[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE GLIDDEN COMPANY, SOYA PRODUCTS DIVISION]

Sterols. X. 17α-Hydroxyprogesterone

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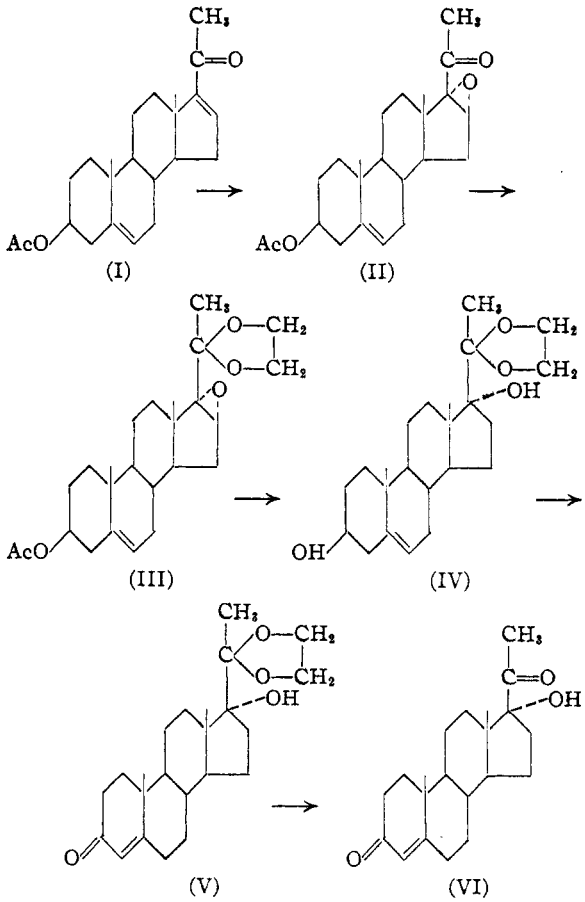
This paper reports the preparation of the first of a series of 17α-hydroxy steroids, the study of which has been under way in this Laboratory for several years.[1] 17α-Hydroxyprogesterone (VI), a naturally occurring hormone of the adrenal cortex, and first isolated therefrom by Pfiffner and North,[2] was chosen as the first objective, primarily for two reasons. It serves as an excellent model for a study of the introduction of the 17α-hydroxy group into pregnenes and pregnanes. Moreover, the intermediates in its preparation were to serve us as intermediates likewise in the preparation of its 21-hydroxy derivative, namely, 17α-hydroxy-11-desoxycorticosterone (Reichstein's Substance S).[3]

Two methods have been described for the partial synthesis of 17α-hydroxyprogesterone. The first of these by Hegner and Reichstein[4] is so involved and gives such poor yields that it can be considered only of academic and historical interest, albeit this excellent work afforded the first exhaustive insight into the chemical behavior of 17α-hydroxyprogesterone. The second synthesis, recently communicated in preliminary form by Kritchevsky and Gallagher,[5] appears to be more amenable to large-scale preparation; however, details are lacking for a critical analysis. Certainly the starting material, pregnan-3α-ol-20-one is not yet a readily available substance.

Recently we communicated a preliminary report[1a] outlining the essential features of a new method for the partial synthesis of 17α-hydroxy steroids. The preparation of 17α-hydroxypregnenolone (XII) from 5,16-pregnadien-3β-ol-20-one, now readily available from pregnenolone[1b] as well as from diosgenin, was described. This procedure, which is described in detail in the present communication, makes 17α-hydroxyprogesterone a readily available substance in quantity for the first time.

