

Fig. 1

reactions of substituted pyridines with 2α-bromocholestan-3-one determining the amount of reductive debromination by isolation of the cholestan-3-one formed.

Discussion

A definitive analytical procedure requires isolation of the pure components of the mixture and it was with this in mind that an analytical scheme was formulated. As Δ^4-cholesten-3-one could be easily separated from Δ^1-cholesten-3-one and cholestan-3-one by thick layer chromatography on silica gel, eluting with ether: benzene (4:96), there only remained the problem of isolating the cholestan-3-one from the Δ^1-ketone. The most obvious approach involved isolation of the mixture of saturated and Δ^1-ketones, ultraviolet analysis for the Δ^1-cholesten-3-one, conversion of the unsaturated component to more polar products by ozonization and finally, isolation of the surviving cholestan-3-one by thick layer chromatography. This procedure, under suitably controlled conditions, was used successfully.

The conditions for the ozonization of the mixture of cholestan-3-one and Δ^1-cholesten-3-one are important. The mixture to be ozonized was dissolved in ethyl acetate; after cooling to -78°, a controlled flow of ozone was passed into the solution for exactly eight minutes after which, a solution of potassium iodide was added to destroy the ozone remaining in solution. Ozone treatment for eight minutes at -78° was found to be sufficient to convert the unsaturated material to more polar products while not attacking the cholestan-3-one to any significant extent. Failure to destroy the excess ozone at -78°, and longer reaction times resulted in attack on the cholestan-3-one. Thick layer chromatography gave a clean separation of cholestan-3-one when two thin layer control plates were run on either side of the thick layer plate in the same tank. Charring of the monitor plates gave the position of the cholestan-3-one band. In one case the thick layer plate was developed in iodine vapour

for 30-60 seconds and the recovered material washed with sodium thiosulphate solution to remove residual iodine. The yields of cholestan-3-one were approximately the same using either method.

Thin layer chromatography revealed that the bands corresponding to Δ^1-cholesten-3-one and Δ^4-cholesten-3-one contained a small amount of each as contaminant in the other. A more exact ultraviolet analysis was carried out by considering the ultraviolet absorption at two different wavelengths; this allowed the contribution of each unsaturated ketone toward the observed absorption curve to be calculated. (The method was checked with synthetic mixtures).

The results, which are briefly summarized in Table I, are in general agreement with those determined earlier (8). The difference between the sum of 3 + 4 + 6 and 100% was accounted for by other products not examined and incomplete recovery from thick layer chromatograms. Examination of the baseline, from thick layer chromatography of the crude ether soluble product obtained in the α-picoline reaction, showed the presence of at least four components.

The yield of cholestan-3-one is quoted as having an upper and lower limit in the γ-collidine case; the upper value is the yield of crude cholestan-3-one containing some impurities from the ozonization while the lower value represents the yield of pure recrystallized product; the true yield is probably about 10%.

The most significant result from this series of reactions is that, although the yields of cholestan-3-one are considerably less than previously reported (8) they are substantially greater than 2% as reported by Nace and Iacona. In addition these yields may be on the low side as

