[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S.A.]

STEROIDS. XXXV.[1] SYNTHESIS OF 11α-HYDROXYPROGESTERONE

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Received April 21, 1952

In the twenty-ninth paper of this series (1) there was described a relatively facile synthesis of 11β-hydroxyprogesterone[3] since it was felt important to make available for biological experiments a simple analog of Δ^4-pregnene-11β,17α,21-triol-3,20-dione (Kendall's Compound F) which appears to be the active hormone secreted by the adrenal cortex (2). It seems of equal importance to prepare the hitherto unknown 11α-hydroxy epimers of this type of adrenal hormone and the present paper is concerned with the synthesis of the simplest one, 11α-hydroxyprogesterone (V) (Δ^4-pregnene-3,20-dione-11α-ol). While this manuscript was being prepared, a report appeared by Peterson and Murray (2a) in which the microbiological oxidation of progesterone to 11α-hydroxyprogesterone (Va) was described. The physical properties of the synthetic compound reported in this paper provide confirmation for the structural assignment of the microbiological product which was based upon oxidation to the known 11-keto-progesterone, the substance's non-identity with 11β-hydroxyprogesterone, and the formation of an acetate.

Until recently, the only known route to 11α-hydroxy steroids consisted of the alkaline isomerization of 11-bromo-12-keto bile acids (3) and the preparation of 11α-hydroxylated cortical hormones would thus involve the degradation of the bile acid side chain. Last year, there were described from this laboratory two novel synthetic methods (4, 5) for the introduction of the 11α-hydroxy group into ring C unsubstituted steroids and it is with the utilization of intermediates prepared by these procedures that this paper is concerned. Since the starting materials are 3β,11α-dihydroxy steroids and the introduction of the essential Δ^4-3-keto moiety would have to proceed through 3-keto-11α-hydroxy intermediates, it was first necessary to collect the basic information on the selective saponification or oxidation of steroidal 3β,11α-dihydroxy derivatives.[4] In the 11β-hydroxy series, it is well known (6) that this grouping is both resistant to esterification and Oppenauer oxidation; the 11α-hydroxy epimers, on the other hand, are readily acetylable (3, 4, 5).

It was now observed in the case of allopregnane-3β,11α-diol-20-one (Ia) (7) that there available at least three routes to the desired 3-keto-11α-hydroxy derivatives II: (a) selective saponification of the 3,11-diacetate Ia to the 3β-

[1] Paper XXXIV, *J. Am. Chem. Soc.*, in press.

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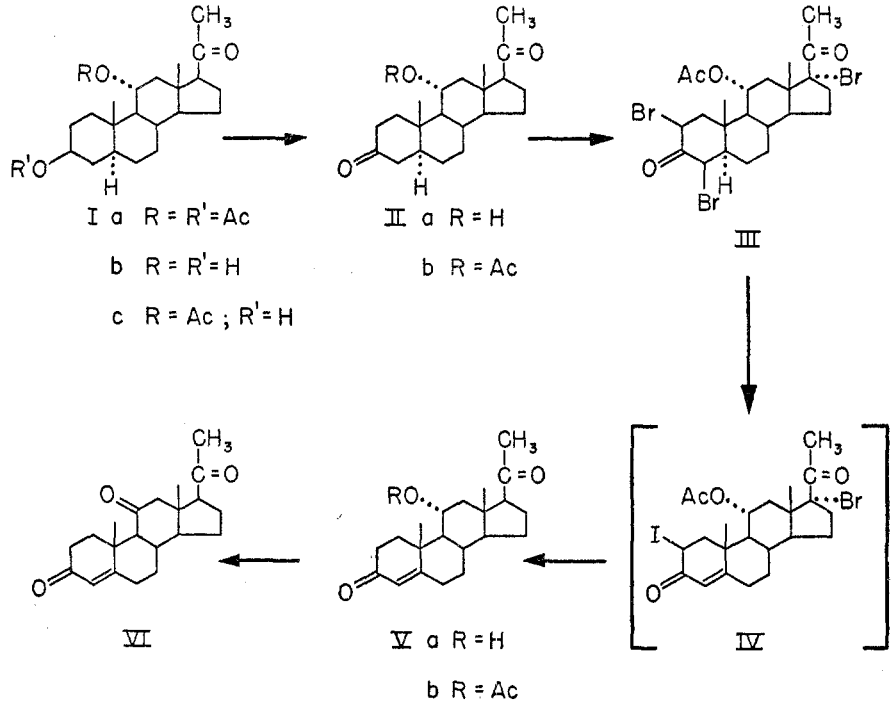
[3] This substance was first prepared by Reichstein and Fuchs (ref. 11) from the adrenal hormone corticosterone.

