[CONTRIBUTION FROM THE CHEMICAL AND BIOLOGICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY]

# Steroidal Cyclic Ketals. XII.[1] The Preparation of $\Delta^{16}$-Steroids

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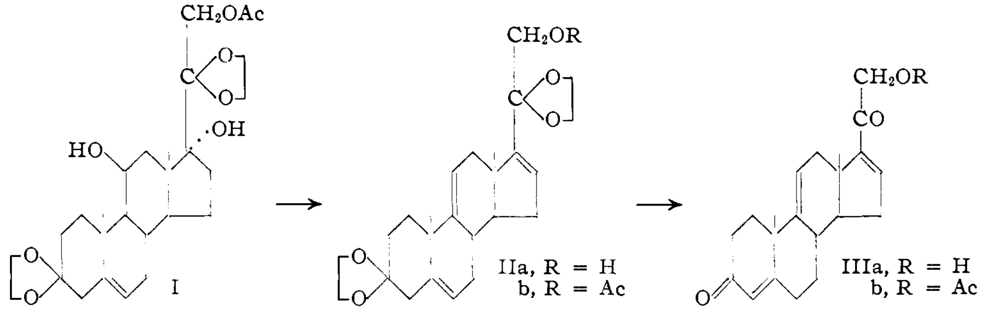
A novel pathway has been developed for the preparation of $\Delta^{16}$-20-keto-steroids. The key reaction was the formation of a $\Delta^{16}$-20-ethylene ketal from a 17$\alpha$-ol-20-ethylene ketal by treatment of the latter with thionyl chloride–pyridine at −5°. Thus, hydrocortisone acetate bisethylene ketal (I) was converted in 42% yield into $\Delta^{5,9(11),16}$-pregnatriene-21-ol-3,20-dione 21-acetate 3,20-bisethylene ketal (IIb), Reichstein's substance S 21-acetate, 3,20-bisethylene ketal (IV) gave $\Delta^{5,16}$-pregnadiene-21-ol-3,20-dione 21-acetate 3,20-bisethylene ketal (Vb), (33% yield), and cortisone acetate bisethylene ketal (VIII) gave $\Delta^{5,16}$-pregnadiene-21-ol-3,11,20-trione 21-acetate 3,20-bisethylene ketal (IXb) (45% yield). Hydrolysis of protective groups afforded $\Delta^{4,9(11),16}$-pregnatriene-21-ol-3,20-dione (IIIa), $\Delta^{4,16}$-pregnadiene-21-ol-3,20-dione (VIa) and $\Delta^{4,16}$-pregnadiene-21-ol-3,11,20-trione (Xa). The 21-acetates (IIIb, VIb and Xb) of these compounds have been prepared. The 11$\beta$-hydroxy analog XIIIa was prepared in the following manner. Compound IXb in tetrahydrofuran was reduced with sodium borohydride to $\Delta^{5,16}$-pregnadiene-11$\beta$,21-diol-3,20-dione-3,20-bisethylene ketal (XI) (81% yield). Hydrolysis with 50% aqueous acetic acid–methanol gave $\Delta^{4,16}$-pregnadiene-11$\beta$,21-diol-3,20-dione (XIIIa) in 93% yield. Its 21-acetate XIIIb also was prepared.

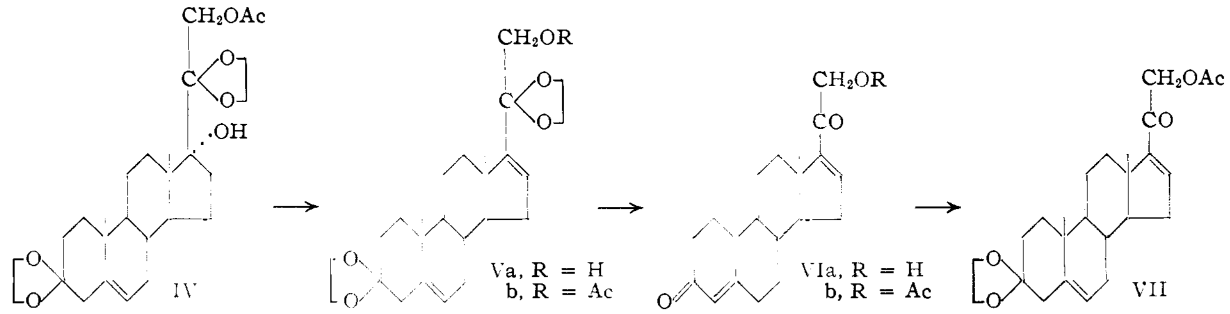
An investigation has been conducted for a method to effect an ionic elimination of a $C_{17}$-$\alpha$-hydroxyl group adjacent to a $C_{20}$-ketal group. The results obtained constitute the basis of this paper.



I

IIa, R = H
b, R = Ac

IIIa, R = H
b, R = Ac



IV

Va, R = H
b, R = Ac

VIa, R = H
b, R = Ac

VII

In a recent publication,[2] there was pointed out that the $C_{17}$-$\alpha$-hydroxyl group in the bisethylene ketal VIII of cortisone acetate was stable to phosphorus oxychloride–pyridine at room temperature. Under these conditions, on the other hand, a $C_{11}$-$\alpha$- or $\beta$-hydroxyl group undergoes an ionic elimination to afford the corresponding $\Delta^{9}$-steroid.[2,3] Thus, if the bisethylene ketal I of hydrocortisone acetate is treated with phosphorus oxychloride–pyridine, there is obtained in excellent yield $\Delta^{5,9(11)}$-pregnadiene-17$\alpha$,21-diol-3,20-dione 21-acetate 3,20-bisethylene ketal.[2]

Now, however, it has been found that, when this reaction is carried out with thionyl chloride–pyridine at −5°, both the $C_{11}$- and $C_{17}$-hydroxyl groups undergo ionic elimination. In this way, the bisketal I was converted into $\Delta^{5,9(11),16}$-pregnatriene-21-ol-3,20-dione 21-acetate 3,20-bisethylene ketal (IIb) in 42% yield. Considerations supporting the structure of this and other $\Delta^{16}$-steroids prepared herein will be discussed collectively later in the paper.

