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A General Synthesis of the Troponoid System Based on Solvolysis of 1,4-Dihydrobenzyl Tosylates[1]

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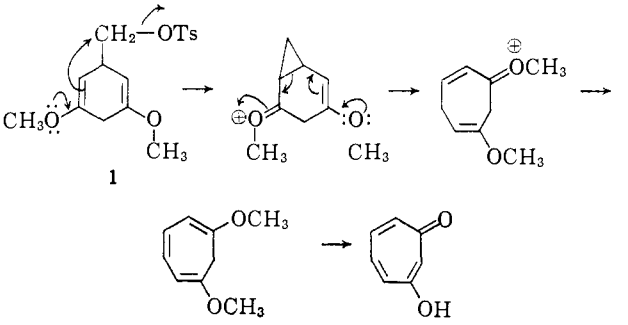
Birch reduction of 3,4,5-trimethoxybenzoic acid gives 3,5-dimethoxy-1,4-dihydrobenzoic acid. Lithium aluminum hydride reduction of the dihydroacid followed by tosylation and solvolysis of the tosylate in pyridine gives a mixture of 1,3-dimethoxycycloheptatrienes which on bromine oxidation gives β-tropolone in 28% average overall yield. This method has been applied to the synthesis of α-tropolone from 2,3-dimethoxybenzoic acid, γ-tropolone from 2,5-dimethoxybenzoic acid, 3-hydroxy-5-methyltropone (a degradation product of a photoproduct obtained from 4-methyltropolone methyl ether) from 3,4,5-trimethoxybenzoic acid and tropone from 3-methoxybenzoic acid. Solvolysis of 3-methoxy-1,4,5,6-tetrahydrobenzyl tosylate gives bicyclo[4.1.0] heptan-2-one, thus providing a facile synthetic entry to this bicyclic system. Solvolysis of 3,5-dimethoxy-1,4-dihydrobenzyl tosylate in acetic acid gives among other products a ketotosylate identified as 3-methoxy-5-oxo-3-cyclohexenylcarbinyl tosylate. This tosylate gives β-tropolone on solvolysis in dilute base. Relative rates of solvolysis of 3,5-dimethoxy-1,4-dihydrobenzyl tosylate, 3,5-dimethyl-1,4-dihydrobenzyl tosylate and 1,4-dihydrobenzyl tosylate show strong rate enhancement (6800) of the homoallylic ionization by a methoxyl group and enhancement by a factor of 46 by the methyl group. Consideration of the relative rates of solvolysis of 1,4-dihydrobenzyl tosylate, 3-methyl-1,4-dihydrobenzyl tosylate and 3,5-dimethyl-1,4-dihydrobenzyl tosylate and of 3-methoxy-1,4-dihydrobenzyl tosylate and 3,5-dimethoxy-1,4-dihydrobenzyl tosylate shows that primary assistance to the homoallylic ionization comes from one, *not both*, double bonds.

The three isomeric tropolones and tropone pose an interesting synthetic problem. Special syntheses have been developed for each compound, but no general method for this class of compounds is available. Satisfactory methods for the synthesis of α-tropolone,[2,4a] γ-tropolone[3] and tropone[4,5] are available. Study of the chemistry of β-tropolone, however, has been stymied by the lack of a useful synthesis of this compound. Our photochemical studies on simple troponoid systems[6,7] required β-tropolone, and in the course of developing a synthesis of β-tropolone we have developed the first generally applicable synthesis of the troponoid system.

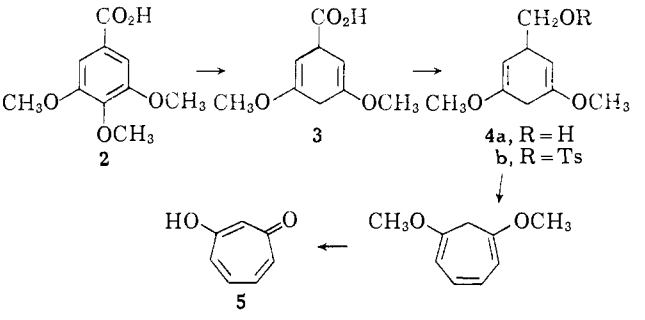
Two syntheses of β-tropolone have been reported.[7,8] Neither of these syntheses has proved practical for the preparation of β-tropolone in adequate quantity for investigation of its chemical, physical and biological properties. The chemistry of α-tropolone[9] and γ-tropolone[6,10,11] has received considerable attention, but the chemical study of β-tropolone has been limited to methylation, bromination and salt formation.[8]

Our approach to the synthesis of the troponoid system was based on the solvolytic ring expansion of 1,4-dihydrobenzyl tosylatesi nitially investigated by Nelson, Fassnacht and Piper.[12] The key feature of the projected β-tropolone synthesis was the solvolytic ring expansion of 3,5-dimethoxy-1,4-dihydrobenzyl tosylate (1). The solvolysis of a tosylate such as 1 raises two interesting questions: (1) Is the ionization assisted by one or both double bonds and (2) what is the effect of a methoxyl substituent on a homoallylic ionization? Introduction of a 6-methyl group enhances the solvolysis rate of cholesteryl tosylate by a factor of 75,[13] so



there was reason to anticipate a substantial rate enhancement by a suitably placed methoxyl substituent. This approach to the synthesis of β-tropolone was particularly appealing because it opened the possibility of synthesizing substituted β-tropolones, α-tropolone, γ-tropolone, tropone and a variety of less highly oxidized seven-membered carbocycles by a single method.

Synthesis of β-Tropolone.—Birch reduction of gallic acid trimethylether (2) gives 3,5-dimethoxy-1,4-dihydrobenzoic acid (**3**).[14] Lithium aluminum hydride reduction of **3** gives the alcohol **4a**. This alcohol shows a doublet in the infrared at 5.95 and 6.06 μ due to the enol ether double bonds. The nuclear magnetic resonance spectrum of **4a** shows two identical olefinic protons



at 5.50 τ and two identical methoxyl groups at 6.41 τ.[15] Treatment of 4a with *p*-toluenesulfonyl chloride in pyridine at 0° gives the tosylate **4b**.[16] This tosylate, though nicely crystalline, is extremely sensitive and proper precaution must be observed if it is not to be used

(1) A preliminary account of this investigation has been published: O. L. Chapman and P. Fitton, *J. Am. Chem. Soc.*, **83**, 1005 (1961).

(2) J. J. Drysdale, W. W. Gilbert, H. K. Sinclair and W. H. Sharkey, *ibid.*, **80**, 3672 (1958).

(3) O. L. Chapman and J. Meinwald, *ibid.*, **80**, 633 (1958).

(4) (a) A. P. TerBorg, R. van Helden and A. F. Bickel, *Rec. trav. chim.*, **81**, 177 (1962); (b) A. P. TerBorg, R. van Helden, A. F. Bickel, W. Renold and A. S. Dreiding, *Helv. Chim. Acta*, **43**, 457 (1960).

(5) T. Ikemi, T. Nozoe and H. Sugiyama, *Chemistry & Industry*, 932 (1960).

(6) O. L. Chapman and D. J. Pasto, *J. Am. Chem. Soc.*, **82**, 3642 (1960).

(7) W. G. Dauben, K. Koch, O. L. Chapman and S. L. Smith, *ibid.*, **83**, 1768 (1961).

