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

STEROIDS. XXIX.[1] SYNTHESIS OF 11β-HYDROXYPROGESTERONE

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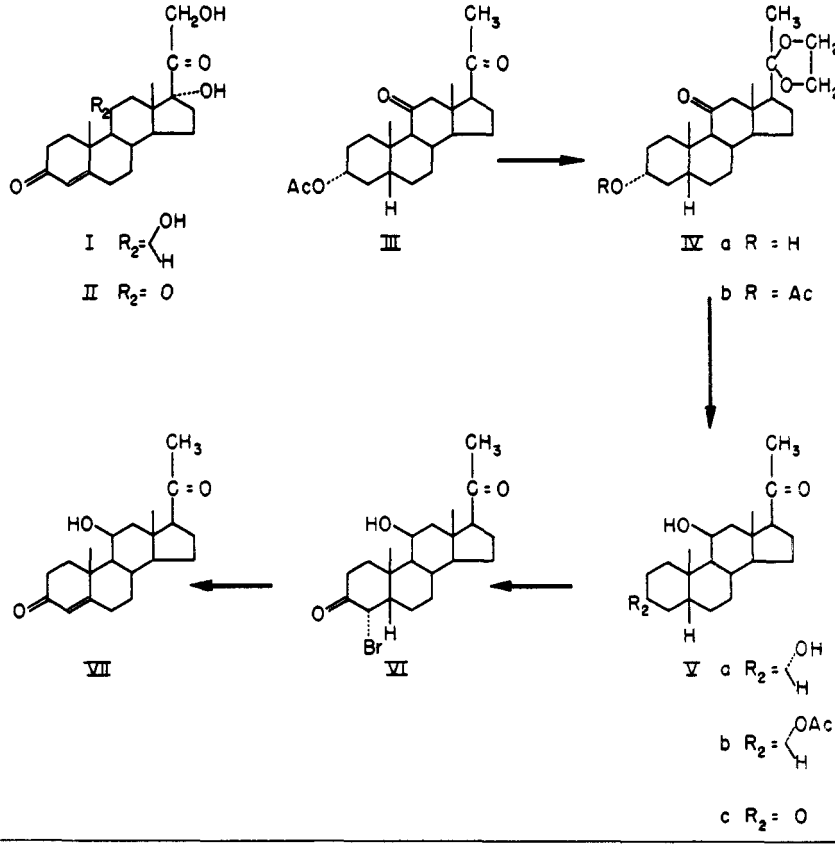
According to recent evidence (1), it appears that Δ^4-pregnene-11β,17α,21-triol-3,20-dione (I) (Kendall's compound F) rather than the 11-keto analog, cortisone (II), is the active hormone secreted by the adrenal gland. This observation makes it very important to study biologically simpler analogs of Kendall's compound F (I). One such derivative would be Δ^4-pregnene-3,20-dione-11β-ol (VII) (11β-hydroxyprogesterone), which still contains the important 11β-hydroxyl function and the Δ^4-3-keto moiety, but lacks the hydroxyl substituents at C-17 and C-21. While 11β-hydroxyprogesterone (VII) has so far not been isolated from natural sources, it could well be one of the intermediates in the biosynthesis or metabolism of Kendall's compound F and it would be of interest to study the fate of the former upon adrenal perfusion or enzymatic incubation.



[1] Paper XXVIII, Djerassi, Mancera, Stork, and Rosenkranz, *J. Am. Chem. Soc.*, **73**, 4496 (1951).

