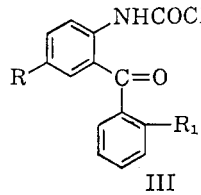
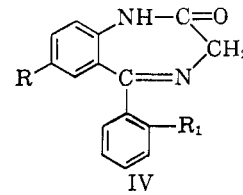
TABLE II



III



IV

			III			IV		
	R	R_1	Yield, %	M.p.	Cryst.[a] from	Yield, %	M.p.	Cryst. from
a	H	H	41	76–77[b]	b. + h.			
b	Cl	H	61	101–103[c]	Cold b. + h.	53	214–215[d]	Hot b.
c	CF_3	H				13	197–201[e]	h.
d	Cl	Cl	74	121–122[c]	b. + h.			
e	H	NO_2	78	201–203[f,g]	m. + e.			
f	CH_3O	H				60	215–218[c]	b. + h.

[a] b. = benzene, h. = hexane, m. = methanol, e. = ether. [b] *Anal.* Calcd. for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 71.61; H, 5.81; N, 10.70. [c] See footnote 1. [d] L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 4936 (1961). [e] G. Saucy and L. H. Sternbach, *Helv. Chim. Acta*, **45**, 2226 (1962). [f] Isolated as hydrobromide. *Anal.* Calcd. for $C_{15}H_{14}BrN_3O_4$: C, 47.38; H, 3.71; N, 11.05. Found: C, 47.93; H, 4.00; N, 11.09. [g] Free base will be described in paper X of this series.

stirred for 2 hr. at room temperature, kept overnight at room temperature and then heated for 1 hr. on a steam bath. The solvent was removed by distillation *in vacuo* and the residue then dissolved in 75 cc. of benzene, washed with dilute hydrochloric acid, water, and dilute sodium bicarbonate. After drying over sodium sulfate, the solvent was removed *in vacuo* and the residue crystallized from ethanol to give 600 mg. (30% yield) of (2-benzoyl-4-chlorophenylcarbamoylmethyl)carbamic acid benzyl ester, m.p. 114–116°. A mixed melting point with material prepared above showed no depression.

(2-Benzoyl-4-chlorophenylcarbamoylmethyl)carbamic Acid Benzyl Ester (IIb) (Acid Chloride Method).—To a solution of 7.1 g. of crude carbobenzoxyglycine chloride[9] in 150 cc. of dry pyridine 7.0 g. of 2-amino-5-chlorobenzophenone was added. After warming for 1 hr. on a steam bath, the solvent was distilled *in vacuo*. The residue was dissolved in methylene chloride and washed successively with dilute hydrochloric acid, water, and dilute sodium carbonate. After drying over sodium sulfate, the solvent was removed *in vacuo* and the residue crystallized from ethanol to give 800 mg. of (2-benzoyl-4-chlorophenylcarbamoylmethyl)carbamic acid benzyl ester, m.p. 109–113°. Recrystallization from ethanol raised the melting point to 114–115°. A mixed melting point with a sample prepared above showed no depression.

5-Chloro-2-glycylamidobenzophenone (IIIb).—A solution of 3.1 g. of (2-benzoyl-4-chlorophenylcarbamoylmethyl)-carbamic acid benzyl ester in 30 cc. of 20% hydrogen bromide in acetic acid[7] was stirred for 35 min. at room temperature. Then 175 cc. of anhydrous ether was added rapidly while stirring. The gummy material that separated was stirred for 10 min., the supernatant liquid decanted, and the product again stirred for 10 min. with 125 cc. of ether. The ether was decanted and the residue dissolved in 100 cc. of water to produce a turbid solution of pH 2.1. This solution was extracted twice with ether and the washings discarded. On addition of ammonia to the aqueous solution to pH 11, a white crystalline product separated. This was extracted with methylene chloride and after drying over sodium sulfate, the methylene chloride was evaporated *in vacuo* at 20° leaving a residue of 1.75 g. Crystallization from cold benzene–hexane gave 1.4 g. (61% yield) of 5-chloro-2-glycylamidobenzophenone, m.p. 101–103°.

