to room temperature, and the final addition was then made. A 1-ml. aliquot of this solution (it is desirable that the phenol content be about 0.05–0.5 mg. for the colorimetric method) was transferred to a 50-ml. volumetric flask, 4 ml. of buffer solution was added, then 5 drops of 36 *N* sulfuric acid and 2 drops of saturated sodium nitrite solution. After 30 to 45 minutes, alcoholic ammonium hydroxide was added while cooling the flask in ice-water. The volume was made up to the mark at room temperature and the solutions were allowed to stand overnight, or at least 5 hours. Colorimetric readings were made with a Klett–Summerson photoelectric colorimeter using a No. 42 violet filter. A small blank correction was necessary. Phenol concentrations were determined from a nearly linear calibration curve, with an accuracy of about 3%.

The rate constants were calculated by standard procedures.[12]

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, THE FLORIDA STATE UNIVERSITY, TALLAHASSEE, FLA.]

Acetolysis of Bicyclo[2.2.2]octyl-2 *p*-Bromobenzenesulfonate and the Absolute Configurations of Bicyclo[2.2.2]octanol-2 and *cis*- and *trans*-Bicyclo[3.2.1]octanol-2

BY H. M. WALBORSKY, M. E. BAUM AND A. A. YOUSSEF

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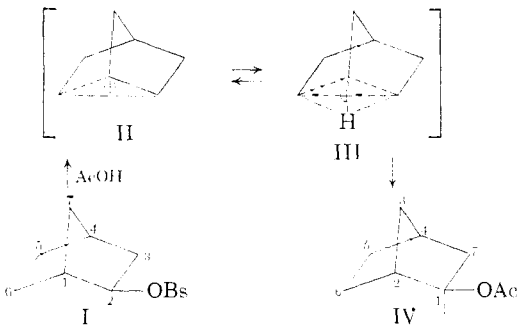
The titrimetric and polarimetric acetolysis rates of bicyclo[2.2.2]octyl-2 *p*-bromobenzenesulfonate have been measured at 25° and found to be 9.07×10^{-6} and 9.4×10^{-6} sec.$^{-1}$, respectively. The acetolysis product was shown to contain, besides bicyclo[2.2.2]octyl-2 acetate, 35 ± 3% of the rearranged bicyclo[3.2.1]octyl-2 acetate. The residual activity found in the acetolysis product of the optically active bicyclo[2.2.2]octyl-2 *p*-bromobenzenesulfonate was shown to reside in both the rearranged and unrearranged alcohols. Retention of activity and configuration in the unrearranged alcohol is discussed in terms of non-classical ion formation. On the basis of the negative Cotton effect exhibited by (−)-bicyclo[3.2.1]octanone-2 and by the application of the Octant rule, absolute configurations have been assigned to (2S)-(+)-bicyclo[2.2.2]octanol-2,(1R:2S:5R)-(−)-*cis*-bicyclo[3.2.1]octanol-2 and (1R:2R:5R)-(−)-*trans*-bicyclo[3.2.1]octanol-2.

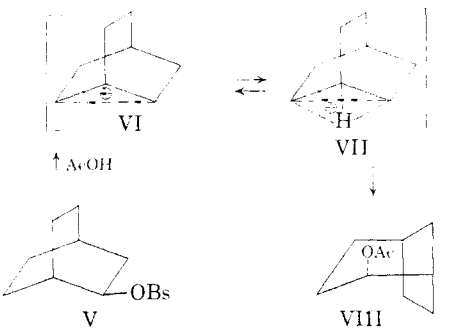
Introduction

The bridged-ion intermediate was originally postulated by Wilson[1] for the transformation of camphene hydrochloride to isobornyl chloride. Subsequent work on the norbornane derivatives gave support to this hypothesis. It was shown that in the acetolysis of optically active *exo*-[2] and *endo*-norbornyl *p*-bromobenzenesulfonate (I)[3] both compounds produced racemic *exo*-norbornyl acetate (IV). This result coupled with the observation that the *exo* isomer solvolyzed 350 times faster than the *endo* was interpreted as evidence for the briged-ion intermediate II.



The skeletal rearrangement (I→IV) implied in the above solvolysis was investigated[4] by tagging the carbon atoms at positions 2 and 3. The results of this experiment demonstrated that rearrangement did occur but that it was more extensive than expected from a bridged-ion such as II. These results could be rationalized by assuming that 55% of the reaction proceeded by II, and 45% by III. The bridged ion III can lead to a 1,3-hydride shift.

The above work prompted the investigation of the analogous bicyclo(2.2.2)octane derivative (V). This system has a number of unique features. In



the first place, if a bridged-ion comparable to II is formed, this ion (VI), in contrast to II, does not possess a plane of symmetry. The bridged ion VII which is analogous to the one proposed by Roberts does, however, possess a plane of symmetry. Secondly, any skeletal rearrangement leads to the formation of an entirely different ring system: a bicyclo(3.2.1)octane derivative (VIII). Finally, this system is essentially free of angle strain, whereas the norbornane system is not.[5] A study of the solvolysis of racemic and optically active V was undertaken to determine the effect of this bridged bicyclic system on the rates as well as on the products of this reaction.

Results

Titrimetric Rates.—Bicyclo(2.2.2)octanol-2 and the *p*-bromobenzenesulfonate ester were prepared as previously described.[6] The solvolysis was conducted in acetic acid, freed of water by reaction with acetic anhydride, and containing sufficient sodium acetate to neutralize the *p*-bromobenzene-

(1) T. P. Nevell, E. de Salas and C. L. Wilson, *J. Chem. Soc.*, 1188 (1939).

