[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF THE SCHERING CORP.]

11-Oxygenated Steroids. X. The Reduction of 21-Benzylidenepregnan-3α-ol-11,20-dione with Various Metal Hydrides[1]

BY EUGENE P. OLIVETO, CORINNE GEROLD AND E. B. HERSHBERG

RECEIVED JUNE 29, 1954

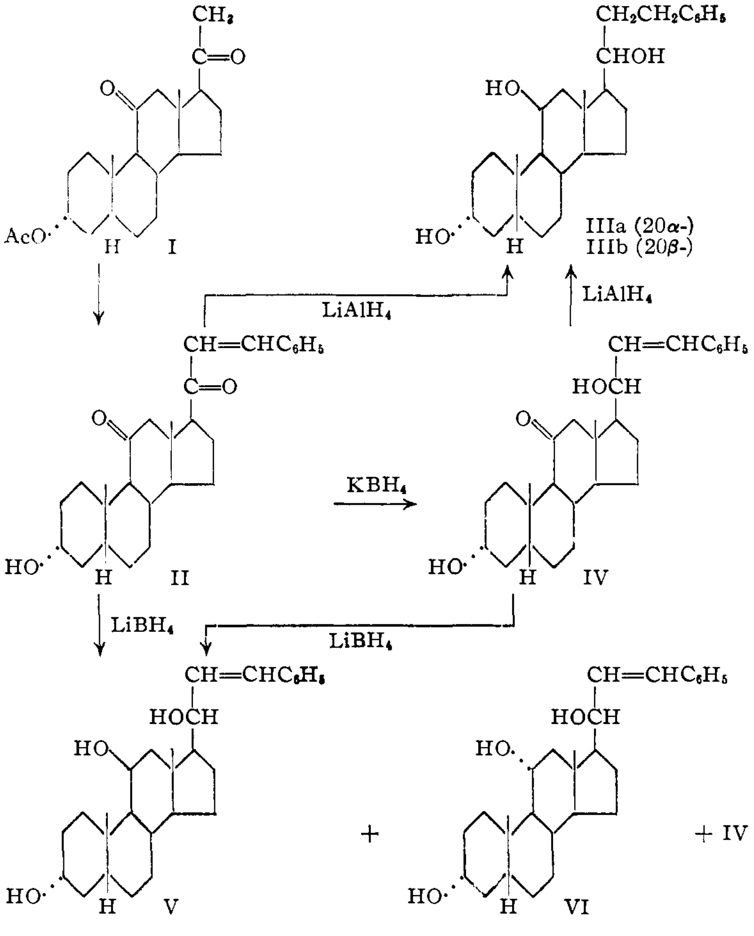
Reduction of 21-benzylidenepregnan-3α-ol-11,20-dione gives the following products: (a) with potassium borohydride, 21-benzylidenepregnane-3α,20β-diol-11-one (IV); (b) with lithium borohydride, a mixture of 21-benzylidenepregnane-3α,11β,20β-triol (V), 21-benzylidenepregnane-3α,11α,20β-triol (VI) and IV; and (c) with lithium aluminum hydride, 21-benzylpregnane-3α,11β,20α-triol (IIIa). Lithium aluminum hydride also reduces IV to the isomeric 21-benzylpregnane-3α,11β,20β-triol (IIIb).

A possible route to 11β-hydroxy steroids which would also possess oxygen functions at C-20 and C-21 involves the preparation of 11,20-diketo-21-benzylidene steroids, reduction of the 11-ketone to an 11β-hydroxyl group, followed by oxidative cleavage (*e.g.*, ozonization) of the benzylidene group. Toward this end, 21-benzylidenepregnan-3α-ol-11,20-dione (II) was prepared by the alkaline condensation of benzaldehyde with pregnan-3α-ol-11,20-dione acetate (I), and its reduction with various metal hydrides was studied.

