amide was crystallized from a benzene–heptane mixture; yield 8.4 g., m.p. 192–195°.

The amide (7.9 g. in 100 ml. of anhydrous tetrahydrofuran) was then treated with 8 g. of lithium aluminum hydride in 100 ml. of ether as described in the general procedure. The resulting $\Delta^5$-3β-hydroxy-17-[(N-piperidino)-methyl] androstene separated as a gel from methylene chloride–hexane. After repeating this process several times there was obtained 6.7 g., m.p. 132–136°, $[\alpha]^{25}D$ −50.7° ($CHCl_3$).

*Anal.* Calcd. for $C_{25}H_{41}ON$: C, 80.80; H, 11.12. Found: C, 80.69; H, 11.51.

A solution of 1.5 g. of amine in 30 ml. of methyl iodide was refluxed for one-half hour. Sixty ml. of ethanol then was added and the methyl iodide was removed by distillation. A small amount of insoluble material was filtered from the hot solution, and the filtrate was concentrated until crystallization began. From the cooled mixture there was obtained 1.25 g. of the methiodide, m.p. 280–282° dec. Recrystallization from methanol raised the m.p. to 282–283° dec., $[\alpha]^{25}D$ −32.1° (ethanol).

*Anal.* Calcd. for $C_{26}H_{44}ONI$: I, 24.71. Found: I, 24.68.

**$\Delta^5$-3β,22-Dihydroxybisnorcholene from the N-Methyl Anilide of $\Delta^5$-3β-Acetoxybisnorcholenic Acid by Lithium Aluminum Hydride Reduction.**—To a solution of 1.57 g. of the N-methyl anilide of $\Delta^5$-3β-acetoxybisnorcholenic acid in 240 ml. of anhydrous tetrahydrofuran was added 5.0 g. of lithium aluminum hydride and the reaction mixture was refluxed overnight. The excess reagent was decomposed in the usual way and the precipitated alumina was removed by filtration. The precipitate was leached with methylene chloride and the extracts were combined with the filtrate. The resulting solution was dried and concentrated. Addition of hexane induced crystallization. There resulted 0.95 g. of $\Delta^5$-3β,22-dihydroxybisnorcholene, m.p. 199–200°, $[\alpha]^{25}D$ −58.6° ($CHCl_3$) [lit. m.p.[3] 196–205° (hemihydrate), $[\alpha]^{25}D$ −55.4° ($CHCl_3$)].

*Anal.* Calcd. for $C_{22}H_{36}O_2$: C, 79.46; H, 10.92. Found: C, 79.04; H, 11.05.

The product was not basic (no precipitate in ethereal hydrogen chloride), was free from nitrogen, and showed no carbonyl bands in the infrared (strong hydroxyl absorption was observed).

BLOOMFIELD, N. J.

[CONTRIBUTION FROM THE MEDICINAL CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES, RESEARCH DIVISION, AMERICAN CYANAMID CO.]

# Steroidal Cyclic Ketals. XVI.[1] 16-Hydroxylated Steroids. II.[2] The Preparation of 16-Keto- and 16β-Hydroxyprogesterone

BY SEYMOUR BERNSTEIN, MILTON HELLER AND STEPHEN M. STOLAR

RECEIVED JUNE 9, 1955

Chromic acid–pyridine oxidation of $\Delta^5$-pregnene-16α-ol-3,20-dione 3,20-bis-ethylene ketal (Ia) afforded the 16-one bis-ketal IIa. Mild acid hydrolysis of IIa gave $\Delta^4$-pregnene-3,16,20-trione (IV), which was converted into the 20-enol acetate V (13% yield) on mild acetylation. Reduction of the 16-one bis-ketal IIa with lithium aluminum hydride resulted in the 16β-ol bis-ketal IIIa, which was hydrolyzed to $\Delta^4$-pregnene-16β-ol-3,20-dione (VIa). Its acetate VIb also was prepared.

In a recent publication[2] from this Laboratory there was reported synthetic pathways to 16α-hydroxyprogesterone and related compounds *via* ethylene ketal intermediates. The latter have lent themselves to a number of interesting transformations which elaborate further the chemistry of the C-16 position. The results obtained form the basis of this paper.

