for 2 hr. The product recovered by dilution and ether extraction was an oil, but a solution in 0.5 ml. of methanol deposited aggregates of small needles (40 mg.). On recrystallization the product melted at 178–182°; λ^{CS_2} 2.90 (OH), 5.73 (ester carbonyl), 5.80 μ (keto group).

Anal. Calcd. for $C_{49}H_{48}O_4$ (460.67): C, 75.60; H, 10.50. Found: C, 75.82; H, 10.41.

5α-Bromocholestane-3β,4β-diol 3-Acetate (12).—A solution of 130 mg. of coprostane-3β-ol-4β,5β-oxide 3-acetate (**16**) in 6 ml. of acetone was treated with 0.26 ml. of 48% hydrobromic acid and kept at 30° for 45 min. Addition of water gave a filterable precipitate which on crystallization from methanol afforded 80 mg. of small prisms, m.p. 143–144.5° dec., α_D +18°. The substance is very sensitive to heat and decomposes somewhat even at room temperature.

Anal. Calcd. for $C_{29}H_{49}O_3Br$ (524.59): C, 66.40; H, 9.41. Found: C, 67.37; H, 9.64.

Acetylation in pyridine (24 hr. at 22°) gave the **3,4-diacetate**, which crystallized from methanol in plates, m.p. 148.5–150.5°, α_D +24°.

Anal. Calcd. for $C_{31}H_{51}O_4Br$ (566.63): C, 65.69; H, 9.09. Found: C, 65.82; H, 9.23.

Cholestane-3β,4β-diol-5α,6α-oxide (14).—A solution of 4 g. of Δ^5-cholestane-3β,4β-diol (m.p. 176°) in 150 ml. of ether was treated with 31.5 ml. of an ethereal solution of 1.1 mol. equiv. of monoperphthalic acid and let stand at 22° for 72 hr. The solution was decanted, washed until neutral, dried and concentrated eventually in 30 ml., after collecting successive crops of precipitate. Crystallization from methanol gave 2.82 g. of crystals, m.p. 184–186°. After several recrystallizations from methanol the oxide **14** was obtained as aggregates of prisms, m.p. 195.5–198°, α_D −39°.

Anal. Calcd. for $C_{27}H_{46}O_3$ (418.64): C, 77.46; H, 11.08. Found: C, 77.59; H, 11.17.

5α-Hydroxy-3,4-secocholestane-3,4-diol Cyclic Acetal-(20).—Cholestane-3β,4β,5α-triol (1.5 g.) was added to a solution of 2 g. of lead tetraacetate in 100 ml. of acetic acid at 22°. After a few hours long needles began to separate and these were found by infrared analysis to consist of a molecular compound of the reaction product **20** and acetic acid. The mixture was let stand overnight and then diluted with water and worked up by ether extraction. Evaporation of solvent left a solid which on crystallization from methanol gave 1.4 g. of needles, m.p. 134–135.5°, α_D −15°; λ^{CS_2} 2.94$_m$ (with a small band at 2.80), 9.07, 9.27, 9.82, 10.14, 10.38, 10.77, 10.92, 11.07 μ.

Anal. Calcd. for $C_{27}H_{46}O_3$ (418.64): C, 77.46; H, 11.08. Found: C, 77.39; H, 11.13.

3,4-Secocholestane-3,4,5-triol (21).—A solution of 1.3 g. of the acetal **20** in 5 ml. of ether was added to a solution of 0.5 g. of lithium aluminum hydride in 10 ml. of ether and the mixture was worked up after standing at 22° for 5 hr. Crystallization of the solid product from aqueous methanol gave 1.14 g. of needles, m.p. 114–116°.

Anal. Calcd. for $C_{27}H_{50}O_3$ (422.67): C, 76.72; H, 11.92. Found: C, 76.93; H, 12.15.

