

NaH) in 100 ml. of glyme was added 2.64 g. (40.0 mmoles) of malononitrile in 50 ml. of glyme. The resulting sodiomalononitrile solution was cooled to -50° and a solution of 4.08 g. (20.0 mmoles) of HCBd in 50 ml. of acetonitrile was added dropwise (1.5 hr.). The color of the reaction solution was first orange, then changed to brown. The reaction solution was allowed to warm to room temperature and was diluted with 1 l. of ether. The gummy, insoluble solid which precipitated was collected and chromatographed on neutral alumina (Woelm). The major product, which was eluted with ethyl acetate and acetonitrile, was a yellow substance, λ_{max} 418 m μ . This yellow product was stirred overnight with 10 g. of tetraethylammonium chloride in acetonitrile. The solution was concentrated to dryness and was extracted with acetone. Tetraethylammonium 2,3-bis(dicyanomethyl)-1,1,4,4-tetracyanobutadienediide (0.52 g., m.p. $205-211^{\circ}$) was recovered from the acetone extract after it was passed through neutral alumina. An analytical sample was prepared by recrystallization from water; $\lambda_{\text{max}}^{\text{KBr}}$ (Et_4N^+ bands not given) 4.56 (s), 6.88 (s), 7.71 (w), and 8.07 (w) μ ; $\lambda_{\text{max}}^{\text{CH}_3\text{CN}}$ 420 m μ (ϵ 20,100), 328 m μ (ϵ 20,100).

Anal. Calcd. for $\text{C}_{30}\text{H}_{48}\text{N}_{10}$: C, 66.6; H, 7.46; N, 25.9. Found: C, 66.7; H, 7.42; N, 26.1.

The dipotassium salt of the bis(dicyanomethyl) compound was prepared by ion exchange and was recrystallized from acetonitrile-ethylene chloride.

Anal. Calcd. for $\text{C}_{14}\text{N}_8\text{K}_2$: C, 46.9; N, 31.3. Found: C, 47.1; N, 31.2.

Tetraethylammonium 1,2,3,4,4-Pentacyanobutadienolate.—A solution of 1.20 g. of sodium bicarbonate in 50 ml. of water was treated with 3.00 g. (14.7 mmoles) of HCBd. The mixture was

stirred 15 min. and was filtered. The dark brown filtrate was treated with 2 g. of tetraethylammonium chloride. The product which precipitated (3.00 g.) was dissolved in methylene chloride, and the solution was diluted with about an equal amount of ether. Yellow tetraethylammonium pentacyanobutadienolate (2.6 g., 55% yield) precipitated. Further dilution of the solution with about 10 volumes of ether caused 0.35 g. of red sodium heptacyanopentadienide (identified by infrared and ultraviolet) to precipitate. An analytical sample of the pentacyanodienolate (m.p. $214.5-216.5^{\circ}$) was prepared by recrystallization from chloroform; $\lambda_{\text{max}}^{\text{KBr}}$ 4.50, 4.55, 6.13, 6.71, 7.75, 9.90, and 13.75 μ ; $\lambda_{\text{max}}^{\text{CH}_3\text{CN}}$ 442 m μ (ϵ 28,600), 424 (25,300), and 266 (3950).

Anal. Calcd. for $\text{C}_{17}\text{H}_{20}\text{N}_5\text{O}$: C, 62.9; H, 6.21; N, 25.9. Found: C, 62.8; H, 6.42; N, 26.3.

A solution of 0.75 g. (4.46 mmoles) of tetracyanofuran¹⁸ in 30 ml. of acetonitrile was stirred overnight at room temperature with 0.30 g. (4.6 mmoles) of KCN. The yellow-brown solution was filtered and was concentrated to dryness. The residue was dissolved in water, and a tacky solid was obtained by addition of a solution of 2.0 g. of Et_4NCl in 10 ml. of water. Yellow crystals of tetraethylammonium pentacyanobutadienolate (0.08 g., m.p. $213-216^{\circ}$) formed on recrystallization of the solid from chloroform. Its identity was confirmed by its infrared spectrum.

Acknowledgments.—The author is greatly indebted to Drs. R. E. Benson, B. C. McKusick, and T. L. Cairns for advice and suggestions and to Dr. H. G. Hoeve for determining the e.s.r. spectrum of hexacyanobutadiene ion radical.

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

The Formation of *cis*- and *trans*-Perhydrobenzofurans from 2-(2-Methoxycyclohexyl)ethanol Derivatives. Reactions Proceeding through Methoxyl Participation¹

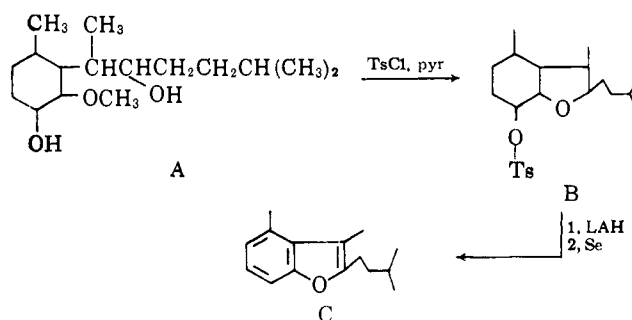
BY STEPHEN E. CANTOR^{2a} AND D. STANLEY TARBELL^{2b}

RECEIVED JANUARY 3, 1964

cis- and *trans*-(2-methoxycyclohexylethanol and homologs have been synthesized and are shown to form *cis*- and *trans*-perhydrobenzofurans when treated with tosyl chloride-pyridine. An oxygen-18 labeling study has shown that the methoxyl oxygen is retained during the cyclization; the hydroxyl oxygen is the one eliminated. The cyclization is believed to involve a cyclic oxonium ion intermediate; this is supported by the isolation of chloro compounds, which could be formed by the attack of chloride ion on a methine carbon atom in the oxonium ion.

We observed,³ during degradative work on the antibiotic fumagillin, a number of reactions in which a perhydrobenzofuran ring was formed, involving interaction of a 2-methoxy group on a cyclohexane ring with an oxygen function on the side chain, with cleavage of the methoxyl group and cyclization. The most important example of this reaction, from the standpoint of the fumagillin work, is illustrated by the transformation of A to B in good yield; B was dehydrogenated to C, whose structure was proved by synthesis.

The present paper describes a study of this type of cyclization on simpler compounds; it is demonstrated that the cyclization can occur from both *cis* and *trans* precursors to form the *cis*- and *trans*-perhydrobenzofurans, and it is shown by oxygen-18 studies that the methoxyl oxygen is the one which is retained in the



cyclization. The reaction is discussed in relation to earlier work on methoxyl participation and methoxonium ion intermediates.

2-Methoxyphenylacetone⁴(D) was most readily prepared by Hauser's⁵ procedure for methyl ketones, by acylation of malonic ester with 2-methoxyphenylacetyl chloride, followed by hydrolysis and decarboxylation. The aromatic ring was reduced catalytically with rhodium-on-alumina⁶ in acetic acid to give the *cis*-ketone E.

(4) J. C. Petropoulos and D. S. Tarbell, *ibid.*, **74**, 1249 (1952).

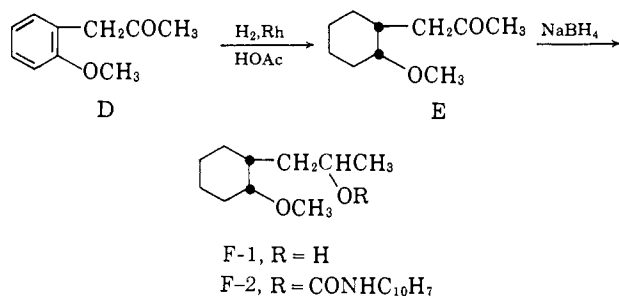
(5) H. G. Walker and C. R. Hauser, *ibid.*, **68**, 1386 (1946).

(6) Cf. C. G. Overberger, L. C. Palmer, B. S. Marks, and N. R. Byrd, *ibid.*, **77**, 4100 (1955); R. Adams, S. Miyano, and D. Fies, *ibid.*, **82**, 1466 (1960).

(1) Aided in part by Grant E-1138 from the National Institutes of Health. Presented in part at the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April 6, 1963.

