INFORMATION TO USERS

This manuscript has been reproduced from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps.

ProQuest Information and Learning
300 North Zeeb Road, Ann Arbor, MI 48106-1346 USA
800-521-0600

SC

NEIGHBOURING DOUBLE BOND PARTICIPATION

IN

EXO 5-HYDROXYBICYCLO[2.2.2] OCT-2-ENE TOSYLATE

BY

S. O'FARRELL

A thesis submitted in partial fulfillment

of the requirements of the degree of

Master of Science

Department of Chemistry

Faculty of Pure and Applied Science

University of Ottawa

Ottawa, Canada

August 1, 1962

Candidate	Supervisor
S. O'Farrell	R. R. Fraser, M.Sc., Ph.D.

PREFACE

This work was undertaken to see if direct participation, in solvolysis reactions, of a β-γ double bond could be observed in the bicyclo[2.2.2]octene system. Such a phenomenon had previously been observed in the bicyclo[2.2.1]heptene system by Winstein, who used the difference in rates of solvolysis of isomeric tosylates and halides as a measure of double bond participation. The aim of the present work was the preparation and acetolysis of the isomeric 5-hydroxybicyclo-[2.2.2]oct-2-ene tosylates. Participation of the double bond in this system was investigated by means of kinetic measurements of the acetolysis and analysis of the products.

The author wishes to thank Dr. R. R. Fraser for his direction of this work, and to express to the National Research Council his appreciation of the grant which supported it.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

The synthesis of the previously unknown exo-5-hydroxybicyclo [2.2.2]oct-2-ene is described, and its behaviour under solvolysis in acetic acid is reported. The end product of the acetolysis is unrearranged and the rate is the fastest yet measured in the bicyclo [2.2.2]octane series. This result supports the theory of homoallylic resonance in the intermediate transition state for the solvolysis reaction.

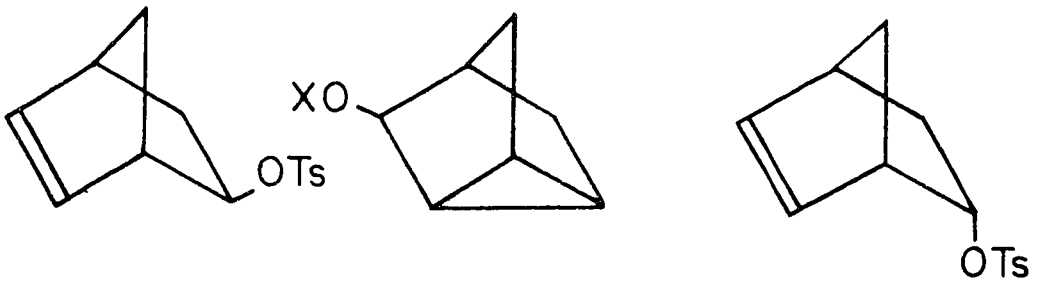
The construction of a preparative-scale vapour-phase chromatograph is described.

INTRODUCTION

The stabilization of a carbonium ion by a β-γ double bond was first noted by Winstein in the course of an investigation into the cholesteryl and cholestanyl systems in 1949 (1, 2). Under certain conditions the solvolysis of cholesteryl tosylate resulted in a compound, the so-called i-ether, possessing a cyclopropyl ring. The solvolysis of cholesteryl tosylate proceeded at a rate one hundred times that of the saturated cholestanyl tosylate, and this acceleration was ascribed to the driving force, or lowering of $\Delta F^{\ddagger}$, produced by the participation of the double bond. The name "homoallylic resonance" was suggested as a description of the phenomenon.

Subsequent work by Winstein (3) on the norbornyl system introduced other examples of homoallylic resonance. The solvolysis of exo norbornenyl tosylate I in acetic acid takes place at a rate which is three hundred times that of cyclohexyl tosylate. The main product of acetolysis has the tricyclic structure IIa. Both of these facts point to a participation of the double bond during the reaction. Winstein points out that the rate difference between exo norbornenyl tosylate I and its endo isomer III is a more exact measure of the driving force contributed by the double bond participation. Although the same homoallylic ion is ultimately formed from both isomers, only in the exo isomer can the double bond participate during the formation of the ion. This assistance is measured by the fact that I acetolyses

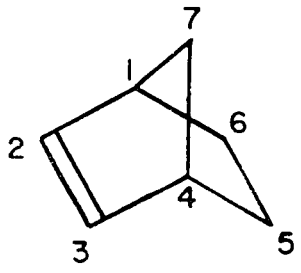
Figure 1

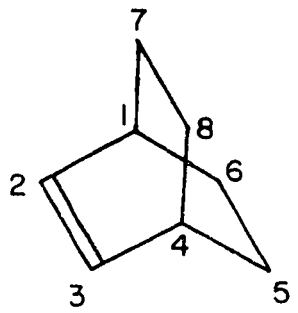


I II III

a x = Ac

b x = H





Numbering of the seven and eight-membered rings.

seven thousand times as quickly as III.

The rates quoted for the saturated norbornyl tosylates (Table I) show that ordinary carbon participation speeds the solvolysis of the exo isomer, but by a factor of only 300 as compared with the endo isomer.

Roberts (4) found that exo norbornenyl chloride solvolysed in 80% aqueous ethanol at a rate which was ten times that of cyclopentyl chloride under the same conditions. The product of solvolysis was the tricyclic alcohol IIb. The ratio of the rate of solvolysis of exo norbornenyl chloride to that of endo norbornenyl chloride was 156. These figures do not show such a notable exo/endo ratio as do Winstein's figures describing the rate of acetolysis of the corresponding tosylates, but there is a general agreement.

Early in 1954, Winstein and Simonetta (5) supported these observations with a set of LCAO calculations which indicated that, in the case of a simple linear homoallyl cation, the electron delocalization energy produced by a movement of the ionic centre towards the double bond exceeded the strain energy required to permit such a movement. In this simple system it was shown that a net gain of 6 to 7 kilocalories per mole was to be expected when the normal interatomic distance between the incipient carbonium ion and the neighbouring double bond had been reduced from 2.5Å to about 2Å. Calculations for the more rigid norbornenyl ion were not attempted.

TABLE I

Some Observed and Calculated Values for the Rate Constant in the Acetolysis of Bicyclic Tosylates

	Adjusted Rate Constants	Relative Rate Constants	Reference	Conditions under which Original Rate Constants were Measured
Exobicyclo[2.2.2]oct-2-en-5-yl tosylate	70×10^{-5} (a)	15,000	Present work	acetolysis of tosylate at 18.2°C.
Endobicyclo[2.2.2]oct-2-en-5-yl tosylate	1.6×10^{-5} (b)	300	(11)	acetolysis of tosylate at 30.07°C.
Bicyclo[2.2.2]oct-2-yl tosylate	1.4×10^{-6} (b)	30	(11)	acetolysis of tosylate at 30.07°C.
Exobicyclo[2.2.1]hept-2-en-5-yl tosylate	1.5×10^{-5}	300	(6)	acetolysis of tosylate at 25°C.
Endobicyclo[2.2.1]hept-2-en-5-yl tosylate	1.9×10^{-9}	.05	(6)	acetolysis of tosylate at 25°C.
Exobicyclo[2.2.1]hept-2-yl tosylate	2.5×10^{-5}	500	(13)	⅓ rate for acetolysis of brosylate at 25°C.
Endobicyclo[2.2.1]hept-2-yl tosylate	7.2×10^{-8}	1.5	(13)	⅓ rate for acetolysis of brosylate at 25°C.
Cyclohexyl tosylate	4.08×10^{-8}	1	(13)	acetolysis of tosylate at 30°C.