7-Chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one (IVb).—A solution of 3.1 g. of (2-benzoyl-4-chlorophenylcarbamoylmethyl)carbamic acid benzyl ester in 30 cc. of 20% hydrobromic acid in glacial acetic acid was stirred for 45 min. at room temperature. On addition of 175 cc. of anhydrous ether, a gummy solid separated. After several minutes, the ether solution was decanted. About 155 cc. of ether was added to the residue and after chilling in an ice bath, 10% sodium hydroxide was added until the mixture was alkaline. The ether layer was separated, washed twice with water, and dried over sodium sulfate. After filtration, the ether solution was concentrated to dryness *in vacuo*. The residue was crystallized from hot benzene to yield 1.05 g. (53%) of 7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one, m.p. 214-215°.

Acknowledgment.—We are indebted to Dr. A. Steyermark and his staff for microanalyses and Dr. A. Motchane and Mr. S. Traiman for the infrared spectra.

(9) M. Bergmann and L. Zervas, *Ber.*, **65**, 1192 (1932).

16-Hydroxylated Steroids. XXIV.[1] 16α,17α-Ortho Esters and Their Transformation Products

JOHN P. DUSZA AND SEYMOUR BERNSTEIN

Organic Chemical Research Section, Lederle Laboratories, A Division of American Cyanamid Co., Pearl River, New York

Received July 23, 1962

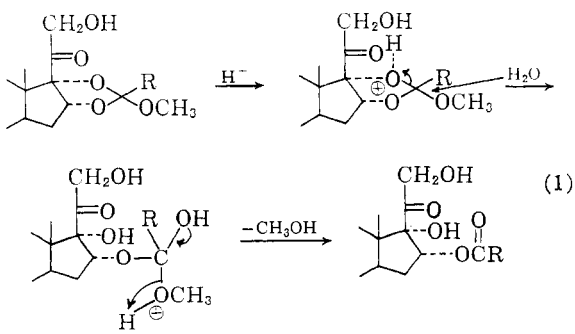
The synthesis of polyhydroxylated steroids has been the subject of an extensive investigation in these laboratories. In addition to their synthesis, considerable effort has been directed to effect selective protection of the various reactive hydroxyl groups in these molecules. We shall discuss in this Note some aspects connected with the use of ortho esters as protective groups and as inter-

(1) Paper XXIII, S. Bernstein, R. B. Brownfield, R. H. Lenhard, S. Mauer, and I. Ringler, *J. Org. Chem.*, **27**, 690 (1962).

mediates for the selective preparation of 16-esters.

The acid-catalyzed reaction of 11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione (I) with trimethyl orthoformate afforded the enol ether ortho ester, 11β,21-dihydroxy-16α,17α-methoxymethylenedioxypregna-3,5-dien-20-one (III). When the reaction was applied in the 9α-fluoro series with II, the corresponding fluorinated derivative IV was obtained.[2,3] As isolated, these compounds formed very stable hydrates which impeded their purification. In each case the crude enol ether ortho ester could be acetylated to give the respective 21-acetates, V and VI, also isolated as solvates. Attempted recrystallization or removal of the incorporated solvent by heating at reduced pressure resulted in part in cleavage of the enol ether function. However, a purification could be achieved by dissolving the crude solvate in methylene chloride and passing this solution rapidly through a synthetic magnesium silicate adsorbent. The compounds were eluted with low concentrations (0–4%) of acetone in methylene chloride. Although the infrared spectra of the crude compounds indicated complete conversion to the enol ether ortho ester, poor recoveries from the columns were encountered. Moreover, the homogeneous fractions so obtained underwent extensive hydrolytic cleavage on rechromatography.

