dles, m.p. 72–73.5° (350 mg., total yield of 59% from the bromoketone).

Oxidation of Methyl Δ^3-Cholenate B.—Oxidation of 1.73 g. of ester was done exactly as before and the crude product was acetylated. The yellowish, glassy acetate mixture (2.05 g.) was then chromatographed on 50 g. of Merck alumina (87 50-ml. fractions). No starting material was encountered, but petroleum ether–benzene (2:1) eluates afforded 100 mg. of solid which on crystallization from methanol gave 70 mg. of plates of **methyl $\Delta^{3,5}$-choledienate**, m.p. 93–96°. The next crystalline fractions (2:1 and 15:10) gave 350 mg. of a mixture which on repeated crystallization gave 80 mg. of **methyl 3α-acetoxy-Δ^4-cholenate**, m.p. 148–150°, mixed m.p. 147–149°. Material recovered from the mother liquors was saponified and found to contain no digitonin-precipitable alcohol. Elution with 1:1 to 1:2 solvent mixtures afforded 260 mg. of material characterized by the infrared spectrum as essentially pure **methyl 3β-acetoxy-Δ^4-cholenate**. Crystallization from methanol gave leaflets (190 mg.), m.p. 142–148°, and the substance on further crystallization formed needles (120 mg.), m.p. 147.5–149°, α_D +20.9° (a mixture with the 3α-epimer melted at 118–132°).

Anal. Calcd. for $C_{27}H_{42}O_4$ (430.61): C, 75.31; H, 9.83. Found: C, 75.51; H, 10.04.

Saponification of this methyl ester acetate and crystallization from methanol and then acetone gave prismatic needles of **3β-hydroxy-Δ^4-cholenic acid**, m.p. 174–176°, undepressed in m.p. on admixture with the above sample. The mother liquor material from crystallizations of the methyl ester acetate was saponified; the product precipitated by digitonin proved to be 3β-hydroxy-Δ^4-cholenic acid.

Benzene–ether eluates gave 230 mg. of an oil that gradually crystallized. Several crystallizations from methanol gave long needles, m.p. 157–159° (10 mg.); the analysis (C, 71.79; H, 8.94) suggests that the substance is a product of further oxidation.

Methyl Lithocholate 3-Benzoate (By Naomi Levy).—A solution of 2.2 g. of methyl lithocholate in 15 ml. of pyridine (dried over potassium hydroxide and distilled) was cooled in an ice-bath during dropwise addition of a solution of 1.3 g. of benzoyl chloride in 10 ml. of benzene. After standing overnight at room temperature, the mixture was worked up and the product crystallized from ethanol, m.p. 74–79°. Two further crystallizations raised the m.p. to 83–85°.

Anal. Calcd. for $C_{32}H_{46}O_4$ (494.69): C, 77.69; H, 9.37. Found: C, 78.00; H, 9.53.

This methyl ester benzoate (1 g.) was pyrolyzed in a sublimation apparatus heated in a Wood's metal-bath at 315–325° under evacuation by an oil-pump. After 1 hr. the white sublimate and oily residue were combined and extracted with ether, and the extract was washed with bicarbonate solution, dried, and evaporated. Chromatography afforded 400 mg. of **methyl Δ^3-cholenate C**, m.p. 69–70°.

CAMBRIDGE 38, MASS.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Stereochemistry of B-Norcoprostane Derivatives[1]

BY TOSHIO GOTO[2]

RECEIVED SEPTEMBER 21, 1959

Reduction of B-norcoprostane-3,6-dione (1) with sodium borohydride affords a separable mixture of the 3α,6α- and 3α,6β-diol (**2**, **3**); hydrogenation gives the 3β,6β-diol (4). Diols **2** and **3** are both cyclized by benzenesulfonyl chloride in pyridine to the 3α,6α-oxide. That the reaction involves no rearrangement was established by conversion of the oxide to B-norcoprostane-6α-ol (12), prepared for comparison through intermediates **5** and **6**. Formation of the same 6α-ol by reduction of diol-**2** 3-tosylate (**7**) establishes the configuration of the diol at C_6. The configuration at C_3 follows from conversion of 1 to the 3α-ol,6-one **10**, which on borohydride reduction gave diol-**2** and on Wolff–Kishner reduction gave the known 3α-ol 11. This evidence establishes that the dione 1 has the 5β-configuration. Experimental correlation of diol **3** with B-norcoprostane-3-one (**15**) by reactions which preclude an inversion at C_8 establishes the 8β-configuration at this center. The configurations of diols **3** and 4 follow from M_D and other considerations.

In 1937, Butenandt and Hausmann[3] encountered a new ketosecodioic acid and found that on brief refluxing with zinc and acetic acid it is cyclized to a diketone. Fieser[4] identified the acid as 6,7-seco-Δ^4-cholestene-3-one-6,7-dioic acid, named the product of cyclization the Butenandt diketone, and characterized it as a B-norstane-3,6-dione. Since the diketone has asymmetric centers at C_5 and C_8 adjacent to the carbonyl group at C_6, four stereoisomers are possible. In the absence of definitive evidence, Fieser provisionally formulated the compound as the B-norcoprostane-3,6-dione of normal 8β-configuration (**1**).

In an investigation of B-norcholesterol, Dauben and Fonken[5] concluded from various transformations that the stanol obtained by hydrogenation has the same configuration at C_5 as the Butenandt diketone. As a means of establishing whether the substances belong to the cholestane or the coprostane series, they investigated the reduction of the corresponding 3-ketone with lithium aluminum hydride and reported that the product is identical with the original 3β-ol. Since the ketone is unhindered, they assumed that the reaction affords the equatorial alcohol. Noting that a 3β-hydroxyl group is equatorial in the B-norcholestane series but axial in the B-norcoprostane series, they concluded that the alcohol is B-norcholestane-3β-ol. Djerassi, *et al.*,[6] however, found the rotatory dispersion curve of the norstane-3-one to resemble the curve of coprostanone rather than that of cholestanone and concluded that the substance is B-norcoprostane-3-one. Recently Dauben and coworkers[7] have resolved the seeming contradiction of evidence by the finding that the product of lithium aluminum hydride reduction is actually a mixture containing about 75% of the 3α-ol. They now regard the product of hydrogenation of B-norcholes-

(1) For a preliminary report of some of the results, see T. Goto and L. F. Fieser, THIS JOURNAL, **81**, 2276 (1959).

(2) Recipient of a Fulbright travel grant on leave from Nagoya University (1957–1959). Present address: Chemical Department, Nagoya University, Chikusa, Nagoya, Japan.

