The first cut was allowed to stand until 120 mg of crystalline trimer was deposited.

The mother liquor was concentrated, and 270 mg of another crystalline product was deposited. Recrystallization from light petroleum ether gave a colorless crystalline product which melted at 117–118°. Thin layer chromatography on silica gel G gave R_f values of 0.23–0.28 in benzene and 0.74–0.81 in $CHCl_3$: λ_{max}^{Nujol} (μ) 6.93, 7.30, 7.35, 8.00, 8.60, 8.75, 8.95, 9.20, 10.04, 10.45, 10.56, 11.32, 11.55, and 11.82; nmr, τ 4.95 (1 H, doublet), 6.35 (2 H, multiplet), 7.55 (4 H, multiplet), 7.9 and 8.0 (two singlets, 4 H and 3 H), 8.1–8.5 (6 H, multiplet), 7.75 (6 H, singlet).

Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.82; H, 8.67; mol wt, 302. Found: C, 75.97; H, 8.77; mol wt, 287.

In another similar run conducted without a nitrogen atmosphere only trimer was isolated.

Diels–Alder Adduct VIII Derived from Quinone Methide.—To 1.08 g of benzoquinone and 1.28 g of tetracyanoethylene in 100 ml of refluxing benzene was added slowly 2.20 g of chroman. After several hours of reflux, the mixture turned a deep purple. After evaporation of the benzene, the solution was chromatographed on a silica gel column with chloroform. The first fraction, a colorless material, was rechromatographed in the same way and sublimed twice: mp 208–210°; yield, 450 mg; λ_{max}^{Nujol} (μ) 4.40 (CN), 6.35, 6.92, 7.10, 8.60, 9.10, 10.30, 10.71, 11.10; nmr, τ 6.30 (singlet, 2 H), 7.40 (triplet, 2 H), 7.75 and 7.80 (singlets, 3 H, methyl), 8.12 (triplet, 2 H), 8.62 (singlet, 6 H).

The Lithium–Liquid Ammonia Reduction of 2-Methyl-2,3-dihydrobenzofuran[1]

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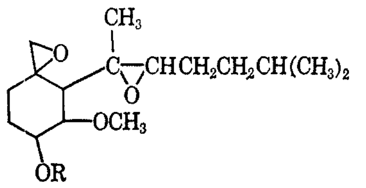
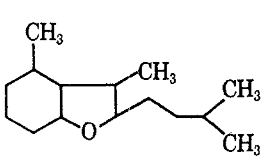
Reduction of 2-methyl-2,3-dihydrobenzofuran (F) with lithium–liquid ammonia in ether-*t*-butyl alcohol yielded as the main product 2,3,4,7-tetrahydro-2-methylbenzofuran (G) along with some hexahydro-2-methylbenzofuran. Dilute acid hydrolysis gave a mixture of saturated and α,β-unsaturated hydroxy ketones, which was converted to 2-(2-hydroxypropyl)cyclohexanone (K, apparently a mixture of diastereoisomers) by catalytic reduction; the hydroxy ketone was obtained by chromatography on alumina in 16% over-all yield from the dihydrobenzofuran F. The structure of K was established by oxidation to the known α-(2-oxocyclohexyl)-acetone (M) and by unambiguous synthesis from the epoxide of 2-allylcyclohexanone ethylene ketal (N). Thus the lithium–liquid ammonia reduction of 2-methyldihydrobenzofuran yields products analogous to those derived from anisole.

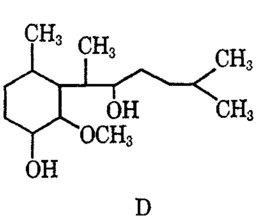
In connection with the synthesis of compounds related to fumagillin[2,3] (A), and particularly of degradation products[2b] such as the alcohol B, the perhydrobenzofuran C, and the monocyclic compound D, we have considered the applicability of the metal–liquid ammonia reduction[4] to phenolic ethers and to 2,3-dihydrobenzofurans.



A, R = $CO(CH{=}CH)_4COOH$
B, R = H



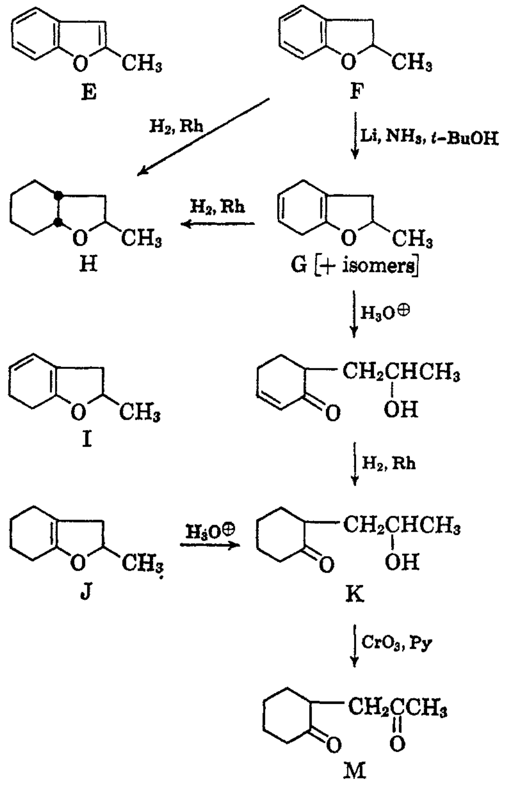
C



D

Hurd[5] showed that an excess of sodium in liquid ammonia reduced 2-methylbenzofuran (E) and the corresponding 2,3-dihydro compound F with ring cleavage to give a good yield of *o*-propylphenol in each case (Scheme I).