(8) R. B. Johns, A. W. Johnson and M. Tišler, *J. Chem. Soc.*, 4605 (1954).

(9) For reviews see: T. Nozoe, Chapter VII in D. Ginsberg (Editor), "Non-benzenoid Aromatic Compounds," Interscience Publishers, Inc., New York, N. Y., 1959; P. L. Pauson, *Chem. Revs.*, **55**, 9 (1955).

(10) O. L. Chapman and D. J. Pasto, *J. Am. Chem. Soc.*, **81**, 3696 (1959).

(11) O. L. Chapman, D. J. Pasto and A. A. Griswold, *ibid.*, **84**, 1213 (1962).

(12) N. A. Nelson, J. H. Fassnacht and J. U. Piper, *ibid.*, **83**, 206 (1961).

(13) R. A. Sueen, *ibid.*, **80**, 3982 (1958).

(14) M. E. Kuehne and B. F. Lambert, *ibid.*, **81**, 4278 (1959).

(15) This confirms the loss of a methoxyl group in the Birch reduction of gallic acid trimethyl ether.

(16) The low temperature is necessary for good yields of the tosylate.

immediately. Solvolysis of **4b** in pyridine[17] gives a mixture of 1,3-dimethoxycycloheptatrienes.[18] Bromine oxidation of the dimethoxycycloheptatriene mixture gives β-tropolone (**5**) in 28% average over-all yield based on gallic acid trimethyl ether. The highest over-all yield obtained in a single run was 51%.

The general utility of this synthetic method for the preparation of derivatives of β-tropolone can be illustrated by the synthesis of 3-hydroxy-5-methyltropone (**6**). This synthesis was important in establishing the structure of the photoproduct **7** obtained *via* **8** from 4-methyltropolone methyl ether.[7] Alkylation of the dihydroacid **3** with potassium amide and methyl iodide gives 1-methyl-3,5-dimethoxy-1,4-dihydrobenzoic acid (**10**).[20] Lithium aluminum hydride reduction of **10** gives the alcohol **11a**. The structure of alcohol **11a** is confirmed by the nuclear magnetic resonance spectrum which shows two olefinic protons at 5.69 τ, two methoxyl groups at 6.43 τ, a $-CH_2-O$ group as a two proton singlet at 6.81 τ, a split two proton signal at 7.33 τ due to the allylic methylene group, an hydroxyl proton at 7.65 τ and a methyl group as a sharp singlet at 8.97 τ. The absence of methine absorption, the singlet methyl absorption and the presence of the allylic methylene protons rigorously fix the location of the methyl group introduced in the alkylation as shown in **10**. Solvolysis of the tosylate **11b** in pyridine gives a mixture of 1,3-dimethoxy-5-methylcycloheptatrienes which is oxidized by bromine in carbon tetrachloride to 3-hydroxy-5-methyltropone identical in absorption spectra and melting point to the sample obtained from the photoproduct **7**.

Synthesis of α-Tropolone.—The synthesis of α-tropolone is based on 2,3-dimethoxybenzoic acid (**12**). Birch reduction of **12** gives 2,3-dimethoxy-1,4-dihydrobenzoic acid (**13**). Expulsion of the buttressed methoxyl group which *a priori* might have been a source of concern is not a serious problem. Reduction of **13** with lithium aluminum hydride gives 2,3-dimethoxy-1,4-dihydrobenzyl alcohol (**14a**). This alcohol shows enol ether double bond absorption in the infrared (5.94 μ) but only normal olefinic absorption at 4.44 τ in the nuclear magnetic resonance spectrum. The nuclear magnetic resonance spectrum of **14a** also shows two non-equivalent methoxyl groups at 6.36 and 6.43 τ. Solvolysis of the tosylate **14b** in refluxing collidine gives a mixture of 1,2-dimethoxycycloheptatrienes which on oxidation with phosphorus pentachloride gives α-tropolone. This synthesis of α-tropolone is convenient and reasonably rapid. It or the recent method of Ter-Borg[4a] will be the method of choice unless one is equipped for handling tetrafluoroethylene.[21]

Synthesis of γ-Tropolone.—Application of the synthetic method to the preparation of γ-tropolone follows the standard pattern (**17-21**) and is based on 2,5-dimethoxybenzoic acid (**17**). The yield of γ-tropolone is not as good as for the other tropolones. The principal difficulty lies in the oxidation of the dimethoxycycloheptatriene to γ-tropolone. Bromine oxidation is only moderately satisfactory because γ-tropolone brominates readily. Other oxidizing agents including tropylium ion have not proved satisfactory.[22] Oxidation of the methoxycycloheptatrienes by hydride ion transfer to tropylium ion and other carbonium ions is under investigation. The preparation of γ-tropolone methyl ether (**22**) by degradation of teloidinone methobromide (**23**)[3] remains the method of choice for preparation of large quantities of γ-tropolone or γ-tropolone methyl ether.

Synthesis of Tropone.—Birch reduction of 3-methoxybenzoic acid (**24**) in our hands gives 3-methoxy-1,4-dihydrobenzoic acid (**25**) rather than the tetrahydroacid

(17) Non-basic solvents have not proved satisfactory for preparative scale solvolysis of 4b.

(18) This mixture may arise in the solvolysis or during the distillation of the crude product. We have recently observed that ethyl tropyl ether isomerizes thermally to 1-ethoxycycloheptatriene.[19] Professor H. J. Dauben has informed us that he also has observed similar isomerizations of alkyl tropyl ethers.

(19) Unpublished observations of O. L. Chapman and G. W. Borden.

(20) A. J. Birch, *J. Chem. Soc.*, 1551 (1950).

(21) An excellent α-tropolone synthesis employing tetrafluoroethylene is available.[2]

(22) We have not been able to accomplish hydride ion transfers between methoxycycloheptatrienes and tropylium ion, although the methoxycycloheptatrienylium ion should be more stable than tropylium ion. Volpin, *et al.*, have succeeded in demonstrating hydride exchange between cycloheptatrienes and tropylium ion.[23]

(23) Z. N. Parnes, M. E. Volpin and D. N. Kursanov, *Tetrahedron Letters*, No. **21**, 20 (1960).

previously described.[14,24] The structure of the dihydroacid (**25**) follows from the nuclear magnetic resonance spectrum. This spectrum shows the carboxylic acid proton as a singlet at -1.92 τ, two olefinic protons at 4.27 τ, a single olefinic proton at 5.27 τ a methine proton as a broad absorption at 6.13 τ, a methoxyl group at 6.47 τ and two methylene protons at 7.25 and 7.37 τ, respectively. Reduction of the dihydroacid **25** gives 3-methoxy-1,4-dihydrobenzyl alcohol (**26a**) which shows enol ether double bond absorption at 5.96 μ in the infrared and two olefinic protons at 4.41 τ, a single olefinic proton at 5.48 τ and a methoxyl group at 6.50 τ in the nuclear magnetic resonance spectrum. Tosylation of **26a** followed by solvolysis of the tosylate **26b** gives a mixture of methoxycycloheptatrienes which is oxidized to tropone (**27**) by bromine in carbon tetrachloride. Acid hydrolysis of the methoxycycloheptatriene mixture gives a mixture of 2,4-cycloheptadienone (**28**) and 3,5-cycloheptadienone (**29**) analogous to that obtained in the degradation of tropinone methoiodide.[25] The mixture of **28** and **29** can be air oxidized to tropone in basic solution. Air oxidation of 2,4-cycloheptadienone to tropone has been reported previously.[26]

Partial reduction of 3-methoxy-1,4-dihydrobenzyl alcohol (**25**) over platinum in methanol gives 3-methoxy-1,4,5,6-tetrahydrobenzyl alcohol (**30a**). This alcohol shows enol ether double bond absorption at 6.03 μ in the infrared and a single olefinic proton at 5.52 τ in the nuclear magnetic resonance spectrum. Solvolysis of the tosylate **30b** gives bicyclo[4.1.0]heptan-2-one (**31**) rather than 4-cycloheptenone (**32**) which might have been anticipated. The bicyclic ketone **31** shows a broad eight proton multiplet at 8.20 τ and a sharply split two proton band at 8.86 τ. The sequence **25**, **30**, **31** provides facile synthetic entry to the parent bicyclo[4.1.0]heptane system.

