tial 105 mg. of the ortho ester XIV with a solvated m.p. < 200°. Slight concentration of the mother liquor afforded an additional 105 mg. of the ortho ester (XIV), also with a solvated m.p. < 200°. The infrared spectrum of this material was identical in all respects to that of an authentic sample.[2]

16α-Acetoxy-9α-fluoro-11β,17α,21-trihydroxypregna-1,4-diene-3,20-dione (XV).—A solution of 16α,17α-(1-ethoxy)-ethylidenedioxy-9α-fluoro-11β,21-dihydroxypregna-1,4-diene-3,20-dione (XIV) (0.1 g.) in methanol (3 ml.) was treated with 10% aqueous hydrochloric acid (0.5 ml.). After standing at room temperature for 5 min., the reaction mixture was neutralized with sodium bicarbonate and most of the methanol removed at reduced pressure. Water was added and the precipitate so obtained was collected and dissolved in ethyl acetate. Evaporation of the dried solution gave 80 mg. of the 16α-acetate XV. Cyrstallization from acetone–hexane yielded 43 mg. of compound, m.p. 230–231°; $[\alpha]^{25}_D$ +63° (methanol); λ_{max} 239 mμ (ε 15,050); infrared spectrum identical to that reported; lit.[2] m.p. 224–228°; $[\alpha]^{22}_D$ +49.7° (methanol); λ_{max} 238 mμ (ε 15,450).

The Reaction of Alkoxalylated Steroid Ketones with Dibenzoyl Peroxide. A Synthesis of 16β-Hydroxytestosterone

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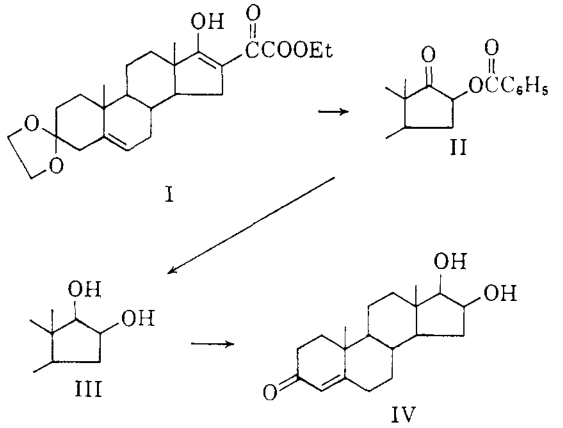
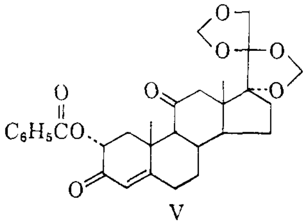
The utility of alkoxalylated or formylated steroid ketones for the introduction of alkyl[1] and cyano[2] groups as well as the halogens,[3,4] including fluorine,[5] is well documented. We now wish to report the direct preparation of certain steroid α-ketol esters *via* the reaction of an alkoxalyl ketone with dibenzoyl peroxide.[6] It may be noted that the benzoyloxylation of various sodio malonates with dibenzoyl peroxide has been reported.[7]

Addition of an equivalent of sodium hydride followed by an equivalent of dibenzoyl peroxide to 16-ethoxalyl-3-ethylenedioxy-17-hydroxyandrosta-5,16-diene (I)[5b,8] and subsequent acetate-induced C-deacylation[5a] afforded a 40% yield of 16β-benzoyloxy-3-ethylenedioxyandrost-5-en-17-one (II). Reduction of this substance with lithium aluminum hydride[9] gave 3-ethylenedioxy-16β,17β-dihydroxyandrost-5-ene (III), which on acid treatment furnished 16β-hydroxytestosterone (IV).[10] The identity of this last substance, as well as the diacetate thereof, was established by mixture melting point comparisons with authentic specimens.[11]