SCHEME I



In the present paper, we find that F is converted by the lithium–*t*-butyl alcohol–ether–liquid ammonia pro-

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[1] Supported by Grant AI-01138 from the National Institutes of Health.

[2] (a) D. S. Tarbell, *et al.*, *J. Am. Chem. Soc.*, **82**, 1005 (1960); (b) *ibid.*, **83**, 3096 (1961); (c) J. R. Turner and D. S. Tarbell, *Proc. Natl. Acad. Sci. U. S.*, **48**, 733 (1962).

[3] S. T. Young, J. R. Turner, and D. S. Tarbell, *J. Org. Chem.*, **28**, 928 (1963).

[4] For reviews, see (a) A. J. Birch, *Quart. Rev.* (London), **4**, 69 (1950); (b) H. Smith, "Organic Reactions in Liquid Ammonia," Interscience Publishers, Inc., 1963, p 237 ff.

[5] C. D. Hurd and G. L. Oliver, *J. Am. Chem. Soc.*, **81**, 2795 (1959).

[6] (a) A. L. Wilds and N. A. Nelson, *ibid.*, **75**, 5360 (1953); (b) H. L. Dryden, Jr., G. M. Webber, R. R. Burtner, and J. A. Cella, *J. Org. Chem.*, **26**, 3237 (1961).

cedure[6] to the tetrahydro compound G and some hexahydro compounds such as J; the products formed are analogous to those from anisole, and little hydrogenolysis is observed.

The ring structure of G was established by catalytic reduction to the perhydro compound[7] H and by a sequence of hydrolysis and catalytic reduction to 2-(2-hydroxypropyl)cyclohexanone (K).

The reduction product of F by the lithium-liquid ammonia procedure[6] contained, from the ultraviolet absorption at 280 mμ, about 4% of starting material; the presence of conjugated product, such as I, was ruled out by the absorption curve.[8]

Vapor phase chromatography of the lithium-ammonia reduction product gave four main peaks, one of which was starting material. Another of the peaks was collected and its infrared spectrum showed a strong band at 1705 cm^{-1} (C=C stretch in a vinyl ether) and no absorption at 3000-3100 cm^{-1}. This was probably the hexahydrobenzofuran J, which would give the hydroxy ketone K on hydrolysis. A compound peak in the vpc showed on collection bands at 1661, 1578, and 692 cm^{-1}, which are not present in the crude reduction product before vpc. Distillation of the crude reduction product through a short Vigreux column showed new bands at these same positions. It is known that 2,5-dihydroanisole is isomerized to the conjugated isomer by heating,[9] and presumably therefore the compound peak consisted of G and a conjugated isomer of it.

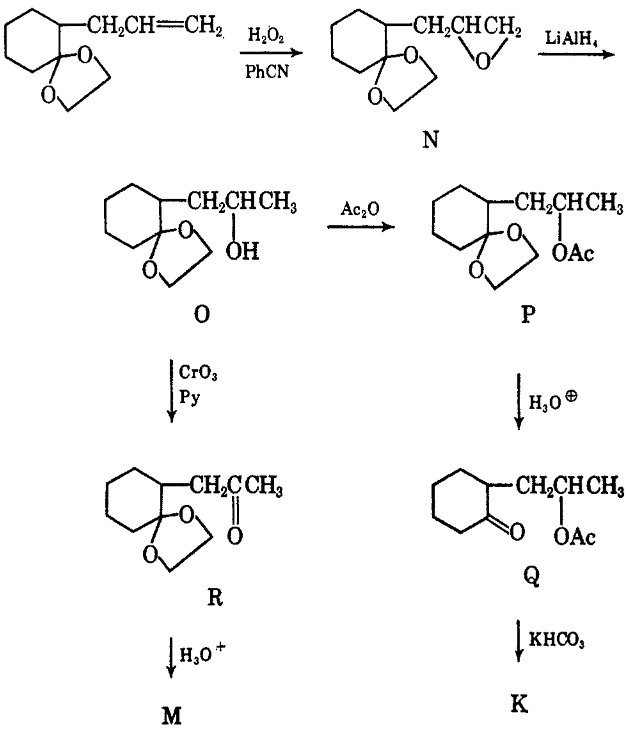
Treatment of the crude reduction product with chloranil gave chloranil hydroquinone and the dihydrobenzofuran F; this indicated that the reduction product contained a dihydro product such as G.[10] Catalytic reduction of the crude liquid ammonia-lithium product gave mainly *cis*-2-methylperhydrobenzofuran, which was consistent with the presence of compounds such as G and hexahydro derivatives.

