cc. of pyridine gave a rotation of +0.02° at 26.7°; *l*, 2 dm.; $[\alpha]^{26.7}D$ +1; *C* = 0.98.

Acetylation of the glucoside in the usual way regenerated the tetraacetate, m. p. and mixed m. p. 174°. Acid hydrolysis yielded *epi*-cholestanol (m. p. and mixed m. p. 186.5–187°) and glucose (osazone).

Separation of the β-Glucosides of Cholestanol and *epi*-Cholestanol.—A mixture containing 95 mg. of each glucoside was stirred for ten minutes with 4 cc. of cold 95% alcohol. The solution was filtered and the undissolved solid washed with 2 cc. of the same solvent. The filtrate and washings were refluxed for eighteen hours with 0.25 cc. of concentrated hydrochloric acid. The product yielded a sterol, m. p. (crude) 182–184° and hence containing about 95% of *epi*-cholestanol (compare Vavon and Jakubowicz[5]). The solid insoluble in alcohol was similarly hydrolyzed (6 cc. of 95% alcohol and 0.25 cc. of concentrated hydrochloric acid) to cholestanol, m. p. (crude) 141°. The recovery of the sterols was practically quantitative.

The separation was, however, less satisfactory when applied to a mixture of sterols, both as regards yields and completeness. A mixture of approximately equal parts of the two sterols was converted into the tetraacetyl-β-glucosides by the Helferich–Evans procedure. The product was hydrolyzed (barium hydroxide) without purification, to the free glucosides, which were exhaustively extracted with boiling petroleum ether (b. p. 30–60°) to remove unchanged sterols. The sterol recovered in this way amounted to 10% of the starting material and gave no Molisch reaction. From the m. p. it contained about 65% of *epi*-cholestanol. The sterol-free glucoside was separated by means of 95% alcohol and the two fractions hydrolyzed by acid as before. The recovered cholestanol was nearly pure but the "*epi*-cholestanol" fraction from the soluble glucoside melted in the crude state at 163–164° and therefore contained about 75% of the *epi*-form. The total recovery of sterols after the separation was 64%.

Summary

1. The synthesis of the glucosides of cholestanol and of *epi*-cholestanol in both α- and β-forms is described, and their structures are proved by hydrolysis.

2. There is no evidence of a connection between the configuration of a cyclic alcohol and its capacity for glucoside formation.

CONVERSE MEMORIAL LABORATORY
CAMBRIDGE, MASSACHUSETTS RECEIVED MAY 1, 1940

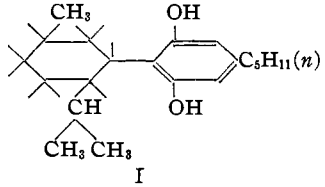
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Structure of Cannabidiol. IV. The Position of the Linkage between the Two Rings[1]

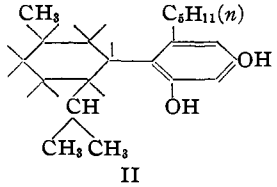
BY ROGER ADAMS, HANS WOLFF, C. K. CAIN AND J. H. CLARK[2]

IN COLLABORATION WITH THE TREASURY DEPARTMENT, NARCOTICS LABORATORY, WASHINGTON, D. C.

Experimental evidence has led to the deduction that tetrahydrocannabidiol has one of the following structures[1]



I



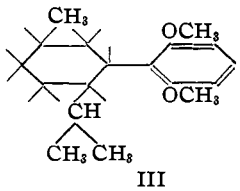
II

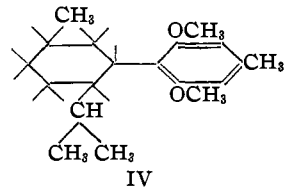
Various chemical methods thus far employed have failed to distinguish between them. Absorption spectra of certain known synthetic compounds of a similar structure have now been observed in order to determine whether these two types of molecular structure may be differentiated by this means. The compounds 2-(3′-menthyl)-1,3-dimethoxybenzene (III), 2-(3′-menthyl)-1,3-dimethoxy-5-methylbenzene (IV), 4-(3′-menthyl)-1,3-dimethoxybenzene (V) and 4-(3′-menthyl)-1,3-dimethoxy-5-methylbenzene (VI) were synthesized by unequivocal methods, and their absorption spectra compared with that of the dimethyl ether of tetrahydrocannabidiol (I or II).