[4] Katz [*Helv. Chim. Acta*, **30**, 883 (1947)] has described the partial saponification of a 3α,11α-diacetoxy *normal* steroid, methyl 3α,11α-diacetoxyetiocholanate.



hydroxy-11α-monoacetate (Ic) followed by chromium trioxide oxidation; (b) selective oxidation at C-3 of the 3,11-diol Ib with N-bromoacetamide; and (c) Oppenauer oxidation of the diol Ib. The resulting allopregnane-3,20-dione-11α-ol (as the acetate IIb) was converted into the desired 11α-hydroxyprogesterone (V) by employing our recently described 3-ketoallo $\rightarrow$ Δ^4-3-keto steroid transformation (8) which involves treatment of a 2,4-dibromo-3-ketoallo steroid with sodium iodide and deiodination of the resulting 2-iodo-Δ^4-3-ketone. The situation was complicated, however, by the fact that it is known (9) that *di*bromination of allopregnane-3,20-dione furnishes the 2,17-dibromo rather than 2,4-dibromo derivative and that it is necessary to *tri*brominate before the requisite 2,4-dibromo moiety is introduced. Since Julian and Karpel (10) reported that a 17-bromo-20-ketone did not react with sodium iodide, it seemed possible that the sodium iodide procedure (8) would succeed in the present instance. Allopregnane-3,20-dione-11α-ol acetate (IIb) was thus tribrominated, the crude 2,4,17-tribromo derivative was refluxed with sodium iodide in ethyl methyl ketone solution and the presumed intermediate 2-iodo-17-bromo-Δ^4-pregnene-3,20-dione-11α-ol acetate (IV) was reduced with chromous chloride. Saponification and chromatographic separation produced the crystalline 11α-hydroxyprogesterone (Va) with $\lambda_{max.}^{EtOH}$ 242 mμ, log ϵ 4.18, $\lambda_{max.}^{CHCl_3}$ 1660 cm.$^{-1}$ (α,β-unsaturated ketone), 1704 cm.$^{-1}$ (20-ketone), and free hydroxyl band. Acetylation furnished the crystalline acetate (Vb) while chromium trioxide oxidation led to the known (11, 12) 11-ketoprogesterone. The physical constants of Va

and Vb were in good agreement with those reported by Peterson and Murray (2a) for the product obtained in the microbiological oxidation of progesterone.

EXPERIMENTAL[5]

Allopregnane-3β,11α-diol-20-one (Ib). A solution of 5.0 g. of allopregnane-3β,11α-diol-20-one diacetate (Ia) (7) in 150 cc. of methanol was refluxed with 5.0 g. of potassium carbonate and 35 cc. of water for one-half hour. After neutralization with acetic acid, concentration, dilution with water, extraction with ether, evaporation to dryness, and recrystallization from hexane-acetone, there was isolated 3.35 g. of the diol Ib with m.p. 177–179°, $[\alpha]_D^{20}$ +60°, $\lambda_{max.}^{CHCl_3}$ 1700 cm.$^{-1}$ and free hydroxyl band.

Anal. Calc'd for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25.

Found: C, 75.60; H, 10.10.