Acid hydrolysis of the crude reduction product (monitored by the disappearance of the strong end absorption and the appearance of a new maximum[11] at 226 mμ), followed by chromatographic separation, gave a mixture of a saturated hydroxy ketone and an α,β-unsaturated hydroxy ketone (infrared bands at 3400, 1710, and 1670 cm^{-1}).

Hydrogenation of the mixture of hydroxy ketones, best in ethyl acetate, gave a product lacking the absorption bands at 3030 and 1670 cm^{-1}, shown by the starting material; purification by chromatography gave the hydroxy ketone K. This material had the correct elemental analysis, strong infrared bands at 3400 and 1710 cm^{-1}, and an nmr spectrum consistent with the assigned structure.

The structure of K was confirmed by an unambiguous synthesis from 2-allylcyclohexanone; one of the intermediates in the synthesis was converted to the known[12] diketone M, and the same diketone was obtained by oxidation of the hydroxy ketone K derived from the dihydrobenzofuran F. The synthetic steps are in Scheme II.

SCHEME II



The elemental analysis of the product obtained by hydrolysis of the keto acetate Q was consistent with the assigned structure, and its infrared and nmr spectra were the same as for the product obtained *via* reduction of F. In addition, tlc showed the same two spots as the hydroxy ketone derived from F (the samples were run side by side on the same plate). The appearance of two spots for each sample of K was apparently due to the presence of both possible diastereoisomers in each product.

Experimental Section[13]

Reduction of 2-Methyl-2,3-dihydrobenzofuran (F) by Lithium and *t*-Butyl Alcohol in Liquid Ammonia.—The procedure used was similar to that of Dryden, *et al.*[6b] To a solution of 8.29 g (0.062 mole) of 2-methyl-2,3-dihydrobenzofuran (F)[14] in 140

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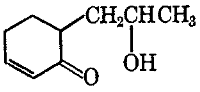
[7] *Cf.* S. E. Cantor and D. S. Tarbell, *J. Am. Chem. Soc.*, **86**, 2902 (1964).

[8] The analogous conjugated dihydroanisole is reported to have λ_{max} 268 mμ (ε 4270): A. J. Birch, *J. Chem. Soc.*, 1551 (1950).

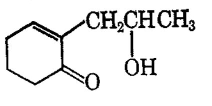
[9] A. P. Krapcho and A. A. Bothner-By, *J. Am. Chem. Soc.*, **81**, 3658 (1959); R. A. Benkeser, *et al.*, *J. Org. Chem.*, **28**, 1094 (1963).

[10] *Cf.* E. A. Braude, L. M. Jackman, and R. P. Linstead, *J. Chem. Soc.*, 3564 (1954).

[11] A conjugated ketone such as



should show λ_{max} 225 mμ, and the isomer



should have λ_{max} *ca.* 237 mμ, on the basis of R. B. Woodward's rules [*J. Am. Chem. Soc.*, **63**, 1123 (1941)].

[12] H. E. Baumgarten, P. L. Creger, and C. E. Villars, *ibid.*, **80**, 6609 (1958). These workers prepared M by alkylation of an enamine of cyclohexanone with α-bromoacetone.

[13] Microanalyses were done by V. Landeryou and A. Revilla of these laboratories, and by Micro-Tech Laboratories, Skokie, Ill. All melting points and boiling points are uncorrected. The infrared spectra of liquids were taken on thin films and those of solids on potassium bromide disks (unless otherwise specified) with a Perkin-Elmer Model 421 spectrophotometer. A Cary recording spectrophotometer Model 11 MS was used to obtain ultraviolet spectra. The nmr spectra were recorded on a Varian A-60 spectrometer in carbon tetrachloride (unless specified otherwise) using tetramethylsilane as an internal standard. Vapor phase chromatography was done on Aerograph A-90-P and A-90-P-2 instruments.

[14] Prepared by cyclization of *o*-allylphenol in HBr-acetic acid: D. S. Tarbell, *Org. Reactions*, **2**, 27 (1944).

ml of *t*-butyl alcohol, 150 ml of anhydrous ether, and 300 ml of distilled liquid ammonia was added 7.0 g (1.0 g-atom) of lithium during 25 min while stirring at reflux. After 6.5 hr, 90 ml of methanol was slowly added to destroy excess lithium. The mixture was allowed to stand overnight while the ammonia was evaporated. To the residue was added 400 ml of water and when the solids had dissolved, the mixture was extracted four times with 100 ml of pentane. The combined extracts were exhaustively washed with water and dried. Removal of the pentane *in vacuo* left 7.5 g of a clear, mobile liquid.

