Reactions of the Bicyclo[2.2.1]heptane System. X. The Composition of Norbornene Oxide and the Course of Its Hydrogenolysis with Various Reagents

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Various lines of evidence presented here show that norbornene oxide is a mixture of *exo*-2,3- (*ca.* 94%) and *endo*-2,3- (*ca.* 6%); the formation of the 2,7-oxide by direct epoxidation of norbornene could not be detected. Reduction of the *exo*-2,3-oxide with lithium aluminum hydride produces a mixture of 2-*exo*- and 7-norborneol, the amount of the 7-component depending on solvent and temperature. Further details bearing on the mechanistic course of this and related rearrangements are discussed.

In the course of studies on the reactions of the titled bicyclic systems[2] it was necessary to synthesize a deuterium labeled *exo*-norbornyl tosylate. The projected synthetic scheme followed the reaction sequence shown in Figure 1.

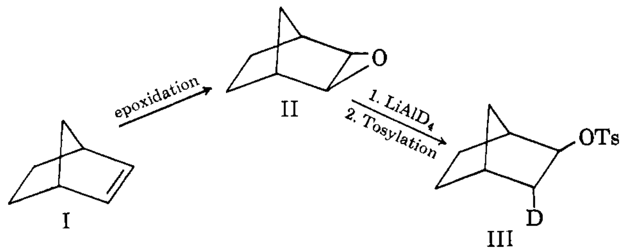

Figure 1

However, it soon became apparent that this scheme was not as straightforward as it seemed, since the product alcohol whose preparation in this manner had been previously reported in the literature,[3] was not a pure substance, but rather a mixture of norborneols. Suspicion as to the source of these impurities was directed at each of the intermediate steps and a thorough reexamination seemed to be required of both the epoxidation of norbornene as well as the reduction of the epoxide with lithium aluminum hydride.

Preliminary Examination of the Solvolysis of the Norbornyl Tosylate Preparation.—The tosylate prepared according to the reaction scheme in Figure 1 was subjected to formolysis at room temperature and worked up in the usual manner[3] to isolate the norbornyl formate product. Vacuum distillation of the crude product yielded far less formate than expected on the basis of the known reaction kinetics.[3] In addition, a residue of more than 12% was recovered which evidently corresponded to a very unreactive tosylate, (IV) (analysis). When this tosylate was recrystallized several times it melted at 54° and gave no substantial depression on determination of the mixed m.p. with authentic 2-*exo*-norbornyl tosylate. However, when IV was subjected to 45 hours heating at 90° in formic acid it still showed no sign of having undergone reaction, in contrast to *endo* (VII) and *exo* (III) tosylates which are completely formolyzed under these circumstances. It was subsequently deduced that IV was the derivative of the previously characterized[4] 7-norborneol (V).

By means of a simple experiment using pure III, prepared by hydration of norbornene and formation of the tosylate, it was established that the 7-norbornyl tosylate had not been formed during the formolysis by some sort of unexpected rearrangement. Consequently, V must have arisen during either or both of the step; in the preparative scheme (Figure 1) prior to tosylations namely, in the epoxidation of I or the lithium aluminum hydride reduction of the epoxide (II).

The Composition of Norbornene Oxide.—The reactions of norbornene (I) under various epoxidizing conditions have appeared to yield only a single product.[5–7] One basis for assigning the *exo*-2,3-structure (II) to this product was the observed formation of *exo*-norborneol on reduction with lithium aluminum hydride. Greene and Rees[8] have observed that other derivatives of norbornene obtained by oxidation with phthaloyl peroxide to possess the 2,7-structure. Soloway and Cristol,[7] however, have rejected the 2,7-epoxy structure for II on the basis of infrared studies founded on the known absorption characteristics of 1,2-, 1,4-, and 1,5-cyclic oxides.[9]

We considered the possibility that norbornene oxide is a mixture contaminated with a small amount of the 2,7-oxide component and undertook to synthesize this substance for characterization purposes. Several vain attempts were made. The first failure occurred in attempting the dehydration of the 2,7-*syn*-diol in a manner analogous to that by which 1,4-cyclohexanediol is converted with basic alumina to the 1,4-epoxide.[10] In subsequent trials neither the dehydrobromination of 2-bromo-7-hydroxynorbornane nor the dehydrotosylation of the monotosylate of the 2,7-*syn*-diol gave the desired 2,7-epoxide.