Chromic acid–pyridine oxidation[3] of $\Delta^5$-pregnene-16α-ol-3,20-dione 3,20-bis-ethylene ketal (Ia)[2] afforded in 80% yield the 16-one bis-ketal IIa, which displayed in the infrared spectrum the expected 5-membered ring carbonyl absorption at 1748 cm.$^{-1}$. The oxime IIb of the 16-one bis-ketal IIa also was prepared and characterized. It was noted that the infrared absorption spectrum of the oxime IIb showed an abnormally weak absorption band in the C=N region at 1670 cm.$^{-1}$.

Mild acid hydrolysis of the 16-one bis-ketal IIa gave $\Delta^4$-pregnene-3,16,20-trione (IV) in fairly good yield. It appeared to exist mainly in an enol form as shown by its complex infrared absorption spectrum (see Experimental) and by its ultraviolet absorption spectrum with bands at 240 and 285 mμ.[4] The expected bathochromic effect of the ultraviolet absorption band in basic solution was observed with a shift of the higher absorption band (285 mμ) to 308 mμ. No shift of the absorption band was noticed on dilution.[5] It was not possible to determine from the above physical data in which direction (or both) enolization might have taken place. Acetylation under mild conditions, however, furnished one of the two possible enol acetates after purification by several crystallizations (perhaps necessary for the separation of both enol acetates). This new compound had an ultraviolet absorption band at 242 mμ (ε 26,400) (the ultraviolet absorption spectrum in basic solution reverted to that of the free enol). Since the bands of the two chromophores combined in the ultraviolet, no information could be obtained from that source as to the direction of enolization. Its infrared absorption spectrum, however, clearly indicated the probable structure. The spectrum in the carbonyl and double bond regions was complex and had bands at 1755, 1725, 1679, 1652 and 1625 cm.$^{-1}$. The band at 1755 cm.$^{-1}$ could best be assigned to the enol acetate grouping,[6] so that the band at 1725 cm.$^{-1}$ must be the result of the conjugated ketone, $\Delta^{17(20)}$-16-one (the $\Delta^4$-3-ketone was, of course, shown by the band at 1679 cm.$^{-1}$). Therefore, the enol acetate was assigned the structure

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[1] Paper XV, W. S. Allen, S. Bernstein, M. Heller and R. Littell, THIS JOURNAL, **77**, 4784 (1955).

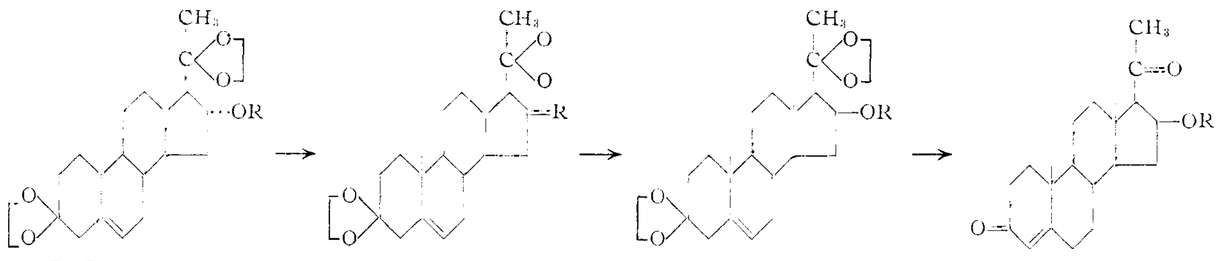
[2] Paper I, S. Bernstein, M. Heller and S. M. Stolar, *ibid.*, **76**, 5674 (1954).

[3] G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, *ibid.*, **75**, 422 (1953).

[4] The value 285 mμ disagrees with that of 277 mμ recorded for the same chromophore system by H. H. Inhoffen, F. Blomeyer and K. Brückner, *Ber.*, **87**, 593 (1954).

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

[6] R. N. Jones, P. Humphries, F. Herling and K. Dobriner, THIS JOURNAL, **74**, 2820 (1952).