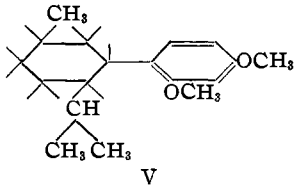
If the methyl group in the benzene ring in compound IV or VI were replaced by *n*-amyl one or the other of the resulting structures would be tetrahydrocannabidiol dimethyl ether, providing the configuration of the asymmetric carbon atoms in the synthetic and natural molecules was the same. These syntheses have not yet been attempted due to the fact that the tetrahydrocannabidiol dimethyl ether is a very high-boiling, viscous oil from which no solid derivatives have as

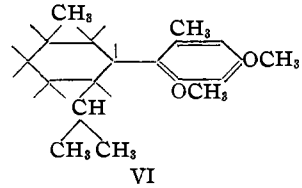
(1) For previous papers see (a) Adams, Hunt and Clark, THIS JOURNAL, **62**, 196 (1940); (b) Adams, Cain and Wolff, *ibid.*, **62**, 732 (1940); (c) Adams, Hunt and Clark, *ibid.*, **62**, 735 (1940).

(2) An abstract of a thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry. Solvay Process Company Fellow, 1939–1940.


III


IV


V


VI

yet been obtained, and the determination of the identity of the synthetic and natural products, therefore, would be difficult. Moreover, olivetol (1,3-dihydroxy-5-*n*-amylbenzene), which is necessary for the syntheses, is not readily accessible.

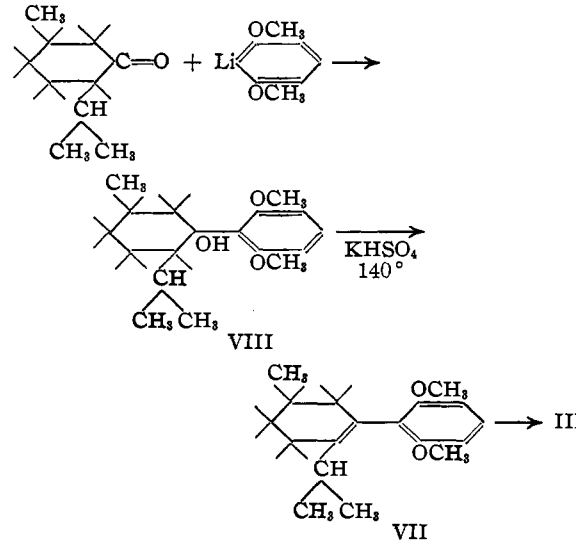
For comparative absorption spectra studies, the corresponding resorcinol and orcinol derivatives (III–VI) are equally valuable and much more easily prepared and purified. The differences in absorption spectra between the 5-methyl and the 5-*n*-amyl substituted resorcinol and their derivatives have been shown previously to be only slight. The curves are shown in Fig. 1.

The absorption spectra of compounds V and VI (D, E and F) with substitution in the 4-position of the benzene ring are markedly different from those of compounds III and IV (B and C) or from that of tetrahydrocannabidiol dimethyl ether (A); the extinction coefficient is higher and at slightly lower wave length. On the other hand, the 2-substituted compounds III and IV (B and C) have absorption spectra very similar to that of tetrahydrocannabidiol dimethyl ether (A). This evidence leads to the selection of structure I as the more probable for tetrahydrocannabidiol. Indirect chemical evidence also favors this formula. Cannabidiol is readily cleaved by pyrolysis with pyridine hydrochloride. Elimination of carbonyl groups located between the hydroxyls in resorcinol takes place quite readily by treatment with hydrochloric acid while corresponding groups in the 4-position are unaffected.[3]

Compound III was prepared from resorcinol dimethyl ether. By reaction with either *n*-butyllithium or phenyllithium, the lithium resorcinol dimethyl ether was obtained with the lithium atom between the methoxyls.[4]

This lithium compound was condensed with *l*-menthone with formation of a mixture of 2-(3′-hydroxy-3′-menthyl)-1,3-dimethoxybenzene (VIII), and 2-(3′-menthen-3′,4′-yl)-1,3-dimethoxybenzene (VII).

