Anal. Calcd. for $C_{15}H_{24}N_4$: C, 69.2; H, 9.3; N, 21.5. Found: C, 69.1; H, 9.5; N, 21.5.

When treated in the same way, the crystalline product failed to give a precipitate on dilution with water. Concentration *in vacuo* left an amorphous residue of 2.76 g. Its infrared spectrum was quite similar to that obtained when 4,6-diacetyl-3-hydroxy-3-methylcyclohexanone was treated in the same manner (above). Thus, the oil and the solid are identified, respectively, as 4,6-dipropionyl-3,7-heptanedione and its intramolecular aldol product, 4,6-dipropionyl-3-ethyl-3-hydroxy-2-methylcyclohexanone.

3,5-Dibenzoyl-2,6-heptanedione.—To a stirred slurry of 48.7 g. (0.300 mole) of benzoylacetone in 250 ml. of ethanol was added 11.5 ml. (0.15 mole) of formalin. The solids dissolved during the next 45 min. After 65 hr., the solution was poured into water, extracted with benzene, dried, and the solvent removed. The oily residue (46.2 g., 91.5%) crystallized on strong cooling. Recrystallization from a small volume of methanol (with seeding) gave 3,5-dibenzoyl-2,6-heptanedione (m.p. 80–81°).

Anal. Calcd. for $C_{21}H_{20}O_4$: C, 75.0; H, 6.0. Found: C, 75.2; H, 6.2.

(C) From β-Ketoamides.—The same general procedure was used for all of the glutaramides prepared: The β-ketoamide was dissolved or, if it was less soluble, slurried in ethanol (a maximum of 500 ml. per mole of amide), and 0.5 equivalent of formalin was added. The slurry was stirred until solution was effected (usually within several hours, although the more insoluble amides never completely dissolved before product began to precipitate). The product usually began separating during the second day, was filtered off after 4–5 days, and purified. Those few products which failed to crystallize were concentrated *in vacuo* or diluted with water to induce precipitation. The products from the four tertiary β-ketoamides used are all oils which, on distillation, behave quite similarly to diethyl α,α'-diacetylglutarate. Table III contains the data on all these substituted diacetylglutaramides.

1:1 Condensation Products. Ethyl α-Hydroxymethyl-α-methylacetoacetate (XI).—A solution of 101 g. (0.700 mole) of ethyl α-methylacetoacetate and 27 ml. (0.35 mole) of formalin in 40 ml. of alcohol was let stand for 10 days. The solution was poured into water, extracted into benzene, dried, and distilled. After a forerun of starting material (35–40 g.), ethyl α-hydroxymethyl-α-methylacetoacetate distilled (b.p. 108–109°/9 mm., $n^{25}\text{D}$ 1.4411); yield, 39 g. (64.0%).

Anal. Calcd. for $C_8H_{14}O_4$: C, 55.2; H, 8.1; mol. wt., 174. Found: C, 55.5; H, 8.2; mol. wt., 185 (ebullioscopic in benzene).

The addition of piperidine or the use of a higher temperature had only a slight effect on the yield.

3-Acetyl-3-penten-2-one (VII).—A mixture of 400 g. (4.00 moles) of 2,4-pentanedione and 170 ml. (3.0 moles) of acetaldehyde was let stand for 1 week and then distilled. Distillation at aspirator pressure (about 10 mm.) appeared to be accompanied by a slow thermal decomposition. Gas chromatographic analysis of the distillate showed that 4% of 2,4-pentanedione and 4% of an unknown component were present as impurities. Distillation under a high vacuum with a low pot temperature gave 3-acetyl-4-penten-2-one as a clear liquid with a pungent odor (b.p. 44–45°/0.04 mm., $n^{25}\text{D}$ 1.4608). Gas chromatographic analysis indicated 96% purity; only 4% of the 2,4-pentanedione was found to contaminate the material. McEntee and Pinder[12] reported b.p. 80–81°/10 mm.

Anal. Calcd. for $C_7H_{10}O_2$: C, 66.6; H, 8.0; mol. wt., 126. Found: C, 66.4; H, 8.1; mol. wt., 126 (mass spectrometer).