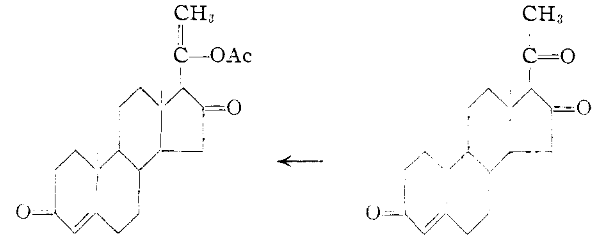


Ia, R = H
b, R = Ac

IIa, R = O
b, R = NOH

IIIa, R = H
b, R = Ac

VIa, R = H
b, R = Ac



V

IV

$\Delta^{4,17(20)}$-pregnadiene-20-ol-3,16-dione 20-acetate (V).[7]

Treatment of $\Delta^5$-pregnene-3,16,20-trione 3,20-bis-ethylene ketal (IIa) with lithium aluminum hydride produced a new alcohol bis-ketal in 85% yield (only product isolated), which differed markedly in melting point and infrared absorption spectrum from the 16α-ol-bis-ketal Ia and must, therefore, be the 16β-ol bis-ketal IIIa. The formation of the latter suggests, thereby, a stereospecific rear attack at this position with lithium aluminum hydride.[8] Preparation of its acetate in the usual manner gave IIIb which also differed in all physical details from the 16α-acetoxy compound Ib, and gave with it a mixed melting point depression.

The 16β-ol bis-ketal IIIa in dilute methanolic sulfuric acid was refluxed for three minutes to afford the free alcohol, $\Delta^4$-pregnene-16β-ol-3,20-dione (VIa). It is interesting to note that as in the case of a 16α-hydroxyl group,[2] it was found possible to hydrolyze the ketal groups under certain acidic conditions and yet not eliminate the 16β-hydroxyl function which is attached to a carbon β to the 20-carbonyl group, and, moreover, is in a *trans* relationship to the 17α-hydrogen.

Molecular rotational analysis has been employed successfully in the past to support assignments of configuration at the C-16 position.[9] Consequently, the compounds described herein were submitted to such an analysis in Table I.

TABLE I

MOLECULAR ROTATION ANALYSIS

| Compound | Ref. | $[\alpha]_D$-(CHCl$_3$) | $M_D$-(CHCl$_3$) | $M_D^{16\alpha\text{-OH-H}}$ |
|---|---|---|---|---|
| $\Delta^4$-Pregnene-3,20-dione | 10 | +200 | +629 | |
| $\Delta^4$-Pregnene-16α-ol-3,20-dione | 2,9c | +157 | +519 | −110 |
| $\Delta^5$-Pregnene-3,20-dione 3,20-bis-ethylene ketal | 11 | −29 | −116 | |
| $\Delta^5$-Pregnene-16α-ol-3,20-dione 3,20-bis-ethylene ketal (Ia) | 3 | −32 | −135 | −19 |
| | | | | $M_D^{16\alpha\text{-OAc-H}}$ |
| $\Delta^4$-Pregnene-16α-ol-3,20-dione 16-acetate | 2,9c | +102 | +380 | −249 |
| $\Delta^5$-Pregnene-16α-ol-3,20-dione 16-acetate 3,20-bis-ethylene ketal (Ib) | | −80 | −370 | −254 |
| | | | | $M_D^{16\text{-one-H}}$ |
| $\Delta^4$-Pregnene-3,16,20-trione (IV) | | +102 | +335 | −294 |
| $\Delta^5$-Pregnene-3,16,20-trione 3,20-bis-ethylene ketal (IIa) | | −154 | −640 | −524 |
| | | | | $M_D^{16\beta\text{-OH-H}}$ |
| $\Delta^4$-Pregnene-16β-ol-3,20-dione (VIa) | | +192 | +635 | +6 |
| $\Delta^5$-Pregnene-16β-ol-3,20-dione 3,20-bis-ethylene ketal (IIIa) | | −27 | −113 | +3 |
| | | | | $M_D^{16\beta\text{-OAc-H}}$ |
| $\Delta^4$-Pregnene-16β-ol-3,20-dione 16-acetate (VIb) | | +103 | +384 | −245 |
| $\Delta^5$-Pregnene-16β-ol-3,20-dione 16-acetate 3,20-bis-ethylene ketal (IIIb) | | 0 | 0 | +116 |

