recovered. The sirupy residue, pale reddish-brown in color, was transferred to a beaker, and placed in the refrigerator for one day. Since no solid appeared, the viscous mass was dissolved in warm 99% ethyl alcohol. The solution was allowed to cool slowly to room temperature, and then placed in the refrigerator. After three days a precipitate was present. This was filtered off and washed with cold alcohol; yield, 6.78 g. After two recrystallizations from 95% ethyl alcohol the product melted at 75.0–75.5°. This compound was presumably diethyl α,β-diphenylglutarate (compound V).

Anal.[16] Calcd. for $C_{21}H_{24}O_4$: C, 74.12; H, 7.06. Found: C, 74.12; H, 6.89.

On hydrolysis with 5% aqueous potassium hydroxide (to which several cc. of ethyl alcohol was added) for eight hours the ester gave a good yield (90%) of the corresponding acid. Neutral equivalent of the acid, calcd. for $C_{17}H_{16}O_4$: 142. Found: 143. The crude acid melted at 192.5–197.5°. The melting points obtained after crystallization from various solvents were as follows: from a mixture of 10% ethanol and 90% water, 195.5–197.5°; from a mixture of 90% ligroin (90–120°) and 10% ethanol, 196.5–197.5°; from a small quantity of absolute ethanol, 207.5–218.5°, with considerable decomposition.

Borsche[7a] reported the melting point of the diethyl glutarate (prepared from ethyl phenylacetate and ethyl cinnamate in the presence of sodium ethoxide) as 92–93°; presumably this was a diastereoisomeric form of the ester obtained by us. The ester obtained by Borsche gave on hydrolysis an acid melting at 230–231°. Meerwein[17] prepared this acid by a different method and found that, by crystallization, several materials could be obtained; one melted at 203–204°, another at 215–224°, and still another at 230–231°.

(16) Microanalysis by Arlington Laboratories, Arlington, Va.

Summary

1. A study has been made of the possibility of using certain simple esters in the Michael type of condensation.

2. It has been found that when a mixture of ethyl acetate and benzalacetophenone is added to sodium triphenylmethyl in ether solution, the ester first undergoes self-condensation (Claisen type) to give acetoacetic ester which then condenses with the benzalacetophenone (Michael type).

3. Both ethyl isobutyrate and ethyl phenylacetate with ethyl cinnamate, on the other hand, give the direct Michael condensation. This reaction is effected either by sodium ethoxide or by sodium triphenylmethyl.

4. The mechanism of these condensations is discussed.

(17) Meerwein, *J. prakt. Chem.*, **97**, 274 (1918).

DURHAM, N. C. RECEIVED APRIL 10, 1940

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

The Preparation of Cholestanol Glucosides with All Four Possible Configurations of the Glucoside Link

BY R. P. LINSTEAD

The view has recently been advanced[1] that the capacity for glucoside formation of the characteristic steroid hydroxyl group (C_3) is profoundly affected by the stereochemical configuration. Miescher and Fischer[1] report that they were unable to prepare glucoside derivatives from *epi*-cholestanol, *epi*-coprostanol or from *epi*-androsterone, whereas isomeric steroids with the normal β-configuration at C_3 yielded glucosides in agreement with previous work.[2] From these results Miescher and Fischer have suggested that the capacity for glucoside formation runs parallel to the ability of steroids to form insoluble digitonides. They have also drawn certain inferences concerning the orientation of the C_3 hydroxyl group with respect to the angular methyl group at C_{10}. These have been criticized by Ruzicka.[3] In the writer's opinion these attempts to orientate the groups at C_3 with those at the neighboring bridgeheads by methods based on steric hindrance are of doubtful value in the present state of our knowledge.

Apart, however, from the debatable question of the interpretation of the facts, there were certain indications that the experimental results might be incorrect. First, among the heart poisons, isomeric glycosides are known with both normal and *epi*-configurations at C_3. Secondly, Dane and Brady[4] have prepared the glycoside of desoxycholic acid which has the *epi*-configuration at C_3. Miescher and Fischer have suggested that Dane and Brady's glucoside involved combination at C_{12} and not at C_3. Thirdly, there is no general

(1) Miescher and Fischer, *Helv. Chim. Acta*, **21**, 336 (1938).

