alkaloidal zone on the chromatogram with the same R_f value as that of thalicarpine was cut from the chromatogram and extracted in a Soxhlet extractor with methanol. The methanolic extract was brought to dryness to leave a resinous residue. The residue was dissolved in 1.5% hydrochloric acid (10 ml.), washed with ether (10 ml.), made alkaline with concentrated ammonium hydroxide, and extracted with ether (30 ml.). The ether extract was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness to yield a yellow oil (0.033 g.), which was crystallized from ethyl acetate to give pale yellow needles (0.013 g.), m.p. 151–153°, $[\alpha]^{21}D$ +131° (*c* 1.30, methanol). The melting point was not depressed on admixture with an authentic sample of thalicarpine. The paper chromatographic behavior, infrared spectrum in chloroform solution, and ultraviolet spectrum were identical with those of the authentic thalicarpine.

[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES, A DIVISION OF AMERICAN CYANAMID CO., PEARL RIVER, N. Y.]

Steroidal Cyclic Ketals. XXV.[1] The Preparation of Steroidal Δ^4-3-Ethyleneketals

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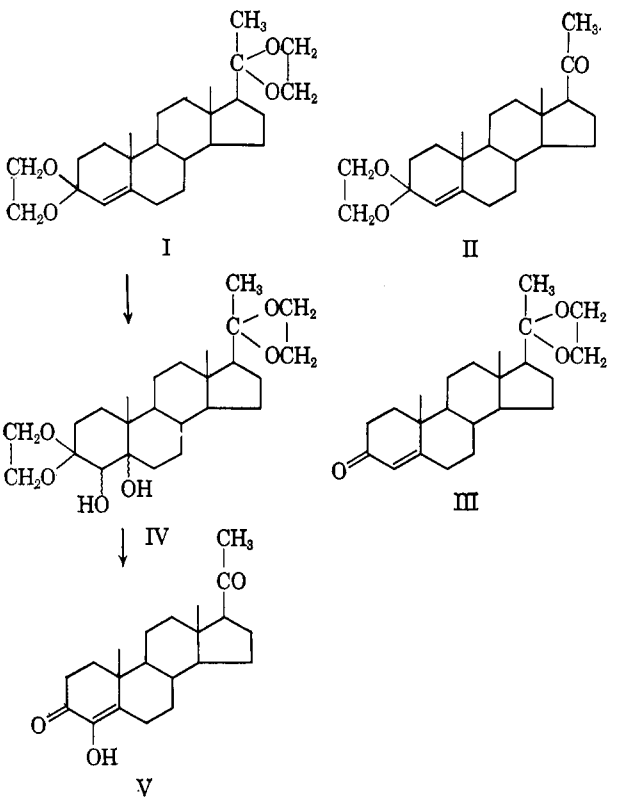
Steroidal Δ^4-3-ethyleneketals have been prepared by substitution of oxalic or preferably adipic acid for *p*-toluenesulfonic acid in the Salmi method for the preparation of steroidal Δ^5-3-ethyleneketals. A possible mechanism is discussed.

When progesterone was ketalized by a modified Salmi[2] procedure, *i.e.*, oxalic acid in place of *p*-toluenesulfonic acid as catalyst, three products were obtained: a 3,20-bisethyleneketal I, a 3-ethyleneketal II, and 20-ethylenedioxypregn-4-en-3-one (III).[3] The unknown compounds I and II did not show absorption in the ultraviolet and exhibited a sharp, weak band in the infrared at 1668 cm.$^{-1}$ which is not shown by Δ^5-3-ethyleneketals. That these compounds I and II were Δ^4-3-ethyleneketals was established when oxidation of the bisethyleneketal I with osmium tetroxide in pyridine[4] gave a dihydroxybisethyleneketal IV from which the known[5] 4-hydroxypregn-4-ene-3,20-dione (V) was obtained by treatment with formic acid. This showed that the dihydroxy bisethyleneketal IV was 3,20-bisethylenedioxypregnane-4ξ,5ξ-diol and that the double bond in the bisethyleneketal I was in the 4,5-position. Thus, compounds I and, consequently, II were assigned the unique structures of 3,20-bisethylenedioxypregn-4-ene (I) and 3-ethylenedioxy-4-en-20-one (II), respectively.

When a solution of the Δ^4-bisethyleneketal I in wet benzene (benzene saturated with water) was shaken with anhydrous magnesium sulfate, the 3-ethyleneketal was removed[6] quantitatively to give 20-ethylenedioxypregn-4-en-3-one (III). The 3-ethyleneketal of 3,20-bisethylenedioxypregn-5-ene (VI)[7] was unaffected by this treatment although the 20-ethyleneketal was removed to a greater or lesser extent according to the time of the reaction to give 3-ethylenedioxypregn-5-en-20-one (VII).[8]

The modified ketalization reaction was applied to several steroids (see Table I). With oxalic acid as catalyst, Δ^4-3-ketones gave either the Δ^4-3-ethyleneketal or a mixture of the Δ^4- and Δ^5-3-ethyleneketals. When oxalic acid was replaced by the weaker adipic acid as catalyst, only the Δ^4-3-ethyleneketal was obtained. In the case of saturated 3-ketosteroids, 5α- and 5β-dihydrocortisone acetate gave good yields of the 3-ethyleneketals but, surprisingly, cholestanone and coprostanone failed to react.

The Δ^4-3-ethyleneketals are stable to base but are extremely sensitive to acid. In contrast to Δ^5-3-ethyleneketals, they are hydrolyzed almost quantitatively in benzene by magnesium sulfate. This enabled the proportions of Δ^4- and Δ^5-3-ethyleneketals in a crude reaction mixture to be determined by comparison of the ultraviolet absorption before and after such treatment of a sample. The Δ^4-3-ethyleneketals ex-



(1) This work has been described in part in a preliminary communication: J. J. Brown, R. H. Lenhard, and S. Bernstein, *Experientia*, **18**, 309 (1962).