(2) S. Winstein and D. Trifan, *J. Am. Chem. Soc.*, **71**, 2953 (1949).

(3) S. Winstein and D. Trifan, *ibid.*, **74**, 1147, 1154 (1952).

(4) J. D. Roberts, C. C. Lee and W. H. Saunders, Jr., *ibid.*, **76**, 4501 (1954).

(5) R. B. Turner, W. R. Meador and R. G. Winkler, *ibid.*, **79**, 4116 (1957).

(6) H. M. Walborsky and D. F. Loncrini, *ibid.*, **76**, 5396 (1954).

sulfonic acid which is liberated during the reaction. The unreacted sodium acetate was titrated with perchloric acid at appropriate time intervals, and the data plotted. The first-order rate constants for the solvolysis of bicyclo(2.2.2)octyl-2 *p*-bromobenzenesulfonate as well as for the comparison compounds are collected in Table I, which lists also the derived values of the thermodynamic quantities of activation, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$. The relative rates at 25° are also shown, taking that of cyclohexyl *p*-bromobenzenesulfonate as unity.

TABLE I

SPECIFIC RATE CONSTANTS[a] AND ACTIVATION PARAMETERS

p-Bromobenzenesulfonate	Temp., °C.	k_1 sec.$^{-1}$	$\Delta H^{\ddagger}$, kcal./mole	$\Delta S^{\ddagger}$, e.u.	Relative rate
Bicyclo(2.2.2)-octyl-2	25.00	9.07×10^{-6}	24.6	1.2	53.0
Bicyclo(2.2.2)-octyl-2	50.97	2.61×10^{-4}			
endo-Bicyclo-(2.2.1)hep-tyl-2[b]	25.00	2.52×10^{-7}	26.0	−1.5	1.5
exo-Bicyclo-(2.2.1)hep-tyl-2[b]	24.96	8.79×10^{-5}			514.0
Cyclohexyl[b]	25.00	1.71×10^{-7}	26.8	0.4	1.0
Cyclopentyl[c]	25.00	6.28×10^{-6}	22.7	−6.3	37.0

[a] All solvolyses were conducted in acetic acid. [b] Ref. 3. [c] H. C. Brown and G. Ham, *J. Am. Chem. Soc.*, **78**, 2735 (1956).

Product Analysis.—Infrared analysis and vapor phase chromatography techniques were used to determine the product composition. The acetate mixture did not lend itself to analysis by either of these methods and was therefore reduced by lithium aluminum hydride to the corresponding alcohols.

The infrared analysis of the alcohol mixture provided only limited information. The analysis showed that the product did not contain any *cis*-bicyclo(3.2.1)octanol-2[7] as evidenced by the absence of a characteristic absorption band[8] at 1065 cm.$^{-1}$. This method could not be used, with certainty, to distinguish between *trans*-bicyclo-(3.2.1)octanol-2[7] and bicyclo(2.2.2)octanol-2.

After much trial and error it was found that a 30% glycerol-on-chromosorb column was effective in separating the mixture of alcohols by vapor phase chromatography. Analysis by this procedure showed the mixture to consist of 35 ± 3% of *trans*-bicyclo(3.2.1)octanol-2 and 65 ± 3% of bicyclo(2.2.2)octanol-2. No *cis*-bicyclo(3.2.1)octanol-2 could be detected.

Polarimetric Rate.—For the work with active *p*-bromobenzenesulfonate esters, bicyclo(2.2.2)octanol-2 was converted to the acid phthalate and resolved *via* its brucine salt to yield upon saponification optically active bicyclo(2.2.2)octanol-2, $(\alpha)^{25}D$ − 7.45 and (+)6.8°, respectively. The (−)-alcohol was converted to the *p*-bromobenzenesulfonate ester, $[\alpha]^{25}D$ +1.2°.

(7) *cis* and *trans* refers to the position of the substituent with respect to the *ethylene bridge*.

(8) A. A. Youssef, M. E. Baum and H. M. Walborsky, *J. Am. Chem. Soc.*, **81**, 4709 (1959).

The polarimetric rate of solvolysis was determined under comparable conditions to that of the titrimetric rate at 25°. When (−)-bicyclo-(2.2.2)-octyl-2 *p*-bromobenzenesulfonate was used the "infinity" reading showed some residual activity (α = +0.09°) (*vide infra*). The data were plotted (see Experimental) and the polarimetric rate constant was calculated to be 9.4 ± 1.4 × 10^{-6} sec.$^{-1}$, which is similar to the titrimetric rate constant, 9.07 ± 0.25 × 10^{-6} sec.$^{-1}$.

Product Analysis.—As noted above the infinity titer showed some residual activity. The solvolysis was run on a larger scale and the mixture of acetates was isolated in 84% yield. The infrared spectrum of the product was identical to that obtained from the solvolysis of the racemic *p*-bromobenzenesulfonate ester. The solvolysis product showed a rotation of $[\alpha]^{25}D$ +0.215° (neat). The question arises as to where this activity resides: is it in the bicyclo(2.2.2)octyl-2 acetate or in the *trans*-bicyclo(3.2.1)octyl-2 acetate, or in both? In order to gain some insight into this question it was decided to reduce the solvolysis mixture to the corresponding alcohol by lithium aluminum hydride and then oxidize the alcohol mixture to the corresponding ketones. The mixture of semicarbazones obtained from the oxidation product mixture had a rotation of $[\alpha]^{25}D$ +0.97° (chloroform, *c* 4.0) after two crystallizations from acetonitrile. This optical activity can only reside in the semicarbazone of bicyclo(3.2.1)octanone-2 since the bicyclo(2.2.2)octanone-2 has a plane of symmetry.