(2) Salway, *J. Chem. Soc.*, **103**, 1026 (1913); MacCorquodale, Steenbock and Adkins, THIS JOURNAL, **52**, 2512 (1930); Lettré and Hagedorn, *Z. physiol. Chem.*, **242**, 210 (1936).

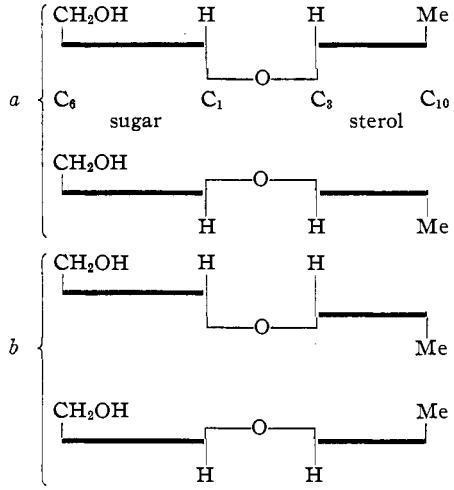
(3) Ruzicka, Furter and Goldberg, *Helv. Chim. Acta*, **21**, 498 (1938).

(4) Dane and Brady, *Z. physiol. Chem.*, **244**, 241 (1936).

reason to expect an abrupt difference in the ease of acetal formation between two epimerides which are esterified with about equal readiness.[5]

In connection with an investigation of cardiac glycosides, now in progress, the writer has re-examined the formation of glucosides from the two cholestanols. It is found that under suitable experimental conditions both the normal and *epi*-forms readily yield glucosides. Miescher and Fischer's suggestion is therefore untenable. Since this work was completed, Gillespie, Macbeth and Mills[6] have described the formation of tetraacetyl β-glucosides from a number of epimeric pairs of alcohols of the cyclohexane series. From these results and those now reported it may be concluded that *there is no evidence of a connection between the configuration of a cyclic alcohol and its capacity for glucoside formation.*

The glucoside link of the cholestanol glucosides connects two asymmetric carbon atoms. Four stereoisomeric modifications are possible, the configurations of which are represented diagrammatically below



[a] First pair: H and Me of sterol *cis*-. [b] Second pair: H and Me of sterol *trans*-. The broad line on the left represents the glucopyranose ring, that on the right ring A of the sterol. The glucoside oxygen is oriented with respect to the CH_2OH at C_5 of the sugar and the angular methyl at C_{10} of the sterol.

All four glucosides have been prepared, both in the free state and as their beautifully crystalline tetraacetyl derivatives. The two α-tetraacetyl glucosides were made by Zemplén's method,[7] the two β-forms by the Helferich–Evans modification[8,9] of the usual silver oxide procedure. The tetraacetyl β-glucoside of cholestanol was also prepared following Miescher and Fischer.[1] The free glucosides were obtained by hydrolysis with barium hydroxide. Their structure was confirmed by hydrolysis to the parent sterol and glucose. Their properties are summarized in Table I.

TABLE I

	Free glucoside M. p., °C.	$[\alpha]_D$ in pyridine	Tetraacetyl derivative M. p., °C.	$[\alpha]_D$ in $CHCl_3$
α-Glucoside of cholestanol	253 dec.	+ 94	184	+114
β-Glucoside of cholestanol	270 dec.	− 17	175	+ 5
α-Glucoside of *epi*-cholestanol	219	+106	130	+ 93
β-Glucoside of *epi*-cholestanol	217	+ 1	174	− 3

The prefixes α- and β- are applied to the glucosides in accordance with Hudson's convention. The prefix β- for normal cholestanol is not used in this paper to avoid confusion. The absolute configurations are unknown. The specific rotations of the eight compounds exhibit a regularity, there being a difference of approximately 100° between the values for the α- and β-forms of each pair.