(2) E. Salmi, *Ber.*, **71**, 1803 (1938); E. Salmi and V. Rannikko, *ibid.*, **72**, 600 (1939).

(3) M. Gut, *J. Org. Chem.*, **21**, 1327 (1956).

(4) J. S. Baran, *ibid.*, **25**, 257 (1960).

(5) R. H. Bible, Jr., C. Placek, and R. D. Muir, *ibid.*, **22**, 607 (1957).

(6) D. N. Robertson, *ibid.*, **25**, 931 (1960), noted that magnesium sulfate is sufficiently acidic to hydrolyze dihydropyran adducts of tertiary alcohols containing an ethynyl group to the alcohol in a few hours.

(7) R. Antonucci, S. Bernstein, R. Littell, K. J. Sax, and J. H. Williams, *ibid.*, **17**, 1369 (1952).

(8) F. Sondheimer, M. Velasco, and G. Rosenkranz, *J. Am. Chem. Soc.*, **77**, 192 (1955).

TABLE I

KETALIZATION OF STEROIDAL KETONES

Compound	Catalyst	Product	Yield,[a] %
Progesterone	A[b]	Δ^4-3-Ethyleneketal	10
	O[c]	Δ^4-3-Ethyleneketal	6
		Δ^4-3,20-Bisethyleneketal	30
		20-Ethyleneketal	21
Reichstein's substance S	A	Δ^4-3-Ethyleneketal	74
	O	Δ^4-3-Ethyleneketal	(24)
		Δ^5-3-Ethyleneketal	45 (72)
Testosterone	A	Δ^4-3-Ethyleneketal	64
	O	Δ^4-3-Ethyleneketal	59
		Δ^5-3-Ethyleneketal	28
6-Dehydrotestosterone	A	$\Delta^{4,6}$-3-Ethyleneketal	14 (55)
Androst-4-ene-3,17-dione	A	No reaction	...
	O	Δ^4-3-Ethyleneketal	30–40
		Δ^4-3,17-Bisethyleneketal	10
Hydrocortisone 21-acetate	A	Δ^4-3-Ethyleneketal	70
	O	Δ^4-3-Ethyleneketal	(55)
		Δ^5-3-Ethyleneketal	23 (27)
Cortisone 21-acetate	A	Δ^4-3-Ethyleneketal	74
	O	Δ^4-3-Ethyleneketal	28
		Δ^5-3-Ethylenketal	67
21-Acetoxy-9α-fluoro-11β,17α-dihydroxypregn-4-ene-3,20-dione	A	Δ^4-3-Ethyleneketal	77
	O	Δ^4-3-Ethyleneketal	65
16α,21-Diacetoxy-9α-fluoro-11β,17α-dihydroxypregn-4-ene-3,20-dione	A	Δ^4-3-Ethyleneketal	50
5α-Dihydrocortisone 21-acetate	A	3-Ketal	81
5β-Dihydrocortisone 21-acetate	A	3 Ketal	87
Cholestanone	A	No reaction	...
	O	No reaction	...
Coprostanone	A	No reaction	...
6α-Hydroxytestosterone 6,17-diacetate	T[d]	Δ^4-3-Ethyleneketal	85
6β-Hydroxytestosterone 6,17-diacetate	T	Δ^4-3-Ethyleneketal	54

[a] Figures in parentheses are based on ultravioleta bsorption data. [b] A = adipic acid. [c] O = oxalic acid. [d] T = *p*-toluenesulfonic acid.

hibit a sharp, weak band in the infrared at about 1668 cm.$^{-1}$.

The molecular rotation differences between several pairs of isomeric Δ^4- and Δ^5-3-ethyleneketals are shown in Table II and are further evidence for the presence of the Δ^4-3-ethyleneketal moiety. The predicted[9] difference (ΔMD) is +492.

TABLE II

MOLECULAR ROTATION DIFFERENCES BETWEEN ISOMERIC Δ^4- AND Δ^5-3-ETHYLENEKETALS

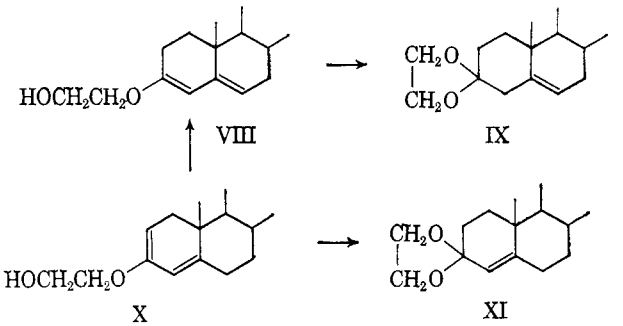
	—MD, 3-ethyleneketal— Δ^4-	Δ^5-	ΔMD ($\Delta^4 - \Delta^5$)
Progesterone	+627	+100[b]	+527
Reichstein's substance S	+495[a]	− 78	+573
Testosterone	+332	−143[c]	+475
Hydrocortisone 21-acetate	+637[a]	+108	+529

[a] The specific rotations for these MD values were determined in 1% pyridine in chloroform; the others were determined in chloroform. [b] See ref. 8. [c] See ref. 10.

(9) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 178.

(10) H. J. Dauben, Jr., B. Löken, and H. J. Ringold, *J. Am. Chem. Soc.*, **76**, 1359 (1954).