All figures are corrected to correspond with the conditions for acetolysis of the relevant tosylate at 25°C. The relative rate constants are rounded off, since there is a considerable error introduced in some instances in converting the rate constant to a value at 25°C.

a. This figure is obtained by multiplying the rate for endobicyclo[2.2.2]oct-2-en-5-yl tosylate by 35, which is the exo/endo ratio at 18.2°C.

b. Calculated by means of thermodynamic data obtained by Goering (11).

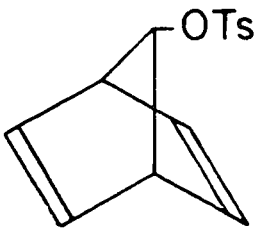
In 1956 Winstein (6) showed that the rate of acetolysis of anti-7-norbornenyl tosylate IV was 10^{11} times that for 7-norbornyl tosylate V, and later (7) that the rates were greatly affected by the position of the double bond, as shown in Table II. These results provide strong evidence for participation of the double bond with reaction at the carbon atom 7.

Meanwhile, a review by Noland (8) suggested that the failure of 5-nitronorbornene VIa to undergo the Nef reaction (9, 10, 11) was due to a homoallylic stabilization of the ionic intermediate VIb, since the reaction occurs normally with 5-nitronorbornane (11). Noland (12) was subsequently able to show that although the classical Nef reaction did not occur in the norbornene case, yet a reaction did proceed, with participation of the double bond to form a nortricyclic intermediate VIc and consequent opening of the 4,5 bond to give a rearranged product VId.

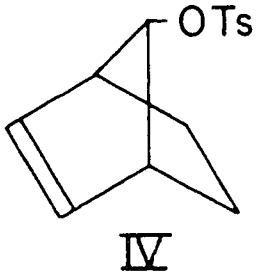
It may now be seen that the concept of homoallylic resonance serves to explain several reactions in the norbornyl and norbornenyl systems. Many of the reactions described above have been carried out in the 2.2.2 -system: for example, the fact that the Nef reaction proceeds normally in the case of 5-nitro-bicyclo[2.2.2]oct-2-ene (12), giving an unrearranged bicyclo[2.2.2]oct-2-ene-5-one, was interpreted as evidence against double bond participation in this system. Also, the earlier failure of Wildman and Saunders (13) to obtain a tricyclic

Table II

Relative rates of acetolysis

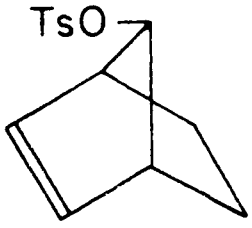


10^{14}

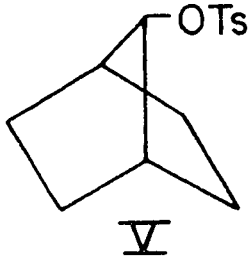


IV

10^{11}



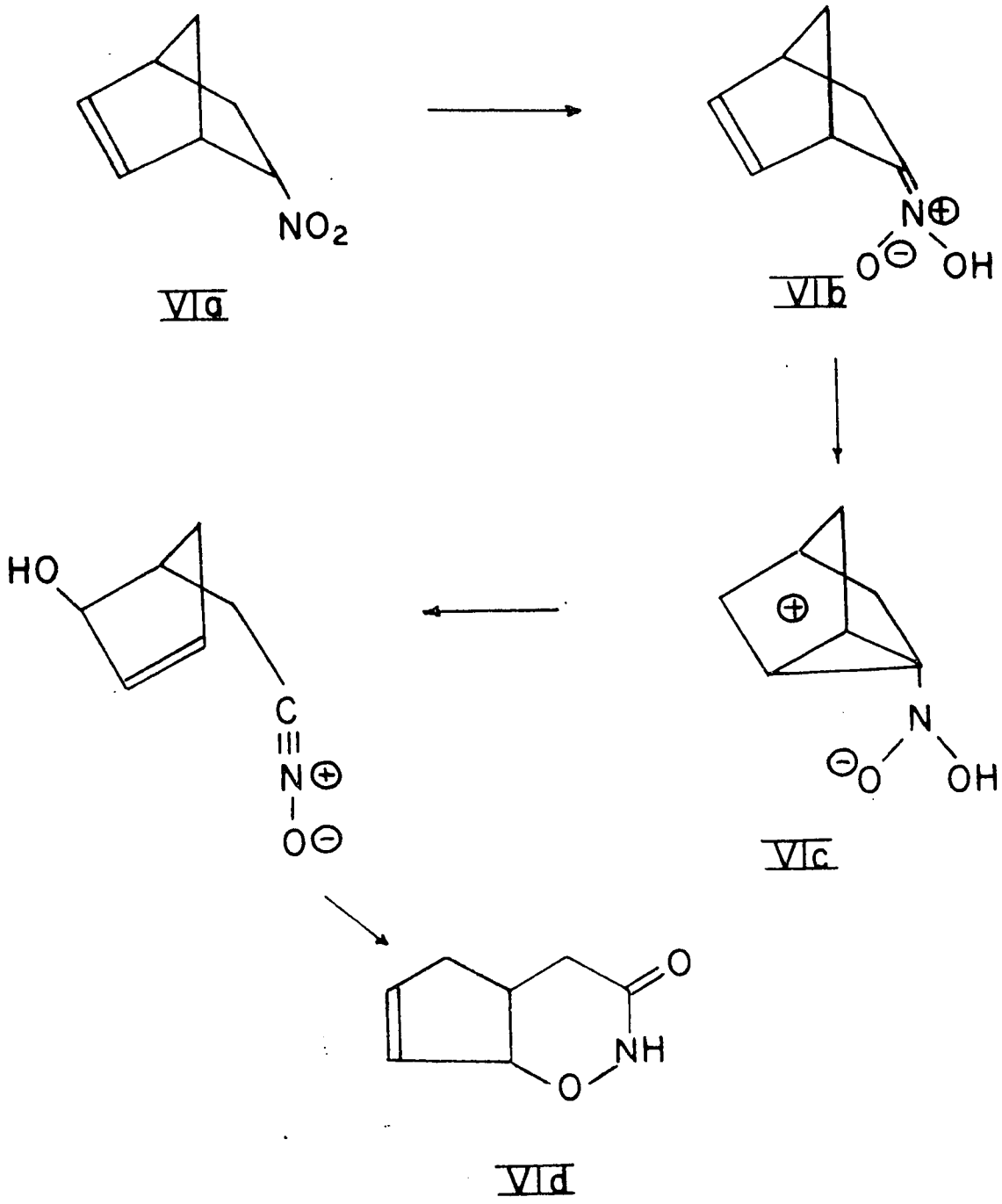
10^{4}



V

1

Figure 2



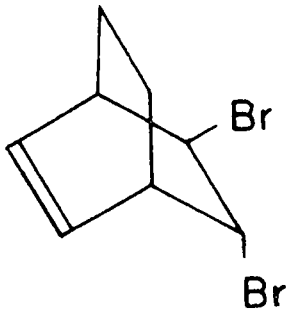
VIa VIb VIc VId

derivative on deamination of 5-amino-bicyclo[2.2.2]oct-2-ene was quoted (12) as evidence against the participation of the double bond in this reaction. However, Grob (14) was able to show that the amine prepared by these workers was the endo isomer, so that participation of the saturated bridge was rather to be expected.