The $\Delta^{5,9(11),16}$-acetate bisketal IIb was saponified, and crude IIa was obtained. It was not characterized, but was treated directly with sulfuric acid in methanol for the hydrolysis of the ketone protective groups. $\Delta^{4,9(11),16}$-Pregnatriene-21-ol-3,20-dione (IIIa) was thereby prepared in almost quantitative yield from the acetate bisketal IIb. Its 21-acetate IIIb was prepared in the usual manner.

These transformations established an essentially novel pathway for the preparation of a $\Delta^{16}$-20-

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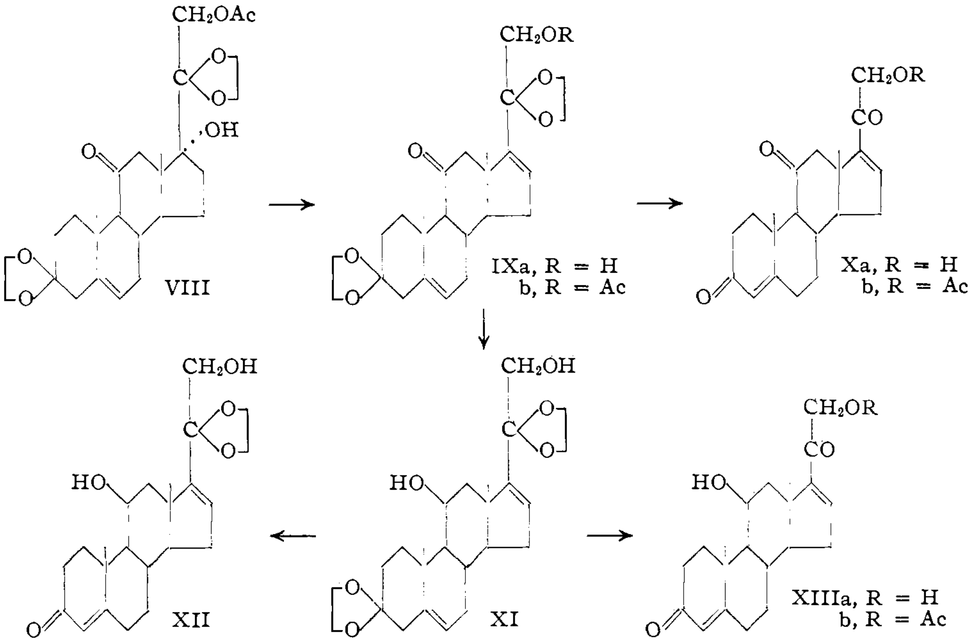
(1) Paper XI, W. S. Allen, S. Bernstein and R. Littell, THIS JOURNAL, **76**, 6116 (1954).

(2) S. Bernstein, R. Littell and J. H. Williams, THIS JOURNAL, **75**, 4830 (1953).

(3) (a) E. Seebeck and T. Reichstein, *Helv. Chim. Acta*, **31**, 2076 (1943); (b) L. Sarett, *J. Biol. Chem.*, **173**, 187 (1948); (c) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, THIS JOURNAL, **74**, 4223 (1951); (d) R. P. Graber, A. C. Haven, Jr., and N. L. Wendler, *ibid.*, **75**, 4722 (1953); (e) S. Bernstein, R. H. Lenhard and J. H. Williams, *J. Org. Chem.*, **19**, 41 (1954); and (f) G. Rosenkranz, O. Mancera and F. Sondheimer, THIS JOURNAL, **76**, 2227 (1954).



ketosteroid, a number of which were subsequently prepared.

Reichstein's substance S 21-acetate 3,20-bisethylene ketal (IV)[4] on treatment with thionyl chloride–pyridine gave in 33% yield $\Delta^{5,16}$-pregnadiene-21-ol-3,20-dione 21-acetate 3,20-bisethylene ketal (Vb). Saponification afforded the 21-olbisketal (Va) which on acid hydrolysis was converted (74% yield) into $\Delta^{4,16}$-pregnadiene-21-ol-3,20-dione (VIa). Acetylation gave the 21-acetate VIb, whose properties were in excellent agreement with those reported for this compound by Cole and Julian.[5,6] These investigators obtained this compound as a by-product in a study of the reduction of $\Delta^{4}$-pregnene-21-ol-3,20-dione-16$\alpha$,17$\alpha$-oxide 21-acetate with chromous chloride in acetic acid.