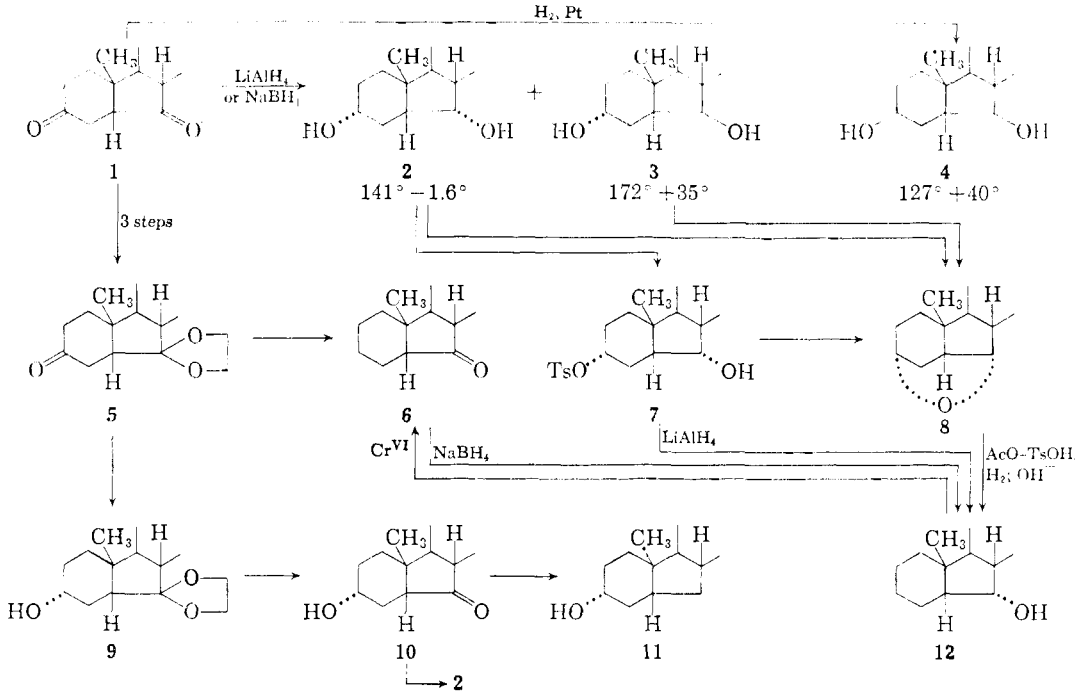
(3) A. Butenandt and E. Hausmann, *Ber.*, **70**, 1154 (1937).

(4) L. F. Fieser, THIS JOURNAL, **75**, 4386 (1953).

(5) W. G. Dauben and G. J. Fonken, *ibid.*, **78**, 4736 (1956).

(6) C. Djerassi, D. Marshall and T. Nakano, *ibid.*, **80**, 4853 (1958).

(7) W. G. Dauben, G. A. Boswell, Jr., and G. H. Berezin, *ibid.*, **81**, 6082 (1959). I am greatly indebted to Professor Dauben for informing me of the recent work.



terol as the axial B-norcoprostane-3β-ol and the Butenandt diketone as of 5β-configuration.

The present work was undertaken[1] prior to this last observation with the idea that the coprostane structure alone presents the possibility for closure of a 3α,6α-oxide bridge. Conversion of the Butenandt diketone into a 3,6-oxide would thus provide unequivocal chemical evidence of the 5β-configuration.

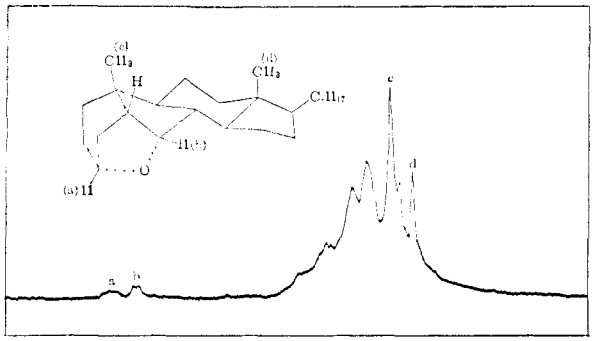


Fig. 1.—N.m.r. spectrum of B-norcoprostane-3α,6α-oxide (in $CDCl_3$ at 40 megacycles per sec., external standard, benzene). Cycles per sec.: a, 82, b, 94 (3β-H and 6β-H); c, 217 (10-CH_3); 229 (13-CH_3).

Reduction of the Butenandt diketone (1) with sodium borohydride in ether–methanol gave a nicely crystalline diol melting at 145–145.5° which, however, proved to be a 1:1 complex of the 3α,6α- and 3α,6β-diols **2** and **3**, resolved by chromatography of the diacetates. A third isomer, the 3β,6β-diol **4**, resulted on hydrogenation. Evidence for the configurations assigned is discussed later. All three diols reverted to **1** on oxidation with dichromate in acetic acid at room temperature.

On treatment with benzenesulfonyl chloride in hot pyridine, diols **2** and **3** both gave a crystalline substance of the formula $C_{26}H_{44}O$, corresponding to an oxide, an unsaturated alcohol or a ketone. The latter two possibilities are eliminated by negative tests with bromine and with tetranitromethane, absence of infrared hydroxyl or carbonyl bands, and transparency at 205–300 mμ. The conclusion that the substance is the 3α,6α-oxide **8** is supported by the n.m.r. spectrum (Fig. 1), which contains resonance peaks at 82 and 94 cycles per second, indicative of hydrogens attached to different oxygen-linked carbons, *i.e.*, the 3β- and 6β-hydrogens. It is evident from the model (Fig. 1) that the oxide bridge forces ring A into the boat conformation. The infrared spectrum (Fig. 2) is distinguished by the presence of several strong bands in the fingerprint region. The possibility that cyclization is attended with a rearrangement is eliminated by the following evidence. The oxide **8** is stable to hydrochloric acid in refluxing methanol–dioxane, but when heated with acetic anhydride and *p*-toluenesulfonic acid it afforded an oily product (the Δ^2- or Δ^3-derivative or a mixture) which on hydrogenation and hydrolysis gave a crystalline alcohol **12** shown to have the alcoholic function at C_6 by oxidation to a ketone **6** recognized from the infrared spectrum (5.76 μ) to have the carbonyl group in a five-membered ring. That the acetolysis of the oxide **8** does not involve a rearrangement was established by preparation of the 6-ketone **6** by another method. The Butenandt diketone reacts with ethylene glycol (and TsOH), as it does with ethanedithiol,[4] with preferential formation of the 3-monoketal (41% yield). The 6-monoethyleneketal **5**, however, was obtained as follows. Partial reduction of the diketone **1** with sodium trimethoxyborohydride gave an oil showing a strong band at 5.76 μ and therefore rich in 3$\alpha\beta$-ol-6-ones. Conversion to the ethyleneketal derivative and oxidation gave a mixture which on chromatographic separation afforded mainly the 6-ketal-3-ketone **5** (34%), along with a smaller amount