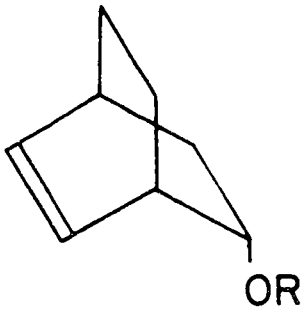
Goering (15) has studied the acetolysis of the tosylate VIIb of endo-5-hydroxybicyclo[2.2.2]oct-2-ene VIIa. The rate of solvolysis is 300 times that of cyclohexyl tosylate, and the product is rearranged to exo-(axial)-bicyclo[3.2.1]oct-3-en-2-ol. Direct participation of the double bond is unlikely, since the geometry would seem to allow participation of only the saturated bridge. Participation of this type appears to lead to rearrangement to a 3.2.1 skeleton.

Grob (16) showed, in 1959, that bromination of bicyclo [2.2.2]octa-2,5-diene resulted in a mixture of two dibromides, one of which, tricyclo[2.2.2.0]octane-3,5-dibromide, had a cyclopropyl ring which indicates double bond participation during the addition reaction. The other dibromide, trans-5,6-dibromobicyclo[2.2.2]oct-2-ene (VIII) solvolysed in 80% aqueous ethanol at 25°C. to give a rate constant of 3.2×10^{-5} sec^{-1}. This is 143 times as fast as cyclopentyl bromide, and over 70 times as fast as exo norbornenyl bromide when solvolysed under the same conditions. The solvolysis product is rearranged to 4-hydroxy-8-bromo-bicyclo[3.2.1]oct-2-ene. Some considerable driving force, again provided by participation of the saturated bridge, is

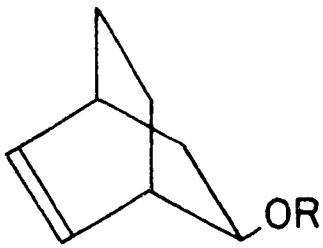
Figure 3



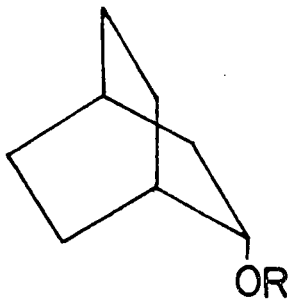
VIII



VII



XI



IX

(a) R = H

(b) R = Ts

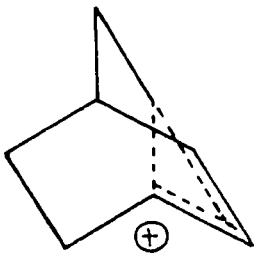
(c) R = Ac

evident in this solvolysis.

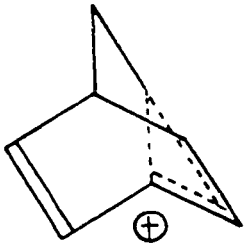
Some consideration of the saturated 2.2.2 -compounds helps to interpret the behaviour of the bicyclooctenes. Walborsky (17) had concluded that no non-classical ion was formed in the reactions of the bicyclo[2.2.2]octanes, since the products of the solvolysis of the tosylate and of the deamination of the amine were unrearranged. He suggested that the angular strain of the 2.2.1 -system played a significant part in the formation of non-classical ions and, hence, that such ions were not to be expected in the relatively strain-free bicyclo[2.2.2]octane system. Re-examination of this work in 1961 (18) showed that the alcohols obtained as products of the hydrolysis of the tosylate of bicyclo[2.2.2]octanol in aqueous acetone contained 45% of bicyclo[3.2.1]octanol and 55% of unrearranged bicyclo[2.2.2]octanol. These results were interpreted as evidence for the existence of the non-classical intermediate XII during the hydrolysis.

Goering's measurement of the rate of acetolysis of the tosylate VIIb (19) showed a rate accelerated to 300 times that of cyclohexyl tosylate. Now, although the rate of acetolysis of the saturated tosylate IXb is enhanced by participation of the same carbon atom that accelerates the acetolysis of VIIb, the former solvolyses at a rate which is ten times smaller than that of the latter. Hence there must be an indirect effect produced by the double bond which probably assists in the carbon participation. This would result in extensive

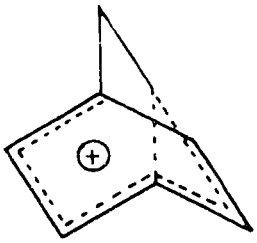
Figure 4



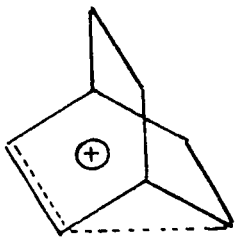
XII



XIII



X



XIV

electron delocalization, as shown in X.

Thus, although it has been suggested that there is no direct participation of the double bond in the solvolytic reactions of derivatives of 5-hydroxybicyclo[2.2.2]oct-2-ene, no experiments have been made to test this point directly. It was therefore interesting to prepare exo-5-hydroxybicyclo[2.2.2]oct-2-ene XIa to see if a direct participation by the double bond would occur during the solvolysis of its tosylate, XIb. From previous work (15, 17) it seems that participation of the saturated bridge results in rearrangement to the 3.2.1 skeleton. Participation of the unsaturated bridge might be expected to give ring closure to a cyclopropyl tricyclic skeleton.

RESULTS

(a) The first requirement was the preparation of the exo alcohol XIa, exo-5-hydroxybicyclo[2.2.2]oct-2-ene. The original preparation of 5-hydroxybicyclo[2.2.2]oct-2-ene was carried out by Alder (20) from vinyl acetate and cyclohexa-1,3-diene. Although the stereochemistry of the reaction was not investigated, it was later assumed (21) that the product was mainly of endo configuration. It seemed possible that this reaction would lead to a mixture of the endo and exo alcohols rather than to a stereochemically pure product, and the preparation was repeated to try and confirm this. However, alcohol prepared by this method could not be separated into two components. Fractional crystallization of the p-nitrobenzoate did not lead to sharply melting fractions, indicating that the material contained too little of the exo alcohol to make possible its isolation.

(b) A possible route to the alcohol was suggested by the work of H. C. Brown (22), who obtained a 63% yield of a mixture of 88% exo and 12% endo 5-hydroxynorbornene by hydroboration of bicycloheptа-2,5-diene followed by hydrogen peroxide oxidation. Hydroboration of bicyclo[2.2.2]oct-2,5-diene yielded 24% of a mixture which, from examination of its infrared spectrum, was estimated to contain both exo and endo 5-hydroxybicyclo[2.2.2]oct-2-ene in the proportion of about 2 exo to 3 endo, in addition to other contaminants. The overall yield of exo

alcohol was judged to be about 5%. In view of the difficulty of preparing the diene, this yield was considered too low to make the method useful.

(c) Eliel (23) reported a method of equilibrating isomeric alcohols by refluxing with lithium aluminium hydride and aluminium trichloride. On refluxing 5-hydroxybicyclo[2.2.2]oct-2-ene prepared by the Diels-Alder reaction, as described (a) on page 13, with this reducing agent, an unidentified material was obtained. The hydroxyl band at 3400 cm^{-1} in the infrared spectrum had a density of 0.05 instead of the expected 0.40, and the NMR spectrum showed an unsymmetrical band between 3.7 and 4.7τ , characteristic of a double bond in an unsymmetrical environment. This evidence showed that the product was not a 5-hydroxybicyclo[2.2.2]oct-2-ene, and indicated the possibility of a rearrangement to bicyclo[3.2.1]oct-3-en-2-ol.