It is of interest to note that the acetate VIb also was prepared in 64% yield directly from the $\Delta^{5,16}$-21-acetate bisketal (Vb) by hydrolysis with 50% aqueous acetic acid in methanol in which both the $C_3$- and $C_{20}$-ketal groups were removed.[7] Also, the 21-acetate VIb in benzene on ketalization afforded only the 3-ethylene ketal VII. This result demonstrated that the steric effect of the 21-acetoxy group on such reactions at the $C_{20}$-ketone group is not altered by the presence of a $\Delta^{16}$-double bond. This steric effect of a 21-acetoxy group has been shown with other steroids.[8,9]

The dehydration reaction was next applied to cortisone acetate bisethylene ketal VIII, the preparation of which has been described already.[1,8] This compound was readily transformed into $\Delta^{5,16}$-pregnadiene-21-ol-3,11,20-trione 21-acetate 3,20-bisethylene ketal (IXb) (45% yield). The $\Delta^{5,16}$-21-ol-bisketal IXa was obtained on saponification. Acid hydrolysis of the latter afforded in 87% yield the free steroid, $\Delta^{4,16}$-pregnadiene-21-ol-3,11,20-trione (Xa). The 21-acetate Xb was prepared in the usual manner, and its properties were in excellent agreement with those obtained for this compound by Dr. Warren F. McGuckin of the Mayo Clinic.[10]

Our attention finally was directed to the preparation of the 11$\beta$-hydroxy XIIIa analog of Xa, and this was accomplished in the following way. $\Delta^{5,16}$-Pregnadiene-21-ol-3,11,20-trione 21-acetate 3,20-bisethylene ketal (IX) in tetrahydrofuran was reduced with a very large excess of sodium borohydride in the presence of sodium hydroxide, and $\Delta^{5,16}$-pregnadiene-11$\beta$,21-diol-3,20-dione 3,20-bisethylene ketal (XI) was obtained in 81% yield. The possible formation in low percentage yield of the 11$\alpha$-epimer in this reduction was not investigated.[1,8] The diol-bisketal XI in glacial acetic acid was heated on a steam-bath for 0.5 hour, and underwent partial hydrolysis to afford in 39% yield $\Delta^{4,16}$-pregnadiene-11$\beta$,21-diol-3,20-dione 20-ethylene ketal (XII). However, hydrolysis of XI in either sulfuric acid–methanol or 50% aqueous acetic acid–methanol removed both ketal groups, and $\Delta^{4,16}$-pregnadiene-11$\beta$,21-diol-3,20-dione (XIIIa) was obtained in 50 or 93% yield, respectively. The free steroid XIIIa was further characterized by the formation of its 21-acetate XIIIb.

The structures of the various $\Delta^{16}$-steroids prepared herein have been assigned on the basis of the following considerations other than elemental analyses: (A) It is now accepted that ionic elimination of a $C_{11}$-hydroxyl group gives rise to a $\Delta^{9(11)}$-steroid.[3]

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[4] R. Antonucci, S. Bernstein and R. Lenhard, THIS JOURNAL, **76**, 2956 (1954).

[5] W. Cole and P. L. Julian, *J. Org. Chem.*, **19**, 131 (1954).

[6] Our preparation was completed prior to the appearance of the Glidden publication.

[7] Hydrolysis of the bisethylene ketal of desoxycorticosterone acetate under these conditions gave rise to a mixture of products which contained a 20-ketal group. At most, only a trace amount of a product was formed which gave a positive ketol test with Blue Tetrazolium.

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

[9] R. Antonucci, S. Bernstein, R. Lenhard, K. J. Sax and J. H. Williams, *ibid.*, **17**, 1369 (1952); see also J. M. Constantin, A. C. Haven, Jr., and L. H. Sarett, THIS JOURNAL, **75**, 1716 (1953).

[10] Private communication.

TABLE I

ULTRAVIOLET ABSORPTION DATA

| Compound | $\lambda_{max}$, m$\mu$ ($\epsilon$) | $\Delta\epsilon$(B − A) | Ref. |
|---|---|---|---|
| $\Delta^{16}$-Pregnene-3,20-dione | 239(9800) | | 14 |
| A. Progesterone | 241(17,000) | | 14 |
| B. $\Delta^{4,16}$-Pregnadiene-3,20-dione | 241(25,200) | +8200 | [b,c] |
| A. $\Delta^{4,9(11)}$-Pregnadiene-17$\alpha$,21-diol-3,20-dione | 237.5–239(16,000) | | 2 |
| B. $\Delta^{4,9(11),16}$-Pregnatriene-21-ol-3,20-dione | 238–239(24,500) | +8500 | [d] |
| A. $\Delta^{4,9(11)}$-Pregnadiene-17$\alpha$,21-diol-3,20-dione 21-acetate | 238.5–240(16,600) | | 2 |
| B. $\Delta^{4,9(11),16}$-Pregnatriene-21-ol-3,20-dione 21-acetate | 239(24,000) | +7400 | [d] |
| A. $\Delta^{4}$-Pregene-17$\alpha$,21-diol-3,20-dione | 240–241(16,650) | | 2 |
| B. $\Delta^{4,16}$-Pregnadiene-21-ol-3,20-dione | 240–241(23,600) | +6950 | [d] |
| A. $\Delta^{4}$-Pregnene-17$\alpha$,21-diol-3,20-dione 21-acetate | 241(17,400) | | 2 |
| B. $\Delta^{4,16}$-Pregnadiene-21-ol-3,20-dione 21-acetate | 238–241(24,200) | +6800 | [d] |
| A. $\Delta^{4}$-Pregnene-17$\alpha$,21-diol-3,11,20-trione | 238(15,600) | | 8 |
| B. $\Delta^{4,16}$-Pregnadiene-21-ol-3,11,20-trione | 238(23,900) | +8300 | [c] |
| A. $\Delta^{4}$-Pregnene-17$\alpha$,21-diol-3,11,20-trione 21-acetate | 238(15,800) | | 14 |
| B. $\Delta^{4,16}$-Pregnadiene-21-ol-3,11,20-trione 21-acetate | 238(24,600) | +8800 | [c] |
| A. $\Delta^{4}$-Pregnene-11$\beta$,17$\alpha$,21-triol-3,20-dione | 242(15,600) | | 8 |
| B. $\Delta^{4,16}$-Pregnadiene-11$\beta$,21-diol-3,20-dione | 241–242(22,600) | +7000 | [d] |
| A. $\Delta^{4}$-Pregnene-11$\beta$,17$\alpha$,21-triol-3,20-dione 21-acetate | 242(16,100) | | 8 |
| B. $\Delta^{4,16}$-Pregnadiene-11$\beta$,21-diol-3,20-dione 21-acetate | 240.5(24,400) | +8300 | [d] |