Treatment of II with potassium borohydride gave a new compound (IV) with an ultraviolet maximum at 254 mμ, and which still contained an 11-ketone; its 3,20-diacetate contained no hydroxyl bands in the infrared spectrum and, therefore, the latter was formulated as 21-benzylidenepregnane-3α,20β-diol-11-one.[2] The preferential reduction[3] of a 20-ketone in an 11,20-diketone by means of sodium borohydride has been reported previously.

In an attempt to obtain the 11β-hydroxy analog of IV, lithium aluminum hydride and lithium borohydride reductions on both II and IV were carried out.

Lithium aluminum hydride reduction of IV either by normal or reverse addition gave a compound which no longer had any ultraviolet absorption characteristic of the $C_6H_5CH{=}CH$— group, contained no carbonyl groups, and which formed a diacetate with acetic anhydride and pyridine. It was therefore assigned the structure 21-benzylpregnane-3α,11β,20β-triol (IIIb). Reduction of II with lithium aluminum hydride also gave a triol of the same type but this compound IIIa and its diacetate differed in their infrared spectra from IIIb and its diacetate; IIIa then is probably 21-benzylpregnane-3α,11β,20α-triol. Unfortunately, the rotations of the triols and their diacetates do not support the assigned structures unequivocally, for the molecular rotations of both diacetates are higher than the corresponding triols. However, the increase is less in the series which has been assigned the 20α-configuration.[4]



The complete reduction of α,β-unsaturated ketones, or α,β-unsaturated alcohols to the saturated alcohols by means of lithium aluminum hydride has been observed before.[5] However, in the case we are reporting, a difference in configuration is

---

[1] Paper IX, H. Herzog, C. C. Payne and E. B. Hershberg, THIS JOURNAL, **76**, 930 (1954).

[2] The assignment of the 20β-configuration is based on: (a) the increase in molecular rotation of the diacetate as compared to the diol [*cf.* L. H. Sarett, *ibid.*, **71**, 1175 (1949)], and (b) the known propensity for sodium borohydride to produce predominantly this configuration in the reduction of a C-20 ketone. [E. P. Oliveto and E. B. Hershberg, *ibid.*, **75**, 488 (1953); O. Mancera, H. Ringold, C. Djerassi, G. Rosenkrantz and F. Sondheimer, *ibid.*, **75**, 1286 (1953)]. It is understood, of course, that these conclusions which are drawn by analogy to other, simpler pregnanes may be rendered invalid by the presence of the 21-benzylidene group in our compounds.

[3] E. P. Oliveto and E. B. Hershberg, ref. 2.

[4] *Cf.* L. H. Sarett, ref. 2; L. F. Fieser and M. Fieser, *Experientia*, **4**, 285 (1948).

[5] F. A. Hochstein and W. G. Brown, THIS JOURNAL, **70**, 3483 (1948).

observed at C-20 in the reduced product, depending on whether the starting material is II or IV. This may be a consequence of: (a) a difference in mechanism in the reduction of II and IV; or (b) a difference in the ease of formation and/or stability of the possible stereoisomeric ring complexes, which have been postulated[5] as being intermediates in the reduction. In any case it is obvious that the reduction of II does not proceed *via* IV.

Lithium borohydride reductions of II and IV also presented interesting features. 21-Benzylidenepregnane-3α,11β,20β-triol (V) could be prepared from IV in good yield by means of this reagent. However, the direct reduction of II to V proceeded in poor yield; two other compounds also were obtained from the reduction: 21-benzylidenepregnane-3α,11α,20β-triol (VI) and 21-benzylidenepregnane-3α,20β-triol-11-one (IV).

This is the second reported instance[6] of the selective reduction of an 11,20-diketone by means of lithium borohydride, and also the first reported isolation of an 11α-hydroxy compound in the reduction of an 11-ketone with this agent.[7]

Experimental[8]

21-Benzylidenepregnan-3α-ol-11,20-dione (II).—This compound, prepared as described previously,[9] had $\epsilon_{\max}^{294}$ 21,800 (95% ethanol). In addition to sodium methoxide,[9] piperidine was also found to be an effective catalyst for the condensation. Its 3-acetate, crystallized from methanol, melted at 207–209° with $[\alpha]_D$ +90.1° (chl.).

