decomposition vessel was placed *ca.* 0.2 g. of *sec*-butyl chlorocarbonate (identified by its infrared spectrum, and mixed melting point of its carbamate derivative, m.p. 94°, with an authentic sample) and an equal amount of redistilled quinoline. The mixture was heated to 70° under a slow nitrogen stream and the carbon dioxide was condensed by liquid nitrogen.

Mass Spectral Data.—The samples of carbon dioxide to be measured in the mass spectrometer were distilled and degassed on a standard high vacuum manifold.

The instrument used was a Consolidated Electrodynamics mass spectrometer, model 21-620. It was found that with this instrument the apparent mass ratios were slightly dependent on the sample pressure in the mass spectrometer. To nullify this effect all samples reported were run at 100-μ sample pressure.

Acknowledgment.—The authors are grateful to Mr. C. A. Whiteman for instruction and assistance in the operation of the mass spectrometer.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER, ROCHESTER 20, N. Y.]

The Chemistry of Some Derivatives of the 7-Oxabicyclo[2.2.1]heptene System, Especially the Epoxy Derivatives (3,8-Dioxatricyclo[3.2.1.0^{2,4}]octanes)[1]

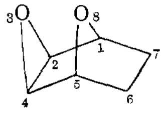
BY MARTIN P. KUNSTMANN,[2] D. STANLEY TARBELL AND ROBERT L. AUTREY

RECEIVED JUNE 18, 1962

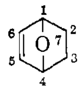
The Diels–Alder addition of ethyl acrylate to furan yields a mixture of the *exo* and *endo* isomers of 2-carbethoxy-7-oxabicyclo[2.2.1]hept-5-ene; variation of the ester function leads to several other derivatives of the 7-oxabicyclo[2.2.1]heptene system. The two epimeric 2-carboxy and 2-carbinyl derivatives have been separated and the configurations established. Epoxidation yields the epoxy compounds, (3,8-dioxatricyclo[3.2.1.0^{2,4}]octanes, or derivatives thereof, formed without Wagner–Meerwein rearrangement. The epoxidation is accompanied by some isomerization of the 2-*endo*-carboxyl group to the 2-*exo* configuration; epoxidation of the 2-carbethoxy and 2-carbinol derivatives is accompanied by some isomerization of the 2-*exo* substituent to the 2-*endo* configuration. Treatment of the dioxatricycloöctanes with various nucleophiles results in products derived from intramolecular nucleophilic displacement; products derived from Wagner-Meerwein rearrangement have not been isolated.

Introduction

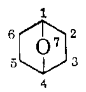
In connection with studies on the antibiotic fumagillin,[3,4] information was needed concerning the behavior of compounds containing a 1,2-epoxide as well as a 1,4-epoxide grouping. The 3,8-dioxatricycloöctane system I is accessible by the Diels–Alder reaction of furan with some appropriate dienophile, followed by epoxidation of the unsaturated bicyclic compound. Some compounds derived from this system have been prepared from the adduct of furan and trifluorocrotonic acid,[5] and from the furan–maleic anhydride adduct.[6,7] The present paper describes the preparation, stereochemistry and properties of a series of 2-substituted 7-oxabicyclo[2.2.1]hept-5-enes (II), and their corresponding saturated derivatives (III). From the bicycloheptenes, members of the dioxatricycloöctane series have been obtained. The results may have some interest in connection with the chemistry of the intensively investigated norbornane-type compounds.



I



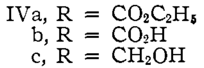
II



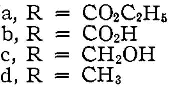
III

Preparation of the 2-Substituted-7-oxabicyclo[2.2.1]hept-5-enes.—Earlier work[8,9] on the furan–maleic anhydride adduct indicated that the equilibrium is unfavorable to the adduct and that a mixture of *endo* and *exo* products is formed. The *endo* is formed more rapidly, but the *exo* adduct is slightly more stable thermodynamically. The same relations were indicated in the present work with the furan–ethyl acrylate adduct; the equilibrium is unfavorable, both *endo* and *exo* forms result, and the latter is favored at elevated temperatures.

Treatment of furan with ethyl acrylate leads to a small yield of the adduct, a mixture of *endo*- and *exo*-2-carbethoxy-7-oxabicyclohept-5-ene (IVa). This mixture was converted into a series of related compounds (IVb to IVf) by standard procedures. The saturated bicycloheptanes (Va to Ve) were obtained by catalytic reduction. The *endo-exo* ratio in the reduced compounds could be determined by vapor phase chromatography (v.p.c.); this technique could not be applied to the unsatu-



IVa, R = $CO_2C_2H_5$
b, R = CO_2H
c, R = CH_2OH
d, R = CH_2OTos
e, R = CH_3
f, R = $C(CH_3)_2OH$



Va, R = $CO_2C_2H_5$
b, R = CO_2H
c, R = CH_2OH
d, R = CH_3
e, R = $C(CH_3)_2OH$

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[1] Aided by Grant E-1138 of the U. S. Public Health Service.

[2] Esso Fellow, 1960–1961; Summer Fellow of the National Science Foundation.

[3] *E.g.*, D. S. Tarbell, R. M. Carman, D. D. Chapman, K. R. Huffman and N. J. McCorkindale, *J. Am. Chem. Soc.*, **82**, 1005 (1960).

[4] D. S. Tarbell, R. M. Carman, D. D. Chapman, S. E. Cremer, A. D. Cross, K. R. Huffman, M. P. Kunstmann, N. J. McCorkindale, J. G. McNally, Jr., A. Rosowsky, F. H. J. Varino and R. L. West, *ibid.*, **83**, 3096 (1961).

[5] E. T. McBee, C. G. Hsu and C. W. Roberts, *ibid.*, **78**, 3389 (1956).

[6] J. Jolivet, *Ann. Chim.*, **5**, 1165 (1960).

[7] Yu. K. Yur'ev and N. S. Zefirov, *Zhur. Obshchei. Khim.*, **31**, 1125 (1961).

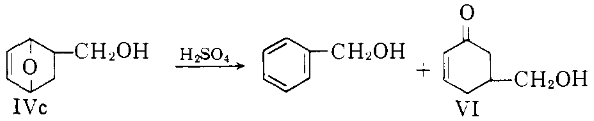
[8] R. B. Woodward and H. Baer, *J. Am. Chem. Soc.*, **70**, 1161 (1948).

[9] J. A. Berson and R. Swidler, *ibid.*, **75**, 1721 (1953).

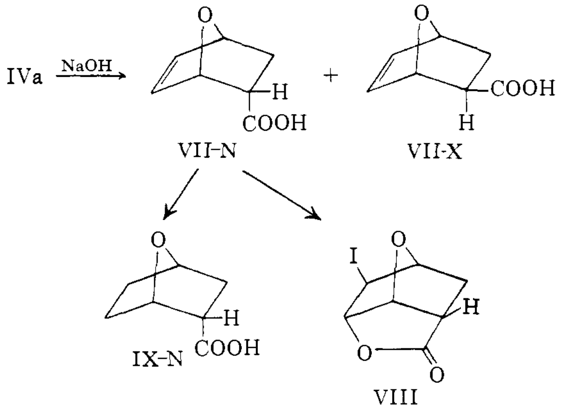
rated compounds, presumably because of dissociation on the column.

The pure *endo* and *exo* isomers were obtained in several cases (see below) and the configuration established by several methods. The cases in which mixtures of *endo* and *exo* isomers were used will be described only cursorily. The v.p.c. examination of Va, the saturated adduct, showed that the *exo* isomer predominated over the *endo* isomer by a factor of 3:2. In the corresponding carbinyl case (Vc) the *exo* form predominated by a 2:1 ratio.

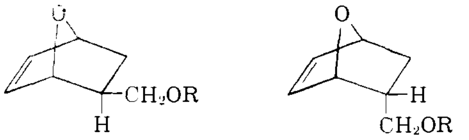
The structure of the adduct IVa was based on analysis, spectra and on the uptake of exactly one mole of hydrogen on catalytic reduction. Further, treatment of the carbinol IVc with sulfuric acid gave benzyl alcohol, characterized as the α-naphthylurethan, and the cyclohexenone derivative VI.[10] The dinitrophenylhydrazone of VI had the reported melting point,[10] and the infrared and n.m.r. spectra of VI were in agreement with the assigned structure; it formed a crystalline *p*-nitrobenzoate. The formation of benzyl alcohol and of the cyclohexenone VI from IVc by treatment with acid can be explained readily.



Separation of *endo-exo* Isomers and Determination of Stereochemistry.—Saponification of the mixed *endo* and *exo* esters IVa yielded a crystalline acid, VII-N,[11] m.p. 98–99°; its configuration was established by conversion to an iodolactone, VIII,[12] m.p. 157°. The infrared spectrum of the iodolactone showed no hydroxyl or olefinic absorption, and had a band at 1780 cm.$^{-1}$, attributable to a γ-lactone. The *endo* acid VII-N was catalytically reduced to the crystalline saturated acid IX-N; the *endo* configuration of VII-N was confirmed by its conversion to the *endo*-carbinol. The *exo*-acid VII-X was not obtained crystalline from the saponification mixture, but its presence was demonstrated by conversion to the *exo*-carbinol.

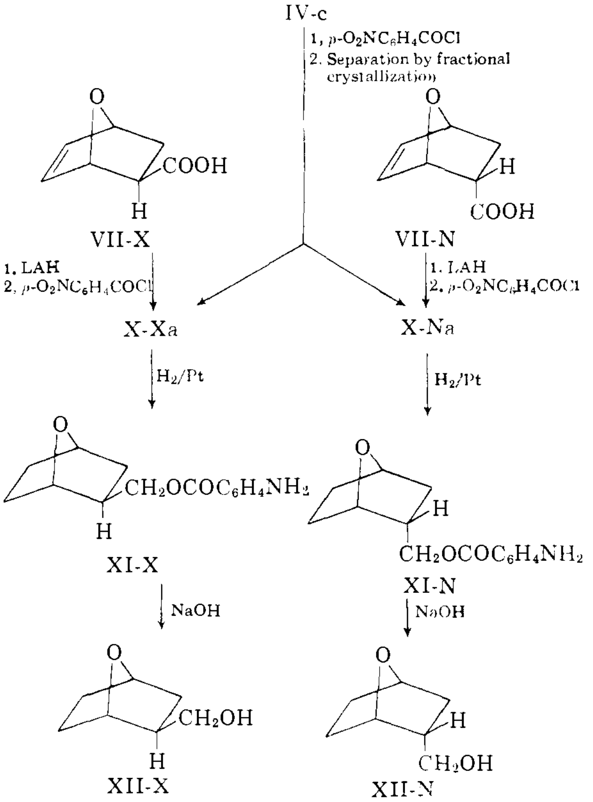


The mixed *endo*- and *exo*-carbinols IVc (R = CH_2OH) were converted to the crystalline *p*-nitrobenzoates, which were separated by crystallization from benzene–hexane into the pure *exo* and *endo* esters, the former predominating in a ratio of 3:1.