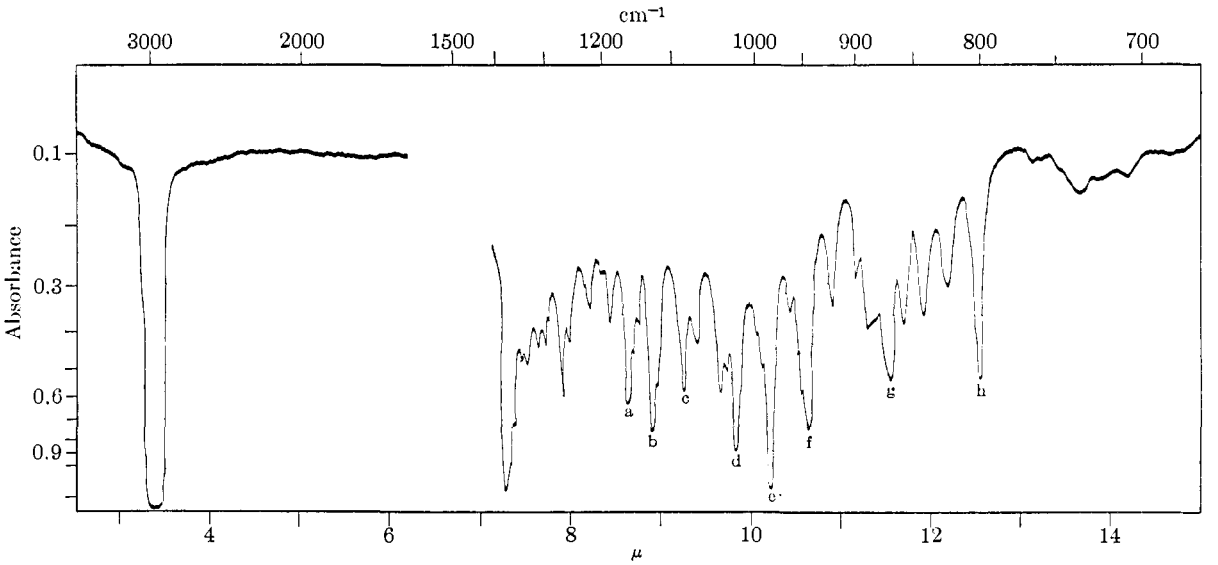


Fig. 2.—Infrared spectrum of B-norcoprostane-3α,6α-oxide (CS_2). Bands (in μ): a, 8.62; b, 8.90; c, 9.22; d, 9.85; e, 10.22; f, 10.65; g, 11.53; h, 12.54.

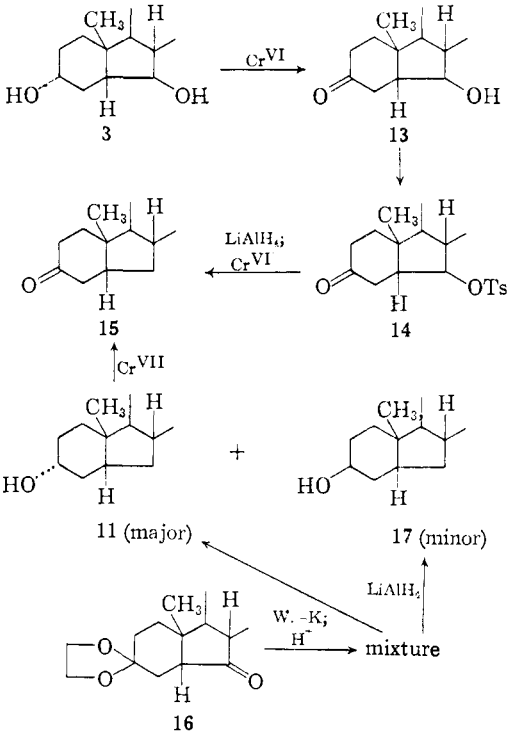
of the 3-monoketal of **1**. Huang-Minlon reduction of **5** and deketalization afforded B-norcoprostane-6-one **6**, identical with the product derived from the oxide. Since acetolysis of the oxide is thus not attended with a rearrangement, the saturated alcohol derived from the oxide corresponds to it in the configuration at C_6 and is B-norcoprostane-6α-ol (**12**).

This 6α-ol is correlated with the 3,6-diol **2** by the observation that the 3-tosylate **7** is reduced smoothly by lithium aluminum hydride to a product identical with the 6α-ol **12**; the configuration of diol **2** at C_6 is thus established as α. The following evidence establishes the configuration at C_3. The 6-ketal-3-one **5** on borohydride reduction gave a single 3-ol **9** which on hydrolysis with perchloric acid afforded a 3-ol-6-one **10**, and this on Huang-Minlon reduction gave a 3-ol identical in constants with an alcohol characterized by Dauben[7] as the 3-epimer of the 3β-ol derived from B-norcholesterol and therefore B-norcoprostane-3α-ol (**11**). Since the precursor olone **10** on reduction yielded diol **2**, this substance is identified as B-norcoprostane-3α,6α-diol.

Fieser[4] converted the Butenandt diketone to the parent B-norstane both by Wolff–Kishner reduction and by desulfurization of the bisethylenethioketal, and Dauben and Fonken[5] obtained an apparently identical hydrocarbon from B-norcholesterol, which has the 8β-configuration of cholesterol. However, even the milder thioketal method might involve change in configuration at C_8, adjacent to a carbonyl group. Thus coprostane-4-one affords cholestane-4-one thioketal, converted on desulfurization to cholestane.[8] Furthermore, it is sometimes difficult to distinguish between isomeric saturated hydrocarbons. Since the experiments cited do not establish unequivocally that the Butenandt diketone has the 8β-configuration, an attempt was made to correlate the diketone with the B-norstane-3-one or 3-ol under conditions precluding configurational change.

(8) R. Stevenson and L. F. Fieser, THIS JOURNAL, **78**, 1409 (1956).