5,16-Pregnadien-3β-ol-20-one acetate (I) was treated at low temperature with one molar equivalent of bromine for protection of the 5,6-double bond and the resulting dibromide, after reaction with perbenzoic acid and debromination with zinc dust, afforded 16,17-oxido-5-pregnen-3β-ol-20-one acetate (II). On treatment of II with ethylene glycol in the presence of *p*-toluenesulfonic acid, the ethylene ketal (III) of 16,17-oxido-5-pregnen-3β-ol-20-one acetate was obtained. Reduction of III with lithium aluminum hydride yielded 5-pregnen-3β,17α-diol-20-one ethylene ketal (IV). Oppenauer oxidation of IV, followed by hydrolysis with dilute acid afforded 17α-hydroxyprogesterone (4-pregnen-17α-ol-3,20-dione) (VI). This surprisingly simple sequence of steps, although described in the experimental portion in small, laboratory preparations, has been carried out in batches of several hundred grams and, with care, results equivalent to or better than those described have been obtained.



6-Methoxy-16-*i*-pregnen-20-one (VIII), prepared from 5,16-pregnadien-3β-ol-20-one *p*-tosylate (VII), afforded an alternative method for protection of the 5,6-double bond. The 16-17-oxide (IX) was treated without isolation with dilute acid in dioxane to yield 16,17-oxido-5-pregnen-3β-ol-20-one (X). The latter, which was also obtained by bicarbonate hydrolysis of II, was converted by Oppenauer oxidation into a new

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(1) (a) For preliminary communication see Julian, Meyer and Ryden, THIS JOURNAL, **71**, 756 (1949); (b) also *cf.* Julian and Karpel, *ibid.*, **72**, 362 (1950).

(2) Pfiffner and North, *J. Biol. Chem.*, **132**, 459 (1940); **133**, lxxvii (1940); **139**, 855 (1941).

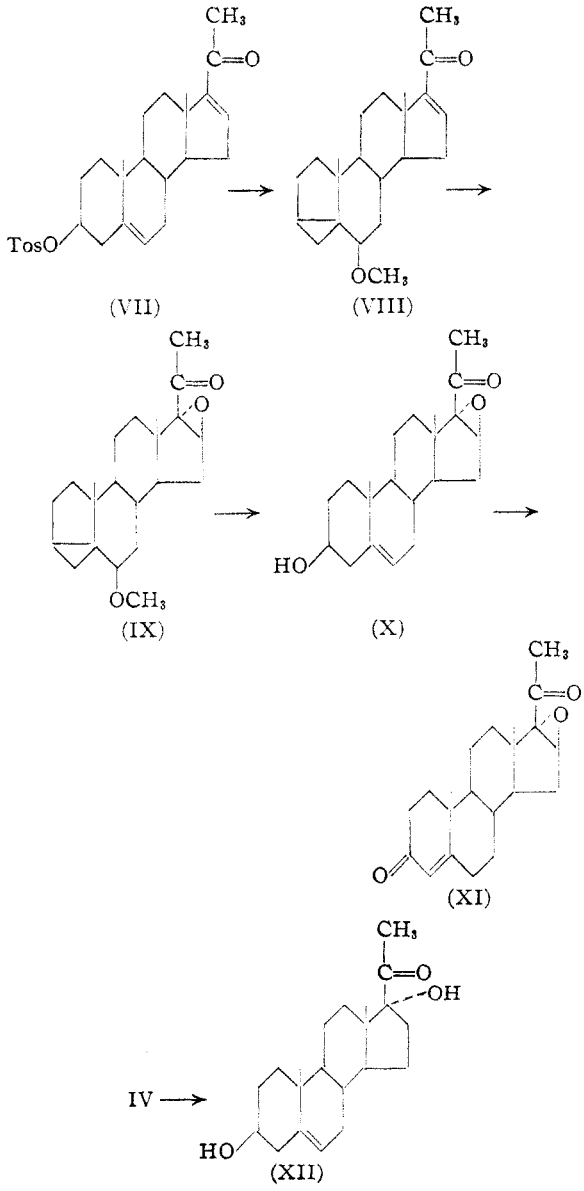
(3) Julian, Meyer, Karpel and Ryden, THIS JOURNAL, **71**, 3574 (1949).