Coördination of the 2,3-oxide with magnesium halide and a hoped for isomerization to the 2,7-oxide, analogous to similar oxide rearrangements in alicyclic systems[11] again encountered failure. The principal product of this reaction was norcamphor.

Since none of the attempts to prepare the 2,7-oxide had proved fruitful, vapor phase chromatographic studies were undertaken in the hope of separating an inhomogeneity in the composition of the epoxide that might be responsible for the mixed composition of the norborneol. It was found, subsequently, that a minor peak corresponding to about 6% of the total accom-

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[1] Fulbright Fellow at the University of Delaware, 1959–1962.

[2] Ph.D. thesis of J. Nyce, University of Delaware, June, 1960.

[3] S. Winstein and D. S. Trifan, *J. Am. Chem. Soc.*, **71**, 2953 (1949); **74**, 1147, 1154 (1952).

[4] S. Winstein, M. Shatavsky, C. Norton, and R. B. Woodward, *ibid.*, **77**, 4183 (1955).

[5] H. Walborsky and D. F. Loncrini, *ibid.*, **76**, 5396 (1954).

[6] H. Kwart and W. G. Vosburgh, *ibid.*, **76**, 5400 (1954).

[7] S. B. Soloway and S. J. Cristol, *J. Org. Chem.*, **25**, 327 (1960).

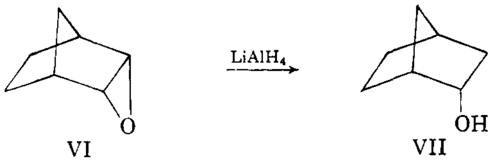
[8] F. D. Greene and W. W. Rees, *J. Am. Chem. Soc.*, **82**, 890 (1960).

[9] W. A. Patterson, *Anal. Chem.*, **26**, 823 (1954).

[10] E. L. Wittbecker, H. K. Hall, Jr., and T. W. Campbell, *J. Am. Chem. Soc.*, **82**, 1218 (1960).

[11] R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959).

panied the dominant oxide peak. This amount comprised less than half of the amount of 7-norbornyl tosylate residual after protracted solvolysis in formic acid and thus this 6% component of the epoxide mixture could not be the progenitor of all the 7-norborneol contaminant of the final product mixture in the reaction series (Figure 1). Furthermore, when this minor fraction was reduced with lithium aluminum hydride it gave neither 2-*exo*-norborneol (III) nor 7-norborneol (V). The mixed melting point and infrared spectrum of the 3,5-dinitrobenzoate prepared from the reduction product identified it as a pure sample of 2-*endo*-norborneol (VII). Consequently, we have assigned to this second (6%) component of the norbornene oxide mixture the 2,3-*endo* structure (VI).



VI VII

When the major (94%) fraction was subjected to vapor phase chromatographic analysis on the same (silicone 200) or other (Ucon-polar and Lac) columns it displayed only a single, symmetrical peak. This gave some confidence in the following inferences: (1) *endo*-VI is the only contaminant of the norbornene oxide; (2) VI is a direct epoxidation product and was not formed on the chromatographic column by thermal isomerization of *exo*-II; and (3) a 2,7-oxide does not form in detectable amounts under the epoxidation conditions employed, a conclusion reached previously by Soloway and Cristol.[7]

It seems fairly clear, also, that the rule of *exo* addition is not as exclusive as had been supposed[12] and that *endo* addition to norbornene may often be an accompanying but slower reaction. We have established this also for other addition reactions. This matter will be discussed as a factor in the mechanism of addition to the bicyclic double bond in a forthcoming article from these laboratories.

Finally, the 2,3-*endo* impurity in norbornene oxide can not be identified as the source of some of the 2-*exo*-7-*anti*-norbornanediol[13] which is formed as a constituent of the acid-catalyzed rearrangement products of the epoxide mixture, II plus VI.

Hydrogenolysis of Norbornene Oxide.—The ring opening of 1,2-epoxides with lithium aluminum hydride is generally accepted to involve an SN2-like displacement mechanism[11] with the AlH_4^- ion performing as the nucleophilic reagent. However, the abnormally great resistance of norbornene oxide to ordinary nucleophilic ring opening (such as with strong hydroxide and alkoxide ion)[14] suggests that the facile reaction with AlH_4^- must be experiencing electrophilic assistance. The very strong tendency of the *exo*-2,3-epoxide (II) to ring opening with electrophilic catalysis has already been amply demonstrated.[5,6] The ability of lithium aluminum hydride to function as an electrophilic reagent has been demonstrated hitherto in hydrogenolysis studies in which this reagent also produces concomitant rearrangement that is not to be noted with other hydrogenolysis reagents.[15] Still another example of the electrophilic activity of lithium aluminum hydride has been elucidated by Corey and co-workers[16] for the case of cholesteryl tosylate undergoing hydrogenolysis to cholestane *via* the cyclocholesteryl cation instead of by direct displacement.