3-Methoxy-5-oxo-3-cyclohexenylcarbinyl Tosylate.—Preliminary measurements of the rate of solvolysis of 3,5-dimethoxy-1,4-dihydrobenzyl tosylate in acetic acid showed that the rate dropped off after 80% completion of the reaction. This observation suggested the presence of a less reactive tosylate. The less reactive tosylate is easily isolated from a preparative scale solvolysis by trituration of the crude solvolysis product with carbon tetrachloride. This tosylate shows ultraviolet absorption maxima at 227 mμ (p-toluenesulfonyl group) and 248 mμ (O—C—CH=C—OCH$_3$)[27] and infrared absorption at 6.12 μ (>C=O) and 6.25 μ (conjugated double bond).[27] This information together with the analysis and the nuclear magnetic resonance spectrum identify the less reactive tosylate as **33**. The nuclear magnetic resonance spectrum of **33** shows four aromatic protons as two identical AB systems at 2.20 and 2.60 τ (J_{AB} 9.0 c.p.s.), a single olefinic proton at 4.67 τ, a $-CH_2-O$ group as a doublet at 6.02 τ, a methoxyl group at 6.32 τ, an aromatic methyl group at 7.56 τ and a five-proton band centered a 7.60 τ due to the remaining two methylene groups and the methine proton. The formation of **33** in the solvolysis of 3,5-dimethoxy-1,4-dihydrobenzyl tosylate (**1**) in acetic acid containing acetic anhydride is interesting. The reaction probably involves acetic anhydride-catalyzed addition of acetic acid to one of the enol ether double bonds giving **34** which can decompose to methyl acetate and **35**. Double bond isomerization to the conjugated position gives **33**. The tosylate **33** does not solvolyze at a conveniently measurable rate at 30°. Solvolysis of the tosylate **33** in dilute sodium hydroxide quite unexpectedly gives β-tropolone. The yield (ultraviolet analysis) is quantitative in dilute solution. The reaction may be viewed as an internal alkylation giving **36** followed by base-catalyzed ring opening to **37** and air-oxidation to β-tropolone. An analogous reaction has been observed in the preparation of 2,4-cycloheptadienone.[26]

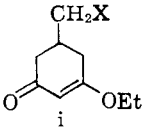
Synthesis of Methyl Substituted 1,4-Dihydrobenzyl Tosylates.—Synthesis of the methyl substituted 1,4-dihydrobenzyl tosylates follows the pattern established for synthesis of the methoxyl substituted 1,4-dihydrobenzyl tosylates. Birch reduction of 3-methylbenzoic acid (**38a**) gives 3-methyl-1,4-dihydrobenzoic acid (**39a**) Lithium aluminum hydride reduction gives the alcohol **40a** which on tosylation gives the tosylate **41a**. A similar sequence of reactions starting with 3,5-dimethylbenzoic acid (**38b**) and benzoic acid (**38c**) gives 3,5-dimethyl-1,4-dihydrobenzyl tosylate (**41b**) and 1,4-dihydrobenzyl tosylate (**41c**), respectively. The prod-

(24) A. J. Birch, P. Hextall and S. Sternhell, *Austral. J. Chem.*, **7**, 256 (1954).

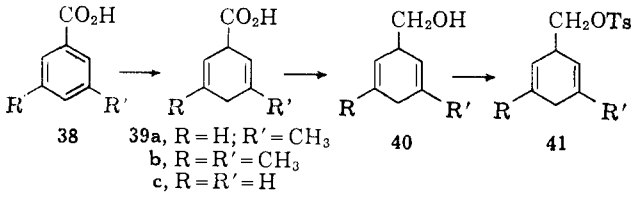
(25) J. Meinwald, S. L. Emerman, N. C. Yang and G. Büchi, *J. Am. Chem. Soc.*, **77**, 4401 (1955).

(26) E. E. van Tamelen and G. T. Hildahl, *ibid.*, **78**, 4405 (1956).

(27) These absorption characteristics compare favorably with compounds



of the type i prepared by the procedure of Kuehne and Lambert.[14]



38 39a, R = H; R' = CH_3 40 41
b, R = R' = CH_3
c, R = R' = H

ucts of solvolysis of 1,4-dihydrobenzyl tosylate have been characterized.[12] Each of the tosylates **41a,b,c** was obtained in crystalline form by low temperature crystallization from ether–petroleum ether. The dihydroacids and dihydroalcohols in the methyl substituted series were much more stable than their counterparts in the methoxyl substituted series.

Solvolysis Rates and Discussion.—The conformation of the 1,4-dihydrobenzyl tosylates is ideal for homoallylic assistance to ionization. The geometry of the homoallylic system in the conformation in which the tosyloxymethyl group is equatorial[28] is quite similar to the geometry of the homoallylic system in cholesteryl tosylate as judged by superimposing Dreiding models of the two systems. Ionization of the 1,4-dihydrobenzyl tosylates could involve assistance by both double bonds (*cf.* **42**) or assistance principally by one double bond (*cf.* **43**). A similar mechanistic dichotomy is encountered in the ionization of pentamethylcyclopentadienyl carbinyl brosylate[29] and tosylate.[30] The solvolysis of 3-methoxy-1,4,5,6-tetrahydrobenzyl tosylate (**30b**) shows that two double bonds are not essential for rapid ionization. The conformation of the tetrahydro-

42 43

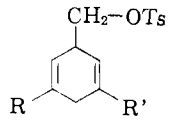
tosylate **30b** is, of course, significantly different from that of the 1,4-dihydrobenzyl tosylates, and this difference must be kept in mind in comparing these systems. The formation of the bicyclic ketone **31** in the solvolysis of **30b** eliminates from consideration a mechanism involving ring expansion by a direct alkyl migration (in which the driving force would be formation of the allyl carbonium ion). A clearer understanding of the details of the ionization of the 1,4-dihydrobenzyl tosylates should be possible through analysis of the relative rates of solvolysis.