(d) The Prevost reaction, as used by Kavadias (24), was used to prepare an iodohydrin from bicyclo[2.2.2]octa-2,5-diene. Iodine powder and silver 3,5-dinitrobenzoate were added to benzene and the suspension was stirred and cooled. The octadiene was then added, and the mixture was stirred for 10 hours at 0°C. After extraction and recrystallization of the product, a yield of 11% of crystalline material was obtained. Elemental analysis corresponded to a compound resulting from the addition of iodonium 3,5-dinitrobenzoate to the olefin, but the spectrographic data quoted in the experimental part indicate that

the product was rearranged to 8-iodo-bicyclo[3.2.1] oct-2-en-4-yl 3,5-dinitrobenzoate.

(e) The exo alcohol was eventually prepared by reduction of the ketone, bicyclo[2.2.2] oct-2-ene-5-one. Dauben (25) and Wheeler (26) have pointed out that the stereochemical course of a hydride reduction may be controlled either by the steric hindrance to the entering reducing agent, as described by Cram (27), or by steric forces acting upon the developing transition-complex, which Dauben calls "product development control". In the case of the reduction of bicyclo[2.2.2]-oct-2-ene-5-one, steric hindrance to the approaching reagent would favour the formation of exo alcohol, while the so-called "product development control" would be expected to favour the more stable alcohol. Equilibration of 5-hydroxybicyclo[2.2.2] oct-2-ene of composition 95:5-endo:exo with sodium and fluorenone according to the procedure of Doering (28) gave, after 48 hours, a 40% yield of alcohol who ratio of epimers was unchanged within the limits of sensitivity of the method of analysis (IR and NMR). This equilibration indicated that the endo alcohol was the more stable.

TABLE III

Proportion of exo-5-hydroxybicyclo[2.2.2]oct-2-ene obtained in reductions of bicyclo[2.2.2]oct-2-ene-5-one

Reducing Agent	Percentage of endo-5-hydroxybicyclo-[2.2.2]oct-2-ene obtained	Percentage of exo-5-hydroxybicyclo-[2.2.2]oct-2-ene obtained
Lithium tri-t-butoxy-aluminium hydride	60	40
Sodium borohydride	68	32
Lithium aluminium hydride	75	25

KINETICS

The kinetics of the acetolysis of endobicyclo[2.2.2]oct-2-en-5-yl tosylate was studied by Goering (19). His method was conventional in that a solution of the tosylate in anhydrous acetic acid was divided into a number of samples, each separately sealed in an ampoule and placed in a constant temperature bath. At intervals a sample was withdrawn and the contents titrated with a solution of sodium acetate in acetic acid, the mixture then being set aside for subsequent identification of reaction products.

This method could not be applied in the present work, since the amount of exo alcohol XIa available was limited. Hence, a somewhat modified technique was used. The sample, dissolved in anhydrous acetic acid, was placed in a water-jacketed cell with a small quantity of indicator, and water from a constant temperature bath was circulated through the cell jacket. The solution was neutralized, at regular intervals, by addition of an acetic acid solution of sodium acetate from a micrometer burette.

To test the reliability of this microanalytical method, the rate of solvolysis of the endo tosylate VIIb was determined first. The rate constant thus obtained was in substantial agreement with that reported by Goering (19).

Goering's figure, corrected to 18.2°C.	6.0×10^{-6} sec^{-1}
Found at 18.2°C.	6.7×10^{-6} sec^{-1}

The uncertainty in the comparison of these figures is ± 10%.

The solvolysis of the exo tosylate XIb followed excellent first-order kinetics, and the rate constant obtained from the graph

$$23.6 \times 10^{-5} \text{ sec}^{-1} \text{ at } 18.2°C.,$$

a rate increase of about 35 times that of the endo tosylate VIIb.

VPC examination of the product of acetolysis of the exo tosylate showed a major constituent, making up about 85% of the total, which was identified as unrearranged exobicyclo[2.2.2]oct-2-en-5-yl acetate. The minor constituent was not identified.

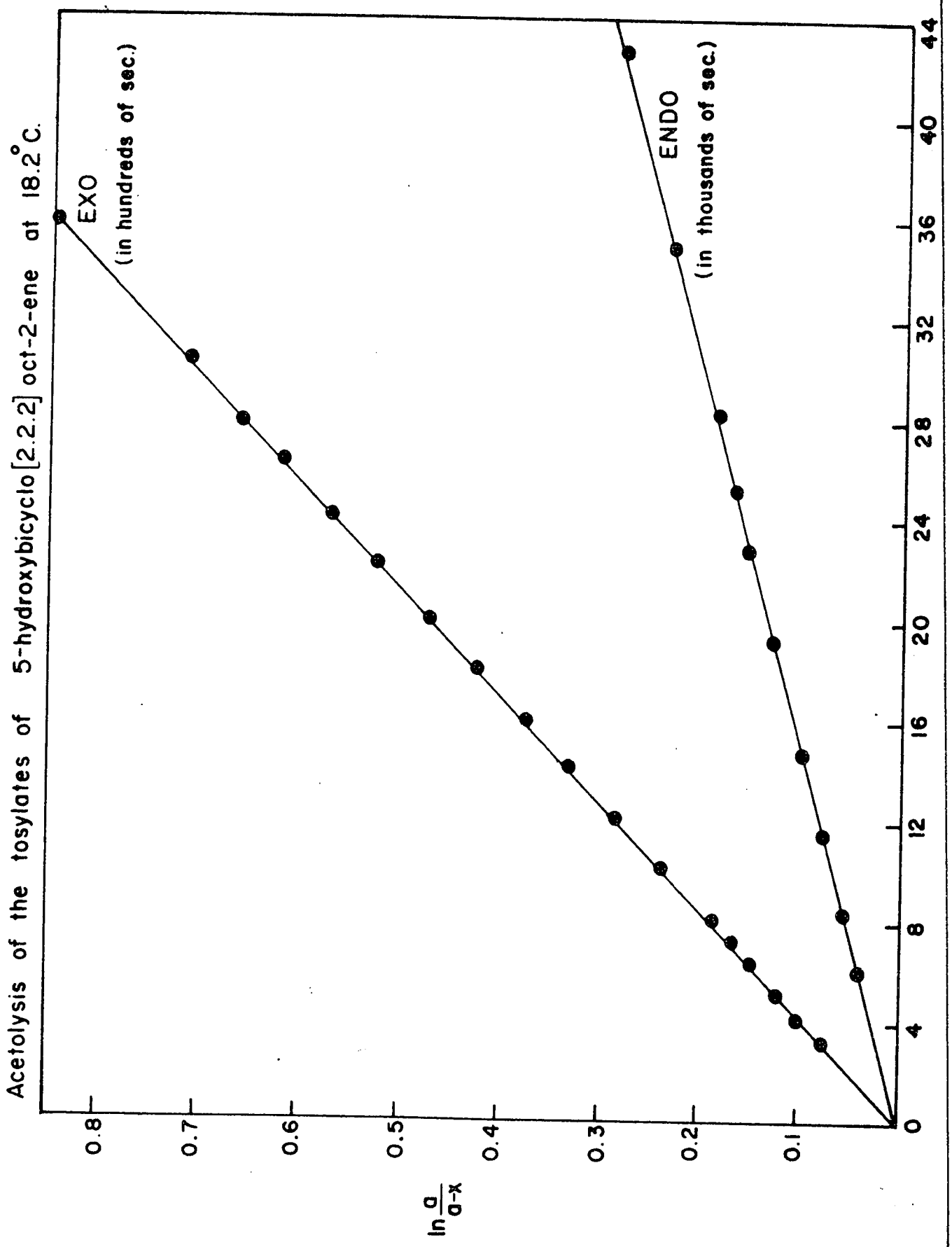

Acetolysis of the tosylates of 5-hydroxybicyclo[2.2.2] oct-2-ene at 18.2°C.
EXO
(in hundreds of sec.)
ENDO
(in thousands of sec.)
$\ln \frac{a}{a-x}$
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
4
8
12
16
20
24
28
32
36
40
44