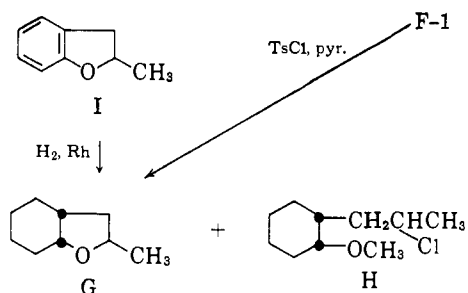
(2) (a) Abbott Laboratories Fellow, 1961-1962; (b) to whom inquiries should be addressed.

(3) (a) D. D. Chapman, S. E. Cremer, R. M. Carman, M. Kunstmann, J. G. McNally, J. A. Rosowsky, and D. S. Tarbell, *J. Am. Chem. Soc.*, **82**, 1009 (1960); (b) D. S. Tarbell, R. M. Carman, D. D. Chapman, S. E. Cremer, A. D. Cross, K. R. Huffman, M. Kunstmann, N. J. McCorkindale, J. G. McNally, Jr., A. Rosowsky, F. H. L. Varino, and R. L. West, *ibid.*, **83**, 3096 (1961).



Reduction in methanol partially reduced the carbonyl group as well as the aromatic ring. The *cis*-ketone E showed a single sharp peak when examined by vapor phase chromatography (v.p.c.); it also formed a crystalline semicarbazone, m.p. 153–154°. Reduction of the carbonyl group in E with sodium borohydride gave the alcohol F-1, which can exist as a mixture of diastereoisomers around the new asymmetric carbon atom carrying the secondary hydroxyl group. Examination by v.p.c. of F-1 appeared to show that the material was homogeneous, but this may have been due simply to lack of separation of the diastereoisomers. The question of homogeneity is discussed below, but F-1 did form a crystalline α -naphthylurethan F-2, m.p. 114–115°.

Treatment of F-1 prepared as above with tosyl chloride in pyridine for 2 days in the dark yielded 34% of the *cis*-perhydrobenzofuran G, 20% of starting material, and 36% of a compound containing chlorine



but no hydroxyl group, which appeared from its elemental analysis to be an impure sample of H and its position isomer, with the chlorine and methoxyl groups interchanged. Mass spectrometric examination of H (by Dr. Glenn Happ) supported the assigned structure; parent mass peaks at 190 and 192 appeared (corresponding to Cl-35 and Cl-37), and the intensity of these peaks decreased rather rapidly. A peak at 140, corresponding to the parent peak for the perhydrobenzofuran G, was present, possibly indicating cyclization of H to G in the mass spectrometer.

The n.m.r. spectrum of H showed a methoxyl group, and one proton at 6.55 τ , which would correspond to the proton under the chlorine atom. The formation of H, or its position isomer, can be readily explained on a mechanistic basis (see below).

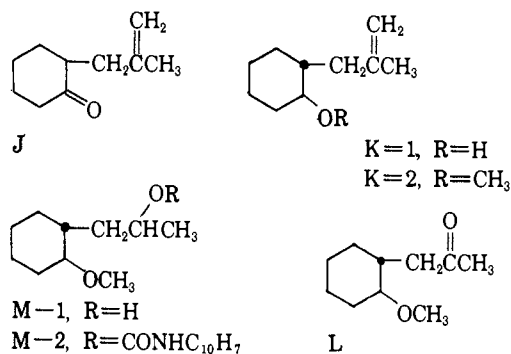
The structure of G was supported by the absence of hydroxyl absorption in the infrared, by the disappearance of methoxyl bands in the n.m.r. spectrum, and by its elemental analysis. Examination by v.p.c. showed two peaks in a ratio of 2:1, which could arise from the two diastereoisomers of G around the methyl-bearing carbon. The n.m.r. spectrum of G showed two pairs of methyl doublets, which supported the idea

that a mixture of diastereoisomers was at hand. This mixture could be due to the fact that the parent alcohol was not homogeneous, or that there had been racemization at the secondary hydroxyl carbon during cyclization, or to both causes.

To examine this situation more thoroughly, the alcohol F-1 was converted to a crystalline acid phthalate ester, which was recrystallized and then saponified to regenerate homogeneous F-1. This was cyclized to G by the previous method; this sample of G showed only one peak by v.p.c. examination, and it showed only one methyl doublet in its n.m.r. spectrum. Hence it appeared to be homogeneous. Its infrared and n.m.r. spectra were identical with those of the material obtained by catalytic reduction of 2-methyl-2,3-dihydrobenzofuran (I); it is assumed that G obtained by these two methods is all *cis*; i.e., the methyl group on C-2 is *trans* to the two hydrogens at the ring junction. It is likely that the mixture of diastereoisomers of G, obtained by cyclization of the alcohol F-1 which had not been purified through the phthalate, was due to the inhomogeneity of the parent alcohol F-1.

The ready cyclization of the *cis* compound F-1, and the fact that the compounds such as B, derived from fumagillin, probably have the *trans* ring juncture,⁷ indicated the desirability of studying the *trans* isomer of F-1; this was synthesized as follows.

Cyclohexanone was converted to 2-methylallyl-cyclohexanone (J) by alkylation with β -methylallyl chloride and sodamide,⁸ and the carbonyl group was reduced to the hydroxyl by repeated treatment with sodium and ethanol.⁹ The alcohol K-1 was assigned the *trans* configuration because reduction under equilibrating conditions should lead to the more stable *trans* form^{9,10}; K-1 was homogeneous in its v.p.c. behavior, and yielded a crystalline 3,5-dinitrobenzoate, m.p. 118–119°. The secondary alcohol K-1 was methylated in 62% yield with sodium hydride-methyl



iodide in dimethylformamide (DMF), and the methoxyl compound K-2 was oxidized to the ketone L in 60% yield by the periodate-osmium tetroxide procedure.¹¹ The ketone L was homogeneous by v.p.c. examina-

(7) The *trans* ring juncture assignment in B and related compounds (ref. 3b) is based on the known stereochemistry of fumagillin (N. J. McCorkindale and J. G. Sime, *Proc. Chem. Soc.*, 331 (1961); J. R. Turner and D. S. Tarbell, *Proc. Natl. Acad. Sci. U. S.*, **48**, 733 (1962)), and on the assumption that the configuration of the carbon-oxygen bond of the methoxyl group is not altered during the cyclization. The oxygen-18 work described below supports this assumption.

(8) Cf. R. Cornubert, *Ann. Chim.*, **16**, 145 (1921); C. A. VanderWerf and L. V. Lemmerman, *Org. Syn.*, **28**, 8 (1948).

(9) J. Colonge and F. Collomb, *Bull. soc. chim. France*, **18**, 24 (1951).

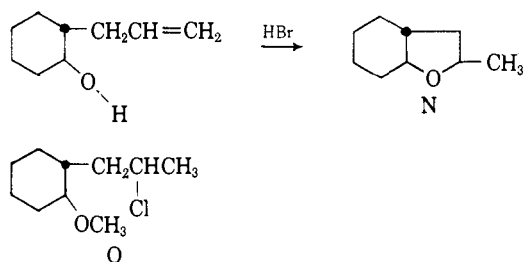
(10) D. H. R. Barton, *J. Chem. Soc.*, 1029 (1953).

(11) R. Pappo, D. S. Allen, Jr., R. V. Lemieux, and W. S. Johnson, *J. Org. Chem.*, **21**, 478 (1956).

tion, and formed a crystalline semicarbazone, m.p. 143–144°, which gave a depression on mixture with the semicarbazone from the *cis*-ketone E. This is in agreement with the assigned *trans* configuration of K, L, and the compounds derived from them.

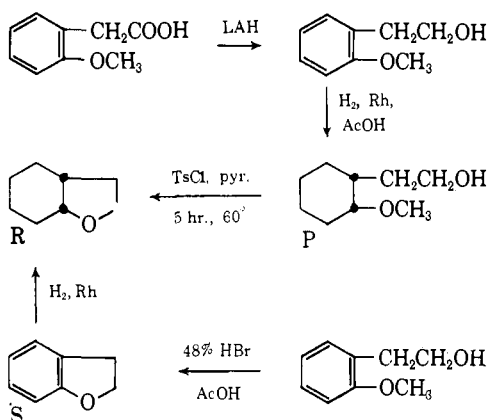
The ketone L was reduced by sodium borohydride to the alcohol M-1, which, like K-1, could consist of a mixture of diastereoisomers, due to the new asymmetric center in the side chain. The alcohol M-1 formed a crystalline α -naphthylurethan, m.p. 121–122°, which showed a depression on mixture melting point with the corresponding derivative F-2 in the *cis* series.