Djerassi and Gorman[11] proposed a mechanism for the formation of Δ^5-3-ethyleneketals in which an intermediate 3,5-dienol ether VIII is formed which ring closes by 1,2-addition to the 3,4-double bond to give the Δ^5-3-ethyleneketal IX. Similarly, the preparation of Δ^4-3-ethyleneketals XI probably involves the formation of an intermediate 2,4-dienol ether X with subsequent ring closure by 1,2-addition to the 2,3-double bond.[12]



It is possible that the intermediate X is also involved in the formation of Δ^5-3-ethyleneketals. By analogy to the isomerization[13] of cholesta-2,4-diene to cholesta-3,5-diene by mineral acids in either polar or nonpolar solvents, the intermediate 2,4-dienol ether X could rearrange to the intermediate 3,5-dienol ether VIII under the influence of the *p*-toluenesulfonic acid used as the catalyst in the reaction. Thus, the formation of a Δ^4-3-ethyleneketal or of a Δ^5-3-ethyleneketal would depend on the rate of ring closure of the 2,4-dienol ether X *vs.* the rate of isomerization of the double bonds. Indeed, although all previous work in the literature had indicated that the use of *p*-toluenesulfonic acid as catalyst would give rise to Δ^5-3-ethyleneketals,[14] we found that ketalization of 6α- and 6β-hydroxytestosterone 6,17-diacetates using this catalyst gave the corresponding Δ^4-3-ethyleneketals. Here the addition reaction predominated the isomerization of the double bonds. Magnesium sulfate hydrolysis of the Δ^4-3-ethyleneketal of 6β-hydroxytestosterone 6,17-diacetate regenerated the parent compound.

Experimental[15]

Melting Points.—All melting points are uncorrected.

Optical Rotations.—Unless noted otherwise, the rotations are for chloroform solutions and were determined at 25°.

Absorption Spectra.—The ultraviolet absorption spectra were determined in methanol. The infrared absorption spectra were carried out in pressed potassium bromide.

Petroleum Ether.—The fraction used had b.p. 60–70°.

Neutral alumina used was Woelm, Activity Grade II.

General Method for the Preparation of Ketals. Method A.—A mixture of steroid (2.0 g.), ethylene glycol (6.0 ml.), adipic acid (200 mg.) or, **method B**, oxalic acid dihydrate (200 mg.), and

(11) C. Djerassi and M. Gorman, *ibid.*, **75**, 3704 (1953).

(12) G. J. Fonken, *J. Org. Chem.*, **26**, 2549 (1961), suggested a similar mechanism for the formation of the $\Delta^{4,6}$-3-ethyleneketals of cholesta-4,6-dien-3-one and ergosta-4,6,22-trien-3-one using *p*-toluenesulfonic acid as catalyst.

(13) H. E. Stavely and W. Bergman, *ibid.*, **1**, 575 (1936).

(14) Subsequent to our preliminary communication,[1] J. W. Dean and R. G. Christiansen, *ibid.*, **28**, 2110 (1963), reported that ketalization of testosterone and of testosterone acetate using a low concentration of *p*-toluenesulfonic acid as catalyst produced mixtures of the corresponding Δ^4- and Δ^5-3-ethyleneketals. They proposed that the Δ^4-3-ethyleneketal is an intermediate in the formation of the Δ^5-3-ethyleneketal based on treatment of the Δ^4-3-ethyleneketal with *p*-toluenesulfonic acid in benzene under ketalization conditions to give the Δ^5-isomer. However, it is possible that the extremely acid-sensitive Δ^4-3-ethyleneketal was first hydrolyzed to the Δ^4-3-ketone followed by reketalization to give the Δ^5-3-ethyleneketal.

(15) Analyses were done by Mr. L. M. Brancone and associates and the spectra and optical rotations were done by Mr. W. Fulmor and associates.

benzene (100 ml.) was stirred and heated under reflux overnight (17–24 hr.), water formed during the reaction being removed by a Dean–Stark moisture trap. The cooled reaction mixture was diluted with benzene and washed with saturated sodium bicarbonate solution. The aqueous phase was extracted with benzene and the combined solvent was washed with water and filtered through a small pad of Celite.[16] Unless noted otherwise, the benzene was evaporated under reduced pressure (water bath temperature *ca.* 60°) without preliminary drying and the residual ketal was purified by crystallization or by adsorption chromatography.

Ketalization of (i) Progesterone. Method A.—The residue was crystallized from a small amount of acetone to give starting material (800 mg.), m.p. 130–132.5°. Concentration of the mother liquor and the addition of petroleum ether gave a further amount (930 mg.) of starting material. Evaporation of this mother liquor gave crude **3-ethylenedioxypregn-4-en-20-one** (II, 310 mg.), contaminated with a small amount of progesterone as shown by the infrared absorption spectrum.

Method B.—The residue was crystallized from acetone–petroleum ether to give crude product (500 mg.), m.p. *ca.* 145–172°. Recrystallization from the same solvent pair gave **20-ethylenedioxypregn-4-en-3-one** (III, 283 mg.), m.p. 192–195°. The oil (2.13 g.) obtained by evaporation of the combined mother liquors was dissolved in petroleum ether (*ca.* 50 ml.) and adsorbed on neutral alumina (160 g.). Fractions of 100 ml. were taken. Fractions 11 and 12 (eluted with 25% ether in petroleum ether) were evaporated and the residues combined (780 mg.). Crystallization from acetone–petroleum ether gave **3,20-bisethylenedioxypregn-4-ene** (I, 530 mg.), m.p. 149–151°, $[\alpha]_D$ +88°[17]; ν_{max} 1668, 1097, and 1085 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{38}O_4$ (402.55): C, 74.59; H, 9.52. Found: C, 74.41; H, 9.78.