Comparison of the rates of solvolysis of the 3-substituted-1,4-dihydrobenzyl tosylates with the 3,5-disubstituted and unsubstituted tosylates should permit a distinction between ionization assisted by both double bonds and ionization assisted primarily by one double bond. If ionization is assisted equally by both double bonds, the rate enhancement factor for two substituents (in the 3,5-positions) should be approximately the square of the rate enhancement factor for a single substituent (in the 3-position). If the ionization is assisted exclusively by one double bond, the difference in solvolysis rate between the monosubstituted and disubstituted tosylates should be the statistical factor two.[31] Comparison of the rates of solvolysis of 3,5-dimethoxy-1,4-dihydrobenzyl tosylate and 3-methoxy-1,4-dihydrobenzyl tosylate and of 3,5-dimethyl-1,4-dihydrobenzyl tosylate and 3-methyl-1,4-dihydrobenzyl tosylate shows in each case that solvolysis of the 3,5-disubstituted tosylates is only a factor of 2–3 more rapid than solvolysis of the 3 substituted tosylates. *This can only mean that the primary assistance to ionization comes from one, not both, double bonds.*

Comparison of the rates of solvolysis of 1,4-dihydrobenzyl tosylate (**41c**), 3,5-dimethyl-1,4-dihydrobenzyl tosylate (**41b**) and 3,5-dimethoxy-1,4-dihydrobenzyl tosylate (**4b**) shows that in these ionizations the methyl group enhances the solvolysis rate by a factor of **46** while the methoxyl group enhances the rate by a factor of 6800. This is the first case in which the electronic effect of a methoxyl group on a homoallylic ionization has been evaluated directly. The factor of 46 rate enhancement by a methyl group in the 1,4-dihydrobenzyl system may be compared with the factor of 75 rate enhancement by a 6-methyl group in cholesteryl tosylate.[13]

TABLE I

SOLVOLYSIS RATES OF 1,4-DIHYDROBENZYL TOSYLATES IN ACETIC ACID



R	R'	T, °C.	k, sec.$^{-1}$	k_{rel} (30°)
H	H	99.6	3.1×10^{-4}	
H	H	82.8	5.1×10^{-5}	
H	H	70.0	1.4×10^{-5}	
H	H	30.0	7.2×10^{-6}[a]	1
CH_3	H	82.8	6.5×10^{-4}	
CH_3	H	70.0	1.7×10^{-4}	
CH_3	H	60.0	6.3×10^{-5}	
CH_3	H	30.0	1.6×10^{-5}[b]	22
CH_3	CH_3	82.8	1.5×10^{-3}	
CH_3	CH_3	70.0	4.7×10^{-4}	
CH_3	CH_3	60.0	1.4×10^{-4}	
CH_3	CH_3	30.0	3.3×10^{-5}[b]	46
CH_3O	H	30.0	1.7×10^{-4}	2400
CH_3O	CH_3O	30.0	4.9×10^{-4}	6800

[a] Extrapolated from data at 99.6° and 70°. [b] Extrapolated from data at 82.8° and 60°.

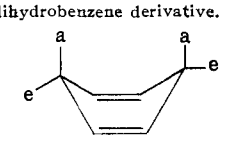
Acknowledgment.—The authors acknowledge financial support of this investigation by a grant (CA-04253) from National Institutes of Health, Department of Health, Education and Welfare.

Experimental

3,5-Dimethoxy-1,4-dihydrobenzoic Acid.[14]—Sodium (120 g.) was added in small pieces to a solution of 3,4,5-trimethoxybenzoic acid (200 g.) and methanol (1,200 ml.) in liquid ammonia (4 l.). When the addition was complete, ammonium chloride (500 g.) was added, and the ammonia was allowed to evaporate at room temperature. The resulting solid was dissolved in ice-water, and the solution was acidified to congo-red with 2 *N* hydrochloric acid at 0°. The solution was extracted with methylene chloride. After drying, the methylene chloride was removed at room temperature giving crude 1,4-dihydro-3,5-dimethoxybenzoic acid (162 g., 93%).

3,5-Dimethoxy-1,4-dihydrobenzyl Alcohol.—Crude 3,5-dimethoxy-1,4-dihydrobenzoic acid (162 g.) was added as a slurry in ether to a suspension of lithium aluminum hydride (68 g.) in ether (500 ml.) under nitrogen. After stirring for 1 hour the excess hydride was decomposed with moist sodium sulfate, and the mixture was filtered. Evaporation of the ether at room temperature gave the crude alcohol. Distillation of the crude product gave 3,5-dimethoxy-1,4-dihydrobenzyl alcohol (145.5 g.), b.p.

(28) It seems reasonable to extend the axial-equatorial concept to the 1,4-positions of a 1,4-dihydrobenzene derivative.



(29) L. DeVries, *J. Am. Chem. Soc.*, **82**, 5242 (1960).

(30) S. Winstein and M. Battiste, *ibid.*, **82**, 5244 (1960).

(31) This statistical factor arises from the fact that in the symmetrical 3,5-disubstituted tosylates the ionization will be facilitated equally by either double bond. In the 3-substituted tosylates this symmetry is not present and a selection between the two double bonds must be made if use is to be made of the 3-substituent.

93–95° at 0.2 mm., m.p. 38–40°, and an unidentified alcohol (20 g.), b.p. 115–117° at 0.2 mm.

Anal. Calcd. for $C_9H_{14}O_3$: C, 63.53; H, 8.24. Found: C, 63.82; H, 8.38.

3,5-Dimethoxy-1,4-dihydrobenzyl Tosylate.—A solution of 3,5-dimethoxy-1,4-dihydrobenzyl alcohol (69.5 g.) and *p*-toluenesulfonyl chloride (81.5 g.) in pyridine (815 ml.) was kept at 0° for 2 days. The solution was then poured into ice-water (3 l.), and the precipitate was collected by filtration, washed well with water and sucked dry. This procedure gave 3,5-dimethoxy-1,4-dihydrobenzyl tosylate (145 g.), m.p. 66–67° dec., λ_{max} 223 mμ. All attempts to dry the tosylate thoroughly led to rapid decomposition. The tosylate when slightly damp could be stored at 0°. The tosylate could be used as such in the next stage of the synthesis. Recrystallization from ether–petroleum ether (b.p. 40–60°) gave colorless crystals, m.p. 77–78° dec.

Anal. Calcd. for $C_{16}H_{20}O_5S$: C, 59.30; H, 6.23. Found: C, 59.27; H, 6.49.

1,3-Dimethoxycycloheptatriene.—3,5-Dimethoxy-1,4-dihydrobenzyl tosylate (145 g.) was dissolved in boiling pyridine (400 ml.) under nitrogen, and the solution was then poured into water (1 l.) and extracted with chloroform (2 × 250 ml.). The combined chloroform fractions were then washed with 2 *N* hydrochloric acid at 0° (ice was repeatedly added) until all the pyridine had been removed and then with water (2 × 500 ml.). The extract was dried, and the chloroform was removed giving the 1,3-dimethoxycycloheptatriene mixture (51.6 g., 76%). This mixture was distilled and the fraction (35.4 g., 57%) b.p. 56–58° at 0.1 mm. was collected. This material showed $\lambda_{max}^{95\%\ EtOH}$ 288 mμ (3.81).

Anal. Calcd. for $C_9H_{12}O_2$: C, 71.00; H, 7.89. Found: C, 71.10; H, 7.54.