Treatment of the *trans*-alcohol M-1 under the same conditions used for the *cis* compound (tosyl chloride–pyridine for 2 days at room temperature) gave an 8% yield of the *trans*-perhydrobenzofuran N, a 70% yield of starting material, and some chlorine-containing material, presumably O. The *trans* compound N was also obtained by the action of 48% hydrobromic acid



in refluxing acetic acid on *trans*-2-allylcyclohexanol, following Colonge and Collomb.⁹ Although this method of synthesis cannot be regarded as a conclusive proof of the structure of N, the results are in agreement with the assigned structure

In order to avoid the complications arising from the asymmetric carbon atom in the side chain of F and M, which becomes C-2 of the perhydrobenzofuran ring system in G and N, the *cis* and *trans* primary alcohols P and V were prepared. The *cis* isomer P was prepared as indicated below, and gave a crystalline α -naphthylurethan, m.p. 132–133°. It was found that P did not cyclize to any appreciable extent when it was treated with tosyl chloride in pyridine for 2 days at room temperature - conditions which cyclized the corresponding secondary alcohol F-1. Treatment of P with the same reagents at 60° for 5 hr. gave the *cis*-perhydrobenzofuran R; no starting material was recovered, but there was some chlorine-containing material formed, as in the earlier cases. The chlorine-containing compound showed no hydroxyl but did

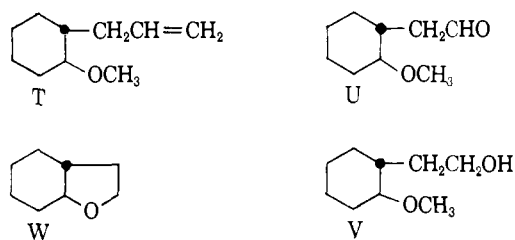


retain its methoxyl group, judging from the spectral properties.

The *cis*-perhydro compound R was also obtained by rhodium reduction of 1,2-dihydrobenzofuran S; the two samples of R gave the same infrared spectrum and v.p.c. retention time. The 1,2-dihydrobenzofuran was most conveniently prepared by the action of 48% hydrobromic acid in refluxing acetic acid on 2-(2-methoxyphenyl)ethanol. Other routes to S gave much poorer yields.

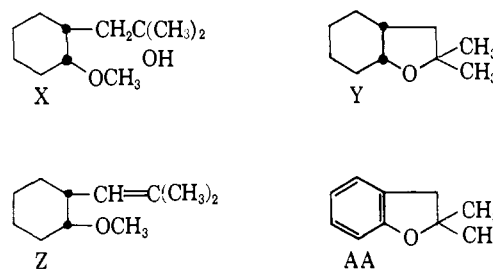
Although the evidence regarding the relative rates of cyclization of the primary alcohol P and the secondary alcohol F-1 is qualitative only, it is certain that the primary alcohol cyclizes more slowly than the secondary alcohol.

The *trans* isomer of P was prepared by periodate–osmium tetroxide oxidation of *trans*-2-allylcyclohexyl methyl ether (T), which was obtained by a sequence similar to that used for K-2. The aldehyde U formed a crystalline semicarbazone, m.p. 143°, and was reduced to the primary alcohol V by sodium borohy-



dride. Treatment of V with tosyl chloride–pyridine gave what appeared to be an impure sample of the *trans*-perhydrobenzofuran W.

The tertiary alcohol X, prepared from the *cis*-ketone E and methylmagnesium iodide, yielded *cis*-2,2-dimethylperhydrobenzofuran (Y), and about 30% of the unsaturated ether Z. The same perhydrobenzofuran Y was obtained by rhodium–alumina reduction of 2,2-dimethyl-1,2-dihydrobenzofuran (AA);



the identity was based on a correspondence of the infrared spectra. The unsaturated compound Z was converted to Y by treatment with HBr–acetic acid; AA was prepared by the cyclization of 2- β -methylallylphenol¹² with HBr–acetic acid.

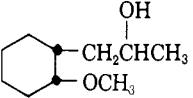
Oxygen-18 Labeling Studies.—The carbonyl oxygen in the ketone E was labeled with oxygen-18 by hydrolyzing the crystalline semicarbazone¹³ of E in water enriched in O-18; the water did not contain excess deuterium. The labeled ketone was reduced, using a sodium borohydride solution made in the O-18 enriched water, to give the hydroxyl-labeled alcohol

(12) Q. R. Bartz, R. F. Miller, and R. Adams, *J. Am. Chem. Soc.*, **57**, 371 (1935).

(13) Cf. M. L. Bender, *ibid.*, **73**, 1626 (1951).

F-1. The presence of the O-18 label in the alcohol F-1 was demonstrated by mass spectrometric study¹⁴; the parent peak for the (unlabeled) alcohol at 172 was too weak to use for isotopic analysis, but the fragment peak at 157 (presumably due to loss of methyl) was large enough to measure. The values for the 157, 158, and 159 peaks are given in Table I; the 159 peak would be derived from O-18 labeled alcohol, and the 158 peak is due to natural abundance of heavy isotopes. The agreement of the calculated value from natural abundances¹⁵ and the found value for the 158 peak makes it clear that this peak is not due to interference by other fragment ions. Table I shows that the labeled alcohol F-1 actually gives about 1% excess of the 159 peak, and this must be attributed to O-18 labeling.

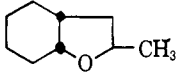
TABLE I

MASS SPECTROMETRIC STUDY ON 			
	157	158	159
Unlabeled	100 ^a	10.2	1.0
Calcd. for natural abundance		10.0% of 157 peak	0.97% of 157 peak
Labeled	100 ^a	10.3	2.0
Calcd. for natural abundance		10.0% of 157 peak	0.86% of 157 peak

^a Peak height normalized to 100.

The results on the cyclized material from the labeled alcohol are given in Table II; the 2-methylperhydrobenzofuran yielded a strong parent peak at 140, and it is clear that there is no appreciable increment in the 142 peak from the labeled alcohol indicating that there is none of the O-18 label remaining in the cyclized material. Therefore we conclude that in the cyclization process the hydroxyl oxygen is the one eliminated, and that the methoxyl oxygen remains in the molecule.

TABLE II

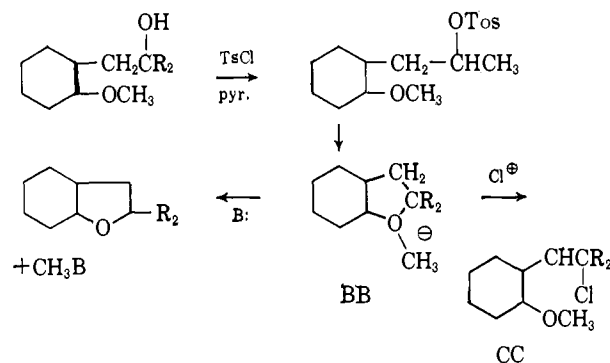
MASS SPECTROMETRIC STUDY ON 			
	140	141	142
Unlabeled	100 ^a	10.8	0.84
Calcd. for natural abundance		10.0% of 140 peak	0.65% of 140 peak
Sample from O-18 labeled precursor	100 ^a	10.5	0.81

^a Peak height normalized to 100.

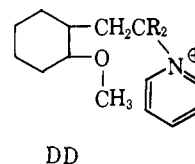
Mechanism of the Cyclization.—The cyclizations reported in this and the preceding papers³ can be reasonably viewed as proceeding through a cyclic oxonium ion, such as BB, which can then lose the methyl group by attack by one of the nucleophiles in solution (chloride ion, pyridine, tosylate ion) to yield the perhydrobenzofuran. Attempts to isolate a methylpyridinium salt by paper chromatography have been unsuccessful. Attack by chloride ion on BB at the appropriate carbon would give the side chain chloride CC, corresponding to H, which was actually isolated.