Although the two products could be separated by fractional distillation followed by crystallization from methanol, it was more convenient to dehydrate the mixture with potassium acid sulfate and to isolate only the menthene derivative (VII). The position of the double bond in this latter compound conceivably might be between the 2′,3′-carbon atoms, but its exact position is of little



VIII

VII

significance since the reduction product will be the same in either case. The hydrogenation of the menthene derivative occurred with difficulty when Raney nickel was used as catalyst and alcohol as a solvent, but readily with platinum oxide in glacial acetic acid to give 2-(3′-menthyl)-1,3-dimethoxybenzene (III). It is noteworthy, however, that hydrogen absorption did not stop completely after addition of one mole of hydrogen but continued at a much slower rate. This was probably due to the fact that after saturation of the double bond in the menthene ring, the resorcinol ring was slowly hydrogenated.

Compound IV was prepared in a similar way to compound III. The position of the lithium in orcinol dimethyl ether was proved by carbonation;

(3) Rosenmund, Buchwald and Deligiannis, *Arch. Pharm.*, **271**, 342 (1933); Limaye and Chate, *Rasaynam*, **1**, 39 (1937); Limaye and Limaye, *ibid.*, **1**, 109 (1937).

(4) (a) Wittig, Pockels and Dröge, *Ber.*, **71**, 1903 (1938); (b) Wittig and Pockels, *ibid.*, **72**, 89 (1939); (c) Gilman, "Metalation and the Related Interconversion Reactions," Eighth Nat. Org. Chem. Symposium, St. Louis, December 30, 1939.

the resulting 2,6-dimethoxy-4-methylbenzoic acid had the same m. p. as previously described.[5]

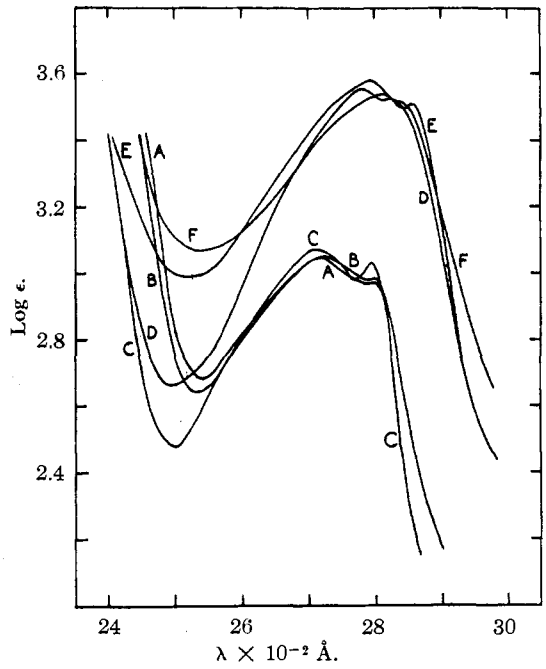


Fig. 1.—A, Tetrahydrocannabidiol dimethyl ether (I or II); B, 2-(3′-menthyl)-1,3-dimethoxy-5-methylbenzene (IV); C, 2-(3′-menthyl)-1,3-dimethoxybenzene (III); D, 4-(3′-menthyl)-1,3-dimethoxybenzene (V) prepared by Suter's method; E, 4-(3′-menthyl)-1,3-dimethoxybenzene (V) prepared by lithium condensation; F, 4-(3′-menthyl)-1,3-dimethoxy-5-methylbenzene (VI).

Compound V was made in an analogous manner from 4-lithium-1,3-dimethoxybenzene (4-lithium resorcinol dimethyl ether) by the action of phenyllithium on 4-bromo-1,3-dimethoxybenzene. This latter substance was synthesized by the following series of reactions: resorcinol dimethyl ether → 4,6-dibromoresorcinol dimethyl ether → 4-bromo-6-lithium resorcinol dimethyl ether → 4-bromoresorcinol dimethyl ether → 4-lithium resorcinol dimethyl ether.[4b]

Compound V was synthesized also by a second procedure. Using the method of condensation of resorcinol with cyclohexanols described by Suter and Smith,[6] a compound, 4-(3′-menthyl)-1,3-dihydroxybenzene, was prepared by condensing resorcinol with *l*-menthol. Methylation gave a dimethyl ether which had the same b. p. and index of refraction as this compound prepared as previously described. Its rotation, however, differed from the compound obtained by condensing 4-lithium resorcinol dimethyl ether with *l*-menthone followed by dehydration and reduction and this difference must be accounted for by the relative configurations of the asymmetric carbons due to the dissimilar procedures used. Moreover, a difference in the absorption spectra of the two preparations was observed (compare D and E) possibly due to the same cause.