Anal. Calcd. for $C_{30}H_{38}O_4$: C, 77.89; H, 8.28. Found: C, 78.06; H, 8.56.

Lithium Aluminum Hydride Reduction of II.—A slurry of 10.0 g. of lithium aluminum hydride in 150 ml. of anhydrous ether was added, over a 30-minute period, to a stirred solution of 10.0 g. of II in 150 ml. of tetrahydrofuran, the temperature being maintained at −10 to −5°. The mixture was allowed to warm up to room temperature and stir overnight. It was then refluxed for one hour, cooled to 0–5°, and 50 ml. of ethyl acetate was added at that temperature. The salts were dissolved by the addition of 10% sulfuric acid, and the mixture extracted with methylene chloride. The extracts were washed neutral, dried over sodium sulfate and evaporated, leaving 9.8 g., m.p. 148–156°. Recrystallization from acetone–hexane yielded 5.2 g. of 21-benzylpregnane-3α,11β,20α-triol (IIIa), m.p. 166–170°. The analytical sample, crystallized twice more, melted at 172–174°, $[\alpha]_D$ +45.9° MeOH, had no ultraviolet absorption and showed no carbonyl peaks in the infrared.

Anal. Calcd. for $C_{28}H_{42}O_3$: C, 78.82; H, 9.92. Found: C, 79.13; H, 10.20.

Its 3,20-diacetate, crystallized from hexane, melted at 152–154°, $[\alpha]_D$ +57.3° (MeOH).

Anal. Calcd. for $C_{32}H_{46}O_5$: C, 75.26; H, 9.08. Found: C, 75.34; H, 9.12.

Potassium Borohydride Reduction of II.—A solution of 2.0 g. of potassium borohydride in 7.5 ml. of water was added to a solution of 2.0 g. of II in 75 ml. of methanol, and the mixture was allowed to stand overnight at room temperature. Concentration of the solution and addition of water gave 1.4 g. of 21-benzylidenepregnane-3α,20β-diol-11-one (IV), m.p. 191–193°, $\epsilon_{\max}^{254}$ 20,700 (95% EtOH). The analytical sample, crystallized from aqueous methanol, melted at 190.6–191.6°, $[\alpha]_D$ +3.8° (chl.), $\epsilon_{\max}^{254}$ 20,800 (95% EtOH). The infrared spectrum indicated the presence of the 11-ketone.

Anal. Calcd. for $C_{28}H_{38}O_3$: C, 79.58; H, 9.06. Found: C, 79.36; H, 9.27.

The 3,20-diacetate, crystallized twice from methanol, melted at 199–201°, $[\alpha]_D$ +11.8° (chl.). Its infrared spectrum showed no hydroxyl peak.

Anal. Calcd. for $C_{32}H_{42}O_5$: C, 75.85; H, 8.36. Found: C, 75.98; H, 8.65.

Additional material was obtained from the reduction filtrate on further dilution with water: 0.58 g., m.p. 110–120°, $\epsilon_{\max}^{254}$ 19,000. Recrystallization from ether gave 0.18 g., m.p. 167–170°. Infrared spectrum studies indicated this to be predominantly the 11-hydroxyl compound, with some 11-ketone still present.

Lithium Borohydride Reduction of IV.—A solution of 18.6 g. of IV in 186 ml. of tetrahydrofuran was cooled to −20° and to it was added a slurry of 18.6 g. of lithium borohydride in 280 ml. of ether. The mixture was allowed to warm up to room temperature and stir overnight, and then was refluxed 2 hours. It was cooled in an ice-bath and the salts dissolved by the addition of 10% sulfuric acid. Methylene chloride was added and the organic extract was washed neutral, dried and evaporated, yielding 18.6 g. of a crystalline residue, m.p. 178–188°. Two recrystallizations from acetone–hexane gave pure 21-benzylidenepregnane-3α,11β,20β-triol (V), m.p. 188–190°, $[\alpha]_D$ +8.2° (chl.), $\epsilon_{\max}^{254}$ 18,900 (95% EtOH). No carbonyl peaks were present in the infrared spectrum.