(14) We are indebted to Dr. G. Happ, of Eastman Kodak Co., for carrying out the mass spectrometric measurements, and for help in their interpretation.

(15) J. H. Beynon, "Mass Spectrometry and its Application to Organic Chemistry," Elsevier Publishing Co., New York, N. Y., 1960.

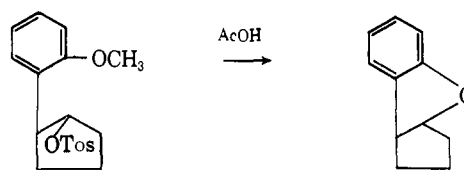


Attack by pyridine at carbon atoms other than the methyl group in BB could lead to a (presumably water-soluble) pyridinium salt, such as DD. The material balance in the reactions examined indicates that appreciable amounts of such a salt are not formed, because most of the material is accounted for. Presumably if products such as DD are formed, they are formed reversibly, and go into the perhydrobenzofuran or to CC irreversibly.



The reactions discussed here belong, of course, within the general frame of reference of solvolyses assisted by suitably located alkoxy groups, studied by Winstein and his collaborators.¹⁶ The kinetic aspects of the current reactions have not been investigated beyond the qualitative observation that the cyclization occurs much more slowly with the primary alcohol P than with the secondary alcohol F-1.

The configuration of the carbon carrying the methoxyl group is evidently not altered during the cyclization; this follows from the labeling experiments showing that the C-O bond in the methoxyl group has not been broken, as well as from the preservation of the *cis* and *trans* relationships in going from the monocyclic methoxyl alcohols to the perhydrobenzofurans. The stereochemical changes at the hydroxyl carbon would be difficult to establish in the present case, because of the two asymmetric carbons elsewhere in the molecule. There is a suggestion that the configuration of this carbon is inverted in the following case,¹⁶ but this is not exactly analogous to the cases we have studied,



because the methoxyl group here is on an aromatic ring.

(16) S. Winstein, E. Allred, R. Heck, and R. Glick, *Tetrahedron*, **3**, 1 (1958); E. L. Allred, Ph.D. Dissertation, University of California, Los Angeles, 1959 (private communication from Professor Winstein); R. Heck, J. C. Corse, E. Grunwald, and S. Winstein, *J. Am. Chem. Soc.*, **79**, 3278 (1957); A. Kirrmann and N. Hamaide, *Bull. soc. chim. France*, **24**, 789 (1957).

Experimental¹⁷

***o*-Methoxyphenylacetone (D).**—(*o*-Methoxyphenyl)acetic acid (28.7 g.) and 60.5 ml. of thionyl chloride were refluxed for 2 hr. until hydrogen chloride ceased being evolved. The temperature was raised and the excess thionyl chloride removed by water pump. Distillation of the residue produced 15 g. (75%) of the desired product, b.p. 136–137° (19 mm.).

This acid chloride was converted to *o*-methoxyphenylacetone (D) according to the procedure of Hauser⁵ for making *o*-nitroacetophenone. A mixture of 3 ml. of absolute alcohol, 0.5 ml. of carbon tetrachloride, and 3.2 g. of magnesium turnings was allowed to react, and 100 ml. of absolute ether was added. To the resulting mixture was added slowly a mixture of 20 g. of diethyl malonate, 18 ml. of absolute ether, and 10 ml. of absolute alcohol. After 3 hr. of reflux, most of the magnesium had dissolved; to this solution was added slowly 20 g. of *o*-methoxyphenylacetyl chloride dissolved in 35 ml. of absolute ether. After 2 hr. of refluxing, 25 g. of concentrated sulfuric acid in 200 ml. of water was added to hydrolyze the complex. The mixture was allowed to stand overnight.

The hydrolyzed reaction mixture was extracted with ether and the combined ether extracts were evaporated to dryness; the residual oil was refluxed for 4 hr. with a mixture of 20 ml. of water, 5 ml. of concentrated sulfuric acid, and 40 ml. of glacial acetic acid. On cooling, the reaction mixture was made basic with 20% aqueous sodium hydroxide and then extracted with ether. The combined ether extracts were dried, filtered, and then evaporated to dryness; the residual oil, 9.3 g. (58%), of a colorless liquid, had b.p. 142° (19 mm.), n_{D}^{25} 1.5218 (lit.⁴ n_{D}^{20} 1.5240). The semicarbazone melted at 146–149° (lit.⁴ 146–147°).

***cis*-1-(2-Methoxycyclohexyl)propan-2-one (B).**—*o*-Methoxyphenylacetone (16 g.) in 30 ml. of glacial acetic acid was hydrogenated at room temperature in the presence of 5 g. of 5% rhodium-on-alumina.

After 10 hr. the uptake of hydrogen ceased, the catalyst was filtered off, and the remaining solution extracted with three 25-ml. portions of ether. The combined ether extracts were washed with six 30-ml. portions of water to remove any excess acetic acid. The ether was dried, removed under vacuum, and the residual liquid distilled to yield 13 g. (78%) of a colorless liquid, b.p. 47–48° (0.8 mm.), n_{D}^{25} 1.4512. Vapor phase chromatography (v.p.c.) on a 5-ft. Ucon Polar column at 147° (He flow 75 cc./min.) gave one sharp peak. The infrared spectrum contained a carbonyl band at 1710 cm.⁻¹, an ether band at 1086 cm.⁻¹, and was devoid of any aromatic bands.

Anal. Calcd. for C₁₀H₁₈O₂: C, 70.54; H, 10.66. Found: C, 70.76; H, 10.64.

The semicarbazone melted, after recrystallization from ethanol-water (3:1), at 152–154°.

Anal. Calcd. for C₁₁H₂₁N₃O₂: C, 58.12; H, 9.31. Found: C, 58.24; H, 9.48.

***cis*-1-(2-Methoxycyclohexyl)propan-2-ol (F-1).**—The *cis*-ketone B (13 g.) was dissolved in 100 ml. of methanol; with stirring, a solution of 3 g. of sodium borohydride in 2 ml. of 2 N sodium hydroxide diluted with 22 ml. of water was added at such a rate so that the temperature did not exceed 25°. The methanol was removed by distillation on a steam bath and the residue diluted with 100 ml. of cold water. The solution was extracted with ether and the ether extracts combined and washed with water, then dried and evaporated. The remaining liquid was distilled to yield 8.3 g. (82%) of a colorless liquid, b.p. 67–68° (0.3 mm.), n_{D}^{25} 1.4610; v.p.c. on a 30% tetramethylene glycol dimethyl ether column at 96° (He flow 52 cc./min.) gave one sharp peak. A 5-ft. Ucon Polar column at 136° (He flow 53 cc./min.) showed two peaks in a ratio of 16:1. The infrared spectrum contained a hydroxyl band at 3330 cm.⁻¹ and an ether band at 1086 cm.⁻¹.

Anal. Calcd. for C₁₀H₂₀O₂: C, 69.72; H, 11.70. Found: C, 70.09; H, 11.69.

(17) All boiling points and melting points are uncorrected. Microanalyses were performed by V. Landeryou of this laboratory as well as Micro-Tech Laboratories (Skokie, Ill.). Nuclear magnetic resonance spectra were taken on a 60-Mc. Varian instrument in chloroform by Dr. L. D. Colebrook. Infrared spectra were determined in the form of liquid films on Perkin-Elmer Models 421 and 21 spectrophotometers. All hydrogenations were carried out with 5% rhodium-on-alumina purchased from Engelhard Industries, Inc. in a Parr hydrogenator. Refractive indices of liquids were measured by means of a conventional water-jacketed Abbe refractometer. The gas chromatographic studies (v.p.c.) were carried out on an Aerograph A-90 instrument.

The α -naphthylurethan F-2 melted at 114–115° after recrystallization from petroleum ether.

Anal. Calcd. for C₂₁H₂₇N₃O₃: C, 73.87; H, 7.97. Found: C, 73.62; H, 7.81.