Allopregnane-3β,11α-diol-20-one 11-monoacetate (Ic). The partial saponification was best accomplished by refluxing 10.5 g. of the diacetate Ia (7) in 200 cc. of methanol for 1½ hours with 3.8 g. (1.4 equivalents) of potassium bicarbonate and 50 cc. of water. After working up as above and recrystallizing from hexane-acetone, there was obtained 7.07 g. (75%) of the 11-monoacetate Ic with m.p. 177–179°, $[\alpha]_D^{20}$ +47°, $\lambda_{max.}^{CHCl_3}$ 1720 and 1704 cm.$^{-1}$ and free hydroxyl band. The infrared spectrum proved to be different from that of Ib and a mixture of Ib and Ic melted at 145–155°.

Anal. Calc'd for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64.

Found: C, 73.72; H, 9.45.

Acetylation of the combined mother liquors afforded 1.8 g. of recovered diacetate Ia with m.p. 168–170°.

Allopregnane-3,20-dione-11α-ol (II). (*a*) *By chromium trioxide oxidation of allopregnane-3β,11α-diol-20-one 11-monoacetate* (Ic). A solution of 5.0 g. of the 11-monoacetate Ic in 200 cc. of acetic acid was treated at 18° dropwise with stirring with a solution of 1.08 g. of chromium trioxide in 100 cc. of 80% acetic acid. After two hours at room temperature, the mixture was diluted with ice water and the precipitate was collected; yield, 4.72 g. (94%), m.p. 173–176°. The analytical sample of *allopregnane-3,20-dione-11α-ol 11-acetate* (IIb) crystallized from hexane-acetone as colorless crystals with m.p. 177–179°, $[\alpha]_D^{20}$ +66°, $\lambda_{max.}^{CHCl_3}$ 1718 and 1700 cm.$^{-1}$, but no free hydroxyl band.

Anal. Calc'd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15.

Found: C, 73.89; H, 9.26.

(*b*) *By Oppenauer oxidation of allopregnane-3β,11α-diol-20-one* (Ib). A mixture of 0.5 g. of the diol Ib in 50 cc. of toluene and 15 cc. of cyclohexanone was dried by distilling off 25 cc., a solution of 1 g. of aluminum isopropoxide in 15 cc. of toluene was added, and the mixture was refluxed for 45 minutes. Acidification, steam-distillation, and extraction of the residue with ether followed by evaporation and recrystallization from hexane-acetone yielded 0.3 g. of *allopregnane-3,20-dione-11α-ol* (IIa) with m.p. 193–195°, $[\alpha]_D^{20}$ +83°, $\lambda_{max.}^{CHCl_3}$ 1700 cm.$^{-1}$ and free hydroxyl band.

Anal. Calc'd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70.

Found: C, 75.63; H, 9.81.

Acetylation with acetic anhydride-pyridine produced the 11-acetate IIb, which proved to be identical (mixture melting point, rotation, infrared spectrum) with that prepared according to (*a*).

(*c*) *By N-bromoacetamide oxidation of allopregnane-3β,11α-diol-20-one* (Ib). A mixture of 0.27 g. of the diol Ib and 0.17 g. of N-bromoacetamide in 15 cc. of acetone (containing

[5] Melting points are uncorrected. Rotations were meaured in chloroform (unless otherwise specified) and ultraviolet absorption spectra in 95% ethanol solution. We are indebted to Srta. Paquita Revaque for these measurements as well as for the infrared spectra (Perkin Elmer Model 12C single beam spectrometer with sodium chloride prism) and to Srta. Amparo Barba for the microanalyses.

1–2% of water) was permitted to stand overnight at room temperature and then diluted with water. Extraction with ether, washing with sodium carbonate solution and water, drying, evaporation, and recrystallization from hexane-acetone gave 0.11 g. of the diketone IIa, which proved to be identical in all respects (including infrared spectrum) with a specimen prepared according to (*b*). Further confirmation of the identity was provided by preparation of the acetate IIb.