β-Tropolone.—The mixture of 1,3-dimethoxycycloheptatrienes (25.6 g.) in chloroform (275 ml.) was cooled to 0°, and a solution of bromine (26.6 g.) in carbon tetrachloride (95 ml.) was added dropwise with stirring. The solvent was removed under reduced pressure, and the resulting gum was heated at 110° for 3 hours with a solution of 48% hydrobromic acid (133 ml.) and water (133 ml.). After cooling, the solution was filtered and then evaporated to dryness. The residue was dissolved in water (110 ml.), filtered and neutralized with 10% aqueous sodium hydroxide. The *p*H of the solution was adjusted to 4, and after standing for 1 hour the pale brown precipitate of β-tropolone (21 g.) was collected. The crude product when recrystallized from ethyl acetate–methanol (1:1) and then from water (after charcoal treatment) gave pure β-tropolone, m.p. 183–183.5°; λ_{max}^{EtOH} 247 mμ (4.49), 254 mμ (4.42), 270 mμ (3.84), 297 mμ (3.68) and 307 mμ (3.59); $\lambda_{max}^{0.05\ N\ NaOH}$ 256 mμ (4.62), 266 mμ (4.58), 294 mμ (3.88) and 303 mμ (3.88).

Anal. Calcd. for $C_7H_6O_2$: C, 68.85; H, 4.92. Found: C, 68.71; H, 4.94.

1-Methyl-3,5-dimethoxy-1,4-dihydrobenzyl Alcohol.—3,5-Dimethoxy-1,4-dihydrobenzoic acid (30 g.) was added to a stirred solution of potassium amide (from 15 g. of potassium) in liquid ammonia (500 ml.). Methyl iodide (75 g.) was added, and the solution was stirred for 30 min. Ammonium chloride (50 g.) was added, and the ammonia was permitted to evaporate at room temperature. The residue was dissolved in water, acidified at 0° and extracted at 0° with methylene chloride. Removal of the methylene chloride after drying gave crude 1-methyl-3,5-dimethoxy-1,4-dihydrobenzoic acid (16.1 g.) which was added as a slurry in ether (50 ml.) to a stirred suspension of lithium aluminum hydride (4.68 g.) in ether (100 ml.) under nitrogen. After stirring for 1 hour the excess hydride was decomposed by addition of saturated sodium sulfate solution. The solution was filtered, and the filtrate was dried over sodium sulfate. Removal of the ether left an oil (13.2 g.) which on distillation gave 1-methyl-3,5-dimethoxy-1,4-dihydrobenzyl alcohol (8.25 g.), b.p. 110° at 0.75 mm.

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.38; H, 8.78.

3-Hydroxy-5-methyltropone.—A solution of 1-methyl-3,5-dimethoxy-1,4-dihydrobenzyl alcohol (8.0 g.) and *p*-toluenesulfonyl chloride (9.1 g.) in pyridine (91 ml.) was kept at 0° for 2 days. The solution was poured into ice-water, and the precipitated tosylate was collected by filtration. The crude tosylate was immediately dissolved in pyridine (25 ml.) and refluxed for 15 min. The solution was cooled, diluted with ether and washed free of pyridine with 2 *N* hydrochloric acid at 0°. Removal of the ether after drying gave crude 5-methyl-1,3-dimethoxycycloheptatriene (4.93 g., mixture of isomers). The crude triene (4.93 g.) in chloroform (50 ml.) was cooled to 0°, and a solution of bromine (5 g.) in carbon tetrachloride (22 ml.) was added dropwise with stirring. The solvent was removed, and the residue was heated at 110° for 3 hours with a solution of 48% hydrobromic acid (25 ml.) and water (25 ml.). After cooling, the solution was filtered and the filtrate was evaporated to dryness. The residue was dissolved in water (20 ml.), filtered and neutralized with 10% sodium hydroxide. The *p*H of the solution was adjusted to 4, and after standing for 1 hour at 0° the precipitate of crude 3-hydroxy-5-methyltropone was collected. The dried, crude product (610 mg.) when recrystallized from water after charcoaling gave pure 3-hydroxy-5-methyltropone, m.p. 139–140°; $\lambda_{max}^{95\%\ EtOH}$ 247, 255, 272, 297 and 312 mμ; $\lambda_{max}^{0.1\ N\ NaOH}$ 257, 267, 295 and 305 mμ.

Anal. Calcd. for $C_8H_8O_2$: C, 70.57; H, 5.92. Found: C, 70.48; H, 6.01.

2,3-Dimethoxybenzyl Alcohol.—Sodium (72 g.) was added in small pieces to a stirred solution of 2,3-dimethoxybenzoic acid (100 g.) and methanol (900 ml.) in liquid ammonia (2 l.). Ammonium chloride (300 g.) was then added, and the ammonia was permitted to evaporate. The solution was acidified at 0° and extracted with methylene chloride. Removal of the methylene chloride after drying gave crude 2,3-dimethoxy-1,4-dihydrobenzoic acid (75.2 g.). The crude dihydroacid (75.2 g.) in ether (500 ml.) was added dropwise to a stirred suspension of lithium aluminum hydride (25 g.) in ether (1.5 l.). The suspension was stirred for 1 hour and then decomposed by addition of moist sodium sulfate. Evaporation of the ether after filtration gave crude 2,3-dimethoxy-1,4-dihydrobenzyl alcohol (48.1 g.). Distillation of the crude alcohol gave pure 2,3-dimethoxy-1,4-dihydrobenzyl alcohol (35.3 g.), b.p. 95–98° at 0.2 mm.

Anal. Calcd. for $C_9H_{14}O_3$: C, 63.53; H, 8.24. Found: C, 63.68; H, 8.14.

1,2-Dimethoxycycloheptatriene.—A solution of 2,3-dimethoxybenzyl alcohol (69.4 g.) and *p*-toluenesulfonyl chloride (89.3 g.) in pyridine (892 ml.) was kept at 0° for 2 days. This solution was poured into ice-water and extracted with ether. Removal of the ether (after drying) at room temperature left a solution of the crude tosylate in pyridine. This solution was immediately added to boiling collidine (1 l.) and refluxed 1 hour. The solution was poured into ice-water and extracted with ether. The ether solution was washed free of pyridine and collidine with 0.1 *N* hydrochloric acid and dried over sodium sulfate. Removal of the ether gave an oil (41.8 g.) which on distillation gave a mixture of 1,2-dimethoxycycloheptatrienes (37.4 g.), b.p. 48–54° at 1.5 mm.

Anal. Calcd. for $C_9H_{12}O_2$: C, 71.00; H, 7.89. Found: C, 71.27; H, 8.05.

α-Tropolone.—1,2-Dimethoxycycloheptatriene (12 g.) was added to a stirred suspension of phosphorus pentachloride (64.8 g.) in dry carbon tetrachloride (30 ml.), and the mixture was stirred overnight. The mixture was poured into methanol (200 ml.) cooled to 0° in an ice-bath, and then the solvent was removed under vacuum. The residue was dissolved in 2 *N* sodium hydroxide (200 ml.) and heated at 100° for 10 minutes. The cooled solution was acidified and continuously extracted with ether for 2 days. Removal of the ether gave crude α-tropolone (6.9 g.). Crystallization from hexane gave pure α-tropolone (3.1 g.), m.p. 50–51°; λ_{max}^{EtOH} 229 (4.35), 234 (4.35), 237 (4.33), 320 (3.85) and 351 mμ (3.70).

