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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, THE UNIVERSITY, ABERDEEN]

Flavothebaone. VI.[1] Oxidation of Nitrogen-Free Products

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The oxidation of flavothebaone trimethyl ether hexahydrodesazamethine, dihydrodesaza-ψ-methine, dihydrodesazaneomethine, and of dihydro-Compound-E with chromic acid, results in the production of aromatic ketones, by oxidation of the methylene group adjacent to the veratrole nucleus. In addition the dihydrodesaza-ψ-methine and dihydro-Compound-E have been oxidized by peroxytrifluoroacetic acid, with attack of the ethylenic linkage. All the reaction products have been satisfactorily formulated on the basis of the structures previously assigned to these nitrogen-free products in the flavothebaone series.

In a search for methods of further degradation of flavothebaone derivatives the oxidation of several nitrogen-free products has been investigated. It was hoped thus to open the ketonic ring of the hexahydrodesazamethine (I) and obtain compounds related to the ψ-methine series. Oxidation of the ketone (I) with chromic acid afforded, however, only 10-oxoflavothebaone trimethyl ether hexahydrodesazamethine (II), which gives a dioxime, and shows the infrared absorption bands characteristic of a saturated carbonyl group (1714 cm.$^{-1}$) and an aromatic carbonyl group (1665 cm.$^{-1}$). The same position is attacked by chromic acid in other compounds of the morphine group, *e.g.*, the conversion of morphine into 10-hydroxymorphine.[2] Attempts to oxidize the diketone (II) further failed. The oxidation of flavothebaone trimethyl ether dihydro-desaza-ψ-methine (III, R = CH_3CO) with chromic acid likewise resulted only in converting the methylene group to carbonyl, the product, oxoflavothebaone trimethyl ether dihydrodesaza-ψ-methine, being given the structure of 11-acetyl-12-ethyl-1,2,7,10-tetramethoxy-5-oxo-5,12-dihydrochrysofluorene (IV, R = CH_3CO). This compound, which readily gives a dioxime, contains one saturated and one highly conjugated unsaturated carbonyl group (infrared bands at 1704 and 1640 cm^{-1}) and has an ultraviolet spectrum (λ_{max} 2,600; 2,950, 3,500 Å, ϵ_{max} 11,200; 15,900; 15,900) very similar to that of piperonylidenedihydroflavothebaone trimethyl ether (V)[3] (λ_{max} 2,600; 2,900; 3,500 Å, ϵ_{max} 12,600; 10,000; 14,100), which contains an analogous conjugated system. Further oxidation of the diketone (IV, R = CH_3CO) could not be effected.

Oxidation of ketones to esters using peroxytrifluoroacetic acid has been successfully accomplished by Sager and Duckworth[4] and by Emmons and Lucas,[5] the latter two workers showing that in the oxidation of methyl alkyl ketones the acetate is invariably formed. Accordingly it was hoped that oxidizing the dihydrodesaza-ψ-methine (III, R = CH_3CO) with this reagent might afford a method of removing the CH_3CO group with access to the neomethine series (*vide infra*). Oxidation of the dihydrodesaza-ψ-methine, $C_{25}H_{28}O_5$, in this way, however, afforded only a very small amount of crystalline material, of composition $C_{25}H_{28}O_7$. The ultraviolet spectrum of this product (λ_{max} 3,050 Å, ϵ_{max} 7,770) indicates that the styrenoid double bond is no longer present, and the infrared spectrum (bands at 1733 and 1690 cm.$^{-1}$) indicates the presence in the molecule of an ester group and a carbonyl group, and the structure VI is accordingly suggested for the compound. Insufficient material was obtained for further investigation.

(1) Part V, *J. Org. Chem.*, **22**, 424 (1957).

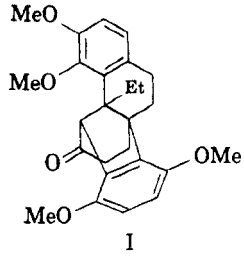
(2) H. Rapoport and S. Masamune, *J. Am. Chem. Soc.*, **77**, 6359 (1955).