***cis*-2-Methylperhydrobenzofuran (G) via Methoxyl Cleavage.**—The secondary *cis*-alcohol F-1 (7.2 g.) was dissolved in 60 ml. of anhydrous pyridine and added to 9.6 g. of *p*-toluenesulfonyl chloride in 60 ml. of anhydrous pyridine. The reaction mixture was allowed to stand in the dark at room temperature for 2 days and then poured onto cracked ice and extracted with ether. The ether portions were combined and washed six times with 25-ml. portions of dilute hydrochloric acid to remove the excess pyridine. The ether solution was dried and evaporated. The remaining liquid was distilled to yield three fractions; the first was a clear, colorless liquid, b.p. 63° (16 mm.), n_{D}^{25} 1.4548 (lit.¹⁸ for *cis-trans* mixture n_{D}^{25} 1.4562). This fraction was the desired *cis*-2-methylperhydrobenzofuran (34%). The infrared spectrum demonstrated that the hydroxyl and methoxyl bands from the precursor alcohol F-1 were gone. A new series of cyclic ether bands were obtained: 1105, 1080, and 1055 cm.⁻¹.

The n.m.r. spectrum also indicated loss of methoxyl with the formation of a cyclic ether. The spectrum contained two sets of methyl doublets at 8.63 and 8.75 τ indicating that the product probably consisted of two diastereoisomers. The v.p.c. showed two large peaks of almost equal areas. As was shown later, neither one of the two peaks corresponded to any *trans*-2-methylperhydrobenzofuran; this was further evidence that the *cis* material contained two diastereoisomers around the carbon bearing the methyl group.

Anal. Calcd. for C₉H₁₆O: C, 77.09; H, 11.50. Found: C, 77.19; H, 11.79.

The second fraction was a colorless liquid, b.p. 98–100° (16 mm.), n_{D}^{25} 1.4603. The material failed to take up any hydrogen or bromine and gave a positive test for chlorine. This material was believed to be a mixture of H and its isomer, yield 36%.

Anal. Calcd. for C₁₀H₁₈OCl: C, 63.01; H, 10.03. Found: C, 64.13; H, 10.35.

A Rast determination indicated that the molecular weight was 190–192 and that the material was monomeric. Although the analysis was unsatisfactory, mass spectrographic analysis proved that a compound with a molecular weight 190 was present. The n.m.r. spectrum not only contained the methoxyl signal at 6.08 τ and the proton on the carbon bearing the methoxyl group, but contained another signal at 6.55 τ , the area of which suggested a single proton on a carbon bearing a chlorine atom. The infrared spectrum showed the presence of the methoxyl group and loss of the hydroxyl group. There was a notable absence of any double bond absorption. The v.p.c. results indicated the presence of two peaks in a 5:4 ratio.

The last fraction (10%) corresponded to the starting alcohol F-1.

Reduction of 2-Methyl-2,3-dihydrobenzofuran (I).—2-Methyl-2,3-dihydrobenzofuran¹⁹ (6.9 g.) was dissolved in 10 ml. of methanol and hydrogenated in the presence of 2 g. of 5% rhodium-on-alumina. The catalyst was filtered off and the methanol removed. The residual liquid was distilled to yield 5.2 g. (73%) of material, b.p. 62° (16 mm.), n_{D}^{25} 1.4559; v.p.c. on a 30% Apiezon L column at 194° (He flow 33 cc./min.) gave only one peak. The sample had an identical infrared and n.m.r. spectrum and identical retention time with the sample of the *cis*-perhydrobenzofuran prepared from the cyclization of the alcohol F-1, prepared through the crystalline acid phthalate (see below).

Separation of the Diastereoisomers of the *cis*-Secondary Alcohol F-1 through the Acid Phthalate.—A mixture of 12.3 g. of the *cis*-secondary alcohol F-1, 41.4 g. of phthalic anhydride, and 30 ml. of dry toluene was refluxed for 5 hr. The toluene was removed under reduced pressure. The residue was dissolved in 95% ethanol and the solution heated to boiling. Some water was added and the solution allowed to cool. An emulsion formed, which on standing produced an oily precipitate. The ethanol was removed by distillation and the residue extracted with a mixture of 90% petroleum ether and 10% benzene. The solution was dried, concentrated, and placed in a cold room for 2 days, after which a solid precipitate formed. The solid was recrystallized twice from a mixture of petroleum ether and benzene and melted at 194–195°. The infrared spectrum (KBr) indicated

(18) J. Entel, C. H. Rouf, and H. C. Howard, *J. Am. Chem. Soc.*, **73**, 4152 (1951).

(19) Prepared following D. S. Tarbell, *Org. Reactions*, **2**, 25 (1944).

the presence of an ester function at 1738 cm.^{-1} and a carboxyl group at 1710 cm.^{-1} ; yield 8.9 g. (39%).

Anal. Calcd. for $\text{C}_{18}\text{H}_{24}\text{O}_5$: C, 67.48; H, 7.55. Found: C, 67.39; H, 7.74.

Hydrolysis of the Purified Phthalate.—The purified acid phthalate (7.82 g.) was treated with 1.70 g. of lithium aluminum hydride in the usual fashion. The dried ethereal solution was removed and the remaining material distilled under vacuum to produce 3.27 g. (80%) of the desired secondary alcohol, n_{D}^{25} 1.4603.

This material was submitted to the same conditions of cyclization which were described previously.

2- β -Methylallylcyclohexanone (J).—3-Chloro-2-methylpropene (184 g.) was allowed to react with 200 g. of cyclohexanone in the presence of 80 g. of finely powdered sodium amide. The procedure is identical with the preparation of 2-allylcyclohexanone.⁸ The yield was 145 g. (49%) of a colorless liquid, b.p. 118° (33 mm.), n_{D}^{25} 1.4669. The infrared spectrum contained a carbonyl band at 1910 cm.^{-1} and a series of bands characteristic of a disubstituted double bond at 1640 , 1290 , and 822 cm.^{-1} .

Anal. Calcd. for $\text{C}_{10}\text{H}_{16}\text{O}$: C, 78.89; H, 10.59. Found: C, 78.64; H, 10.42.

The 2,4-dinitrophenylhydrazine melted at 115 – 116° after recrystallization from 95% ethanol.

Anal. Calcd. for $\text{C}_{18}\text{H}_{20}\text{N}_4\text{O}_4$: C, 57.82; H, 6.07. Found: C, 57.61; H, 6.33.

trans-(2- β -Methylallyl)cyclohexanol (K-1).—To a cold solution of β -methylallylcyclohexanone and 500 ml. of 95% ethanol sodium was added over a period of 3 hr. After the sodium ceased to react, a small portion of water was cautiously added and the ethanol removed by distillation. The organic layer was separated from the sodium hydroxide layer and then placed again in 500 ml. of fresh 95% ethanol. This procedure was repeated four times to convert all of the ketone to the desired alcohol.

The ethanol was removed by distillation on a steam bath and the basic solution extracted with three 50-ml. portions of ether. The ether was washed with three 25-ml. portions of water, dried, and the solvent was removed. The residual liquid was distilled to yield 23 g. (75%) of a colorless material, b.p. 67° (0.3 mm.), n_{D}^{25} 1.4610. The infrared spectrum contained a hydroxyl band at 3220 cm.^{-1} and bands at 1640 , 1290 , and 882 cm.^{-1} , characteristic of the disubstituted double bond; v.p.c. analysis on a 5-ft. Ucon Polar column at 109° (He flow 55 cc./min.) showed only one peak.

Anal. Calcd. for $\text{C}_{10}\text{H}_{18}\text{O}$: C, 77.86; H, 11.76. Found: C, 78.10; H, 11.63.

The 3,5-dinitrobenzoate melted at 118 – 119° after recrystallization from 95% ethanol.

Anal. Calcd. for $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_6$: C, 58.61; H, 5.79. Found: C, 58.24; H, 5.78.

trans-(2-Methoxy-1- β -methylallyl)cyclohexane (K-2).—To a mixture of 20 ml. of dimethylformamide and 30 ml. of anhydrous ether was added slowly 2.88 g. of a 52% mineral oil dispersion of sodium hydride. *trans*-(2- β -Methylallyl)cyclohexanol (8.0 g.) in 10 ml. of anhydrous ether was slowly added to the mixture. After 2 hr. the mixture was heated under reflux for 3 hr. and allowed to stand at room temperature overnight. The flask was cooled in an ice bath and 14.1 g. of methyl iodide was introduced through a dropping funnel. A slurry of sodium iodide was formed. The solution was stirred for 6 hr. and then allowed to stand overnight.