(4) Hegner and Reichstein, *Helv. Chim. Acta*, **24**, 828 (1941).

(5) Kritchevsky and Gallagher, *J. Biol. Chem.*, **179**, 507 (1949).

derivative of progesterone, namely, 16,17-oxidoprogesterone (XI). As expected, this steroid showed no progestational activity at a level of 25 mg. in the modified Clauberg assay by the McPhail technique. The possibility of androgenic activity for comparison with that of 17α-hydroxyprogesterone[2] is under investigation.

5-Pregnene-3β,17α-diol-20-one (XII), previously prepared by a more laborious route by Fuchs and Reichstein,[6] was easily obtained by hydrolysis of its ethylene ketal (IV).



Experimental[7]

16,17-Oxido-5-pregnen-3β-ol-20-one Acetate (II).—A solution of 50.0 g. of 5,16-pregnadien-3β-ol-20-one acetate (I) in 500 ml. of chloroform was chilled in a Dry Ice–acetone-bath and then treated dropwise under good agitation with a solution of 22.4 g. of bromine in 250 ml. of chloroform over a period of one-half hour. After the complete disappearance of the bromine color, the solution was allowed to warm up to room temperature and then concentrated *in vacuo* with gentle warming to a heavy sirup. This was dissolved in 825 ml. of a benzene solution containing 55 mg. of perbenzoic acid per ml. and then allowed to stand in the dark at room temperature for nineteen hours.[8] The solution was diluted with ether and washed with 5% sodium hydroxide solution and water. The crystalline residue remaining after concentration of the dried solution *in vacuo* was taken up in 450 ml. of ether and 300 ml. of acetic acid, warmed and debrominated with zinc dust added portionwise. To complete the reaction, the mixture was refluxed for fifteen minutes, a fresh portion of zinc dust was then added and the mixture was refluxed for another ten minutes. After dilution with water, the zinc was separated and the ethereal layer was washed with water, 5% sodium hydroxide solution and water until neutral. The solid residue, after removal of solvent from the dried solution, gave upon crystallization from methanol 29.2 g. (56%) of white, crystalline solid melting at 152–155°. Several recrystallizations from methanol afforded plates melting at 154–155°; $[\alpha]^{26}D$ −9.0° (54.2 mg. made up to 5 ml. with chloroform, αD −0.098°, *l*, 1 dm.).

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.43; H, 8.72.

By re-debromination of the mother liquor an additional crop of several grams of less-pure material may be obtained. In one experiment (35 g. of starting material) where the mother liquor was debrominated with chromous chloride[9] there was obtained 2 g. of the original diene.

5,16-Pregnadien-3β-ol-20-one *p*-Tosylate (VII).—5,16-Pregnadien-3β-ol-20-one was prepared from the acetate (I) by hydrolysis with potassium bicarbonate in aqueous methanol. The use of methanolic potassium hydroxide led to considerable color formation and lowered yield.

A mixture of 4.85 g. of 5,16-pregnadien-3β-ol-20-one and 4.85 g. of *p*-tosyl chloride in 10 ml. of anhydrous pyridine was allowed to stand for about twenty hours. The mixture was then taken up in ether–methylene chloride and washed with dilute hydrochloric acid, water, sodium bicarbonate solution and water. The residue remaining after removal of solvent *in vacuo* from the dried solution was crystallized from acetone; 5.67 g. (95%) of fine needles melting at 163–165° dec. Several recrystallizations from acetone gave material melting at 163–164° dec.; $[\alpha]^{29}D$ − 36.3° (45.5 mg. made up to 5 ml. with chloroform, αD − 0.33°, *l*, 1 dm.).

Anal. Calcd. for $C_{28}H_{36}O_4S$: C, 71.76; H, 7.74. Found: C, 71.71; H, 7.86.