In the present instance, the formation of an alcohol product (V) of the hydrogenolysis clearly implicates the electrophilic characteristic of the lithium aluminum hydride and stamps the rearrangement leading to its formation as a typical Wagner–Meerwein change. Furthermore, as seen from the results in Table I, the use of more polar solvents at higher temperatures greatly increases the ease of reaction and the proportion of the rearrangement product.

Table I

Amount[a] of 7-Norborneol Formed by Reduction of 2,3-Norbornene Oxide

Reagent	Solvent	% 7-Alcohol
$LiAlH_4$	N-Ethylmorpholine	16
$LiAlH_4$	Tetrahydrofuran[b]	8
Na	Ethanol	0

[a] Determined by solvolyzing the tosylate mixture in 60% ethanol–water for 2 hr. at 30°. The titration[3] is corrected for the amount of the 2-*endo*-tosylate. [b] Bartlett and Giddings[17] report that in ether solvent with reflux times as long as 72 hr. the 7-alcohol rearrangement product is eliminated.

Bartlett and Giddings[17] have formulated a mechanism for the reduction of benznorbornene oxide in which the electrophilic character of the lithium aluminum hydride is attributed to the lithium cation. We prefer, instead, to assign the electrophilic function to the aluminum atom of an aluminum hydride molecule, arising as a component of an equilibrium with lithium hydride and lithium aluminum hydride normally considered to be displaced in the direction of forming aluminum hydride to an undetectable extent. In the presence of oxide (II) we may assume the establishment of a second equilibrium leading to the formation of an oxide–aluminum hydride complex as shown in Figure 3. The latter may be considered to originate all the possible reaction paths indicated in Figure 3 to lead to normal (*trans*) or rearranged reduction product.

The reaction course shown in Figure 3 is more attractive for several reasons. For one, trivalent aluminum complexes are very much stronger Lewis acids than lithium cations could be, especially since the latter undoubtedly exist in tight ion-multiplet association with AlH_4^- contraions. Secondly, we have attempted to test the possibility that an alkali cation can function as an electrophilic reagent by carrying out the hydrogenolysis of norbornene oxide with sodium in ethanol where a considerable concentration of sodium ethoxide is present. Failure to identify any 7-norborneol in

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[12] See for further discussion L. Kaplan, H. Kwart, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **82**, 2341 (1960).

[13] H. Krieger, *Suomen Kemistilehti*, **B31**, 340 (1958).

[14] Unpublished results of W. A. Vosburgh from these laboratories, 1954.

[15] See for examples and other references H. Kwart and G. Null, *J. Am. Chem. Soc.*, **81**, 2765 (1959).

[16] E. J. Corey, H. G. Howell, A. Boston, R. L. Young, and R. A. Sneen, *ibid.*, **78**, 5036 (1956).

[17] P. D. Bartlett and W. P. Giddings, *ibid.*, **82**, 1240 (1960). These authors also noted the contamination of the 2-norborneol with 7-norborneol resulting from reduction of norbornene oxide with lithium aluminum hydride. No further detail is given except the statement that infrared studies were done. Our work (reported here), which confirms their assignment, was completed prior to the appearance of their article (ref. 14).