The yields of acetyl glucosides (both α- and β-forms) from *epi*-cholestanol were very little lower than those from cholestanol under the same conditions, but the *epi*-derivatives were considerably more difficult to isolate. The tetraacetyl α-glucoside of *epi*-cholestanol gave particular trouble owing, apparently, to ready deacetylation, and a triacetyl derivative was isolated from the crude reaction product. The acetyl glucosides of *epi*-cholestanol are much more soluble in organic solvents than are the corresponding derivatives of cholestanol, and tend to form gels. There is a similar difference between the solubilities of the free glucosides, and it is possible to separate cholestanol from *epi*-cholestanol by taking advantage of this. The large effect on the solubility brought about by a small configurational change in a compound of high molecular weight (550) is noteworthy. The results fall into line with Noller's recent demonstration[10] that the basis of the digitonin precipitation method lies not in the fact that *epi*-compounds do not form digitonides but that their derivatives are more soluble than those of the corresponding normal (β-) compounds.

(5) Vavon and Jakubowicz, *Bull. soc. chim.*, [4] **53**, 581 (1933).
(6) Gillespie, Macbeth and Mills, *J. Chem. Soc.*, 243 (1940).
(7) Zemplén and Gerecs, *Ber.*, **63**, 2720 (1930).
(8) Helferich and Klein, *Ann.*, **450**, 219 (1926); Helferich, Bohn and Winkler, *Ber.*, **63**, 989 (1930).
(9) Reynolds and Evans, THIS JOURNAL, **60**, 2559 (1938).
(10) Noller, *ibid.*, **61**, 2717 (1939).

Experimental[11]

Materials.—Cholestanol and *epi*-cholestanol were prepared by Ruzicka's modification[12] of Vavon's method.[5] The specific rotations of the pure anhydrous sterols (two separate preparations of each[13]) are shown below:

Sample	Cholestanol A	Cholestanol B	*Epi*-Cholestanol A	*Epi*-Cholestanol B
Concn.	1.45	4.03	5.94	1.92	5.25
Temp., $t°$	25.2	26.6	24.3	26.5	25.4
$[\alpha]_D^{t°a}$	+23	+22	+20	+27	+25

[a] Determined in pure chloroform, 2-dm. tube.

The previously recorded values are: for cholestanol,[14] $[\alpha]^{22}D$ +28.8 (in ether, $C = 4$); and for *epi*-cholestanol[15] $[\alpha]^{15}D$ +33.95 (solvent not stated, $C = 0.32$). The lower values now found were not due to contamination of the samples with cholesterol, for their melting points were correct (cholestanol, 142°; *epi*-cholestanol, 187°), and they showed no Liebermann–Burchard reaction and did not decolorize bromine in chloroform. α-Tetraacetylbromoglucose was prepared by the methods of Freudenberg[16] and of Levene and Raymond,[17] which were about equally convenient.

α-Glucoside of Cholestanol.—A mixture of cholestanol (3.00 g., dried at 100°), tetraacetylbromoglucose (3.18 g., 1 equiv.), 1.17 g. of mercuric acetate (5% deficiency; dried over phosphorus pentoxide) and 35 cc. of dry benzene was refluxed for three hours with exclusion of water. The bulk of the solvent was then removed and the crystalline mass was washed with small quantities of dry ether until free from colored and sticky impurities. The residue was the almost pure tetraacetyl glucoside, m. p. 177–179°, 2.19 g. (40%). Two crystallizations from absolute alcohol yielded the pure **tetraacetyl-α-glucoside of cholestanol** as bold stellate clusters of transparent prismatic needles; m. p. 183.5–184°.

Anal. Calcd. for $C_{41}H_{66}O_{10}$: C, 68.5; H, 9.3. Found: C, 68.5; H, 9.3. *Rotation.* 211.5 mg. dissolved in 25 cc. of chloroform gave a rotation of +1.92° at 25.3°; *l*, 2 dm.; $[\alpha]^{25.3}D$ +114, $C = 0.846$.

The tetraacetyl glucoside was soluble to *ca.* 2.5% in boiling alcohol, almost insoluble in the cold. It gave a positive Molisch reaction, negative Liebermann–Burchard reaction and failed to reduce boiling Fehling solution.