The ultraviolet spectrum in 95% ethanol showed strong end absorption and a band at 280 mμ, attributed to the presence of 4% of the starting material. The infrared spectrum showed bands, among others, at 3030, 1721, 1705 (1721 > 1705), 1695 (sh), 1640, 669, and 662 cm^{-1}. All of these bands were attributed to double bonds. A very strong band at 1200 cm^{-1} (C=C—O) was also present.

Distillation of 2.53 g of the crude product through a Vigreux column gave 2.03 g of distillate: bp 66.5–68° (10 mm). The infrared spectrum of the distillate showed the same bands as in the crude product, but new bands were discernible at 1661, 1578, and 692 cm^{-1}.

Vpc of the crude reduction product on a 5 ft × 0.25 in. 20% Ucon Polar on Chromosorb P column (column temperature 111°, flow rate 75 cc of He/min) showed major peaks at 8.5, 13.5 and 15.9 (incompletely resolved), and 19.6 min in a ratio of 1.0: 3.1:0.36. The peak at 13.5 min was larger than that at 15.9 min; since they were not completely resolved, their combined area is given in the relative ratios. Other small peaks appeared at 0.5, 1.0, 6.8, 7.3, and 9.4 min. Samples of the peak at 8.5 min and the compound peak at 13.5–15.9 min were collected by vpc. The infrared spectrum of the former showed bands at 1705 (s), 1695 (sh), and 1198 cm^{-1} (s); no band appeared between 3000 and 3100 cm^{-1}. The liquid collected from the compound peak at 13.5–15.9 min showed strong infrared bands at 1721, 1661, 1578, 1205, and 1195 cm^{-1}. Weak bands at 3030 and 1640 cm^{-1} and medium bands at 692, 669, and 662 cm^{-1} were also present.

After distillation or vpc of the crude reduction product, the appearance of infrared bands at 1661, 1578, and 692 cm^{-1}, not present in the spectrum of the crude product, indicated the formation of a new product during these operations.

The compound eluted at 19.6 min was identified as starting material by comparison of its infrared spectrum and vpc retention time with a known sample of F.

Acidification of the aqueous layer after the pentane extraction gave 60 mg of an unidentified oil. This fact showed that formation of phenolic material by hydrogenolysis was not appreciable.

Hydrogenation of the Lithium–Ammonia Reduction Product of 2-Methyl-2,3-dihydrobenzofuran.—A solution of 0.288 g of the distilled reduction product in 20 ml of methanol was hydrogenated at atmospheric pressure at 25° over 0.085 g of 5% rhodium on alumina. After 9.8 hr the catalyst was removed and the methanol distilled to leave a liquid residue which was taken up in a few milliliters of ether and dried. Evaporation of the ether gave 0.241 g of a mobile liquid. Analysis by vpc on a 15-ft 20% Craig column showed several peaks; the largest peak (63% of the total area of all the peaks) was collected by vpc. The infrared spectrum and vpc retention time of this material were identical with those of *cis*-2-methylperhydrobenzofuran obtained on hydrogenation of 2-methyl-2,3-dihydrobenzofuran over rhodium on alumina.[7]

Dehydrogenation of the Lithium–Ammonia Reduction Product of 2-Methyl-2,3-dihydrobenzofuran by Chloranil.—A solution of 0.364 g of the reduction product and 0.583 g of chloranil in 15 ml of dry benzene was refluxed for 2.2 hr. Tan needles (0.321 g) were collected after cooling in ice; they melted, after recrystallization from a benzene–ethanol mixture, at 239–243°, and had an infrared spectrum identical with that of an authentic sample of 2,3,5,6-tetrachlorohydroquinone.

Evaporation of the solvent from the reaction mixture left a residue; after extraction twice with 10 ml of petroleum ether (bp 30–60°), 0.25 g of a dark green solid remained, which was not investigated further.

Evaporation of the petroleum ether extract gave 0.30 g of an oil. Examination by vpc on a 10-ft 30% Apiezon column showed two peaks in a ratio of about 5:1. The major component was identified as 2-methyl-2,3-dihydrobenzofuran by identity of its infrared spectrum and vpc retention time with those of an authentic sample.

Hydrolysis of the Lithium–Ammonia Reduction Product of 2-Methyl-2,3-dihydrobenzofuran.—A solution of 4.47 g of the reduction product in 70 ml of 95% ethanol, 17.5 ml of water, and 0.35 ml of 18% hydrochloric acid was allowed to stand at room temperature for 13 hr. The solution was neutralized with potassium carbonate and concentrated to leave two layers. Salt was added to saturate the aqueous layer, and the mixture was extracted three times with ether. The combined extracts were washed with brine and dried to give on evaporation of the ether 5.1 g of an oil.

The product, dissolved in 10 ml of benzene, was chromatographed on 300 g of Woelm neutral alumina, activity II. Elution with 650 ml of benzene gave 1.05 g of an oil. The early fractions were shown by their infrared spectra to contain 2-methyl-2,3-dihydrobenzofuran. The later fractions showed no hydroxyl or carbonyl bands in their infrared spectra, but showed strong bands in the 1150–1050-cm^{-1} region.