When the enantiomorph of the above *p*-bromobenzenesulfonate ester was solvolyzed, reduced and oxidized, the semicarbazone obtained had a rotation equivalent in magnitude but opposite in sign, $[\alpha]^{25}D$ −0.92° chloroform, (*c* 3.4).

In order to determine whether the bicyclo-(2.2.2)octanol-2 retained any activity it was necessary to separate this mixture by v.p.c. on a preparative scale. The retention times of the alcohols in this mixture are only 1.7 minutes apart and the peaks overlapped considerably. A mixture (750 mg., $[\alpha]^{25}D$ +3.41°) was chromatographed, to yield 6 mg. of 96% pure bicyclo(2.2.2)octanol-2, which was dextrorotatory. The observed rotation corresponds to 82 ± 15% retention of activity and configuration (see Experimental).

The other component of the mixture, *trans*-bicyclo(3.2.1)octanol-2, was isolated (4 mg.) in 98% purity and was levorotatory.

Discussion

In the bicyclo(2.2.1)heptyl systems rate enhancement has been observed in the solvolysis of the *exo* and *endo* isomers. That the *exo* isomer solvolyzed faster than the *endo* has been interpreted in terms of carbon participation[9] and/or relief of steric strain.[9,10] The general topic has been discussed in a recent review.[11]

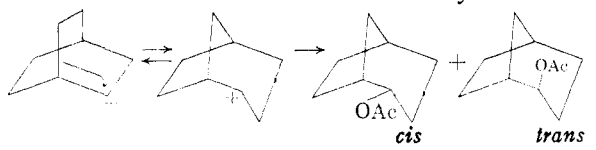
(9) S. Winstein, B. K. Morse, E. Grunwald, H. W. Jones, J. Corse, D. Trifan and H. Marshall, *ibid.*, **74**, 1127 (1952).

(10) See H. C. Brown, *Science*, **103**, 385 (1949); H. C. Brown and R. S. Fletcher, *J. Am. Chem. Soc.*, **71**, 1845 (1949), for a general discussion.

(11) A. Streitwieser, Jr., *Chem. Revs.*, **56**, 571 (1956).

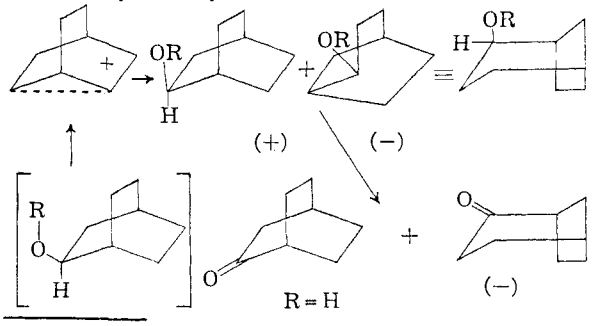
Unfortunately *exo* and *endo* isomerism is not possible in the bicyclo(2.2.2)octyl system and therefore a direct test of the above phenomenon cannot be made. From the data in Table I it can be argued that very little, if any, rate enhancement is occurring. At 25° the acetolysis of bicyclo-(2.2.2)octyl-2 *p*-bromobenzenesulfonate is 53 times faster than the cyclohexyl *p*-bromobenzenesulfonate and the cyclopentyl *p*-bromobenzenesulfonate is 37 times faster than the cyclohexyl derivative. These results can be rationalized on the basis of I-strain as applied to 5- and 6-membered rings.[12] On the other hand, lack of significant rate enhancement need not necessarily exclude carbon participation in the transition state.[13] It should be noted that product analysis shows that 35% of the products is rearranged bicyclo(3.2.1)octanol-2.

In order to ascertain whether or not carbon participation or non-classical ion formation is occurring to any appreciable extent, the solvolysis of the optically active bicyclo(2.2.2)octyl-2 *p*-bromobenzenesulfonate was undertaken to determine the stereochemical course of the reaction. The acetolysis of the optically active *p*-bromobenzenesulfonate ester yielded an optically active acetate mixture which was reduced to the corresponding optically active alcohols. The alcohol mixture consisted of 65% bicyclo(2.2.2)octanol-2 and 35% *trans*-bicyclo(3.2.1)octanol-2. Important to note is the complete absence of *cis*-bicyclo(3.2.1)-octanol-2. It has been previously demonstrated that the *cis*-bicyclo(3.2.1)octanol-2 is the thermodynamically more stable isomer.[8] The complete absence of the *cis* isomer provides evidence that rearrangement to an open carbonium ion is unlikely since under these circumstances one would expect to obtain a mixture consisting largely of the *cis* isomer. The observation that only the *trans*



cis *trans*

is formed is consistent with the prediction based on the formation of a non-classical ion. Since the non-classical ion is dissymmetric, the product formed, besides being *trans*, should also be optically active. Oxidation of the alcohol mixture did indeed produce an optically active ketone. The activity could only reside in the bicyclo(3.2.1)octanone-2, since the bicyclo(2.2.2)octanone-2 possesses a plane of symmetry.

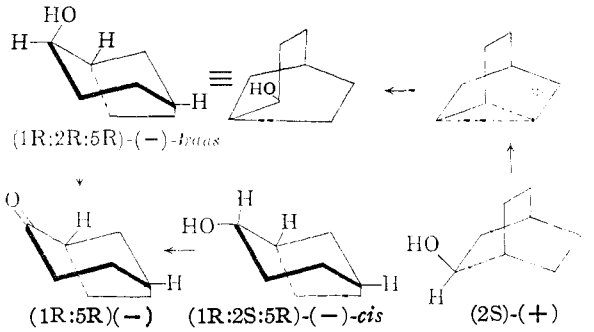


(12) H. C. Brown and G. Ham, *J. Am. Chem. Soc.*, **78**, 2735 (1956).
(13) M. J. S. Dewar, *Ann. Reports*, **48**, 118 (1951).