Selective removal of the enol ether function in the presence of the ortho ester grouping was accomplished only with moderate success. In the 9α-fluoro series, the corresponding Δ^4-3-ones, VII and VIII, were obtained through brief acid treatment (*p*-toluenesulfonic acid–dioxane; perchloric acid–aqueous dioxane). Experiments in the 9α-hydrogen series were not conclusive. Brief acid treatment usually resulted in incomplete hydrolysis of the enol ether function,[4] while prolonged reaction conditions also partially hydrolyzed the ortho ester grouping to a 16α-ester. One possible mechanism for the formation of such 16-esters may be generally illustrated as follows. Protonation of the 17-oxygen would be assisted by the presence of the 20-carbonyl group. The attack of water would then bring about the cleavage of the cyclic ortho ester and give rise to, *e.g.*, a formate (R = H).[5,6]



(1)

The acid hydrolysis (*p*-toluenesulfonic acid–dioxane; hydrochloric acid–methanol) of 11β,21-dihydroxy-3-methoxy-16α,17α-methoxymethylenedioxypregna-3,5-dien-20-one (III) or of its 9α-fluoro analog IV gave the respective 16α-formates, IX and X. To demonstrate that there still remained a readily acylable hydroxyl group, treatment of X with pyridine and acetic anhydride afforded the mixed ester XI. The structure assigned to XI was supported by the hydrolysis of 21-acetoxy-9α-fluoro-3-methoxy-16α,17α-methoxymethylenedioxypregna-3,5-dien-20-one (VI) to the identical mixed ester. In this manner the formate ester was shown to be at C-16 and the acetate ester at C-21. Vigorous hydrolysis of VI (hydrochloric acid–methanol) afforded 21-acetoxy-9α-fluoro-11β,16α,17α-trihydroxypregn-4-ene-3,20-dione (XII).[7]

Finally, the extension of the partial hydrolysis of a 16,17-ortho ester function to provide a 16α-acetate was studied. For this purpose, 9α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione (XIII) in dioxane was treated with triethyl orthoacetate in the presence of 72% perchloric acid to give the known ortho ester XIV. The latter in methanol on hydrolysis with 10% aqueous hydrochloric acid was converted into the desired 16α-acetoxy-9α-fluoro-11β,17α,21-trihydroxypregna-1,4-diene-3,20-dione (XV).[2]

Experimental

Melting points are uncorrected. The ultraviolet spectra were determined in methanol and the rotations in the solvents specified. The infrared absorption spectra were determined in pressed disks of potassium bromide. The authors are indebted to William Fulmor and associates for the infrared, ultraviolet absorption, and optical rotation data. We wish also to thank Louis M. Brancone and associates for the analyses.

11β,21-Dihydroxy-3-methoxy-16α,17α-methoxymethylenedioxypregna-3,5-dien-20-one (III).—One gram of 11β,16α,17α-trihydroxypregn-4-ene-3,20-dione (I) was suspended in dioxane (10 ml.), trimethyl orthoformate (1.0 ml.) and methanol (4 drops). Two drops of 70% perchloric acid were added; solution was obtained in 1 min. and the reaction

(2) The reaction of ortho esters with steroidal 16α,17α-glycols [L. L. Smith and M. Marx, *J. Am. Chem. Soc.*, **82**, 4625 (1960)] in $\Delta^{1,4}$-3-one systems has been reported. References to cyclic ortho esters in other than the steroid field have been collected in this reference.