The material in fractions 13 and 14 (eluted with 25% ether in petroleum ether) totaled 490 mg. and consisted mainly of progesterone and some 3-ethylenedioxypregn-4-ene-20-one (II) as shown by infrared analysis.[18]

Fractions 15 and 16 (eluted with 25% ether in petroleum ether) were combined and evaporated and the residue was crystallized from acetone–petroleum ether to give **3-ethylenedioxypregn-4-en-20-one** (II, 132 mg.), m.p. 163–165°, $[\alpha]^{30}_D$ +175°[19]; ν_{max} 1700, 1668, and 1091 cm.$^{-1}$. One further crystallization from the same solvents gave the sample for analysis, m.p. 164–165.5°.

Anal. Calcd. for $C_{23}H_{34}O_2$ (358.50): C, 77.05; H, 9.56. Found: C, 76.83; H, 9.63.

Fractions 21 through 24 (eluted with 50% ether in petroleum ether) were evaporated and the residues combined. Crystallization from acetone–petroleum ether gave an additional amount of **20-ethylenedioxypregn-4-en-3-one** (III, 190 mg.), m.p. 195–197°; ν_{max} 1678, 1627, 1070, and 1053 cm.$^{-1}$; $[\alpha]_D$ +101°; lit.[3] m.p. 189–191°, $[\alpha]^{26}_D$ +119°.

Fractions 27 and 28 (eluted with ether) were evaporated and the residues were combined and recrystallized from acetone–petroleum ether to give progesterone (38 mg.), m.p. 120.5–123.5°.

3,20-Bisethylenedioxypregnane-4ζ,5ζ-diol (**IV**).—A solution of 3,20-bisethylenedioxypregn-4-ene (625 mg., 1.55 mmoles) in pyridine (5 ml.) was treated with osmium tetroxide (415 mg., 1.63 mmoles). The reaction mixture was stirred at room temperature for 1.5 hr. and then kept in the dark for 12 days.[4] A solution of sodium bisulfite (900 mg.) in water (15 ml.) and pyridine (12.5 ml.) was added and the reaction mixture was stirred for 2 hr. and 40 min. It was then extracted several times with chloroform and the combined extracts were washed with water and dried (sodium sulfate). Evaporation yielded a glass which was dissolved in acetone–petroleum ether; re-evaporation afforded a white crystalline solid (675 mg.), m.p. 169–174°, ν_{max} 3500 cm.$^{-1}$ (no Δ^4-absorption). Recrystallization from acetone–petroleum ether gave 3,20-bisethylenedioxypregnane-4ζ,5ζ-diol (609 mg.) in a solvated state, m.p. 169–176°.

Anal. Calcd. for $C_{25}H_{40}O_6$ (436.57): C, 68.77; H, 9.24. Found: C, 68.02, 67.71; H, 9.31, 9.29.

4-Hydroxypregn-4-ene-3,20-dione (**V**).—A solution of 3,20-bisethylenedioxypregnane-4ζ,5ζ-diol (IV, 485 mg.) in formic acid (5 ml. 98–100%) was heated under reflux for 1 hr. and was then poured into hot water. The mixture was cooled overnight before the material which had separated was collected and washed with water to afford crude product (334 mg.), m.p. 194–215°. Two crystallizations from acetone–petroleum ether and one from acetone gave pure 4-hydroxypregn-4-ene-3,20-dione (142 mg.), m.p. 229–232°, $[\alpha]_D$ +177°, λ_{max} 277 mμ (ε 12,500); ν_{max} 3450, 1707, 1670, and 1640 cm.$^{-1}$ [lit.[5] m.p. 226–228°, $[\alpha]_D$ +177°, λ_{max} 277 mμ (ε 11,500)].

20-Ethylenedioxypregn-4-en-3-one (**III**).—A solution of 3,20-bisethylenedioxypregn-4-ene (I, 20 mg.) in wet benzene (10 ml.) was shaken for 1 hr. with anhydrous magnesium sulfate (1.0 g.). The mixture was filtered through Celite[16] and the solvent was evaporated. The infrared spectrum of the residue was identical with that of 20-ethylenedioxypregn-4-en-3-one. Crystallization of the residue from acetone–petroleum ether gave the product (8 mg.), m.p. 189–192.5°.

3-Ethylenedioxypregn-5-en-20-one (**VII**).—A solution of 3,20-bisethylenedioxypregn-5-ene (400 mg.) in wet benzene (200 ml.) was shaken at room temperature for 1 hr. with anhydrous magnesium sulfate (20 g.). After filtration through Celite[16] and evaporation of the filtrate, the residue (380 mg.) was dissolved in benzene (2 ml.) and petroleum ether (48 ml.) was added. The solution was chromatographed on neutral alumina (30 g.). Elution with 30% benzene in petroleum ether afforded starting material (142 mg., shown by the infrared spectrum) followed by a mixture (62 mg.) of starting material and 3-ethylenedioxypregn-5-en-20-one (shown by the infrared spectrum). Continued elution with 30% benzene in petroleum ether and then with 50% benzene in petroleum ether gave material (167 mg.) which upon crystallization from acetone–petroleum ether gave 3-ethylenedioxypregn-5-en-20-one (78 mg.), m.p. 182.5–184.5°; ν_{max} 1710 and 1095 cm.$^{-1}$ (lit.[8] m.p. 180–181°).

When the reaction was carried out for 17 hr. chromatography was not required. Thus the crude residue from 3,20-bisethylenedioxypregn-5-ene (1.0 g.) was crystallized from acetone–petroleum ether to give 3-ethylenedioxypregn-5-en-20-one (670 mg.), m.p. 170–179°.