X–Xa, R = $p\text{-}O_2NC_6H_4CO$ X–Na, R = $p\text{-}O_2NC_6H_4CO$
X–Xb, R = H X–Nb, R = H

Treatment of the pure *p*-nitrobenzoates with lithium aluminum hydride yielded the pure *exo*- and *endo*-carbinols, X-Xb and X-Nb. Their configurations were established by conversion of the *exo*- and *endo*- acids VII–X and VII–N to the carbinols by lithium aluminum hydride reduction. The identities were shown by mixture melting points of the *p*-nitrobenzoates, since the carbinols were liquids. The assigned configurations of the carbinols were also supported by their behavior on treatment with perphthalic acid (see below). Both the *endo* and *exo* forms of the carbinol gave a shift of the hydroxyl stretching frequency to higher frequency with dilution; hence, intramolecular hydrogen bonding was absent in both forms, and no conclusions about configuration could be drawn from hydrogen bonding behavior.



Catalytic reduction of the pure *p*-nitrobenzoates (X-Xa and X-Na) gave the crystalline *p*-aminobenzoates of 2-hydroxymethyl-7-oxabicyclo[2.2.1]-heptane (XI-X and XI-N), and saponification yielded the corresponding carbinols (XII-X and XII-N).

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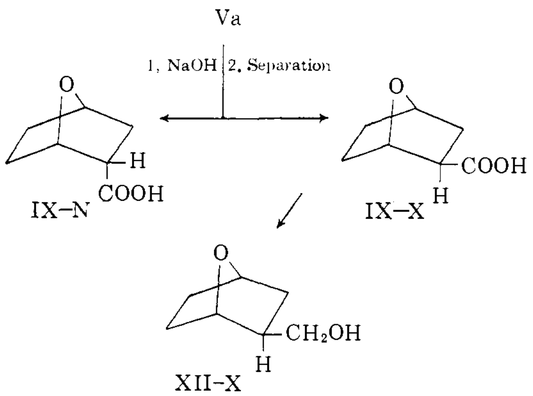
[10] E. E. van Tamelen and G. T. Hildahl, *J. Am. Chem. Soc.*, **78**, 4405 (1956).

[11] Pure isomers will be indicated by the suffix N (for *endo*) and X (for *exo*).

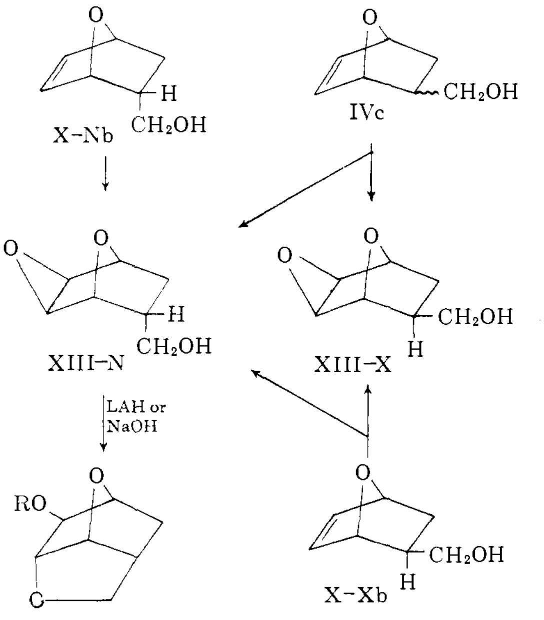
[12] *Cf.* E. E. van Tamelen and M. Shamma, *ibid.*, **76**, 2315 (1954).

The mixture of saturated *exo*- and *endo*-acids Vb, obtained by the hydrolysis of the saturated ester Va, was separated by removal of the crystalline *endo*-acid IX-N from the mixture. The crude saturated *exo*-acid IX-X, which was not obtained crystalline, was converted with lithium aluminum hydride to the *exo*-carbinol XII-X.



IX-N
IX-X
XII-X

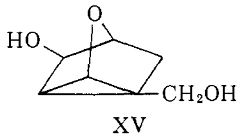
Epoxidation to the 3,8-Dioxatricyclooöctane System.—Treatment of several of the bicycloheptene derivatives (IV) with monoperphthalic acid[13] gave members of the 3,8-dioxatricyclooöctane series (I). Thus, the mixed *endo*- and *exo*-carbinols, containing an excess of *exo* (see above), yielded a mixture of epoxides, consisting of about three parts of the 6-*endo* compound XIII-N to one part of the 6-*exo* isomer XIII-X.[14] The pure *endo*-carbinol X-Nb yielded only thhe *endo* tricyclic compound, but the pure *exo*-carbinol X-Xb gave a mixture of the *endo* and *exo* tricyclic compounds XIII-N and XIII-X.



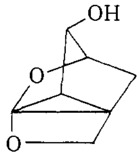
X-Nb
IVc
XIII-N
XIII-X
X-Xb

XIVa, R = H
b, R = COCH$_3$

The structures XIII-X and XIII-N were assigned on the basis of the following facts. The compounds showed an infrared band at 855 cm.$^{-1}$, which is in agreement with observations on numerous other compounds containing fused epoxide rings.[15] They gave a positive thiosulfate test for 1,2-epoxides[16] and formed a monoacetate which had no free hydroxyl group. The n.m.r. spectrum showed no vinyl or aldehydic hydrogens, and showed a total of seven of the ten hydrogens on oxygen and carbon bearing oxygen. These observations rule out tricyclene-like structures such as XV, structures derived from a Wagner–Meerwein rearrangement[8,17] such as XVI, and bicyclic structures containing carbon-carbon unsaturation or aldehyde groups.



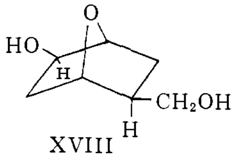
XV



XVI

The epoxidation must have occurred, therefore, without rearrangement of the carbon skeleton.[18] The epoxide group was assigned the *exo* configuration because electrophilic substitution in bicycloheptenes and 7-oxabicycloheptenes occurs from the side of the methylene or oxygen bridge.[7,8,15b,c,19]

The epoxide structure of XIII-X and XIII-N was indicated by further transformations. Treatment of the mixture of epoxides XIII-X and XIII-N with lithium aluminum hydride gave a mixture of a diol XVIII and the tricyclic compound XIVa. The formation of the mixture indicated that XIII was a mixture of *endo* and *exo* isomers, XIII-X giving rise to the diol XVIII, and XIII-N to XIVa. The secondary hydroxyl group in compound XVIII was assigned the *exo* configuration since it resulted from the attack of hydride on the *exo*-epoxide; the hydroxymethyl group was assigned the *exo* configuration also since the *endo* group should attack the epoxide to form XIVa.[15c]



XVIII

The latter (XIVa) was the sole product when XIII-N, prepared from the pure *endo*-carbinol, was treated with lithium aluminum hydride; it was also formed from the *endo-exo* mixture, XIII-N and

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[13] Prepared by the method of E. E. Royals and L. L. Harrell, Jr., *J. Am. Chem. Soc.*, **77**, 3405 (1955).

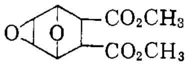
[14] The numbering in structure I is used.

[15] (a) S. B. Soloway and S. J. Cristol, *J. Org. Chem.*, **25**, 327 (1960); (b) J. Meinwald and G. A. Wiley, *J. Am. Chem. Soc.*, **80**, 3667 (1958); (c) H. B. Henbest and B. Nicholls, *J. Chem. Soc.*, 221 (1959); (d) H. H. Gunthard, H. Heusser and A. Furst, *Helv. Chim. Acta*, **36**, 1900 (1953).

[16] W. C. J. Ross, *J. Chem. Soc.*, 2257 (1950).

[17] J. C. Martin and P. D. Bartlett, *J. Am. Chem. Soc.*, **79**, 2533 (1957).

[18] The oxidation of the maleate–furan adduct with peracid was reported[6] to give the compound XVII.

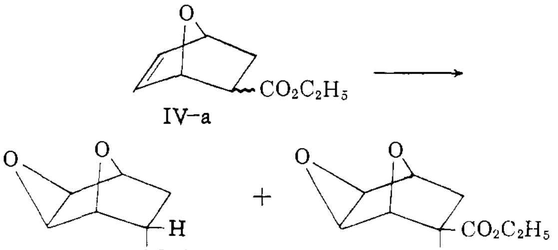


[19] (a) G. Stork, *et al.*, *J. Am. Chem. Soc.*, **75**, 384 (1953); (b) H. M. Walborsky and D. F. Loncrini, *ibid.*, **76**, 5396 (1954); (c) S. B. Soloway, H. Kwart and P. von R. Schleyer, Jr., *ibid.*, **82**, 2341 (1960); (d) S. J. Cristol, *et al.*, *ibid.*, **79**, 6035 (1957); (e) J. A. Berson and R. Swidler, *ibid.*, **76**, 4060 (1954); (f) J. A. Berson, *ibid.*, **76**, 5748 (1954); (g) J. D. Roberts, F. O. Johnson and R. A. Carboni, *ibid.*, **76**, 5692 (1954).

XIII-X, by treatment with 20% aqueous alkali, periodic acid, 2% sulfuric acid or ammonium thiocyanate. The structure assigned to XIVa was in agreement with the structures and configurations assigned to X-Nb and XIII-N; XIVa formed a crystalline monoacetate XIVb, which had no free hydroxyl, and XIVa was stable to the action of lithium aluminum hydride. It had lost the epoxide band at 855 cm.$^{-1}$. The n.m.r. spectrum showed that seven of the ten hydrogens were on oxygen and on carbon bearing oxygen. This ruled out structure XVI, which might result from a Wagner–Meerwein rearrangement[8,17] during the epoxide opening.

Acetylation of the mixed epoxides XIII–X and XIII-N gave a mixture of two crystalline acetates in a 2:1 ratio; the more abundant one was identical with the acetate of the cyclic ether XIVb and evidently was formed by isomerization of the epoxide XIII-N to XIVa followed by acetylation. The second acetate was the acetate of XIII-X; it had the epoxide band at 852 cm.$^{-1}$. The ratio of the two acetates was approximately the same as the ratio of the two products XIVa and XVIII formed by hydride treatment of the mixed epoxides.

Epoxidation of the mixed *exo*- and *endo*-esters IVa yielded a mixture containing approximately 60% of the *endo*-ester XIX-N, and 40% of the *exo*-ester XIX-X. The ratio was based on the ratio of products obtained when the mixture was treated with lithium aluminum hydride; this yielded the ether XIVa and the diol XVIII, both formed apparently by reduction of the ester to a primary alcohol group, followed by reaction of each epimer XIII-N and XIII-X as described above.