6-Methoxy-16-*i*-pregnen-20-one (VIII).—A solution of 6.76 g. of the *p*-tosylate (VII) and 17 g. of freshly-fused potassium acetate in 175 ml. of anhydrous methanol was refluxed for three hours and then poured into one liter of water. The aqueous suspension was extracted with ether and the extract was washed with water, dilute sodium carbonate solution and then water until neutral. Upon removal of solvent from the dried solution, there remained 5.11 g. of a viscous straw-colored oil. This crude *i*-steroid was employed as such for further work.

A one-gram sample of the crude *i*-steroid was dissolved in 30 ml. of hexane and chromatographed on 10 g. of activated alumina wetted with hexane. Elution with 100 ml. of hexane gave 760 mg. of an oily material which solidified upon standing in the refrigerator. Trituration of the solid with cold methanol gave a white crystalline product

(6) Fuchs and Reichstein, *Helv. Chim. Acta*, **24**, 804 (1941).

(7) Carbon-hydrogen analyses by Micro-Tech Laboratory, Skokie, Illinois.

(8) The disappearance of perbenzoic acid was followed by iodometric titration of samples removed at suitable intervals. During the period of reaction, a total of 1.1 molar equivalents of perbenzoic acid was consumed.

(9) Julian, Cole, Magnani and Meyer, THIS JOURNAL, **67**, 1728 (1945).

melting at 58–60°; $[\alpha]^{29}D$ + 87.4° (68.1 mg. made up to 5 ml. with chloroform, αD + 1.191°, *l*, 1 dm.).

To further characterize the crude material, the *i*-steroid was converted to the 3β-methoxy derivative. A solution of 200 mg. of the oil in 12 ml. of methanol containing one drop of concentrated sulfuric acid was refluxed for one hour. Upon cautious addition of water and chilling, crystals separated. Several recrystallizations of the solid material from aqueous methanol gave colorless needles of **3β-methoxy-5,16-pregnadien-20-one** melting at 166–168°; $[\alpha D]^{30}D$ −38.7° (24.9 mg. made up to 5 ml. with chloroform, αD − 0.193°, *l*, 1 dm.).

Anal. Calcd. for $C_{22}H_{32}O_2$: C, 80.44; H, 9.82. Found: C, 80.21; H, 9.66.

The same 3β-methoxy derivative was obtained directly from the *p*-tosylate (VII) by reaction of the latter with methanol.

16,17-Oxido-5-pregnen-3β-ol-20-one (X). (a) From 6-Methoxy-16-*i*-pregnen-20-one.—A solution of 1.60 g. of oily 6-methoxy-16-*i*-pregnen-20-one in 20 ml. of benzene containing 78 mg. of perbenzoic acid per ml. was allowed to stand at room temperature for seventeen hours. After dilution with ether, the solution was washed with 5% sodium hydroxide solution and then water until neutral. Upon removal of solvent from the dried solution, there remained 1.63 g. of a pale yellow sirup. The crude *i*-steroid oxide (IX) was dissolved in 30 ml. of purified dioxane, diluted with 5 ml. of water containing one drop of concentrated sulfuric acid and refluxed for one hour. The mixture was then poured into 300 ml. of water and the solid was separated by filtration; 1.10 g. of white solid melting at 170–180°. Several recrystallizations from ether–petroleum ether (b. p. 35–60°) and from acetone gave fine, white needles melting at 189–190°; $[\alpha]^{28}D$ + 1.7° (30.1 mg. made up to 5 ml. with chloroform, αD + 0.01°, *l*., 1 dm.).

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 75.80; H, 9.04.

Reaction of the crude *i*-steroid oxide (IX) with methanol in the presence of sulfuric acid gave **16,17-oxido-3β-methoxy-5-pregnen-20-one**; colorless plates melting at 188–190° after several recrystallizations from methanol; $[\alpha]^{30}D$ −6.5° (57.9 mg. made up to 5 ml. with chloroform, αD − 0.075°, *l*, 1 dm.).

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.58; H, 9.74.