Table 1

Products from Reaction of 2α-Bromocholestan-3-one with Pyridines

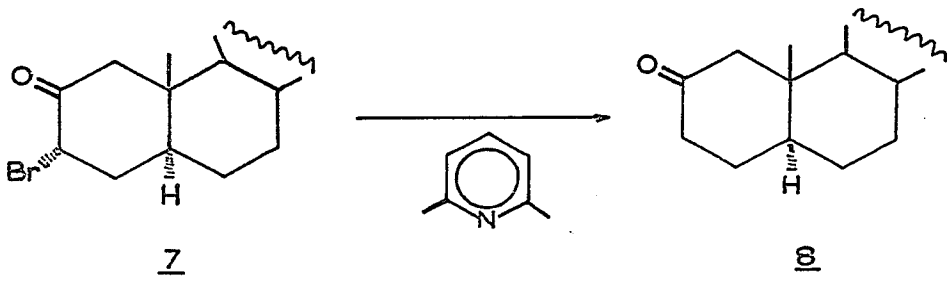
Amine	Normal bp, °C	Pyridinium salt, %		Amine.HBr %		Ether soluble frac., %		Cholestan-3-one 4, %		Δ^1-Ketone 3, %	Δ^4-Ketone 6, %
Pyridine	115	-	(82)[a]	Not. detm.		-	(15)	-	(10)	- (4.7)	- (0)
γ-Picoline	145	-	(88)	-	(9.3)	-	(12.6)	-	(2)	- (9)	- (1.5)
β-Picoline	144	80	(82)	12	(13)	14	(14)	<1.8	(2)	9 (10)	3 (2)
α-Picoline[b]	129	10	(-)	92	(-)	87	(-)	<3.5	but real	26 (-)	35 (-)
2,4-Lutidine[b]	157	0	(0)	97	(95)	97	(100)	trace	(20)	37 (55)	26 (25)
2,6-Lutidine[b]	144	0	(0)	89	(94)	89	(100)	7	(46)	36 (24)	40 (30)
γ-Collidine[b]	171	0	(0)	99	(103)	98	(99)	5.8-14.7[c]	(37)	41 (38)	33 (25)
Pyrolysis of γ-Picolinium salt						94	(89)	9	(29)	30 (15)	33 (44)

[a]All values given in parentheses are those taken from the earlier work described in the reference (8).

[b]The difference between the sum of 6 + 3 + 4 and 100% is accounted for by pyridinium salts, other products formed in the reaction which were not examined, and incomplete recovery from thick layer chromatograms.

[c]The higher figure is the crude 4 containing some impurities from the ozonization reaction; the lower figure is the yield of pure 4. The true yield of 4 will lie somewhere in between and is estimated to be about 10%.

cholestan-3-one is slightly attacked by ozone despite the carefully controlled conditions. The formation of a reduction product in the reaction of 2α-bromocholestan-3-one with 2,6-lutidine and γ-collidine is not without precedent. The most relevant example is the reaction of 3α-bromocholestan-2-one(7)with 2,6-lutidine (16) which gave a 28% (pure by tlc) yield of cholestan-2-one (8). An attempt to debrominate 1a-bromo-cis-hexahydrofluorenone (11)(9)with refluxing γ-collidine resulted in formation of 31% of the saturated ketone 10. The failure of 9 to undergo a simple E2 elimination was ascribed to the equatorial position of the bromine, a conformation in which no adjacent hydrogen is trans



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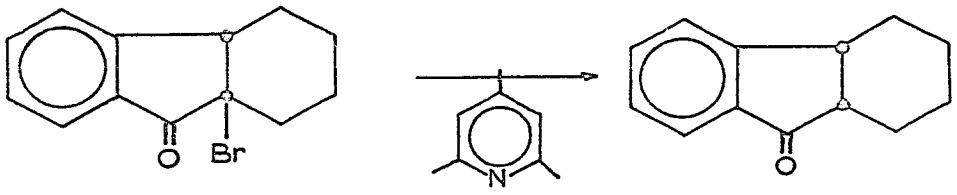

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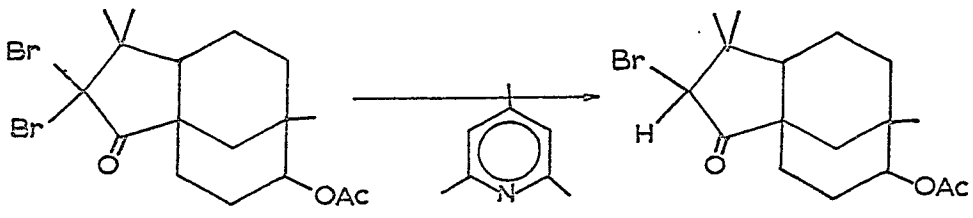