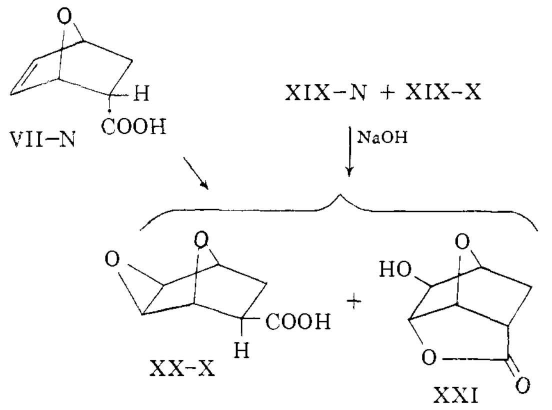


IV–a

XIX–N

XIX–X

Epoxidation of the pure *endo*-acid VII–N gave a mixture of the epoxy acid XX-X and the crystalline hydroxylactone XXI. The action of aqueous sodium hydroxide on the mixed *endo*- and *exo*-epoxy esters XIX-N and XIX-X formed a mixture of the epoxy acid XX-X and the hydroxylactone XXI also. The structure of the lactone was assigned on the basis of the infrared spectrum: a hydroxyl band at 3350 cm.$^{-1}$, a carbonyl band at 1780 cm.$^{-1}$ (γ-lactone) and no epoxide band. The n.m.r. spectrum showed five of the eight protons to be on oxygen and on carbon bearing oxygen, in agreement with structure XXI. The structure of XX-X was assigned on the basis of the epoxide band at 858 cm.$^{-1}$ and the carboxyl band at 1725 cm.$^{-1}$ in the infrared, and on the failure of the compound to lactonize.



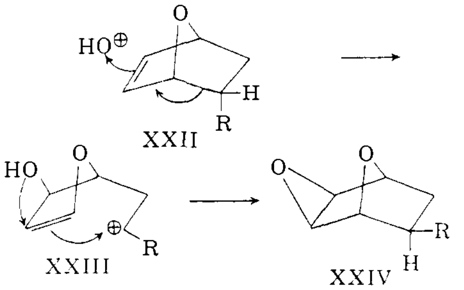
VII–N

XX–X

XXI

Epimerization during Epoxidation.—The results of the epoxidation of the *endo*-acid VII-N and of the *exo*-carbinol X-Xb showed that there was partial epimerization of the group at C-2 of the oxabicycloheptene nucleus. Because the epimerization during epoxidation and subsequent treatments of VII-N must have occurred during the epoxidation step, we suggest that, in all cases showing epimerization, it occurred during epoxidation. In general, epimerization during lithium aluminum hydride treatment is unlikely. The epimerization with VII-N changed the *endo*-carboxyl to the *exo* configuration. In contrast, the pure *endo*-carbinol X-Nb gave only the *endo* epoxidized product XIII-N. The epoxidation of the mixed carbinols IVc could be shown to be accompanied by epimerization of the *exo*-carbinol group to the *endo* configuration, by a consideration of the *endo–exo* ratio in the starting material IVc and in the products XIII-N and XIII-X. Therefore the epoxidation reaction favored the formation of product with an *exo*-carboxyl group, but with an *endo*-carbinol group.

The epimerization could be explained by several mechanisms. One mechanism could involve formation of a carbonium ion and recyclization with altered stereochemistry at C-2, as



XXII

XXIII

XXIV

The plausibility of this sequence is supported by two considerations. An intermediate of structure XXIII may be stabilized by R = –COOH through α-lactone[20] formation, and by R = –CH_2OH through epoxide formation. The transformation from XXIII to the closed epoxide XXIV is supported by the analogy of the closure of Δ^3-cyclopentenylethyl arenesulfonates to the bicycloheptyl nonclassical ion.[21]

[20] W. A. Cowdrey, E. D. Hughes and C. K. Ingold, *J. Chem. Soc.*, 1208 (1937); S. Winstein and H. J. Lucas, *J. Am. Chem. Soc.*, **61**, 1576 (1939); S. Winstein, *ibid.*, **61**, 1635 (1939).

[21] (a) R. G. Lawton, *ibid.*, **83**, 2399 (1961); (b) P. D. Bartlett and S. Bank, *ibid.*, **83**, 2591 (1961).

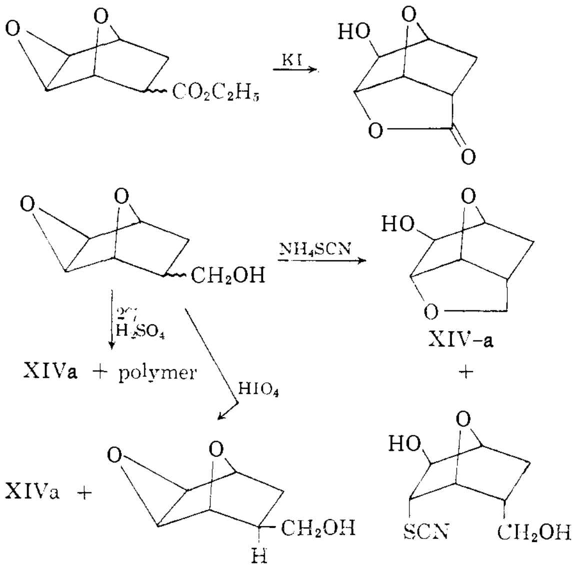
It is not possible, however, to rule out epimerization through an "internal" dissociation of the oxabicycloheptene, of the type demonstrated by Berson.[22]

It is not clear from consideration of either of these alternatives why in the case of the acid the *exo*-carboxyl is favored, while in the alcohol the *endo*-carbinol is favored. Indeed, it is not obvious why both *endo*-acid VII-N and *endo*-alcohol X-Nb are not converted directly, on epoxidation, to the lactone XXI and cyclic ether XIVa, respectively (*cf.* ref. 15c).

The positive thiosulfate test for 1,2-epoxides and the spectral data appear to be satisfactory evidence that the assigned epoxide structures are correct and that a Wagner–Meerwein rearrangement is not involved.

Ring Opening Reactions of the Dioxatricyclooctanes.—The action of lithium aluminum hydride on the *endo*-epoxide XIII-N to give the cyclic ether XIVa, and the formation of the lactone XXI, which have been described above, represent intramolecular displacement reactions on the epoxide group. The positive thiosulfate reaction on the epoxides represents an intermolecular displacement by the very powerful nucleophile thiosulfate ion on the epoxides.

Numerous other attempts to open the epoxide rings by other nucleophiles led to products derived from intramolecular displacement reactions, of the *endo* isomers. Products derived from Wagner–Meerwein rearrangement,[8,17] were not isolated, although they may have been formed.



Experimental[23]

Diels–Alder Reaction between Ethyl Acrylate and Furan; Formation of 2-Carbethoxy-7-oxabicyclo[2.2.1]hept-5-ene (IVa).—Furan (30 ml.) and ethyl acrylate (25 ml.), both stabilized with 0.025% hydroquinone, were mixed and refluxed for several weeks. Excess reactants were evaporated under reduced pressure at room temperature, to leave 11.3 g. of crude adduct IVa. This was distilled (50° (10^{-2} mm.)) to yield 7.2 g. of a pure colorless oil, n^{23}_{D} 1.4664. The infrared spectrum showed bands at 3040, 1725 and 698 cm.$^{-1}$.

Anal. Calcd. for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.40; H, 7.24.

Compound IVa was a mixture of *exo* and *endo* isomers, as shown by the vapor phase chromatogram of the reduced compound Va.

Catalytic Reduction of IVa; Formation of 2-Carbethoxy-7-oxabicyclo[2.2.1]heptane (Va).—To palladium-on-charcoal (5%, 500 mg.) in 95% ethanol was added 3.00 g. of the unsaturated ester IVa. Uptake of hydrogen ceased at the theoretical amount after 4 hours. The product, 3.05 g. of a colorless oil, was taken up in ether; the ether solution was put through alumina (10 g., act. I,[24] Woelm, neutral), and then the residue after evaporation of the ether was evaporatively distilled (50° (10^{-2} mm.)) to yield 2.8 g. of pure Va, n^{25}_{D} 1.4560. The infrared spectrum showed no bands at 3040 and 698 cm.$^{-1}$; it did show a band at 1730 cm.$^{-1}$.

The vapor phase chromatogram (5′ Ucon Polar column, 158°, 40 cc./min.) showed two peaks with retention times of 9.9 and 15.3 min. having areas in the ratio 3:2. These are probably the *exo* and *endo* isomers, respectively.

Anal. Calcd. for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.63; H, 8.33.

Treatment of IVa with Methylmagnesium Iodide; Formation of 2-α-Hydroxyisopropyl-7-oxabicyclo[2.2.1]hept-5-ene (IVf).—The ester IVa (21.0 g.) in 75 ml. of ether was added dropwise to the Grignard reagent from 7.05 g. of magnesium and 41.2 g. of methyl iodide in 25 ml. of ether. The reaction mixture was stirred overnight, then decomposed with 25 ml. of water and 150 ml. of 10% sodium sulfate solution. The aqueous layer was continuously extracted for 2 days with ether. The ethereal extract then was shaken with anhydrous sodium sulfate and sodium bisulfite, filtered, and the ether removed to yield 17.6 g. of crude material. This was vacuum distilled (82–88° (0.2 mm.)) to yield 11.7 g. of pure IVf, n^{25}_{D} 1.4854. There appeared to be some decomposition during the distillation. The infrared spectrum showed bands at 3350, 3050, 1140 and 688 cm.$^{-1}$.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.12; H, 9.15.

Compound IV-f appeared to be a mixture of *exo* and *endo* isomers, as shown by the vapor phase chromatogram of the reduced compound Ve.

Catalytic Reduction of IVf; Formation of 2-α-Hydroxyisopropyl-7-oxabicyclo[2.2.1]heptane (Ve).—Three grams of impure IVf was reduced with hydrogen over palladium exactly as described above for IVa. The product, 3.3 g. of a brownish, thin oil, was chromatographed on 60 g. of alumina (Fisher). A first fraction (541 mg.) seemed from its infrared spectrum to be a mixture of Ve and the corresponding methyl ketone arising from incomplete addition of the Grignard reagent. The main fraction, 2.02 g., Ve, was twice evaporatively distilled (50° (10^{-2} mm.)) to yield 1.70 g. of colorless oil, n^{25}_{D} 1.4741. The infrared spectrum showed bands at 3340 and 1140 cm.$^{-1}$, and no bands at 3050 and 688 cm.$^{-1}$. The vapor phase chromatogram (5-½′ Flexol 8N8 on Chromosorb, 150°, 40 cc./min.) showed two peaks with retention times of 49.3 and 78 min., the areas of which were in the ratio 4:1.

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.05; H, 10.21.

Treatment of IVa with Lithium Aluminum Hydride; Formation of 2-Hydroxymethyl-7-oxabicyclo[2.2.1]hept-5-ene (IVc).—To 2.0 g. of lithium aluminum hydride in 100 ml. of ether was added, dropwise, 5.00 g. of the unsaturated

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[22] J. A. Berson and R. Swidler, *J. Am. Chem. Soc.*, **75**, 1721 (1953); J. A. Berson, R. D. Reynolds and W. A. Jones, *ibid.*, **78**, 6049 (1956); J. A. Berson, A. Remanick and W. A. Mueller, *ibid.*, **82**, 5501 (1960); J. A. Berson and A. Remanick, *ibid.*, **83**, 4947 (1961).