(b) **From 16,17-Oxido-5-pregnen-3β-ol-20-one Acetate.**—A solution of 5.0 g. of 16,17-oxido-5-pregnen-3β-ol-20-one acetate in 400 ml. of methanol was treated with 5.0 g. of potassium bicarbonate in 75 ml. of water and then refluxed for one and one-quarter hours. The solution was then concentrated *in vacuo* to about 100 ml. and diluted with 500 ml. of water. The solid was separated by filtration, washed with water and dried. This material, 4.38 g. melting at 188–190° after softening at 180°, gave, upon recrystallization from methanol, 4.04 g. (91%) of needles which melted at 189–191° and showed no depression in melting when admixed with a sample of the material described above.

16,17-Oxidoprogesterone (16,17-Oxido-4-pregnene-3,-21-dione) (XI).—A solution of 4.0 g. of 16,17-oxido-5-pregnen-3β-ol-20-one in 200 ml. of dry toluene and 40 ml. of freshly-distilled cyclohexanone was distilled to remove traces of moisture (about 20 ml. of distillate was collected). It was then treated dropwise, under reflux, with 2.0 g. of aluminum isopropoxide in 25 ml. of toluene over a period of ten minutes. After one-half hour of reflux, the boiling solution was treated with 0.5 ml. of glacial acetic acid in 5 ml. of toluene. After one hour of steam distillation and the addition of a small quantity of sodium chloride, the suspension was extracted with ether–chloroform. The ethereal layer was washed well with water, dried and concentrated and the residue was taken up in ether and concentrated until a heavy mass of crystals had separated. An equal volume of petroleum ether (b. p. 35–60°) was added and the solid was separated; 2.47 g. melting at 203–205°. By concentration of the mother liquor an additional crop of 0.37 g. (total yield 71.5%), m. p. 198–202°, was obtained. Several recrystallizations from aqueous methanol gave colorless prisms, melting at 205–207°; $[\alpha]^{27}D$ + 160.8° (34.5 mg. made up to 5 ml. of chloroform, αD + 1.11°, *l*, 1 dm.).

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.50; H, 8.68.

Ethylene Ketal of 16,17-Oxido-5-pregnen-3β-ol-20-one Acetate (III).—A mixture of 1.50 g. of the oxide compound (II), 1.50 g. of freshly-distilled ethylene glycol and 50 ml. of benzene was distilled until traces of moisture had been removed. After the addition of 100 mg. of *p*-toluenesulfonic acid monohydrate, the reaction mixture was refluxed with agitation for four hours during which time the water was continually separated in a Bidwell–Sterling moisture collector. The mixture was then diluted with ether and washed with water, dilute sodium bicarbonate solution and then water. After the addition of a few drops of pyridine, the dried solution was concentrated and the residue crystallized by trituration with methanol; 850 mg. (51%) of white solid melting at 185–190° after softening slightly lower. Several recrystallizations from benzene–methanol (containing one drop of pyridine) gave thick, needle-like prisms melting at 195–197°; $[\alpha]^{27}D$ −37.8° (56.0 mg. made up to 5 ml. with chloroform, αD − 0.424°, *l*, 1 dm.).

Anal. Calcd. for $C_{25}H_{36}O_5$: C, 72.08; H, 8.72. Found: C, 71.92; H, 8.67.

From the original mother liquor there was obtained 190 mg. (12.5%) of crude starting material (m. p. 135–140°) which can be reprocessed for additional ketal.