The non-classical ion intermediate requires that the bicyclo(2.2.2)octanol-2 portion of the solvolysis product should be active, and that furthermore the configuration should be retained. Separation of the alcohol mixture by vapor phase chromatography yielded a sample of bicyclo(2.2.2) octanol of 96% purity whose sign of rotation showed that retention of configuration had occurred and whose magnitude of rotation indicated the possibility of complete retention. Unfortunately, the size of the sample used and the small rotation observed permits us only to say that retention occurred to the extent of 82 ± 15%. This datum cannot exclude the open carbonium ion entirely, but it certainly permits one to say that if the open carbonium plays a role, it is only to a minor extent and that the non-classical or bridged-ion intermediate plays the major role in the reaction. The rate of solvolysis was also followed by polarimetric means and it was observed that the polarimetric rate is very similar to the titrimetric rate. Whether internal return occurs or not cannot be measured by our limited data, but may well prove to be important in this reaction, as it has in others.[3]

Our data also do not permit us to draw any conclusions with regard to C_6–C_2 hydrogen shifts since the amount of retention of optical activity in the bicyclo(2.2.2)octanol-2 could accommodate the occurrence of a hydride shift leading to a small amount of racemization

Absolute Configurations:



A sample of *cis*-bicyclo(3.2.1)octanol-2 was converted to the acid phthalate and resolved *via* its brucine salt to yield after hydrolysis (−)-*cis*-bicyclo(3.2.1)octanol-2, $[\alpha]^{25}D$ −8.2°. The alcohol was oxidized by chromic anhydride to the ketone, $[\alpha]^{24}D$ −55°. It will be recalled that (−)-*trans*-bicyclo(3.2.1)octanol-2 was isolated from the solvolysis product of the *p*-bromobenzenesulfonate ester of (+)-bicyclo(2.2.2)octanol-2 and that oxidation of this rearranged alcohol gave the (−)-ketone, isolated as its semicarbazone derivative.

The optical rotatory dispersion of the (−)-bicyclo(3.2.1)octanone-2 (Fig. 1) shows that this ketone exhibits a negative cotton effect. Application of the octant rule[14] provides one with the absolute configuration of the (−)-ketone as 1R:5R. Since the (−)-*cis*-and (−)-*trans*-bicyclo(3.2.1)-octanol-2 have been oxidized to the (−)-ketone their absolute configurations are 1R:2S:5R and 1R:2R:5R, respectively.

(14) W. Moffit, A. Moscowitz, R. B. Woodward, W. Klyne and C. Djerassi, unpublished work cited by C. Djerassi in "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960.

Based on the mechanism proposed for the rearrangement of the *p*-bromobenzenesulfonate ester of (+)-bicyclo(2.2.2)octanol-2 to (−)-*trans*-bicyclo(3.2.1)octanol-2, the absolute configuration of (+)-bicyclo(2.2.2)octanol-2 is assigned the 2S configuration.

Acknowledgment.—This work was supported in part by research grant CY-4065, National Institutes of Health, Public Health Service. We wish to thank Dr. M. O'Dwyer for obtaining the rotatory dispersion data and Prof. E. Grunwald for many helpful discussions.

Experimental[15]

Bicyclo(2,2,2)octene-2 was prepared by condensation of 1,3-cyclohexadiene and ethylene following the procedure described by Walborsky and Loncrini.[6]

Water-free Peracetic Acid.[16]—Phosphorus pentoxide (120 g.) was suspended in 500 ml. of anhydrous benzene and cooled in ice. Peracetic acid (30%, 150 ml.) was added carefully with stirring and cooling. The cold solution was filtered and stored in the ice-box until used.

2,3-Epoxybicyclo(2.2.2)octane.[6]—To 50 g. of bicyclo-(2.2.2)octene-2 and 5 g. of anhydrous sodium acetate in 125 ml. of anhydrous benzene was slowly added 500 ml. of anhydrous peracetic acid in benzene over a period of 2 hours. The temperature of the mixture was kept below 20° during the addition. The reaction mixture was allowed to remain at room temperature for 2 hours, freed from excess of peracetic acid by washing with dil. alkali, water and dried over anhydrous sodium sulfate. Evaporation of the solvent *in vacuo* gave 50 g. (87%) of product which was purified by sublimation; m.p. 190–192° (s.t.).

Bicyclo(2.2.2)octanol-2.[6]—2,3-Epoxybicyclo(2.2.2) octane (46 g.) was reduced by lithium aluminum hydride in the usual manner. The best yield was obtained when the decomposition was effected with ammonium chloride solution. Working up the reaction mixture gave the alcohol 45 g. (95%), m.p. 208–210° (s.t.). **The *p*-nitrobenzoate,** m.p. 96–98°, **the *p*-bromobenzenesulfonate** ester,[6] m.p. 80–81° and the acetate,[8] b.p. 105° at 20 mm., 61–62° (2 mm.), $n^{25}D$ 1.4705, were prepared.