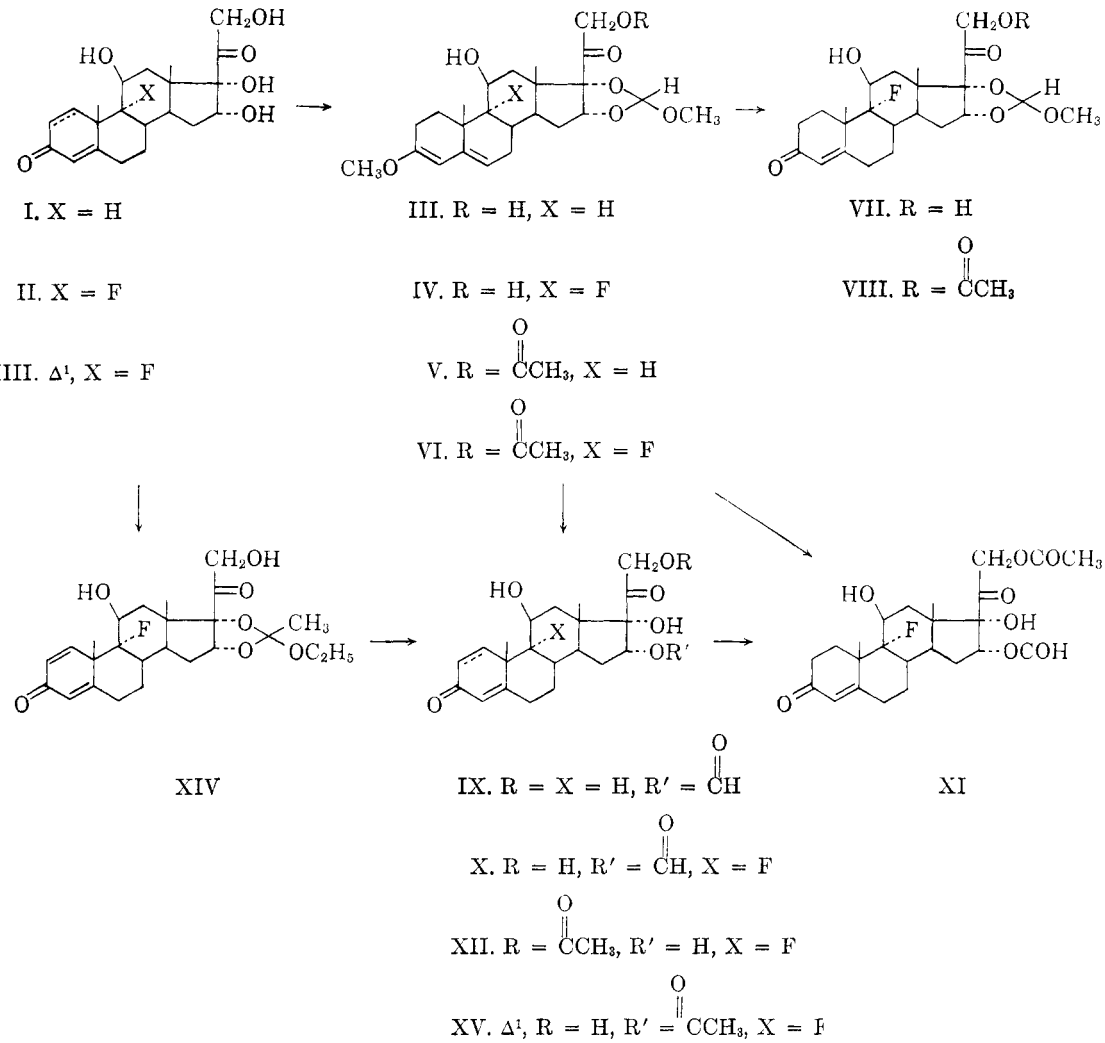
(3) The reaction of the steroid dihydroxyacetone side chain with ortho esters has recently been reported [R. Gardi, R. Vitali, and A. Ercoli, *Tetrahedron Letters*, 448 (1961)] to give the 17α,21-cyclic ortho esters.

(4) The ease of hydrolysis of the $\Delta^{3,5}$-enol ether appears to be influenced by Ring C substituents. The presence of a C-11 β-hydroxyl group contributes to its instability which is increased by the addition of a C-9 fluorine atom, such that compounds III, IV, V, and VI are hydrolyzed noticeably on standing at room temperature even after removal of the solvating molecules.