[23] All boiling points and melting points are uncorrected. Elemental microanalyses were performed by T. Montzka and V. Landeryou of this Laboratory, and by Micro-Tech Laboratories (Skokie, Ill.) and F. Pascher (Bonn, Germany). Nuclear magnetic resonance spectra were taken on a 60 Mc. Varian instrument by Dr. L. Colebrook of this Laboratory and by Varian Associates (Palo Alto, Calif.). Infrared spectra were determined on samples in the form of liquid films, carbon tetrachloride solutions or potassium bromide disks on a Perkin-Elmer model 21 spectrophotometer. Ultraviolet spectra were determined in 95% ethanol on a Beckman DU spectrophotometer. Vapor phase chromatography was carried out on an Aerograph model A-90C instrument with helium as the carrier gas.

[24] The activity of the alumina corresponds to the Brockman scale. *Cf.* E. Lederer and M. Lederer, "Chromatography," Elsevier Press, New York, N. Y., 1953, p. 28.

ester IVa in 50 ml. of ether. After completion of the addition, the suspension was stirred for 1 day. The excess hydride and salts were destroyed by the addition of a saturated sodium sulfate solution. The precipitate was filtered and washed with ether; the ethereal solution was dried with anhydrous sodium sulfate, and evaporated under reduced pressure to yield 3.70 g. of crude IVc. This was distilled (50° (10^{-2} mm.)) to afford 3.4 g. of pure IVc, n^{25}D 1.4923. The infrared spectrum showed bands at 3250, 3050, 1030 and 705 cm.$^{-1}$. Compound IVc appeared to be a mixture of *exo* and *endo* isomers, as shown by the vapor phase chromatogram of the reduced compound Vc. Chromatography on alumina (act. I, Woelm, neutral) afforded no separation of isomers.

Anal. Calcd. for $C_7H_{10}O_2$: C, 66.62; H, 7.99. Found: C, 66.48; H, 8.23. The analyst reported the sample to be very hygroscopic.

Catalytic Reduction of IVc; Formation of 2-Hydroxymethyl-7-oxabicyclo[2.2.1]heptane (Vc).—The unsaturated primary alcohol IVc (1.00 g.) was reduced by hydrogen over 200 mg. of palladium-on-charcoal. The usual workup yielded 1.0 g. of crude material which was poured over alumina (10 g., act. I, Woelm, neutral) and eluted with ether. The resulting product was evaporatively distilled (50° (10^{-2} mm.)) to yield 825 mg. of pure Vc, n^{25}D 1.4823. The infrared spectrum showed bands at 3200 and 1040 cm.$^{-1}$, and no bands at 3050 and 705 cm.$^{-1}$.

Anal. Calcd. for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.29; H, 9.38.

The vapor phase chromatogram (5′ Ucon Polar column, 158°, 42 cc./min.) showed two peaks with retention times of 15.0 and 21.4 min. and areas in the ratio 13:7. At 145°, 56 cc./min., the two peaks had retention times of 10.2 and 14.2 min.

Treatment of the Saturated Ester Va with Lithium Aluminum Hydride; Formation of Vc.—One-half gram of Va was reduced by lithium aluminum hydride in ether as described above for IVa. The usual workup gave 375 mg. of crude oil which was distilled (50° (10^{-2} mm.)) to yield 305 mg. of Vc, n^{25}D 1.4820. The infrared spectrum was identical with that of Vc obtained by the catalytic reduction of IVc.

The vapor phase chromatogram (5′ Ucon Polar column, 158°, 40 cc./min.) showed two main peaks with retention times of 15.2 and 21.8 min., the areas of which were in the ratio 13:7. The retention times agree with those for Vc obtained from IVc; a mixture of Vc from the two sources showed only two peaks.

Treatment of the Unsaturated Primary Alcohol IVc with *p*-Toluenesulfonyl Chloride–Pyridine; Formation of the *p*-Toluenesulfonate IVd.—To 34.0 g. of freshly crystallized *p*-toluenesulfonyl chloride in 30 ml. of pyridine was added 10.2 g. of the unsaturated primary alcohol IVc in 30 ml. of pyridine. The mixture stood for 3 hours; then it was poured onto 200 g. of crushed ice and left for an hour. The mixture was then extracted with three 100-ml. portions of ether. The ethereal solution was washed with 100 ml. of 10% aqueous hydrochloric acid, 100 ml. of water and 100 ml. of 10% aqueous sodium bicarbonate; then it was dried with anhydrous sodium sulfate and evaporated under reduced pressure to yield 22.8 g. of a brownish, viscous oil which was carried onto the next step without further purification. The infrared spectrum showed no hydroxyl absorption, a shoulder at 3030–3040 cm.$^{-1}$, and bands at 1350, 1175 and 705 cm.$^{-1}$.

Treatment of IVd with Lithium Aluminum Hydride; Formation of 2-Methyl-7-oxabicyclo[2.2.1]hept-5-ene (IVe).—To a stirred suspension of 3.0 g. of lithium aluminum hydride in 100 ml. of anhydrous ether the 22.8 g. of the crude tosylate IVd in 100 ml. of anhydrous ether was added in 3 hours. The mixture was stirred an additional 3 hours. Isolation of the crude product in the usual manner afforded 10 g. of a liquid with a strong sharp odor. This was dissolved in petroleum ether (b.p. 37–51°) and poured through a column of alumina (10 g., act. I, Woelm, neutral). The resulting 6.1 g. of colorless liquid was taken up in 20 ml. of ether, and washed with 10 ml. of 10% aqueous hydrochloric acid, 10 ml. of water and 10 ml. of 10% aqueous sodium bicarbonate. The dried ethereal solution was distilled, and the portion boiling between 118–124° (3.84 g.) was collected, n^{30}D 1.4612. The infrared spectrum showed no hydroxyl band, and bands at 3030 and 698 cm.$^{-1}$. The nuclear magnetic resonance spectrum showed two hydrogens in the vinyl region (3.86 τ), two hydrogens in the region for those on carbon bearing oxygen (5.0–7.0 τ), and six hydrogens in the saturated region (7.5–9.6 τ). There were two methyl peaks (8.90 and 9.18 τ, both doublets), supporting the fact that IVe was a mixture of *exo* and *endo* isomers.

Anal. Calcd. for $C_7H_{10}O$: C, 76.32; H, 9.15. Found: C, 76.44; H, 9.25.

Catalytic Reduction of IVe; Formation of 2-Methyl-7-oxabicyclo[2.2.1]heptane (Vd).—Two hundred milligrams of IVe was reduced by hydrogen over 200 mg. of palladium-on-charcoal in methanol suspension. The mixture was filtered and the filtrate was diluted with an equal volume of water. This solution was continuously extracted with petroleum ether (b.p. 37–51°) overnight. The petroleum ether was concentrated and the concentrate put through a column of alumina (10 g., act. I, neutral Woelm) using petroleum ether for elution. The eluate was twice distilled, the portion boiling between 110–115° being collected, to yield 980 mg. of a colorless liquid, n^{30}D 1.4520. The infrared spectrum showed no hydroxyl band and no vinyl proton or *cis*-disubstituted double bond band. The vapor phase chromatogram (5–$^1/_2$′ Flexol 8N8 on Chromosorb, 151°, 40 cc./min.) showed two peaks with retention times of 6.4 and 7.4 min., with areas in the ratio 3:2.

Anal. Calcd. for $C_7H_{12}O$: C, 74.95; H, 10.78. Found: C, 75.16; H, 10.94.

Formation of the *p*-Nitrobenzoate Esters of IVc; Separation of the *exo* (X-Xa) and endo (X-Na) Isomers by Fractional Crystallization.—In 30 ml. of dry pyridine, IVc (10.0 g.) was treated with freshly crystallized *p*-nitrobenzoyl chloride (15.0 g.). After the initial reaction had subsided, the mixture was warmed on the steam-bath for half an hour, then poured onto ice, allowed to stand for an hour, then centrifuged. The centrifugate was washed with 100 ml. of 5% sodium bicarbonate solution, and two 100-ml. portions of water. The precipitate was dried overnight over sodium hydroxide under reduced pressure; it afforded 22.73 g. of solid material. This was dissolved in benzene, treated with charcoal, filtered, and crystallized from a benzene–hexane solution.

The first crop of crystals contained 11.9 g. of material, m.p. 128–135°. Recrystallization from benzene–hexane afforded 11.78 g. of X-Xa, m.p. 135–137°.

The second crop of crystalline material contained 1.9 g., m.p. 92–97°. Recrystallization from benzene–hexane afforded 1.87 g. of X-Na, m.p. 97–98°. A mixture melting point between X-Xa and X-Na was depressed (78–105°).

Subsequent crystallizations and recrystallizations yielded 70 mg. more of X-Xa and 1.45 g. more of X-Na. The total yield of X-Xa was 11.85 g. and of X-Na, 3.32 g.

Anal. Calcd. for $C_{14}H_{13}O_5N$: C, 61.09; H, 4.76; N, 5.09. Found for X-Xa: C, 60.93; H, 4.96; N, 5.15. Found for X-Na: C, 61.06; H, 5.00; N, 4.99.

The infrared spectra of the two were similar except for a few small shifts in bands, and differing relative intensities. Both showed a band at 3040 cm.$^{-1}$, a band around 1710 cm.$^{-1}$ (X-Xa at 1710 cm.$^{-1}$, X-Na at 1715 cm.$^{-1}$) and bands around 1530 and 1340 cm.$^{-1}$ (X-Xa at 1525 and 1340 cm.$^{-1}$, X-Na at 1530 and 1340 cm.$^{-1}$). There were bands at 1027 and 1011 cm.$^{-1}$ for each compound, but for X-Xa, the 1027 cm.$^{-1}$. band was more intense than the 1011 cm.$^{-1}$ band, whereas the reverse was true of X-Na. The ultraviolet spectra for the two compounds were quite similar. For X-Xa, the spectrum showed ϵ_{259} 1.4 × 10^4 and ϵ_{220} 4.2 × 10^3. For X-Na, the spectrum showed ϵ_{259} 1.9 × 10^4 and ϵ_{220} 5.5 × 10^3.

Cleavage of X-Xa with Lithium Aluminum Hydride; Isolation of the *exo* Unsaturated Primary Alcohol X-Xb.—To lithium aluminum hydride (1.5 g.) in 20 ml. of ether was slowly added 3.00 g. of X-Xa in 20 ml. of a 1:1 mixture of ether and tetrahydrofuran; the mixture was stirred and refluxed for 4 hours after completion of the addition. From the usual workup, 1.89 g. of product was obtained. This was extracted with 20 ml. of water, the mixture was filtered and the precipitate washed with water. The aqueous solution was treated with charcoal, filtered, and continuously extracted with ether for 1 day. The dried ethereal extract was evaporated under reduced pressure to yield 965 mg. of crude oil in ether solution. This was put through alumina (10 g., act. II, neutral, Woelm), then evaporatively distilled (50° (10^{-2} mm.)) to yield 885 mg. of colorless X-Xb,

$n^{28.5}\text{D}$ 1.4917. The infrared spectrum showed bands at 3250, 3050, 1030 and 705 cm.$^{-1}$. It also showed bands at 863 and 680 cm.$^{-1}$ which were present in the spectrum of IVc, but absent in that of X–Xb. This was the only readily observable difference in the spectra of the two isomers.