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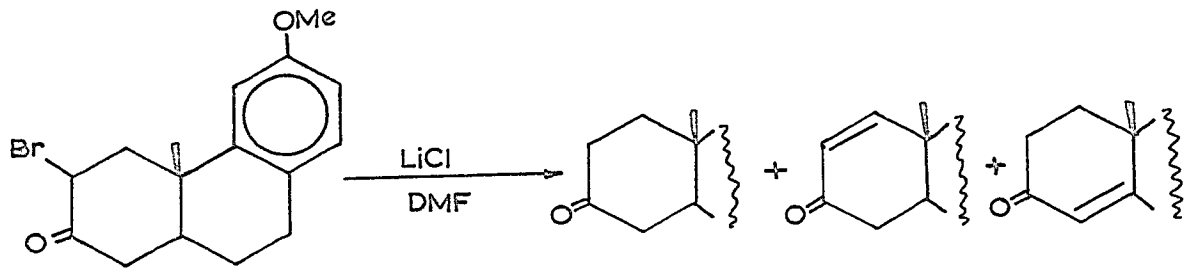
coplanar with respect to bromine. Reductive debromination of the caryophyllene derivative 11 (12) also occured in 22% yield with refluxing γ-collidine. The mechanism by which the saturated ketone is formed is not immediately obvious expecially as the oxidation state of the bromide is left unchanged in the overall reaction. A reasonable mechanism would be reversible formation of a bromopyridinium ion and the enolate anion of cholestan-3-one. Rebromination of the cholestan-3-one could give both 2α- and 4α-bromocholestan-3-one while bromination of the monobromide could give mixtures of dibromides. This mechanism would be most convenient in that it would not only provide an explanation for the saturated ketone, but also for the Δ^4-cholesten-3-one; the latter would arise, not by rearrangement, but simply by dehydrobromination of 4α-bromocholestan-3-one. This mechanism is unlikely on several grounds: the yield of γ-collidine hydrobromide is almost quantitative and no products have been found which would result from elimination of two molecules of hydrogen bromide although this statement must be qualified by the observation that some highly polar products were found in the α-picoline reaction whose genesis is unknown. Further chemical evidence against the 'bromopyridinium ion' mechanism is provided by the reaction of γ-collidine with 2α-bromocholestan-3-one in the presence of β-naphthol, a bromine acceptor. If an equilibrium between bromopyridinium ion and the enolate anion of cholestan-3-one is being set up then the addition of a positive bromine trapping agent will favour formation of cholestan-3-one by removal of the positive bromine from the bromopyridinium ion. Analysis of the product from such a reaction showed no change in the cholestan-3-one yield relative to reaction in the absence of β-naphthol. The possibility that

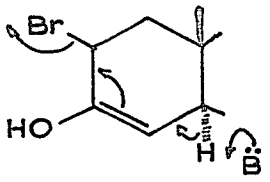
1-bromo-2-naphthol might be debrominated by γ-collidine as soon as it was formed, was excluded by showing that it survived under the reaction conditions used to dehydrobrominate the bromo ketone.

It seems that the Δ^4-cholesten-3-one arises by direct rearrangement from 2α-bromocholestan-3-one. There could not have been enough 4α-bromocholestan-3-one present as an impurity (8) to give rise to 25-40% yields of Δ^4-cholesten-3-one, and both Δ^1-and Δ^4-cholesten-3-one are stable under the reaction conditions as expected; each ketone could be recovered in 97% yield after refluxing in γ-picoline with added γ-picolinium salt 2 (R=Me) and γ-picoline hydrobromide (8). As pointed out previously, it is unlikely that the Δ^4-cholesten-3-one arises *via* bromination of cholestan-3-one by bromopicolinium ion to give 4α-bromocholestan-3-one. Other examples in which a rearranged elimination product is formed are known. Apart from the example mentioned earlier of the conversion of 1 to a mixture of 3 and 6 only (6), rearranged elimination products have been observed using a mixture of lithium chloride in dimethylformamide. The phenanthrene derivative 15 gives the saturated ketone 16 as well as the normal 17 and rearranged 18 unsaturated ketones (13). It is postulated



15 16 17 18

that the rearranged product could arise via a vinylogous dehydrohalogenation of the enol, 19 but there are other possibilities: e.g. formation of a zwitterionic intermediate 19a.