3,4-Secocholestane(3α,5α)(3β,4)-dioxide = Desoxoketone 104 (22).—A solution of *t*-butyl chromate was prepared by addition of 1 g. of chromic anhydride in portions with ice cooling to 2.2 g. of *t*-butyl alcohol and dilution with benzene to a volume of 20 ml.; the benzene solution was separated from a small aqueous layer and dried. Eight ml. of this solution was added to a suspension of 1 g. triol **21** in 20 ml. of benzene. The mixture was let stand at 22° for 48 hr. The solution then was shaken with 5 ml. of water containing 1.5 g. of sodium bisulfite and 20 ml. of 10% sulfuric acid until the color changed from brown to green. The yellowish organic layer was separated and processed as usual. On chromatography of the oily product on 20 g. of alumina, 4:1 petroleum ether–benzene eluates gave 260 mg. of an oil of infrared spectrum identical with that of desoxoketone 104, but it could not be induced to crystallize. This was rechromatographed on 10 g. of alumina and 9:1 petroleum ether–benzene and gave fractions which were oils but which when digested with methanol gave 80 mg. of crystals, m.p. 51–53°; a mixture with desoxoketone 104 melted at 51–56° and the infrared and n.m.r. spectra were identical; λ^{Chf} 6.74, 9.02, 9.87, 10.08, 11.10 μ.

Cholestane-3β,4β,5α,6β-tetraol (23).—A solution of 0.17 g. of cholestane-3β,4β-diol-5α,6α-oxide (**14**) in 13 ml. of tetrahydrofuran was treated with 0.8 ml. of 30% perchloric acid at 22° for 8 hr. Dilution with water gave a white precipitate which was washed well and crystallized from aqueous methanol and then from aqueous acetone. It separated as a microcrystalline powder, m.p. 173–176° (sample dried in vacuum at 110° for 15 hr.).

Anal. Calcd. for $C_{27}H_{48}O_4$ (436.65): C, 74.26; H, 11.08. Found: C, 74.62; H, 11.19.

4-Methoxy-4,5,6β-trihydroxy-3,4-secocholestane-3-ol Cyclic Acetal (24).—The crude tetraol **23** (550 mg.) was added to 30 ml. of acetic acid containing 0.05 mole of lead tetraacetate and the mixture worked up. Ether extraction gave a solid residue, which was refluxed for 2 hr. with 5 ml. of methanol containing 10 drops of concd. hydrochloric acid. Ether extraction gave a crude solid which was dissolved in 10 ml. of benzene and 20 ml. of petroleum ether and chromatographed on 12 g. of alumina. Ether eluates afforded 190 mg. of needles which on recrystallization from petroleum ether afforded needles, m.p. 118–120°, α_D −43°; λ^{Chf} 2.80$_w$, 9.02$_s$, 9.22$_s$, 10.25$_s$, 10.37$_s$, 11.08$_s$ μ.

Anal. Calcd. for $C_{28}H_{48}O_4$ (448.66): C, 74.95; H, 10.78; CH_3O, 6.92. Found: C, 74.47; H, 10.89; CH_3O, 7.09.

4-Methoxy-4,5-dihydroxy-3,4-secocholestane-3-ol-6-one Cyclic Acetal (25).—A solution of 50 mg. of sodium dichromate dihydrate in 0.5 ml. of acetic acid was added to a solution of 110 mg. of **24** in 1.5 ml. of benzene and 2 ml. of acetic acid with ice cooling. The mixture was let stand at 22° for 5 hr., and ether extraction gave an oil which solidified. Crystallization from petroleum ether afforded prisms, m.p. 120–121.5°, α_D −23°, λ^{CS_2} 5.80, 9.04, 9.20, 9.80, 9.97, 10.31 (broad), 11.05 μ.

Anal. Calcd. for $C_{28}H_{46}O_4$ (446.65): C, 75.29; H, 10.38. Found: C, 75.15; H, 10.44.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Reactions of Ketone 104

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RECEIVED SEPTEMBER 8, 1959

Several transformations of the ketone are now interpretable on the basis of the structure 1. Typical reactions involve acetolysis to the unsaturated acetoxy ketone **2** and electrophilic attack of the double bond to give products **3, 9** and **10**.