Bicyclo(2.2.2)octyl-2 Acid Phthalate.—Bicyclo(2.2.2)-octanol-2 (30 g., 0.238 mole) was mixed with an equimolar quantity of resublimed phthalic anhydride (35.2 g.) and the mixture dissolved in 90 ml. of anhydrous pyridine. After being heated in an oil-bath at 100° for 4.5 hours, the reaction mixture was poured into 500 ml. of cold water and extracted thoroughly with benzene. The combined benzene extract was washed several times with 10% sulfuric acid, water, and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a solid (47.6 g., 70% yield) which was recrystallized from benzene and few drops of low boiling point petroleum ether; m.p. 155°.

Anal. Calcd. for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 70.06; H, 6.70.

Product Analysis in the Solvolysis of Bicyclo(2.2.2)-octyl-2-*p*-Bromobenzenesulfonate.—Pure bicyclo(2.2.2)-octyl-2 *p*-bromobenzenesulfonate (6 g., 0.0173 mole) was allowed to react in 550 ml. of dry glacial acetic acid containing sodium acetate (0.0313 *M*) for 600 minutes (*ca.* 12 half-lives) at 50°. The cooled solution was diluted with 1.5 l. of water and extracted three times with 200-ml. portions of pentane. The aqueous layer was diluted again with 1 l. of water and extracted similarly with pentane. The combined pentane extract was washed thoroughly with water, allowed to stand for 2 hours over anhydrous sodium carbonate and then dried over anhydrous sodium sulfate. The pentane solvent was stripped through a 12" column and the residue was distilled without an attempt at fractionation, to give a colorless liquid (2.4 g., 82.7%), b.p. 60–61° (2 mm.), $n^{23}D$ 1.4702.

Reduction of the Acetolysis Product.—To a slurry of 1.1 g. of lithium aluminum hydride in 25 ml. of anhydrous ether was added a solution of 2.0 g. (0.00119 mole) of the solvolysis acetate in 15 ml. of ether and allowed to stir at room temperature for 30 hours. The reaction mixture was decomposed carefully with water and worked up in the usual manner to give 1.3 g. (85%) of the solvolysis alcohol, m.p. 195–206° (s.t.).

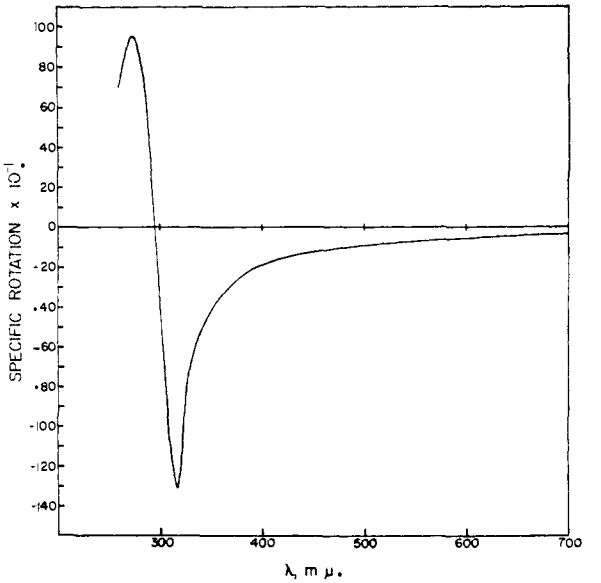


Fig. 1.—Rotatory dispersion curve of (—)-bicyclo[3.2.1]-octanone-2 (dioxane).

Analysis of the Alcohols by Vapor Phase Chromatography.—The retention times of pure *trans*-bicyclo(3.2.1)octanol-2 and pure bicyclo(2.2.2)-octanol-2, on a 3-ft. 30% glycerol-on-chromosorb column, were found to be 13.9 and 15.6 minutes, respectively. The optimum resolution was found to be at 93° with a flow rate of 200 ml./min. of helium gas as a carrier.

The alcohol from the solvolysis reaction was dissolved in absolute ethanol and passed through the column under the above conditions. Two peaks were obtained, beside the air and the solvent peaks, at 13.9 and 15.6 minutes, which overlapped partially. The areas under the two peaks were traced and their ratios were determined by weighing and by the use of a planimeter. The percentage of *trans*-bicyclo(3.2.1) octanol-2 from three different runs was 35 ± 3%.

Resolution of Bicyclo(2.2.2)octyl-2 Acid Phthalate.—Racemic bicyclo(2.2.2)octyl-2 acid phthalate (47 g.) was dissolved in a minimum of hot ethyl acetate and an equivalent amount of brucine was added. After standing overnight, feather-like crystals started to separate and after three days a total of 35 g. of the salt were filtered off. Another 23 g. separated out which were crystallized from ethyl acetate and combined with the first crop. The combined amount of the brucine salt was then recrystallized from ethyl acetate several times until a constant melting point, 135–145°, and a constant degree of rotation were obtained. The rotations observed for three consecutive crystallizations were, $[\alpha]^{25}D$ −25.90°, −26.14° and −26.70° (chloroform; *c*, 0.12, 0.15, 0.14), respectively. The amount of the brucine salt at this stage decreased to 47 g.

The brucine salt (47 g.) was dissolved in benzene and shaken three times with 50-ml. portions of 2 *N* hydrochloric acid. The benzene layer was washed with water and extracted with sodium bicarbonate solution. Acidification of the cold aqueous solution with cold dilute sulfuric acid liberated the acid phthalate which was filtered and dried. A total of 19 g. was recovered, m.p. 150–155°, $[\alpha]^{25}D$ −6.40° (chloroform, *c* 0.52).

The original ethyl acetate mother liquor which contained the other diasteroisomer was decomposed with hydrochloric acid and purified through the sodium salt as described above to give the enantiomorphic acid phthalate enantiomorph (15 g.).

Several fractional crystallizations of the individual enantiomorphs were carried out with each of the partially resolved acid phthalates until a constant melting point, 157–158°, and a constant degree of rotation was achieved.