(3) K. W. Bentley, J. Dominguez, and J. P. Ringe, *J. Org. Chem.*, **22**, 418 (1957).

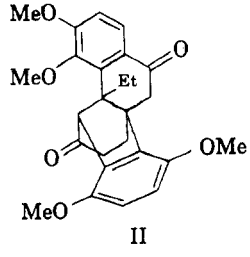
(4) W. F. Sager and A. Duckworth, *J. Am. Chem. Soc.*, **77**, 188 (1955).

(5) W. D. Emmons and G. B. Lucas, *J. Am. Chem. Soc.*, **77**, 2287 (1955).

Oxidation of flavothebaone trimethyl ether dihydrodesazaneomethine (III, R = OH) with chromic acid followed the same course as the oxidation of the dihydrodesaza-ψ-methine (III, R = CH_3CO), the product, oxoflavothebaone trimethyl ether dihydrodesazaneomethine, being given the structure of 12-ethyl-11-hydroxy-1,2,7,10-tetramethoxy-5-oxo-5,12-dihydrochrysofluorene (IV, R = OH). The ultraviolet spectrum of this product (λ_{max} 2,550; 2,900; 3,500 Å, ϵ_{max} 15,100; 13,800, 11,300) is very similar to that of the diketone (IV, R = CH_3CO), and as the infrared spectrum shows that it contains only one carbonyl group (highly conjugated, band at 1640 cm.$^{-1}$) and one hydroxyl group (band at 3585 cm.$^{-1}$), it is clear that the sterically hindered —CH(OH)— group of the neomethine derivative resists oxidation. Unlike other neomethine derivatives this substance resists dehydration on heating with formic acid, the product of the reaction being the formate ester, and doubtless this may be attributed to the fact that the driving force behind the other dehydrations in the neomethine series, the establishment of a new aromatic system, is absent in this case.



I



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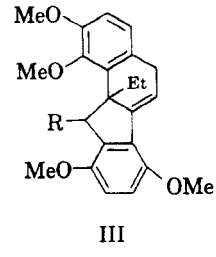

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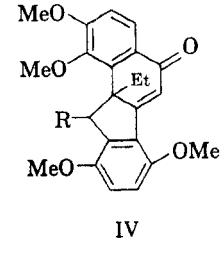

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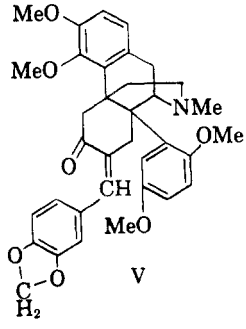

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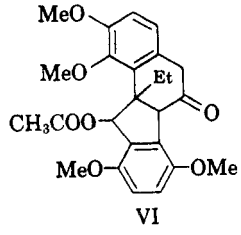

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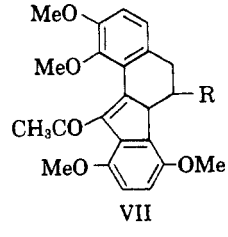

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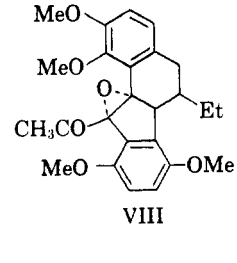

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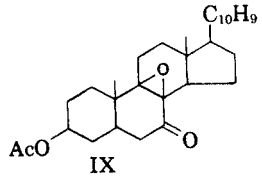

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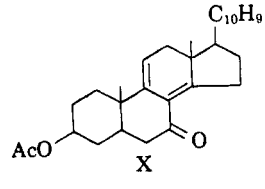

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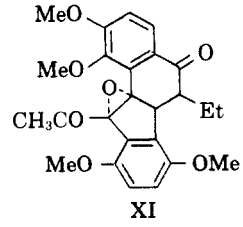