It may be seen from the table that the molecular rotational differences due to 16α-hydroxyl and 16α-acetoxyl groups are in the expected negative directions, although the $\Delta^5$-pregnene-16α-ol-3,20-dione 3,20-bis-ethylene ketal (Ia) has a smaller $\Delta M_D(-19)$ than expected from the average ($\Delta M_D^{16\alpha\text{-OH-H}}$ *ca.* −60 in alcohol) given by Fukushima and Gallagher.[10b] However, we have experienced a number of anomalous molecular rotational differences from ethylene ketal derivatives in

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(7) C. W. Marshall and T. F. Gallagher, THIS JOURNAL, **71**, 2325 (1949), have prepared the same chromophoric system in $\Delta^{17(20)}$-pregnene-3α,12α,20-triol-16-one 3α,12α,20-triacetate which has an ultraviolet absorption band at 249 mμ (ε 11,200).

(8) H. Hirschmann, F. B. Hirschmann and M. A. Daus, *J. Biol. Chem.*, **178**, 751 (1949), obtained solely the 16β-hydroxyl configuration upon reduction of a steroid 16-one with platinum or Raney nickel or aluminum isopropylate. A. Bowers, T. G. Halsall and G. C. Sayer, *J. Chem. Soc.*, 3070 (1954), obtained a mixture of 16α and 16β-hydroxyl compounds using lithium aluminum hydride on a triterpenoid, although these authors noted one case in which only a 16β-hydroxyl function was formed.

(9) (a) H. Hirschmann and F. B. Hirschmann, *J. Biol. Chem.*, **184**, 259 (1950); (b) D. K. Fukushima and T. F. Gallagher, THIS JOURNAL, **73**, 196 (1951); (c) D. Perlman, E. Titus and J. Fried, *ibid.*, **74**, 2126 (1952).

(10) E. Fernholz, *Ber.*, **67**, 2027 (1934).

(11) R. Antonucci, S. Bernstein, R. Lenhard, K. J. Sax and J. H. Williams, *J. Org. Chem.*, **17**, 1369 (1952).

this Laboratory.[12] The molecular rotational difference ($\Delta M_D^{16\text{-one-H}}$ −294, −524) of the 16-ketone compounds (IV, IIa) are in the anticipated negative direction.[13] The lower value for $\Delta^4$-pregnene-3,16,20-trione (IV), perhaps, is due to the enol formation already mentioned. The molecular rotational differences of the 16β-hydroxy compounds (IIa and VIa) are in the expected positive direction, but of considerably smaller values than observed in previous work (reference 10b recorded an average $\Delta M_D^{16\beta\text{-OH-H}}$ +40 in alcohol). While the $\Delta M_D$ for $\Delta^5$-pregnene-16β-ol-3,20-dione 16-acetate 3,20-bis-ethylene ketal (IIIb) is of a reasonable magnitude (reference 10b recorded $\Delta M_D^{16\beta\text{-OAc-H}}$ +100 in alcohol), the free dione 16-acetate VIb furnished a marked deviation with a $\Delta M_D$ −245. If the data found for the 16β-substituted bis-ketals (IIIa and IIIb) are discounted because of the previously mentioned abnormalities of these types of compounds, the unexpected results with $\Delta^4$-pregnene-16β-ol-3,20-dione (VIa) and its acetate VIb may be explained conveniently on the basis of "vicinal action" between the 17β-acetyl side chain and the 16β-substituent.

Infrared absorption data have been reported in the Experimental. The usual group absorption bands have been indicated: hydroxyl (*ca.* 3500 cm.$^{-1}$), carbonyl (1755–1675 cm.$^{-1}$), double bonds (1660–1610 cm.$^{-1}$), acetate (1260–1170 cm.$^{-1}$), and one of the C–O stretching bands of the ketal group (*ca.* 1100 cm.$^{-1}$).

ADDED IN PROOF.—Since submission of this manuscript, G. E. Arth, G. I. Poos and L. H. Sarett, THIS JOURNAL, **77**, 3834 (1955) (in particular, footnote 9 of that paper) have clarified the difference between our results and those of Inhoffen[4] with respect to the ultraviolet absorption spectrum of a 16,20-dione.