(15) Melting points and boiling points are uncorrected. Analyses were performed by E. Thommen, Basel, Switzerland.

(16) L. Horner and E. Jurgens, *Ber.*, **90**, 2184 (1957).

In this manner, 15.5 g. of levoratatory bicyclo(2.2.2)octyl-2 acid phthalate $[\alpha]^{25}D$ −7.03° (chloroform, *c* 0.521), and 8 g. of the dextrorotatory enantiomorph $[\alpha]^{25}D$ + 6.86° (chloroform, *c* 0.643), were obtained.

Anal. Calcd. for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 70.31; H, 6.80.

Conversion of Bicyclo(2.2.2)octyl-2 Acid Phthalates Enantiomorphs to the Corresponding Alcohols.—In a typical experiment 8.3 g. of optically pure (−)-bicyclo-(2.2.2)octyl-2 acid phthalate, m.p. 157–158°, was dissolved in a solution of 10 g. of sodium hydroxide in 75 ml. of water and steam distilled. The liberated alcohol was collected together with *ca.* 200 ml. of water. The solid alcohol (2.5 g.) was filtered off and the aqueous solution after being saturated with sodium chloride, was extracted 4 times with 50-ml. portions of pentane. The combined pentane extract was washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent *in vacuo* gave 1.1 g. of additional alcohol, a total of 3.6 g. (94%), m.p. 210–211°. The alcohol was purified by sublimation and crystallization from pentane; m.p. 216–217° (s.t.), $[\alpha]^{25}D$ −7.45° (chloroform, *c* 0.750).

Similarly, 7 g. of optically pure bicyclo(2.2.2)octyl-2 acid phthalate (+) was converted to the corresponding alcohol, $[\alpha]^{25}D$ +6.80° (chloroform, *c* 0.615).

Anal. Calcd. for $C_8H_{14}O$: C, 76.12; H, 11.18. Found: C, 76.19; H, 11.01.

(+)-Bicyclo(2.2.2)octyl-2 *p*-Bromobenzenesulfonate.—To 1.5 g. of optically pure (−)-bicyclo(2.2.2)octanol-2 dissolved in 10 ml. of anhydrous pyridine was added gradually and with cooling and stirring 3.1 g. of recrystallized and dried *p*-bromobenzenesulfonyl chloride. After being left in the ice-box for 65 hours, the reaction mixture was poured on ice, and the separated crystalline solid (3.8 g., 93%) was filtered and dried. After three crystallizations from low-boiling petroleum ether, it gave m.p. 88–88.5°, $[\alpha]^{25}D$ + 1.2° (glacial acetic acid, *c* 1.40).

Anal. Calcd. for $C_{14}H_{17}O_3Br$: C, 48.70; H, 4.96. Found: C, 48.49; H, 5.05.

When the above reaction was repeated with 0.4 g. of the alcohol and the reaction mixture in pyridine was left only 20 hours, bicyclo(2.2.2)-octyl-2 *p*-bromobenzenesulfonate was obtained in 72.7% yield with an identical activity.

(+)-Bicyclo(2.2.2)octyl-2 Acetate.—Optically pure (+)-bicyclo(2.2.2)octanol-2 (1.5 g.) was dissolved in a mixture of 10 ml. of redistilled acetic anhydride and 15 ml. of glacial acetic acid and heated in an oil-bath at 75° for 7 hours. The reaction mixture was poured on ice and extracted 4 times with 50-ml. portions of ether. The combined ethereal extract was washed with water, and with a saturated solution of sodium bicarbonate and dried over anhydrous sodium sulfate. The solvent was stripped through a fractionating column and the residue was distilled *in vacuo* to give 1 8 g. (90%) of (+)-bicyclo(2.2.2)octyl-2 acetate, b.p. 58–59° (2 mm.), $[\alpha]^{26}D$ +4.03° (neat), $n^{25}D$ 1.4705.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.37; H, 9.59. Found: C, 71.23; H, 9.56.

Acetolysis of (−)-Bicyclo(2.2.2)octyl-2 *p*-Bromobenzenesulfonate in Glacial Acetic Acid.—Optically pure (−)-bicyclo(2.2.2)octyl-2 *p*-bromobenzenesulfonate (7 g.) was solvolyzed in 800 ml. of dry glacial acetic acid containing sodium acetate (0.032 *M*) in a bath at 50° for 15 hours. The reaction mixture was worked up in a similar manner to that of the racemic compound. The resulting acetate (2.9 g., 84%) had b.p. 60° at 2 mm., $n^{25}D$ 1.4702, $[\alpha]^{25}D$ +0.215° (neat).

Product Analysis.—The mixture of (+)-acetates obtained from the solvolysis of (−)-bicyclo(2.2.2)octyl-2 *p*-bromobenzenesulfonate was reduced to the corresponding alcohols by lithium aluminum hydride in the usual manner. The product of the reduction was sublimed *in vacuo* without fractionation; m.p. 185–201°, $[\alpha]^{25}D$ +3.41° (chloroform, *c* 10.0).

The alcohol mixture (0.75 g.) was separated by use of a preparative vapor phase chromatography column[17] employing the same conditions mentioned under analysis of the racemic product. Bicyclo(2.2.2)octanol-2 (6.2 mg., 96 ± 1% pure) and 2 mg. of *trans*-bicyclo(3.2.1)octanol-2 (98 ± 1% pure) were obtained. The activity of the samples was measured at 25°, with a recording Rudolf optical rotatory dispersion apparatus and using pure dioxane as the solvent.