Elution by anhydrous ether gave 0.089 g of an oil in the first 275 ml of eluate; the infrared spectrum of this material showed no hydroxyl or carbonyl bands. The next 775 ml of ether eluted 1.09 g of an oil whose infrared spectrum showed bands at 3400, 1710, and 1670 cm^{-1}. The early fractions contained little of the material responsible for the 1670-cm^{-1} band, while the later fractions showed an increase in this material.

Elution with a 19:1 ether–methanol mixture gave 1.17 g of an oil in a total of 500 ml of eluate. The infrared spectrum of this material showed strong bands at 3400 and 1670 cm^{-1}, and a weak band at 1710 cm^{-1}. Elution with 200 ml of methanol then gave 0.26 g of a viscous yellow oil.

The main ether fraction (1.09 g) and the oil (1.17 g) eluted by 19:1 ether–methanol were combined and utilized to prepare 2-(2-hydroxypropyl)cyclohexanone (K) by hydrogenation (see below).

The hydrolysis at room temperature was also followed by monitoring the ultraviolet spectrum. A solution of 0.011 g of the reduction product in 100 ml of 90% aqueous ethanol showed the strong end absorption characteristic of enol ethers. On addition of 0.3 ml of 18% hydrochloric acid, the end absorption disappeared and a new band at 226 mμ appeared, which reached a maximum after 78 min.

Hydrogenation of the Hydroxy Ketone Mixture from the Hydrolysis of the Lithium–Ammonia Reduction Product of F. 2-(2-Hydroxypropyl)cyclohexanone (K). A. Hydrogenation in Acetic Acid with 5% Rhodium on Alumina Catalyst.—A solution of 0.723 g of the mixture of the hydroxy ketones in 10 ml of glacial acetic acid was hydrogenated at 25° and 1 atm over 0.33 g of 5% rhodium on alumina. After 1.6 hr the catalyst was removed, and the solution in 100 ml of water was neutralized with sodium bicarbonate. Extraction three times with 35 ml of ether gave, after being washed with water and dried, 0.446 g of a yellow oil, whose infrared spectrum showed bands at 3400 and 1710 cm^{-1}; however, bands at 3030 and 1670 cm^{-1}, present in the starting material, were absent.

The total product was chromatographed on 15 g of Woelm neutral alumina, activity II. Elution with 80 ml of benzene gave 0.143 g of an oil, whose infrared spectrum showed the absence of hydroxyl and carbonyl bands. Elution with 60 ml of 1:1 benzene–ether gave 0.136 g of K. Methanol eluted 0.16 g of a yellow, tacky resin.

The hydroxy ketone K was evaporatively distilled at 0.05 mm (bath temperature 88°). The infrared spectrum of this compound showed strong bands at 3400 (OH), 1710 (C=O), 1080, 1050, 965, and 942 cm^{-1}. The nmr spectrum showed a doublet at δ 1.25 (O-CH-CH$_3$), a multiplet centered at δ 4.25 (-O-CH), a singlet at δ 3.10 (OH), and a broad envelope at δ 1.0–2.5. The infrared and nmr spectra were the same as those shown by K synthesized from 2-allylcyclohexanone (see below). Tlc on silica gel G showed two spots on development with ether. A sample of K synthesized from 2-allylcyclohexanone showed on the same plate the same two spots.

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.02; H, 10.31.

B. Hydrogenation in Ethyl Acetate with 5% Palladium-on-Charcoal Catalyst.—A solution of 1.277 g of the hydroxy ketone mixture in 30 ml of ethyl acetate was hydrogenated over 0.25 g of 5% palladium on charcoal at 20° and 1 atm. The mixture was worked up as above and was chromatographed on 39 g of Woelm neutral alumina, activity II. Elution with 150 ml of benzene gave 0.25 g of an oil. The first four fractions showed a strong band at 1710 cm^{-1}, but only a weak hydroxyl band near 3400 cm^{-1}. The latter two fractions had strong bands at 3400 and 1710 cm^{-1}, showing that the hydroxy ketone K was starting to elute. A 1:1 benzene–ether mixture (150 ml) gave 0.55 g of the hydroxy ketone K. This material showed the same infrared spectrum as the product obtained by hydrogenation in acetic acid over rhodium on alumina.

Further elution with 100 ml of 1:1 ether–benzene gave 0.075 g of an oil, which was shown by its infrared spectrum to be the ketone K contaminated with a small amount of α,β-unsaturated ketone (weak band at 1670 cm^{-1}). Elution with ether and finally methanol gave 0.22 g of an oil whose infrared spectrum showed strong bands at 3400 and 1670 cm^{-1}. Apparently the hydrogenation of the α,β-unsaturated ketone of the ketone mixture was not complete.