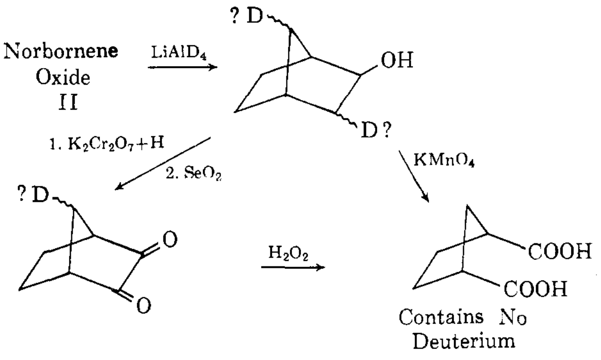

Figure 2

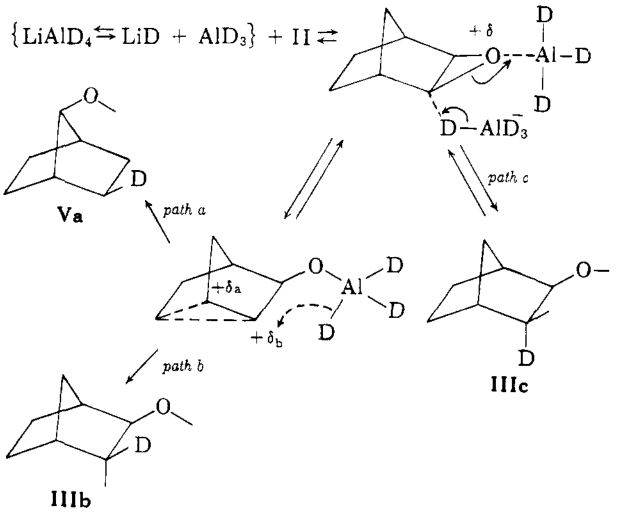

Figure 3

the product would seem to indicate that the Wagner–Meerwein rearrangement of the oxide (II) is not susceptible to catalysis by sodium cations. We have also carried out this reaction in toluene medium using only one equivalent of sodium (two g.-atoms) and slightly more than one equivalent (two moles) of *t*-butyl alcohol[18a] with smaller yield but with results quite similar to those observed for the reaction in ethanolic medium. A different result with the use of lithium cations here could not have been anticipated.

Finally, we must consider other evidence that compels rejection of a rearrangement mechanism of the epoxide *via* electrophilic catalysis by lithium cations.[17,18a] Normally oxides (other than ethylene and propylene) react in a pinacol like rearrangement under the influence of electrophilic catalysts such as RMgX, R_2Zn, MgX_2, ZnX_2, etc. On the other hand, the corresponding lithium reagents (RLi) give normal addition products with all oxides, the rearrangement reaction clearly requires greater coördinating ability than lithium cation can supply, although it is quite sensitive to the coördinating activity of magnesium, zinc, aluminum, and other Lewis acid centers in complex ions.

We have speculated, also, that the rearrangement of *exo*-norbornene oxide (II) during lithium aluminum hydride reduction may be more deep seated than indicated in Figure 3, involving possibly a series of Nametkin changes such as are often encountered in carbonium ion reactions in the related camphane series.[18b] To test for the occurrence of such a possibility, we undertook to trace the distribution of deuterium incorporated into the 2-norborneol during reduction of II with lithium aluminum deuteride. The rationale of this experiment is analogous to that upon which Roberts and co-workers based their appreciation of the scrambling of a labeled atom when carbonium ion reactions occur on the norbornane skeleton.[19]

The two alternative schemes by which the deuterium trace was accomplished are outlined in Figure 2. The recovery of the completely undeuterated end product of both degradation lines, *cis*-1,3-cyclopentanedicarboxylic acid, signifies that all of the 2-norborneol had been deuterated in the C-3 position and confirms that the course of reaction producing (V) is a simple Wagner–Meerwein probably passing thru path *a*, Figure 3.

The question of whether the *exo*-2-norborneol is formed *via trans* displacement on the aluminum-oxy complex in path *c*, or *via* the bridged ion intermediate through path *b* has been settled by the finding that the deuterium in the deuterated 2-norborneol product has the *endo* configuration of (IIIc) rather than the *exo* configuration (IIIb).

Experimental

The preparation of most of the compounds used was carried out according to procedures given in the various pertinent references designated above. The properties of these agreed very well with those reported in the literature. All melting point and boiling point values given below are uncorrected.

Preparation of *exo*-Norbornyl Tosylate.—Though Winstein and Trifan[3] have prepared the *endo*-tosylate no report of the *exo*-tosylate exists in the literature. A crude yield of this tosylate (92%) was obtained following the procedure of ref. 3. After being washed with a small amount of *n*-pentane on a Büchner funnel, the m.p. was 52.5–53.5°; 53–54° after one recrystallization from *n*-pentane.

Anal. Calcd. for $C_{14}H_{18}O_3S$: C, 63.16; H, 6.77. Found: C, 62.97; H, 6.59.