The plan was to partially oxidize B-norcoprostane-3α,6β-diol (**3**) to the 3-ketone **13** and remove the 6β-hydroxyl group by reduction of the tosylate **14**. Oxidation of **3** with dichromate at 0° gave a mixture probably containing several products, but a nicely crystalline product, m.p. 144–144.5°,



was easily isolated in moderate yield by crystallization from methanol. The same substance was obtained from the Butenandt diketone **1** by reduction to a mixture of diols **2** and **3** and partial oxidation at 4°, and by partial reduction of **1** with sodium trimethoxyborohydride at 0° (lower yield). The infrared spectrum showed both a band for a 3-keto group and a weaker band for a 6-keto group.

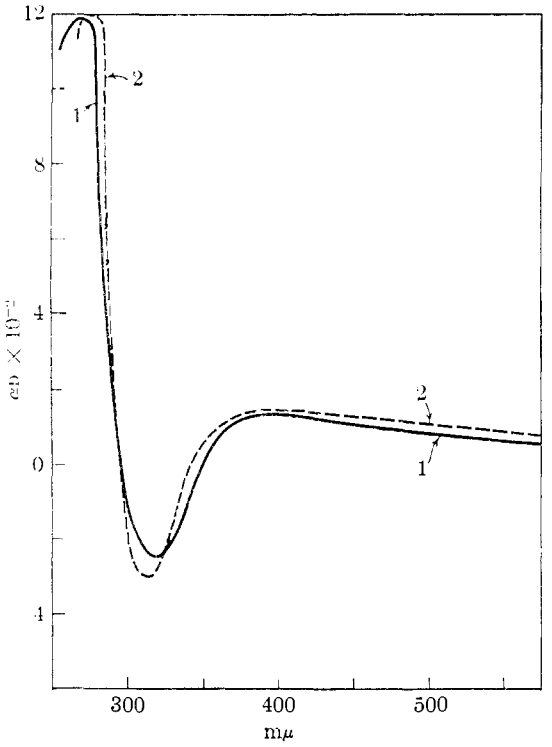


Fig. 3.—Rotatory dispersion curves of B-norcoprostane-3-one obtained (1) by the Wolff–Kishner method and (2) by the tosylate method.

On further oxidation the substance afforded the diketone **1** in quantitative yield. These observations suggested that the product is a molecular complex (probably 1:1) of the desired 6β-ol-3-one **13** and the Butenandt diketone, and indeed it was split easily into these components by chromatography. The 6β-ol-3-one was converted into the tosylate **14** and this was reduced with lithium aluminum hydride and the 3-keto group was restored by dichromate oxidation. Unlike the case of the unhindered 3-tosylate **7,** reported above, reduction of **14** proceeded poorly and the product was a mixture. Components isolated by chromatography were the desired 6-membered ring ketone **15,** the 3α, 6α-oxide **8,** and the Butenandt diketone. Probably the tosylate is reduced in part to the 3α,6β-diol 6-tosylate and the tosyl group is either eliminated to give the oxide, hydrolyzed to the 3α,6β-diol or reduced to the 3α-ol; the latter products are then oxidized to the dione and 3-one.

Since the tosylate reduction might have involved a rearrangement of the nucleus, it was necessary to establish that the end product is indeed the B-norstane-3-one formulated (**15**). The route to B-norcoprostane-3α-ol (**11**) formulated above (via **5, 9** and **10**) affords this substance in very low yield and actually was worked out at a later date. The route chosen involved conversion of the Butenandt diketone to the 3-ethyleneketal **16,** Wolff–Kishner reduction and acid hydrolysis. After several crystallizations the product melted at 61°, whereas the 3-one obtained by the tosylate method melts at 65.5°. No depression was noted in mixed melting point determinations, and the infrared curves were superimposable. However, the rotatory dispersion curves, kindly determined by Y. Inoue at Nagoya University, showed differences beyond the limit of experimental error. The ketonic product was therefore reduced, and chromatography on alumina afforded two alcohols. Oxidation of the major component gave a ketone, m.p. 71°, identical (infrared, mixed m.p.) with **15,** obtained by the tosylate method. The rotatory dispersion curves for the two samples, and for the B-norcoprostane-3-one[6] obtained by Dauben and Fonken[5] from B-norcholesterol are almost identical (Fig. 3) and such differences as exist are attributable to traces of impurities. Constants found for the ketone **15** and 3α-ol **11** agree well with those reported by Dauben.[7] The minor alcohol accompanying **11** corresponds in constants with a substance characterized by Dauben as B-norcholestane-3β-ol (**17**).[7] The Wolff–Kishner reduction thus is attended with partial inversion at C_5, but an inversion at either C_5 or C_8 is precluded in the correlation of diol **3** with the 3-one **15** through the tosylate **14.** Since **15** is correlated with cholesterol, the conclusion may be drawn that diol **3** and the Butenandt diketone have the 8β-configuration.

There remains for consideration the configurations of diols **3** and **4.** Since **3** can be cyclized to the 3α,6α-oxide, one of the hydroxyl groups must be α, and since the 3α,6α-diol is known (**2**), the substance must be the 3α,6β- or the 3β,6α-diol. That the former assignment is correct is evident from various pieces of evidence. If hydride reduction of the Butenandt diketone follows the usual course of affording exclusively the equatorial 3-alcohol, the common products **2** and **3** must have the same configuration at C_3. A model shows that a 6α-hydroxyl group is more hindered than a 6β-hydroxyl, and indirect evidence cited in the Experimental part indicates that, under conditions such that diol **2** gives the 3-monotosylate in good yield, diol **3** gives a ditosylate. A further argument is based upon comparison with the third diol (**4**) resulting on hydrogenation of the Butenandt diketone. Since adsorption of the molecule on the catalyst surface requires attack of both carbonyl groups from the same side, and since the substance is not the 3α,6α-diol, the 3β,6β-assignment is indicated. In the cholestane and coprostane series the difference in α_D between a 3α-ol and a 3β-ol is small, whereas with 6- and 7-alcohols the difference between epimers is large. In accordance with this rule and with the assignments, the α_D difference between **2** and **3** is 35.5° and between **3** and **4** is 5°. Molecular rotation relationships for the compounds studied are indicated in Table I.

Acknowledgments.—This work was supported by grants from the National Cancer Institute of the National Institutes of Health (C1696 Endo) and Research Corporation. I wish to thank Professor Louis F. Fieser for the privilege and inspiration of working in his laboratory.

Experimental[9]

The Butenandt diketone (**1**) was prepared according to Fieser[4] except that the mixture of acids resulting on zinc

(9) For experimental procedures, see L. F. Fieser, T. Goto and B. K. Bhattacharyya, THIS JOURNAL, **82**, 1700 (1960), note 19.