**Acknowledgment.**—We wish to thank Messrs. Louis M. Brancone, Samuel S. Modes, John Heider and Alex N. Prezioso for the analyses, and Messrs. William Fulmor and George Morton and Miss Anne Callaghan for the optical rotations and infrared absorption spectra.

## Experimental

*Melting Points:* All melting points are uncorrected, and were determined with uncalibrated Anschütz thermometers. *Optical Rotations:* The solvent was chloroform. *Absorption Spectra:* The ultraviolet absorption spectra were determined in absolute alcohol (unless otherwise noted) with a Beckman spectrophotometer (model DU) or a Cary recording spectrophotometer (model 11S). The infrared absorption spectra (pressed potassium bromide) were determined with a Perkin–Elmer spectrophotometer (model 21). *Petroleum Ether:* The fraction used had a b.p. 60–70° (Skellysolve B). *All evaporations were carried out under reduced pressure.*

**$\Delta^5$-Pregnene-16α-ol-3,20-dione 16-Acetate 3,20-Bis-ethylene Ketal (Ib).**—A solution of 0.2 g. of the 16α-ol bis-ketal Ia in 2.5 ml. of pyridine and 1 ml. of acetic anhydride was allowed to stand at room temperature for 68 hours, poured into water, filtered and washed with water to give 0.18 g. of solid. Three crystallizations from acetone–petroleum ether yielded 0.12 g. of the acetate Ib, m.p. 249–251°; $\nu_{max}$ 1730, 1260 and 1097 cm.$^{-1}$; $[\alpha]^{25}_D$ −80° (*c* 1.094), $[M]_D$ −370.

*Anal.* Calcd. for $C_{27}H_{40}O_6$ (460.59): C, 70.40; H, 8.75. Found: C, 70.22; H, 8.86.

**$\Delta^5$-Pregnene-3,16,20-trione 3,20-Bis-ethylene Ketal (IIa).**—To a solution of 0.12 g. of the 16α-ol bis-ketal Ia in 2 ml. of pyridine was added a solution of 0.12 g. of chromic anhydride in 4 ml. of pyridine. After standing 16 hours at room temperature, the solution was added to water, filtered, and the filtrate was extracted with ethyl acetate. The residue from the filtration was boiled in ethyl acetate, filtered, and the filtrate was combined with the previous extracts. After treatment with Norite, the dried extract was evaporated. Three crystallizations from methanol gave 0.05 g. of the trione bis-ketal IIa, m.p. 211–215°; $\nu_{max}$ 1748 and 1102 cm.$^{-1}$, $[\alpha]^{25}_D$ −154° (*c* 0.799), $[M]_D$ −640.

*Anal.* Calcd. for $C_{25}H_{36}O_6$ (416.54): C, 72.08; H, 8.71. Found: C, 71.86; H, 9.00.

In another run 0.625 g. (80%) of IIa, m.p. 210.5–215°, was obtained from 0.79 g. of Ia.

**$\Delta^5$-Pregnene-3,16,20-trione 3,20-Bis-ethylene Ketal 16-Oxime (IIb).**—To a solution of 0.15 g. of hydroxylamine hydrochloride and 0.3 g. of sodium acetate in 15 ml. of methanol and 2 ml. of water was added 0.15 g. of the trione bis-ketal IIa, and the mixture was refluxed for 10 minutes. The resultant mixture was added to water and the solid was collected to give 0.135 g., m.p. 239–249° dec. Three crystallizations from methanol afforded 0.075 g. of the oxime IIb, m.p. 266.5–267.5° dec.; $\nu_{max}$ 3410, 1670 (weak) and 1098 cm.$^{-1}$; $[\alpha]^{25}_D$ −127 (*c* 0.505), $[M]_D$ −550.

*Anal.* Calcd. for $C_{25}H_{37}NO_5$ (431.55): C, 69.57; H, 8.64; N, 3.25. Found: C, 69.38; H, 8.41; N, 3.09.

In another run conducted as above except that the refluxing period was 6 hours, 1.04 g. of IIb, m.p. 260.5–262.5° dec., was obtained from 1 g. of IIa.