There was an observable shift of the hydroxyl frequency of X–Xb in the infrared upon dilution from a 1% solution (CCl_4) to a 0.06% solution. The hydroxyl band shifted from 3420 to 3600 cm.$^{-1}$. For the 1% soultion the relative intensity of the 3420 cm.$^{-1}$ band to the 3600 cm.$^{-1}$ band was 2:1; for the 0.06% solution, it was 1:3.

Cleavage of X–Na with Lithium Aluminum Hydride; Isolation of X–Nb.—To lithium aluminum hydride (1.0 g.) in 20 ml. of ether was slowly added a solution 1.00 g. of X–Na in 10 ml. of ether and enough tetrahydrofuran to dissolve the compound. This reaction was treated essentially as described above for X–Xa: the initial crude product (880 mg.) afforded 380 mg. of slightly yellow oil which was distilled (50° (10^{-2} mm.)) (without purification through alumina) to give 310 mg. of colorless X–Nb, $n^{29}\text{D}$ 1.4969. The infrared spectrum showed bands at 3250, 3050, 1030 and 705 cm.$^{-1}$; it showed no bands at 863 and 680 cm.$^{-1}$.

There was an observable shift in the hydroxyl frequency of X–Nb in the infrared upon dilution from a 1% solution (CCl_4) to a 0.06% solution; the hydroxyl band shifted from 3420 to 3600 cm.$^{-1}$. For the 1% solution the relative intensity of the 3420 cm.$^{-1}$ band to the 3600 cm.$^{-1}$ band was 2:1; for the 0.06% solution it was 1:3.

Catalytic Reduction of X-Xa; Formation of the *p*-Aminobenzoate XI-X.—One gram of X-Xa in methanol was reduced by hydrogen over palladium-on-charcoal. Uptake ceased promptly at the theoretical 4 equivalents. Following the usual workup, 970 mg. of a viscous colorless oil was obtained which immediately began to crystallize. Recrystallization from benzene–hexane afforded 900 mg. of white crystals, m.p. 122–127°. A small portion was recrystallized from methanol for an analytical sample, m.p. 132–133°. The infrared spectrum showed bands at 3400, 1680 and 1626 cm.$^{-1}$. The ultraviolet spectrum showed two maxima; ϵ_{259} 2.2 × 10^4, ϵ_{222} 8.9 × 10^3.

Anal. Calcd. for $C_{14}H_{17}O_3N$: C, 67.99; H, 6.93; N, 5.66. Found: C, 67.98; H, 7.05; N, 5.64.

Catalytic Reduction of X-Na; Formation of XI-N.—As described for X–Xa, X–Na (1.00 g.) was reduced. The usual workup gave 950 mg. of a viscous brownish oil, which immediately began to crystallize. Crystallization from benzene–hexane afforded 880 mg. of brownish crystals, m.p. 124–130°. A small portion was recrystallized from methanol for the analytical sample, m.p. 131–132.5°. The mixture melting point with XI-X was 123–132°. The infrared spectrum of XI–N was very similar to that of XI–X; only an intensity reversal of two bands was noticed. For XI–X, a band at 1317 cm.$^{-1}$ had a greater intensity than a band at 1303 cm.$^{-1}$; the reverse was true for XI–N. The ultraviolet spectrum for XI–N showed two maxima: ϵ_{259} 2.2 × 10^4, ϵ_{222} 8.6 × 10^3.

Anal. Calcd. for $C_{14}H_{17}O_3N$: C, 67.99; H, 6.93; N, 5.66. Found: C, 67.79; H, 7.05; N, 5.76.

Saponification of XI-X; Isolation of the *exo* Saturated Primary Alcohol XII-X.—To 5 ml. of 10% aqueous sodium hydroxide plus 1 ml. of dioxane was added XI–X (820 mg.) and the resulting mixture was heated on the steam-bath for 6 hours. The mixture was cooled, filtered, treated with charcoal, filtered, and continuously extracted with ether for 2 days. The dried ethereal solution was evaporated under reduced pressure to yield 245 mg. of a pale yellow oil. This was evaporatively distilled to yield 194 mg. of colorless XII–X, $n^{28}\text{D}$ 1.4803. The infrared spectrum showed no band at 745 cm.$^{-1}$, whereas the spectra of Vc and XII-N showed a band at 745 cm.$^{-1}$. There was an observable shift in the hydroxyl frequency of XII-X in the infrared upon dilution from a 1% solution (CCl_4) to a 0.06% solution; it shifted from 3420 to 3600 cm.$^{-1}$. The relative intensity of the 3420 cm.$^{-1}$ band to the 3600 cm.$^{-1}$ band for the 1% solution was 4:1, for the 0.06% solution it was 1:3.

The vapor phase chromatogram of this oil (5′ Ucon Polar column, 145°, 56 cc./min.) showed one main peak with a retention time of 10.2 min. Adding XII-X to Vc (mixture of isomers) enhanced the peak at 10.2 min.

Saponification of XI-N; Isolation of the *endo* Saturated Primary Alcohol XII-N.—The *endo-p*-aminobenzoate (840 mg.) was saponified as described for the *exo*-ester. The crude colorless alcohol (339 mg.) was distilled (50° (10^{-2} mm.)) to afford 285 mg. of XII-N, $n^{28.5}\text{D}$ 1.4825. The infrared spectrum of XII-N showed no band at 728 cm.$^{-1}$, whereas the spectra of Vc and XII-X showed a band at 728 cm.$^{-1}$. There was an observable shift in the hydroxyl frequency of XII-N in the infrared (3420 to 3600 cm.$^{-1}$) upon dilution from a 1% solution (CCl_4) to a 0.06% solution. The relative intensity of the 3420 cm.$^{-1}$ band to the 3600 cm.$^{-1}$ band for the 1% solution was 2:1; for the 0.06% solution it was 1:3.

The vapor phase chromatogram of XII–N (5′ Ucon Polar column, 145°, 56 cc./min.) showed one main peak with a retention time of 14.2 min. Adding XII-N to Vc (mixture of isomers) enhanced the peak at 14.2 min.

Hydrolysis of IVa; Formation of the *endo* and *exo* Isomers of 2-Carboxy-7-oxabicyclo[2.2.1]hept-5-ene (VII-N and VII-X).—Undistilled IVa (30 g.) was stirred with 50 ml. of 10% aqueous sodium hydroxide at room temperature for 1 day. The aqueous solution was acidified with concd. hydrochloric acid and then continuously extracted with ether for 1 day. The dried ethereal extract was evaporated under reduced pressure to yield 24 g. of a brown oil in which crystals slowly formed. This was triturated with 3:1 petroleum ether–ether solution, dissolved in ether, treated with charcoal, filtered and crystallized from petroleum ether–ether. A total of 13.62 g. of crystalline material was obtained. This was chromatographed over alumina (200 g. of act. I, neutral Woelm alumina deactivated with 16 ml. of 10% aqueous acetic acid). The first fraction, eluted with 1:1 petroleum ether–ether, consisted of 1.375 g. of a mobile liquid which the infrared spectrum showed to be unhydrolyzed ester IVa.

A small portion of this ester was treated with lithium aluminum hydride. The infrared spectrum and the *p*-nitrobenzoate derivative (m.p. 97–98°) of the resulting alcohol showed it to be identical with X–Nb; this indicated that the unhydrolyzed ester had the *endo* configuration.

Saponification of 500 mg. of this ester yielded 375 mg. of a yellowish oil, which was heated *in vacuo* (50° (10^{-2} mm.)) to give 130 mg. of a crystalline sublimate. Recrystallization from benzene–hexane afforded 120 mg. of the *endo* unsaturated acid VII–N, m.p. 97–97.5° (mixture melting point with the second fraction from the chromatography was undepressed: m.p. 97–98.5°).

The second fraction from the column, which was eluted with 1:3 petroleum ether–ether through ether, consisted of 7.960 g. of crystalline VII-N, m.p. 96.5–99.5°. A small portion of this was crystallized from benzene–hexane for analysis, m.p. 98–99.5°. The infrared spectrum showed bands at 1700 and 700 cm.$^{-1}$. The n.m.r. spectrum showed one hydrogen at -1.11 τ, two hydrogens at 3.61 τ, two hydrogens in the 4.7–5.1 τ region, and three hydrogens in the 6.5–8.6 τ region.

Anal. Calcd. for $C_7H_8O_3$: C, 60.00; H, 5.75. Found: C, 60.15; H, 5.71.

A third fraction was eluted from the column with chloroform, and contained 105 mg. of an oil, the infrared spectrum of which was very similar to that of VII–N. This was treated with lithium aluminum hydride to yield an oil whose infrared spectrum was identical with that of the unsaturated primary alcohol X-Xb, and whose *p*-nitrobenzoate derivative corresponded to X–Xa, m.p. 134–137°. A mixture melting point with X–Xa was undepressed.

Treatment of VII-N with Iodine in Basic Medium; Formation of the Iodolactone VIII.—A solution of 770 mg. of VII–N in 15 ml. of 7% aqueous sodium bicarbonate was treated with 15 ml. of water containing 1.27 g. of iodine and 4.98 g. of potassium iodide. This solution was allowed to stand for 1 hour, then it was extracted with three 25-ml. portions of chloroform. The combined chloroform extracts were then washed with 25 ml. of 10% aqueous sodium bisulfite, dried with sodium sulfate, and the chloroform was evaporated under reduced pressure to give 320 mg. of a white solid, m.p. 150–154°. Crystallization from ethyl acetate gave white crystals, m.p. 157–157.5°. The infrared spectrum showed no hydroxyl or olefinic bands; it had a band at 1780 cm.$^{-1}$.

Anal. Calcd. for $C_7H_7O_3I$: C, 31.60; H, 2.65. Found: C, 31.68; H, 2.72.

Treatment of VII-N with Lithium Aluminum Hydride; Formation of the *endo* Unsaturated Primary Alcohol X-Nb.—One gram of the unsaturated acid VII–N was reduced by 1.0

g. of lithium aluminum hydride in ether, essentially as described above for the ester IVa. The crude oil produced (400 mg.) was distilled (45° (10^{-2} mm.)) to afford 360 mg. of an oil whose infrared spectrum was identical with that of the *endo* unsaturated primary alcohol X–Nb. The *p*-nitrobenzoate of the oil, m.p. 96–97.5°, gave no depression upon admixture with X–Na.

Catalytic Reduction of VII–N; Formation of *endo*-2-Carboxy-7-oxabicyclo[2.2.1]heptane (IX-N).—The acid VII-N (500 mg.) was reduced by hydrogen over 100 mg. of palladium-on-charcoal as described for the reduction of the ester Va. The 540 mg. of crude material upon sublimation (65° (10^{-2} mm.),) yielded 475 mg. of crystalline material, m.p. 75–78.5°. The analytical sample, m.p. 78–79.5°, was prepared by two crystallizations from benzene–hexane. The infrared spectrum showed a band at 1710 cm.$^{-1}$ and no band at 700 cm.$^{-1}$.