Ketalization of (ii) Reichstein's Substance S. Method A.—The residual glass which crystallized upon addition of ether was crystallized from acetone–petroleum ether containing a trace of pyridine to give **3-ethylenedioxy-17α,21-dihydroxypregn-4-en-20-one** (1.67 g.), m.p. 186–196°. Three further crystallizations gave the analytical sample (960 mg.), m.p. 192–196° with effervescence, $[\alpha]_D$ +127°; (1% pyridine in chloroform); ν_{max} 3510, 1719, 1670, and 1099 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{34}O_5$ (390.50): C, 70.74; H, 8.78. Found: C, 70.90; H, 8.80.

Method B.—One gram of Reichstein's Substance S was used in this reaction. The cooled solution was washed with saturated sodium bicarbonate solution and water and dried (sodium sulfate). The solid obtained by evaporation of solvent was collected with the aid of ether and crystallized from acetone to give **3-ethylenedioxy-17α,21-dihydroxypregn-5-en-20-one** (500 mg.) as plates, m.p. 220–225°. The analytical sample had m.p. 227–228°, $[\alpha]_D$ −20°; ν_{max} 3450, 1708, and 1109 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{34}O_5$ (390.50): C, 70.74; H, 8.78. Found: C, 70.60; H, 8.83.

The acetate 21-acetoxy-3-ethylenedioxy-17α-hydroxypregn-5-en-20-one had m.p. 264–268°, undepressed on mixing with an authentic sample.[20]

In another experiment with 2 g. of Reichstein's Substance S, the reaction mixture was cooled and the material which separated was collected and washed with benzene, saturated sodium bicarbonate solution, and water, and dried to give **3-ethylenedioxy-17α,21-dihydroxypregn-5-en-20-one** (1.02 g., 45% yield, m.p. 220–228°). The benzene phase of the reaction mixture was treated as in the General Method to give a solid (1.26 g.), m.p. 168–195°, λ_{max} 241–242 mμ (ε 1500). A solution of this solid (20 mg.) in wet benzene (10 ml.) was shaken for 1 hr. with anhydrous magnesium sulfate (1 g.). The filtered solution was evaporated and the residue had λ_{max} 241–242 mμ (ε 8600). Comparison of the extinction coefficients before and after treatment

(16) Celite is a Johns–Manville registered trademark for diatomaceous silica products.

(17) The rotation value is for a rechromatographed sample, m.p. 147–150°. The original sample was found to have reverted appreciably to the Δ^4-3-ketone on standing.

(18) Hydrolysis of the latter compound, either on the column or during evaporation, would account for the appearance of progesterone at this point.

(19) The rotation value is for a sample, m.p. 158–161°, obtained from another run, the analytical sample having reverted to the Δ^4-3-ketone on standing. The infrared spectrum was identical with that of the analytical sample.

(20) R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell, and J. H. Williams, *J. Org. Chem.*, **18**, 70 (1953).

(Δ^4-3-one, 16,650) indicated that the ketalization had proceeded in 96% yield, the ratio of Δ^5-3-ketal to Δ^4-3-ketal being about 3 to 1.

(iii) **Testosterone. Method A.**—The residual solid, m.p. 182–221°, was collected with the aid of ether to give 1.47 g. of material, m.p. 217–225°. Crystallization from acetone afforded **3-ethylenedioxyandrost-4-en-17β-ol** (1.28 g.), m.p. 224–229°. Evaporation of the initial ether filtrate followed by crystallization of the residue from acetone gave an additional amount of product (70 mg.), m.p. 209–219°. This mother liquor was evaporated and the residual solid [(670 mg., λ_{max} 241 mμ (ε 15,000)] was dissolved in benzene (30 ml.) and adsorbed on neutral alumina (40 g.). The material eluted with 10 and 25% ether in benzene was crystallized from aqueous acetone to give testosterone (400 mg.), m.p. 147–152°.

Method B.—The residue (2.29 g.) obtained, m.p. 156–218°, λ_{max} 242 mμ (ε 2000), was dissolved in methylene chloride (10 ml.), and ether (5 ml.) was added. After standing for 1 hr. at room temperature, the material which separated was collected, washed with ether, and crystallized from acetone to give **3-ethylenedioxyandrost-4-en-17β-ol** (1.14 g.), m.p. 226–230.5°. The analytical sample had m.p. 227–232°, $[\alpha]^{30}D$ +100°; ν_{max} 3490, 1667, and 1092 cm.$^{-1}$ (lit.[14] m.p. 225–232°, $[\alpha]D$ +95.1°).

Anal. Calcd. for $C_{21}H_{32}O_2$ (332.47): C, 75.86; H, 9.70. Found: C, 75.32; H, 9.83.

An additional amount of crude product (100 mg.), m.p. 193–212°, was obtained from the initial methylene chloride–ether mother liquor by evaporation followed by crystallization of the residue from acetone. This last mother liquor was evaporated and the residue (860 mg.), m.p. 169–175°, was dissolved in benzene (30 ml.) and adsorbed on neutral alumina (50 g.). The material eluted with 10% ether in benzene crystallized from acetone–petroleum ether to give **3-ethylenedioxyandrost-5-en-17β-ol** (480 mg.), m.p. 183.5–185.5° (lit.[7] m.p. 185–188°). The material eluted with 25% ether in benzene was crystallized from aqueous acetone to give testosterone (74 mg.), m.p. 151–154°.