Figure 5

DISCUSSION

Goering (19) concludes that the rate of solvolysis of endobicyclo[2.2.2]oct-2-en-5-yl tosylate is between 100 and 1000 times that which would be expected if participation of the double bond did not take place. If one accepts the intermediate XII as proposed for the ionization of endobicyclo[2.2.2]oct-5-yl tosylate IXb, then it seems that solvolysis of the unsaturated compound would involve XIII in the absence of double bond participation, and X where the double bond does participate. The salt effect is less than 5%, which is typical of an S_n1 reaction. Attack at the carbon atom 2 would be expected, and this would give the observed product, bicyclo[3.2.1]oct-2-en-5-yl acetate.

The maximum rate enhancement would be expected where direct participation of the double bond occurs, as is evident in the solvolysis of exo-norbornenyl tosylate. This expectation is fulfilled, since exobicyclo[2.2.2]oct-2-en-5-yl tosylate XIb solvolyses 35 times as fast as endobicyclo[2.2.2]oct-2-en-5-yl tosylate VIIb. However, in the solvolysis of XIb one might expect that some tricyclo[2.2.2.0]-octanyl acetate would be formed. Only exobicyclo[2.2.2]oct-2-en-5-yl acetate XIc was identified. Apparently the tricyclic compound is too highly strained to allow its formation to compete significantly with the formation of XIc. That the double bond participates in the

ionization of XIb is shown, first, by the acceleration of solvolysis and, secondly, by the fact that the reaction proceeds with at least 85% retention of configuration, since XIc and not VIIc is the product of solvolysis. It is therefore concluded that the solvolysis of the tosylate of exo-5-hydroxybicyclo[2.2.2]oct-2-ene occurs with participation of the neighbouring β-γ double bond. The transition state for the solvolysis can thus be best represented by XIV. Table I shows that the rate of acetolysis of exobicyclo[2.2.2]oct-2-en-5-yl tosylate is 15,000 times that of cyclohexyl tosylate under the same conditions; while the rate of acetolysis of endobicyclo[2.2.2]oct-2-en-5-yl tosylate is 300 times that of cyclohexyl tosylate.

EXPERIMENTAL

All infrared spectra were recorded on a Perkin-Elmer Model 137B Infracord. The NMR spectra were measured on a Varian V-4302 NMR spectrometer. All melting points and boiling points are uncorrected.

BICYCLO[2.2.2]OCT-2-ENE-5-OL

(a) The method used is that of Alder and Rickert (20). Into a Carius tube were sealed 16 grams (0.2 moles) of crude 60% cyclohexa-1,3-diene, prepared according to J. Hine et al (29), and 13 grams of vinyl acetate. The tube was kept at 190°C. for 40 hours, then chilled in dry ice/acetone and opened, and the liquid distilled. The fraction boiling at 91° - 94°C. (9mm.) was reserved and hydrolysed at room temperature for 12 hours with 2 equivalents of sodium hydroxide in 5% solution in 60% aqueous methanol. This solution was then acidified with 10% sulphuric acid and the methanol removed at 25°C. under reduced pressure. The remaining solution was extracted with ether, and the combined extracts were washed with 5% aqueous potassium bicarbonate and two changes of water. The ethereal solution was dried over anhydrous magnesium sulphate.

Because of the unusually high vapour pressure of the 2.2.2 - bicyclic compounds, care must be used in evaporating off solvents. In this case the ether was distilled off at atmospheric pressure, through

a 20 cm. column. There remained 1.3 grams (0.012 moles) of a white crystalline solid, a yield of 6% bicyclo[2.2.2]oct-2-en-5-ol.

The melting point was diffuse, about	125°C.	
The reported melting point was	167.5° - 169°C.	(18)
The melting point of p-nitrobenzoate was	104° - 109°C.	
The reported melting point was	109.8° - 110.8°C.	(13, 8)

Fractional recrystallization of the p-nitrobenzoate from ethanol/water resulted in some divergence of melting points, but no sharply melting fraction was obtained. The infrared spectrum of the alcohol showed lines at

3500 3000 1400 1175 1100 1065 1060 990 940 860 712 and 693 cm^{-1}.

Preparation of Bicyclo[2.2.2]octa-2,5-diene

Bicyclo[2.2.2]octa-2,5-diene was prepared exactly according to the method described by Grob (14). The route used was through the acid, acid chloride, isocyanate, urethane, N-methyl amine, N,N-dimethyl amine, and thermal decomposition of the N-oxide of the N,N-dimethyl amine. From 85 grams of acid, 40 grams of urethane were obtained.

Melting point	100°C. - 102°C.
Reported melting point	107°C. - 108°C.

From 30 grams of urethane were produced 6 grams of diene, a white, waxy, semi-liquid substance of no exact melting point. The infrared spectrum

showed peaks at

3000 1590 1360 1222 1153 1120 912 866 826 710 and 670 cm^{-1}.

This spectrum corresponded well with that illustrated by Grob (14).

(b) Hydroboration of bicyclo[2.2.2]octa-2,5-diene

The following procedure is that of H. C. Brown (22). Bicyclo[2.2.2]octa-2,5-diene (2.1 grams, 20mM) was dissolved in 50 ml. of ether, 55 mg. (2.5mM) of lithium borohydride were added, and the mixture was allowed to stand for some hours at 0°C. Maintaining the mixture at this temperature, a solution of 460 mg. of boron trifluoride etherate in 5 ml. of ether was added over 60 minutes, with stirring. The mixture was allowed to reach room temperature and, after a further hour, the excess diene, together with the ether, was evaporated off at atmospheric pressure. The residual solid was redissolved in ether and the solution was brought to 5°C. in the cold room. To this was added 4.5 ml. of 3M sodium hydroxide solution, followed by 5 ml. of 15% hydrogen peroxide added dropwise, with stirring, over an hour. The ether layer was separated, washed with water and dried over anhydrous magnesium sulphate. Upon evaporation of the solvent there remained 0.5 grams of resinous non-crystalline solid. The infrared spectrum showed lines at

3500 3000 1380 1160 1090 1060 1030 990 950 934 860 710 697 cm^{-1}. The line at 697 cm^{-1} is indicative of exo alcohol; that at 710 is due to endo.

This product could not be crystallized, but on the evidence of the infrared spectrum it was identified as a mixture of exo and endo 5-hydroxybicyclo[2.2.2]oct-2-ene with resinous contaminants.