Similarly, reaction of molar equivalents of dibenzoyl peroxide, potassium *t*-butoxide, and the 2-methoxalyl derivative of 17α,20;20,21-bismethylenedioxypregn-4-ene-3,11-dione,[12] followed by treatment with potassium acetate, afforded an 8% yield of 2α-benzoyloxy-17α,20;20,21-bismethylenedioxypregn-4-ene-3,11-dione (V). The assignment of the α-configuration to the benzoyloxy substituent in V was made on the basis of the molecular rotation contribution (+58°) of this group.[13]



V

Experimental[14]

16β-Benzoyloxy-3-ethylenedioxyandrost-5-en-17-one (II).—To a magnetically stirred suspension of 0.293 g. (12.2 mmoles) of sodium hydride in 100 ml. of benzene was added

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[1] J. A. Hogg, F. H. Lincoln, R. W. Jackson, and W. P. Schneider, *J. Am. Chem. Soc.*, **77**, 6401 (1955).

[2] H. M. Kissman, A. S. Hoffman, and M. J. Weiss, *J. Org. Chem.*, **26**, 2610 (1961).

[3] H. Ruschig, *Ber.*, **88**, 878 (1955).

[4] 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, *J. Am. Chem. Soc.*, **77**, 4436 (1955).

[5] (a) H. M. Kissman, A. M. Small, and M. J. Weiss, *ibid.*, **81**, 1262 (1959); (b) H. M. Kissman, A. M. Small, and M. J. Weiss, *J. Org. Chem.*, **26**, 973 (1961); (c) A. H. Nathan, J. C. Babcock, and J. A. Hogg, *ibid.*, **24**, 1395 (1959); (d) A. H. Nathan, B. J. Magerlein, and J. A. Hogg, *ibid.*, **24**, 1517 (1959); (e) J. Edwards and H. J. Ringold, *J. Am. Chem. Soc.*, **81**, 5262 (1959).

[6] The two-step preparation of α-ketol esters from alkoxalyl steroid ketones is well known; *cf.* ref. 3.

[7] S.-O. Lawesson and T. Busch, *Acta. Chem. Scand.*, **13**, 1716 (1959).

[8] Spectral evidence suggests that this ethoxalyl derivative exists in the enol form depicted by I.

[9] J. Fishman, *J. Am. Chem. Soc.*, **82**, 6143 (1960).

[10] (a) A. Butenandt, J. Schmidt-Thomé, and T. Weiss, *Ber.*, **72B**, 417 (1939); (b) H. L. Herzog, M. J. Gentles, A. Basch, W. Cascarelli, M. E. A. Zeitz, and W. Charney, *J. Org. Chem.*, **25**, 2177 (1960); (c) R. M. Dodson and S. Mizuba, *ibid.*, **27**, 698 (1962).

[11] These samples were kindly supplied by Professor R. M. Dodson of the University of Minnesota and Dr. S. Mizuba of G. D. Searle & Co.

[12] C. E. Holmlund, L. I. Feldman, H. M. Kissman, and M. J. Weiss, *J. Org. Chem.*, **27**, 2122 (1962).

[13] 2β-Acetoxy substituents show a marked levorotatory effect (−514 to −586); F. Sondheimer, St. Kaufmann, J. Romo, H. Martinez, and G. Rosenkranz, *J. Am. Chem. Soc.*, **75**, 4712 (1953).

a solution of 5.25 g. (12.2 mmoles) of 16-ethoxalyl-3-ethylenedioxy-17-hydroxyandrosta-5,16-diene (I)[5b] in 100 ml. of benzene. After the hydrogen evolution had ceased, a solution of 2.96 g. (12.2 mmoles) of dibenzoyl peroxide in benzene was added at 0°. The mixture was allowed to warm to room temperature and stirred for 2.5 days. The resulting mixture was distributed between additional benzene and a 1% potassium hydroxide solution. The benzene solution was washed repeatedly with the alkali until it gave a negative test for an enol with ferric chloride. The dried organic layer was taken to dryness and the residue was treated with 5.0 g. of sodium acetate in 200 ml. of boiling methanol for 1 hr. The solution was taken to near dryness and distributed between methylene chloride and water. The dried organic layer was evaporated, and the residue was recrystallized twice from acetone–petroleum ether to give 1.675 g. of white needles, m.p. 210–215°. The combined mother liquors were taken to dryness, and the residue was chromatographed on silica gel. The solid eluted by benzene–ether (95:5) was recrystallized from acetone–petroleum ether to give 0.494 g. (40% total yield) of white needles, m.p. 210–215°. Material from a similar experiment had m.p. 210–215°; $[\alpha]^{25}_{\mathrm{D}}$ +35°; $\lambda_{\max}$ 230 mμ (ϵ 15,500); $\lambda_{\max}$ 5.70, 5.80, 6.22, 6.30, 7.80, 8.97, 13.94 μ; positive blue tetrazolium test.