TABLE I

MOLECULAR ROTATIONS

	M_D	Δ
B-Norcoprostane[4]	+ 36	6α-OH:
-6α-ol	− 74	−110
-3α-ol	+ 83	
-3α,6α-diol	− 6	− 89
-3-one	+ 76	6β-OH:
-6β-ol-3-one	+224	+148
-3α-ol	+ 83	
-3α,6β-diol	+137	+ 54
-6α-ol	− 74	3α-OH:
-3α,6α-diol	− 6	+68
-6-one	+125	
-3α-ol-6-one	+185	+60

dust reduction was extracted with a 10% solution of potassium bicarbonate rather than the sodium salt since the potassium salt of dihydro-Butenandt acid is more soluble in water and extraction is facilitated; addition of sodium chloride to the extract then precipitates the sodium salt. Forty grams of cholesterol yielded 5.0 g. of Butenandt diketone, m.p. 116–118°, λ^{CS_2} 5.75, 5.82 μ, and 4.2 g. of dihydro-Butenandt acid sodium salt.

Borohydride Reduction of 1.—A stirred solution of 5 g. of 1 in 50 ml. each of ether and methanol was treated at 12–16° with 1.5 g. of sodium borohydride, the solution was stirred for 1 hr. and let stand overnight. Extraction with ether afforded an oil which on digestion with petroleum ether afforded 4 g. of product, m.p. 136–140°. Crystallization from aqueous methanol gave 2.1 g. of needles, m.p. 140.5–142°. Further crystallization afforded the 1:1 complex of B-norcoprostane-3α,6α-diol (**2**) and the 3α,6β-diol (**3**), m.p. 145–145.5°, α_D +14° Chf.

Anal. Calcd. for $(C_{26}H_{46}O_2)_2$ (781.26): C, 79.94; H, 11.87. Found: C, 79.90; H, 11.74.

For separation, 1.16 g. of complex was acetylated with 6 ml. each of acetic anhydride and pyridine and the acetate recovered and adsorbed from petroleum ether on a column of 40 g. of alumina; 2:1 petroleum ether–benzene eluted 460 mg. of crystalline diol **3** diacetate, and a 1:1 mixture eluted 620 mg. of oily diol **2** diacetate.

B-Norcoprostane-3α,6α-diol (2).—The oily diacetate (620 mg.) was cleaved with lithium aluminum hydride in ether and gave an initially oily product which solidified on digestion with acetone and gave 420 mg. of solid, m.p. 128–131°. Several crystallizations from methanol gave plates, m.p. 140–141.5°, α_D −1.6° Chf.

Anal. Calcd. for $C_{26}H_{46}O_2$ (390.63): C, 79.94; H, 11.87. Found: C, 79.91; H, 11.95.

A solution of 200 mg. of **2** in 2 ml. each of benzene and acetic acid was treated at ice-bath temperature with 200 mg. of sodium dichromate in 2 ml. of acetic acid and let stand overnight at 24°. The product on crystallization from methanol afforded 170 mg. of needles of the Butenandt diketone, m.p. and mixed m.p. 116–117°.

B-Norcoprostane-3α,6β-diol (3).—Cleavage of the crystalline diacetate as before and crystallization from acetone afforded plates, m.p. 170–172°, α_D +35° Chf.

Anal. Calcd. for $C_{26}H_{46}O_2$ (390.63): C, 79.94; H, 11.87. Found: C, 80.04; H, 11.97.

The diacetate, purified by crystallization from methanol of the product obtained by chromatography, formed leaflets, m.p. 93–94°, α_D +37.8° Chf.

Anal. Calcd. for $C_{30}H_{50}O_4$ (474.70): C, 75.90; H, 10.62. Found: C, 75.77; H, 10.60.

Lithium Aluminum Hydride Reduction of 1.—A solution of 1 g. of 1 in 25 ml. of ether was added by drops to a refluxing solution of 200 mg. of lithium aluminum hydride in 50 ml. of ether. After refluxing for 1 hr., excess hydride was destroyed with methanol and the mixture worked up. Digestion of the oily product with petroleum ether gave a crystalline paste, which afforded 500 mg. of crystalline powder, which sintered at 135° and melted at 153°. Crystallization from acetone gave a mixture of needles and plates, which were separated mechanically and recrystallized from acetone. The substance forming needles, m.p. 145–145.5°, was identified as the 1:1 complex of **2** and **3** and that forming plates, m.p. 170–172°, as the diol **3**.

B-Norcoprostane-3β,6β-diol (4).—A mixture of 1.5 g. of dione **1** and 150 mg. of platinum oxide in 30 ml. of acetic acid absorbed 195 ml. of hydrogen in 24 hr. The filtered solution on evaporation in vacuum left an oil, and this was refluxed in 18 ml. of ethanol for 12 hr. with 1 g. of Girard reagent and 2 ml. of acetic acid. Dilution with water and extraction with ether gave a pasty product which was dissolved in 2 ml. of acetone and kept at 0–3° overnight for crystallization. A further crystallization from aqueous acetone gave 500 mg. of aggregates of small needles, m.p. 111–115°. Several recrystallizations from ether–petroleum ether gave glistening needles, m.p. 126–127.5°, α_D +40.1°.

Anal. Calcd. for $C_{26}H_{46}O_2$ (390.63): C, 79.94; H, 11.87. Found: C, 79.98; H, 11.66.

B-Norcoprostane-3α,6α-diol 3-Tosylate (7).—*p*-Toluenesulfonyl chloride (170 mg.) was added with ice cooling to a solution of diol **2** (150 mg.) in 3 ml. of pyridine and the mixture was kept at 0–5° for 18 hr. Addition of ice-water and extraction with ether gave a solid product which crystallized from ether–petroleum ether in needles (110 mg.), m.p. 118.5–119.5°, α_D +1.7° Chf.

Anal. Calcd. for $C_{33}H_{52}O_4S$ (544.75): C, 72.75; H, 9.62. Found: C, 72.43; H, 9.51.

When the molecular complex of **2** and **3** was tosylated as above, the product, obtained in good yield, was a molecular complex of diol **2** 3-tosylate and diol **3** 3,6-ditosylate. It formed slender needles, m.p. 114–115.5°.

Anal. Calcd. for $C_{33}H_{52}O_4S \cdot C_{40}H_{58}O_6S_2$ (1243.79): C, 70.47; H, 8.98; S, 7.65. Found: C, 70.49; H, 8.92; S, 7.73.