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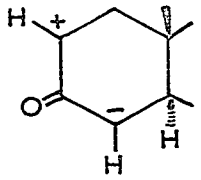

19a

Other examples are the treatment of 1-bromo-A-norcholestan-2-one with lithium chloride and dimethylformamide to give Δ^3-A-norcholesten-2-one in 92% yield (14), and the reaction of 2α-bromocholestan-3-one with dimethylsulphoxide to give saturated ketone, Δ^1- and Δ^4-ketone and several oxidation products (10).

The product analyses amply demonstrate the importance of the pyridine structure. One α-methyl group drastically reduces the amount of quaternary salt formation in favour of elimination. Further methyl substitution has no great effect unless the resulting pyridine has two α-methyl groups, at which point the yield of reduction product becomes significant and no quaternary salt is formed. These results are probably a reflection of the increased steric hindrance of nitrogen approach to the sites at which displacement or elimination is initiated.

It can be concluded unequivocally that in those α-halo-ketones where displacement or dehydrohalgenation by an α-substituted pyridine is retarded for stereochemical reasons, reductive debromination becomes a significant product forming pathway.

Experimental

2α-Bromocholestan-3-one. (9)

A solution of bromine (13.5 g., 85 mmoles.) and 18 drops of 48% hydrobromic acid in 60 ml. of glacial acetic acid was added slowly to a stirred solution of cholestan-3-one (30 g., 75 mmoles) in 80 ml. of glacial acetic acid maintained at 25°C or below. The bromoketone, which crystallized during the addition, was collected and washed. Recrystallization from ethanol: acetone (5:1) yielded 27.5 g, (76%) m.p. 166-167° [lit. (9) m.p. 168-169] . Tlc on silica gel plates eluted with ether: benzene (5:95) indicated the presence of cholestan-3-one as an impurity. Pure 2α-bromocholestan-3-one was obtained by chromatography of 2.0 g. of crude bromoketone on a 25 mm. diameter column of silica gel (100 g.) eluting with benzene: petroleum ether (b.p. 30-60°) mixtures (1:3 to 1:1).

The degree of purity was assessed by tlc comparison with a set of synthetic mixtures of known cholestan-3-one content run on one plate. Using a concentration of 200γ/spot, 0.5% of cholestan-3-one could be detected reliably.

Substituted Pyridines

The purity was ascertained from their nmr spectra. 2,6-Lutidine and α-and β-picoline were of greater than 99% purity, but it was necessary to purify γ-collidine and 2,4-lutidine *via* their hydrobromide or hydrochloride salts (8). Anhydrous hydrogen chloride was passed into a solution of γ-collidine in 600 ml. of petroleum ether (b.p. 60-80°) until the solution became solid. After filtration, the filtrate was again treated with

hydrogen chloride until no more precipitate appeared. The combined pink solid (90 g.) was recrystallized from methanol: ethyl acetate to give 59 g. (m.p. 294-296°). The pure γ-collidine hydrochloride was dissolved in 400 ml. of distilled water and treated with 100 ml. of 10% aqueous sodium hydroxide solution. Vacuum distillation of the ethereal extract afforded 37.2 g. of pure γ-collidine (b.p. 60-61/12 mm.). 2,4-Lutidine was purified via a similar procedure using the hydrobromide salt.

Reaction of Cholestan-3-one with Ozone

Cholestan-3-one (10 mg. pure by tlc) was dissolved in 25 ml. of redistilled ethyl acetate and, after cooling to -78°C, treated with ozone for 8 min. At the end of this time 10 ml. of 25% aqueous potassium iodide solution was added and the solution shaken vigorously until the temperature rose above the freezing point. After washing the organic solution with 25 ml. of 25% aqueous sodium thiosulphate solution and water, drying and evaporation gave cholestan-3-one which was assessed for purity by tlc. Cholestan-3-one (Rf. 0.24 in ether: benzene(3:97))recovered from a 4 min. treatment with ozone showed no evidence of decomposition while that from an 8 min. treatment showed a trace of decomposition product with Rf. 0.09 and at the baseline in the same solvent.