2,5-Dimethoxy-1,4-dihydrobenzoic Acid.—Sodium (36 g.) was added in small pieces to a solution of 2,5-dimethoxybenzoic acid (53 g.) and methanol (450 ml.) in liquid ammonia (1.5 l.). Ammonium chloride (150 g.) was then added, and the ammonia was permitted to evaporate at room temperature. The residue was dissolved in ice-water (2 l.) and made acid to congo red at 0° by addition of 2 *N* hydrochloric acid. The solution was extracted with methylene chloride. Removal of the solvent after drying gave crude 2,5-dimethoxy-1,4-dihydrobenzoic acid (50.2 g.).

2,5-Dimethoxy-1,4-dihydrobenzyl Alcohol.—Crude 2,5-dimethoxy-1,4-dihydrobenzoic acid (50.2 g.) was added as a slurry in ether to a suspension of lithium aluminum hydride (25 g.) in ether (200 ml.). After stirring for 1 hour at room temperature the excess hydride was decomposed with moist sodium sulfate. Evaporation of the ether after filtration gave the crude alcohol (26.8 g.). Distillation of the crude alcohol gave pure 2,5-dimethoxy-1,4-dihydrobenzyl alcohol (15.55 g.), b.p. 82–83° at 0.2 mm.

Anal. Calcd. for $C_9H_{14}O_3$: C, 63.53; H, 8.24. Found: C, 63.71; H, 8.55.

1,4-Dimethoxycycloheptatriene.—A solution of 2,5-dimethoxy-1,4-dihydrobenzyl alcohol (36 g.) and *p*-toluenesulfonyl chloride (45.9 g.) in pyridine (459 ml.) was kept at 0° for 2 days. The solution was poured in water, and the precipitate was collected by filtration, washed with water and sucked dry. The precipitate was immediately dissolved in boiling collidine (500 ml.), and the solution was refluxed 30 min. The solution was poured into water (2 l.) and extracted with ether. The ether solution was washed free of collidine with 0.1 *N* hydrochloric acid and then dried. Removal of the ether left an oil (28.3 g.) which on distillation gave a mixture of 1,4-dimethoxycycloheptatrienes (19.42 g.), b.p. 90–95° at 2 mm.

Anal. Calcd. for $C_9H_{12}O_2$: C, 71.00; H, 7.89. Found: C, 70.84; H, 7.82.

γ-Tropolone.—The mixture of 1,4-dimethoxycycloheptatrienes (8.1 g.) in chloroform (45 ml.) was cooled to 0°, and bromine (8.4

g.) in carbon tetrachloride (30 ml.) was added dropwise with stirring. The solvent was removed under vacuum, and the residual oil was heated at 110° for 3 hours with 48% hydrobromic acid (48 ml.) and water (48 ml.). This solution was filtered and evaporated to dryness. The residue was dissolved in water (48 ml.) and neutralized with 10% sodium hydroxide solution. The solution was acidified (*p*H 4) and cooled. The crude precipitate of γ-tropolone (6.10 g.; λ_{max}^{EtOH} 230, 334 mμ) was collected and dried. Recrystallization of the crude product from ethyl acetate–methanol (1:1) and then water with a little charcoal gave pure γ-tropone as a pale yellow, crystalline solid, m.p. 209–211°. Methylation of the product with diazomethane gave γ-tropolone methyl ether identical in infrared and ultraviolet absorption with an authentic sample. Acid hydrolysis of the methyl ether gave γ-tropolone λ_{max}^{EtOH} 230 and 334 mμ and $\lambda_{max}^{0.1\ N\ NaOH}$ 360 mμ.

3-Methoxy-1,4-dihydrobenzyl Alcohol.—Sodium (144 g.) was added in small pieces to a solution of 3-methoxybenzoic acid (200 g.) and methanol (1800 ml.) in liquid ammonia (4 l.). Ammonium chloride (600 g.) was then added, and the ammonia was permitted to evaporate at room temperature. The residue was dissolved in water, made acid to congo red at 0° and extracted with methylene chloride. Evaporation of the methylene chloride after drying gave crude 3-methoxy-1,4-dihydrobenzoic acid (160 g.). The crude dihydroacid was dissolved in ether (200 ml.) and added to a suspension of lithium aluminum hydride (80 g.) in ether (600 ml.) under nitrogen. After stirring for 1 hour, the excess hydride was decomposed. After filtration, evaporation of the ether gave an oil (110 g.). Distillation of this oil gave 3-methoxy-1,4-dihydrobenzyl alcohol (92.5 g.), b.p. 93–96° at 0.2 mm., and an unidentified alcohol (3.5 g.).

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.71; H, 8.83.

Methoxycycloheptatriene.—A solution of 3-methoxy-1,4-dihydrobenzyl alcohol (50 g.) and *p*-toluenesulfonyl chloride (75.0 g.) in pyridine (750 ml.) was kept at 0° for 2 days. The solution was then poured into water and extracted with chloroform. The chloroform solution was washed free of pyridine with water and dried. Removal of the chloroform at room temperature left an oil. This oil was refluxed in pyridine (1 l.) under nitrogen for 1 hour. The solution was poured into ice-water and extracted with chloroform. The chloroform solution was washed free of pyridine with 2 *N* hydrochloric acid. Removal of the chloroform left an oil (23.2 g.). Distillation of this oil gave a mixture of methoxycycloheptatrienes as a pale yellow oil (16.4 g.), b.p. 67–70° at 20 mm., λ_{max}^{EtOH} 289 mμ (3.54).

Anal. Calcd. for $C_8H_{10}O$: C, 78.69; H, 8.20. Found: C, 78.77; H, 7.91.

Tropone.—The methoxycycloheptatriene mixture (6.75 g.) in chloroform (75 ml.) at 0° was oxidized by dropwise addition of bromine (7.0 g.) in carbon tetrachloride (25 ml.). Removal of the solvent left a gum. Water was added, and the resulting acidic solution was made basic (*p*H 8) and extracted with chloroform. Removal of the chloroform after drying gave crude tropone; λ_{max}^{EtOH} 223, 227, 231, 235, 237 and 305 mμ.

Acid Hydrolysis of Methoxycycloheptatriene.—Methoxycycloheptatriene (52 mg.) was refluxed 2 hours in 1 *N* ethanolic sulfuric acid (5 ml.). During this time the ultraviolet absorption maximum at 289 mμ decayed. An aliquot of this solution was made strongly alkaline and heated at 60° for 2 minutes giving rise to the characteristic ultraviolet spectrum of tropone (225, 227, 231, 235, 238 and 307 mμ). The remainder of the solution was diluted with ether and washed free of acid with saturated sodium bicarbonate solution. Removal of the ether after drying left a residue which showed infrared carbonyl absorption (5.90, 6.02, 6.16 and 6.31 μ) closely resembling that of a mixture of 3,5-cycloheptadienone and 2,4-cycloheptadienone prepared by base-catalyzed degradation of tropinone methiodide.[25]

Bicyclo[4.1.0]heptan-2-one.—A solution of 3-methoxy-1,4-dihydrobenzyl alcohol (10 g.) in methanol was added to a suspension of prereduced platinum oxide (0.5 g.) in methanol (20 ml.). The hydrogenation was stopped after 1.1 equivalents of hydrogen had been absorbed. The solution was filtered and combined with a similar hydrogenation of 13 g. of 3-methoxy-1,4-dihydrobenzyl alcohol. Distillation of the combined crude product after removal of the methanol gave 3-methoxy-1,4,5,6-tetrahydrobenzyl alcohol (14.4 g., b.p. 102–104° at 2.75 mm.).