B-Norcoprostane-3α,6α-oxide (8).—Benzenesulfonyl chloride (270 mg.) was added dropwise to a solution of 70 mg. of B-norcoprostane-3α,6α-diol (**2**) in 2 ml. of pyridine at 90–100°. After continued heating for 1 hr., the reaction mixture was treated with 1 ml. of water, heated on the steam-bath for 5 min., extracted with ether, and the oily product was chromatographed on 1.2 g. of alumina. Petroleum ether eluted 4 mg. of oily unsaturated material, and petroleum ether–benzene (8:2–2:1) eluates gave 33 mg. of crystalline oxide **8**. Purified by repeated crystallization from methanol, the oxide formed needles, m.p. 85.5–86.5°, α_D +30.5° Chf.

Anal. Calcd. for $C_{26}H_{44}O$ (372.61): C, 83.80; H, 11.90. Found: C, 83.64; H, 11.85; mol. wt. (Rast) 363.

The 3α,6β-diol **3** (70 mg.) treated in the same way gave 14 mg. of crystalline oxide **8**. A solution of 150 mg. of B-norcoprostane-3α,6α-diol 3-tosylate (**7**) in 2.3 ml. of pyridine was heated on the steam-bath for 40 min., after which extraction with ether and chromatography afforded 10 mg. of the oxide **8**.

A solution of 20 mg. of oxide in 2 ml. of methanol and 1 ml. of dioxane containing 3 drops of concd. hydrochloric acid was refluxed for 5 hr., after which ether extraction afforded unchanged starting material.

B-Norcoprostane-6α-ol (12). (a) From the Oxide 8.—A mixture of 600 mg. of **8**, 300 mg. of *p*-toluenesulfonic acid and 20 ml. of acetic anhydride was heated on the steam-bath for 30 min. and then poured onto ice-water. After standing overnight ether extraction gave a brown oil which was chromatographed on 18 g. of alumina. Petroleum ether–benzene (3:1) eluates afforded 370 mg. of an oil which showed acetate infrared bands and λ^{EtOH} 210 mμ (4,000). A solution of this substance in acetic acid in the presence of 30 mg. of platinum oxide absorbed 27 ml. of hydrogen. A solution of the oily product of hydrogenation in 20 ml. of 95% methanol containing 1 g. of potassium hydroxide was refluxed for 18 hr. and extracted with ether. Treatment of the oily product with methanol afforded 140 mg. of needles, m.p. 102–103°, and chromatography of the mother liquor afforded a second crop (110 mg.) of crystals, m.p. 101–102°. Recrystallization from methanol gave long needles, m.p. 102.5–103.5°, α_D −19.8° Chf.

Anal. Calcd. for $C_{26}H_{46}O$ (374.63): C, 83.35; H, 12.38. Found: C, 83.32; H, 12.30.

(b) **From B-Norcoprostane-3α,6α-diol 3-Tosylate (7).**—A solution of 46 mg. of **7** and 50 mg. of lithium aluminum hydride in 10 ml. of ether was refluxed for 6 hr. Decomposition of excess reagent (methanol) and extraction as usual gave a solid which on crystallization from methanol gave

20 mg. of long needles, m.p. 99.5–101°; undepressed in m.p. on admixture with sample (a).

(c) **From B-Norcoprostane-6-one (6).**—Reduction of **6** (40 mg.) with sodium borohydride in ether–methanol and two crystallizations from methanol gave needles, m.p. 95–98°; a mixture with sample (a) melted at 95–101°.

B-Norcoprostane-6-one (6) from B-Norcoprostane-6α-ol (12).—A chilled solution of 130 mg. of **12** in 1.5 ml. each of benzene and acetic acid was treated with a solution of 130 mg. of sodium dichromate in 1.5 ml. of acetic acid and was let stand overnight at 24°. The product, collected by ether extraction and crystallized from methanol, formed needles, m.p. 97–98° (110 mg.). Recrystallization from methanol gave long needles, m.p. 98–98.5°, α_D +33.6° Chf., λ^{CS_2} 5.76 μ.

Anal. Calcd. for $C_{26}H_{44}O$ (372.61): C, 83.80; H, 11.90. Found: C, 83.59; H, 11.79.

B-Norcoprostane-3,6-dione 6-Ethyleneketal (5).—A solution of 4 g. of B-norcoprostane-3,6-dione in 80 ml. each of ether and methanol containing 0.8 ml. of 10% sodium hydroxide was treated at 5–8° with 1.8 g. of sodium trimethoxyborohydride and let stand at the same temperature for 2 hr. The mixture was diluted with water, acidified with acetic acid, and extracted with ether. A solution of the oily reduction product, 0.2 g. of *p*-toluenesulfonic acid and 3.5 g. of ethylene glycol in 100 ml. of benzene was refluxed under a water separator for 12 hr. The oily reaction product, an oil (4.8 g.), was dissolved in 30 ml. of pyridine and the solution was added with ice cooling to a solution of 2.5 g. of chromic anhydride in 50 ml. of pyridine. After standing at 24° for 18 hr., the solution was diluted with water and extracted with ether. The extract was washed thoroughly with water and with saturated sodium chloride solution, evaporated, and the product was chromatographed on 140 g. of alumina. Petroleum ether–benzene (14:11–13:12) eluates gave 310 mg. of the oily 3,6-bisethyleneketal; 1:1 petroleum ether–benzene eluates gave 250 mg. of crystals of the 3-monoethyleneketal (**16**), and elution with 8:17 petroleum ether–benzene and with benzene gave material which on crystallization from methanol formed long needles, m.p. 117–119.5° (1.4 g.). The fully purified substance melted at 120–121°; λ^{CS_2} 5.82, 9.50 μ.

Anal. Calcd. for $C_{28}H_{45}O_3$ (430.65): C, 78.09; H, 10.77. Found: C, 77.76; H, 10.83.

For conversion to B-norcoprostane-6-one (6), a mixture of 200 mg. of **5**, 1 ml. of ethanol, 4 ml. of triethylene glycol, 400 mg. of potassium hydroxide and 0.2 ml. of hydrazine was heated in an oil-bath at 200–210° for 1 hr. under a stream of nitrogen. Dilution with water and extraction with ether gave the oily desoxoketal, which was treated in 10 ml. of tetrahydrofuran with 1.5 ml. of 25% perchloric acid. The solution was let stand at 24° for 17 hr. Extraction with ether and crystallization from methanol gave needles, m.p. 94–96°, α_D +32.4°, undepressed in m.p. on admixture with B-norcoprostane-6-one from **6**.

B-Norcoprostane-3,6-dione 3-Ethyleneketal (16).—A solution of 4 g. of the dione **1**, 1.5 g. of ethylene glycol and 0.1 g. of *p*-toluenesulfonic acid in 100 ml. of benzene was refluxed for 3 hr. under a water separator. The reaction product, a semi-solid, when chromatographed as in the preparation of **5** afforded a little oily bisketal, 70 mg. of **5** and 1.84 g. of crystals of **16**. Recrystallized from methanol, the substance was obtained as needles, m.p. 112.5–113.5°; λ^{CS_2} 5.76, 9.08 μ.