When the condensation was carried out in the presence of piperidine, the product obtained in 89.4% crude yield was 4,6-diacetyl-3-hydroxy-3,5-dimethylcyclohexanone (m.p. 108.5–109.5°). Knoevenagel[7] reported m.p. 108° but incorrectly assigned to this material the structure 3,5-diacetyl-4-methyl-2,6-heptanedione.

3-Acetyl-4-hexen-2-one.—A mixture of 100 g. (1.00 mole) of 2,4-pentanedione and 58.1 g. (1.00 mole) of propionaldehyde was treated twice daily with 2-drop portions of diethylamine. Phase separation occurred on the third day. The next day the volatiles were removed *in vacuo* and the residue was distilled, yielding 60.2 g. (43.0%) of 3-acetyl-4-hexen-2-one (b.p. 59–61°/6 mm., $n^{25}\text{D}$ 1.4875). McEntee and Pinder[12] reported b.p. 82°/14 mm.

3-Acetyl-4-hepten-2-one.—Similarly, a mixture of 50.1 g. (0.500 mole) of 2,4-pentanedione and 22.1 ml. (0.25 mole) of butyraldehyde was treated twice daily for 5 days with 5-drop portions of piperidine, concentrated *in vacuo*, and distilled, yielding 32.8 g. (85.0%) of 3-acetyl-4-hepten-2-one (b.p. 90–92°/18 mm., $n^{25}\text{D}$ 1.4809). Payne[14] reported b.p. 83–84°/8 mm., $n^{20}\text{D}$ 1.4840.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.1; H, 9.2. Found: C, 70.3; H, 9.3.

Condensation of Chloral with Ethyl Acetoacetate.—A solution of 65.1 g. (0.500 mole) of ethyl acetoacetate and 36.7 g. (0.250 mole) of freshly distilled chloral in 25 ml. of ethanol was let stand 1 week, poured into water, extracted into ether, dried, and the volatiles, including most of the remaining ethyl acetoacetate, removed *in vacuo*. The residue (about 5 ml.) was distilled, giving about 3 g. of a colorless oil (b.p. 110–118°/0.3–0.4 mm., $n^{25}\text{D}$ 1.4730).

Anal. Found: C, 38.0; H, 4.0. Calcd. for $C_8H_9Cl_3O_3$ (ethyl α-acetyl-γ,γ,γ-trichlorocrotonate): C, 37.0; H, 3.5. Calcd. for $C_{14}H_{19}Cl_3O_6$ [diethyl α,α'-diacetyl-β-(trichloromethyl)glutarate]: C, 43.2; H, 4.9.

The Osmium Tetroxide-catalyzed Hydroxylation of Furan–Maleic Anhydride Adducts[1]

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Diels–Alder adducts of maleic anhydride with furan, 2-methylfuran, 2-acetoxyfuran, and 2-bromofuran have been hydroxylated by osmium tetroxide in the presence of 30% hydrogen peroxide in *t*-butyl alcohol to provide the corresponding unsubstituted and 1-substituted 5,6-dihydroxy-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic acids. The probable stereochemistry of the products is discussed.

The hydroxylation of Diels–Alder adducts provides a facile route for the preparation of polyhydroxycyclohexanes. When the diene employed in the Diels–Alder reaction is a furan, then hydroxylation of the adduct affords a derivative of cyclohexane carrying hydroxyl groups or potential hydroxyl groups on at least four contiguous carbon atoms.[2] This investigation was undertaken to prepare intermediates suitable for further elaboration into naturally occurring polyhydroxycyclohexanes.

The use of furan and substituted furans as dienes in the Diels–Alder reaction, particularly with maleic an-

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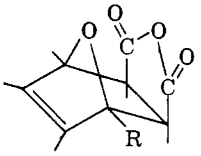
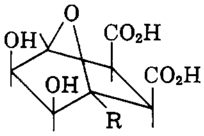
[1] This paper represents part of a thesis submitted by John L. Fischer to the Graduate College of the University of Illinois, 1959, in partial fulfillment of the requirements for the degree of Master of Science. This work was supported in part by a grant from the Research Board of the Graduate College of the University of Illinois: grant no. 05-19-82.