XI

The allocation of structures of two compounds in the flavothebaone series, namely Compound-E (VII, R = $CH{=}CH_2$) and dihydro-Compound-E (VII, R = Et),[6] rests on rather scanty evidence, and these structures have been further probed by the oxidation of dihydro-Compound-E. Oxidation of this substance, $C_{25}H_{28}O_5$, with either peroxytrifluoroacetic acid, or with chromic acid, affords dihydro-Compound-E_1, $C_{25}H_{28}O_6$, which no longer shows stilbenoid absorption (λ_{max} 2,900 Å, ϵ_{max} 5,020), and contains a saturated carbonyl group (infrared band at 1708 cm.$^{-1}$) in place of the unsaturated carbonyl group of the starting material; this confirms the view that the stilbenoid and α,β-unsaturated ketone double bonds of Compound-E and dihydro-Compound-E are one and the same. In addition the marked change in optical rotation is going from dihydro-Compound-E ($[\alpha]_D$ −68°) to dihydro-Compound-E_1 ($[\alpha]_D$ + 248°) suggests the establishment of new centers of dissymmetry in the latter, and this compound is accordingly formulated as (VIII). In the steroid field α,β-unsaturated ketones are known to afford epoxides by chromic acid oxidation as well as by oxidation with peracids,[7,8] and in this field epoxides between fully substituted carbon atoms are much more stable than other sorts of epoxides. For example Staveley and Bollenback[9] found, in the course of studies on α-spinasterol, that the epoxide (IX) is stable to boiling acetic acid, although it is dehydrated to (X) by heating with hydrochloric acid and acetic acid. The epoxide (VIII), however, was found stable to acid and base-catalysed dehydration. Further, epoxides such as (IX) do not react with the normal ketonic reagents due to steric hindrance

(6) K. W. Bentley, J. Dominguez, and J. P. Ringe, *J. Org. Chem.*, **22**, 409 (1957).

(7) O. Rosenheim and H. King, *Nature*, **139**, 1015 (1937).

(8) V. Petrow, *J. Chem. Soc.*, 998 (1939).

(9) H. E. Staveley and G. N. Bollenback, *J. Am. Chem. Soc.*, **65**, 1600(1943).

of the carbonyl group by the oxide ring,[7,8] and in agreement with the formulation (VIII), dihydro-Compound-E_1 fails to give an oxime or a dinitrophenylhydrazone.

Further oxidation of dihydro-Compound-E_1 with chromic acid yields the diketone dihydro-Compound-E_2, $C_{25}H_{26}O_7$, (XI) which contains one saturated and one aromatic carbonyl group (infrared bands at 1702 and 1675 $cm.^{-1}$) and forms a mono-2,4-dinitrophenylhydrazone. The satisfactory accommodation of these facts on the basis of the structure (VII, R = Et) for dihydro-Compound-E may be regarded as strong support for this formulation, and hence for the structure (VII, R = $CH{=}CH_2$) for Compound-E.

EXPERIMENTAL

Oxidation of flavothebaone trimethyl ether hexahydrodesazamethine. A solution of chromium trioxide (2 g.) in 90% acetic acid (8 ml.) was slowly added to a cooled solution of flavothebaone trimethyl ether hexahydrodesazamethine (5 g.) in acetic acid (40 ml.). A brown precipitate rapidly formed and the mixture was heated for 20 min. on the steam bath, when a deep green solution was obtained. Water was added and the precipitated product (4.8 g.) was collected and washed with 2*N* sodium carbonate solution and then with water. Recrystallization of the product from methanol afforded 10-*oxoflavothebaone trimethyl ether hexahydrodesazamethine* (II) as white prisms, m.p. 219–220°, $[\alpha]_D^{21}$ +174° ($CHCl_3$, c. 0.43).

Anal. Calcd. for $C_{26}H_{28}O_6$: C, 71.4; H, 6.5. Found: C, 71.3; H, 6.7.

The *dioxime*, prepared by heating a solution of the diketone, hydroxylamine hydrochloride, and sodium acetate in 80% ethanol, was obtained as white prisms, m.p. 255°, on recrystallization from ethanol.

Anal. Calcd. for $C_{26}H_{30}O_6N_2$: C, 66.8; H, 6.5; N, 6.0. Found: C, 66.1; H, 6.5; N, 5.9.