(5) The appearance of 16α-esters has been noted (ref. 2) under ortho ester forming conditions. These may have arisen from subsequent hydrolysis of the cyclic orthoester according to equation 1 where R is an alkyl group.

(6) The acid hydrolysis of 17α,21-ortho ester (ref. 3) led to a mixture of 17α- and 21-esters. In this case preferential protonation of either the 17 or 21-oxygen might not be expected.

(7) Prepared through acetylation of the 16α,17α-borate complex [L. J. Leeson, J. A. Lowery, G. M. Sieger, and S. Muller, *J. Pharm. Sci.*, **50**, 606 (1961)] with no physical constants supplied.



was allowed to proceed for an additional 1 min. The reaction was terminated by the addition of pyridine (1.0 ml.). The entire reaction mixture was poured into water and filtered to provide 1.03 g. of the enol ether ortho ester III. The infrared spectrum of this material indicated complete conversion to the enol ether.

The dried solid was dissolved in methylene chloride and chromatographed on Florisil[8] (40 g.). The material eluted in the late 2% acetone–methylene chloride fractions (4 × 100 ml.) and the early 4% acetone–methylene chloride fractions (3 × 100 ml.) was combined to give 0.35 g. of enol ether orthoester. An aliquot of the 2% acetone–methylene chloride eluates gave material of m.p. 176–177° (dried *in vacuo*); $[\alpha]^{25}D$ −18° (1% pyridine in chloroform); λ_{max} 237 mμ (ε 21,900); $\lambda_{max}^{MeOH-HCl}$ 244 mμ (ε 19,500 based on regenerated Δ4-3-one); ν_{max} 3520, 3480, 1728, 1665, 1640 and 1175 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{34}O_7$ (434.51): C, 66.34; H, 7.89. Found: C, 65.89; H, 7.99.

9α-Fluoro-11β,21-dihydroxy-3-methoxy-16α,17α-methoxymethylenedioxypregna-3,5-dien-20-one (IV).—To a suspension of 9α-fluoro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione (II) (2.0 g.) in dry dioxane (20 ml.), trimethyl orthoformate (2.0 ml.) and absolute methanol (0.1 ml.) was added concentrated sulfuric acid (0.1 ml.). The mixture became homogeneous in 5 min. and the reaction time was extended another 15 min. at which time the solution had become dark red. The reaction was terminated by the addition of pyridine (1.2 ml.) which dissipated most of the color. The light yellow reaction mixture was poured into water and filtered to give the crude enol ether ortho ester IV (2.2 g.).

The crude material was dissolved in methylene chloride and chromatographed on Florisil.[8] The desired material was eluted with the later 2% acetone–methylene chloride fractions (5 × 100 ml.) and the 4% acetone–methylene chloride fractions (18 × 100 ml.) to give a total of 1.011 g. of crystalline material. Numerous attempts at recrystallization of this material were unsuccessful. A combination of the 2% acetone fractions provided 0.7 g. of product IV which, after being dried *in vacuo*, exhibited a m.p. of 197–206°[9]; $[\alpha]^{25}D$ ±0° (1% pyridine in chloroform); λ_{max} 240 mμ (ε 20,600); ν_{max} 3500, 1730, 1670, 1645, 1240, and 1175 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{33}O_7F$ (452.50): C, 63.70; H, 7.35; F, 4.20. Found: C, 63.36; H, 7.45; F, 4.17.

21-Acetoxy-11β-hydroxy-3-methoxy-16α,17α-methoxymethylenedioxypregna-3,5-dien-20-one (V).—A solution of 11β,21-dihydroxy-3-methoxy-16α,17α-methoxymethylenedioxypregna-3,5-dien-20-one (III) (1.05 g.) in pyridine (5.0 ml.) was treated with acetic anhydride (3.0 ml.). After standing overnight at room temperature, the reaction mixture was poured into water and extracted with ether.