[2] See Yu. K. Yur'ev and N. S. Zefirov, *J. Gen. Chem. USSR*, **31**, 629 (1961) for the hydroxylation of the furan–vinylene carbonate adduct to afford derivatives of inositol.

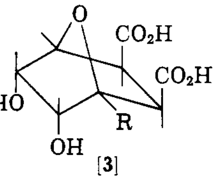
hydride as the dienophile, has been amply reviewed.[3] Adducts of maleic anhydride and the furans employed in this investigation were prepared as described in the literature for furan,[4] 2-methylfuran[5] and 2-acetoxyfuran.[6a] The maleic anhydride addition product of 2-bromofuran is described in the literature[7]; however, that paper is a Communication to the Editor and since a further description of this work has not been forthcoming, the preparation is recorded in the Experimental section. The stereochemistry of the latter three adducts may be assigned by analogy with the known configuration of the furan–maleic anhydride adduct. When maleic anhydride and furan react in ether solution, the product isolated has the *exo–cis* configuration [**1a**].[8,9]



[**1**]



[**2**]



[**3**]

a, R = H—; **b**, R = CH_3—; **c**, R = $\overset{\overset{O}{\|}}{C}H_3CO$—; **d**, R = Br—

Although it has not been rigorously established what effect substituents in the 2-position of furan have on the steric course of the Diels–Alder reaction, it is probable that the adducts have the *exo-cis* configuration also [**1b**, **1c**, and **1d**].[10]

The hydroxylation of maleic anhydride–furan adducts has received little attention[2,11,12] although such reactions with other Diels–Alder adducts have been reported.[13] The adducts employed in this study were hydroxylated using the method described by Milas[14] which involves oxidation by a catalytic amount of osmium tetroxide in the presence of hydrogen peroxide in *t*-butyl alcohol. In this medium, osmium tetroxide transforms the olefinic double bond into the osmate ester of a glycol which in turn is converted by peroxide into the *cis*-glycol with concomitant regeneration of osmium tetroxide. Instead of using the anhydrous conditions specified by Milas, these hydroxylations were carried out in the presence of 30% aqueous hydrogen peroxide.[15] An acetone or acetone–ether solvent was employed because of the relative solubilities of the reactants and products in this medium. Although the reaction mixture was homogeneous initially, the hydroxylated compound precipitated as the reaction proceeded and could be separated easily by filtration. During the course of the reaction, the water present in the reaction medium hydrolyzed the anhydride functional group so that the product isolated was the corresponding dicarboxylic acid.[16],

The Stereochemistry of the Glycols.—It has been established that hydroxylations with osmium tetroxide produce a *cis*-glycol.[17] However, in the case of the hydroxylated compounds described in this paper, two *cis*-glycols are possible, *viz.*, **2** and **3**. A choice can be made by applying Alder's rule of *exo*-addition.[18] Because the hydroxylation proceeds *via* the osmate ester of the glycol,[17] steric considerations for this intermediate strongly suggest the hydroxylated compounds have the configuration shown in 2—*e.g.*, the *exo-cis*-glycol. For the formation of this product, there is less steric interference between osmium tetroxide and the oxygen bridge than between that reagent and the two carbon bridge.

By hydroxylating the furan–maleic anhydride [**1a**] adduct with 30% hydrogen peroxide in formic acid, Jolivet[11b] isolated a 60% yield of a dihydroxy dicarboxylic acid melting at 230° isomeric with the substance reported here melting at 200°. In all probability the 230° compound has the *trans*-glycol configuration since reactions with hydrogen peroxide in formic acid have been shown to result in *trans* hydroxylation.[19] In this context it is disconcerting to note that treatment of **1a** with 30% hydrogen peroxide in 85% formic acid at 28° has been reported to afford a 75% yield of the *oxirane* derivative, *exo*-5,6-epoxy-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic acid.[12f] In view of the data obtained by Jolivet,[11b] it is rather disquieting that this epoxide was found to be stable to hydrolytic conditions and failed to yield the *vic*-glycol.