Oxidation of flavothebaone trimethyl ether dihydrodesaza-ψ-methine. (a) *With chromic acid.* A solution of chromium trioxide (0.8 g.) in 90% acetic acid (8 ml.) was slowly added to a cooled solution of flavothebaone trimethyl ether dihydrodesaza-ψ-methine (2 g.) in acetic acid (40 ml.). The mixture, which became deep blue, was heated for 10 min. on the steam bath, when a deep green solution was obtained. Water was added to the mixture and the product collected. After washing with sodium carbonate solution and water, the product was recrystallized from methanol, when 1.4 g. of *oxoflavothebaone trimethyl ether dihydrodesaza-ψ-methine* (IV, R = CH_3CO) was obtained as a light brown rods, m.p. 235°, $[\alpha]_D^{22}$ +350° ($CHCl_3$, c. 0.94).

Anal. Calcd. for $C_{25}H_{26}O_6$: C, 71.1; H, 6.2. Found: C, 70.7; H, 6.3.

The *dioxime*, prepared from the diketone and hydroxylamine hydrochloride in ethanol and pyridine, was obtaned as white prisms, m.p. 261° (dec.), $[\alpha]_D^{23}$ +436° ($CHCl_3$, c. 0.84), on recrystallization from ethanol.

Anal. Calcd. for $C_{25}H_{28}O_6N_2$: C, 66.3; H, 6.2; N, 6.2. Found: C, 65.8; H, 6.2; N, 5.8.

(b) *With peroxytrifluoroacetic acid.* Trifluoroacetic anhydride (3.0 g.) was added slowly, with shaking, to a cooled suspension of 87% hydrogen peroxide (0.44 ml.) in methylene chloride (4 ml.). Disappearance of the hydrogen peroxide phase indicated the completion of the formation of the peracid. The resulting solution was added to flavothebaone trimethyl ether dihydrodesaza-ψ-methine (2.5 g.) in methylene chloride (10 ml.) over a period of 10 min. The exothermic reaction was moderated by ice-bath cooling and the dark green-blue solution was kept for 10 min. after the final addition of peracid. An equal volume of chloroform was then added to the reaction mixture and the solution washed successively with water, 2*N* sodium carbonate solution, and aqueous sodium chloride. The dried solution was then evaporated to dryness. The residual dark tar was dissolved in benzene and the solution chromatographed on alumina; a bright orange band was eluted with benzene. Evaporation of the eluate and recrystallization of the residue from methanol afforded 0.08 g. of a compound believed to be *11-acetoxy-12-ethyl-1,2,7,10-tetramethoxy-6-oxo-5,6,12,13-tetrahydrochrysofluorene* (VI) as pale brown prisms, m.p. 232°, $[\alpha]_D^{20}$ −231° ($CHCl_3$, c. 0.28).

Anal. Calcd. for $C_{25}H_{28}O_7$: C, 68.1; H, 6.4. Found: C, 67.8; H, 6.3.

Oxidation of flavothebaone trimethyl ether dihydrodesazaneomethine. A solution of chromium trioxide (0.9 g.) in 90% acetic acid (8 ml.) was slowly added to a cooled solution of flavothebaone trimethyl ether dihydrodesazaneomethine (2.3 g.) in acetic acid (100 ml.). After 10 min. the mixture was heated at 60° for 5 min., when a deep green solution was obtained. Water was then added and the product collected, washed with sodium carbonate and water, and recrystallized from methanol, when *oxoflavothebaone trimethyl ether dihydrodesazaneomethine* (IV, R = OH) was obtained as pale yellow prisms, m.p. 193–194°, $[\alpha]_D^{23}$ +219° ($CHCl_3$ c. 0.76).

Anal. Calcd. for $C_{23}H_{24}O_6$: C, 69.7; H, 6.1. Found: C, 69.7; H, 6.2.

Attempted dehydration of oxoflavothebaone trimethyl ether dihydrodesazaneomethine. A solution of oxoflavothebaone trimethyl ether dihydrodesazaneomethine (0.5 g.) in acetic anhydride (6 ml.) and 100% formic acid (3 ml.) was heated under reflux for 3 hr., during which time the solution turned deep red. Water was added to the reaction mixture and the precipitated product was collected and recrystallized from ethanol, when the *formate ester* of oxoflavothebaone trimethyl ether dihydrodesazaneomethine was obtained as pale brown plates, m.p. 252° (dec.), $[\alpha]_D^{20}$ +418° ($CHCl_3$, c. 0.44).