(iv) **6-Dehydrotestosterone. Method A.**—The residue was crystallized from acetone–petroleum ether to give 1.93 g. of material, m.p. 156–179°; λ_{max} 239 mμ (ε 13,700) and 284 mμ (ε 14,100) [55% yield based on λ_{max} 238 mμ (ε 25,500) for the $\Delta^{4,6}$-3-ketal (see below)]. The crystallized material and the residue from the mother liquor were combined to give a total of 2.09 g. which was dissolved in hot benzene (100 ml.). On cooling, crystals (1.27 g.), m.p. 193–196°, separated. The infrared spectrum was identical with that of starting material. The benzene filtrate was adsorbed on neutral alumina (108 g.). The material eluted with 15% ether in benzene was crystallized from acetone–petroleum ether to give **3-ethylenedioxyandrost-4,6-dien-17β-ol** (316 mg.), m.p. 179–181°. The analytical sample had m.p. 178–181°, $[\alpha]D$ +87° (1% pyridine in chloroform); λ_{max} 232 mμ (ε 23,600; shoulder), 238 (25,500), and 248 (15,500; inflection); ν_{max} 3510, 1652, 1623, and 1096 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{30}O_2$ (330.45): C, 76.32; H, 9.15. Found: C, 76.22; H, 9.30.

Elution with 20 and 25% ether in benzene afforded an additional amount of starting material (540 mg.), m.p. 197–201°.

Hydrolysis of the $\Delta^{4,6}$-3-ketal with perchloric acid in acetone gave 6-dehydrotestosterone, m.p. 197–200°, in high yield.

(v) **Androstenedione. Method B.**—One gram of androstenedione was used in the reaction. The oily residue was dissolved in benzene (25 ml.) and petroleum ether (25 ml.) and adsorbed on neutral alumina (60 g.). The material (190 mg.) eluted with 50% benzene in petroleum ether was crystallized from acetone–petroleum ether to give **3,17-bisethylenedioxyandrost-4-ene** (70 mg.), m.p. 126–129°, ν_{max} 1665 and 1090 cm.$^{-1}$. This compound proved to be unstable during recrystallization (several months in the refrigerator) from the same solvents, **17-ethylenedioxyandrost-4-en-3-one** (17 mg.), m.p. 146–148° (lit.[21] m.p. 146.2–148°), being obtained. The compound had ν_{max} 1673, 1624, 1108, and 1095 cm.$^{-1}$. Further elution with 50% benzene in petroleum ether and with benzene afforded material (510 mg.) from which **3-ethylenedioxyandrost-4-en-17-one** (340 mg.), m.p. 141–146°, was obtained upon crystallization from acetone–petroleum ether. The analytical sample had m.p. 146–148.5°, $[\alpha]D$ +160° (1% pyridine in chloroform); ν_{max} 1745, 1668, and 1094 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{30}O_3$ (330.45): C, 76.32; H, 9.15. Found: C, 76.32; H, 9.25.

(vi) **Hydrocortisone Acetate. Method A.**—The residual glass was treated with ether and evaporation gave a solid, m.p. 195–210°, which was crystallized from acetone–petroleum ether containing a small amount of pyridine to give **21-acetoxy-3-ethylenedioxy-11β,17α-dihydroxypregn-4-en-20-one** (1.56 g.), m.p. 212–218°. The analytical sample, m.p. 212–217°, had $[\alpha]D$ +142° (1% pyridine in chloroform), λ_{max} 241 mμ (ε 800, concentration 100 γ/ml.); ν_{max} 3490, 1750, 1722, 1660, 1233, and 1097 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{36}O_7$ (448.54): C, 66.94; H, 8.09. Found: C, 66.44; H, 8.50.

Method B.—The residual glass A (2.02 g.) had λ_{max} 240 mμ (ε 1800; calcd. as 11% hydrocortisone acetate). A solution of residue A (1.02 g.) in benzene (250 ml.) was shaken for 2.5 hr. with anhydrous magnesium sulfate (25 g.). The mixture was filtered through a small pad of Celite[16] and evaporation of the filtrate gave a residual glass B (370 mg.) having λ_{max} 242 mμ (ε 3100; calcd. as 19% hydrocortisone acetate). The filter pad was slurried with water and the mixture of Celite[16] and organic material obtained by filtration was dried overnight at 90°. The mixture was extracted with acetone and evaporation of solvent followed by crystallization of the residue from methanol gave hydrocortisone acetate (447 mg.), m.p. 216–219°. The residue (104 mg.) from the mother liquor had λ_{max} 242 mμ (ε 17,100).

The residue B (370 mg.) was subjected to partition chromatography[22] on Celite (185 g.),[16] the solvent system consisting of 20 parts (by volume) of petroleum ether (b.p. 90–100°), 5 parts of ethyl acetate, 3 parts of methanol, and 2 parts of water. Fractions of 20 ml. were taken. Fractions 14 through 48 were combined and evaporated and the residue was crystallized from acetone–petroleum ether to give **21-acetoxy-3-ethylenedioxy-11β,17α-dihydroxypregn-5-en-20-one** (185 mg.), m.p. 223–239° (solvated). Recrystallization from ethyl acetate–heptane gave the analytical sample (153 mg.), m.p. 224–241° (solvated), raised to 236–241° upon drying *in vacuo* at 140° overnight; $[\alpha]D$ +24°; ν_{max} 3490, 1754, 1725, 1645, 1233, and 1108 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{36}O_7$ (448.54): C, 66.94; H, 8.09. Found: C, 66.48; H, 8.30.

Fractions 75 through 94 were combined and evaporated to give hydrocortisone acetate (53 mg.), m.p. 216–219°.

A portion of the remainder of residue A (250 mg.) was subjected to partition chromatography in an attempt to isolate the Δ^4-3-ketal. However, only hydrocortisone acetate, m.p. 216–219°, was obtained, the unstable Δ^4-3-ketal probably being hydrolyzed during the chromatography.