**$\Delta^5$-Pregnene-16β-ol-3,20-dione 3,20-Bis-ethylene Ketal (IIIa).**—A solution of 0.201 g. of the trione bis-ketal IIa in 75 ml. of anhydrous ether was added dropwise over a period of 15 minutes to a stirred mixture of 0.4 g. of lithium aluminum hydride in 40 ml. of absolute ether. After the mixture was refluxed for 1.5 hours with stirring, it was cooled, water was added cautiously, and the layers were separated. The water layer was extracted with ether and ethyl acetate, and the extract was dried and evaporated. Two crystallizations from acetone–petroleum ether furnished 0.083 g. (41%) of the 16β-ol bis-ketal IIIa, m.p. 223.5–226.5°; $\nu_{max}$ 3550 and 1097 cm. $^{-1}$; $[\alpha]^{24}_D$ −27° (*c*, 0.852], $[M]_D$ −113.

*Anal.* Calcd. for $C_{25}H_{38}O_5$ (418.55): C, 71.74; H, 9.15. Found: C, 71.46; H, 9.21.

In another reduction with 0.98 g. of the ketone IIa after decomposition of the complex with saturated sodium potassium tartrate solution, the mixture was filtered and the filtrate was extracted as above. The residue was boiled for 1 hour with ethyl acetate and filtered and the filtrate was combined with the previous extract. Evaporation gave 0.745 g., m.p. 231.5–234°,[14] and 0.086 g., m.p. 224–227° (85%), of IIIa.

**$\Delta^5$-Pregnene-16β-ol-3,20-dione 16-Acetate 3,20-Bis-ethylene Ketal (IIIb).**—Acetylation of the 16β-ol bis-ketal (IIIa. 0.1 g.) in pyridine (3 ml.) and acetic anhydride (1 ml.) was conducted in the usual manner at room temperature to give 0.101 g. of solid, m.p. 216.5–220°. Three crystallizations from acetone–petroleum ether yielded 0.048 g. of the acetate IIIb, m.p. 260.5–261.5°; $\nu_{max}$ 1740, 1252 and 1095 cm.$^{-1}$; $[\alpha]_D^{25}$ ±0° (*c* 1.126), $[M]_D$ ±0°.

*Anal.* Calcd. for $C_{27}H_{40}O_6$ (460.59): C, 70.40; H, 8.75. Found: C, 70.36; H, 8.95.

Admixture melting point of the acetates Ib and IIIb showed non-identity, m.p. 222–226°.

**$\Delta^4$-Pregnene-3,16,20-trione (IV).**—A solution of the trione bis-ketal (IIa, 0.3 g.) in acetone (50 ml.) was treated with *p*-toluenesulfonic acid monohydrate (0.1 g.) and allowed to stand 16 hours at room temperature. Sodium bicarbonate was added. The mixture was swirled a few minutes and filtered. The filtrate was evaporated at room temperature. Two crystallizations of the residue from dilute acetone gave 0.18 g. (76%) of the trione IV, m.p. 177.5–180°; $\lambda_{max}$ 240 mμ (ε 16,900) and 285 mμ (ε 5,430);

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[12] R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell and J. H. Williams, *J. Chem. Soc.*, **18**, 70 (1953); S. Bernstein, R. Littell and J. H. Williams, *ibid.*, **18**, 1418 (1953).

[13] W. Klyne, *J. Chem. Soc.*, 2916 (1952), and M. N. Huffman and M. H. Lott, THIS JOURNAL, **75**, 4327 (1953) (see also previous papers by the latter investigators) have pointed out the large negative increment in optical rotation ($\Delta M_D$ *ca.* −450 to −500) conferred on a steroid molecule by a 16-ketone.

[14] This higher melting point was invariably reached on later runs.

$\lambda_{\max}^{1\%\ \text{KOH in abs. EtOH}}$ 241 m$\mu$ ($\epsilon$ 16,650) and 308 m$\mu$ ($\epsilon$ 20,100); $\nu_{\max}$ 1760, 1682, 1655 and 1610 cm.$^{-1}$; $[\alpha]^{25}\text{D}$ +102° (*c* 0.956), $[M]\text{D}$ +335.