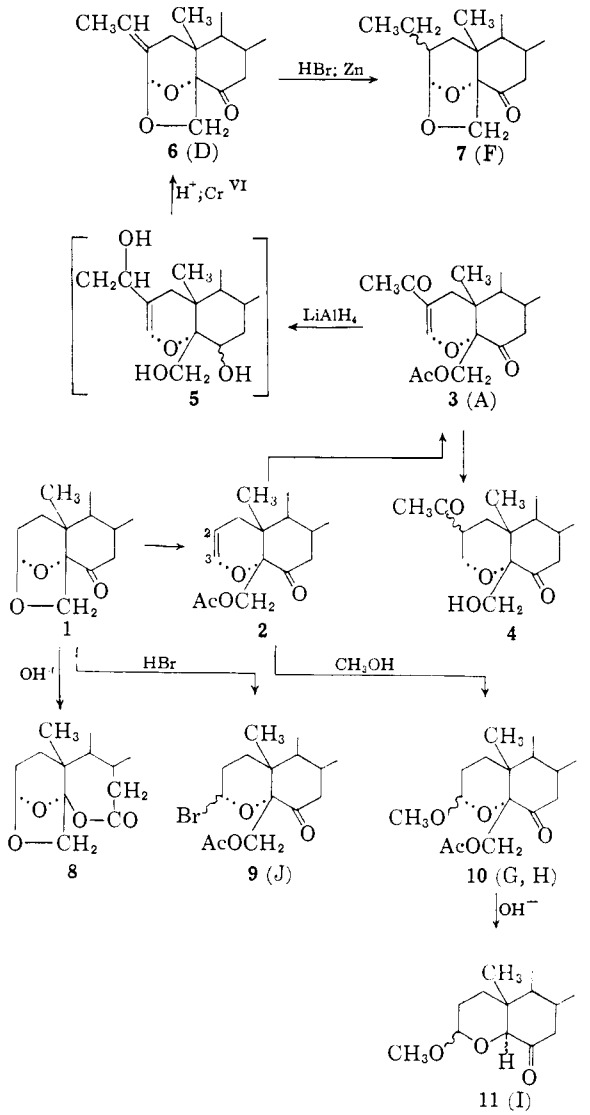
Following elucidation of the structure of ketone 104 as 3,4-secocholestane-6-one-(3α,5α)(3β,4)-dioxide (**1**),[2] it is possible to interpret a series of transformations encountered (B. K. B.) in an early search for a clue to the structure. The key intermediate to most of the products is the previously described[2] olefin acetate **2**, obtainable in good yield by heating the ketone **1** with acetic anhydride and aluminum chloride at a temperature

(1) See notes 2 and 3 of preceding paper, ref. 2.

(2) L. F. Fieser, T. Goto and B. K. Bhattacharyya, THIS JOURNAL, **82**, 1700 (1960).

of about 140°. The acetolysis is analogous to the conversion of a sapogenin to a pseudosapogenin acetate,[3] which is effected under similar conditions. That the 6-keto group plays no part was established by formation of an olefin acetate analogous to **2** on acetolysis of desoxoketone 104. Acetolysis of **1** in the presence of *p*-toluenesulfonic acid gives compound A, assigned[2] formula **3**, along with some of the olefin acetate **2**, from which it is evidently derived by Friedel–Crafts acylation; a small amount of A was detected in the crude olefin acetate on examination of the infrared spectrum. In the transformation of **2** into **3** the electrophile $CH_3C^+{=}O$ preferentially attacks the more negative carbon (C_2) of the vinyl ether linkage.

When the reaction mixture resulting on acetolysis in the presence of the sulfonic acid was decomposed with methanol rather than with water, the product



contained compound A and a difficultly separable mixture of isomeric compounds G and H, which we now regard as 3-epimers of the structure **10**. Analyses indicate that each compound contains one methoxyl and one acetoxyl group, and each forms a monoöxime. Since the methoxy compounds appeared in place of olefin acetate **2** it is evident that they arose by addition to the double bond of this substance, again with preferential attack by electrophilic H^+ at C_2. On treatment with hydrogen bromide, compound G reverts to ketone 104. Compounds G and H (**10**) on treatment with alcoholic alkali afforded compound I, and the analytical evidence indicated that the reaction involves replacement of $C_3H_5O_2$ by H, which corresponds to that expected for hydrolysis of **10** to the α-hydroxymethyl ketone and reverse aldolization to **11** (compare the preceding paper[2]: conversion of **6** into **7**). Formula **11** for compound I is supported by the fact that the infrared spectra of the substance and of the alcohol derived from it by borohydride reduction contain strong bands characteristic of an acetal linkage, as shown by the following comparison with synthetic 3-methoxy-4-oxacholestane[2]:

Compound I (**11**)	8.80	9.48	9.54		11.23 μ
Dihydro I	8.94	9.51	9.63	9.69	11.16
3-Methoxy-4-oxacholestane	8.89	9.48	9.67		11.24

Another transformation product (J) obtained by treatment of ketone 104 with hydrogen bromide in acetic anhydride–chloroform probably arises in an attack by bromide ion of the 3-carbonium ion derived from **1** to give **9**, analogous to the methoxy compound **10**. That ketone 104 is unaffected by refluxing with methanolic sulfuric acid[4] means that the cyclic acetal form predominates at equilibrium in the presence of hydrogen ion. In the presence of acetic anhydride the equilibrium is displaced by acetylation and the acetal linkage is opened easily.