Anal. Calcd. for $C_{28}H_{34}O_5$ (450.55): C, 74.64; H, 7.61. Found: C, 74.45; H, 7.72.

3-Ethylenedioxy-16β,17β-dihydroxyandrost-5-ene (III).—To a magnetically stirred slurry of 0.760 g. (20 mmoles) of lithium aluminum hydride in 25 ml. of ether was added dropwise a solution of 0.900 g. (2.0 mmoles) of 16β-benzoyloxy-3-ethylenedioxyandrost-5-en-17-one (II) in 30 ml. of benzene. The mixture was heated at reflux temperature for 1 hr. and allowed to stand at room temperature for 1.5 hr. The excess hydride was destroyed by addition of ethyl acetate, and the mixture was treated with a 5% hydrochloric acid solution and extracted with methylene chloride. The dried extract was evaporated, and the residue was triturated with ether and filtered to give 0.575 g. (83% yield) of white crystals, m.p. 228–231°. A sample was recrystallized twice from acetone–petroleum ether to give white crystals, m.p. 226–228°; no significant absorption in the ultraviolet at 20 γ/ml.; $\lambda_{\max}$ 2.88, 9.09 μ.

Anal. Calcd. for $C_{21}H_{32}O_4$ (348.47): C, 72.38; H, 9.26. Found: C, 71.59, 71.18; H, 9.13, 9.10.

16β-Hydroxytestosterone (IV).—A solution of 0.500 g. (1.44 mmoles) of 3-ethylenedioxy-16β,17β-dihydroxyandrost-5-ene (V) in 20 ml. of methanol containing 1 ml. of 8% sulfuric acid solution was heated at reflux temperature for 2 hr. The solution was diluted with 30 ml. of water and evaporated until solid separated. The mixture was extracted with methylene chloride, and the combined extracts were washed with sodium bicarbonate solution, dried, and taken to dryness. The residue was crystallized from acetone–petroleum ether to give 0.283 g. of long needles, m.p. 182–184°. Concentration of the mother liquor gave an additional 39 mg. of needles. Material from a similar experiment was obtained as white needles, m.p. 188–189°; a mixture with 16α-hydroxytestosterone melted at 160–168°.[15] The material had $[\alpha]^{25}_{\mathrm{D}}$ +105°, +93° (methanol); $\lambda_{\max}$ 240 mμ (ϵ 15,800); $\lambda_{\max}$ 3.02, 6.08, 6.20 μ. Reported values are m.p. 172–173°,[10a] 179–182°,[10b] and 183.5–185.5°[10c] $[\alpha]_{\mathrm{D}}$ +101°, +94 (dioxane),[10b] +103°.[10c]

Anal. Calcd. for $C_{19}H_{28}O_3$ (304.41): C, 74.96; H, 9.27. Found: C, 74.52; H, 9.69.

This material formed a diacetate, obtained from methanol as white needles, m.p. 205–206°; $[\alpha]^{25}_{\mathrm{D}}$ +90°; $\lambda_{\max}$ 240 mμ (ϵ 16,500); $\lambda_{\max}$ 5.75, 5.97, 6.18, 7.95, 8.10 μ. (Reported values are m.p. 201–202.5°,[10b] 204–205.5°;[10c] $[\alpha]^{25}_{\mathrm{D}}$ +88°,[10b] +90°[10c].)