Anal. Calcd. for $C_{24}H_{24}O_7$: C, 67.9; H, 5.7. Found: C, 67.6; H, 5.6.

Oxidation of dihydro-compound-E. (a) *With peroxytrifluoroacetic acid.* A solution of peroxytrifluoroacetic acid, prepared from trifluoroacetic anhydride (1.6 g.) and 87% hydrogen peroxide (0.24 ml.), in methylene chloride was slowly added with constant shaking to a solution of dihydro-Compound-E (2 g.) in methylene chloride (6 ml.), the exothermic reaction being moderated by ice-bath cooling. The deep violet solution was allowed to stand for 5 min. in the ice bath after the final addition of peracid, then poured into water (25 ml.) and chloroform (20 ml.) added. The organic layer was separated and washed well with aqueous sodium carbonate, aqueous sodium dithionite (this changed the color from violet to light orange), and water. The dried solution was evaporated to dryness and the residue crystallized from methanol. Recrystallization from the same solvent afforded *dihydro-Compound-E_1* (VIII) as white prisms m.p. 193–194°, $[\alpha]_D^{20}$ +248° ($CHCl_3$, c. 0.6).

Anal. Calcd. for $C_{25}H_{28}O_6$: C, 70.7; H, 6.7. Found: C, 70.7; H, 6.8. This substance could not be induced to form an oxime or a dinitrophenylhydrazone.

(b) *With chromic acid.* A solution of chromium trioxide (0.07 g.) in 90% acetic acid (4 ml.) was slowly added to a solution of dihydro-Compound-E (0.3 g.) in acetic acid (12 ml.). A deep red solution was obtained; this was kept for 10 min. at room temperature, and then heated on the steam bath for 20 min. The product was precipitated with water, collected, and recrystallized from methanol, when 0.13 g. of dihydro-Compound-E_1 was obtained as white prisms, m.p. 193–194°, alone or mixed with the product of the peracid oxidation; $[\alpha]_D^{20}$ +243° ($CHCl_3$, c. 0.45).

This compound was recovered unchanged after boiling for

4 hr. with 100% formic acid, and after boiling for 4 hr. with potassium hydroxide in ethanol and in 2-ethoxyethanol.

Further oxidation of dihydro-Compound-E_1. Dihydro-Compound-E_1 (1 g.) in acetic acid (30 ml.) was oxidized with a solution of chromium trioxide (0.4 g.) in 90% acetic acid (4 ml.). The product was precipitated with water and recrystallized from ethanol, when 0.4 g. of *dihydro-Compound-E_2* (XI) was obtained as white prisms, m.p. 224°, $[\alpha]_D^{20}$ +304° ($CHCl_3$, c. 0.60).

Anal. Calcd. for $C_{25}H_{26}O_7$: C, 68.5; H, 6.0. Found: C, 68.5; H, 6.0.

The *2,4-dinitrophenylhydrazone* was obtained as red needles, m.p. 261° on recrystallization from a mixture of ethanol and chloroform.

Anal. Calcd. for $C_{31}H_{30}O_{10}N_4$: C, 60.2; H, 4.9; N, 9.1. Found: C, 59.9; H, 4.7; N, 8.9.

ABERDEEN, SCOTLAND

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S. A.]

Steroids. LXXXV.[1] Synthesis of 4-Methyl and 4,4-Dimethyl Hormone Analogs[2]

H. J. RINGOLD AND G. ROSENKRANZ

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4,4-Dimethyl-Δ^5-androsten-3-one derivatives have been prepared by alkylation of testosterone and 17α-methyltestosterone. The dihydroallo compounds are derived by catalytic hydrogenation of the Δ^5-3-ones while the corresponding 3β,17β-diols are obtained by borohydride reduction of the saturated and unsaturated ketones. Evidence is presented for the stereochemical course of catalytic and of hydride reduction, and molecular rotation discrepancies are discussed. 4-Methyltestosterone has been synthesized by alkaline cyclization of the reaction product of ethyl Grignard reagent and the enol lactone derived from ozonolysis of testosterone.