A small portion of wet ether was added cautiously, then 75 ml. of water to dissolve the sodium and the dimethylformamide. The water layer was extracted five times with 25-ml. portions of cold water to remove traces of dimethylformamide. The ether was dried and removed to yield a residual liquid which was distilled to give 6.2 g. (62%) of material, b.p. 65° (13 mm.), n_{D}^{25} 1.4628. The infrared spectrum of the ether showed a strong methoxyl band at 1080 cm.^{-1} ; v.p.c. analysis on a 5-ft. Ucon Polar column at 109° (He flow 71 cc./min.) showed two peaks in a ratio 16:1.

Anal. Calcd. for $\text{C}_{11}\text{H}_{20}\text{O}$: C, 78.51; H, 11.98. Found: C, 78.32; H, 11.85.

trans-1-(2-Methoxycyclohexyl)propan-2-one (L).—To a stirred solution of 8.4 g. of the unsaturated ether K-2 and 25 mg. of osmic acid in 150 ml. of a mixture of purified dioxane and 150 ml. of water was added 21 g. of powdered sodium metaperiodate during a 30-min. period. The mixture was stirred for an additional 6 hr. and then 50 ml. of water added to dissolve the remaining sodium metaperiodate. As the reaction proceeded, sodium iodate precipitated out. The mixture was filtered, the filter cake

washed with ether, and the ether and filtrate were combined and washed with seven 50-ml. portions of water to remove the dioxane. The ether layer was dried and removed to yield a dark liquid. This residual liquid was distilled to yield 5.4 g. (60%) of a colorless liquid, b.p. 105 – 106° (10 mm.), n_{D}^{25} 1.4550. V.p.c. on a 5-ft. Ucon Polar column at 110° (He flow 75 cc./min.) gave two peaks in a ratio of 1:19 at 28.9 and 37.9 min. The peak at 28.9 min. corresponded to the previously prepared *cis*-ketone E. The large peak at 37.9 min. represented 95% of the material.

Anal. Calcd. for $\text{C}_{10}\text{H}_{18}\text{O}_2$: C, 70.54; H, 10.66. Found: C, 70.69; H, 10.59.

The semicarbazone melted at 143 – 145° after recrystallization from 95% ethanol.

Anal. Calcd. for $\text{C}_{11}\text{H}_{21}\text{N}_2\text{O}_2$: C, 58.12; H, 9.31. Found: C, 58.06; H, 9.45.

A mixture of the semicarbazone of the *cis*-ketone E and the *trans*-ketone L was prepared; a mixture melting point showed a depression of 115 – 140° .

trans-1-(2-Methoxycyclohexyl)propan-2-ol (M-1).—A procedure similar to the one used to prepare F-1 was employed. The sodium borohydride reduction of 4.5 g. of the *trans*-ketone L produced 4.0 g. (88%) of a colorless liquid, b.p. 114° (12 mm.), n_{D}^{25} 1.4610. The infrared spectrum contained a hydroxyl band at 3330 cm.^{-1} . V.p.c. on a 5-ft. Ucon Polar column at 114° (He flow 75 cc./min.) gave one large peak at 35.9 min., whereas the *cis*-alcohol F-1 gave one peak at 49.2 min.

Anal. Calcd. for $\text{C}_{10}\text{H}_{20}\text{O}_2$: C, 69.72; H, 11.70. Found: C, 69.48; H, 11.61.

The α -naphthylurethan M-2 melted at 121 – 122° after recrystallization from petroleum ether. A mixture of the α -naphthylurethan of the *cis*-alcohol F-1 and the *trans*-alcohol M-1 was prepared. A mixture melting point showed a depression of 91 – 111° .

Anal. Calcd. for $\text{C}_{21}\text{H}_{27}\text{NO}_3$: C, 73.87; H, 7.97. Found: C, 74.01; H, 8.08.

Formation of trans-2-Methylperhydrobenzofuran (N) via Methoxyl Cleavage.—The *trans*-alcohol M-1 (2.2 g.) in 20 ml. of anhydrous pyridine was added to 2.5 g. of recrystallized *p*-toluenesulfonyl chloride in 20 ml. of pyridine. The flask was left at room temperature in the dark for 2 days and then worked up in the same manner used in the *cis* series. The residual liquid was analyzed by v.p.c. on a 5-ft. Ucon Polar column. The first peak, 8%, was the desired *trans*-2-methylperhydrobenzofuran as was shown later by comparison with an authentic sample. The refractive index was 1.4559 at 23° which was in fair agreement with that recorded,⁹ 1.4612 at 20° . The infrared spectrum contained bands at 1143, 1085, and 1070 cm.^{-1} indicative of cyclic ether.

Anal. Calcd. for $\text{C}_9\text{H}_{16}\text{O}$: C, 77.09; H, 11.50. Found: C, 77.24; H, 11.61.

The second peak (12%) was collected from the v.p.c.; a sodium fusion showed a positive test for chlorine. The infrared indicated the loss of hydroxyl and the retention of the original methoxyl group.

The last fraction corresponded to the starting alcohol and represented 70% of the material.

Preparation of trans-2-Methylperhydrobenzofuran (N) from trans-2-Allylcyclohexanol.—The previously prepared *trans*-2-allylcyclohexanol, n_{D}^{25} 1.4761 (lit. n_{D}^{25} 1.4758),⁹ 5 g., was refluxed in 20 ml. of acetic acid and 10 ml. of 48% hydrobromic acid for 25 min. The hot solution was poured onto ice and extracted three times with 50-ml. portions of ether. The ether was washed with three 50-ml. portions of cold water, dried, and removed to yield a yellowish residue. This residual liquid was distilled to yield two fractions: the first fraction, 1.14 g. (25%), was the *trans*-2-methylperhydrobenzofuran, b.p. 62° (18 mm.), n_{D}^{25} 1.4557. The infrared spectrum contained bands at 1143, 1085, and 1068 cm.^{-1} . The v.p.c. retention time of this material was identical with that for the *trans*-2-methylperhydrobenzofuran prepared by methoxyl cleavage. The refractive indices of the two samples differed by only 0.002.

The second fraction from the distillation, 3.48 g., b.p. 135° (18 mm.), n_{D}^{25} 1.4887, when submitted to sodium fusion and analyzed for halogen showed a positive test for bromine. The infrared spectrum contained a band at 678 cm.^{-1} and a strong acetate carbonyl band at 1737 cm.^{-1} . The material was not further characterized.

trans-(2-Methoxy-1-allyl)cyclohexane (T).—The procedure was identical with the one employed for the preparation of *trans*-(2-methoxy- β -methylallyl)cyclohexane. Distillation produced 12

g. (52%) of a colorless liquid, b.p. 57–59° (13 mm.), n_D^{20} 1.4548. The infrared spectrum contained bands at 1640, 990, and 922 cm^{-1} indicative of a terminal methylene group. The methoxyl group absorbed at 1082 cm^{-1} .

Anal. Calcd. for $\text{C}_{10}\text{H}_{18}\text{O}$: C, 77.86; H, 11.76. Found: C, 77.72; H, 11.81.

Preparation of *cis*-1-(2-Methoxycyclohexyl)propan-2-one-O-18.—A 5 *N* solution of aqueous hydrochloric acid containing 1.54% oxygen-18 was prepared by passing dry hydrogen chloride gas through water containing 1.54% oxygen-18. The water contained only a negligible percentage of deuterium oxide; after titration the solution was diluted with an equal portion of the oxygen-18 water to form a 5 *N* solution.

To 46 ml. of this 5 *N* solution was added 5.91 g. of the semicarbazone of *cis*-1-(2-methoxycyclohexyl)propan-2-one, and this mixture was heated on a steam bath for 25 min. The hot solution was poured onto ice and extracted with three 25-ml. portions of ether. The ether was washed with five 20-ml. portions of cold water, dried, and removed to yield 2.53 g. (59%) of the desired ketone N. The infrared spectrum of this ketone did not show any carbon–deuterium stretching. The material was not purified but used directly in the next step.