Anal. Calcd. for $C_{23}H_{32}O_5$ (388.49): C, 71.10; H, 8.30. Found: C, 71.31; H, 8.42.

On treatment with acetone–perchloric acid the diol gave an acetonide, obtained from petroleum ether as needles, m.p. 189–191°; $[\alpha]^{25}_{\mathrm{D}}$ +120°; $\lambda_{\max}$ 240 mμ (ϵ 13,600); $\lambda_{\max}$ 6.00, 6.19, 7.29, 7.34, 9.46, 11.58 μ. Reported values are m.p. 183–184°,[10a] 185–187°,[10b] and 183.5–187°.[10c]

Anal. Calcd. for $C_{22}H_{32}O_3$ (344.48): C, 76.70; H, 9.36. Found: C, 76.83; H, 9.42.

2α-Benzoyloxy-17α,20;20,21-bismethylenedioxypregn-4-ene-3,11-dione (V).—A solution of 224 mg. (2.0 mmoles) of potassium *t*-butoxide and 977 mg. (2.0 mmoles) of 3-hydroxy-2-methoxalyl-17α,20;20,21-bismethylenedioxypregn-2,4-dien-11-one[12] was treated with a solution of 484 mg. (2.0 mmoles) of dibenzoyl peroxide in 25 ml. of benzene. The resulting mixture was stirred at room temperature for 23 hr. and then distributed between methylene chloride and water. The dried organic solution was taken to dryness, and the residue was treated with 1.00 g. of potassium acetate in 25 ml. of boiling methanol for 1 hr. The solution was taken to dryness; the product was isolated with methylene chloride and chromatographed on a silica gel column (1.2 × 16.5 cm.). Elution with benzene–ether (9:1) gave in fractions 3 and 4 (100 ml. each) a solid that was rechromatographed on a silica gel column (1.0 × 17 cm.). Elution with benzene–ether (9:1), 50 ml. fractions being collected, gave in fraction 2 material which was recrystallized from methanol to give 87 mg. (8% yield) of white needles, m.p. 203–205°; $[\alpha]^{25}_{\mathrm{D}}$ +74°; $\lambda_{\max}$ 233 mμ (ϵ 30,500); $\lambda_{\max}$ 5.85, 6.15, 6.22, 6.29, 7.85, 8.88, 9.10, 14.02 μ; positive blue tetrazolium test.

Anal. Calcd. for $C_{30}H_{34}O_8$ (522.57): C, 68.95; H, 6.56. Found: C, 68.50; H, 6.37.

Acknowledgment.—We are indebted to Mr. L. Brancone and his staff for the microanalyses and to Mr. W. Fulmor and his staff for the spectral and polarimetric data.

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[14] Melting points were taken in an open capillary tube and are uncorrected values. The ultraviolet spectra were determined in methanol on a Cary recording spectrophotometer and the infrared spectra (pressed potassium bromide disks) were carried out with a Perkin–Elmer spectrophotometer (Model 21). Polarimetric data were obtained in chloroform solution unless stated otherwise. All evaporations were carried out under reduced pressure, and the petroleum ether used was that fraction boiling at 60–70°.

[15] (a) W. J. Adams, D. K. Patel, V. Petrow, and I. A. Stuart-Webb, *J. Chem. Soc.*, 297 (1956); (b) We are indebted to Dr. C. E. Holmlund of these laboratories for a specimen of this material.

Aza-Aromatic Substitution. II. Debromination and Isomerization of 3-Bromoquinoline at Higher Temperatures

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In rationalizing the selective and facile bromination of quinoline at C-3 by the decomposition of the 1:1 quinoline–bromine complex, it was postulated that C-3 was attacked in preference to C-6 because of the favorable circumstances for a bridged bromonium ion transition state at C-3 (I).[1] By the principle of microscopic reversibility

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[1] Paper I of this series: J. J. Eisch, *J. Org. Chem.*, 27, 1318 (1962).