Compound VI could not be successfully synthesized from 4-bromoorcinol dimethyl ether. Several attempts failed. However, it was formed by the direct condensation of orcinol and *l*-menthol in the presence of phosphoric acid followed by methylation.

The methods of synthesis used for compounds III–V are applicable not only to the eventual synthesis of tetrahydrocannabidiol dimethyl ether but also to the formation of molecules in which one or two double bonds are present in the menthyl residue. It is possible that cannabidiol dimethyl ether might be synthesized through this route.

Tetrahydrocannabidiol dimethyl ether was prepared by reduction of cannabidiol dimethyl ether with platinum oxide catalyst in glacial acetic acid at ordinary pressure.

Experimental

A very convenient form of apparatus (devised by Hans Wolff) for preparing and reacting lithium compounds is shown in Fig. 2. The apparatus consists of flask A in which the phenyllithium or butyllithium is formed, and flask B in which the lithium exchange reaction occurs. Subsequent condensation with the selected reactant is also

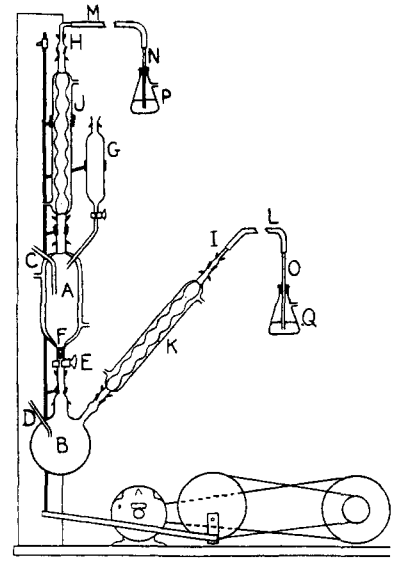


Fig. 2.

(5) Herzig and Wenzel, *Monatsh.*, **24**, 897 (1903).
(6) Suter and Smith, THIS JOURNAL, **61**, 166 (1939).

carried out in flask B. Flasks A and B are connected to each other by a ground glass joint. C and D are gas inlets through which dry oxygen-free nitrogen is passed into A or B. Flask A is surrounded by a jacket through which either cold water or steam may be passed when desired. By immersing flask B in an oil-bath, the mixture therein can be heated. Efficient agitation when desired is rendered possible by attachment of the complete apparatus to a shaking machine.

In order to separate the small residue of unreacted lithium when the butyllithium or phenyllithium passes through the stopcock E from flask A into flask B, a small amount of glass wool F is placed on top of the stopcock (at least 2 mm. bore in order to prevent clogging by the lithium halide formed in the reaction). Through separatory funnel G the butyl or phenyl halides are added. Glass tubes H and I are attached with ground joints to the top of condensers J and K. In order to secure flexibility during agitation, rubber tubes L and M are connected on the one side to glass tubes H and I and on the other to glass tubes N and O. The latter lead to mercury traps P and Q which permit the reaction to be carried out under slight nitrogen pressure.

A description of the preparation of 2-(3'-hydroxy-3'-menthyl)-1,3-dimethoxybenzene will serve to clarify in detail how the apparatus is employed.

2-(3'-Hydroxy-3'-menthyl)-1,3-dimethoxybenzene (VIII).—Into flask A was run 20 cc. of dry ether through separatory funnel G. A vigorous stream of dry oxygen-free nitrogen was passed through C into flask A. The condenser J was detached and 1.52 g. of lithium (pressed and washed with dry ether and cut under nitrogen–ether atmosphere) was introduced into flask A, then the condenser J replaced. A solution of 9.2 g. of *n*-butyl chloride in 30 cc. of dry ether was placed in separatory funnel G. A third of this solution was added at once to flask A and the apparatus agitated. The reaction usually started in two to three minutes with evolution of heat and the appearance of cloudiness in the solution. The remainder of the butyl chloride solution was then added slowly (during thirty minutes). Agitation was continued for another hour after which time only a very small amount of lithium was unreacted.

A nitrogen stream was passed into flask B, stopcock E then was opened and the ether solution of butyllithium allowed to flow from A into B. Agitation sometimes was necessary at this point to loosen the precipitated salt in A in order to allow the influx of the solution.