Reduction of compound A (**3**) with lithium aluminum hydride and decomposition of excess reagent with dilute hydrochloric acid gave a product which failed to crystallize but which on oxidation gave a crystalline ketone, compound D. Strong bands (in addition to a keto band at 5.80 μ) at 9.04, 9.47, 9.72, 10.09 and 10.98 μ clearly indicate the presence of the cyclic acetal structure, which is further supported by the presence of a band at 6.72μ associated with scissoring vibrations of the 4-CH_2 group.[1] This evidence, coupled with the analysis and the fact that the substance readily adds hydrogen bromide to give the monobromo compound E, suggests that D has the structure **6**. The position indicated for the double bond is consistent with the appearance of a band at 11.87 μ (835 cm.$^{-1}$), characteristic of a trisubstituted olefin. The bromo compound E is probably the 2-bromo derivative of the saturated compound F (**7**), into which it is converted on reduction with zinc and acetic acid.

Whereas the olefin acetate **2** adds bromine smoothly and is hydrogenated readily, compound A (**3**), in which the double bond is part of a β-diketone enol ether system, does not add bromine and it absorbed hydrogen (Pt, HOAc) only very

(3) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp. 549–550.

(4) L. F. Fieser and B. K. Bhattacharyya, THIS JOURNAL, **75**, 4418 (1953).

slowly and afforded the saturated product **4** in low yield. The product of deacetylation (acid hydrolysis) was obtained only as an oil, but the infrared spectrum supports the structure assigned. The substance is the 2-acetyl derivative of a parent keto alcohol previously described (formula **6** of first paper[2]), and like this substance it shows bands at 2.78 μ (OH), and at 9.25 and 9.36 μ (tetrahydropyran ring). The keto band at 5.84 μ is about twice as strong as that of the parent substance, and a band not present appears at 7.37 μ (methyl vibration of CH_3CO–C).

The alcohol[4] formed on lithium borohydride reduction of ketone 104 would be expected to be the axial 6β-ol resulting from attack on the α-side, and this assumption is supported by the following M_D increments for introduction at C_6 of the OH, OAc and keto groups: −91, −161, −165; in the cholestane series the increments for the 6β-OH, 6β-OAc and 6-keto groups are −50, −110, −113.[5] The lactone[4] formed on peroxide oxidation of ketone 104 probably has the structure **8**, since it is usually the more highly substituted carbon atom which migrates to oxygen in such reactions.[6]

Acknowledgments.—See preceding paper.[2]

Experimental[7]

Compound D (6).—To 50 ml. of a solution prepared by refluxing 1 g. of lithium aluminum hydride with 100 ml. of ether and decanting was added a solution of 210 mg. of compound A in 20 ml. of ether; a white precipitate separated immediately. After refluxing for 2 hr. the excess hydride was decomposed by addition of alcohol, ice and dilute hydrochloric acid. Extraction with ether gave a glassy product (205 mg.), and since in previous trials this had afforded no solid on crystallization or chromatography, it was dissolved in 1.5 ml. of benzene and the solution cooled, treated with 1.5 ml. of acetic acid, and then with a cold solution of 170 mg. of sodium dichromate dihydrate in 1.7 ml. of acetic acid, added dropwise. After 16 hr. at 8°, the mixture was worked up in the usual way and gave 195 mg. of brownish gum, which was chromatographed. A solid eluted by 9:1 petroleum ether–benzene was crystallized from methanol–acetone (m.p. 97–98°, 102 mg., 55%) and then from methanol. It formed small plates, m.p. 97.4–98.4°, α_D −89.7° Chf; λ^{Chf} 5.80, 6.72$_m$, 9.04, 9.47, 9.72, 10.09, 10.95, 11.01, 11.97 μ; tests with ferric chloride and tetranitromethane negative; no ultraviolet absorption.

Anal. Calcd. for $C_{29}H_{46}O_3$ (442.66): C, 78.68; H, 10.47. Found: C, 78.75, 78.55; H, 10.55, 10.35; OCH_3, none.