Reaction of 2α-Bromocholestan-3-one with γ-Collidine

2α-Bromocholestan-3-one (3.209 g., 6.9 mmoles.) in 10 ml. of γ-collidine was refluxed for 18 hr. (Oil-bath 195-200°). After cooling and addition of 75 ml. of ether, filtration afforded crystalline γ-collidine hydrobromide (1.43 g., 98%). The ethereal solution was washed with two 25-ml. portions of 10% sulphuric acid to remove γ-collidine,

dried and evaporated to give 2.588 g. of a brown gum (98%), which was dissolved in carbon tetrachloride and made up to 10 ml. volumetrically. The stock solution (1 ml.) was thick layer chromatographed in ether: benzene (4:96). Separation of the two zones yielded 160 mg. of mainly Δ^1-cholesten-3-one + cholestan-3-one and 68 mg. of mainly Δ^4-cholesten-3-one. Calculations from the ultraviolet absorptions of these zones at 220 and 250 mμ and from those of authentic specimens, Δ^1-cholesten-3-one: λ_{max}^{EtOH} 230 mμ (ε11,050) and Δ^4-cholesten-3-one: λ_{max}^{EtOH} 241 mμ (ε16,500) showed that the Δ^1-cholesten-3-one band contained 64% Δ^1-cholesten-3-one and 11.3% of Δ^4-cholesten-3-one while the Δ^4-cholesten-3-one band actually contained 76% Δ^4-cholesten-3-one and 9% Δ^1-cholesten-3-one. Full data for these calculations are tabulated in Tables 2 and 3.

A solution of 1 ml. of the stock solution in 20 ml. of redistilled ethyl acetate was cooled to -78° (acetone: solid carbon dioxide) and ozonized for 8 min. At the end of this time the reaction was quenched by addition of 10 ml. of 25% aqueous potassium iodide solution. After shaking the mixture until it reached room temperature, it was washed with 25 ml. of 25% aqueous sodium thiosulphate solution, separated and dried over magnesium sulphate. Filtration and evaporation left 306 mg. of amber gum which was separated on thick layer plates developed in ether: benzene (4:96). The position of the cholestan-3-one was ascertained by charring monitor plates run in the same tanks as the thick layer plates. White, crystalline impure cholestan-3-one (38 mg., 14.7%), m.p. 100-112°, was recovered. Two recrystallizations from 95% ethanol gave 11 mg. (4%) of pure cholestan-3-one, m.p. 126-128°, undepressed on admixture with authentic cholestan-3-one, m.p. 129-130°. Tlc of the recrystallized

product gave a single spot with the same Rf. as authentic cholestan-3-one.

Reaction of 2α-Bromocholestan-3-one with γ-Collidine (E.W.W.)

The bromo ketone 1 (1.00 g., 2.15 mmoles.) was refluxed with 4 ml. of purified γ-collidine for 12 hr. to give a pale amber solution which, after cooling, dilution with ether and filtration, afforded 430 mg. (99%) of γ-collidine hydrobromide. After removing the γ-collidine by extraction with dilute hydrochloric acid, the ethereal filtrate was evaporated to give 810 mg. (98%) of amber-coloured, partly crystalline product. Thick layer chromatography of 358 mg. of the crude product on ethyl acetate: petroleum ether (b.p. 60-80) (15:85) yielded 223 mg. (62% of total product) of a mixture of 3 and 4 and 118 mg. (33% of total product) of 6. Part of the 3 and 4 zone (213 mg.) was rechromatographed on thick plates and developed in reagent grade chloroform (contained 0.75% of ethanol). The zone just ahead of the blue band under ultraviolet light was separated and extracted to yield 20.1 mg. (5.8% of total product) of crystalline cholestan-3-one whose tlc spot showed only the faintest trace of 3. The blue zone yielded 193 mg. of Δ^1-cholesten-3-one which still contained cholestan-3-one.