(c) Attempted Equilibration of 5-hydroxybicyclo[2.2.2]oct-2-ene

The following method is that of E. Eliel (23). A mixture of 380 mg. of lithium aluminium hydride and 4 grams of anhydrous aluminium chloride was refluxed with 300 mg. of alcohol, prepared by method (a), page 22, in 50 ml. of ether for 20 hours. Acetone (0.01 ml.) was added to the purple solution, which was then stirred for a further 2 hours. The liquid was poured into an excess of 5% aqueous sodium hydroxide and extracted with ether. The ethereal solution was washed with water and dried over anhydrous magnesium sulphate. Upon evaporation of the solvent there remained 254 mg. (85%) of crystalline material. The infrared spectrum showed lines at

3500_{vw} 2950 1440 1200 1040 1000 800 768 and 720 cm^{-1}.

From the unsymmetrical absorption pattern in the olefinic region of the NMR spectrum of this product it was concluded that the alcohol had rearranged to bicyclo[3.2.1]octenol.

(d) Reaction of bicyclo[2.2.2]octa-2,5-diene with Iodine and Silver Benzoate

An attempt was made to prepare the alcohol by means of the

Prevost reaction. The procedure is taken from Kavadias (24). A mixture of 100 ml. of benzene, 5.08 grams (20mM) of iodine in fine powder and 6.38 grams (20mM) of freshly prepared silver 3,5-dinitrobenzoate was stirred for 1 hour at 26°C. and cooled to 5°C. Then 3.9 grams (20mM) of bicyclo[2.2.2]octa-2,5-diene in benzene were added with stirring, and the mixture was stirred at 0°C. for 10 hours, and for a further 2 hours with the cooling bath removed. The solution was then filtered off and the filtrate washed with water, aqueous potassium bicarbonate solution, aqueous sodium thiosulphate solution and water. It was then dried with anhydrous magnesium sulphate, and the solvent was evaporated through a 20 cm. column at atmospheric pressure. The remaining syrup was dissolved in hot chloroform, an equal portion of ethanol was added and the solution was set aside to crystallize. Grey-white silvery leaflets crystallized out. After 3 recrystallizations from carbon tetrachloride the melting point was 160° - 164°C. The total yield was 4 grams (11%).

Analysis

Calculated for $C_{15}H_{13}N_2I$: C, 40.56%; H, 2.96%; N, 6.31%; I, 28.60%.

Found: C, 40.63%; H, 3.23%; N, 6.51%; I, 26.48%.

The infrared spectrum of the product showed lines at

3180 3000 1740 1640 1550 1344 1275 1165 1080 970

945 925 765 cm^{-1}.

The NMR spectrum showed an olefinic band between 3.3 and 4.0τ which had the asymmetry associated with the 3.2.1 skeleton. The product was

therefore characterized as 8-iodo-bicyclo[3.2.1]oct-2-en-4-yl 3,5-dinitrobenzoate.

(e) Reduction of Bicyclo[2.2.2]oct-2-en-5-one with Lithium Tri-t-butaxyaluminium Hydride

Following the procedure of H. C. Brown (22), 2 ml. of t-butanol, dried over sodium, were added to 400 mg. of lithium aluminium hydride in 50 ml. of dried ether at 0°C. Then 351 mg. of bicyclo[2.2.2]oct-2-ene-5-one (see preparation, page 29) were added and the mixture was stirred for 2 hours at 0°C. and then for 2 hours at room temperature. The mixture was poured into 5% aqueous sodium hydroxide, which was extracted with ether. The ethereal extracts were washed with 3 changes of water and dried over anhydrous magnesium sulphate. Upon evaporation of the solvent there remained 339 mg. (96%) of a whitish crystalline substance, bicyclo[2.2.2]oct-2-en-5-ol.

(f) Reduction of Bicyclo[2.2.2]oct-2-en-5-one with Sodium Borohydride

A mixture of 930 mg. of sodium borohydride and 655 mg. of potassium acetate was dissolved in 50 ml. of water. To this solution was added a solution of 391 mg. of bicyclo[2.2.2]oct-2-ene-5-one in 50 ml. of ether. This mixture was shaken vigorously for 3 days at room temperature, about 23°C., ether being added from time to time to maintain the original volume. The mixture was then extracted with ether. The ethereal solution was washed with 3 changes of water and

dried over anhydrous magnesium sulphate. Evaporation of the solvent left 363 mg. (93%) of bicyclo[2.2.2]oct-2-en-5-ol.

(g) Reduction of Bicyclo[2.2.2]oct-2-en-5-one with Lithium Aluminium Hydride

A mixture of 120 mg. of lithium aluminium hydride and 350 mg. of bicyclo[2.2.2]oct-2-ene-5-one was stirred in 50 ml. of dry ether for 2 hours at 0°C. and for 2 hours at room temperature. The mixture was poured into 5% aqueous sodium hydroxide, which was extracted with ether. When the ethereal extracts were washed with 3 changes of water and dried over anhydrous magnesium sulphate, and the solvent was evaporated, there remained 240 mg. (69%) of crystalline bicyclo[2.2.2] oct-2-en-5-ol.

Analysis

The products obtained under (e), (f) and (g), pages 27 and 28, were analysed in the Pye Argon Vapour Phase Chromatograph, using a Carbowax 20M column supported on firebrick. The column temperature was 130°C., the input pressure 8 lb./sq.in., and the detector voltage 1250 v. Each showed a minor and a major constituent. The major constituent was considered to be endo alcohol; the minor, exo. This identification was later verified when known samples had been prepared.

The proportions were as follows:

	Endo	Exo
(e)	60%	40%
(f)	68%	32%
(g)	75%	25%

BICYCLO[2.2.2]OCT-2-EN-5-ONE

(h) The method of Wildman (30) was used to make 5-nitrobicyclo-[2.2.2]oct-2-ene from nitroethylene and cyclohexa-1,3-diene. The product was distilled at 120°C. and 15mm. pressure. From this material the Nef reaction (30) yielded a yellow, waxy substance melting between 40° and 70°C.

(i) Following the procedure of Barett et al (31), a 10% solution of bicyclo[2.2.2]oct-2-en-5-ol (prepared according to method (a), page 22,) in pyridine was added to twice the volume of a 10% solution of chromium trioxide in pyridine. The mixture was allowed to stand for 48 hours at room temperature, about 26°C. Sufficient water was added to dissolve solids, and the solution was extracted with a mixture of equal parts of ether and benzene. The extracts were washed with 3 changes of water and dried over anhydrous magnesium sulphate. When the solvent was evaporated, a brown, waxy solid remained in 80% yield. This was purified by sublimation to give an almost white, waxy solid.

melting point 63° to 72°C. The infrared spectrum showed strong absorption at

3000 1730 1440 1005 1060 860 704 cm^{-1}.

VPC examination of the product of the above reaction (i), using the Perkin-Elmer columns A and K, showed a single peak. A mixture of this product with the original alcohol gave two peaks under the same conditions. Lithium aluminium hydride reduction of the products of the reactions described under (h) and (i) gave bicyclo[2.2.2]oct-2-en-5-ol. These products, (h) and (i), were therefore considered to be bicyclo[2.2.2]oct-2-en-5-one.