*Anal.* Calcd. for $C_{21}H_{28}O_3$ (328.44): C, 76.79; H, 8.59. Found: C, 76.43; H, 8.81.

**$\Delta^{4,17(20)}$-Pregnadiene-20-ol-3,16-dione 20-Acetate** (V).—A solution of 0.215 g. of the trione IV in 5 ml. of pyridine and 3 ml. of acetic anhydride was allowed to stand 16 hours at room temperature, poured into water, extracted with ether and ethyl acetate, and the combined extracts were treated with Norite and dried. Evaporation gave an oil. Six crystallizations from dilute acetone afforded 0.032 g. (13%) of the enol acetate V, m.p. 203–203.5°; $\lambda_{\max}$ 242 m$\mu$ ($\epsilon$ 26,400); $\lambda_{\max}^{1\%\ \text{KOH in abs. EtOH}}$ 241 m$\mu$ ($\epsilon$ 16,400) and 308 m$\mu$ ($\epsilon$ 21,200); $\nu_{\max}$ 1755, 1725, 1679, 1652, 1625 and 1170 cm.$^{-1}$; $[\alpha]^{24}\text{D}$ −30° (*c* 0.531), $[M]\text{D}$ −112.

*Anal.* Calcd. for $C_{23}H_{30}O_4$ (370.47): C, 74.56; H, 8.16. Found: C, 74.83; H, 8.36.

**$\Delta^4$-Pregnene-16$\beta$-ol-3,20-dione** (VIa).—To a refluxing mixture of 0.83 g. of the 16$\beta$-ol bis-ketal IIIa in 100 ml. of methanol was added 6 ml. of 8% (v./v.) sulfuric acid. The reaction was allowed to proceed for 3 minutes and then was added to ice-water. The mixture was filtered to give 0.54 g. of solid, m.p. 188–194.5°. Several crystallizations from acetone–petroleum ether gave 0.245 g. of the 16$\beta$-ol dione VIa, m.p. 202–203°; $\lambda_{\max}$ 240 m$\mu$ ($\epsilon$ 16,500); $\nu_{\max}$ 3420, 1712, 1658 and 1615 cm.$^{-1}$; $[\alpha]^{25}\text{D}$ +192° (*c* 1.91), $[M]\text{D}$ +645.

*Anal.* Calcd. for $C_{21}H_{30}O_3$ (330.45): C, 76.32; H, 9.15. Found: C, 76.06; H, 9.02.

**$\Delta^4$-Pregnene-16$\beta$-ol-3,20-dione 16-Acetate** (VIb).—A solution of 272 mg. of VIa in 4 ml. of pyridine and 2 ml. of acetic anhydride was allowed to stand at room temperature for 16 hours, poured into ice-water, and filtered to give 264 mg. of crude acetate VIb, m.p. 185–193°. Several crystallizations from acetone–petroleum ether yielded 110 mg. (36%) of VIb, m.p. 202–203°; $\lambda_{\max}$ 240 m$\mu$ ($\epsilon$ 17,100); $\nu_{\max}$ 1745, 1721, 1680, 1625 and 1250 cm.$^{-1}$; $[\alpha]^{25}\text{D}$ +103° (*c* 0.3), $[M]\text{D}$ +384.

The analytical sample was obtained necessarily by sublimation, otherwise the analytical results invariably indicated solvation.

*Anal.* Calcd. for $C_{23}H_{32}O_4$ (372.49): C, 74.16; H, 8.66. Found: C, 74.19; H, 8.80.

PEARL RIVER, NEW YORK

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY]

# Terpenoids. XVII.[1] The Cactus Triterpenes Thurberogenin and Stellatogenin[2]

BY CARL DJERASSI, E. FARKAS,[3] L. H. LIU[3] AND G. H. THOMAS[3]

RECEIVED MARCH 5, 1955

Degradative evidence is presented on the basis of which it is suggested that the two cactus triterpenes thurberogenin and stellatogenin possess structures XLII and XLIII based on a betulinic acid skeleton.