D-Oxime, crystallized four times from methanol, formed short needles, m.p. 175.2–175.8°.

Anal. Calcd. for $C_{29}H_{47}O_3N$ (457.67): C, 76.10; H, 10.34; N, 3.06. Found: C, 75.70; H, 10.34; N, 3.35.

D-2,4-Dinitrophenylhydrazone crystallized from ethanol–ethyl acetate as small, yellowish-orange prisms, m.p. 210.8–211.2°.

Anal. Calcd. for $C_{35}H_{50}O_6N_4$ (622.78): C, 67.50; H, 8.09; N, 9.60. Found: C, 67.64; H, 8.20; N, 9.60.

Compound E.—One ml. of a 32% solution of hydrogen bromide in acetic acid was poured onto 70 mg. of compound D. Within a few minutes the crystals had changed to a thick oil, which after some time began to become crystalline. After 16 hr. at 25°, ice and water were added and the mixture extracted with ether. Evaporation of the washed and dried extract left a solid, and three crystallizations from methanol containing a little acetone gave 48 mg. (58%) of needles, m.p. 138.4–139°, α_D −44.0° Chf; λ^{Chf} 5.80, 6.72, 8.97, 9.47, 9.68, 10.05, 11.10 μ.

Anal. Calcd. for $C_{29}H_{47}O_3Br$ (523.59): C, 66.53; H, 9.05; Br, 15.26. Found: C, 66.47; H, 9.08; Br, 15.32.

Compound F (7).—For reduction, a solution of 116 mg. of compound E in 3.3 ml. of acetic acid was heated on the steam-bath and 0.33 g. of zinc dust was added in small portions during 20–25 min. and heating was continued for another hour. The product, collected by ether extraction and crystallized once from methanol, melted at 89–91° (57 mg., 58%). Recrystallized from methanol, it formed slender needles, m.p. 91.8–92.4°, α_D −50.2° Chf; λ^{Chf} 5.81, 6.72$_m$, 8.99, 9.42, 9.72, 10.07, 11.12 μ.

Anal. Calcd. for $C_{29}H_{48}O_3$ (444.67): C, 78.32; H, 10.88. Found: C, 78.42; H, 10.90.

Compound G (10).—As in the preparation of A, a mixture of 5 g. of ketone 104, 75 ml. of acetic anhydride and 2.3 g. of *p*-toluenesulfonic acid was let stand at room temperature for 84 hr. The excess anhydride was then decomposed by slow addition of methanol over a period of 7 hr. The mixture was then diluted, extracted with ether, and the product crystallized from petroleum ether (30–60°). This afforded 1.19 g. of compound A, m.p. 146–147°. The mother liquor was then chromatographed on 100 g. of alumina (100-ml. fractions). Fractions 6–12 (3:1 and 1:1 petroleum ether–benzene), m.p. 141–145°, combined and crystallized twice from methanol, afforded 600 mg. that when rechromatographed gave 500 mg. (8%) of compound G, m.p. 140–141°. Fractions 18–30 (1:1 petroleum ether–benzene and benzene) on two crystallizations from methanol gave 1.34 g. of compound A.

Compound G on further crystallization formed elongated prisms, m.p. 140.2–140.8°, α_D −6.3° Chf., λ^{Chf} 5.80 μ.

Anal. Calcd. for $C_{30}H_{50}O_5$ (490.70): C, 73.43; H, 10.27; OCH_3, 6.32. Found: C, 73.63, 73.57; H, 10.39, 10.18; OCH_3, 6.54.

A mixture of 110 mg. of compound G, 1 ml. of chloroform and 2 ml. of 32% hydrogen bromide in acetic acid was let stand at room temperature for 24 hr. (homogeneous solution) and then taken up in ether. After washing with water and bicarbonate solution, the solution was dried and evaporated and the residue chromatographed. The material eluted by 9:1 petroleum ether–benzene crystallized from methanol to give 40 mg. of needles of ketone 104, m.p. 123–124°, identified by mixed m.p. determination, rotation, and infrared spectrum. A solid eluted by 3:1 petroleum ether–benzene on crystallization from acetone melted at 191.5–193°; no test for unsaturation and no ultraviolet or infrared carbonyl absorption.

G-Oxime crystallized from methanol in needles, m.p. 199.5–201°.