The 6.2-mg. sample of (+)-bicyclo(2.2.2)octanol-2 was dissolved in 1 ml. of dioxane and the dispersion curve was measured and compared with the curve obtained from an optically pure ($[\alpha]^{25}D$ −7° ($CHCl_3$)) authentic sample of bicyclo(2.2.2)octanol-2 of an identical concentration. Specific rotations were calculated every 10 mμ in the region 300–600 mμ. for both the authentic sample and the solvolysis alcohol. From these data the percentage retention of activity was determined at each point and then averaged to obtain the average percentage retention. The average mean deviation was determined. The result of this analysis showed that retention of activity had occurred to the extent of 82 ± 15%.

The *trans*-bicyclo(3.2.1)octanol-2 was shown to have negative rotation but, due to the small sample (2 mg.) and the large errors involved, the magnitude of rotation was not determined.

Oxidation of the Solvolysis Alcohols.—The mixture of (+)-alcohols obtained from the reduction of the solvolysis product, without purification, was oxidized by chromic anhydride in acetic acid in the usual manner. The mixture of ketones was steam distilled from the reaction mixture and the distillate was saturated with sodium chloride, extracted thoroughly with ether, the ethereal layer washed and dried over anhydrous sodium sulfate. Evaporation of the solvent *in vacuo* gave the ketones, m.p. 158–60°.

The crude ketone (0.20 g.), in 2 ml. of ethanol was heated for 2 minutes on the steam-bath with semicarbazide hydrochloride (0.30 g.) and sodium acetate (0.30 g.) dissolved in 1 ml. of water. On dilution with water, the semicarbazone precipitated (0.26 g., 90%), m.p. 186–187°. It was recrystallized twice from acetonitrile; m.p. 191–192°, $[\alpha]^{25}D$ −0.97° (chloroform, *c* 4.00).

Anal. Calcd. for $C_9H_{15}N_3O$: C, 59.64; H, 8.34; N, 23.19. Found: C, 59.38; H, 8.42; N, 23.37.

The same set of experiments were repeated starting with the acetate obtained from the solvolysis of (+)-bicyclo-(2.2.2)octyl-2 brosylate. The resulting semicarbazone gave $[\alpha]^{25}D$ +0.92° (chloroform, *c* 3.38).

***cis*-Bicyclo(3.2.1)octyl-2 Acid Phthalate.**—*cis*-Bicyclo-(3.2.1)octanol-2 (10 g.) prepared as previously described[8] was converted to the acid phthalate following the procedure used for bicyclo(2.2.2)octyl-2 acid phthalate. Bicyclo-(3.2.1)octyl-2 acid phthalate (17 g.) was recrystallized from benzene–petroleum ether (30–60°); m.p. 114–117°.

Anal. Calcd. for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 70.31; H, 6.63.

Resolution of *cis*-bicyclo(3.2.1)octyl-2 Acid Phthalate.—The acid phthalate (15 g.) was dissolved in the minimum amount of acetone and an acetone solution of brucine alkaloid (21.5 g., 1 equ.) was added. The salt separated immediately was dissolved in a mixture of acetone and methanol and allowed to stand in the ice-box overnight to yield 23 g. of a crystalline solid, m.p. 120–124°, $[\alpha]^{24}D$ −22.7° (chloroform, *c* 1.4). After two recrystallizations from 2-butanone and one crystallization from ethyl acetate, 10 g. of the salt was decomposed in the usual manner to give the active acid phthalate (3.5 g.) which was further purified by extraction with a saturated solution of sodium bicarbonate followed by acidification. The acid phthalate had m.p. 107–110°, $[\alpha]^{24}D$ −11.6° (chloroform, *c* 1.55), and its infrared spectrum was identical with that of the racemic bicyclo(3.2.1)-octyl-2 acid phthalate.

(−)-*cis*-Bicyclo(3.2.1)octanol-2.—Bicyclo(3.2.1)octyl-2 acid phthalate (3 g.) was dissolved in 40 ml. of 10% sodium hydroxide and steam distilled. The distillate was saturated with sodium chloride and extracted thoroughly with ether, washed and dried. Evaporation of the solvent gave the alcohol (0.9 g.), m.p. 178–180° (s.t.), $[\alpha]^{24}D$ −8.2° (chloroform, *c* 1.4). Vapor phase chromatography showed that active bicyclo(3.2.1)octanol-2 consists of 95 ± 1% of the *cis* isomer. On a 3-ft. glycerol column (30% glycerol-on-chromosorb) at 93° with a helium flow-rate of 200 ml./min., the *cis* isomer has a retention time of 18.2 minutes.

(−)-Bicyclo(3.2.1)octanone-2.—Active bicyclo(3.2.1)-octanol-2 was oxidized as previously described[8] to the corresponding ketone. The ketone was purified by sublimation and chromatography on an alumina column; m.p. 125–126° (s.t.), $[\alpha]^{24}D$ −55.5° (chloroform, *c* 4.0), λ_{max}

(17) The separation was performed by Dr. W. F. Ulrich, Beckman Instrument Co.

TABLE II

SOLVOLYSIS OF BICYCLO(2.2.2)OCTYL-2 *p*-BROMOBENZENESULFONATE[a] AT 25 ± 0.05°

Time, sec.	$(a - x)$	$\frac{2.303}{(\log a/a - x)}$	k_1, sec.$^{-1}$ × 10^6
0	3.420	0.00	..
25,500	2.722	.2281	8.95
27,200	1.827	.6264	9.32
106,800	1.310	.9599	8.99
169,500	0.756	1.5096	8.91
284,400	0.253	2.6040	9.16
		Av.	9.07 ± 0.25

[a] 0.02850 *M*.