(8) Florisil, a trade name of the Floridin Corporation for a synthetic magnesium silicate adsorbent.

(9) The broad melting point ranges exhibited by IV and VI may well be ascribed to their instability, see ref. 4. It should be noted that in ortho ester formation a new asymmetric center is generated, and consequently the melting points of IV and VI may also be a reflection of the existence of an unresolved epimeric mixture.

The ether extract was washed with a saturated saline solution and dried. Evaporation of the solvent gave a semicrystalline residue which was dissolved in methylene chloride and chromatographed on Florisil[8] (30 g.). The early methylene chloride fractions (25 ml.) were combined to give 0.29 g. of desired material V, which after being dried *in vacuo* exhibited m.p. 194–196°; $[\alpha]^{25}D$ −17° (1% pyridine in chloroform); λ_{max} 238 mμ (ε 20,200); ν_{max} 3570, 1758, 1658, 1632, 1233, and 1170 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{36}O_8$ (476.55): C, 65.53; H, 7.67. Found: C, 65.89; H, 7.74.

21-Acetoxy-9α-fluoro-11β-hydroxy-3-methoxy-16α,17α-methoxylenedioxypregna-3,5-dien-20-one (VI).—A solution of 9α-fluoro-11β,21-dihydroxy-3-methoxy-16α,17α-methoxymethylenedioxypregna-3,5-dien-20-one (IV) (1.96 g.) in dry pyridine (15 ml.) and acetic anhydride (10 ml.) was allowed to stand at room temperature for 20 hr. The reaction mixture was poured into water and was extracted thoroughly with ether. The extract was washed with a saturated saline solution, dried (sodium sulfate), and evaporated to give a glass. The latter was dissolved in methylene chloride and chromatographed on Florisil[8] (60 g.).

The desired material was eluted with methylene chloride (10 × 100 ml.), and amounted to 1.1 g. of crystalline 21-acetate VI. A portion (0.3 g.) of this material was rechromatographed to yield 75 mg.; m.p. 176–194°[9] which could not be recrystallized; $[\alpha]^{25}D$ +2° (1% pyridine in chloroform); λ_{max} 240 mμ (ε 18,300); ν_{max} 3570, 1740, 1667, 1642, and 1238 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{35}O_8F$ (494.54): C, 63.15; H, 7.14; F, 3.84. Found: C, 63.17; H, 7.52; F, 3.79.

9α-Fluoro-11β,21-dihydroxy-16α,17α-methoxymethylenedioxypregn-4-ene-3,20-dione (VII).—To a solution of 9α-fluoro-11β,21-dihydroxy-3-methoxy-16α,17α-methoxymethylenedioxypregn-4-ene-3,20-dione (IV) (0.89 g.) in dioxane (10 ml.) was added a solution of *p*-toluenesulfonic acid (0.375 g.) in dioxane (2 ml.). After standing at room temperature for 5 min., the reaction mixture was poured into water and filtered. After several crystallizations from acetone–petroleum ether, there was obtained 0.16 g. of the product VII, m.p. 222–223°; $[\alpha]^{25}D$ +139° (methanol); λ_{max} 239 mμ (ε 16,000); ν_{max} 3500, 1740, 1667, and 1184 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{31}O_7F$ (438.48): C, 63.00; H, 7.13; F, 4.34. Found: C, 62.77; H, 7.31; F, 4.10.