(vii) **Cortisone Acetate. Method A.**—Crystallization of the residue from acetone containing a trace of pyridine yielded **21-acetoxy-3-ethylenedioxy-17α-hydroxypregn-4-ene-11,20-dione** (1.64 g.), m.p. 231–239°. Three recrystallizations from acetone–petroleum ether containing a trace of pyridine gave the analytical sample (1.19 g.), m.p. 237–244°, $[\alpha]D$ +159° (1% pyridine in chloroform); ν_{max} 3460, 1760, 1738, 1715, 1668, 1234, and 1092 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{34}O_7$ (446.52): C, 67.24; H, 7.68. Found: C, 67.34; H, 7.94.

Method B.—The reaction mixture was heated under reflux for 4.5 hr. during which time solution took place followed by separation of the product. The cooled mixture was washed with saturated sodium bicarbonate solution and the solid, collected by filtration, was washed with water and benzene–methanol (1:1) to give **21-acetoxy-3-ethylenedioxy-17α-hydroxypregn-5-ene-11,-20-dione** (1.29 g.), m.p. 276–282° (lit.[10] m.p. 267–268.5°). The infrared spectrum was identical with that of an authentic sample.[20] The benzene–methanol wash was evaporated and the residue was heated with acetone and, after cooling, was collected by filtration to give an additional amount of the Δ^5-3-ketal (175 mg.), m.p. 276–281°. Concentration of the filtrate and addition of petroleum ether yielded **21-acetoxy-3-ethylenedioxy-17α-hydroxypregn-4-ene-11,20-dione** (145 mg.), m.p. 235–246°. The benzene phase was treated as described in the General Method and the residue obtained was crystallized from acetone–petroleum ether to give a further amount of the Δ^4-3-ketal (460 mg.), m.p. 237–244°. The infrared spectra of these two fractions were identical with that of the product in method A.

(viii) **21-Acetoxy-9α-fluoro-11β,17α-dihydroxypregn-4-ene-3,20-dione. Method A.**—The combined solvent extract was dried (sodium sulfate), filtered through Celite,[16] and evaporated.

(21) H. L. Herzog, M. A. Jevnik, M. E. Tully, and E. B. Hershberg, *J. Am. Chem. Soc.*, **75**, 4425 (1953).

(22) R. Littell and S. Bernstein, *ibid.*, **78**, 984 (1956).

The residual glass was crystallized from acetone–petroleum ether to give product (460 mg.), m.p. 220° dec. The Celite[16] and sodium sulfate from the above filtration were washed thoroughly with acetone. The crystalline material (1.25 g.), m.p. 219–224°, 225° dec., obtained by removal of solvent was crystallized from acetone–petroleum ether to give **21-acetoxy-3-ethylenedioxy-9α-fluoro-11β,17α-dihydroxypregn-4-en-20-one** (1.06 g.), m.p. 229–232°, 233° dec. Two additional crystallizations gave m.p. 230–233°, 234° dec., $[\alpha]_D$ +76° (pyridine); ν_{max} 5300, 1753, 1737, 1675, and 1085 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{35}FO_7$ (466.53): C, 64.36; H, 7.56; F, 4.07. Found: C, 64.86; H, 7.32; F, 3.98.

Method B.—Ten grams of 21-acetoxy-9α-fluoro-11β,17α-dihydroxypregn-4-ene-3,20-dione was ketalized. The dried (sodium sulfate) benzene extract was evaporated and the residue crystallized from acetone–petroleu mether to give **21-acetoxy-3-ethylenedioxy-9α-fluoro-11β,17α-dihydroxypregn-4-en-20-one** (7.18 g.), m.p. 234–236°, 236–239° dec. The infrared spectrum was identical with that of the analytical sample obtained in method A.

(ix) 16α,21-Diacetoxy-9α-fluoro-11β,17α-dihydroxypregn-4-ene-3,20-dione. Method A.—The residue was crystallized from acetone–petroleum ether to give product (1.17 g.), m.p. 237–245°, 246° dec. Three recrystallizations from the same solvents yielded **16α,21-diacetoxy-3-ethylenedioxy-9α-fluoro-11β,17α-dihydroxypregn-4-en-20-one** (590 mg.), m.p. 251–258°, 261° dec., $[\alpha]_D$ +95° (pyridine); ν_{max} 3470, 1725, 1712 (shoulder), 1668, 1250, 1125, and 1082 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{37}FO_9$ (524.57): C, 61.82; H, 7.11; F, 3.62. Found: C, 62.10; H, 7.37; F, 3.68.

(x) 5β-Dihydrocortisone Acetate. Method A.—The residue obtained from the ketalization of 1.0 g. of 5β-dihydrocortisone acetate was crystallized from acetone–petroleum ether to give **21-acetoxy-3-ethylenedioxy-17α-hydroxy-5β-pregnane-11,20-dione** (970 mg.), m.p. 218.5–225°. The analytical sample m.p. 217.5–224°, had $[\alpha]^{26}_D$ +87°; ν_{max} 3480, 1750 (shoulder), 1725 (shoulder), 1711, 1236, and 1097 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{36}O_7$ (448.54): C, 66.94; H, 8.09. Found: C, 66.83; H, 8.13.

(xi) 5α-Dihydrocortisone Acetate. Method A.—One gram of 5α-dihydrocortisone acetate was used. The cooled reaction mixture which contained separated product was diluted with benzene and ethyl acetate. The solution was washed with saturated sodium bicarbonate solution and water and dried (sodium sulfate). The solution was filtered through Celite[16]; evaporation yielded **21-acetoxy-3-ethylenedioxy-17α-hydroxy-5α-pregnane-11,-20-dione** (700 mg.), m.p. 262–270°. An additional amount of product (200 mg.), m.p. 263–269°, was obtained by extracting the filter cake with hot acetone. Crystallization from acetone gave the analytical sample, m.p. 273–279°, $[\alpha]_D$ +79°; ν_{max} 3435, 1754, 1732, 1710, 1232, and 1105 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{36}O_7$ (448.54): C, 66.94; H, 8.09. Found: C, 66.85; H, 8.30.