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[3] (a) K. Alder, "Newer Methods of Preparative Organic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1948, p. 381; (b) M. C. Kloetzel, *Org. Reactions*, **4**, 1 (1948); (c) H. L. Holmes, *Org. Reactions*, **4**, 60 (1948); (d) A. P. Dunlop and F. N. Peters, "The Furans," Reinhold Publishing Corp., New York, N. Y., 1953, pp. 54–64; (e) J. G. Martin and R. K. Hill, *Chem. Rev.*, **61**, 537 (1961).

[4] O. Diels and K. Alder, *Ber.*, **62**, 554 (1929); See also ref. 3b, p. 43.

[5] K. Alder and K. H. Backendorf, *Ann.*, **535**, 101 (1938).

[6] (a) N. Clauson-Kaas and N. Elming, *Acta Chem. Scand.*, **6**, 560 (1952); (b) M. P. Cava, C. L. Wilson, and C. J. Williams, Jr., *J. Am. Chem. Soc.*, **78**, 2303 (1956).

[7] M. G. Van Campen, Jr., and J. R. Johnson, *ibid.*, **55**, 430 (1933).

[8] R. B. Woodward and H. Baer, *ibid.*, **70**, 1161 (1948).

[9] (a) H. Kwart and I. Burchuk, *ibid.*, **74**, 3094 (1952) and (b) J. A. Berson and R. Swidler, *ibid.*, **75**, 1721 (1953) present data relevant to *endo–exo* interconversions of bicyclic Diels–Alder adducts.

[10] It should be noted that Alder and Backendorf assigned the *endo–cis* configuration to the maleic anhydride–2-methylfuran adduct (ref. 4.), by analogy with their incorrect assignment of that configuration to the maleic anhydride–furan adduct. Later Mel'nikov and Kraft (see ref. 12b) assumed this adduct [**1b**] had the *exo–cis* structure and more recently, Yur'ev and Zefirov (see ref. 12f) summarized the evidence for assigning the *exo–cis* configuration to this adduct.

[11] (a) R. McCrindle, K. H. Overton, and R. A. Raphael, *J. Chem. Soc.*, 1560 (1960); (b) J. Jolivet, *Ann. chim.*, [13], **5**, 1165 (1960); see also J. Jolivet, *Compt. rend.*, **243**, 2085 (1956) for a preliminary account.

[12] By contrast other addition reactions have been described for the olefinic function present in these adducts: (a) Bromine, J. A. Berson and R. Swidler, *J. Am. Chem. Soc.*, **76**, 4060 (1954); (b) Chlorine, N. N. Mel'nikov and V. A. Kraft, *J. Gen. Chem. USSR*, **26**, 227 (1956), **29**, 949 (1959); (c) Hypobromous acid, ref. 11b; (d) Hypochlorous acid, ref. 11b; (e) Hydrogen, ref. 5 and 8; (f) Epoxidation, Yu. K. Yur'ev and N. S. Zefirov, *J. Gen., Chem.* **31**, 772, 1125 (1961).

[13] (a) K. Alder and G. Stein, *Ann.*, **504**, 216 (1933); (b) H. Kwart and W. G. Vosburgh, *J. Am. Chem. Soc.*, **76**, 5400 (1954); (c) R. Grewe, A. Heinke, and C. Sommer, *Chem. Ber.*, **89**, 1978 (1956); (d) W. Rigby, *J. Chem. Soc.*, 2452 (1956); (e) K. B. Wiberg and K. A. Saegebarth, *J. Am. Chem. Soc.*, **79**, 2822 (1957); (f) E. E. Smissman, J. T. Suh, M. Oxman, and R. Daniels, *ibid.*, **81**, 2909 (1959); **84**, 1040 (1962); (g) ref. 2.

[14] N. A. Milas and S. Sussman, *J. Am. Chem. Soc.*, **58**, 1302 (1936), **59**, 2345 (1937). See also ref. 13c and F. D. Gunstone, "Advances in Organic Chemistry," Vol. 1, Interscience Publishers, Inc., New York, N. Y., 1960, p. 103.

[15] See M. Mugdan and D. P. Young, *J. Chem. Soc.*, 2988 (1949) for comments regarding the unimportance of using an anhydrous medium.

[16] It is of interest to note that oxmium tetroxide hydroxylation of the maleic anhydride-2-acetoxyfuran adduct under anhydrous conditions was reported to afford a product with an intact anhydride group (ref. 11a).