Anal. Calcd. for $C_7H_{10}O_3$: C, 58.73; H, 7.04. Found: C, 59.03; H, 7.03.

Hydrolysis of the Saturated Ester Va; Formation of the Saturated Acid Vb, and Separation into the Two Isomers IX-N and IX-X.—The saturated ester Va (500 mg.) was stirred with 0.2 g. of sodium hydroxide in 5 ml. of water until all the insoluble oil had dissolved. The solution was then acidified and continuously extracted with ether. The dried ethereal extract was concentrated under reduced pressure to give 398 mg. of an oil, which was distilled (60° (10^{-2} mm.)) to yield 310 mg. of a thick colorless oil (mixture of IX-N and IX-X), which was sent for analysis before separation of the isomers was achieved.

Anal. Calcd. for $C_7H_{10}O_3$: C, 58.73; H, 7.04. Found: C, 58.65; H, 7.13.

This oil was subjected to a crystallization from benzene–hexane (seeded with IX-N obtained from VII–N). A crystalline material (140 mg.), m.p. 69–76°, was obtained. After several recrystallizations from benzene–hexane, the melting point was 78–79.5°. A mixture melting point with IX-N obtained by the catalytic reduction of VII–N showed no depression.

The material recovered from the mother liquor of the original crystallization (150 mg. of a viscous oil) was treated with lithium aluminum hydride in ether. Usual workup gave 100 mg. of an oil. The vapor phase chromatogram of this oil (5′ Ucon Polar column, 145°, 56 cc./min.) showed one main peak with a retention time of 10.2 min. and a smaller one with a retention time of 14.5 min. Addition of the pure *exo* saturated primary alcohol XII–X to this oil enhanced the peak at 10.2 min., while addition of the *endo* isomer XII-N enhanced the peak at 14.5 min. These results indicate that the oil from the lithium aluminum hydride reduction consisted of both isomers, mainly the *exo*, and hence that the material recovered from the mother liquor which did not crystallize was mainly the *exo* isomer of the saturated acid IX–X.

Treatment of IVc with Monoperphthalic Acid in Chloroform; Formation of 6-Hydroxymethyl-3,8-dioxatricyclo-[3.2.1.0^{2,4}]octane (Mixture of *endo* and *exo* Isomers, XIII-N and XIII–X).—To an excess of freshly prepared monoperphthalic acid[18] in cold chloroform was added 12.2 g. of IVc. The solution was kept at 5° for 2 days, during which time phthalic acid slowly precipitated. Purified 2-pentene (2 ml.) was added and the mixture was left at room temperature for 2 hours, then filtered, and the chloroform and other volatile materials were removed under reduced pressure. The residual oil was passed over alumina (50 g., Merck), with chloroform, and the eluate was evaporated to give 16 g. of crude material. This was evaporatively distilled (65–70° (10^{-2} mm.) to give 11.5 g. of quite viscous material.

A 2 g. portion of material was chromatographed on alumina (40 g., Merck); the mixture of epoxides, XIII–N and XIII–X, was eluted with chloroform through 9:1 chloroform–methanol, and contained 2.06 g. of material, which was evaporatively distilled (65° (10^{-2} mm.)) for a pure sample, $n^{25.5}$D 1.5035. The infrared spectrum showed bands at 3300 and 855 cm.$^{-1}$. The n.m.r. spectrum showed a total area in the region 5.0–7.0 τ corresponding to seven hydrogens and a total area in the region 7.5–9.0 τ corresponding to three hydrogens. This compound gave a positive epoxide test with sodium thiosulfate.[16] The vapor phase chromatogram (5′ Ucon Polar column, 156°, 46 cc./min.) showed a single peak with a retention time of 26.6 min. Other work shows, however, that the epoxide is a mixture of the *endo* (XIII–N) and *exo* (XIII–X) isomers.

Anal. Calcd. for $C_7H_{10}O_3$: C, 59.13; H, 7.09. Found: C, 58.81; H, 7.28. The analyst reported the material to be very hygroscopic.

Treatment of the Epoxy Alcohol (XIII-N and XIII-X Mixture) with Lithium Aluminum Hydride; Formation of the Isomeric Cyclic Ether XIVa and the Reduced Compound *exo* - 2 - Hydroxymethyl - *exo* - 5(or 6) - hydroxy - 7 - oxabicyclo[2.2.1]heptane (XVIII).—To a stirred refluxing suspension of lithium aluminum hydride (1.0 g.) in 100 ml. of purified tetrahydrofuran was added dropwise the epoxy alcohol (2.00 g.) obtained from IVc in 50 ml. of purified tetrahydrofuran. The mixture was stirred and refluxed for 1 day after completion of the addition. The crude oily product was chromatographed on alumina (15 g., act. II, Woelm, neutral) to yield two fractions.

The first fraction, eluted with chloroform, contained 1.48 g. of a viscous oil. This was evaporatively distilled (60° (10^{-2} mm.)) to give 1.27 g. of pure XIVa, n^{30}D 1.5009. The infrared spectrum showed a band at 3250 cm.$^{-1}$, and no band at 855 cm.$^{-1}$. The n.m.r. spectrum showed one hydrogen at 5.18 τ (triplet), one hydrogen at 5.83 τ (doublet), and a total of five hydrogens between 6.0–6.7 τ, giving a total of seven hydrogens in the region of the spectrum for those on oxygen and on carbon bearing oxygen; there were three hydrogens in the region 7.5–9.0 τ. The epoxide test of XIVa, with sodium thiosulfate was negative. There was an observable shift in the hydroxyl frequency of XIVa (3420 to 3560 cm.$^{-1}$) in the infrared upon dilution from a 1% solution (CCl_4) to a 0.06% solution. The relative intensity of the 3420 cm.$^{-1}$ band to the 3560 cm.$^{-1}$ band for the 1% solution was 1:1; for the 0.06% solution it was 1:3. The vapor phase chromatogram (5′ Ucon Polar column, 156°, 46 cc./min.) showed a single peak with a retention time of 26.7 min.

Anal. Calcd. for $C_7H_{10}O_3$: C, 59.13; H, 7.09. Found: C, 59.01; H, 7.22.

An acetate was prepared from XIVa according to procedure 11B in Shriner, Fuson and Curtin.[25] The acetate was extracted with ether and passed over alumina (5 g., act. I, Woelm, neutral) in petroleum ether. It was then crystallized from benzene–hexane to afford crystalline XIVb, m.p. 79–80°. The infrared spectrum of this acetate showed a band at 1725 cm.$^{-1}$, and no hydroxyl or epoxide bands. The epoxide test with sodium thiosulfate was negative.

Anal. Calcd. for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.92; H, 6.71.

The second fraction, eluted with methanol, contained 0.50 g. of a viscous oil. This was evaporatively distilled (70° (10^{-2} mm.)) to yield 250 mg. of colorless XVIII, n^{30}D 1.4979. The infrared spectrum showed a band at 3200 cm.$^{-1}$ and no band at 855 cm.$^{-1}$. The n.m.r. spectrum showed a total of seven hydrogens in the region 5.4–7.0 τ and a total of five hydrogens in the region 7.9–9.1 τ.

Anal. Calcd. for $C_7H_{12}O_3$: C, 58.31; H, 8.39. Found: C, 58.27; H, 8.20.

An acetate was prepared as for the first fraction; crystallization from benzene–hexane gave material, m.p. 44–47°. When these crystals were cooled quickly after having been above their melting point, they gave a crystalline material, m.p. 65–67°. The infrared spectrum of this acetate showed a band at 1725 cm.$^{-1}$ and no hydroxyl or epoxide bands.

Anal. Calcd. for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07. Found: C, 58.19; H, 7.26.

A sample of XIVa was quantitatively recovered unchanged (identity proved by comparison of infrared spectra and acetates) after treatment for 3 days with lithium aluminum hydride in boiling tetrahydrofuran.

When the epoxy alcohol (XIII–N and XIII–X mixture) was treated with lithium aluminum hydride in ether in an analogous manner, essentially no reaction took place as, judged from the infrared spectrum of the reaction product.

Treatment of X-Xb with Monoperphthalic Acid in Chloroform, Followed by Lithium Aluminum Hydride Reduction of the Resulting Epoxide.—In a manner analogous to the

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[25] R. L. Shriner, R. C. Fuson and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th Edition, John Wiley and Sons, Inc., New York, N. Y., 1956, p. 212.

treatment of IVc with monoperphthalic acid, X-Xb (3.16 g.) was so treated. The workup gave 3.5 g. of crude oil, distilled at 65° (10^{-2} mm.) to yield 3.02 g. of a viscous oil whose infrared spectrum was very similar to that for the mixture of XIII-N and XIII-X obtained from IVc, except that it had only a relatively small band at 705 cm.$^{-1}$ whereas the spectrum for the mixture had a relatively larger one.

As described earlier, 1.00 g. of the above-formed epoxide was treated with 1.0 g. of lithium aluminum hydride; the usual workup gave 1.08 g. of a crude oil. Chromatography on alumina (15.0 g., act. II, Woelm, neutral) afforded two fractions.

The first fraction, eluted with chloroform, contained 357 mg. of XIVa, as judged from its infrared spectrum, and its acetate, m.p. 80.5–81° (mixture melting point with XIVb was undepressed).

The second fraction, eluted with methanol, contained 642 mg. of XVIII as judged by its infrared spectrum and its acetate, m.p. 64.5–66° (mixture melting point with acetate of XVIII previously obtained was undepressed).

Treatment of X-Nb with Monoperphthalic Acid in Chloroform, Followed by Lithium Aluminum Hydride Reduction of the Resulting Epoxide.—As above, X-Nb (600 mg.) was treated with an excess of the peracid in cold chloroform. Workup gave a crude viscous oil, which was distilled (60° (10^{-2} mm.)) to yield 575 mg. of a viscous oil whose infrared spectrum was very similar to that for the mixture of XIII-N and XIII-X, except that it had no band at 684 cm.$^{-1}$ whereas the spectrum for the mixture had one.

Lithium aluminum hydride (0.5 g.) reduction of 400 mg. of the above-formed epoxide gave only one fraction when the crude reaction product was chromatographed on alumina. This fraction, eluted with chloroform, contained 380 mg. of XIVa as judged from its infrared spectrum and its acetate, m.p. 79–80.5° (mixture melting point with XIVb was undepressed).

Treatment of the Epoxy Alcohol (Mixture of XIII-N and XIII-X) with Acetic Anhydride and Sodium Acetate; Formation of the Two Isomeric Acetates, XIVb and the Acetate of XIII-X.—The epoxy alcohol (1.00 g.) was acetylated with sodium acetate–acetic anhydride at room temperature. The crude product after passage in chloroform over alumina (10 g., act. II, neutral, Woelm) was 1.2 g. of a viscous oil which crystallized slowly. This material was chromatographed on alumina (15 g., act. I, neutral, Woelm) to yield two fractions.