287 (ε 18); *RD* in dioxane (*c* 2.73), 23–24°: $(\alpha)_{700}$ −36.5, $(\alpha)_{589}$ −52, $(\alpha)_{317}$ −1306, $(\alpha)_{275}$ + 949, $(\alpha)_{260}$ +700.

The semicarbazone was prepared in the usual manner,[8] m.p. 167–69°, $(\alpha)_D$ −31.0° (chloroform, *c* 4.7).

Kinetics: Solvents.—The acetic acid was purified by refluxing with chromic anhydride, azeotropic distillation with benzene and collection of the purified acetic acid. The water content was determined by cryoscopy and sufficient acetic anhydride was added to make the solvent anhydrous and in addition to compensate for the water that is formed when sodium carbonate is allowed to react with acetic acid to make the standardized sodium acetate solution. The concentration of acetic anhydride was further determined by Kilpi's anthranilic acid method.

Titrations.—Analyses were performed with approximately 0.05 *N* standard perchloric acid and sodium acetate in glacial acetic acid. The standard perchloric acid was prepared from 60% aqueous acid which was compared with Bureau of Standards potassium acid phthalate. The sodium acetate reagent was obtained by dissolving reagent grade sodium carbonate in glacial acetic acid. Titrations were carried out with 5-ml. micro-burets. The best indicator was found to be brom phenol blue (1% solution in glacial acetic acid) and the end-point was approached from the acid side. The standard sodium acetate and perchloric acid were compared from time to time; the perchloric acid titer was found to be constant over a long period of time.

Rate Measurements.—The compound to be solvolyzed was weighed into a volumetric flask and made up to volume with the sodium acetate solutions (0.03–0.04 *M*). The amount of material used was calculated so that the solution would still contain sodium acetate at the end of the reaction. About 6-ml. portions of the solutions were sealed in ampoules and immersed in a suitable thermostat. At suitable time intervals an ampoule was removed and the reaction was interrupted by immersing it into ice. The ampoule was then brought to room temperature by placing in a beaker containing water, opened and a 5-ml. aliquot was removed, brought to acidity with perchloric acid and then titrated with standard sodium acetate to a bright faint yellow end-point.

First-order rate constants k, where $k = \frac{1}{t} \ln (a/a\text{-}x)$, a being the initial concentration in moles/liter of the material, t the elapsed time, and x the concentration of consumed base, were calculated. The results are summarized in the Tables II and III.

Polarimetric Measurements.—Polarimetric determinations carried out in this work were done with the aid of a Bellingham and Stanley model type polarimeter and a 2-dcm. polarimeter tube (unless specified). The measurements were carried out in a completely dark room using the sodium D line (λ 5893 Å.) (unless specified).

TABLE III

SOLVOLYSIS OF BICYCLO(2.2.2)OCTYL-2 *p*-BROMOBENZENE SULFONATE[a] AT 50.97 ± 0.05°

Time, sec.	$(a - x)$	$\frac{2.303}{(\log a/a - x)}$	k_1, sec.$^{-1}$ 10^4
0	4.419	0.00	..
18,000	2.637	.5166	2.87
36,000	1.690	.9613	2.67
54,000	1.105	1.2864	2.57
72,000	0.714	1.8231	2.53
94,800	0.445	2.259	2.42
		Av.	2.61 ± 0.26

[a] 0.02838 *M*.

Rate of Solvolysis of (−)-Bicyclo(2.2.2)octyl-2 *p*-Bromobenzenesulfonate.—(−)-Bicyclo(2.2.2)octyl-2-*p*-bromobenzenesulfonate was weighed in a volumetric flask (high concentration suitable for polarimeter reading) and made up to mark with pure glacial acetic acid containing sodium acetate (calculated to react completely with the liberated *p*-bromobenzenesulfonic acid). The flask was thermostated in the bath at 25° and at suitable time intervals readings were taken in the following way. The solution was filtered off from the suspended particles by decantation into a specially designed filtration apparatus (which was thermostated during filtration) and a weak pressure of nitrogen was applied. The clear solution was transferred quickly and quantitatively to the polarimeter tube which was also thermostated by having water from the bath circulating around it. The average of ten readings from both sides of the tube was recorded which showed a maximum deviation of ±0.010° from each separate reading. The solution was returned back to the flask and thermostated. The green mercury light with suitable filter was used, and polarimetric rate constants were calculated using the equation

$$2.303 \log 10 \frac{\alpha_0 - \alpha_\infty}{\alpha_t - \alpha_\infty} = kt$$

Table IV summarizes the results obtained in a typical run.

TABLE IV

RATE OF SOLVOLYSIS OF (−)-BICYCLO(2.2.2)OCTYL-2 *p*-BROMOBENZENESULFONATE[a] AT 25 ± 0.05°

Time, sec.	α	$\left(\frac{\alpha_0 - \alpha_\infty}{\alpha t - \alpha_\infty}\right)$	$\frac{2.303 \log}{\left(\frac{\alpha_0 - \alpha_\infty}{\alpha t - \alpha_\infty}\right)}$	k_1, sec.$^{-1}$ × 10^6
0	−0.155	1	0	...
13,020	− .128	1.122	0.1152	8.90
28,920	− .97	1.310	.2701	9.30
70,920	− .049	1.760	.5670	8.00
117,120	+ .021	3.550	1.267	10.80
160,120	+ .045	5.440	1.6941	10.60
.....	+ .090	...	....	...
			Av.	9.4 ± 1.4

[a] Brosylate = 0.276 *M*; NaOAc = 0.302 *M*.