Oxidation of 2-(2-Hydroxypropyl)cyclohexanone (K) to α-(2-Oxocyclohexyl)acetone (M).—To 4.7 ml of ice-cold, stirred anhydrous pyridine, 0.415 g of chromium trioxide was added in portions. To the yellow suspension, 0.210 g of the hydroxy ketone K (from the lithium–ammonia reduction of F) in 1.2 ml of pyridine was added. After 0.5 hr the stirring and cooling were stopped. When the mixture had stood at room temperature for 22 hr, 25 ml of water was added. Extraction with ether followed by washing of the combined extracts with water and brine gave 0.164 g of an oil after drying and evaporation of the ether.

Vpc of the product mixture on a 5 ft × 0.25 in. 20% Ucon Polar on Chromosorb P column (column temperature 158°, flow rate 65 cc of He/min) showed the major component at a retention time of 21.8 min. An authentic sample of α-(2-oxocyclohexyl)acetone (see below) showed a retention time of 21.9 min under the same conditions. Injection of the crude product mixture in 50-μl portions and collection of the peak at 21.8 min gave 0.015 g of a liquid, which had an infrared spectrum identical with that of authentic α-(2-oxocyclohexyl)acetone. Treatment of this liquid with 2,4-dinitrophenylhydrazine in phosphoric acid–ethanol[15] gave a product, mp 203–205° (from methanol–chloroform). The bis-2,4-dinitrophenylhydrazone obtained from authentic M melted at 205.5–207° (methanol–chloroform).

2-Allylcyclohexanone Ethylene Ketal.—2-Allylcyclohexanone[16] (53 g) was converted to the ethylene ketal in the usual way with ethylene glycol and *p*-toluenesulfonic acid in benzene. The product was distilled through a 46-cm Vigreux column; two fractions were collected at 89–90.5° (8.5 mm), 7.1 g, and 90.5–92.5° (8.5 mm), 48.8 g (70% yield, $n^{25}\mathrm{D}$ 1.4720). Analysis by vpc on a 5-ft Ucon Polar column showed the first fraction to contain about 90% product, while the second fraction was homogeneous. The infrared spectrum showed medium bands at 3080 and 1650 cm^{-1}, and strong bands at 1090, 998, and 910 cm^{-1}.

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.27; H, 9.92.

Epoxide of 2-Allylcyclohexanone Ethylene Ketal (N).—The method used was that of Payne.[17] To 166 ml of absolute methanol was added 60.5 g (0.332 mole) of 2-allylcyclohexanone ethylene ketal, 28.8 g of benzonitrile, and 5.5 g of potassium bicarbonate. To this was added 18.85 g of 50% hydrogen peroxide, and the solution was stirred at room temperature in a water bath for 78 hr. After addition of 280 ml of water, the solution was extracted three times with 180 ml of chloroform. The combined extracts were washed three times with 160 ml of water, and after drying the chloroform was distilled from the solution until the internal temperature was 85°. After addition of 60 ml of hexane, the precipitated benzamide was removed, and by a simple distillation material of bp 60–126° (2–3 mm) was collected. Redistillation through a spinning-band column gave a forerun of 6.3 g; 14.1 g of starting material, bp 74.5–78° (1 mm); and 32.5 g, bp 119–122° (1 mm) ($n^{25}\mathrm{D}$ 1.4770), 64% based on unrecovered starting material. The product gave a positive test for epoxide with a 0.2 *M* thiosulfate in 50% aqueous acetone containing phenolphthalein.[18] The infrared spectrum showed bands at 3040, 1258, 925, and 838 cm^{-1} all characteristic of an epoxide.[19] A very strong band also appeared at 1092 cm^{-1}. The nmr spectrum showed the dioxolane ring protons as a singlet at δ 3.88, the methylene protons of the epoxide as multiplets centered at δ 2.28 and 2.57, and the methinyl epoxide proton as a multiplet centered at δ 2.78.

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 67.05; H, 9.34.

2-[2-Hydroxypropyl)cyclohexanone Ethylene Ketal (O).—To 2.0 g (5.27 × 10^{-2} mole) of lithium aluminum hydride in 60 ml of dry ether was added 24.0 g (0.121 mole) of the epoxide N in 60 ml of ether during 1 hr. The mixture was then stirred and refluxed for 25 hr. With cooling 40 ml of water was slowly added and the mixture was poured into 250 ml of 10% potassium hydroxide. The aqueous layer was separated from the organic layer and extracted four times with ether. The combined extracts, after being washed with brine, were combined with the organic layer and dried. Evaporation of the ether left 22.5 g of liquid which, after distillation through a spinning-band column, gave 1.7 g, bp 79.5–80° (0.2 mm), and 16.9 g, bp 78–79° (0.09 mm). The latter fraction ($n^{25}\mathrm{D}$ 1.4770) showed one peak on vpc on a Ucon Polar column and amounted to a 70% yield.

The infrared spectrum showed strong bands at 3420 (OH), 1092 (ketal), 1018, 943, and 921 cm^{-1}, and the product gave a positive iodoform test.

Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.06. Found: C, 66.22; H, 10.00.