Ethylene Ketal of 17α-Hydroxypregnenolone (5-Pregnen-3β,17-α-diol-20-one) (IV).—A stirred suspension of 1.50 g. of lithium aluminum hydride in 150 ml. of dry ether was treated dropwise with a solution of 3.0 g. of the oxido-ketal (III) in 50 ml. of dry benzene and 200 ml. of dry ether over a period of ten minutes. After stirring for one-half hour, the reaction mixture was refluxed and stirred for an additional hour. It was then decomposed by cautious addition of water and washed free of alkali with water. The ethereal solution was dried, treated with several drops of pyridine and concentrated to dryness *in vacuo*. The residue was crystallized from acetone yielding 2.0 g. of white solid melting at 180–183°. The mother liquor yielded an additional 180 mg. melting at 175–178° (total yield 80.5%). For analysis, a sample was recrystallized several times from acetone; colorless prisms melting at 185–187°; $[\alpha]^{26}D$ −44.8° (13.5 mg. made up to 5 ml. with chloroform, αD −0.121°, *l*, 1 dm.).

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.63; H, 9.70.

17α-Hydroxypregnenolone (5-Pregnene-3β,17α-diol-20-one (XII).—A suspension of 300 mg. of the ketal (IV) in 10 ml. of methanol, 2 ml. of water and 0.5 ml. of concd. sulfuric acid was refluxed for forty-five minutes. During this period the starting material was replaced by a less soluble crystalline substance. The mixture was then chilled, diluted with 8 ml. of water and the solid was separated. After drying, the white solid, 220 mg. (83%), melted at 245–250° after sintering about 230°. Several recrystallizations from methanol gave fine prisms melting at 265°.[6] The melting point is not distinct and will vary considerably with the rate of heating; $[\alpha]^{28}D$ −34.4° (9.3 mg. made up to 5 ml. with 1 part of dioxane and 2 parts of ethanol, αD − 0.064°, *l*, 1 dm.).

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.87; H, 9.69. Found: C, 75.42; H, 9.84.

Acetylation of a sample of the 17α-hydroxypregnenolone with acetic anhydride–pyridine gave the 3-acetoxy derivative; fine needles melting at 232–234°[6] after several recrystallizations from benzene–petroleum ether (b. p. 35–60°).

17α-Hydroxyprogesterone (4-Pregnen-17α-ol-3,20-dione) (VI).—A solution of 2.32 g. of the ketal (IV) in 120 ml. of dry toluene and 24 ml. of cyclohexanone was dis-

tilled for a short period to remove traces of moisture. It was then treated dropwise, at the boiling point under reflux, with a solution of 1.25 g. of aluminum isopropoxide in 15 ml. of toluene over a period of five minutes. After one-half hour of reflux, the solution was diluted with water and ether. The ethereal layer was washed with 2% sodium hydroxide solution and then water until neutral. The ether was removed and the residue was steam distilled for one hour. The solid was separated after adding a small amount of sodium chloride and chilling. The air-dried, crystalline solid weighed 2.67 g. and melted at 190–195°. This crude material was dissolved in 100 ml. of methanol; the solution was filtered and treated with a solution of 2 ml. of concd. sulfuric acid in 20 ml. of water. The solution was then refluxed for one-half hour during which time the color changed to deep violet. It was then poured into one liter of water and extracted with ether. The extract was washed well with water, dried and concentrated. The residue upon crystallization from ether–petroleum ether (b. p. 35–60°) gave 1.38 g. (67%) of crystalline material melting at 200–208° after softening somewhat lower. Recrystallization from acetone yielded material (1.05 g.) melting at 210–215°. Further recrystallization from acetone gave diamond-shaped plates melting at 213–215°; $[\alpha]^{22}D$ + 97.2 (9.9 mg. made up to 2 ml. with chloroform, αD − 0.481°, *l*, 1 dm.); ϵ_{240} − 17,800 (methanol).

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.07; H, 9.05.

In one experiment, the intermediate **ketal of 17α-hydroxyprogesterone** (V) was purified. Several recrystallizations from methanol gave fine, white plates melting at 212–216°.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.76; H, 9.02.

No improvement in yield of 17α-hydroxyprogesterone was obtained by conducting the hydrolysis at room temperature for two hours or by purifying the intermediate ketal.

Summary

A new partial synthesis of 17α-hydroxyprogesterone is described.