[a] Solvent is alcohol or absolute alcohol except as indicated. [b] D. K. Fukushima and T. F. Gallagher, THIS JOURNAL, **73**, 196 (1951). [c] Solvent is methanol. [d] This work.

(B) In a recent paper[11] from this Laboratory, it was proven by chemical means that the double bond of a $\Delta^{16}$-20-ketosteroid does not rearrange when its 20-carbonyl group was condensed with ethylene glycol. This behavior was in marked contrast to the coincident rearrangement of the double bond during the formation of the ethylene ketal of a $\Delta^{4}$-3-ketosteroid.[12] Thus, on this basis, it is reasonable to assume that the elimination of a $C_{17}$-hydroxyl group adjacent to a $C_{20}$-ketal group gives rise to the corresponding $\Delta^{16}$-20-ketal. Further chemical evidence on this structural feature has been obtained during the course of a related investigation, and will be presented in the near future.[13]

(C) The free steroids (IIIa, VIa, Xa and XIIIa) and their respective acetates (IIIb, VIb, Xb and XIIIb) contain two isolated $\alpha,\beta$-unsaturated ketonic chromophores, namely, $\Delta^{4}$-3-ketone and $\Delta^{16}$-20-ketone. Ultraviolet absorption analysis played an important role in substantiating the structures of these compounds. Dorfman[14] in a noteworthy paper on the ultraviolet absorption spectra of steroids states that a $\Delta^{4}$-3-ketone *generally* absorbs selectively at 241 m$\mu$ with an *average* molecular extinction coefficient of 16,600 (*e.g.*, progesterone, $\lambda_{max}$ 241 m$\mu$, $\epsilon$ 17,000), whereas, a $\Delta^{16}$-20-ketone absorbs selectively at 240 m$\mu$ with an *average* molecular extinction of 10,500 (*e.g.*, $\Delta^{16}$-pregnene-3,20-dione, $\lambda_{max}$ 239 m$\mu$, $\epsilon$ 9800). $\Delta^{4,16}$-Pregnadiene-3,20-dione which contains both chromophores absorbs selectively at 241 m$\mu$, with a molecular extinction coefficient of 25,200. Introduction of a $\Delta^{16}$-20-ketonic chromophore in progesterone results in an increase in the extinction coefficient of the order of +8200 ($\Delta\epsilon$). The spectra of the new $\Delta^{16}$-steroids are in good agreement with the observations discussed above, and show a $\Delta\epsilon$ which ranges from +6800 to 8800 (Table I).

(D) The transformations were followed readily by infrared absorption analysis which further supported the assigned structures. Infrared data are reported in the Experimental. Besides the hydroxyl and carbonyl bands, we have indicated the following double bond bands: $\Delta^{16}$ (non-conjugated) at 1630–1638 cm.$^{-1}$; $\Delta^{16}$ (conjugated with $C_{20}$-ketone) at 1588–1600 cm.$^{-1}$; $\Delta^{4}$ (conjugated with $C_3$-ketone) at 1620–1630 cm.$^{-1}$, and $\Delta^{5}$ at 1680 cm.$^{-1}$. We have also indicated one of the principal "C–O" stretching bands of the ketal function at approximately 1100 cm.$^{-1}$.

(E) All the compounds containing a $C_{17}$-ketol group gave a positive Blue Tetrazolium test, diagnostic for such a group. Moreover, compounds containing the $\Delta^{16}$-$C_{17}$-ketol group gave a positive Porter–Silber color test. This finding is in agreement with the observation of Mattox, Mason and co-workers[15] that such a group as present in $\Delta^{16}$-pregnene-3$\alpha$,21-diol-11,20-dione 3,21-diacetate does give such a positive test.

**Bioassays.**[16]—In the electrolyte assay (K/Na ratio) on adrenalectomized rats, $\Delta^{4,9(11),16}$-pregnatriene-21-ol-3,20-dione (IIIa), $\Delta^{4,16}$-pregnadiene-21-ol-3,20-dione (VIa) and $\Delta^{4,16}$-pregnadiene-11$\beta$,-21-diol-3,20-dione (XIIIa) exhibited no activity

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[11] S. Bernstein, M. Heller and S. M. Stolar, THIS JOURNAL, **76**, 5674 (1954).

[12] E. Fernholz and H. E. Stavely, Abstracts of the 102nd Meeting of the American Chemical Society, Atlantic City, N. J., September 8–12, 1941, p. M39; Fernholz, U. S. Patents 2,356,154 (August 22, 1944) and 2,378,918 (June 26, 1945); R. Antonucci, S. Bernstein, R. Littell, K. J. Sax and J. H. Williams, *J. Org. Chem.*, **17**, 1341 (1952); and G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953).

[13] W. S. Allen and S. Bernstein, in process of preparing manuscript for publication.

[14] L. Dorfman. *Chem. Revs.*, **53**, 47 (1953).