PREPARATIVE VAPOUR PHASE CHROMATOGRAPHY

The stationary phase, 20% Carbowax 20M on 80-mesh Chromosorb, was held in stainless steel U-tubes, each leg of which was 86 cm. long. Three such U-tubes were joined in series by ¼" stainless steel tubing to give a total path length of 516 cm. Swagelok fittings with stainless steel ferrules were used to connect up the tubing. This column, together with the detector and the independently heated injector block, was kept in an air oven heated to 120° - 130°C. The injector block was raised to 200°C. The carrier gas used was nitrogen, admitted at an inlet pressure of 5 lb./sq.in. The gas passed through a preheating loop of ¼" tubing in the oven before being admitted to the detector.

This detector was a stainless steel block drilled with two passages, in each of which was mounted a glow plug. Each plug formed one arm of a Wheatstone bridge, the other arms being two 25 w. fixed resistors shunted by a Helipot. The values of these fixed resistors were selected to match the resistances of the glow plugs. The output from this bridge went to a 10 mv. recorder.

The effluent gas was bubbled through ether at -70°C. The ether was removed when 2/3 of the first peak had passed through, and replaced with fresh ether when 1/3 of the following peak had passed.

The exo-5-hydroxybicyclo[2.2.2]oct-2-ene separated by vapour-phase chromatography from the mixture prepared by method (f), page 27, was recrystallized once from petroleum ether (boiling point 39° - 41°C.) and sublimed. The melting point was then 175° - 175.7°C.

Analysis:	Calculated for $C_8H_{12}O$:	C, 77.37%; H, 9.74%.
	Found:	C, 77.10%; H, 9.62%.

The NMR spectrum of this compound is shown in Fig. 6. The peaks are assigned as follows. The multiplet at 3.86τ is due to the olefinic protons. The peak at 6.37τ is assigned to the proton on the 5-carbon atom. The broad absorption at 7.8τ is due to the bridgehead protons and the complex absorption at higher field to the remaining 5 protons. On catalytic hydrogenation, a white, crystalline solid was obtained, bicyclo[2.2.2]octanol, melting at 225° - 226°C. (Lit. m.p. 229.9° -

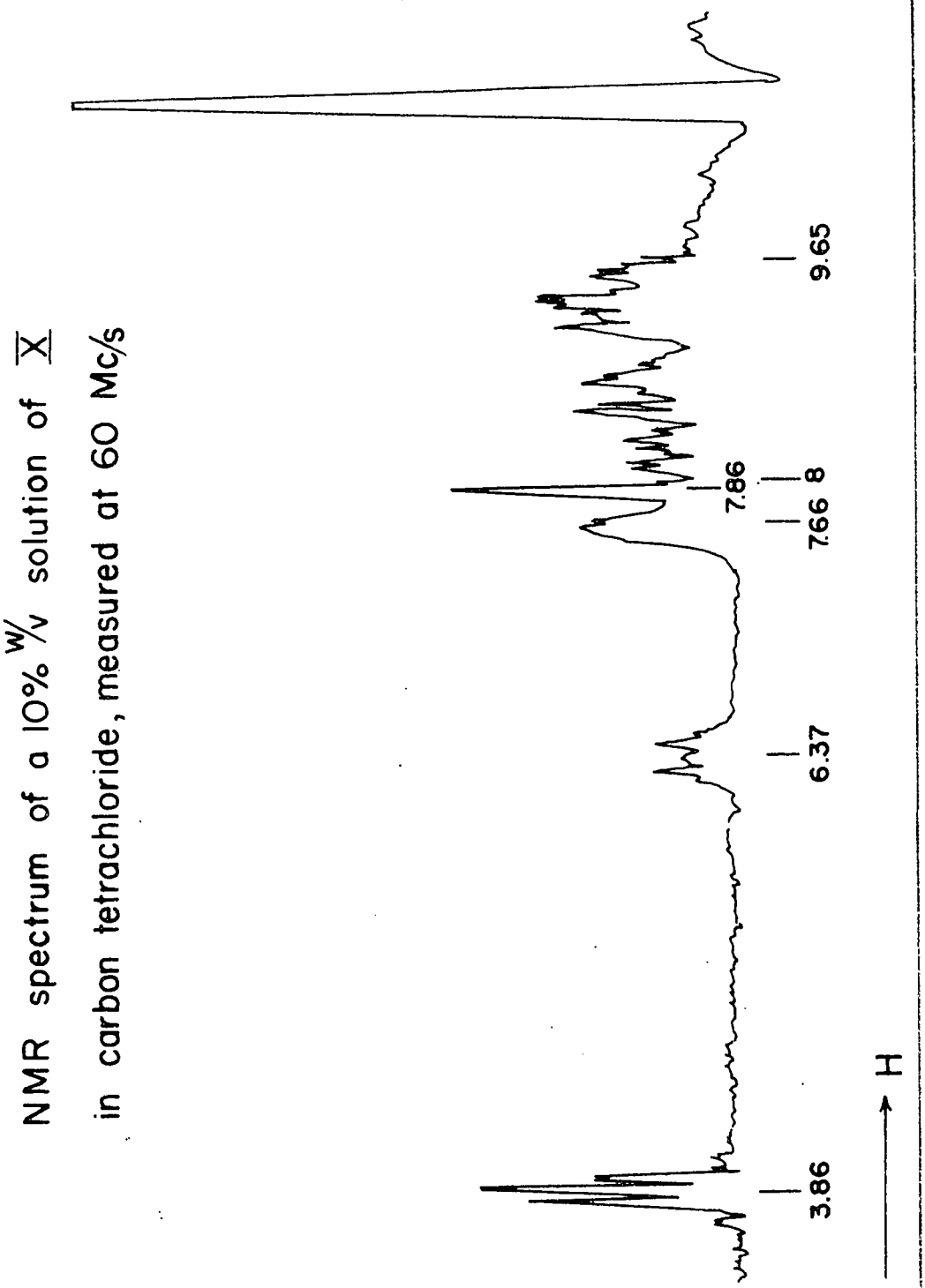

NMR spectrum of a 10% w/v solution of X
in carbon tetrachloride, measured at 60 Mc/s
9.65
7.86
7.66 8
6.37
3.86
H

Figure 6

222.2°C. (18).) The endo-5-hydroxybicyclo[2.2.2]oct-2-ene from the vapour-phase chromatography was recrystallized and sublimed in the same way. The melting point was 168.1° - 168.8°C. Goering reports 167.5° - 169°C. (15). Hydrogenation of the endo isomer also yielded a white crystalline solid, bicyclo[2.2.2]octanol, melting at 224.5° - 226°C. A mixture of the two hydrogenation products melted at 225° - 226°C.

Spectrographic Examination

The infrared spectra showed lines as follows:

EXO alcohol 1065 1044 1006 950 905 650 and 697 cm^{-1}.

ENDO alcohol 1387 1080 1053 1028 650 and 712 cm^{-1}.

The lines at 697 and 712 were found useful in analysis of unknown mixtures of alcohols.

The NMR spectra showed symmetrical olefinic peaks, at 3.86τ for the exo, and 3.90τ for the endo. The shift of the 5-carbon proton was from 6.25τ for the endo to 6.37τ for the exo. This shift corresponded in magnitude and direction with that observed in the bicyclo[2.2.1]heptenes by R. R. Fraser (32), and serves to confirm the stereochemical assignment.