Reaction of 2α-Bromocholestan-3-one with γ-Collidine in the Presence of β-Naphthol

2α-Bromocholestan-3-one (247 mg., 0.53 mmole.) and 171 mg. (1.19 mmoles) of recrystallized β-naphthol were refluxed in 5 ml. of γ-collidine for 18 hr. Dilution with 75 ml. of ether and filtration gave γ-collidine hydrobromide (93 mg., 100%). After washing with 10% aqueous

sodium hydroxide solution and 10% hydrochloric acid to remove β-naphthol and γ-collidine, the ethereal extract was evaporated to give 198 mg. (100%) of product. Ozonization and isolation of the cholestan-3-one using the procedure previously described gave 22 mg. (11%) of impure cholestan-3-one. Tlc in ether: benzene (4:96) showed cholestan-3-one (Rf. 0.22) and impurities at Rf. 0.1, 0.05 and the baseline.

Reaction of 1-Bromo-2-naphthol with γ-Collidine

A solution of 1-bromo-2-naphthol (14.6 mg., 0.065 mmole.) in 2 ml. of γ-collidine saturated with γ-collidine hydrobromide was refluxed for 18 hr. under nitrogen. The resulting pale amber solution was cooled, diluted with ether and extracted with two 5 ml. portions of 10% sulphuric acid. After drying, evaporation of the ethereal solution yielded 15.2 mg. of an oil. Analysis by tlc run in ether: benzene (5:95) showed that most of the starting material remained unchanged though a little β-naphthol had been formed.

Cholestan-3-one Isolation: Iodine as Indicator

Thick layer chromatography of cholestan-3-one (75 mg.) in ether: benzene (5:95) and development in iodine vapour until a faint yellow band appeared (30-60 sec.) gave cholestan-3-one (60 mg.) with m.p. 128-130° (Authentic 129-130°) .

Ozonization of a sample of crude product from the γ-collidine reactions (868 mg.), in ethyl acetate at -78° for 8 min. gave, after the usual work up procedure a crude product which was separated by tlc. The ethereal extract of the cholestan-3-one band, as revealed by iodine vapour, was washed with 10 ml. of 10% aqueous sodium thiosulphate

solution and, after drying, evaporated to give 96 mg. of crude cholestan-3-one. Two recrystallizations from acetone gave 18 mg. (2.0%) of small colourless prisms, m.p. 125-127°, Rf. 0.24 in ether: benzene (6:94).

Reaction of 2α-Bromocholestan-3-one with 2,6-Lutidine

2α-Bromocholestan-3-one (614 mg., 1.32 mmoles.) in 10 ml. of 2, 6-lutidine was refluxed for 22 hr. under a nitrogen atmosphere. Dilution with 75 ml. of ether and filtration gave 219 mg. (89%) of 2, 6-lutidine hydrobromide. Evaporation of the ethereal solution, after extraction with two 20-ml. portions of a 10% sulphuric acid solution, left a pale yellow solid (451 mg, 89%) which was analysed as described for the γ-collidine reaction.

Reaction of 2α-Bromocholestan-3-one with 2,4-Lutidine

2α-Bromocholestan-3-one (545 mg., 1.17 mmoles.) in 5 ml. of 2, 4-lutidine was refluxed for 5.5 hr. Dilution with ether and filtration gave 213 mg. (97%) of 2, 4-lutidine hydrobromide. Evaporation of the filtrate after acid extraction left 437 mg. (97%) of dark greenish brown gum which was analysed as described for the γ-collidine reaction.

Reaction of 2α-Bromocholestan-3-one with α-Picoline

2α-Bromocholestan-3-one (1.592 g., 3.43 mmoles.) and 10 ml. of α-picoline were refluxed for 19 hr. under nitrogen. Addition of 100 ml. of ether: water mixture (3:1) followed by filtration afforded 194 mg. (10%) of the water insoluble α-picolinium salt of 2α-bromocholestan-3-one, m.p. 332-334° dec. (when placed on the hot stage at 185°). The salt was shown to be different from the analogous pyridinium salt by mixed melting point (325-332°) and from the β-and γ-picolinium salts by nmr. The

filtrate was separated and the aqueous layer combined with that from a further aqueous wash of the ethereal layer. Acidification and addition of a 10% aqueous silver nitrate solution precipitated silver bromide, (592 mg.) from which the yield of α-picolinium bromide was calculated to be 92%. The ether soluble product (1.148 g., 88%) was isolated and analysed as described for the γ-collidine reaction.