11α-Hydroxyprogesterone (*Δ⁴-pregnene-3,20-dione-11α-ol*) (Va). A solution of 4.1 g. (3.1 equivalents) of bromine in 40 cc. of glacial acetic acid was added dropwise to a solution of 3.0 g. of allopregnane-3,20-dione-11α-ol acetate (IIb) in 70 cc. of acetic acid containing 5 drops of 4 *N* hydrogen bromide in acetic acid. After five hours at room temperature, the mixture was poured into ice water and the precipitated tribromo derivative (III) (4.75 g.) was collected, washed well with water, and dried. The dried material was refluxed for 14 hours with 6.5 g. of sodium iodide in 125 cc. of ethyl methyl ketone and then kept at room temperature for an additional 12 hours. After dilution with water, the product was extracted with ether, washed with sodium thiosulfate solution and water, and the ether was removed under reduced pressure. The crude residue ($\lambda_{max.}^{EtOH}$ 240 mμ, log ε 4.09), dissolved in 100 cc. of acetone, was treated in an atmosphere of carbon dioxide with a solution of chromous chloride prepared (8) from 35 g. of chromic chloride. After 20 minutes at room temperature, water was added, the mixture was extracted with ether, washed with water until neutral, dried, and evaporated. The resulting yellowish oil ($\lambda_{max.}^{EtOH}$ 240 mμ, log ε 4.07) was saponified by refluxing for 30 minutes with 2.0 g. of potassium carbonate in 100 cc. of methanol and 20 cc. of water and after extraction with chloroform, it was chromatographed on 150 g. of ethyl acetate-washed alumina. Recrystallization of the pooled chloroform-benzene (7:3) eluates from ether-hexane afforded 0.425 g. of *11α-hydroxyprogesterone* (Va) with m.p. 165–167°, $[\alpha]_D^{20}$ +169°, $\lambda_{max.}^{EtOH}$ 242 mμ, log ε 4.18, $\lambda_{max.}^{CHCl_3}$ 1704 and 1660 cm.$^{-1}$ and free hydroxyl band; reported for the microbiological oxidation product (2a): m.p. 166–167°, $[\alpha]_D^{25}$ +179°, $\lambda_{max.}^{EtOH}$ 242 mμ, log ε 4.19.

Anal. Calc'd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15.

Found: C, 76.63; H, 9.43.

Acetylation with acetic anhydride-pyridine for one hour on the steam-bath followed by recrystallization from hexane-acetone led to *11α-hydroxyprogesterone acetate* (Vb) with m.p. 173–175°, $[\alpha]_D^{20}$ +138° (acetone), $\lambda_{max.}^{EtOH}$ 240 mμ, log ε 4.18, $\lambda_{max.}^{CHCl_3}$ 1724, 1700 and 1670 cm.$^{-1}$, no free hydroxyl band; reported (2a): m.p. 175–177°, $[\alpha]_D^{24}$ +143° (acetone).

Anal. Calc'd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66.

Found: C, 74.15; H, 8.78.

Oxidation of Va with chromium trioxide for two hours at room temperature in acetic acid yielded 60% of 11-ketoprogesterone with m.p. 170–172°, $[\alpha]_D^{20}$ +238°, $\lambda_{max.}^{CHCl_3}$ 1708 and 1670 cm.$^{-1}$ but no free hydroxyl band; reported (11): m.p. 172–174°, $[\alpha]_D^{17}$ +238.5° (acetone); (2a): m.p. 174–176°, $[\alpha]_D^{25}$ +227°.

SUMMARY

Allopregnane-3β,11α-diol-20-one (I) can be converted into allopregnane-3,20-dione-11α-ol (II) by three procedures: (a) by Oppenauer oxidation of the 3β,11α-diol; (b) by N-bromoacetamide oxidation of the 3β,11α-diol; and (c) by partial saponification of the 3β,11α-diacetate and subsequent chromium trioxide oxidation. Tribromination of allopregnane-3,20-dione-11α-ol acetate (IIb) followed by treatment with sodium iodide and reduction with chromous chloride produced 11α-hydroxyprogesterone (V), which has recently (2a) been isolated in the microbiological oxidation of progesterone.

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