Solvolysis in Formic Acid.—The deuterio tosylate (26.5 g., 0.1 mole) (prepared by reaction of norbornene oxide with lithium aluminum deuteride according to ref. 6 and tosylation by the procedure above) was dissolved in 100 g. of formic acid (99–100%) at room temperature (25–26°). No heat was generated during solution of the tosylate. The solution became dark red after standing at room temp. for 70 hr. After quenching the reaction with ice-water, the organic layer was extracted with *n*-hexane. Evaporation of solvent yielded 13.2 g. of a brown-colored oil. Vacuum distillation of this oil afforded *exo*-norbornyl formate boiling at 71–73°, 120 mm. The yield was 8.6 g., 61.4%; residue 3.3 g. Since the yield of formate was less than expected and the residue was more than expected, the dark residue was cooled with *n*-hexane in a refrigerator. The crystals that separated were recrystallized from *n*-hexane–ether (1:1) to give colorless crystals. The yield was 0.8 g.; m.p. 54–56°; mixed melting point with *exo*-norbornyl tosylate, 50–53°. This was not considered a great depression of melting point in a class of compounds renowned for large cryoscopic constants. However, infrared spectra of the two samples were different. The colorless crystals were proven to be 7-norbornyl tosylate in the following way. The tosylate isolated from the distillation was further treated with boiling formic acid for 48 hr. to solvolyze any *endo*-tosylate (VII) that may have been present. After the usual work-up procedure, the separated crystals had m.p. 56.5–57.3°. A mixed melting point and comparison of the infrared spectra with an authentic sample of 7-tosylate established its identity, (*vide infra*). We could isolate no residual tosylate after identical

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[18] (a) This experiment was carried out in response to a suggestion of a referee who considered it likely that the ethanol medium had damped the electrophilic character of the sodium cations. (b) See for some examples S. Nametkin, *et al.*, *J. prakt. Chem.*, **124**, 144 (1930); *Ber.*, **66**, 511 (1933); A. I. Sivkoff, *J. Gen. Chem. USSR*, **15**, 70 (1945); and, particularly, A. Lipp and G. Stutzinger, *Ber.*, **65**, 241 (1932).

[19] J. D. Roberts and C. C. Lee, *J. Am. Chem. Soc.*, **73**, 5998 (1951); J. D. Roberts, C. C. Lee, and W. H. Saunders, Jr., *ibid.*, **76**, 4501 (1954).

treatment of pure 2-*exo*-norbornyl tosylate (10 g.) with 40 g. of formic acid.

Oxidation of the Solvolyzed Product.—Norborneol derived from formic acid solvolysis after saponification of the formate ester was oxidized by two methods. In the first method, 0.8 g. of norborneol was oxidized with 1.6 g. of potassium dichromate and 1.4 g. of sulfuric acid in 4 g. of water at room temperature by stirring for 6 hr. The norcamphor isolated (0.5 g.) was treated with 0.5 g. of selenium dioxide in 1.5 cc. of xylene at refluxing temperature for 4 hr., then after filtering off the selenium which separated, the yellow xylene solution was treated with 2 g. of 30% hydrogen peroxide and a catalytic amount of sodium bicarbonate at room temp. (20–25°) for 2 hr. Upon working up in the customary fashion 320 mg. of crude acid was obtained, which was recrystallized from benzene, and then from water; final m.p. 119–120°.

In the second method norborneol was oxidized by a procedure modified from that given by Roberts, *et al.*[19] The solution consisting of 5 cc. of pentane and 1.0 g. of norborneol was placed in a pressure bottle with a neoprene stopper. To this was added 40 cc. of a 20% potassium hydroxide solution containing 4 g. of potassium permanganate while cooling with dry ice-saturated aqueous sodium chloride mixture. After being stirred magnetically for 5 hr. at a temperature below $-5°$, the excess reagent was reduced with sodium bisulfite at a temperature below 0°. Acidification of the aqueous layer followed by continuous extraction with ether gave 510 mg. of crude acid. This was crystallized first from benzene, then from water, and finally vacuum sublimed; m.p. 121°, infrared spectrum superimposable on that of *cis*-1,3-cyclopentanedicarboxylic acid.

Oxidation of the Products of Lithium Aluminum Deuteride Reduction of II.—The potassium permanganate oxidation reaction sequence was carried out on the alcohol product of reduction of norbornene oxide with lithium aluminum deuteride. The final dibasic acid product contained no deuterium. The experimental evidence bearing on the identification of the deuterated 2-norborneol as (IIIc) will be discussed in a future article on a closely related subject.