Stopcock E then was almost completely closed. The tube I attached to the condenser K was removed temporarily and replaced by a separatory funnel with ground joint. A solution of 13.8 g. of resorcinol dimethyl ether[7] in 30 cc. of dry ether then was introduced all at once through this separatory funnel, which was then removed and replaced by the glass tube I leading through L and O to the mercury trap Q. The stopcock E now was closed completely and the mixture shaken for one hour.

Stopcock E again was opened just slightly and a solution of 16 g. of *l*-menthone in 20 cc. of dry ether was added dropwise with agitation of the apparatus from the same separatory funnel used for the addition of the resorcinol dimethyl ether. The reaction took place with evolution of sufficient heat to reflux the ether. After fifteen minutes, flask B was disconnected from flask A, from condenser K, and from gas inlet D. The contents were poured into a beaker containing 200 g. of ice water.

The two layers were separated and the aqueous layer was extracted several times with ether. The ether extracts were washed with water containing 3 cc. of glacial acetic acid, and then with water. After drying over anhydrous magnesium sulfate, the ether was evaporated and the residue distilled under reduced pressure. A small carborundum column was used. The fraction b. p. 142–168° (4 mm.) was collected; yield 7.1 g. On adding to this distillate a small amount of ethanol and scratching, a crystalline compound separated. It was recrystallized several times from boiling ethanol to which just enough water was added to effect a slight cloudiness which disappeared on addition of a few drops of ethanol; white crystals, m. p. 59–60° (cor.).

Anal. Calcd. for $C_{18}H_{28}O_3$: C, 73.92; H, 9.67. Found: C, 73.63; H, 9.79. *Rotation.* 0.0437 g. made up to 5 cc. with 95% ethanol at 27° gave α_D −0.15°; *l*, 1; $[\alpha]^{27}D$ −17°.

2-(3'-Menthen-3',4'-yl)-1,3-dimethoxybenzene (VII).—The pure carbinol just described or the fraction from which the carbinol was obtained was heated with a small amount of fused potassium acid sulfate at 140–160° (bath temperature) for about one hour (until no more water was evolved) and distilled, b. p. 123–125° (2 mm.). On crystallization from 80% ethanol, white crystals resulted, m. p. 88° (cor.). The yield was essentially quantitative.

Anal. Calcd. for $C_{18}H_{26}O_2$: C, 78.77; H, 9.55. Found: C, 78.87; H, 9.48. *Rotation.* 0.0417 g. made up to 5 cc. with 95% ethanol at 27° gave α_D +0.24°; *l*, 1; $[\alpha]^{27}D$ +29°.

2-(3'-Menthyl)-1,3-dimethoxybenzene (III).—A solution of 1.54 g. of 2-(3'-menthen-3',4'-yl)-1,3-dimethoxybenzene in 50 cc. of glacial acetic acid was treated with 50 mg. of platinum oxide catalyst. Reduction was carried out at atmospheric pressure; hydrogen was absorbed readily (about two hours). After filtration, the glacial acetic acid was evaporated *in vacuo*. On addition of methanol and a few drops of water and on cooling to −20°, the oily residue crystallized. The compound was recrystallized several times from 90% methanol, m. p. 46° (cor.).

Anal. Calcd. for $C_{18}H_{28}O_2$: C, 78.20; H, 10.22. Found: C, 78.31; H, 10.43. *Rotation.* 0.0475 g. made up to 5 cc. with 95% ethanol at 26° gave α_D −0.42; *l*, 1; $[\alpha]^{26}D$ −45°.

1,3-Dimethoxy-5-methylbenzene (Orcinol Dimethyl Ether).—To 45 g. of orcinol dissolved in 250 cc. of methanol 18 g. of sodium was added slowly and the mixture refluxed for twenty minutes. Through the top of the reflux condenser, 100 g. of dimethyl sulfate was added very cautiously from a dropping funnel. Enough dimethyl sulfate was added to obtain a color change from deep yellow to light yellow, and then a 30% aqueous sodium hydroxide solution until the solution was alkaline. The addition of dimethyl sulfate and sodium hydroxide was repeated alternately. To the final alkaline solution, water was added. The orcinol dimethyl ether was extracted with ether, the ether washed with sodium hydroxide solution, dried and distilled, b. p. 110–112° (17 mm.); yield 48 g.

(7) Flood and Nieuwland, THIS JOURNAL, **60**, 2566 (1928).