A solution of 3-methoxy-1,4,5,6-tetrahydrobenzyl alcohol (14.2 g.) and *p*-toluenesulfonyl chloride (21 g.) in pyridine (210 ml.) was kept at 0° for 4 days. The solution was diluted with methylene chloride and washed with water. Removal of the methylene chloride left a solution of the tosylate in pyridine. This solution was diluted to 400 ml. with pyridine and refluxed 1 hour. This solution was diluted with methylene chloride and washed free of acid with 2 *N* hydrochloric acid. Removal of the methylene chloride after drying gave an oil (10.1 g.) which on distillation (85–90° at 16 mm.) gave bicyclo[4.1.0]heptan-2-one (6.1 g.); 3.30 μ (cyclopropane C—H), 5.91 μ (< C=O). Preparation of the 2,4-dinitrophenylhydrazone in the usual manner gave bicyclo[4.1.0]heptan-2-one 2,4-dinitrophenylhydrazone, m.p. 158–159° (reported[32] 158°).

3-Methoxy-5-oxo-3-cyclohexenylcarbinyl Tosylate.—A solution of 3,5-dimethoxy-1,4-dihydrobenzyl tosylate (10 g.) in acetic acid (90 ml.) containing sodium acetate (8 g.) and acetic anhydride (10 ml.) was kept at 30° for 2 hours. The solution was then diluted with ether and washed free of acid with 10% sodium bicarbonate solution. Evaporation of the ether left an oil (8.1 g.). Trituration of this oil left crystalline 3-methoxy-5-oxo-3-cyclohexenylcarbinyl tosylate (2–3 g.), m.p. 87–88°, λ_{max}^{EtOH} 227 (4.26) and 248 mμ (4.24).

Anal. Calcd. for $C_{15}H_{18}O_5S$: C, 58.06; H, 5.81; $-OCH_3$, 10.00. Found: C, 58.33; H, 6.10; $-OCH_3$, 9.86.

Conversion of 3-Methoxy-5-oxo-3-cyclohexenylcarbinyl Tosylate to β-Tropolone.—An aliquot (5 ml.) of a stock solution of 3-methoxy-5-oxo-3-cyclohexenylcarbinyl tosylate (15 mg.) in 100 ml. of 95% ethanol was diluted to 50 ml. with 0.1 *N* sodium hydroxide solution. This solution was heated at 80° for 90 min., cooled and acidified. The ultraviolet spectrum of this solution showed the characteristic maxima of β-tropolone. The extinction (32,200) at 246 mμ indicated quantitative formation of β-tropolone (ε 246 mμ 31,000).

A solution of 3-methoxy-5-oxo-3-cyclohexenylcarbinyl tosylate (140 mg.) in 1 *N* sodium hydroxide (10 ml.) was refluxed 2 hours. Air was bubbled through the solution during this period. The solvent was removed, and the residue was dissolved in water (2 ml.) and acidified to *p*H 4 with 2 *N* hydrochloric acid. The precipitate of crude β-tropolone was collected by filtration. Recrystallization from water gave pure β-tropolone, m.p. 181–183°, mixed melting point with authentic β-tropolone 182–184°. The ultraviolet spectrum of the product was identical to that of authentic β-tropolone.

3-Methyl-1,4-dihydrobenzoic Acid.—Sodium (90 g.) was added in small pieces to a stirred solution of 3-methylbenzoic acid (100 g.) and methanol (1 l.) in liquid ammonia (3 l.). Ammonium chloride (430 g.) was added, and the reaction was worked up in the usual manner giving crude 3-methyl-1,4-dihydrobenzoic acid (95.2 g.). A sample of the acid was recrystallized twice from ether–petroleum ether (b.p. 60–80°) giving pure 3-methyl-1,4-dihydrobenzoic acid, m.p. 87–88°.

Anal. Calcd. for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.61; H, 7.32.

3-Methyl-1,4-dihydrobenzyl Alcohol.—Crude 3-methyl-1,4-dihydrobenzoic acid (90 g.) in ether was added to a stirred suspension of lithium aluminum hydride (38 g.) in ether (2 l.). Work up in the usual manner gave an oil (65.3 g.) which on distillation gave 3-methyl-1,4-dihydrobenzyl alcohol (60.3 g.), b.p. 97–98° at 11 mm.

Anal. Calcd. for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.47; H, 9.96.

3-Methyl-1,4-dihydrobenzyl Tosylate.—A solution of 3-methyl-1,4-dihydrobenzyl alcohol (30 g.) and *p*-toluenesulfonyl chloride (53 g.) in pyridine (530 ml.) was kept at 0° for 2 days. The solution was diluted with ether and washed free of pyridine with 0.1 *N* hydrochloric acid. Removal of the ether after drying gave the crude tosylate. The tosylate was purified by crystallization from ether–petroleum ether at −70°.

Anal. Calcd. for $C_{15}H_{18}O_3S$: C, 64.70; H, 6.52. Found: C, 64.55; H, 6.33.

3,5-Dimethyl-1,4-dihydrobenzoic Acid.—Sodium (82 g.) was added in small pieces to a stirred solution of methanol (800 ml.) and 3,5-dimethylbenzoic acid (100 g.) in liquid ammonia (2 l.). Ammonium chloride (400 g.) was added, and the ammonia was permitted to evaporate at room temperature. The residue was dissolved in water, acidified and extracted in the usual manner. The crude product was recrystallized from ether–petroleum ether (b.p. 60–80°) giving 3,5-dimethyl-1,4-dihydrobenzoic acid (95 g., m.p. 138.5–139°).

Anal. Calcd. for $C_9H_{12}O_2$: C, 71.00; H, 7.89. Found: C, 71.29; H, 8.09.

3,5-Dimethyl-1,4-dihydrobenzyl Alcohol.—A solution of 3,5-dimethyl-1,4-dihydrobenzoic acid (95 g.) in ether (500 ml.) was added dropwise to a suspension of lithium aluminum hydride (38 g.) in ether (1 l.). After stirring for 1 hour at room temperature the excess hydride was decomposed with saturated sodium sulfate solution. Removal of the ether gave the crude alcohol as an oil (69.2 g.). Distillation of the crude alcohol gave 3,5-dimethyl-1,4-dihydrobenzyl alcohol (61.9 g., b.p. 110° at 11 mm.).

Anal. Calcd. for $C_9H_{14}O$: C, 78.20; H, 10.20. Found: C, 78.41; H, 10.43.

3,5-Dimethyl-1,4-dihydrobenzyl Tosylate.—A solution of 3,5-dimethyl-1,4-dihydrobenzyl alcohol (30 g.) and *p*-toluenesulfonyl chloride (45 g.) in pyridine (450 ml.) was kept at 0° for 2

(32) G. Stork and J. Ficini, *J. Am. Chem. Soc.*, **83**, 4678 (1961).

days. The solution was poured into ice-water, and the precipitate of crude tosylate was collected. Recrystallization from ether–petroleum ether (b.p. 60–80°) gave 3,5-dimethyl-1,4-dihydrobenzyl tosylate (59.2 g.), m.p. 53.5–54°.