Anal. Calcd. for $C_{28}H_{40}O_3$: C, 79.20; H. 9.50. Found: C, 78.97; H, 9.52.

Acetylation of V with acetic anhydride and pyridine at room temperature gave, on water precipitation, a solid of m.p. 97–108°. Attempts to crystallize this material were unsuccessful. However, with methanol, a characteristic gel was obtained, which was shown to be homogeneous upon chromatography on Florisil; its infrared spectrum indicated the presence of a hydroxyl group and two acetate groups.

Lithium Borohydride Reduction of II.—Direct reduction of 10.0 g. of II with lithium borohydride by the procedure described above gave, after acetone–hexane crystallization, 3.92 g., m.p. 177–180°. Acetylation of 2.0 g., followed by crystallization from methanol, gave 0.73 g., m.p. 172–185°. An infrared spectrum showed a strong 11-carbonyl peak and no hydroxyl absorption, indicating that this material was predominantly IV diacetate. Concentration of the methanolic filtrate gave the gel characteristic of V diacetate; the infrared spectrum showed hydroxyl and acetate absorption, but no 11-carbonyl.

The residue from the original acetone–hexane crystallization of the reduction product, gave, upon acetylation, 5.56 g., m.p. 175–200°. Recrystallization from methylene chloride–methanol gave 1.28 g., m.p. 230–235°. The infrared spectrum showed complete acetylation, with no ketone or hydroxyl absorption; this compound is presumably 21-benzylidenepregnane-3α,11α,20β-triol triacetate. The analytical sample melted at 232–235°, $[\alpha]_D$ −35.0° (chl.), $\epsilon_{\max}^{254}$ 18,900 (95% EtOH).

Anal. Calcd. for $C_{34}H_{46}O_6$: C, 74.15; H, 8.42. Found: C, 73.87; H, 8.53.

Lithium Aluminum Hydride Reduction of IV.—The reduction of 3.0 g. of IV with $LiAlH_4$ in the manner described above, gave 2.73 g. of a resin which crystallized upon treatment with ether to give 1.11 g., m.p. 165–172°. One further crystallization from aqueous acetone raised the m.p. to 170–173°, $[\alpha]_D$ +28.9° MeOH; this material had no ultraviolet absorption. The infrared spectrum, while showing the absence of carbonyl functions, indicated that this material was different from IIIb.

The 3,20-diacetate, according to its infrared spectrum, contained a free hydroxyl, no ketone carbonyl, but was different from IIIb. Its rotation was +58.3° (MeOH), but it could not be crystallized for analysis.

BLOOMFIELD, NEW JERSEY

---

[6] N. L. Wendler. Huang-Minlon and M. Tishler, THIS JOURNAL, **73**, 3818 (1951).

[7] Lithium aluminum hydride is known to give varying amounts of 11α-hydroxy compounds when an 11-ketone is reduced [R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell and J. Williams, *J. Org. Chem.*, **18**, 70 (1953); R. Levin, B. Magerlein, A. McIntosh, A. Hanze, G. Fonken, J. Thompson, A. Searcy, M. Scheri and E. Gutsell, THIS JOURNAL, **76**, 546 (1954)]. Reduction of cortisone bis-ethylene ketal with lithium borohydride produces an 11-hydroxy isomer ratio similar to that obtained with lithium aluminum hydride [H. Herzog, unpublished results from these laboratories].

[8] All m.p.'s are corrected. All rotations were taken in a one-decimeter tube at a concentration of *ca.* 1%. Analyses and optical data were obtained by the Microanalytical and Physical Chemistry Departments of these Laboratories.

[9] R. B. Turner, V. R. Mattox, W. F. McGuckin and E. C. Kendall, THIS JOURNAL, **74**, 5814 (1952).