Reaction of 2α-Bromocholestan-3-one with β-Picoline

A solution of 2α-bromocholestan-3-one (2.788 g., 6.00 mmoles.) and 10 ml. of β-picoline was refluxed for 3 hr. and, after dilution with 75 ml. of ether, filtered to give 2.969 g. of crystals which were triturated with water and filtered again. There remained 2.680 g. (80%) of the water-insoluble β-picolinium salt of 2α-bromocholestan-3-one. Evaporation of the aqueous filtrate gave 123 mg. (12%) of crystalline β-picolinium hydrobromide. The ether soluble product (326 mg, 14%) was isolated and analysed as described in the γ-collidine reaction.

Pyrolysis of the γ-Picolinium salt of 2α-Bromocholestan-3-one

Pyrolysis of 259 mg. (0.48 mmole.) of pure salt was carried out in a 1cm. diam. pyrex tube at 300-320° (0.02mm). Complete decomposition occurred within 4 hr. (residue 1.7 mg.). The sublimate consisted of 24.9 mg. of starting material and 151.9 mg of ether-soluble product which was analysed as in the γ-collidine reaction.

Table 2

Analysis of Δ^1-cholesten-3-one band by Ultraviolet*

Base	collidine	2,6-lutidine	2,4-lutidine	α-picoline	β-picoline	pyrolysis
Absorb. @ 220 mμ	0.528	0.424	0.503	0.438	0.520	0.442
Absorb. @ 250 mμ	0.290	0.177	0.199	0.187	0.208	0.182
Wt. taken for UV	2.96	2.13	2.25	2.41	2.30	2.25
Wt. Δ^1- mg./100 ml.	1.89	1.67	2.02	1.72	1.95	1.76
Wt. Δ^4- mg./100 ml.	0.33	0.07	0.05	0.09	0.23	0.07
Δ^1-as % of band	64	79	90	71.6	90	78.5
Δ^4- as % of band	11.3	3.4	2.0	3.7	2.39	3.0
Wt. material recov. from Δ^1-band	1.601 g.	189.5 mg.	167.3 mg.	451.5 mg.	226 mg.	60.5 mg.
Total wt. / Δ^1-prod.	1.084 g.	184 mg.	164 mg.	368 mg.	206.5 mg.	48 mg.
Total wt. / Δ^4-prod.	690 mg.	200 mg.	117.4 mg.	499 mg.	73.4 mg.	55.3 mg.

Table 3

Analysis of Δ^4-cholesten-3-one band by Ultraviolet*

Base	collidine	2,6-lutidine	2,4-lutidine	α-picoline	β-picoline	pyrolysis
Absorb @ 220 mμ	0.274	0.405	0.332	0.315	0.337	0.380
Absorb @ 250 mμ	0.456	0.641	0.552	0.675	0.591	0.698
Wt. taken for UV	1.63	2.25	1.89	2.05	2.08	2.40
Wt. Δ^1- mg./100 ml.	0.153	0.310	0.183	zero	0.106	0.024
Wt. Δ^4- mg./100 ml.	1.23	1.72	1.50	1.98	1.62	1.96
Δ^1- as % of band	9.4	13.8	9.7	zero	5.1	1.25
Δ^4- as % of band	75.5	76.5	79.5	96.0	78.0	81.0
Wt. (mg.) of material recov. from Δ^4-band	677	251	144	479	87.6	66.5

* Note: 'Wt. taken for UV' is in mg./100 ml. of 95% EtOH.
'Wt. Δ^1-mg./100 ml.' refers to the wt./100 ml. 95% EtOH as calculated from the absorbance figures.
Wt. material recovered from Δ^1-band refers to the wt. recovered by removal of the appropriate band from the thick layer plate in each reaction.

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