[15] V. R. Mattox, H. L. Mason, A. Albert and C. F. Code, THIS JOURNAL, **75**, 4869 (1953).

[16] The bioassays were carried out under the direction of Dr. Ralph I. Dorfman at the Worcester Foundation for Experimental Biology, Shrewsbury, Mass. We are pleased to acknowledge this collaboration on the biological phase of the work.

at both the 6- and 25-μg. dose levels, where desoxycorticosterone gave significantly positive results. Compound VIa was inactive also at the 100-μg. level.

Also, $\Delta^{4,16}$-pregnadiene-11β,21-diol-3,20-dione (XIIIa) in the thymus involution assay (adrenalectomized and ovariectomized mice) appeared to give a statistically significant decrease in the thymus weight. However, its activity was of a low order when compared with those of cortisone and hydrocortisone.

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## Experimental

**Melting Points.**—All melting points are uncorrected, and were determined with uncalibrated Anschütz thermometers.

**Optical Rotations.**—The sample was dissolved in chloroform (unless otherwise noted) to make a 2-ml. solution, and the rotation was determined in a 1-dm. semi-micro tube at wave length 5893 Å. (*D*).

**Absorption Spectra.**—The ultraviolet spectra were determined in absolute alcohol (unless otherwise noted) with a Beckman spectrophotometer (model DU). The infrared spectra (Nujol mull or pressed potassium bromide as indicated) were determined with a Perkin–Elmer spectrophotometer (model 21).

**Petroleum Ether.**—The fraction used had a b.p. 60–70° (Skellysolve B).

**$\Delta^{5,9(11),16}$-Pregnatriene-21-ol-3,20-dione 21-Acetate 3,20-Bisethylene Ketal (IIb).**—Hydrocortisone acetate bisketal (I) (1.5 g.) was dissolved in 30 ml. of dry pyridine, chilled to −5°, and 6 ml. of thionyl chloride was added. The mixture was allowed to stand at −5° for 16 hours, and then poured into ice-water. The oily mixture was extracted with 2 liters of ether, the extract was washed with saturated saline solution, dried and was evaporated under reduced pressure. The oily residue was crystallized from acetone–methanol, and the yield was 0.58 g. (42%), m.p. 123–123.5°. Recrystallization from acetone–methanol changed the melting point to 119–120°; ultraviolet: $\lambda_{\max}$ none; infrared: $\lambda_{\max}^{\text{Nujol}}$ 1742, 1633, 1252 and 1090 cm.$^{-1}$; $[\alpha]^{25}\mathrm{D}$ +3° ($\alpha\mathrm{D}$ +0.05°, 14.61 mg.), $[M]\mathrm{D}$ +14.

*Anal.* Calcd. for $C_{27}H_{36}O_6$ (456.56): C, 71.02; H, 7.95. Found: C, 71.08; H, 8.20.

**$\Delta^{4,9(11),16}$-Pregnatriene-21-ol-3,20-dione (IIIa).**—The $\Delta^{5,9(11),16}$-acetate bisketal IIb (430 mg.) was refluxed 0.5 hour with 15 ml. of 2% alcoholic potassium hydroxide. Water was added, and the mixture was extracted with 1 liter of chloroform. The extract was washed to neutral with saturated saline solution, dried and was evaporated under reduced pressure. The crystalline residue IIa dissolved in 40 ml. of methanol was treated with 4 ml. of 8.5% (v./v.) sulfuric acid, and the mixture was refluxed for 1 hour. The cooled mixture was neutralized with saturated sodium bicarbonate solution, and crystals appeared upon further cooling. These were collected by filtration, and washed well with water. The yield was 305 mg. (99%), m.p. 204–209°. Recrystallization from acetone–ether raised the melting point to 215–218°; ultraviolet: $\lambda_{\max}$ 238–239 mμ ($\epsilon$ 24,500); infrared: $\lambda_{\max}^{\text{Nujol}}$ 3460, 1674, 1620, 1598 and 1094 cm.$^{-1}$; $[\alpha]^{24}\mathrm{D}$ +194° ($\alpha\mathrm{D}$ +2.43°, 25.09 mg.), $[M]\mathrm{D}$ +632.

*Anal.* Calcd. for $C_{21}H_{26}O_3$ (326.42): C, 77.27; H, 8.03. Found: C, 77.49; H, 8.27.

**$\Delta^{4,9(11),16}$-Pregnatriene-21-ol-3,20-dione 21-Acetate (IIIb).**—The $\Delta^{4,9(11),16}$-free steroid IIIa was acetylated in the usual manner at room temperature with acetic anhydride and pyridine. Recrystallization of the crude product from acetone–petroleum ether gave pure IIIb, m.p. 126–127°; ultraviolet: $\lambda_{\max}$ 239 mμ ($\epsilon$ 24,000); infrared: $\lambda_{\max}^{\text{Nujol}}$ 1752, 1682, 1620, 1588, 1220 and 1088 cm.$^{-1}$; $[\alpha]^{24}\mathrm{D}$ +166° ($\alpha\mathrm{D}$ +0.94°, 10.34 mg.), $[M]\mathrm{D}$ +611.

*Anal.* Calcd. for $C_{23}H_{28}O_4$ (368.45): C, 74.97; H, 7.66. Found: C, 74.90; H, 7.64.