Anal. Calcd. for $C_{28}H_{46}O_3$ (430.65): C, 78.09; H, 10.77. Found: C, 78.18; H, 10.75.

3α-Hydroxy-B-norcoprostane-6-one 6-Ethyleneketal (9).—A solution of 1.06 g. of the 6-ketal **5** in 25 ml. each of ether and methanol was treated at 25° with 0.25 g. of sodium borohydride and let stand for 1 hr., when 1 ml. of acetone was added. The solution was concentrated to 20 ml., and addition of water caused separation of 910 mg. of crystals, m.p. 121.5–123°. Recrystallization from aqueous methanol afforded short prisms, m.p. 124–125°, α_D −11.0° Chf.

Anal. Calcd. for $C_{28}H_{48}O_3$ (432.66): C, 77.72; H, 11.18. Found: C, 77.54; H, 11.19.

3α-Hydroxy-B-norcoprostane-6-one (10).—A solution of 910 mg. of the ketal **9** in 45 ml. of tetrahydrofuran containing 3 ml. of 25% perchloric acid was let stand at 25° for 12 hr. Ether extraction afforded an oil which crystallized from petroleum ether. Recrystallization from petroleum ether gave aggregates of needles, m.p. 116–117.5°, α_D +47.6° Chf, λ^{CS_2} 5.77 μ.

Anal. Calcd. for $C_{26}H_{44}O_2$ (388.61): C, 80.35; H, 11.41. Found: C, 80.04; H, 11.44.

Recrystallization from petroleum ether sometimes gave long, slender needles, m.p. 88.5–90°, α_D + 49.3°. The two forms gave the same rotatory dispersion curve and appear to be polymorphic.

Anal. Calcd. for $C_{26}H_{44}O_2$ (388.61): C, 80.35; H, 11.41. Found: C, 80.15; H, 11.32.

Oxidation of **10** with dichromate in acetic acid gave the 3,6-dione **1**, m.p. and mixed m.p. 113.5–115°. Reduction of **10** (200 mg.) with sodium borohydride in ether–methanol gave an oil which was acetylated (Ac_2O–Py, 25° overnight) and chromatographed (6 g. alumina). Petroleum ether–benzene (2:1 and 1:1) eluates gave an oily acetate which was not identified. Petroleum ether–benzene (1:2) then eluted 60 mg. of another oily acetate which on cleavage with lithium aluminum hydride in ether gave a product which crystallized from aqueous methanol in plates, m.p. 132–137°. Recrystallization gave material, m.p. 139–140.5°, identical with B-norcoprostane-3α,6α-diol (**2**), as described above.

Complex of B-Norcoprostane-6β-ol-3-one (13) and Dione 1.—An iced solution of 50 mg. of sodium dichromate in 0.5 ml. of acetic acid was added to a solution of 50 mg. of **3** in 1 ml. each of benzene and acetic acid and the mixture was let stand at 2–3° for 10 hr. After addition of water, extraction with ether gave a solid which crystallized from methanol in leaflets, m.p. 137–141° (15 mg.). Further crystallizations of the complex raised the m.p. to 144–144.5°.

Anal. Calcd. for $C_{26}H_{42}O_2 \cdot C_{26}H_{44}O_2$ (775.21): C, 80.56; H, 11.18. Found: C, 80.36; H, 11.16.

The complex is available more readily from dione **1** as follows. The dione (19.5 g.) was reduced with sodium borohydride as described above and the crystalline mixture of diols **2** and **3** was dissolved in 200 ml. each of benzene and acetic acid and the solution was treated at 4° with a cold solution of 15 g. of sodium dichromate in 100 ml. of acetic acid. After standing at 2–3° for 6 hr. the solution was diluted and extracted with ether. Evaporation left a semi-solid residue which on crystallization from ether–petroleum ether gave 4.83 g. of the complex, m.p. 140–142°. The mother liquor material was oxidized at room temperature, and crystallization of the product gave 12.92 g. of dione **1**, m.p. 116–117°. Similar oxidation of the complex gave **1**, m.p. 116–117°, almost quantitatively.

In another experiment a solution of 0.5 g. of dione **1** in 10 ml. of methanol containing 0.1 ml. of 10% sodium hydroxide was treated with 0.2 g. of sodium trimethoxyborohydride at 0°. After 1 hr. at 0°, excess hydride was decomposed by addition of a few drops of acetic acid, and water was added. Extraction with ether and crystallization from aqueous methanol gave 150 mg. of material, m.p. 98–108°. Several crystallizations from acetone gave leaflets of the complex, m.p. 143–144°.

B-Norcoprostane-6β-ol-3-one (13).—The complex (320 mg.) was adsorbed from benzene onto 10 g. of alumina. Benzene–ether (9:1 to 1:1) eluates gave 160 mg. of crystals of dione **1**, m.p. 115–116°, and ether eluates gave 130 mg. of **13**. The fully purified substance crystallized from ether–petroleum ether in needles, m.p. 151.5–152°, α_D +57.5° Chf.; λ^{CS_2} 2.84, 5.83 μ.

Anal. Calcd. for $C_{26}H_{44}O_2$ (388.61): C, 80.35; H, 11.41. Found: C, 80.14; H, 11.44.

The 6-tosylate 14 was prepared by adding 200 mg. of *p*-toluenesulfonyl chloride with ice cooling to a solution of 200 mg. of **13** in 4 ml. of pyridine and allowing the mixture to stand at 2–3° for 18 hr. and at room temperature for 6 hr. Addition of ice-water caused separation of crystalline tosylate, and recrystallization from ether–petroleum ether gave slender needles, m.p. 148–149°.

Anal. Calcd. for $C_{33}H_{50}O_4S$ (542.73): C, 73.03; H, 9.29. Found: C, 71.84; H, 9.06.

B-Norcoprostane-3-one (15).—A solution of 200 mg. of the 6-tosylate **14** in 10 ml. of ether was added dropwise to a boiling solution of 200 mg. of lithium aluminum hydride in 10 ml. of ether and the solution was refluxed for 12 hr., treated with a little acetone, and worked up as usual. The

resulting oil was oxidized with dichromate in benzene–acetic acid at 25° and the product chromatographed on 5 g. of alumina. Petroleum ether eluates gave 70 mg. of B-norcoprostane-3α,6α-oxide (8), and petroleum ether–benzene (1:1) eluates gave 30 mg. of oily ketone 15. When covered with methanol and let stand at 2–3° the material crystallized in needles (m.p. 60–63°). Recrystallization from methanol raised the m.p. to 64.5–65.5°, α_D +37.1° Chf, λ^{CS_2} 5.82 μ.