Preparation of 5-hydroxybicyclo[2.2.2]oct-2-ene Tosylates

The tosylates of the alcohols were prepared by the method of

Goering (18) by allowing alcohol and freshly recrystallized tosyl chloride to react in dry pyridine solution for 3 to 4 days at 5°C. The reaction mixture was then poured into ice water, and the mixture was extracted with redistilled petroleum ether (39° - 41°C.). The extracts were washed with 2 changes of water, dried over anhydrous magnesium sulphate, and the solvent was evaporated off. The endo tosylate was obtained as a white crystalline mass on recrystallization. It melted at 59° - 60°C., as compared with Goering's tosylate, which melted at 66.3° - 66.6°C. The crystals were quite unstable, darkening rapidly at room temperature. They were stored and manipulated in the cold room at 5°C.

The exo tosylate could not be crystallized and was used as a clear, colourless oil. It was even more unstable than its isomer, darkening very rapidly at room temperature to an intense blue colour. The infrared spectra were as follows:

EXO 1360 1180 1170 1095 974 928 913 830 814 702 cm^{-1}.

ENDO 1360 1184 1174 1100 1085 995 968 (band 930-900) 875 840 815 710 and 688 cm^{-1}.

Solvolysis

Acetic acid was dried by distillation with a calculated

portion of acetic anhydride, as described by Goering (18). A small quantity (5 ml.) of this dried distilled acid was placed in the reaction cell. The temperature of this portion was allowed to fall until equilibrium was reached at 18.2° ± .05°C. A small quantity of indicator (bromophenol blue) was added, followed by about 20 mg. of bicyclo[2.2.2]oct-2-en-5-yl tosylate. The resultant solution was stirred at all times by a teflon-covered stirring bar. The reaction mixture was titrated with .03M sodium acetate in anhydrous acetic acid, delivered from a micrometer burette accurate to ± .002 ml. The time of titration was marked at the end of the operation. Infinity titers fell about 10% short of the weight of ester added at the start. No attempt was made to keep the reaction mixture dry, and this may have shifted the observed end point of the titration. In every case at least 10 titrations were made and the reaction run to 50% completion (endo) and 80% completion (exo).

The product of solvolysis was extracted with petroleum ether, and washed with water, bicarbonate, and further water. It was then dried over anhydrous magnesium sulphate, and much of the solvent was evaporated off. VPC examination of the remaining solution, on the Perkin-Elmer column "A" at 175°C., showed 85% of a major constituent. The infrared spectrum of the product showed lines at

	1362	1235	1037	1013	954	864	704	cm^{-1}.
Known exo acetate	1362	1235	1037	1013	954		704	cm^{-1}.
endo acetate	1370	1246	1025			855	706	cm^{-1}.

The exo acetate was prepared by mixing solutions of exo alcohol (20 mg.) in pyridine and acetyl chloride in pyridine at 0°C. and reacting at 5°C. for 3 days. The acetate was extracted with petroleum ether and washed, dried over anhydrous magnesium sulphate, and the solvent evaporated off. The infrared spectrum of the residue was then obtained. Unfortunately, the limited supply of exo alcohol prevented the preparation of an analytical sample of the acetate. This procedure identifies the major reaction product of the acetolysis of exobicyclo[2.2.2]oct-2-en-5-yl tosylate as unrearranged acetate.

CLAIMS TO ORIGINAL RESEARCH

(1) exo-5-Hydroxybicyclo[2.2.2]oct-2-ene was synthesized and isolated in a pure state.

(2) exo-5-Hydroxybicyclo[2.2.2]oct-2-ene tosylate was prepared.

(3) Kinetic measurements were made of the solvolysis of this tosylate in anhydrous acetic acid at 16.2°C. The rate was 23.6×10^{-5} sec^{-1}.

(4) It has been established that homoallylic resonance takes place in the bicyclo[2.2.2]oct-2-ene system.

(5) A preparative vapour-phase chromatograph was constructed.

BIBLIOGRAPHY

(1)	S. Winstein and R. Adams	J. Am. Chem. Soc.	70,	838 (1948)
(2)	J. Hine "Physical Organic Chemistry", McGraw-Hill, 1956			pp. 307-309
(3)	S. Winstein, B.M. Walborsky and K. Schreiber	J. Am. Chem. Soc.	72,	5795 (1950)
(4)	F.D. Roberts, W. Bennett and R. Armstrong	J. Am. Chem. Soc.	72,	3329 (1950)
	F.D. Roberts and W. Bennett	J. Am. Chem. Soc.	76,	4623 (1954)
(5)	M. Simonetta and S. Winstein	J. Am. Chem. Soc.	76,	18 (1954)
(6)	S. Winstein and M. Shatavsky	J. Am. Chem. Soc.	78,	592 (1956)
(7)	S. Winstein and C. Ordronneau	J. Am. Chem. Soc.	82,	2084 (1960)
(8)	W.E. Noland and W.C. Wildman	Chem. Rev.	55,	137 (1955)
(9)	W.E. Parham, W.T. Hunter and R.J. Hanson	J. Am. Chem. Soc.	73,	5068 (1951)
(10)	E.E. Van Tamelen and R.J. Thiede	J. Am. Chem. Soc.	74,	2615 (1952)
(11)	W.C. Wildman and C.R. Hemminger	J. Org. Chem.	17,	1641 (1952)

(12)	W.E. Noland, J.H. Cooley and P.A. McVeigh	J. Am. Chem. Soc.	79,	2977 (1957)
(13)	W.C. Wildman and D.R. Saunders	J. Am. Chem. Soc.	76,	947 (1954)
(14)	C.A. Grob, H. King and A. Gagneux	Helv. Chem. Acta.	40,	130 (1957)
(15)	H.L. Goering, R.W. Greiner and M.F. Sloan	J. Am. Chem. Soc.	83,	1391 (1961)
(16)	A. Gagneux and C.A. Grob	Helv. Chem. Acta.	42,	1753 and 2006 (1959)
(17)	H.H. Walborsky	Experientia	9,	209 (1953)
(18)	H.L. Goering and M.F. Sloan	J. Am. Chem. Soc.	83,	1397 (1961)
(19)	H.L. Goering and M.F. Sloan	J. Am. Chem. Soc.	83,	1992 (1961)
(20)	K. Alder and H.F. Rickert	Annalen	543,	1 (1940)
(21)	F.G. Martin and R.K. Hill	Chem. Rev.	61,	537 (1961)
(22)	H.C. Brown and G. Zweifel	J. Am. Chem. Soc.	81,	5632 (1959)
(23)	E. Eliel and M.N. Rerick	J. Am. Chem. Soc.	82,	1367 (1960)
(24)	G. Kavadias	Ph.D. Thesis, University of Ottawa		(1960)

(25)	W.G. Dauben, G.J. Fonken and D.S. Noyce	J. Am. Chem. Soc.	78.	2579	(1956)
(26)	O.H. Wheeler and J.L. Mateos	Can. J. Chem.	36.	1431	(1958)
(27)	D.J. Cram and F.D. Green	J. Am. Chem. Soc.	75.	6005	(1953)
(28)	W. von E. Doering and T.C. Aschner	J. Am. Chem. Soc.	71.	838	(1949)
(29)	J. Hine, J.A. Brown, L.H. Zalkow, W.E. Gardner and M. Hine	J. Am. Chem. Soc.	77.	594	(1955)
(30)	W.C. Wildman and D.R. Saunders	J. Org. Chem.	19.	501	(1954)
(31)	W.F. Johns, R.M. Lukes and L.H. Sarett	J. Am. Chem. Soc.	76.	5026	(1954)
(32)	R.R. Fraser	Can. J. Chem.	40.	78	(1962)