(87%). This procedure is far more satisfactory than that described by Ludwinowsky and Tambor.[8]

2 - (3' - Hydroxy - 3' - menthyl) - 1,3 - dimethoxy - 5-methylbenzene.—This compound was prepared in a manner similar to 2-(3'-hydroxy-3'-menthyl)-1,3-dimethoxybenzene. To phenyllithium prepared from 1.52 g. of lithium and 15.2 g. of bromobenzene in 80 cc. of dry ether was added 15.2 g. of orcinol dimethyl ether in 50 cc. of dry ether. After three hours of shaking, 16 g. of *l*-menthone in 30 cc. of dry ether was added and the product isolated in the manner previously described, yield 8 g. The carbinol was in the fraction boiling above 156° (2 mm.). After several crystallizations from ethanol containing enough water to allow crystallization, white crystals were obtained, m. p. 66.5°.

Anal. Calcd. for $C_{19}H_{30}O_3$: C, 74.46; H, 9.88. Found: C, 74.80; H, 10.04. *Rotation.* 0.0209 g. made up to 5 cc. with 95% ethanol at 27° gave α_D −0.07°; *l*, 1; $[\alpha]^{27}D$ −17°.

2 - (3' - Menthen - 3',4' - yl) - 1,3 - dimethoxy - 5-methylbenzene.—The carbinol or the mixture from which the carbinol was obtained was dehydrated with a little potassium acid sulfate. The product boiled at 132–133° (2 mm.). It was crystallized from methanol, white crystals, m. p. 103.5–104° (cor.).

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.14; H, 9.79. Found: C, 79.07; H, 9.83. *Rotation.* 0.0468 g. made up to 5 cc. with 95% ethanol at 28° gave α_D +0.38°; *l*, 1; $[\alpha]^{28}D$ +40°.

2 - (3' - Menthyl) - 1,3 - dimethoxy - 5 - methylbenzene (IV).—Hydrogenation of 2-(3'-menthen-3',4'-yl)-1,3-dimethoxy-5-methylbenzene was carried out with platinum oxide catalyst and glacial acetic acid at atmospheric pressure (about two hours). The resulting compound was crystallized from methanol containing some water; white crystals, m. p. 60–61° (cor.).

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.55; H, 10.42. Found: C, 78.31; H, 10.32. *Rotation.* 0.0459 g. made up to 5 cc. with 95% ethanol at 28° gave α_D −0.33°; *l*, 1; $[\alpha]^{28}D$ −36°.

2,6-Dimethoxy-4-methylbenzoic Acid.—To butyllithium prepared from 0.84 g. of lithium and 5.5 g. of *n*-butyl chloride, 7.6 g. of 1,3-dimethoxy-5-methylbenzene (orcinol dimethyl ether) was added. After shaking for fifteen minutes a large excess of finely powdered dry-ice was cautiously added. When the mixture reached room temperature, 100 cc. of dilute sulfuric acid was added and the product was extracted with ether. The ether was evaporated and the residue dissolved in 15% aqueous sodium hydroxide. After washing several times with ether, the alkaline solution was acidified. White crystals precipitated which were purified by recrystallization from dilute ethanol, m. p. 178–179° (cor.); yield 2.6 g. The melting point previously was reported as 178°.[5]

4 - (3' - Hydroxy - 3' - menthyl) - 1,3 - dimethoxybenzene.—4,6-Dibromoresorcinol dimethyl ether was prepared by bromination of resorcinol dimethyl ether,[9] yield 81% of purified product, m. p. 138–140°. Conversion of the dibromo derivative to 4-bromoresorcinol dimethyl ether and then to 4-lithium resorcinol dimethyl ether was carried out according to the general procedure of Wittig.[4]

To phenyllithium prepared from 2.8 g. of lithium and 31.3 g. of bromobenzene in 150 cc. of dry ether (time of preparation, one and one-half hours) was added 32.5 g. of monobromoresorcinol dimethyl ether. After forty minutes, 30 g. of *l*-menthone in 50 cc. of ether was introduced. The mixture was decomposed with ice water, the ether layer washed with water containing a few drops of glacial acetic acid and then with pure water. The ether solution was dried over anhydrous magnesium sulfate and distilled. The product b. p. 145–148° (2 mm.) was collected: $n^{20}D$ 1.5292; yield 37 g. (86% based on 4-bromoresorcinol dimethyl ether).