[17] W. A. Waters in H. Gilman "Organic Chemistry," Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1953, page 1156; R. Criegee, *Ann.*, **522**, 75 (1936); R. Criegee, B. Marchand, and H. Wannowius, *ibid.*, **550**, 99 (1942).

[18] K. Alder and G. Stein, *ibid.*, **515**, 185 (1935), **525**, 183 (1936); K. Alder, H. Wirtz, and H. Koppelberg, *ibid.*, **601**, 138 (1956); see also ref. 12a.

[19] E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 356.

Experimental[20]

Preparation of Adducts of Furans and Maleic Anhydride [I].—Furan, obtained from E. I. du Pont Co., and 2-methylfuran, supplied by the Quaker Oats Co., were purified by distillation prior to use. 2-Bromofuran[21] and 2-acetoxyfuran[6b] were synthesized by the methods described in the literature.

***exo-cis*-7-Oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride [1a],**[4] ***exo-cis*-1-methyl-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride [1b],**[5] **and *exo-cis*-1-acetoxy-7-oxabicyclo-[2.2.1]-hept-5-ene-2,3-dicarboxylic anhydride [1c]**[6a] were prepared from maleic anhydride and the appropriate furan by methods recorded in the literature.

***exo-cis*-1-Bromo-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic Anhydride [1d].**—To a solution of 5.5 g. (0.037 mole) of 2-bromofuran in 10 ml. of ether was added 3.7 g. (0.038 mole) of powdered maleic anhydride. The flask was stoppered and stirred magnetically for 15 min. when a clear solution was obtained. After remaining overnight at room temperature, the flask was unstoppered and stirring resumed until crystals appeared. The white suspension was refrigerated for 2 days and the solid, isolated by filtration, weighed 7.8 g. (85%) and melted at 119–120° (lit.,[7] m.p. 116°).

Purification of *t*-Butyl Alcohol.—The alcohol was shaken for 48 hr. with solid potassium permanganate, filtered, dried with magnesium sulfate, and distilled from fresh solid potassium permanganate directly into the glass stoppered bottle used for the preparation of the osmium tetroxide catalyst solution.[22]

Osmium Tetroxide Catalyst Solution.—The contents of a 1-g. sealed vial of osmium tetroxide (Merck) was dissolved in 200 ml. of purified *t*-butyl alcohol. The pale green solution was treated with 3 drops of 30% hydrogen peroxide and allowed to remain at room temperature for 1 day. If the solution became dark, the dropwise addition of 30% hydrogen peroxide was repeated until the pale green color persisted. This solution is stable for at least one year at room temperature. Each milliliter contains 2×10^{-5} mole of osmium tetroxide.

***exo-cis*-5,6-Dihydroxy-*exo-cis*-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic Acid [2a].**—To a solution of 1 g. (6.0 mmoles) of **1a**, in 8 ml. of reagent grade acetone (Mallinckrodt) were added 2 ml. of absolute ether (Mallinckrodt) and a mixture of 1 ml. of catalyst solution and 1 ml. of 30% hydrogen peroxide (9.8 mmoles). The reaction mixture became brown and the flask was stoppered and kept in a water bath at 30° for 24 hr. At that time a white solid was present in an amber solution. An additional 10 ml. of absolute ether was added and the suspension was cooled in an ice bath for 4 hr. The solid obtained by filtration was washed with ether and dried in air.

This crude product was treated with 15 ml. of warm methanol and filtered to remove 50 mg. of a white solid which did not melt even when heated to 315° and was not investigated further. The methanolic filtrate was concentrated to 10 ml., absolute ether was added to precipitate the product which was recrystallized from methanol, methanol–isoamyl acetate or 50% aqueous dioxane. The crystalline material was dried for 10 hr. *in vacuo* at 80° over phosphorus pentoxide and provided 0.65 g. (50%) of product. A wide melting point range is obtained for this material unless the sample is introduced into a bath preheated to 195°, m.p. 199–200° dec.

Anal. Calcd. for $C_8H_{10}O_7$: C, 44.04; H, 4.62. Found: C, 44.48; H, 5.11.