A solution of the tetraacetate (1.00 g.) in 75 cc. of hot alcohol was treated with 40 cc. of approximately 0.2 *N* barium hydroxide. After nineteen hours at room temperature the product was acidified with very dilute hydrochloric acid. The solid glucoside was washed with dilute acid and water, dried and crystallized from pyridine. The **α-glucoside of cholestanol** formed fine silky needles, insoluble in water and the usual organic solvents except pyridine: m. p., indefinite, about 253° with decompn., after preliminary sintering and darkening, yield, almost quantitative.

Anal. Calcd. for $C_{33}H_{58}O_6$: C, 71.9; H, 10.6. Found: C, 71.5; H, 10.7. *Rotation.* 316.4 mg. dissolved in 25 cc. of pyridine gave a rotation of +2.38° at 26.7°; *l*, 2 dm.; $[\alpha]^{26.7}D$ +94; $C = 1.267$.

The glucoside (110 mg.) was re-acetylated by refluxing it for thirty minutes with the same weight of anhydrous sodium acetate and 6 cc. of acetic anhydride. Dilution of the product with water yielded leaflets of the tetraacetate, identical with that described above.

The free glucoside (410 mg.) was refluxed for sixteen hours with a mixture of 11 cc. of alcohol, 0.5 cc. of hydrochloric acid and 0.5 cc. of water. The clear solution so obtained was treated with aqueous alkali until only barely acid, and the alcohol was boiled off. The solid which separated from the cold solution was extracted with ether and identified as cholestanol by m. p. and mixed m. p. (142°). The glucose in the aqueous solution was identified as the osazone.

β-Glucoside of Cholestanol.—The reaction was performed in a 3-necked flask fitted with a Hershberg stirrer, reflux condenser, dropping funnel and drying tube. A mixture of cholestanol (3.00 g.), silver oxide[8] (2.00 g.), anhydrous calcium sulfate (7.5 g.) and alcohol-free chloroform (15 cc.) was stirred at room temperature for an hour. Iodine (1 g.) was then added, followed by a solution of 3.18 g. of tetraacetylbromoglucose in 8 cc. of pure chloroform. Stirring was continued for twenty-three hours at room temperature and finally for an hour at the boiling point. The product was left overnight, filtered through charcoal and freed from solvent under reduced pressure. The residue was stirred with dry ether (50 cc.) and the white solid (3.40 g.) collected, and washed with a little dry ether. One crystallization from absolute alcohol gave bold transparent prismatic needles of the **tetraacetyl-β-glucoside of cholestanol**; m. p. 175°, yield 3.10 g. (56%). The compound closely resembled the tetraacetyl derivative of the α-glucoside in solubility, crystalline form and color reaction. A mixture of the two melted at 155–158°.

*Anal.** Calcd. for $C_{47}H_{66}O_{10}$: C, 68.5; H, 9.3. Found: C, 68.9; H, 9.5. *Rotation.* 237.6 mg. dissolved in 25 cc. of chloroform gave a rotation of +0.09° at 24.7°; *l*, 2 dm.; $[\alpha]^{24.7}D$ +5; $C = 0.95$. A quantitative hydrolysis gave: % acetyl, 24.7; calcd. (4 CH_3CO), 23.9.

The same compound, m. p. and mixed m. p. 174°, was prepared by Miescher and Fischer's procedure. They report a yield of 51% of crude glucoside, and a m. p. of 174–175°.

Hydrolysis of the acetyl derivative (1.60 g.) with aqueous alcoholic barium hydroxide as described above for the α-isomeride gave the **β-glucoside of cholestanol**, yield 1.06 g. (86%). It crystallized from pyridine–alcohol in thin needles tending to felt. It slowly decomposed from 240° upward and the m. p. varied with the rate of heating. The highest value observed was *ca.* 270° (bath at 250°). The glucoside also could be crystallized from boiling acetone, in which it was very sparingly soluble.

*Anal.** Calcd. for $C_{33}H_{58}O_6$: C, 71.9; H, 10.6. Found: C, 71.2; H, 10.7.[18] *Rotation.* 252.1 mg. in 25 cc. of

(11) All melting points are corrected. The microanalyses marked with an asterisk were kindly carried out by Lyon Southworth.