Anal. Calcd. for $C_{18}H_{28}O_3$: C, 73.92; H, 9.67. Found: C, 74.30; H, 9.67. *Rotation.* 0.107 g. made up to 5 cc. with 95% ethanol at 27° gave α_D −22°; *l*, 1; $[\alpha]^{27}D$ −10.3°.

4 - (3' - Menthen - 3',4' - yl) - 1,3 - dimethoxybenzene.—The pure carbinol was dehydrated with potassium acid sulfate. The product had a b. p. of 140–142° (2 mm.); $n^{20}D$ 1.5345.

Anal. Calcd. for $C_{18}H_{26}O_2$: C, 78.77; H, 9.55. Found: C, 78.87; H, 9.58. *Rotation.* 0.0476 g. made up to 5 cc. with 95% ethanol at 25° gave α_D +50°; *l*, 1; $[\alpha]^{25}D$ +52°.

4-(3'-Menthyl)-1,3-dimethoxybenzene.—A. The reduction of 2.41 g. of 4-(3'-menthen-3',4'-yl)-1,3-dimethoxybenzene was carried out with platinum oxide catalyst in glacial acetic acid at room temperature. After one mole of hydrogen was absorbed, which took six hours, the material was distilled; b. p. 142–145° (2 mm.), $n^{20}D$ 1.5215. It showed no optical rotation.

Anal. Calcd. for $C_{18}H_{28}O_2$: C, 78.20; H, 10.22. Found: C, 78.38; H, 10.08.

4-(3'-Menthyl)-1,3-dihydroxybenzene.—To a solution of 55 g. of resorcinol (0.5 mole) in 125 g. of 85% phosphoric acid heated at 140° (oil-bath temperature), was added with mechanical stirring 78 g. of *l*-menthol (0.5 mole) in 110 g. of phosphoric acid previously heated together on a steam cone. The addition took forty-five minutes. Stirring and heating at 140° was continued for three hours, after which 300 cc. of water was added and the mixture extracted with benzene. The benzene was extracted with a 15% aqueous sodium hydroxide solution; the alkaline layer was acidified with dilute sulfuric acid and extracted with benzene. The solvent was evaporated and the product distilled, yield 45 g. The distillate was refractionated; the main fraction boiled 188–190° (2 mm.); $n^{20}D$ 1.5451.

Rotation. 0.0365 g. made up to 5 cc. with 95% ethanol at 25° gave α_D −0.05°; *l*, 1; $[\alpha]^{25}D$ −6.9°.

4-(3'-Menthyl)-1,3-dimethoxybenzene.—B. To 8 g. of the dihydroxy compound just described in 150 cc. of methanol, 3.4 g. of sodium was added slowly and the mixture refluxed. Through the reflux condenser 20 g. of dimethyl sulfate was added gradually from a dropping funnel. On further addition of a small amount of dimethyl sulfate, the reaction mixture turned acid (color change). Sufficient 30% aqueous sodium hydroxide solution was added to render the solution alkaline, and dimethyl sulfate again was introduced. Finally, sodium hydroxide was added in

(8) Ludwinowsky and Tambor, *Ber.*, **39**, 4039 (1906).
(9) Hönig, *ibid.*, **11**, 1041 (1878).

excess; the methylation was complete when the alkaline solution was only light yellow. Water was introduced, the mixture extracted with ether, the ether layer washed three times with 10% sodium hydroxide solution, dried and distilled, b. p. 143–156° (2 mm.). The distillate was fractionated and the main fraction boiled 143–145° (2 mm.), $n^{20}D$ 1.5210.

Anal. Calcd. for $C_{18}H_{28}O_2$: C, 78.20; H, 10.22. Found: C, 78.17; H, 10.18. *Rotation.* 0.0428 g. made up to 5 cc. with 95% ethanol at 26° gave αD −0.05°; *l*, 1; $[\alpha]^{26}D$ −5.8°.

4 - (3′ - Menthyl) - 1,3 - dihydroxy - 5 - methylbenzene.—The procedure used was similar to that for preparing 4-(3′-menthyl)-1,3-dihydroxybenzene. From 31 g. of orcinol, 65 g. of phosphoric acid (85%) and 39 g. of *l*-menthol was obtained the product, b. p. 188–190° (2 mm.); $n^{20}D$ 1.5545, yield 7 g.

Rotation. 0.0845 g. made up to 5 cc. with 95% ethanol at 28° gave αD −0.20°; *l*, 1; $[\alpha]^{28}D$ −16°.