Anal. Calcd. for $C_{30}H_{51}O_5N$ (505.72): C, 71.24; H, 10.17; N, 2.77; OCH_3, 6.13. Found: C, 71.53; H, 10.29; N, 2.40; OCH_3, 6.62.

Compound H (10).—In the preparation of compound G, the mother liquor remaining from crystallization of fractions 6–12 was evaporated and the residue combined with fraction 5 (m.p. 123–125°) and chromatographed as before. Fractions 10–18, m.p. 145–147°, were combined and crystallized twice from methanol to give 328 mg. of H, m.p. 145°. Recrystallized, the substance formed stout needles, m.p. 145.6°, α_D +27.7° Chf (*c* 1.77), λ^{Chf} 5.80 μ.

Anal. Calcd. for $C_{30}H_{50}O_5$ (490.70): C, 73.43; H, 10.27; OCH_3, 6.32. Found: C, 73.48, 73.67; H, 10.39, 10.39; OCH_3, 6.18.

A mixture of compounds G and H melted at 139–142°; the infrared spectra are markedly different in the fingerprint region.

H-Oxime crystallized from methanol in prismatic needles, m.p. 208.6–209°.

Anal. Calcd. for $C_{30}H_{51}O_5N$ (505.72): C, 71.24; H, 10.17; N, 2.77. Found: C, 71.30; H, 10.08; N, 2.77.

Compound I (11).—A hot solution of 120 mg. of compound G in 5 ml. of methanol was treated with 1.5 ml. of Claisen alkali and let stand at room temperature for 16 hr. After the mixture had been worked up, crystallization from methanol furnished small blades, m.p. 133.6–134.6°, α_D + 83° Chf. Compound H, treated in the same way, gave an identical product, m.p. 134.9–135.2°, α_D +83.7° Chf (*c* 1.46); λ^{CS_2} 5.76, 8.80, 9.48, 9.54, 11.23 μ.

Anal. Calcd. for $C_{27}H_{46}O_3$ (418.64): C, 77.46; H, 11.08; OCH_3, 7.40. Found: C, 77.25, 77.31, 77.29; H, 11.16, 11.25, 10.85; OCH_3, 8.16, 7.42.

(5) D. H. R. Barton and W. Klyne, *Chemistry & Industry*, 755 (1948).

(6) W. von E. Doering and L. Speers, THIS JOURNAL, **72**, 5515 (1950).

(7) Preparative experiments by B. K. B. except as noted; infrared data by T. G.

The 2,4-dinitrophenylhydrazone was eluted from a column of alumina with benzene and crystallized from ethyl acetate–methanol. It formed small yellow needles, m.p. 140.6–142°.

Anal. Calcd. for $C_{33}H_{50}O_6N_4$ (598.76): C, 66.19; H, 8.42. Found: C, 66.76; H, 8.62.

Compound J (9).—A solution of 125 mg. of ketone 104 in 0.5 ml. of chloroform and 0.5 ml. of acetic anhydride was cooled in Dry Ice–acetone and about 0.8 ml. of hydrogen bromide was condensed on top of the mixture. After standing for 48 hr. at 0° the mixture was taken up in ether and the solution washed wth water and bicarbonate solution, dried and evaporated, and the residue chromatographed. A fraction eluted by 3:1 petroleum ether–benzene afforded 9 mg. of crystals, m.p. 138–144°. In another run, conducted for 24 hr., 1 g. of ketone 104 afforded 40 mg. of product after extensive chromatography. Four recrystallizations from methanol gave small prisms, m.p. 149.2–149.8°, α_D +21.4° Chf; λ^{Chf} 5.73, 5.80.

Anal. Calcd. for $C_{29}H_{47}O_4Br$ (539.58): C, 64.55; H, 8.78; Br, 14.81. Found: C, 64.94; H, 8.86; Br, 14.56.

Variations of the above procedure either gave lower yields or furnished no crystalline material.

Alcohol 104.—The glassy alcohol previously reported[4] eventually solidified, and three crystallizations from methanol (seed may be required) raised the m.p. to 105.6–106.4° α_D −19.4° Chf.

Anal. Calcd. for $C_{27}H_{46}O_3$ (418.64): C, 77.46; H, 11.08. Found: C, 76.96; H, 10.94.