While the 4,4-dimethyl moiety is common in the triterpene series (*e.g.* lanosterol, euphol and β-amyrin) the only such steroidal compounds known have been just recently synthesized in the cholesterol[3] and ergosterol[4] series. As part of a broad program directed towards the correlation of steroid structure with activity we have had occasion to prepare a number of novel 4,4-dimethyl substituted androgen analogs as well as 4-methyltestosterone.

Treatment of testosterone (Ia) and 17α-methyltestosterone (Ib) with excess potassium *tert*-butoxide and methyl iodide in *tert*-butanol for several hours at room temperature[5] led in *ca.* 70% yield to 4,4-dimethyl-Δ^5-androsten-17β-ol-3-one (IIa) and to 4,4,17-trimethyl-Δ^5-androsten-17β-ol-3-one (IIb). These unsaturated ketones, in methanol solution, were smoothly hydrogenated at 25° and atmospheric pressure over a palladium-carbon catalyst to the corresponding dihydroallo derivatives, 4,4-dimethyldihydrotestosterone (IIIa) and 4,4,17-trimethyldihydrotestosterone (IIIb). Sodium borohydride reduction of the Δ^5-3-ketones (IIa and IIb) and of the 3-keto dihydro compounds (IIIa and IIIb) led in high yield to the respective Δ^5-3β-ols (IVa and IVb) and to the saturated 3β-ols (Va and Vb). Alternately, the saturated alcohol Va was prepared by catalytic hydrogenation of 4,4-dimethyl-Δ^5-androstene-3β,17β-diol (IVa), establishing that, as one would expect, reduction of the 5,6-double bond followed the same stereochemical course in the case of both the 3-ketone and the 3β-alcohol and further, hydride reduction of the 3-ketone led to the 3β-ol in the saturated as well as the unsaturated series.

Although, to our knowledge, there are no literature reports of the double bond hydrogenation of a steroidal Δ^5-3-ketone, the rings A/B *trans* configuration may be assigned to compounds III and V with certainty based on the following considerations: (1) catalyst absorption on the α-face of C-5,6 (which would lead to the A/B *trans* compound) is not sterically hindered, while the combination of a C-4β-axial methyl and a C-10 angular methyl group markedly hinders β-face approach to C-5,6; (2) the rotatory dispersion curves of IIIa and IIIb are identical with those of authentic 4,4-dimethyl-3-keto-A/B *trans* terpenes;[6] and (3) in all cases hydrogenation of a steroid Δ^5-3β-alcohol leads to the A/B *trans* compound.[7] That the alcohols IV and V are indeed the 3β (equatorial) alcohols follows from the recorded[3] lithium alumi-

(1) Paper LXXXIV, H. J. Ringold and G. Rosenkranz, *J. Org. Chem.*, **22**, 99 (1957).

(2) Presented at the 129th Meeting of the American Chemical Society, Dallas, Tex., April 1956.

(3) R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives, and R. B. Kelly, *J. Am. Chem. Soc.*, **76**, 2852 (1954).

(4) G. Cooley, B. Ellis, and V. Petrow, *J. Chem. Soc.*, 2998 (1955).

(5) These reaction conditions are those reported by Woodward, Barton, and co-workers, reference 3, in their elegant conversion of cholesterol to lanosterol.

(6) We are grateful to Professor C. Djerassi for the determination of rotatory dispersion curves of these compounds. For a description of this useful technique, see C. Djerassi, E. W. Folz, and A. E. Lippman, *J. Am. Chem. Soc.*, **77**, 4354 (1955).

(7) *e.g.* The hydrogenation of cholesterol leads exclusively to cholestanol [R. Willstätter and E. W. Mayer, *Ber.*, **41**, 2199 (1908)], and that of dehydroepiandrosterone to androstan-3β-ol-17-one [A. Butenandt, H. Dannenberg, G. Hanisch, and H. Kudszus, *Z. physiol. Chem.*, **237**, 57 (1935)].