The *dimethyl ester* was obtained by treating the acid with diazomethane, m.p. 202–204°.

Anal. Calcd. for $C_{10}H_{14}O_7$: C, 48.78; H, 5.73. Found: C, 48.86; H 5.39.

***exo-cis*-5,6-Dihydroxy-*exo-cis*-1-methyl-7-oxabicyclo[2.2.1]-heptane-2,3-dicarboxylic Acid [2b].**—To a solution of 1 g. (5.5 mmoles) of **1b**, in 3 ml. of acetone was added a mixture of 1 ml. of the osmium tetroxide catalyst solution and 1 ml. of 30% hydrogen peroxide. The brown reaction mixture was kept in a stoppered flask at 30° for 24 hr. The light colored solution was concentrated to 2 ml., and 2 ml. of methanol and 8 ml. of isoamyl acetate were added. The solution was heated and the methanol allowed to evaporate slowly until the product began to precipitate. The mixture was allowed to cool, was filtered, and dried.

Recrystallization was accomplished by dissolving the solid in a minimum of methanol, adding four volumes of isoamyl acetate and concentrating the solution on a steam bath until crystals appeared. The mixture was cooled and filtered and the solid was dried *in vacuo* over phosphorus pentoxide for 8 hr. at 80°. The yield was 0.40 g. (31%), m.p. 184° dec.

Anal. Calcd. for $C_9H_{12}O_7$: C, 46.55; H, 5.21. Found: C, 46.79; H, 5.37.

***exo-cis*-5,6-Dihydroxy-*exo-cis*-1-acetoxy-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic Acid [2c].**—A solution of 1 ml. of catalyst solution in 1 ml. of 30% hydrogen peroxide was added to a solution of 1 g. (4.4 mmoles) of **1c**, in 8 ml. of acetone and 2 ml. of absolute ether. The flask was stoppered and maintained at 30° for 24 hr. White crystals appeared and precipitation was completed by adding 10 ml. of absolute ether and refrigerating the mixture overnight. Recrystallization from methanol–isoamyl acetate as described above afforded 0.70 g. (54%), m.p. 155–156° dec.

Anal. Calcd. for $C_{10}H_{12}O_9 \cdot H_2O$: C, 40.82; H, 4.80; neut. eq. 147.1. Found: C, 41.02; H, 4.85; neut. eq., 145.0, 146.0.

Three recrystallizations from methanol–isoamyl acetate yielded material melting at 171° dec.

Anal. Calcd. for $C_{10}H_{12}O_9$: C, 43.48; H, 4.38; Found: C, 43.10; H, 4.62.

***exo-cis*-5,6-Dihydroxy-*exo-cis*-1-bromo-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic Acid [2d].**—To a solution of 1 g. (4.0 mmoles), of **1d** in 5 ml. of acetone and 5 ml. of ether was added to a mixture of 1 ml. of catalyst solution and 1 ml. of 30% hydrogen peroxide. The brown reaction mixture was kept at 30° for 24 hr., then at room temperature for 48 hr. Precipitation was completed by adding 10 ml. of ether and refrigerating overnight. Filtration yielded 0.60 g. of product and an additional 0.30 g. was obtained from the filtrate. Recrystallization was accomplished by dissolving the crude product in hot 9:1 methanol–acetone, adding an equal volume of isoamyl acetate and allowing the solution to evaporate slowly on a steam bath. The solid was dried *in vacuo* at 80° for 8 hr. over phosphoric anhydride and weighed 0.80 g. (67%) m.p. 212–213° dec.

Anal. Calcd. for $C_8H_9O_7Br$: C,3 2.35; H, 3.05; neut. equi., 148.6. Found: C, 32.65; H, 3.51; neut. equi., 152.5.

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[20] All melting points and boiling points are uncorrected.

[21] D. G. Manly and E. D. Amstutz, *J. Org. Chem.*, **21**, 516 (1956); A. F. Shepard, N. R. Winslow, and J. R. Johnson, *J. Am. Chem. Soc.*, **52**, 2083 (1930).

[22] Unless impurities were removed by this procedure, the catalyst solution was unstable; it turned black and was not suitable for the hydroxylation reactions.