4-(3′-Menthyl)-1,3-dimethoxy-5-methylbenzene (VI).—The dihydroxy compound was methylated in a similar way to the corresponding resorcinol derivative. The product had a b. p. 167–169° (2 mm.); $n^{20}D$ 1.5238; yield, 2.5 g. of dimethyl ether from 3.2 g. of dihydroxy compound.

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.55; H, 10.42. Found: C, 77.50; H, 9.62. *Rotation.* 0.0861 g. made up to 5 cc. with 95% ethanol at 28° gave αD −0.25°; *l*, 1; $[\alpha]^{28}D$ −14.5°.

Cannabidiol Dimethyl Ether.—The following preparation of this compound is superior to that previously described[1c] in that it is less tedious and also gives a purer product as indicated by a spread of only 0.0004 unit between the refractive indices of the first and last of seven fractions cut arbitrarily in the course of the distillation.

A solution of 14.78 g. of cannabidiol in 100 cc. of acetone was treated with 25 g. of anhydrous potassium carbonate and 20 g. (3 moles) of methyl iodide. The mixture was refluxed for five days, poured into 500 cc. of water, and extracted with three 100-cc. portions of petroleum ether (b. p. 30–60°). The solvent was evaporated and the product distilled at 2 mm. The product, which weighed 15.16 g., was treated with the same amounts of reagents mentioned above and refluxed for two days longer. Cannabidiol dimethyl ether was isolated from the reaction mixture as described above and distilled, b. p. 168–170° (2 mm.) (bath temperature 190–200°); yield 13.88 g., $n^{20}D$ 1.5243.

Rotation. 0.0525 g. made up to 5 cc. with 95% ethanol at 28° gave αD −1.51°; *l*, 1; $[\alpha]^{28}D$ −144°.

Tetrahydrocannabidiol Dimethyl Ether.—A solution of 6.07 g. of cannabidiol dimethyl ether in 150 cc. of glacial acetic acid was reduced with hydrogen at 2–3 atm. pressure using 0.1 g. of platinum oxide. Hydrogen corresponding to 2.03 moles per mole of cannabidiol dimethyl ether was absorbed in thirty minutes, after which no pressure change was noted in an additional twenty-five minutes.

The acetic acid was removed *in vacuo* and the tetrahydrocannabidiol dimethyl ether, an almost colorless viscous oil, was distilled, b. p. 167–170° (2.5 mm.) (bath temperature 180–190°); yield 5.12 g.; $n^{20}D$ 1.5109; d^{20}_4 0.9618.

Anal. Calcd. for $C_{21}H_{32}(OCH_3)_2$: C, 79.71; H, 11.05; OCH_3, 17.91. Found: C, 79.58; H, 11.00; OCH_3, 18.18. *Rotation.* 0.0573 g. made up to 5 cc. with 95% ethanol at 29° gave αD −0.34°; *l*, 1; $[\alpha]^{29}D$ −30°.

Summary

1. The absorption spectrum of tetrahydrocannabidiol dimethyl ether was shown to be very similar to that of 2-(3′-menthyl)-1,3-dimethoxybenzene and of 2-(3′-menthyl)-1,3-dimethoxy-5-methylbenzene but different from that of 4-(3′-menthyl)-1,3-dimethoxybenzene and 4-(3′-menthyl)-1,3-dimethoxy-5-methylbenzene. It was concluded, therefore, that the menthyl residue in tetrahydrocannabidiol dimethyl ether was linked to the olivetol between the methoxyl groups.

2. The synthetic compounds were prepared by unequivocal methods. The 2-lithium resorcinol or orcinol dimethyl ethers were condensed with menthone. The tertiary alcohols thus produced were dehydrated to the corresponding olefins and the olefins reduced with platinum oxide and hydrogen.

3. In a similar manner 4-lithium resorcinol dimethyl ether was converted to 4-(3′-menthyl)-1,3-dimethoxybenzene. This compound and the 4-(3′-menthyl)-1,3-dimethyl-5-methylbenzene were also made by direct condensation of *l*-menthol and resorcinol or orcinol followed by methylation.

4. Tetrahydrocannabidiol dimethyl ether was prepared by the reduction of cannabidiol dimethyl ether in glacial acetic acid with platinum oxide catalyst.

URBANA, ILLINOIS RECEIVED MAY 16, 1940