**$\Delta^{5,16}$-Pregnadiene-21-ol-3,20-dione 21-Acetate 3,20-Bisethylene Ketal (Vb).**—A solution of Reichstein's substance S 21-acetate bisethylene ketal (IV) (0.5 g.) in 10 ml. of pyridine was treated at −5° with 2 ml. of purified thionyl chloride. The mixture was allowed to stand at −5° for 16 hours, and then at room temperature for 1 hour. Finally it was rechilled to −5°, and poured into ice-water. The oily mixture was extracted with ether as above. Crystallization of the oily residue from methanol yielded 0.16 g. (33%), m.p. 126–129.5°. Recrystallization from acetone–methanol gave pure Vb, m.p. 131–132°; ultraviolet: $\lambda_{\max}$ none; infrared: $\lambda_{\max}^{\text{Nujol}}$ 1738, 1630, 1226 and 1088 cm.$^{-1}$; $[\alpha]^{25}\mathrm{D}$ −34° ($\alpha\mathrm{D}$ −0.14°, 8.1 mg.), $[M]\mathrm{D}$ −156.

*Anal.* Calcd. for $C_{27}H_{38}O_6$ (458.57): C, 70.71; H, 8.35. Found: C, 70.63; H, 8.60.

**$\Delta^{5,16}$-Pregnadiene-21-ol-3,20-dione 3,20-Bisethylene Ketal (Va).**—The $\Delta^{5,16}$-21-acetate 3,20-bisketal (Vb) (60 mg.) was refluxed for 0.5 hour with 10 ml. of 2.5% alcoholic potassium hydroxide. The addition of water yielded 50 mg. (92%), m.p. 193–210°. Recrystallization from acetone–petroleum ether gave pure Va, m.p. 191–194°; ultraviolet: $\lambda_{\max}$ none; infrared: $\lambda_{\max}^{\text{Nujol}}$ 3570, 1630 and 1095 cm.$^{-1}$; $[\alpha]^{24}\mathrm{D}$ −46° ($\alpha\mathrm{D}$ −0.21°, 9.10 mg.), $[M]\mathrm{D}$ −191.

*Anal.* Calcd. for $C_{25}H_{36}O_5$ (416.54): C, 72.08; H, 8.71. Found: C, 72.35; H, 8.93.

**$\Delta^{4,16}$-Pregnadiene-21-ol-3,20-dione (VIa).**—The $\Delta^{5,16}$-bisketal (Va) (450 mg.) was refluxed for 1 hour with 6 ml. of 8% (v./v.) sulfuric acid in 100 ml. of methanol. Water was added, and the methanol was removed by distillation under reduced pressure. The residual mixture was extracted with 500 ml. of chloroform, and the extract was washed with 2% sodium bicarbonate solution and with saturated saline solution. The dried extract was evaporated under reduced pressure, and the residue was crystallized from acetone–petroleum ether. The yield was 260 mg. (74%), m.p. 227–232°. Recrystallization from acetone–petroleum ether sharpened the melting point to 229–232°. This compound (VIa) gave a positive α-ketol test with Blue Tetrazolium and a positive Porter–Silber test; ultraviolet: $\lambda_{\max}$ 240–241 mμ ($\epsilon$ 23,600); infrared: $\lambda_{\max}^{\text{KBr}}$ 3472, 1672, 1666, 1622, 1592 and 1090 cm.$^{-1}$; $[\alpha]^{24}\mathrm{D}$ +148° ($\alpha\mathrm{D}$ +1.16°, 15.71 mg.), $[M]\mathrm{D}$ +485.

*Anal.* Calcd. for $C_{21}H_{28}O_3$ (328.44): C, 76.79; H, 8.59. Found: C, 76.78; H, 8.80.

**$\Delta^{4,16}$-Pregnadiene-21-ol-3,20-dione 21-Acetate (VIb). A.**—The free steroid VIa was acetylated in the usual manner at room temperature with acetic anhydride and pyridine. The crude acetate was recrystallized from ether, m.p. 153–154°; ultraviolet: $\lambda_{\max}$ 238–241 mμ ($\epsilon$ 24,200); infrared: $\lambda_{\max}^{\text{Nujol}}$ 1748, 1684, 1626, 1595 and 1240 cm.$^{-1}$; $[\alpha]^{25}\mathrm{D}$ +142°($\alpha_{\mathrm{D}}$ +1.04°, 14.71 mg.), $[M]\mathrm{D}$ +525.[17]

*Anal.* Calcd. for $C_{23}H_{30}O_4$ (370.47): C, 74.56; H, 8.16. Found: C, 74.31; H, 8.32.

**B.**—The $\Delta^{5,16}$-21-acetate bisketal Vb (150 mg.) was refluxed for 0.5 hour with 15 ml. of 50% acetic acid in 10 ml. of methanol. Water (100 ml.) was added to the cooled solution which was then extracted with 300 ml. of chloroform. The extract was washed with a saturated sodium bicarbonate solution and a saturated saline solution. The dried extract was evaporated under reduced pressure, and the residue was crystallized from methanol-water; 77 mg. (64%), m.p. 131–140°. Recrystallization from acetone–petroleum ether raised the melting point to 149–151°. The compound gave a positive α-ketol test with Blue Tetrazolium; ultraviolet: $\lambda_{\max}$ 240–241 mμ ($\epsilon$ 23,100). Its infrared spectrum was identical to that of the acetate VIb prepared above (A).