Anal. Calcd. for $C_{16}H_{20}O_3S$: C, 65.78; H, 6.90. Found: C, 65.92; H, 7.06.

1,4-Dihydrobenzyl Tosylate.—1,4-Dihydrobenzyl tosylate was prepared as previously described[12] except that the crude tosylate was purified by crystallization from ether–petroleum ether (b.p. 40–60°) at −50°.[33]

(33) 1,4-Dihydrobenzyl tosylate was not obtained in crystalline form in the earlier work.[12]

Anal. Calcd. for $C_{14}H_{16}O_3S$: C, 63.60; H, 6.10. Found: C, 63.56; H, 6.07.

Rate Measurements.—The tosylates were solvolyzed as 0.03 *M* solutions in acetic acid 0.06 *M* in sodium acetate. The consumption of sodium acetate was followed by titration with perchloric acid in acetic acid as previously described[34] using the ampoule technique.[34] The sodium acetate solution was prepared by refluxing sodium carbonate (6.36 g.) in glacial acetic acid (1900 ml.) and acetic anhydride (100 ml.) for 2 hours. Temperatures were measured with a thermometer calibrated by the National Bureau of Standards.

(34) S. Winstein, C. Hanson and E. Grunwald, *J. Am. Chem. Soc.*, **70**, 812 (1948).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF OREGON, EUGENE, ORE.]

The Mechanism of the Prins Reaction. II. The Solvolysis of *trans*-2-Hydroxymethylcyclohexyl Brosylate and *trans*-2-Acetoxymethylcyclohexyl Brosylate[1]

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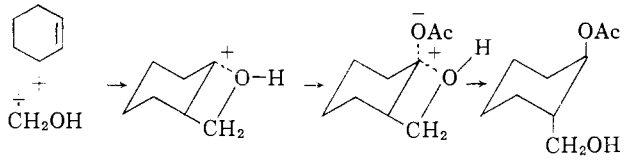
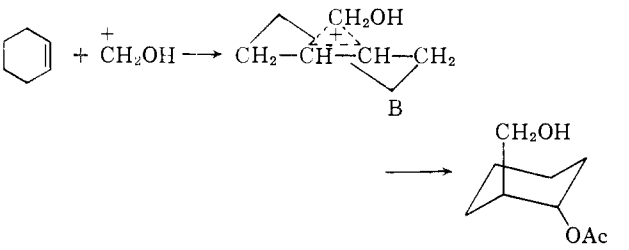
The preparation and solvolysis of *trans*-2-hydroxymethylcyclohexyl brosylate and *trans*-2-acetoxymethylcyclohexyl brosylate is reported. The solvolysis of *trans*-2-hydroxymethylcyclohexyl brosylate in aqueous dioxane yields mainly 3-hydroxymethylcyclohexene and a mixture of the *cis*- and *trans*-2-hydroxymethylcyclohexanols containing 40% of the *trans* isomer. The large amount of net retention of configuration is ascribed to the intervention of cyclic ions A or **B**. Acetolysis of *trans*-2-acetoxymethylcyclohexyl brosylate in the presence of added acetate gives 3-acetoxymethylcyclohexene and the diacetate of *cis*-2-hydroxymethylcyclohexanol, while in the absence of added acetate the olefin is accompanied by a mixture of the acetates of the *cis*- and *trans*-2-hydroxymethylcyclohexanols containing 70% of the *trans* isomer. It is suggested that in both cases the bridged ion C is formed. In the presence of high concentrations of acetate ion, the cyclic ion C suffers displacement at the primary carbon to give the *cis*-diacetate, while in the absence of acetate ion acetic acid reacts at C-1 to give the *trans*-diacetate. It is also possible that both the *cis*- and *trans*-diacetates arise from the corresponding orthodiacetates. Evidence for the cyclic intermediate C was obtained by isolating the ethyl orthoacetate of *cis*-2-hydroxymethylcyclohexanol from the solvolysis of *trans*-2-acetoxymethylcyclohexyl brosylate in anhydrous ethanol. It is concluded that there are two possible stereoselective paths for the acid-catalyzed reaction of formaldehyde with olefins to produce 1,3-diol derivatives. In acetic acid solutions, the reaction may proceed by a mechanism involving neighboring acetate, but since the reaction is also highly stereoselective in aqueous mixtures another path is available through ions similar to A or B.

The mechanism of the Prins reaction has been the subject of several investigations.[2–6] One example of the Prins reaction, the sulfuric acid-catalyzed reaction of cyclohexene and formaldehyde in acetic acid solution, has been studied quite extensively.[2,3,6,7] The mixture of products from the reaction is quite complex, but the main products are derivatives of *trans*-2-hydroxymethylcyclohexanol and none of the *cis* isomer is found.

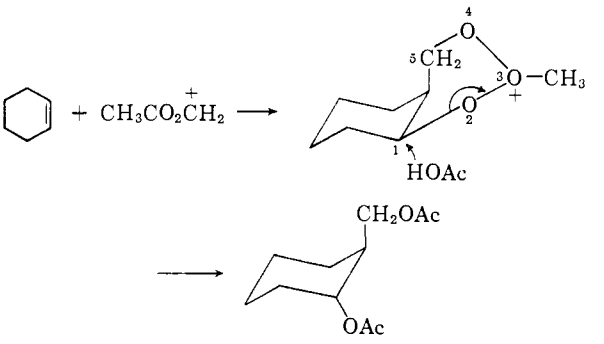
The stereospecificity of the Prins reaction is not consistent with a simple carbonium ion mechanism. We should like to consider three types of mechanisms. The first accounts for the stereospecificity by suggesting a solvated trimethylene oxide[5] intermediate or an intramolecularly solvated carbonium ion in which the principal solvation comes from the oxygen of a hydroxyl group in a four-membered ring.[2] This mechanism, proposed by Blomquist and Wolinsky,[2] is



In a previous report from these laboratories[6] we suggested an alternate mechanism which more readily rationalizes the formation of the side products. The intermediate which controls the stereochemistry of the reaction is the three-membered cyclic ion B, similar to the intermediates formulated for other examples of electrophilic addition to double bonds.



We should like to add a third mechanism for consideration. In acetic acid solution the attacking species might arise from hydroxymethyl acetate by protonation and loss of water. This species would be capable of



(1) Supported in part by the Petroleum Research Fund of the American Chemical Society, 915-A4, and a Faculty Research Grant from the Graduate School of the University of Oregon.

(2) A. T. Blomquist and J. Wolinsky, *J. Am. Chem. Soc.*, **79**, 6025 (1957).

(3) E. Smissman and R. A. Mode, *ibid.*, **79**, 3447 (1957).

(4) E. E. Smissman and D. T. Witiak, *J. Org. Chem.*, **25**, 471 (1960).

(5) H. W. Zimmerman and J. English, Jr., *J. Am. Chem. Soc.*, **75**, 2367 (1953).

(6) L. J. Dolby, *J. Org. Chem.*, **27**, 2971 (1962).

(7) J. Matti, *Bull. soc. chim. France*, [4] **51**, 974 (1932); S. Olsen and H. Padberg, *Z. Naturforsch.*, **1**, 448 (1946); S. Olsen, *ibid.*, **1**, 671 (1946); S. Olsen, *Angew. Chem.*, **59**, 32 (1947); S. Olsen, *Z. Naturforsch.*, **3b**, 314 (1948).