(12) Ruzicka, Brüngger, Eichenberger and Meyer, *Helv. Chim. Acta*, **17**, 1407 (1934).

(13) I am indebted to Dr. W. S. Johnson for assistance in the preparation of the two cholestanols.

(14) Willstätter, *Ber.*, **41**, 2199 (1908).

(15) Windaus, *ibid.*, **47**, 2388 (1914).

(16) Freudenberg, Noë and Knopf, *ibid.*, **60**, 241 (1927).

(17) Levene and Raymond, *J. Biol. Chem.*, **90**, 247 (1931).

(18) Like many other glucosides the compound is difficult to obtain in the completely anhydrous state. For analysis it was dried at 100° (2 mm.) over phosphorus pentoxide.

pyridine gave a rotation of −0.35° at 24.4°; *l*, 2 dm.; $[\alpha]^{24.4}D$ −17; *C* = 1.08.

Re-acetylation of the glucoside yielded the same tetra-acetyl derivative, m. p. and mixed m. p. 174°, in excellent yield. Hydrolysis with aqueous alcoholic hydrochloric acid gave cholestanol (m. p. and mixed m. p. 141–142°) and glucose (osazone).

α-Glucoside of *epi*-Cholestanol.—The isolation of the pure tetraacetyl derivative of this glucoside gave considerably more trouble than did that of the other three isomerides. (i) The Zemplén condensation was carried out exactly as already described for cholestanol but, after preliminary experiments, the method of isolation of the acetyl glucoside was altered to the following. The product was freed from the bulk of the benzene, diluted with two volumes of ligroin (b. p. 90–120°) and allowed to stand overnight. The solution was filtered from the brown precipitate of mercury salt and freed from solvent under reduced pressure. The sticky residue was extracted with boiling petroleum ether (b. p. 30–60°) which left a small resin. The solution was filtered through charcoal and the solvent was removed. The residue (5.02 g.) was re-acetylated by boiling it for ninety minutes with 5 g. of anhydrous sodium acetate and 50 cc. of acetic anhydride. Dilution of the product gave a semi-solid mass, which was dissolved in alcohol, and the solution diluted with water. The solid so obtained was collected by filtration, washed with water and crystallized from alcohol (charcoal). This yielded a gel which slowly passed into a solid. The solid was the crude tetraacetyl glucoside, m. p. 110–117°, 2.43 g. After a number of crystallizations from alcohol the pure **tetraacetyl-α-glucoside** of *epi*-cholestanol was obtained as bold clusters of transparent prisms, m. p. 130°.

Anal. Calcd. for $C_{41}H_{66}O_{10}$: C, 68.5; H, 9.3. Found: C, 68.6; H, 9.5. *Rotation.* 200.1 mg. dissolved in 25 cc. of chloroform gave a rotation of +1.48 at 24.8°; *l*, 2 dm.; $[\alpha]^{24.8}D$ +92.5; *C* = 0.80.

The compound was insoluble in water, moderately soluble in the alcohols and sparingly soluble in petroleum ether. It depressed the m. p. (133°) of β-pentaacetyl-glucose and did not reduce Fehling solution. Its purification was made difficult by the great tendency of the slightly impure material to separate from the usual solvents as a gel. It is probable that the impurity was partly deacetylated material caused by very easy hydrolysis.

(ii) In an earlier preparation the crude reaction product was allowed to solidify without "re-acetylation." It was then separated into two portions by extraction with cold ligroin. The insoluble portion after crystallization from alcohol yielded the tetraacetyl derivative, m. p. 130°, described above. The ligroin solution gave a thick oil which solidified slowly and changed to a caseous solid when stirred with 90% alcohol. Crystallization from absolute alcohol (charcoal) gave fernlike clusters of opaque needles, m. p. 86–88° after previous softening. The substance depressed the m. p. of tetraacetylbromoglucose (89°), did not reduce Fehling solution, and gave a positive Molisch reaction. It has been identified as the **triacetyl α-glucoside of *epi*-cholestanol.**

*Anal.** Calcd. for $C_{39}H_{64}O_9$: C, 69.2; H, 9.5. Found: C, 69.0; H, 9.5.