**$\Delta^{5,16}$-Pregnadiene-21-ol-3,20-dione 21-Acetate 3-Ethylene Ketal (VII).**—A mixture of the 21-acetate VIb (0.5 g.), 30 ml. of benzene, 3 ml. of ethylene glycol and 15 mg. of *p*-toluenesulfonic acid monohydrate was treated in the conventional manner (6 hours reflux). The residue obtained upon evaporation of the benzene extract was crystallized

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(17) Cole and Julian[5] have recorded the following constants for VIb: m.p. 152°, $\lambda_{\max}^{\text{methanol}}$ 241 mμ ($\epsilon$ 25,200), $[\alpha]\mathrm{D}$ +148° (chloroform).

from acetone–methanol. The yield was 0.27 g. (49%), m.p. 184–188°. Recrystallization from acetone–petroleum ether raised the melting point to 190–192°; ultraviolet: $\lambda_{\max}$ 239.5 m$\mu$ ($\epsilon$ 8,800); infrared: $\lambda_{\max}^{\mathrm{KBr}}$ 1760, 1688, 1590, 1216 and 1082 cm.$^{-1}$; $[\alpha]^{25}\mathrm{D}$ $-23°$ ($\alpha\mathrm{D}$ $-0.14°$, 12.00 mg.), $[M]\mathrm{D}$ $-95$.

*Anal.* Calcd. for $C_{25}H_{34}O_5$ (414.52): C, 72.43; H, 8.27. Found: C, 72.39; H, 8.51.

$\Delta^{5,16}$-**Pregnadiene-21-ol-3,11,20-trione 21-Acetate 3,20-Bisethylene Ketal (IXb).**—Cortisone acetate bisethylene ketal (VIII) (0.3 g.) dissolved in 10 ml. of pyridine was treated with 2 ml. of thionyl chloride in the manner described above (16 hours at $-5°$). Evaporation of an ether extract gave an oily residue which was crystallized from methanol; 130 mg. (45%), m.p. 113–114°. Recrystallization from acetone–methanol gave pure IXb, m.p. 114–115°; ultraviolet: $\lambda_{\max}$ none; infrared: $\lambda_{\max}^{\mathrm{Nujol}}$ 1744, 1715, 1680, 1638, 1246 and 1090 cm.$^{-1}$; $[\alpha]^{25}\mathrm{D}$ $-13°$ ($\alpha\mathrm{D}$ $-0.19°$, 14.46 mg. in 1 ml. of chloroform), $[M]\mathrm{D}$ $-61$.

*Anal.* Calcd. for $C_{27}H_{36}O_7$ (472.56): C, 68.62; H, 7.68. Found: C, 68.77; H, 7.84.

$\Delta^{5,16}$-**Pregnadiene-21-ol-3,11,20-trione 3,20-Bisethylene Ketal (IXa).**—The 21-acetate 3,20-bisketal (IXb) was saponified with 2.5% alcoholic potassium hydroxide to yield the bisketal IXa, m.p. 157.5–161° (from acetone–petroleum ether); ultraviolet: $\lambda_{\max}$ none; infrared: $\lambda_{\max}^{\mathrm{Nujol}}$ 3520, 3354, 1710, 1680, 1630 and 1100 cm.$^{-1}$; $[\alpha]^{25}\mathrm{D}$ $-15°$ ($\alpha\mathrm{D}$ $-0.15°$, 19.66 mg.), $[M]\mathrm{D}$ $-65°$.

*Anal.* Calcd. for $C_{25}H_{34}O_6$ (430.52): C, 69.74; H, 7.96. Found: C, 69.73; H, 8.18.

$\Delta^{4,16}$-**Pregnadiene-21-ol-3,11,20-trione (Xa).**—The 3,20-bisketal IXa (1.7 g.) was refluxed for 40 minutes with 10 ml. of 8% (v./v.) sulfuric acid in 100 ml. of methanol. The addition of water gave crystals which were collected; 1.21 g. (87%), m.p. 231–234°. Recrystallization from acetone–ether lowered the melting point to 223–228°; ultraviolet: $\lambda_{\max}^{\mathrm{MeOH}}$ 238 m$\mu$ ($\epsilon$ 23,900); infrared: $\lambda_{\max}^{\mathrm{Nujol}}$ 3410, 1714, 1678, 1630, 1592 and 1082 cm.$^{-1}$; $[\alpha]^{24}\mathrm{D}$ $+236°$ ($\alpha\mathrm{D}$ $+2.33°$, 19.78 mg.), $[M]\mathrm{D}$ $+807$.

*Anal.* Calcd. for $C_{21}H_{26}O_4$ (342.42): C, 73.66; H, 7.66. Found: C, 73.80; H, 7.84.

$\Delta^{4,16}$-**Pregnadiene-21-ol-3,11,20-trione 21-Acetate (Xb).**—The free steroid Xa was acetylated in the usual manner at room temperature to give Xb, m.p. 189–190° (from acetone–methanol); ultraviolet: $\lambda_{\max}^{\mathrm{MeOH}}$ 238 m$\mu$ ($\epsilon$ 24,600); infrared: $\lambda_{\max}^{\mathrm{Nujol}}$ 1738, 1710, 1670, 1622, 1598 and 1258 cm.$^{-1}$; $[\alpha]^{24}\mathrm{D}$ $+213°$ ($\alpha\mathrm{D}$ $+1.78°$, 16.75 mg.), $[M]\mathrm{D}$ $+818$.[18]

*Anal.* Calcd. for $C_{23}H_{28}O_5$ (384.45): C, 71.85; H, 7.34. Found: C, 71.76; H, 7.48.