2-(2-Acetoxypropyl)cyclohexanone Ethylene Ketal (P).—The alcohol O (9.41 g) was acetylated at room temperature with acetic anhydride and pyridine. After the usual work-up, distillation through a Vigreux column yielded three fractions: bp 101–102.5° (0.35 mm), 0.54 g ($n^{25}\mathrm{D}$ 1.4622); bp 102.5–104.5° (0.35 mm), 7.6 g ($n^{25}\mathrm{D}$ 1.4618); bp 104.5–105.5° (0.35 mm), 1.1 g ($n^{25}\mathrm{D}$ 1.4618); total yield 81%. Vpc on a 15 ft × 0.25 in. 25% Ucon Polar column (column temperature 188°, flow rate 125 cc of He/min) showed the same two peaks for each fraction. The peak ratios differed for each fraction, being 2:1, 1.5:1, and 1:1, respectively. The appearance of two peaks was due to the presence of both possible diastereoisomers.

The infrared spectrum of the second fraction showed strong bands at 1743 (ester C=O) and 1095 cm^{-1} (C–O of dioxolane ring).

The nmr spectrum of the second fraction showed a singlet at δ 3.88 (proton of dioxolane ring), a singlet at δ 1.97 (acetate methyl), and a multiplet centered at δ 4.93 (methinyl proton of carbinol carbon). Doublets at δ 1.18 and 1.23 (J = 6.6 cps for both) were assigned to the terminal methyl of the propyl side chain (one for each diastereoisomer). The ratio of the peak heights of corresponding branches of the doublets was 1.3:1.

Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.43; H, 9.11. Found: C, 64.61; H, 9.18.

2-(2-Acetoxypropyl)cyclohexanone (Q).—A solution of 5.57 g (0.23 mole) of the acetoxy ketal P in 25 ml of 80% acetic acid was let stand at room temperature for 22 hr. After the solution was diluted with water, it was extracted three times with ether. The combined extracts were washed with water, bicarbonate solution, again with water, and finally brine. The ether solution was dried and gave, on solvent evaporation, 4.05 g of an oil. Distillation through a spinning-band column gave 2.1 g of product: bp 66–69° (0.3 mm), $n^{24}\mathrm{D}$ 1.4533. Analysis by vpc on a Ucon Polar column showed only one peak; the pot residue (1.2 g) was also shown to be mainly the same material.

The infrared spectrum showed bands at 1740 (ester) and 1715 cm^{-1} (ketone), as well as strong bands at 1372 and 1245 cm^{-1}. The nmr spectrum showed a doublet at δ 1.18 (CH_3-CH-O), a singlet at δ 1.92 (acetate methyl), and a multiplet centered at δ 4.83 (HC-OAc).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.58; H, 9.11.

2-(2-Hydroxypropyl)cyclohexanone (K). Hydrolysis of 2-(2-Acetoxypropyl)cyclohexanone (Q).—To a solution of 1.65 g of Q in 49 ml of absolute methanol was added 1.68 g of potassium bicarbonate in 19.7 ml of water. The solution was refluxed for 110 hr, and was then concentrated on a rotary evaporator to about one-third of the initial volume. After addition of 35 ml of water, the mixture was extracted three times with ether, and the combined extracts were washed with saturated brine. The solution was dried and the solvent was removed at

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[15] A. I. Vogel, "Practical Organic Chemistry," 3rd ed, Longmans, Green and Co., London, 1961, p 344.

[16] Prepared in 60% yield by the method of C. A. Vanderwerf and L. V. Lemerman, *Org. Syn.*, **28**, 8 (1948); vpc examination showed that the product was at least 99% pure.

[17] G. B. Payne, *Tetrahedron*, **18**, 763 (1962).

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

[19] K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1962, p 36.

reduced pressure to leave 1.037 g of a liquid, which was chromatographed on Woelm neutral alumina, activity II. Elution with 125 ml of petroleum ether gave 0.240 g of liquid; solvents of increasing polarity through ether gave 0.721 g of liquid. The infrared spectrum of the first fraction showed it to be mainly K, but the presence of a few additional bands suggested the presence of an impurity. The larger fraction was evaporatively distilled at 0.5 mm (bath temperature 60°) to provide analytically pure K. The spectral and analytical properties of K are described above.

2-(2-Oxopropyl)cyclohexanone Ethylene Ketal (R).—To 17.5 ml of dry, ice-cold, stirred pyridine, 1.55 g (1.55×10^{-2} mole) of chromium trioxide was added in small portions during 20 min. To the resultant yellow suspension, 1.00 g (5.0×10^{-3} mole) of the ketal alcohol O in 2.5 ml of pyridine was added; the mixture was stirred for 0.5 hr in an ice bath, and then at room temperature for 5.5 hr. The brown mixture was taken up in 125 ml of water and extracted four times with ether; the combined extracts were washed four times with ice-cold 3.7% hydrochloric acid, followed immediately by 30 ml of 10% sodium carbonate in two portions, and finally with water and saturated brine. The ether was dried and was removed at reduced pressure. The total residue was chromatographed on Woelm neutral alumina, activity I. Elution with 425 ml of ether gave 0.546 g of product, which was evaporatively distilled at 0.2 mm (bath temperature 75°) to give 0.477 g of R (48% yield). Vpc on a 5-ft 20% Ucon Polar column showed purity of about 99%. Analytically pure material was obtained by preparative vpc.