21-Acetoxy-9α-fluoro-11β-hydroxy-16α,17α-methoxymethylenedioxypregn-4-ene-3,20-dione (VIII).—A solution of 21-acetoxy-9α-fluoro-11β-hydroxy-3-methoxy-16α,17α-methoxymethylenedioxypregna-3,5-dien-20-one (VI) (0.6 g.) in dioxane (6.0 ml.) and water (0.6 ml.) was treated with 2 drops of 72% perchloric acid. After standing for 2 min. at room temperature, the reaction mixture was treated with pyridine (0.5 ml.) and poured into water. The precipitated solid was collected and dried. The material was dissolved in methylene chloride and chromatographed on Florisil.[8] The material eluted by 4% acetone–methylene chloride, and 6% acetone–methylene chloride was combined and crystallized from ether–petroleum ether to give 0.36 g. of a material VIII with a solvated m.p. 125–130°, with effervescence; $[\alpha]^{25}D$ +192° (methanol); λ_{max} 239 mμ (ε 14,700); ν_{max} 3450, 1758, 1667, and 1238 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{33}O_8F$ (480.51): C, 62.48; H, 6.92; F, 3.96. Found: C, 65.00, 64.80; H, 8.23, 7.93; F, 3.50.

16α-Formyloxy-11β,17α,21-trihydroxypregn-4-ene-3,20-dione (IX).—Three hundred milligrams of 11β,21-dihydroxy-3-methoxy-16α,17α-methoxymethylenedioxypregna-3,5-dien-20-one (III) was dissolved in dioxane (10 ml.) and treated with a solution of *p*-toluenesulfonic acid monohydrate (0.19 g.) in dioxane (20 ml.). After 5 min. of standing at room temperature, the reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with saturated saline and dried. Evaporation gave a residue which upon crystallization from acetone–petroleum ether gave 0.13 g. of the 16-formate IX, m.p. 200–202°. Another crystallization gave the analytical sample, m.p. 201–203°; $[\alpha]^{25}D$ +114° (methanol); λ_{max} 242 mμ (ε 16,000); ν_{max} 3490, 1723, 1655, and 1198 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{30}O_7$ (406.46): C, 65.01; H, 7.44. Found: C, 65.01; H, 7.49.

9α-Fluoro-16α-formyloxy-11β,17α,21-trihydroxypregn-4-ene-3,20-dione (X).—One gram of 9α-fluoro-11β,21-dihydroxy-3-methoxy-16α,17α-methoxymethylenedioxypregna-3,5-dien-20-one was dissolved in methanol (30 ml.) and to this solution was added 0.5 *N* hydrochloric acid (4 ml.). After standing 5 min. at room temperature, the solution was poured into water and neutralized with aqueous sodium bicarbonate. The methanol was partially removed at reduced pressure and the precipitate was collected to give 0.5 g. of the formate X. Crystallization from acetone gave 225 mg., m.p. 252–254°. The melting point was raised to 257–259° after a subsequent crystallization; $[\alpha]^{25}D$ +101° (methanol); λ_{max} 239 mμ (ε 16,300); ν_{max} 3500, 1738, 1680–1670, and 1174 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{29}O_7F$ (424.45): C, 62.25; H, 6.89; F, 4.48. Found: C, 62.34; H, 7.14; F, 4.69.

21-Acetoxy-16α-formyloxy-9α-fluoro-11β,17α-dihydroxypregn-4-ene-3,20-dione (XI).—A. 21-Acetoxy-9α-fluoro-11β-hydroxy-3-methoxy-16α,17α-methoxymethylenedioxypregna-3,5-dien-20-one (VI) (0.8 g.) was dissolved in dry dioxane (10 ml.). To this solution was added *p*-toluenesulfonic acid monohydrate (0.31 g.) in dioxane (2.0 ml.). After standing at room temperature for 5 min., the reaction mixture was poured into water and filtered. Crystallization of this solid from acetone–petroleum ether gave 0.105 g. of the desired product XI, m.p. 228–235°. Recrystallization raised the m.p. to 239–241°; $[\alpha]^{25}D$ +92° (chloroform); λ_{max} 239 mμ (ε 17,000); ν_{max} 3430, 1750, 1672, 1245, and 1178 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{31}O_8F$ (466.49): C, 61.79; H, 6.71; F, 4.08. Found: C, 62.09; H, 6.93; F, 4.12.