$\Delta^{5,16}$-**Pregnadiene-11$\beta$,21-diol-3,20-dione 3,20-Bisethylene Ketal (XI).**—The 3,20-bisketal IXb (600 mg.) was refluxed for 20 hours with 800 mg. of sodium borohydride in 50 ml. of tetrahydrofuran containing 7 ml. of 2.5% sodium hydroxide solution. After the addition of water, the tetrahydrofuran was removed by distillation under reduced pressure, and the aqueous residue was extracted with 500 ml. of chloroform. The extract was washed with saturated saline solution, dried, and was evaporated under reduced pressure. The gummy residue was crystallized from acetone–petroleum ether yielding 445 mg. (81%), m.p. 187.5–189°. Recrystallization from acetone–petroleum ether gave pure XI, m.p. 189–191°; ultraviolet: $\lambda_{\max}$ none; infrared: $\lambda_{\max}^{\mathrm{Nujol}}$ 3500, 1630 and 1098 cm.$^{-1}$; $[\alpha]^{24}\mathrm{D}$ $-33°$ ($\alpha\mathrm{D}$ $-0.19°$, 11.45 mg.), $[M]\mathrm{D}$ $-143$.

*Anal.* Calcd. for $C_{25}H_{36}O_6$ (432.54): C, 69.42; H, 8.39. Found: C, 69.48; H, 8.43.

$\Delta^{4,16}$-**Pregnadiene-11$\beta$,21-diol-3,20-dione 20-Ethylene Ketal (XII).**—A mixture of the 3,20-bisketal XI (1.0 g.) and 20 ml. of glacial acetic acid was heated on a steam-bath for 0.5 hour. After being cooled the mixture was neutralized with sodium bicarbonate, and was extracted with 500 ml. of chloroform. The extract was washed with saturated saline solution, dried, and evaporated under reduced pressure. Crystallization of the residue from acetone–petroleum ether gave 0.35 g. (39%) of the monoketal XII, m.p. 229–233°. Recrystallization from acetone–petroleum ether raised the m.p. to 238–240.5°; ultraviolet: $\lambda_{\max}$ 242 m$\mu$ ($\epsilon$ 16,100); infrared: $\lambda_{\max}^{\mathrm{KBr}}$ 3365, 1666, 1623 and 1036 cm.$^{-1}$; $[\alpha]^{24}\mathrm{D}$ $+149°$ ($\alpha\mathrm{D}$ $+1.70°$, 22.82 mg. in 2 ml. of pyridine), $[M]\mathrm{D}$ $+ 578$.

*Anal.* Calcd. for $C_{23}H_{32}O_5$ (388.49): C, 71.10; H, 8.30. Found: C, 71.18; H, 8.51.

$\Delta^{4,16}$-**Pregnadiene-11$\beta$,21-diol-3,20-dione (XIIIa).** A.—The 3,20-bisketal XII (250 mg.) was refluxed for 1 hour with 4 ml. of 8% (v./v.) sulfuric acid in 40 ml. of methanol. After the addition of water, the methanol was removed by distillation under reduced pressure, and the aqueous solution was extracted with 500 ml. of chloroform. The extract was washed with a saturated sodium bicarbonate solution and with a saturated saline solution. The dried extract was evaporated under reduced pressure, and the oily residue was crystallized from acetone–ether to yield 100 mg. (50%), m.p. 154–156°. Pure XIIIa was obtained by recrystallization from acetone–petroleum ether; m.p. 158–160°. The compound gave a positive $\alpha$-ketol test with Blue Tetrazolium, and a positive Porter–Silber test; ultraviolet: $\lambda_{\max}$ 241–242 m$\mu$ ($\epsilon$ 22,600); infrared: $\lambda_{\max}^{\mathrm{Nujol}}$ 3480, 1690, 1660, 1626, 1600 and 1102 cm.$^{-1}$; $[\alpha]^{24}\mathrm{D}$ $+200°$ ($\alpha\mathrm{D}$ $+0.94°$, 9.42 mg.), $[M]\mathrm{D}$ $+688$.

*Anal.* Calcd. for $C_{21}H_{28}O_4$ (344.44): C, 73.22; H, 8.19. Found: C, 73.28; H, 8.44.

B.—In another run a solution of the 3,20-bisketal XII (2.0 g.) in 100 ml. of methanol and 50 ml. of 50% aqueous acetic acid was refluxed for 1 hour. It was cooled, neutralized with sodium bicarbonate, and the methanol was distilled under reduced pressure. The product was extracted from the residual mixture with 1 l. of chloroform. The extract was washed with saturated saline, dried, and evaporated under reduced pressure. The residue was crystallized from acetone–petroleum ether to give 1.48 g. (93% yield), m.p. 164–165°; positive Blue Tetrazolium test.

$\Delta^{4,16}$-**Pregnadiene-11$\beta$,21-diol-3,20-dione 21-Acetate (XIIIb).**—The free steroid XIIIa was acetylated in the usual manner to yield XIIIb, m.p. 148–149° (from acetone–petroleum ether–ether); ultraviolet: $\lambda_{\max}$ 240.5 m$\mu$ ($\epsilon$ 24,400); infrared: $\lambda_{\max}^{\mathrm{Nujol}}$ 3544, 1760, 1680, 1624, 1592, 1220 and 1072 cm.$^{-1}$; $[\alpha]^{24}\mathrm{D}$ $+191°$ ($\alpha\mathrm{D}$ $+1.58°$, 16.60 mg.), $[M]\mathrm{D}$ $+737$.

*Anal.* Calcd. for $C_{23}H_{30}O_5$ (386.47): C, 71.48; H, 7.82. Found: C, 71.58; H, 8.10.

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(18) McGuckin[10] has characterized Xb as follows: m.p. 183–184°, $\lambda_{\max}^{\mathrm{alc.}}$ 237–238 m$\mu$ ($\epsilon$ 25,200); $[\alpha]\mathrm{D}$ $+200°$ (dioxane), $+$ 220° (alc.), $+$ 194° (acetone).