6α- and 6β-Hydroxytestosterone 17-Monoacetates.—The enol acetate of testosterone acetate was prepared in high yield by the method used to prepare the enol acetate of 19-nortestosterone acetate.[23] A solution of the enol acetate (10 g.) in ether (350 ml.) was treated[24] with monoperphthalic acid in ether (112 ml., 0.357 *N*) and the mixture was heated under reflux for 3 hr. The cooled reaction mixture was washed several times with saturated sodium bicarbonate solution and, while washing, an oil separated in the aqueous phase which crystallized on standing to afford 6β-hydroxytestosterone 17-monoacetate (1.68 g.), m.p. 198–205°. The ether solution was washed with water, dried (magnesium sulfate), and concentrated with simultaneous addition of petroleum ether. An additional amount (2.93 g.) of the 6β-hydroxy compound, m.p. 193–202°, separated. Recrystallization of the combined fractions from acetone–petroleum ether gave the 6β-hydroxy compound (3.39 g.),[24] m.p. 207.5–210°. The initial ether–petroleum ether mother liquor afforded a postprecipitate of crude product (2.98 g.), m.p. 147–177°, which, after several crystallizations from acetone–petroleum ether, gave an additional amount (770 mg.) of the 6β-hydroxy compound, m.p. 203–207°. All mother liquors were combined and evaporated and a solution of the residue in methylene chloride (50 ml.) was adsorbed on Florisil (250 g.).[25] The material eluted with 6% acetone in methylene chloride was crystallized from acetone–petroleum ether to give 6β-hydroxytestosterone 17-monoacetate (1.71 g.), m.p. 203–208°. The material eluted with 8 and 10% acetone in methylene chloride was crystallized from acetone–petroleum ether to give 6α-hydroxytestosterone 17-monoacetate (590 mg.),[26] m.p. 218–225°.

Ketalization of (xii) 6α-Hydroxytestosterone 6,17-Diacetate.—6α-Hydroxytestosterone 6,17-diacetate was prepared by the action of acetic anhydride–pyridine overnight on 6α-hydroxytestosterone 17-monoacetate. The diacetate was crystallized from aqueous acetone and had m.p. 188.5–191°, $[\alpha]_D$ +76.5°, λ_{max} 236 mμ (ε 14,200); ν_{max} 1733, 1675, 1616, 1239, and 1224 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{32}O_5$ (388.49): C, 71.10; H, 8.30. Found: C, 70.59; H, 8.53.

The diacetate (500 mg.) was subjected to the usual ketalization conditions with benzene (25 ml.), ethylene glycol (1.5 ml.), and *p*-toluenesulfonic acid (10 mg.). After 4 hr. the product (550 mg.), m.p. 212–219°, was isolated. Crystallization from acetone–petroleum ether gave the Δ^4-3-ethyleneketal of 6α-hydroxytestosterone 6,17-diacetate (469 mg.), m.p. 226–229°. The compound had $[\alpha]_D$ +72° (1% pyridine in chloroform); ν_{max} 1739, 1667, 1242, 1095, 1062, 1042, and 1020 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{36}O_6$ (432.54): C, 69.42; H, 8.39. Found: C, 69.27; H, 8.44.

(xiii) 6β-Hydroxytestosterone 6,17-Diacetate.—The diacetate,[24] m.p. 137.5–140°, was prepared by the action of acetic anhydride–pyridine overnight on 6β-hydroxytestosterone 17-monoacetate. The diacetate (500 mg.) was ketalized as above. After 4 hr. the reaction mixture was cooled, methylene chloride was added, and the mixfure was washed with aqueous sodium bicarbonate solution and water and dried (sodium sulfate). Evaporation of solvent followed by crystallization of the residue (infrared spectrum showed some Δ^4-3-ketone) from *n*-hexane gave crude product (350 mg.), m.p. 159–169°. Recrystallization from aqueous methanol gave the Δ^4-3-ethyleneketal of 6β-hydroxytestosterone 6,17-diacetate (300 mg.), m.p. 171–175°. The analytical sample had m.p. 172–177°, $[\alpha]_D$ +40° (1% pyridine in chloroform); ν_{max} 1739, 1658, 1242, 1094, and 1027 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{36}O_6$ (432.54): C, 69.42; H, 8.39. Found: C, 69.03; H, 8.50.

Hydrolysis of the Δ^4-3-Ethyleneketal of 6β-Hydroxytestosterone 6,17-Diacetate.—The Δ^4-3-ethyleneketal (25 mg.) and anhydrous magnesium sulfate (2.5 g.) were stirred in wet benzene (25 ml.) for 2 hr. The mixture was filtered and solvent was evaporated. Crystallization of the residue from aqueous methanol gave 6β-hydroxytestosterone 6,17-diacetate (15 mg.), m.p. 129–132°; λ_{max} 236 mμ (ε 13,000). The infrared spectrum was identical with that of an authentic sample.

(23) L. Velluz, B. Goffinet, and G. Amiard, *Tetrahedron*, **4**, 241 (1958).

(24) J. Romo, G. Rosenkranz, C. Djerassi, and F. Sondheimer, *J. Org. Chem.*, **19**, 1509 (1954).

(25) Florisil is the Floridin Co. registered trademark for a synthetic magnesium silicate.

(26) J. P. Dusza, J. P. Joseph, and S. Bernstein, *J. Org. Chem.*, **27**, 4046 (1962).