It is possible that this compound was not obtained quite free from the tetraacetate. Its acetylation yielded the tetraacetyl derivative, m. p. (crude) 122–124°, mixed m. p. 124–126°.

(iii) Another method for the preparation of the pure tetra-acetate was to hydrolyze the gel-forming mixture, m. p. *ca.* 115° (see i above) with alcoholic aqueous barium hydroxide to the free glucoside. This was washed with water to remove glucose and with boiling petroleum ether to remove sterol. It was then reacetylated. The acetyl derivative after one crystallization from alcohol melted at 129°, and at 129–129.5° in admixture with the pure tetra-acetate.

The pure tetraacetate was hydrolyzed with alcoholic aqueous barium hydroxide and the free glucoside isolated as already described. The **α-glucoside of *epi*-cholestanol** was readily soluble in hot alcohol and crystallized on cooling in tufts of small needles, m. p. 219° without appreciable decomposition.

*Anal.** Calcd. for $C_{33}H_{58}O_6$: C, 71.9; H, 10.6. Found: C, 72.2; H, 10.7. *Rotation.* 68.4 mg. dissolved in 25 cc. of pyridine gave a rotation of +0.58° at 26.5°; *l*, 2 dm.; $[\alpha]^{26.5}D$ +106°; *C* = 0.27.

The pure glucoside also was obtained by hydrolyzing the crude gel-forming tetraacetate and crystallizing the product from alcohol. Hydrolysis of the free glucoside (80 mg.) with aqueous alcoholic hydrochloric acid yielded 50 mg. of *epi*-cholestanol, m. p. (crude) 184°, mixed m. p. 185°, together with glucose, identified as the osazone.

β-Glucoside of *epi*-Cholestanol.—The condensation was performed in exactly the same way as with cholestanol. After the removal of the chloroform a caseous solid was obtained which hardened on being extracted with cold petroleum ether (b. p. 20–40°). The residue when crystallized from ligroin (b. p. 90–120°) gave needles, m. p. *ca.* 166°. The extract deposited the same substance in a purer form (m. p. 169–171°). The combined yield of crystalline material was 2.5 g. from 3.0 g. of *epi*-cholestanol (45%). Two further crystallizations from ligroin (b. p. 90–120°) gave the pure **tetraacetyl-β-glucoside** of *epi*-**cholestanol**, long thin needles, felting when dry, m. p. 173°.

*Anal.** Calcd. for $C_{41}H_{66}O_{10}$: C, 68.5; H, 9.3. Found: C, 68.0; H, 9.3. *Rotation.* 291 mg. dissolved in 25 cc. of chloroform gave a rotation of −0.08° at 27.2°; *l*, 2 dm.; $[\alpha]^{27.2}D$ −3; *C* = 1.16.

This compound, either before or after crystallization from ligroin, formed a gel when attempts were made to crystallize it from alcohol. After two days the gel began to yield starfish-shaped crystals, the individual needles being curved owing to the strain from the contracting gel.

Hydrolysis of the tetra-acetate with aqueous alcoholic barium hydroxide as before yielded the free **β-glucoside** of *epi*-**cholestanol**. This was insoluble in water and ligroin, easily soluble in hot alcohol and cold pyridine. A concentrated solution in hot alcohol tended to form a gel on cooling. The substance was best crystallized by cautious addition of water to a dilute solution in alcohol or pyridine. It formed long hairy needles, m. p. 216–217° without decomposition. A mixture with the α-glucoside of *epi*-cholestanol melted at 205°.

*Anal.** Calcd. for $C_{33}H_{58}O_6$: C, 71.9; H, 10.6. Found: C, 71.3; H, 10.8.[13] *Rotation.* 245.5 mg. dissolved in 25

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

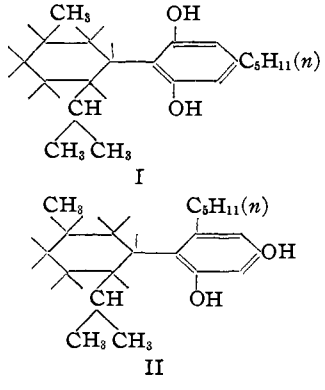
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

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.