CHICAGO, ILLINOIS RECEIVED SEPTEMBER 16, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, IMPERIAL COLLEGE, LONDON]

Stereochemistry of the Cholesterol Dichlorides[1]

BY D. H. R. BARTON* AND E. MILLER

During the last twenty years, intensive study of the stereochemistry of steroidal compounds has led to solution of many of the important problems in this field.[2] It is generally agreed that the determination of the stereochemistry of halogen derivatives is more difficult than that of the corresponding hydroxylic compounds. This is illustrated in the steroid field by the relatively recent solution[3,4] of the problem of the orientation of the cholesteryl and cholestanyl 3-halides, as compared with the long accepted configurations of the corresponding 3-alcohols. Again the stereochemistry of the 5,6-dihydroxy-derivatives of cholestanol is known with certainty,[2] but the configurations of the corresponding dihalides have not hitherto been elucidated.

In order to remedy this deficiency in our knowledge attention was first directed to the two cholesterol dichlorides. One of these, which is readily obtained by the addition of chlorine to cholesterol[5] (or better, the corresponding esters), has been known for many years.[6] Its method of formation implies that it must be a *trans*-dichloride[7] and this is confirmed[8] by its resistance to dehydrochlorination on refluxing with methanolic caustic potash. The second dichloride of cholesterol was first prepared (as the benzoate) by Berg and Wallis[9] by the action of iodobenzene dichloride[10] on cholesteryl benzoate. It was shown by these authors that alkaline reagents provoked a facile elimination of hydrogen chloride, an observation that we have fully confirmed, there being formed 6-chlorocholest-5-en-3β-ol. Since the molecular rotation differences recorded by Berg and Wallis for the acylation of the latter were not in good agreement with those expected, we have redetermined the relevant rotations (Table I) and have found that, in fact, the agreement for the constitution assigned is satisfactory. The behavior of the new cholesterol dichloride benzoate is best explained if the two chlorine atoms are in the *cis*-relationship. At first we were unable to obtain reproducible results during its preparation using the iodobenzene dichloride reagent. Instead of the *cis*-dichloride benzoate of Berg and Wallis the ordinary *trans*-dichloride benzoate was isolated. In the end it was discovered that the reagent can react by two different mechanisms, both of which lead to the addition of two chlorine atoms to the

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(1) This paper is Part XIV in our series on the "Application of the Method of Molecular Rotation Differences to Steroids." It was supported, in part, by a Research Grant from the Chemical Society, London.

(2) See "Natural Products Related to Phenanthrene," by L. F. Fieser and M. Fieser, 3rd edition, especially Chapter X (by R. B. Turner).

(3) Shoppee, *J. Chem. Soc.*, 1138, 1147 (1946).

(4) Dodson and Riegel, *J. Org. Chem.*, **13**, 424 (1948); compare E. Bergmann, *Helv. Chim. Acta*, **20**, 590 (1937).

(5) For an improved preparation of the benzoate see Exptl. section.

(6) Mauthner, *Monatsh.*, **15**, 85, 362 (1894); **27**, 421 (1906).

(7) *Inter alia*, Michael, *J. prakt. Chem.*, **52**, 344 (1895); McKenzie, *J. Chem. Soc.*, **101**, 1196 (1912); Terry and Eichelberger, THIS JOURNAL, **47**, 1067 (1925); Roberts and Kimball, *ibid.*, **59**, 947 (1937); Lucas and Gould, *ibid.*, **63**, 2541 (1941).

(8) Hückel, Tappe and Legutke, *Ann.*, **543**, 191 (1940); Cristol, THIS JOURNAL, **69**, 338 (1947); compare Hughes, Ingold, *et al.*, *J. Chem. Soc.*, 2093 (1948).

(9) Berg and Wallis, *J. Biol. Chem.*, **162**, 683 (1946).

(10) Garvey, Halley and Allen, THIS JOURNAL, **59**, 1827 (1937).