Preparation of *cis*-1-(2-Methoxycyclohexyl)propan-2-ol-O-18.—The labeled ketone, in methanol, was treated with a sodium borohydride solution that had been prepared from 4 g. of sodium borohydride, 20 ml. of water containing 1.54% oxygen-18, and 1 ml. of a 2 *N* sodium hydroxide solution also prepared from oxygen-18 water. The material was worked up in the usual fashion. Vacuum distillation of the product gave material which was identical with the unlabeled alcohol. Mass spectrographic analysis proved that the material contained 1% of oxygen-18 in the hydroxyl group.

***cis*-2-Methylperhydrobenzofuran from the Oxygen-18 Alcohol.**—The cyclization reaction was carried out in the usual fashion and the work-up was identical to those that had been carried out previously. Mass spectrographic analysis of the *cis*-2-methylperhydrobenzofuran showed that no excess oxygen-18 was present.

***cis*-1-(2-Methoxycyclohexyl)ethanol (P).**—*o*-Methoxyphenylethanol (10 g., prepared by a lithium aluminum hydride reduction of the commercially available *o*-methoxyphenylacetic acid), was dissolved in 40 ml. of glacial acetic acid and hydrogenated at room temperature, in the presence of 4.5 g. of 5% rhodium-on-alumina. After 6 hr., the uptake of hydrogen ceased, the catalyst was filtered off, and the remaining solution extracted with three 20-ml. portions of petroleum ether. The combined ether extracts were washed with five 30-ml. portions of cold water to remove any traces of acetic acid. The ether was dried and removed to yield, after distillation, 8 g. (78%) of a colorless liquid, b.p. 56–57° (0.7 mm.), n_D^{20} 1.4638. The infrared spectrum contained a hydroxyl band at 3.05 μ (3310 cm^{-1}) and was devoid of any aromatic character; v.p.c. on a 5-ft. Ucon Polar column of a 15-ft. Apiezon L column caused the material to undergo cyclization to perhydrobenzofuran as was shown later by comparison with an authentic sample.

Anal. Calcd. for $\text{C}_9\text{H}_{18}\text{O}_2$: C, 68.31; H, 11.47. Found: C, 68.10; H, 11.30.

The α -naphthylurethan melted, after recrystallization from petroleum ether, at 132–135°.

Anal. Calcd. for $\text{C}_{19}\text{H}_{25}\text{O}_3\text{N}$: C, 72.35; H, 7.99. Found: C, 72.45; H, 7.90.

Formation of *cis*-Perhydrobenzofuran (R).—The *cis* primary alcohol P (3.12 g.) in 15 ml. of anhydrous pyridine was added to 4.2 g. of *p*-toluenesulfonyl chloride in 15 ml. of anhydrous pyridine. The reaction mixture was stirred at 60° (oil bath) for 5.5 hr. The hot solution was then poured onto cracked ice and worked up in the usual fashion. The ether was dried and removed; an infrared spectrum of the crude residue indicated complete loss of the hydroxyl function and a complete absence of any absorption due to a double bond. Distillation of the residue led to two fractions: the first was the desired *cis*-perhydrobenzofuran (R), b.p. 66–68° (15 mm.), n_D^{20} 1.4648 (lit.²⁰ for *cis-trans* mixture was 1.4680); v.p.c. analysis on a 12-ft. 25% Ucon Polar column gave two peaks in a 4:1 ratio; the larger peak, as was later demonstrated, corresponded in retention time with an authentic sample of *cis*-perhydrobenzofuran prepared by an unambiguous synthesis.

The second fraction from the distillation, b.p. 95–98° (15 mm.), gave a positive test for chlorine. The infrared spectrum indicated that the methoxyl group was present, but that the hydroxyl had disappeared. This material was not characterized further.

2,3-Dihydrobenzofuran by the Acid Cleavage and Cyclization of *o*-Methoxyphenylethanol.²¹—*o*-Methoxyphenylethanol (4 g., 0.026 mole) in 12 ml. of 48% hydrobromic acid and 20 ml. of acetic acid was refluxed for 6 hr. The hot solution was poured onto ice and extracted with three 20-ml. portions of petroleum ether. The combined ether extracts were washed with several portions of cold water and dried. Removal of the ether left a pink oil which was distilled to yield 2.3 g. (74%) of the desired 2,3-dihydrobenzofuran, n_D^{20} 1.5482.

Reduction of 2,3-Dihydrobenzofuran to the *cis*-Octahydro Compound R.—2,3-Dihydrobenzofuran (2 g.) was dissolved in 30 ml. of methyl alcohol and hydrogenated in the presence of 0.8 g. of 5% rhodium-on-alumina. The catalyst was filtered off and the material worked up in the usual fashion; v.p.c. on a 25% Ucon Polar column at 162° (He flow 100 cc./min.) gave one peak, which had an identical retention time with the *cis*-perhydrobenzofuran prepared through methoxyl cleavage. Their infrared spectra were similar and their refractive indices varied only by one unit in the fourth decimal place.

Preparation of *trans*-1-(2-Methoxycyclohexyl)acetaldehyde (U).—To a stirred solution of 9.76 g. (0.063 mole) of *trans*-1-allyl-2-methoxycyclohexane and 15 mg. of osmic acid in 150 ml. of a mixture of two volumes of purified dioxane to one volume of water was added 26.9 g. (0.126 mole) of sodium metaperiodate, over a period of 1 hr. The reaction mixture was allowed to stir for 3 hr., during which time an additional 75-ml. portion of water was added. The standard work-up procedure was employed. Distillation of the black residue gave 4.4 g. (43%) of a colorless material, b.p. 79° (1.5 mm.), n_D^{20} 1.4548. V.p.c. analysis showed that the material was nearly pure and that less than 1% of the unsaturated starting material remained. The infrared spectrum contained a carbonyl band at 1720 cm^{-1} .

Anal. Calcd. for $\text{C}_9\text{H}_{16}\text{O}_2$: C, 69.19; H, 10.32. Found: C, 69.48; H, 10.39.

***trans*-1-(2-Methoxycyclohexyl)ethanol (V).**—The *trans*-aldehyde U (2.15 g.) was dissolved in 20 ml. of methanol and treated with an excess of sodium borohydride. After the standard work-up procedure, a colorless liquid was obtained, which was distilled to yield 1.95 g. (93%), b.p. 64° (12 mm.), n_D^{20} 1.4598. The infrared spectrum contained a hydroxyl peak at 3385 cm^{-1} .

Anal. Calcd. for $\text{C}_9\text{H}_{18}\text{O}_2$: C, 68.31; H, 11.47. Found: C, 68.27; H, 11.16.

The α -naphthylurethan, after recrystallization from petroleum ether, melted at 124–125°.

Anal. Calcd. for $\text{C}_{19}\text{H}_{25}\text{NO}_3$: C, 72.35; H, 7.99. Found: C, 72.09; H, 7.80.

A mixture of the urethans of the *cis*-primary alcohol and of the *trans*-primary alcohol was prepared. A mixture melting point showed a depression of 89–117°.

Formation of *trans*-Perhydrobenzofuran (W).—The *trans*-primary alcohol V (3.39 g.) was dissolved in 15 ml. of anhydrous pyridine and added to 4.48 g. of *p*-toluenesulfonyl chloride in 15 ml. of anhydrous pyridine. The reaction mixture was stirred at 63° for 5.5 hr. The hot solution was poured onto cracked ice and worked up in the usual fashion. An infrared spectrum of the crude material demonstrated that some starting material had not reacted and that some unsaturated material was present; bands were present at 1640 and 895 cm^{-1} . Distillation led to three fractions: the first, 1.43 g. (51%), b.p. 170–173°, n_D^{20} 1.4619, was mainly the desired *trans*-perhydrobenzofuran.

Anal. Calcd. for $\text{C}_8\text{H}_{14}\text{O}$: C, 76.14; H, 11.18. Found: C, 78.51; H, 11.81.

The analysis was incorrect because the unsaturated material produced in the reaction contaminated the sample. The infrared spectrum showed the cyclic ether bands at 1184, 1142, 1090, and 1160 cm^{-1} ; v.p.c. analysis on a 25% Ucon Polar column at 152° (He flow 75 cc./min.) gave two peaks in a 2.5:1 ratio. The retention times of these two peaks differed from the retention times for the two peaks obtained from the *cis*-perhydrobenzofuran.