Reduction of Norbornene Oxide with Sodium and Alcohol.—To 100 ml. of warm ethyl alcohol solution of 10 g. of norbornene epoxide was added 10 g. of sodium with vigorous stirring. The solution turned dark red; after complete consumption of the metal, 160 cc. of water was added, and the solution was extracted with *n*-pentane. After evaporation of *n*-pentane and working up in the manner described above for the norborneol preparations 1.9 g. of crystals was recovered. Tosylation in the usual way (*vide supra*) of 770 mg. of this alcohol (infrared) afforded 1.37 g. of crystalline product, which, after desiccation, melted at 54.5–55.5°. The infrared spectrum of this tosylate and mixed melting point with authentic 2-*exo*-norborneol tosylate completed the identification. The purity of the tosylate as determined by the titrimetric method was > 96%.

Preparation of the *p*-Nitrobenzoate of 7-Norborneol and Isolation of 7-Norbornyl *p*-Nitrobenzoate from the Product of Lithium Aluminum Hydride-reduced Norbornene Oxide.—The authentic 7-norborneol was prepared by the procedure of Walborsky.[5] The derivative was prepared by a standard method, using 230 mg. of 7-norborneol and 550 mg. of *p*-nitrobenzoyl chloride in 2 cc. of pyridine. The crude product (450 mg.) was recrystallized from alcohol, m.p. 106–107°. The mother liquor from the recrystallization of *p*-nitrobenzoate prepared from lithium aluminum hydride-reduced norborneol was evaporated to dryness. After five recrystallizations (two from 80% aq. alcohol and three from *n*-hexane) yellowish crystals were obtained which melted at 105–106°. The m.p. was not depressed when mixed with the authentic specimen.[5] The pure 2-*exo*-norbornyl *p*-nitrobenzoate melts at 85.5–86.5°, and 2-*endo*-norbornyl *p*-nitrobenzoate at 79–80°. The tosylate prepared from 40 mg. of pure 7-alcohol and 60 mg. of *p*-toluenesulfonyl chloride in 3 ml. of pyridine melted at 54.5–55.3° did not depress the m.p. of the tosylate recovered after solvolysis of the tosylates mixture in formic acid (*vide supra*) and had a superimposable infrared spectrum.

Gas Chromatographic Separation of 2,3-Norbornene Oxide.—The 50% acetone solution of norbornene oxide was repeatedly separated on an analytical F and M 300 chromatograph equipped with an F and M silicone 200 on Chromosorb (15-ft.) column by injection of 80–90 μl. at a time at 130°. About 50 mg. of the minor fraction (oily solid) was collected in this fashion and reduced with 100 g. of lithium aluminum hydride in 2 ml. of N-ethylmorpholine. The infrared spectra was nearly identical with that of 2-*endo*-norborneol (VII). The crude product was converted to the 3,5-dinitrobenzoate derivative using 200 mg. of 3,5-dinitrobenzoyl chloride in 1 ml. of pyridine. After recrystallization first from alcohol, and then acetonitrile, lustrous plate crystals were obtained which melted at 116–117°; the m.p. was not depressed when mixed with an authentic sample (m.p. 121°) of *endo*-norbornyl 3,5-dinitrobenzoate. The same derivative prepared from authentic 2-*exo*-norborneol melts at 103.5–104.5° (lit., 104–105°) and that of 7-norborneol at 130–131°. The infrared spectrum was also superimposable on that of the derivative of 2-*endo*-norborneol.

The quantitative analysis of norbornene oxide was performed on a 10-ft. Ucon-polar column at 133°. Two distinct peaks were obtained, corresponding to 94% of *exo* isomer and 6% of *endo* isomer. When the pure *exo* isomer was injected into either the Ucon-polar or silicone 200 columns under the conditions specified above, no isomerization of the *endo* isomer could be detected.

Attempted Preparation of 2,7-Epoxide.—The mixture of 7-*syn*- and *anti*-2-*exo*-norbornane diol was prepared according to the procedure given by Kwart and Vosburgh.[6] The 7-*syn* compound was separated by Krieger's method.[13] The crude mixture gave 39 g. of the *anti*-7-alcohol starting with 96.2 g. of norbornene oxide. The monotosylation was performed in the usual manner (*vide supra*) using 23 g. of diol and 37.2 g. of *p*-toluenesulfonyl chloride in pyridine. The viscous oil thus obtained showed an hydroxyl group and a sulfonate group in its infrared spectra. This was treated in the manner described in the literature[10] for preparing similar oxetones. Only a complex mixture resulted which displayed hydroxyl, carbonyl, and olefin functions in its infrared spectra. No further investigations were performed.