In the first paper of this series[4] we described the isolation from the cactus *Lemaireocereus thurberi* of a new triterpene which was named "thurberogenin." The substance possessed the empirical formula $C_{30}H_{46}O_3$, formed a monoacetate and in the infrared exhibited a band at *ca.* 5.65 $\mu$ which was assigned to a five-membered lactone ring. Subsequently, an investigation of *Lemaireocereus stellatus*[5] and other cacti[5,6] led to the isolation of another triterpene lactone, "stellatogenin" ($C_{30}H_{48}O_4$) which could be correlated[5] with thurberogenin. Since stellatogenin is much more abundant as well as more widely distributed[5,6] this has made available a sufficient supply of these two triterpenes so that degradation studies could be initiated and these form the subject of the present paper. It should be noted that except for the cactus triterpene dumortierigenin,[7] no triterpenes so far have been encountered in nature which possess a lactone ring.

**Reactions of the Double Bond.**—Thurberogenin gives essentially no color with tetranitromethane[8] and does not show[7] any high terminal ultraviolet absorption typical[9] of the 12–13 double bond of triterpenes of the $\alpha$- and $\beta$-amyrin series (I, II). Nevertheless, the presence of a reactive double bond could be demonstrated by several reactions: (a) thurberogenin (X) can be hydrogenated with platinum oxide in glacial acetic acid to a dihydro derivative (XI); (b) thurberogenin can be oxidized readily with perbenzoic acid to yield an epoxide (XII)[5]; (c) selenium dioxide in acetic acid transforms thurberogenin acetate into an $\alpha,\beta$-unsaturated aldehyde (XIV) ($\lambda_{\max}^{\text{EtOH}}$ 222 m$\mu$, log $\epsilon$ 4.01) which in turn can be hydrogenated with palladium to a dihydroaldehyde (XV).

These reactions eliminate completely from consideration an $\alpha$-(I) or $\beta$-amyrin (II) skeleton, since those triterpenes[10] behave differently under such conditions, but rather suggest that thurberogenin belongs to the rare class of lupeol triterpenes of which only three members are known[10]: lupeol

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[1] Paper XVI, C. Djerassi, G. H. Thomas and H. Monsimer, THIS JOURNAL, **77**, 3579 (1955).

[2] (a) We are indebted to the Division of Research Grants of the U. S. Public Health Service for generous financial assistance (Grant No. G-3863) in support of this work. (b) Presented at the XIV International Congress of Pure and Applied Chemistry, Zürich, July 22, 1955.

[3] Postdoctorate research fellow at Wayne University.

[4] Paper I, C. Djerassi, L. E. Geller and A. J. Lemin, THIS JOURNAL, **75**, 2254 (1953).

[5] Paper XI, C. Djerassi, L. H. Liu, E. Farkas, A. E. Lippman, A. J. Lemin, L. E. Geller, R. N. McDonald and B. J. Taylor, *ibid.*, **77**, 1200 (1955).

[6] To be published.

[7] Paper VI, C. Djerassi, E. Farkas, A. J. Lemin, J. C. Collins and F. Walls, THIS JOURNAL, **76**, 2969 (1954). While a definite decision cannot as yet be made whether the intact lactone ring is indeed present in the plant glycosides or whether it is produced during the acid hydrolysis, it was shown in that paper that the lactone ring of dumortierigenin, thurberogenin and stellatogenin could not have been formed in the manner recorded for the oleanolic acid → iso-oleanolic acid lactone (XXII) transformation (*cf.* D. H. R. Barton and N. J. Holness, *J. Chem. Soc.*, 78 (1952)).

[8] The earlier reported (ref. 4) light yellow color may have been due to some contamination, possibly with oleanolic acid.

[9] T. G. Halsall, *Chemistry & Industry*, 867 (1951).

[10] For the sake of brevity, references to the original literature are not given when they apply to well-known reactions of pentacyclic triterpenes since these are summarized quite adequately in review articles by O. Jeger (in L. Zechmeister's "Progress in the Chemistry of Organic Natural Products," Springer, Vienna, 1951, Vol. 7, p. 1) and by D. H. R. Barton (in E. H. Rodd, "Chemistry of Carbon Compounds," Elsevier Press, Houston, Texas, 1953, Vol. IIB, p. 726).