The first fraction, eluted with petroleum ether, contained 630 mg. of a crystalline material, m.p. 79–80.5°. Mixture melting point with XIVb was undepressed.

The second fraction, eluted with 1:1 petroleum ether–ether, contained 300 mg. of an oil which crystallized slowly on standing. This material was recrystallized from benzene–hexane to give crystals, m.p. 67.5–69°, the acetate of XIII-X. The infrared spectrum showed no hydroxyl band; it showed bands at 1725 and 852 cm.$^{-1}$. It had a band at 680 cm.$^{-1}$, but none at 705 cm.$^{-1}$.

Anal. Calcd. for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.76; H, 6.47.

Treatment of IVa with Monoperphthalic Acid in Chloroform; Formation of 6-Carbethoxy-3,8-dioxatricyclo[3.2.1.0^{2,4}]octane (Mixture of *endo* and *exo* Isomers XIX-N and XIX-X).—Freshly distilled IVa (2.50 g.) was treated with an excess of freshly prepared monoperphthalic acid in cold chloroform. The usual workup gave 3 g. of oil, which was passed over a short column of alumina (15 g., Merck) with ether and then distilled (70° (10^{-2} mm.)) to afford 2.5 g. of oil. This was chromatographed on alumina (50 g., Merck); a small forerun was eluted with 1:1 petroleum ether–ether. The epoxy ester (mixture of XIX-N and XIX-X) was eluted with ether and 9:1 ether–methanol; a total of 2.045 g. of material was collected, which was distilled (65° (10^{-2} mm.)), $n^{25.5}\text{D}$ 1.4741. The infrared spectrum showed bands at 1720 and 855 cm.$^{-1}$. This compound gave a positive epoxide test with sodium thiosulfate.

Anal. Calcd. for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.68; H, 6.73.

The vapor phase chromatogram (5′ Ucon Polar column, 160°, 72 cc./min.) showed a single somewhat broad peak with a retention time of 12.5 min. Other work shows, however, that the epoxy ester is actually a mixture of *endo* and *exo* isomers XIX-N and XIX-X.

Treatment of the Epoxy Ester (Mixture of XIX-N and XIX-X) with Lithium Aluminum Hydride; Formation of XIVa and XVIII.—The epoxy ester (3.00 g.) was treated with 1.5 g. of lithium aluminum hydride in boiling tetrahydrofuran. Usual workup gave 2.5 g. of an oil which was chromatographed on alumina (50 g. act. II, neutral, Woelm) to yield two fractions.

The first fraction, which was eluted with 4:1 ether–chloroform through chloroform, contained 1.47 g. of a viscous oil, which was distilled (60° (10^{-2} mm.)) to yield 1.29 g. of material, $n^{30}\text{D}$ 1.5008. This was shown to be identical with XIVa by its infrared spectrum and its acetate, m.p. 78.5–80° (mixture melting point with XIVb was undepressed).

The second fraction, eluted with 4:1 chloroform–methanol through methanol, contained 920 mg. of a viscous oil, which was distilled (70° (10^{-2} mm.)) to yield 780 mg. of material, $n^{30}\text{D}$ 1.4976. This was shown to be identical with XVIII by its infrared spectrum and its acetate, m.p. 44–47° and 64–66° (mixture melting point with the acetate of XVIII was undepressed).

When the epoxy ester was treated with lithium aluminum hydride in ether in a manner analogous to the above reduction, the product obtained was the epoxy alcohol mixture (XIII-N and XIII-X).

Treatment of VII-N with Monoperphthalic Acid in Chloroform: Formation of *exo*-6-Carboxy-3,8-dioxatricyclo[3.2.1.0^{2,4}]octane (XX-X) and the Hydroxylactone XXI.—Freshly crystallized VII-N (1.60 g.) was treated with an excess of monoperphthalic acid in cold chloroform. The crude solid (2.2 g.) was dissolved in chloroform, filtered, and crystallized from chloroform–hexane to yield 950 mg. of crystalline material. Repeated attempts to isolate more crystalline material from the mother liquor failed. The crystalline material was triturated with three 2-ml. portions of ether to give 550 mg. of ether-soluble material and 390 mg. of ether-insoluble material.

The ether-soluble material was crystallized from chloroform–hexane to yield 438 mg. of crystalline XX-X, m.p. 124–129°. Recrystallization gave 392 mg., m.p. 131–132°. The infrared spectrum showed bands at 1725 and 858 cm.$^{-1}$.

Anal. Calcd. for $C_7H_8O_4$: C, 53.85; H, 5.16. Found: C, 53.72; H, 5.30.

The ether-insoluble material was crystallized from chloroform–hexane to give 363 mg. of XXI, m.p. 113–116°. A recrystallization yielded 321 mg., m.p. 115–117°. The infrared spectrum showed bands at 3350 and 1780 cm.$^{-1}$, and no band at 858 cm.$^{-1}$. The n.m.r. spectrum showed one hydrogen at 4.68 τ (triplet), two hydrogens at 5.55 τ (triplet), two hydrogens at 6.3 τ (broad multiplet) and three hydrogens in the region 7.2–8.3 τ.

Anal. Calcd. for $C_7H_8O_4$: C, 53.85; H, 5.16. Found: C, 53.72; H, 5.15.

Treatment of the Epoxy Acid XX-X with Lithium Aluminum Hydride; Formation of XVIII.—In a manner analogous to the reduction of the epoxy alcohol formed from IVc, 500 mg. of the epoxy acid XX-X was treated with 0.5 g. of lithium aluminum hydride. The usual workup gave 380 mg. of oil which was chromatographed on alumina (10 g., act. II, neutral, Woelm). One main product was obtained (310 mg.) which was eluted with 4:1 chloroform–methanol through methanol. The infrared spectrum was identical with that of XVIII, and the acetate, m.p. 64.5–66.5°, gave no melting point depression when mixed with the acetate of XVIII.

Treatment of the Epoxy Ester (Mixture of Isomers) with Aqueous Sodium Hydroxide; Formation of the Epoxy Acid XX-X and the Hydroxylactone XXI.—The epoxy ester (1.00 g.) was treated as described in the saponification of IVa. The dried ether solution yielded 685 mg. of crystalline material. This was triturated with three 2-ml. portions of ether, to give 369 mg. of ether-insoluble material and 296 mg. of ether-soluble material.

The ether-insoluble material, m.p. 115–117.5°, was recrystallized from chloroform–hexane to give crystals, m.p. 116–117°. The infrared spectrum of this material was identical with that of XXI, and a mixture melting point of the two was undepressed.

The ether-soluble material was washed with 2 ml. of benzene, and crystallized from chloroform–hexane to yield 227 mg. of crystalline material, m.p. 131–132°. The infrared spectrum was identical to that of the epoxy acid

XX-X, and a mixture melting point of the two was undepressed.

Treatment of the Epoxy Alcohol (Mixture of XIII-N and XIII-X) with Dilute Mineral Acid; Formation of the Cyclic Ether XIVa.—To 30 ml. of 2% aqueous sulfuric acid was added 1.00 g. of the epoxy-alcohol, and the resulting solution was refluxed for 1 hour, during which time a brown precipitate formed. The mixture was cooled and filtered. The brown precipitate (105 mg.) seemed to be a polyphenolic material; it was soluble in dimethylformamide, seemed stable to hot acid, but turned black in hot 10% sodium hydroxide.

The aqueous filtrate was continuously extracted with ether for 2 days, and the ethereal extract was evaporated under reduced pressure to yield 1 g. of crude material. This was chromatographed on alumina (10 g. act. II, neutral, Woelm); two fractions were obtained.

The first fraction, eluted with chloroform, contained 590 mg. of a viscous oil, whose infrared spectrum was identical with that of the cyclic ether XIVa, and whose acetate, m.p. 80.5–81°, showed no melting point depression when mixed with XIVb.

The second fraction, eluted with methanol, contained 100 mg. of an ill-defined viscous oil. The infrared spectrum showed carbonyl absorption (strong band at 1668 cm.$^{-1}$ with shoulder at 1690 cm.$^{-1}$), hydroxyl absorption (3200 cm.$^{-1}$), and no epoxide absorption. It gave a negative ferric chloride test, and did not form any well-defined derivative with 2,4-dinitrophenylhydrazine reagent.

Treatment of the Epoxy Alcohol (Mixture of XIII-N and XIII-X) with Periodic Acid: Formation of the Cyclic Ether XIVa.—To 10 ml. of water containing 3.20 g. of periodic acid dihydrate was added 2.00 g. of the epoxy alcohol, and the solution was left at room temperature for 1 day. This was then continuously extracted with chloroform for 2 days and the dried chloroform extract was evaporated under reduced pressure to give 2.3 g. of a yellow oil, which was chromatographed on alumina (40 g., act. III, neutral, Woelm); two main fractions were obtained.

The first fraction, eluted with 4:1 ether–chloroform contained 1.34 g. of a viscous oil whose infrared spectrum was identical with that of the cyclic ether XIVa and whose acetate, m.p. 80.5–82°, showed no melting point depression when mixed with XIVb.

The second fraction, eluted with 9:1 chloroform–methanol, contained 390 mg. of a viscous oil whose infrared spectrum was very similar to that for the mixture of XIII-N and XIII-X, except that it had only a band at 684 cm.$^{-1}$ and no band at 705 cm.$^{-1}$.

Treatment of the Epoxy Alcohol (Mixture of XIII-N and XIII-X) with Aqueous Sodium Hydroxide; Formation of XIVa.—To 25 ml. of 20% aqueous sodium hydroxide was added 650 mg. of the epoxy alcohol and the resulting solution was refluxed for 1 day. The cooled alkaline solution was extracted with four 30-ml. portions of chloroform. The acidified aqueous extract was extracted with four 25-ml. portions of chloroform. The dried extracts were evaporated under reduced pressure: the alkaline solution yielded 570 mg. of a viscous oil, while the acidic solution yielded 130 mg. of yellow oil.

The product from the alkaline extract was chromatographed on alumina (10 g., act. III, neutral, Woelm); two fractions were obtained. The first fraction, eluted with 9:1 ether–chloroform, contained 180 mg. of viscous oil whose infrared spectrum was identical with that of XIVa, and whose acetate, m.p. 79.5–81°, showed no melting point depression when mixed with XIVb. The second fraction, eluted with chloroform, contained 300 mg. of a viscous oil whose infrared spectrum was very similar to that of starting material; it showed bands at both 705 and 684 cm.$^{-1}$.

The product from the acidic extract was chromatographed on alumina (10 g., act. III, neutral, Woelm). Only one fraction, eluted with 9:1 ether–chloroform, was obtained, and contained 105 mg. of a viscous oil whose infrared spectrum was identical with that of XIVa, and whose acetate, m.p. 80–81°, showed no melting point depression when mixed with XIVb.

When the epoxy alcohol was refluxed with 10% aqueous sodium hydroxide for 13 hours and the products isolated as described above, only starting material (85%) could be recovered.