Anal. Calcd. for $C_{26}H_{44}O$ (372.61): C, 83.80; H, 11.90. Found: C, 83.33; H, 11.52.

Elution of the column with ether gave 30 mg. of crystalline dione 1.

A purer sample of B-norcoprostane-3-one (15) was obtained by dichromate oxidation of B-norcoprostane-3α-ol (11) in benzene–acetic acid at 25°. Crystallized from methanol, it formed needles, m.p. 70–71°, α_D +20.5° Chf, λ^{CS_2} 5.82 μ (Found: C, 84.01; H, 12.01). The two samples showed no depression in m.p. on admixture, and the infrared spectra were identical.

B-Norcoprostane-3α-ol (11).—A mixture of 700 mg. of B-norcoprostane-3,6-dione 3-ethyleneketal (16), 1.4 g. of potassium hydroxide, 1 ml. of hydrazine, 7 ml. of ethanol and 10 ml. of triethylene glycol was refluxed for 30 min. and the condenser was removed and the solution heated at 200–208° for 1 hr. in a hydrogen atmosphere. The resulting ketal, an oil (680 mg.), was dissolved in 7 ml. of tetrahydrofuran and the solution was treated at 25° with 2.5 ml. of 25% perchloric acid and allowed to stand overnight. The crude product was an oil, but on chromatography on 15 g. of alumina, petroleum ether–benzene (6:4) eluates gave 390 mg. of crystalline ketone (needles). Several crystallizations raised the m.p. only to 60–61°, and hence the material was reduced with lithium aluminum hydride in ether and the mixture of 3-ols was chromatographed on 12 g. of alumina. Petroleum ether–benzene (1:4) eluates gave 130 mg. of crystals of the 3α-ol 11, which on recrystallization from aqueous methanol formed aggregates of fine needles, m.p. 93–94.5° (a companion substance is described below).

Anal. Calcd. for $C_{26}H_{46}O$ (374.63): C, 83.35; H, 12.38. Found: C, 83.41; H, 12.13.

A product identical with the 3α-ol 11 was obtained by lithium aluminum hydride reduction of 50 mg. of the 3-one 15 (m.p. 64.5–65.5°, derived from 14). Chromatography of the crude product gave an oil, a solution of which in methanol when let stand at 2–3° gave crystals, m.p. 70–80°. Recrystallization gave aggregates of small crystals, m.p. and mixed m.p. 92–94.5°. Huang-Minlon reduction of 100 mg. of B-norcoprostane-3α-ol-6-one (10) and chromatography gave an oil of infrared spectrum identical with that of 11 (prepared from 16).

B-Norcholestane-3β-ol (17).—Following the chromatograph fractions affording B-norcoprostane-3α-ol (11), benzene eluates afforded 60 mg. of 17, which crystallized from methanol in needles, m.p. 129–131°.

Anal. Calcd. for $C_{26}H_{46}O$ (374.63): C, 83.35; H, 12.38. Found: C, 83.29; H, 12.24.

Dichromate oxidation of 17 (35 mg.) and digestion of the product with methanol gave the corresponding 3-one, m.p. 85–90°. Recrystallization from methanol yielded needles, m.p. 90–93°, α_D +44°.

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[CONTRIBUTION FROM THE DIVISION OF CHEMICAL RESEARCH, G. D. SEARLE AND CO.]

4-Oxasteroid Analogs

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RECEIVED SEPTEMBER 23, 1959

The keto-acid IIa and lactonol IIIa obtained from ozonization of testosterone benzoate have been transformed into a series of epimeric saturated lactones (V and VI), pseudoesters (VIII) and a pseudoacid chloride (VII). Methods for interconverting the keto-acid and the lactonol are discussed.

As part of a general investigation into the effects of changes in the basic carbon skeleton of steroids on their physiological properties, we have prepared a number of androstane derivatives having an oxygen in place of a carbon at the 4-position. Compounds of this type have been prepared previously as intermediates in the series of reactions leading to the introduction of radioactive carbon into the steroid molecule[2] and in certain total synthetic schemes,[3] but in only one case[2a] have the reactions of these compounds been explored to any extent.

When testosterone benzoate (I) was ozonized according to Turner,[2a] the reported product, m.p. 150.5–151.5°, $[\alpha]_D$ +81°, was obtained in the first experiment but a new isomeric material, m.p. 175–176°, $[\alpha]_D$ +127°, was obtained on all subsequent oxidations. Since the rotations of the substances differed and the infrared spectra were not identical, it was clear that this was not a case of polymorphism. It was found that the lower melting isomer could be converted to the new material by heating it above its melting point. The tautomeric keto-acid IIa and lactonol IIIa structures were assigned to the high and low melting materials, respectively, on the basis of their infrared spectra. Compound IIIa had a lactone carbonyl band (5.74 μ) which was clearly resolved from the ester carbonyl absorption and a highly bonded hydroxyl (3.08 μ), while IIa showed only broad unresolved carbonyl absorption (5.83–5.88 μ) and no discernible band in the hydroxyl region.[4,5]

Further evidence for the tautomeric relationship of the two ozonization products of testosterone benzoate is the identity of the materials obtained from them on further reaction. Treatment of either IIa or IIIa with acetyl chloride and acetic anhydride led to 17β-benzoyloxy-4-oxaandrost-5-en-3-one (IV)[2a] which exhibited a strong infrared

(1) Western Utilization Research and Development Division, Agricultural Research Service, U. S. Dept. of Agriculture, Albany 10, Calif.

(2) (a) R. B. Turner, THIS JOURNAL, **72**, 579 (1950); (b) G. I. Fujimoto, *ibid.*, **73**, 1856 (1951); (c) R. D. H. Heard and P. Ziegler, *ibid.*, **73**, 4036 (1951); (d) M. Uskokovic, R. I. Dorfman and M. Gut, *J. Org. Chem.*, **23**, 1947 (1958).

(3) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, THIS JOURNAL, **74**, 4223 (1952).

(4) Similar ozonizations of cholest-4-ene-3-one (ref. 2a) and 17β-benzoyloxy-19-norandrost-4-en-3-one (A. J. Birch, *Chemistry & Industry*, 615 (1951)) gave products whose spectra indicated that they were in the keto-acid form.

(5) The spectral characteristics of IIIa agree with those reported by Uskokovic, Dorfman and Gut (ref. 2d) for the acidic ozonization product of progesterone to which they have assigned structure IIIb (5β-OH).