B. A solution of 9α-fluoro-16α-formyloxy-11β,17α,21-trihydroxypregn-4-ene-3,20-dione (X) (0.11 g.) in pyridine (1.0 ml.) and acetic anhydride (1.0 ml.) was allowed to stand at room temperature for 17 hr. and then poured into water and filtered. Several crystallizations of this material from acetone–petroleum ether gave the 16-formate 21-acetate XI, m.p. 239–241°; $[\alpha]^{25}D$ +85° (chloroform); λ_{max} 239 mμ (ε 18,000). Its infrared spectrum was identical to that of A above.

Anal. Calcd. for $C_{24}H_{31}O_8F$ (466.49): C, 61.79; H, 6.71; F, 4.08. Found: C, 61.73; H, 6.68; F, 4.12.

21-Acetoxy-9α-fluoro-11β,16α,17α-trihydroxypregn-4-ene-3,20-dione (XII).—A solution of 21-acetoxy-9α-fluoro-11β-hydroxy-3-methoxy-16α,17α-methoxymethylenedioxypregna-3,5-dien-20-one (VI) (0.20 g.) in methanol (10 ml.) was refluxed for 10 min. with 0.5 *N* hydrochloric acid (2.5 ml.). Water then was added to the point of turbidity and upon cooling there precipitated the desired 21-acetate XII. After several crystallizations from acetone–petroleum ether 100 mg. were obtained, m.p. 239–241°; $[\alpha]^{25}D$ +123° (methanol); λ_{max} 239 mμ(ε 16,500); ν_{max} 3430, 1753, 1728, 1675, 1630, and 1232 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{31}O_7F$ (438.48): C, 63.00; H, 7.13; F, 4.34. Found: C, 63.54; H, 7.23; F, 4.38.

16α,17α-(1-Ethoxy)ethylidenedioxy-9α-fluoro-11β,21-dihydroxypregna-1,4-diene-3,20-dione (XIV).—To a suspension of 9α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-3,20-dione (XIII, 0.5 g.) in dry dioxane (5 ml.), triethylorthoacetate (0.5 ml.) and anhydrous ethanol (4 drops) was added 72% perchloric acid (2 drops). In 5 min. the reaction mixture had become essentially clear and this then was filtered into a flask containing pyridine (0.5 ml.). The addition of water gave a very fine suspension which was collected after the addition of solid sodium chloride. The moist precipitate was dissolved in methylene chloride and dried over sodium sulfate. Evaporation of the solvent and recrystallization of the residue from acetone–hexane provided an ini-

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

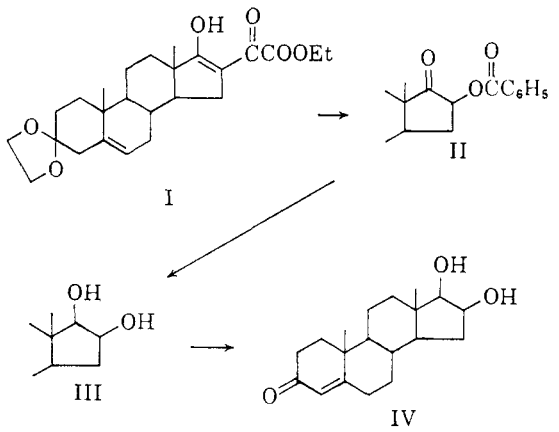
GEORGE R. ALLEN, JR., AND MARTIN J. WEISS

Organic Chemical Research Section,
Lederle Laboratories Division,
American Cyanamid Company, Pearl River, New York

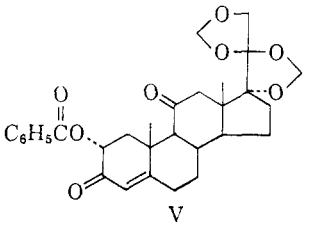
Received July 19, 1962

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[1] 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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(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.

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