Treatment of the Epoxy Alcohol (Mixture of XIII-N and XIII-X) with Ammonium Thiocyanate.—To a mixture of 80 ml. of 95% ethanol and 12.0 g. of ammonium thiocyanate was added 4.0 g. ofthe epoxy alcohol. The resulting mixture was refluxed for 2 days during which time the solution slowly turned dark brown. The cooled solution was diluted with 100 ml. of water and the solution continuously extracted with chloroform for 2 days. The chloroform extract was treated with charcoal, filtered, and evaporated under reduced pressure to leave 4.80 g. of a viscous brown oil. This was chromatographed on alumina (100 g., act. II, neutral, Woelm).

The first fraction, eluted with 1:1 ether–chloroform through chloroform, contained 3.08 g. of a viscous oil whose infrared spectrum was identical with that of XIVa, and whose acetate, m.p. 80–81°, showed no melting point depression when mixed with XIVb.

The second fraction, eluted with 19:1 chloroform–methanol, contained 525 mg. of a viscous oil whose infrared spectrum was very similar to that of unreacted starting material; the band at 684 cm.$^{-1}$ was much larger in comparison with the band at 705 cm.$^{-1}$ than in the spectrum of the starting material.

The third fraction, eluted with 1:1 chloroform–methanol, contained 175 mg. of a crystalline material which was extremely hygroscopic, and liquefied very quickly upon exposure to the atmosphere. The infrared spectrum of this material showed strong bands at 3300 and 2050 cm.,$^{-1}$[26] and no band at 855 cm.$^{-1}$.

When the epoxyalcohol was treated with ammonium thiocyanate in refluxing 1-butanol instead of ethanol, a slightly higher percentage (10%) appeared to form a thiocyanate derivative (although it was never isolated in pure form) as judged from the infrared spectra of the reaction products; the yield of XIVa in this case was about 60–65%. Much more decomposition appeared to occur under these conditions, and it hindered the isolation of any derivative.

When the epoxyalcohol was treated with ammonium thiocyanate in refluxing methanol, no derivative was observed; the reaction product appeared to be composed of starting material (85–90%) and some cyclic ether XIVa (10–15%).

Treatment of the Epoxyester (Mixture of XIX-N and XIX-X) with Potassium Iodide in 3-Heptanone.—To a mixture of 1.0 g. of powdered potassium iodide in 30 ml. of 3-heptanone was added 500 mg. of the epoxyester, and the resulting mixture refluxed for 2 days. The cooled mixture was diluted with 20 ml. of chloroform, and filtered; the filtrate was evaporated under reduced pressure. The residue was triturated with petroleum ether–ether to remove remaining traces of 3-heptanone; this left 465 mg. of residue which was chromatographed on alumina (15 g., act. I, neutral, Woelm).

The first fraction, eluted with chloroform, contained 420 mg. of an oil whose infrared spectrum was identical with that of starting material.

The second fraction, eluted with methanol, contained 30 mg. of an oil whose infrared spectrum showed it to be a mixture of a γ-lactone and some other material, probably the iodohydrin formed by the opening of the epoxide. The infrared spectrum showed strong hydroxyl absorption at 3250 cm.$^{-1}$, strong carbonyl absorption at 1780 (γ-lactone) and 1720 cm.$^{-1}$, increased absorption around 1100 cm.$^{-1}$ (secondary hydroxyl) and no absorption at 855 cm.$^{-1}$. The test for halogen (sodium fusion) was positive.

Treatment of IVc with Aqueous Mineral Acid; Formation of Benzyl Alcohol and 5-Hydroxymethylcyclohex-2-enone (VI).—To 20 ml. of 10% aqueous sulfuric acid was added 5.0 g. of IVc and the resulting solution refluxed for 2 hours. A dried ether extract yielded 4.037 g. of a mobile oil, which was chromatographed on alumina (80 g., act. I, neutral, Woelm).

The first fraction, eluted with ether, contained 682 mg. of a thin colorless oil whose infrared spectrum was identical with that of benzyl alcohol. The α-naphthylurethan derivative, m.p. 132.5–134.5°, showed no melting point depression on admixture with an authentic sample.

The second fraction, eluted with chloroform through 4:1 chloroform–methanol, contained 3.218 g. of a yellow oil. This was subjected to distillation (75° (10^{-2} mm.)) from

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(26) L. J. Bellamy, "The Infra-Red Spectra of Complex Molecules," 2nd Edition, John Wiley and Sons, Inc., New York, N. Y., 1958, p. 347. The range 2090-2020 cm.$^{-1}$ is reported as the range of absorption of the thiocyanate group.

which 500 mg. of a clear mobile oil was obtained; the rest of the material did not distil and appeared polymeric. The infrared spectrum of the distillate showed bands at 3250, 3050 and 1660 cm.$^{-1}$. The ultraviolet spectrum showed a maximum at 225–226 mμ, ϵ 6.1 × 10^3.

Anal. Calcd. for $C_7H_{10}O_2$: C, 66.62; H, 7.99. Found: C, 66.45; H, 8.17.

A *p*-nitrobenzoate derivative, after recrystallization from chloroform–hexane, gave crystals, m.p. 99–100°. The n.m.r. spectrum of the *p*-nitrobenzoate showed four hydrogens at 1.78 τ (aromatic), one hydrogen at 3.0 τ (multiplet), one hydrogen at 5.9 τ (doublet), two hydrogens at 5.63 τ (doublet), and five hydrogens in the region 7.0–8.0 τ.

Anal. Calcd. for $C_{14}H_{13}O_5N$: C, 61.09; H, 4.76; N, 5.09. Found: C, 61.35; H, 4.82; N, 5.10.

A 2,4-dinitrophenylhydrazone, m.p. 134–140°, was prepared.[10] After crystallization from methanol, a red solid, m.p. 146–148°, was obtained; its melting point corresponds to that reported for the 2,4-dinitrophenylhydrazone of 5-hydroxymethylcyclohex-2-enone, m.p. 147–148.5°.[10]

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF ROCHESTER, ROCHESTER, N. Y.]

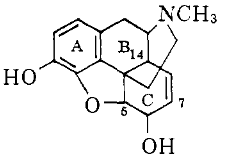
The Closure of the Oxide Bridge in the Morphine Series[1]

BY MARSHALL GATES AND MARVIN S. SHEPARD[2]

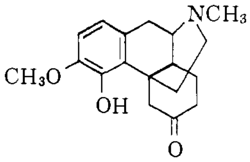
RECEIVED JUNE 13, 1962

The dibromination of *cis* and *trans*-dihydrothebainone and of *cis*-dihydrocodeinone has been shown in all probability to yield the corresponding 1,7-dibromo derivatives. The tribromination of *cis*-dihydrothebainone leads not to *cis* 1,5,7 or 1,7,7-tribromodihydrothebainone but directly to *cis*-1,7-dibromodihydrocodeinone. The role of these substances in closure of the oxide bridge from C_4 to C_5 and in other reactions is discussed.

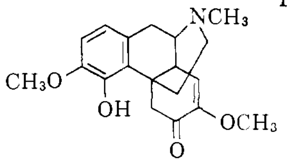
The oxide bridge which characterizes morphine (I) and related alkaloids of opium is open in a number of degradation products of these alkaloids, *e.g.*, *cis*- and *trans*[3]-dihydrothebainone (II and III), and is missing in the structurally related alkaloids sinomenine[4] (IV) and hasubanonine.



I



II rings, B/C *cis*
III rings, B/C *trans*

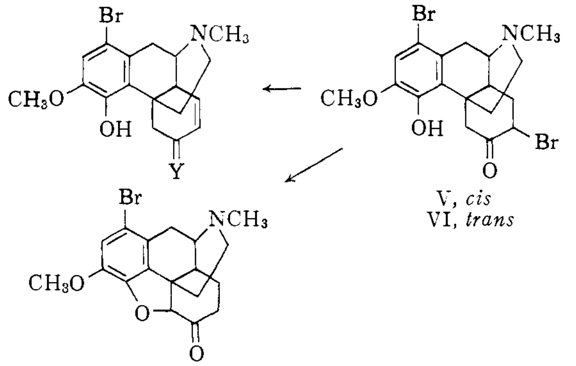


IV

The reclosure of this oxide bridge has assumed importance in several synthetic efforts.[5,6] It was first accomplished by Schöpf[7,8] by dibromination of II followed by treatment with alkali, and proceeds smoothly in high yield with *cis*-dihydrothebainone and with other substances with the natural configuration at C-14 (rings B/C *cis*). With *trans*-dihydrothebainone (III), however, the closure is difficult and only moderate yields are obtained.[9]

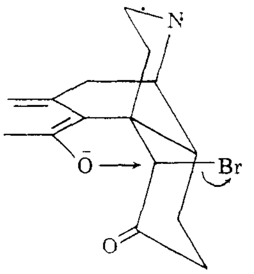
We had originally attributed the much smoother cyclization of *cis*-dibromodihydrothebainone with alkali to the more favorable spatial relationship of the displacing phenoxide ion and the bromine, assumed to be at position 5 in both C_{14}-epimers. Axial bromine at C_5 in the *cis* compound is ideally situated for displacement by phenoxide, whereas neither configuration of bromine at C_5 in the *trans* isomer is susceptible to easy displacement.

IX, *cis*, Y = NNH $C_6H_3(NO_2)_2$
X, *cis*, Y = O

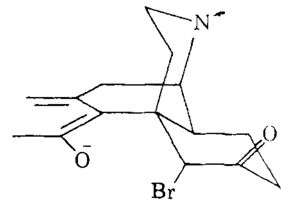


V, *cis*
VI, *trans*

VII, *cis*
VIII, *trans*



cis



trans

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(1) Taken in part from the Ph.D. dissertation of Marvin S. Shepard, University of Rochester, 1958.

(2) American Cyanamid Fellow, 1957–1958; Charles Pfizer Fellow, Summer, 1958.

(3) Now that the stereochemistry of these substances is known with certainty, we prefer to use the descriptive term "*trans*-dihydrothebainone" for this substance and analogous names for related substances rather than any of the less rational trivial names heretofore proposed (C. Schöpf and F. Borkowsky, *Ann.*, **458**, 148 (1927); L. Small and G. L. Browning, *J. Org. Chem.*, **3**, 618 (1939); K. W. Bentley and A. E. Wain, *J. Chem. Soc.*, 967 (1952); H. Rapoport and J. B. Lavigne, *J. Am. Chem. Soc.*, **75**, 5329 (1953)).

(4) Configurations shown in this paper have no significance in the absolute sense. Sinomenine and morphine belong to enantiomorphic series.

(5) L. Small, H. M. Fitch and W. E. Smith, *J. Am. Chem. Soc.*, **58**, 1457 (1936). Methyldihydromorphinone (Metopon), first described by these authors, was for a time produced commercially by a process which involved a ring closure of this type as one of its steps.

(6) M. Gates and G. Tschudi, *ibid.*, **78**, 1380 (1956).

(7) C. Schöpf and T. Pfeifer, *Ann.*, **483**, 157 (1930).

(8) C. Schöpf, T. Pfeifer and H. Hirsch, *ibid.*, **492**, 213 (1932).

(9) M. Gates and G. M. K. Hughes, *Chemistry & Industry*, 1506 (1956).