The second fraction, 0.12 g. (4.8%), b.p. 175–195°, gave a positive test for chlorine. The infrared spectrum demonstrated

(20) N. I. Shuikin, I. I. Demitriev, and T. P. Dobrynina, *J. Gen. Chem. U.S.S.R.*, **10**, 967 (1940); *Chem. Abstr.*, **35**, 2508 (1941).

(21) Cf. G. Chatelus and P. Cagniant, *Compt. rend.*, **224**, 1777 (1947).

that the methoxyl group was present. This material was not characterized.

cis-1-(2-Methoxycyclohexyl)-2-methylpropan-2-ol (X).—To 0.0675 mole of methylmagnesium bromide in ether was added 6.4 g. (0.038 mole) of *cis*-1-(2-methoxycyclohexyl)propan-2-one (E) in 50 ml. of ether. The ketone solution was added cautiously and the ether was allowed to reflux gently. The reaction mixture was refluxed for 0.5 hr., cooled, and treated with 13 ml. of a saturated solution of ammonium chloride. The ether was removed and the residue was distilled to yield 5.75 g. (82%) of a colorless liquid, b.p. 67–68° (0.8 mm.), n_D^{20} 1.4612. The infrared spectrum showed hydroxyl absorption at 3398 cm^{-1} ; v.p.c. analysis failed to detect the tertiary alcohol because it underwent elimination on the acid-washed column.

Anal. Calcd. for $\text{C}_{11}\text{H}_{22}\text{O}_2$: C, 70.92; H, 11.90. Found: C, 70.67; H, 11.80.

cis-2,2-Dimethylperhydrobenzofuran (Y) via Methoxyl Cleavage.—The tertiary alcohol X (3.8 g.) in 15 ml. of anhydrous pyridine was added to 4.34 g. of *p*-toluenesulfonyl chloride in 15 ml. of anhydrous pyridine. The solution remained at room temperature for 2 days. After the usual work-up procedure, an infrared spectrum of the crude residue indicated that the alcohol function had disappeared. There was also evidence of double bond absorption. Distillation of the liquid residue gave two products; the first was the desired *cis*-2,2-dimethylperhydrobenzofuran (Y) (30%), b.p. 63–65° (19 mm.), n_D^{20} 1.4528, as was shown by comparison with an authentic sample. The infrared spectrum contained bands at 1177, 1149, 1099, and 998 cm^{-1} indicative of the cyclic ether. The v.p.c. results indicated that the material was very pure (98%), and it had an identical retention time with the authentic sample of *cis*-2,2-dimethylperhydrobenzofuran.

Anal. Calcd. for $\text{C}_{10}\text{H}_{18}\text{O}$: C, 77.86; H, 11.76. Found: C, 78.29; H, 11.97.

The second fraction, b.p. 67–72° (19 mm.), n_D^{20} 1.4577, was homogeneous as shown by v.p.c. analysis. The infrared spectrum of this material contained a strong band at 1640, and bands at 926 and 878 cm^{-1} indicative of a trisubstituted double bond. This unsaturated compound represented 60–63% of the material.

cis-3-(2-Methoxycyclohexyl)-2-methyl-2-propene (Z).—The tertiary alcohol X (1.8 g.) was heated under reflux for 3 hr. and then distilled to yield 1.4 g. of a colorless material, b.p. 68–70° (18 mm.), n_D^{20} 1.4570. The infrared spectrum contained strong bands at 1640, 926, and 878 cm^{-1} ; v.p.c. analysis indicated that the material was at least 98% pure.

Anal. Calcd. for $\text{C}_{11}\text{H}_{20}\text{O}$: C, 78.51; H, 11.98. Found: C, 78.04; H, 11.67.

cis-2,2-Dimethylperhydrobenzofuran from Z.—The unsaturated compound Z (1 g.) was refluxed in a mixture of 5 ml. of 48% hydrobromic acid and 20 ml. of acetic acid for 0.5 hr. The hot solution was poured onto ice and extracted with three 20-ml. portions of ether. The ether extracts were combined, washed with five 20-ml. portions of cold water, and dried. The ether was filtered and removed to yield a pink residue, which was distilled to yield 0.41 g. (44%) of a colorless liquid, b.p. 67–68° (19 mm.), n_D^{20} 1.4524. This material had an identical infrared spectrum and v.p.c. retention time with the *cis*-2,2-dimethylperhydrobenzofuran prepared by the methoxyl cleavage of the tertiary alcohol X.

Preparation of 2,2-Dimethyl-2,3-dihydrobenzofuran (AA).— β -Methylallylphenol (15 g.), n_D^{20} 1.5512 (lit. n_D^{20} 1.5534)¹² was refluxed in 60 ml. of glacial acetic acid and 30 ml. of 48% hydrobromic acid. The standard work-up procedure was employed to yield, after distillation, 8 g. (54%), b.p. 68–70° (12 mm.), n_D^{20} 1.5160 (lit.¹² n_D^{20} 1.5190).

2,2-Dimethylperhydrobenzofuran (Y).—The aromatic material AA (5 g.) was hydrogenated in the presence of 2 g. of 5% rhodium-on-alumina. After 4 hr. the absorption of hydrogen ceased and the catalyst was filtered off. The acetic acid solution was extracted with three 20-ml. portions of petroleum ether, washed with five 25-ml. portions of cold water, and dried. The ether was filtered and removed to yield 3.5 g. of the desired *cis*-2,2-dimethylperhydrobenzofuran, b.p. 67° (20 mm.); n_D^{20} 1.4528. V.p.c. analysis on a 30% Apiezon L column at 136° (He flow 82 cc./min.) gave three peaks: two minor ones (less than 1%) and a large peak which corresponded to the retention time of the *cis*-2,2-dimethylperhydrobenzofuran produced by the cyclization of the tertiary *cis*-alcohol X. The infrared spectra of the two materials were identical.

[CONTRIBUTION FROM THE PUERTO RICO NUCLEAR CENTER AND THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PUERTO RICO, RÍO PIEDRAS, PUERTO RICO]

The Wolff-Kishner Reaction of Hydrazones¹

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Kinetic and thermodynamic data for the base-catalyzed, homogeneous Wolff-Kishner reaction of negatively substituted hydrazones are presented. The nonlinearity of the Hammett plot is interpreted in terms of solvation effects in the transition state.

Introduction

Previously obtained² kinetic results for the base-catalyzed, homogeneous Wolff-Kishner reaction of diaryl ketone hydrazones were shown³ to obey the Hammett equation. However, that study was limited to positively or mildly negatively substituted hydrazones, and it was of interest, therefore, to extend the series to include strongly negatively substituted compounds. It was immediately apparent that the kinetic results obtained with the latter type hydrazones were not in agreement with those predicted on the basis of the Hammett relationship. In this paper we wish to report the more recent results and to offer an explanation for the nonlinearity of the Hammett plot.

(1) Experimental data from the Ph.D. Thesis of C. M. H., Duquesne University, 1956. All inquiries should be directed to H. H. S. at PRNC, San Juan, Puerto Rico.

(2) H. H. Szmant, H. F. Harnsberger, T. J. Butler, and W. P. Barie, *J. Am. Chem. Soc.*, **74**, 2724 (1952).

(3) H. H. Jaffé, *Chem. Rev.*, **63**, 191 (1953).

Experimental and Results

The apparatus and experimental procedure in carrying out the kinetic study were essentially identical with those described in the preceding publication² in this series. Special precautions were observed to exclude atmospheric oxygen from the base and the reaction mixture, and the apparatus was flushed thoroughly with nitrogen before each kinetic run. The base concentration was determined at the end of each kinetic experiment and the run was discarded when a serious loss of base was found to have taken place. The temperatures were recorded on a thermometer which was calibrated against a National Bureau of Standards calibrated set of Anschütz thermometers. The kinetic results are summarized in Table I and representative, linear $\ln k/T$ vs. $1/T$ plots are shown in Fig. 1–2. The enthalpies and entropies of activation were calculated by means of the Eyring equation and are listed in Table II.