The infrared spectrum showed strong bands at 1717 (ketone), 1088 (ketal), 948, and 924 cm^{-1}. The nmr spectrum showed a singlet at δ 2.02 (CH_3—C=O) and a singlet at δ 3.83 (protons of dioxolane ring).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.40; H, 9.28.

The **semicarbazone**, after two recrystallizations from ethanol-water and sublimation at 0.08 mm (bath temperature 140°), melted at 154.5–155.5°.

Anal. Calcd for $C_{12}H_{21}N_3O_3$: C, 56.45; H, 8.29. Found: C, 56.64; H, 8.28.

α-(2-Oxocyclohexyl)acetone (M).—A solution of 0.451 g (2.28×10^{-3} mole) of R in a mixture of 2 ml of 95% ethanol and 1 ml of water containing 2 drops of 37% hydrochloric acid was refluxed for 1.1 hr. The reaction mixture was then diluted with water and extracted three times with ether. The combined ether extracts were washed with saturated bicarbonate, water, and finally with saturated brine. After the ether was dried, it was evaporated to give 0.172 g of an oil.

Vpc on a 5 ft × 0.25 in. 20% Ucon Polar on Chromosorb P column (column temperature 153°, flow rate 75 cc of He/min) showed the product at 11.0 min, preceded by several small peaks. The total crude product was injected in 25–30-μl portions, and the peak at 11.0 min was collected to give 0.078 g of the diketone M of 99+% purity (n^{25}_{D} 1.4615, lit.[12] n^{25}_{D} 1.4655).

The infrared spectrum showed a band at 1710 cm^{-1}, with a shoulder at 1725 cm^{-1}, strong bands at 1165 and 1130 cm^{-1}, and a weak, sharp band at 3400 cm^{-1}. The nmr spectrum showed a singlet at δ 2.08 (CH_3—C=O) and complex absorption at δ 1.5–3.0.

The bis-2,4-dinitrophenylhydrazone was prepared as above and had the same properties as the derivative obtained from the oxidation product of the hydroxy ketone K.

The Oxidative Coupling Reactions of 2,6-Xylenol with Activated Manganese Dioxide[1]

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Dimeric and polymeric products are obtained by the reaction of 2,6-xylenol and activated manganese dioxide. The tail-to-tail dimer, 2,2′,6,6′-tetramethyl-*p,p*′-biphenol, is formed when a molar excess of 2,6-xylenol is treated with the activated oxide, whereas the head-to-tail polymer is the principal product with excess oxide. The head-to-tail dimer, 4-(2′,6′-xylenoxy)-2,6-xylenol, reacts with the oxide to afford polymer and small amounts of 2,6-xylenol and the tail-to-tail dimer. Low molecular weight oligomer is converted by means of the oxide to higher molecular weight oligomer, 2,6-xylenol, the tail-to-tail dimer, and 3,3′,5,5′-tetramethyldiphenoquinone. Similar findings were obtained with silver oxide, lead dioxide, copper–pyridine, and basic ferricyanide. These observations and other considerations support a quinol–ether mechanism for this type of reaction rather than a nonclassical electron-transfer mechanism.

Activated manganese dioxide is a reagent used widely in organic syntheses for the specific oxidation of benzylic or allylic alcohols to aldehydes or ketones. This and other reactions of this material have been reviewed by Evans.[2a] Factors influencing the rate and specificity of the allylic oxidation have been well examined by Gritter,[2b,c] and modes of activity have been investigated by Pratt[3] and Henbest.[4] Recently, activated manganese dioxide has been applied as an agent for oxidative coupling in several enzyme-miming syntheses of phenolic natural products such as diploicin,[5] dehydrogriseofulvin,[6,7] and picrolichenic acid.[8] In the present investigation, an examination of the oxidative coupling reactions of activated manganese dioxide and a less elegant phenol, 2,6-xylenol, has been made in order to expand the scope of this reaction and to clarify the general mode of oxidative polymerization of phenols.

The oxidative polymerization of 2,6-xylenol has been accomplished heretofore by silver oxide[9] and a copper-pyridine complex.[10] The studies of the latter system have shown that the reaction involves free-radical intermediates and a stepwise polycondensation wherein the polymerization of dimer, trimer, or oligomer may be obtained without monomer. These observations prompted an unusual mechanistic proposal.[11]

Results

Activated manganese dioxide reacts with 2,6-xylenol (I) to form a polyphenylene ether (II), 2,2′,6,6′-tetra-

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[1] Presented in part at the 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1965; Abstracts, p 15S.

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