5β-Acetoxymethyl-4-oxa-Δ²-coprostene (T. G.).—A mixture of 100 mg. of desoxyketone 104, 100 mg. of aluminum chloride and 2 ml. of acetic anhydride was boiled gently for 3 hr., cooled, decomposed with ice and water and extracted with ether. Chromatography on 3 g. of alumina afforded oily 4:1 petroleum ether–benzene fractions which solidified when rubbed with methanol. Crystallization from methanol gave needles, m.p. 74–77° (17 mg.).

Anal. Calcd. for $C_{29}H_{48}O_3$ (444.67): C, 78.32; H, 10.88. Found: C, 78.02; H, 10.70.

Desacetyldihydro A (4), by T. G.—A solution of 1 g. of compound A (**3**) in 30 ml. of acetic anhydride when hydrogenated in the presence of 50 mg. of platinum oxide absorbed 52 ml. of hydrogen at 22° in 2 hr. The filtered solution was evaporated, ether was added and evaporated several times to remove acetic acid, and treatment of the residue with methanol afforded 300 mg. of starting material, m.p. 142–144°. Chromatography of the mother liquor afforded 530 mg. of oily product which was hydrolyzed by refluxing for 2 hr. with 6 ml. of methanol and 1.5 ml. of concd. hydrochloric acid. Ether extraction gave an oil which afforded solid when digested with petroleum ether. Two crystallizations from methanol gave 80 mg. of crystals, m.p. 149–152°; λ^{CS_2} 2.80$_w$, 5.83$_s$, 7.40$_m$, 9.25$_m$, 9.35 mμ.

Anal. Calcd. for $C_{29}H_{48}O_4$ (460.87): C, 75.60; H, 10.50. Found: C, 75.54; H, 10.66.

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[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

The Base-catalyzed Condensation of Progesterone with Ethyl Oxalate

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RECEIVED SEPTEMBER 10, 1959

Methoxide-catalyzed acylation of progesterone (I) by ethyl oxalate occurs at C-2 and C-21 in a relatively indiscriminate manner to give a mixture of 2-mono-, 21-mono- and 2,21-bis-ethoxalyl derivatives.

The base-catalyzed condensation of pregnane derivatives with oxalate esters affords a method for the introduction of 21-hydroxy (or acetoxy),[2a,b] 1-dehydro[2c] and 2-alkyl[3] groupings into the steroid molecule[4]; moreover, it is the basis of a procedure whereby the dihydroxyacetone side-chain may be elaborated from the simple 17β-acetyl side-chain.[2b] In view of the importance of these moieties in steroidal hormones possessing anti-inflammatory activity, it is of interest to ascertain the practicality of effecting a preferential acylation at one of the two reaction sites (C-2 and C-21) available in a 4-pregnen-3,20-dione. Moreover, it is of interest to determine what effect the presence of other groupings might have on the course of this reaction. Preferential ethoxalylation at C-21 already has been reported[2b] for 11-ketoprogesterone, 11α-hydroxyprogesterone and 11β-hydroxyprogesterone.[5] In contrast, we have found in the course of other work that 9(11)-dehydro-16α,17α-isopropylidenedioxyprogesterone reacts with ethyl oxalate, in the presence of 1.1 equivalents of sodium methoxide exclusively at C-2, although in the presence of an additional molar equivalent of methoxide, ethoxalylation takes place at C-21 as well to give a 2,21-bis-ethoxalyl derivative.[6] Moreover, Bernstein, Brown and co-workers have observed that the 9α-fluoro-11β-hydroxy-16α,17α-isopropylidenedioxyprogesterone undergoes preferential ethoxalylation at C-2.[7] Since 16α,17α-isopropylidenedioxyprogesterone also reacts selectively at C-2,[8] it may be concluded that the presence of the 16α,17α-isopropylidenedioxy group inhibits ethoxalylation at C-21. Furthermore, we have found that 9(11),16-bisdehydroprogesterone undergoes preferential C-21 ethoxalylation rather poorly and that the predominant reaction is a concurrent ethoxalylation at C-2 and at C-21.[9] The results of

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(2) (a) H. Ruschig, *Ber.*, **88**, 878 (1955); (b) J. A. Hogg, P. F. Beal, A. H. Nathan, F. H. Lincoln, W. P. Schneider, B. J. Magerlein, A. R. Hanze and R. W. Jackson, THIS JOURNAL, **77**, 4436 (1955); (c) J. A. Hogg, F. H. Lincoln, A. H. Nathan, A. R. Hanze, W. P. Schneider, P. F. Beal and J. Korman, *ibid.*, **77**, 4438 (1955).

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