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The only synthesis of 11β-hydroxyprogesterone (VII) is that of Reichstein and Fuchs (2), who prepared it by treatment of the 21-tosylate of corticosterone with sodium iodide followed by reductive removal of the 21-iodo group. For the preparation of relatively large amounts for biological investigations, it appeared desirable to employ a more readily available starting material and the presently described synthesis of 11β-hydroxyprogesterone (VII) starts from pregnan-3α-ol-11,20-dione acetate (III), an intermediate in the commercial synthesis (3) of cortisone. Conversion of III to the 20-ethylene ketal 3-acetate (IVb), followed by reduction with lithium aluminum hydride afforded the ketal of pregnane-3α,11β-diol-20-one, which was not isolated but was treated in acetone solution with *p*-toluenesulfonic acid (conditions which do not cause dehydration of the labile 11β-hydroxy group) producing pregnane-3α,11β-diol-20-one (Va) in 92% over-all yield (based on III). As was to be expected on the basis of earlier experiments (4), lithium aluminum hydride reduction of the 11-keto group gave almost exclusively the 11β-hydroxy isomer and in accordance with that formulation, only a 3-monoacetate (Vb) was formed on acetylation. By contrast, 11α-hydroxy steroids are readily acetylated under those conditions (5). Selective oxidation of the diol Va by Oppenauer's procedure (6) led smoothly to pregnan-11β-ol-3,20-dione (Vc), which was monobrominated at C-4 (VI) and dehydrobrominated by the semicarbazide variation (7) of the Mattox-Kendall reaction (8) giving 11β-hydroxyprogesterone (VII). The physical constants were in good agreement with those reported by Reichstein and Fuchs (2) for the specimen prepared from corticosterone and the infrared spectrum demonstrated the presence of a free hydroxyl group as well as Δ^4-3-keto and 20-keto functions.

EXPERIMENTAL[3]

Pregnane-3α,11β-diol-20-one (Va). A solution of 15 g. of pregnan-3α-ol-11,20-dione 3-acetate (III) in 525 cc. of dry benzene and 15 cc. of ethylene glycol was refluxed with 1.0 g. of *p*-toluenesulfonic acid employing a water separator (9). After 12 hours, the separation of water was complete and the mixture was washed with dilute bicarbonate solution, water, dried over sodium sulfate, and evaporated. In one experiment, the oily ketal acetate IVb was saponified with 5% methanolic sodium hydroxide (4 hours, room temperature) and the resulting *pregnan-3α-ol-11,20-dione 20-ethylene ketal* (IVa) was recrystallized from hexane-acetone; m.p. 143–145° (Kofler), $[\alpha]_D^{20}$ +60° (acetone).

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

Found: C, 73.18; H, 9.55.

The oily ketal acetate IVb was dissolved in 1.2 l. of dry ether and added dropwise to a mixture of 6.4 g. of lithium aluminum hydride and 800 cc. of ether, refluxed for 2 hours, and then allowed to stand at room temperature for the same period of time. The excess reagent was decomposed with ethyl acetate, and the ether solution was washed well with Rochelle salt solution, dried over sodium sulfate and evaporated. The residue was dissolved immediately in 400 cc. of acetone and kept at room temperature overnight with 1.6 g. of *p*-toluenesulfonic acid. After neutralizing with sodium carbonate and concentrating to about one-third the original volume, water was added and the solid was collected; yield,

[3] Melting points are uncorrected. Unless noted otherwise, rotations were determined in chloroform and ultraviolet absorption spectra in 95% ethanol solution. We are grateful to Srta. Paquita Revaque and staff for these measurements as well as for the infrared spectra (Perkin-Elmer model 12C spectrometer with sodium chloride prism). Thanks are due to Srta. Amparo Barba for the microanalyses.

12.5 g. (92%), m.p. 208–213°, $[\alpha]_D^{20}$ +118°. Two recrystallizations afforded the analytical sample of the diol Va with m.p. 216–218° (Kofler), $[\alpha]_D^{20}$ +123°.

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

Found: C, 75.18; H, 9.98.

Pregnane-3α,11β-diol-20-one 3-monoacetate (Vb) was prepared in the usual manner (acetic anhydride-pyridine, 1 hour, steam-bath) and recrystallized from methanol; m.p. 180–182°, $[\alpha]_D^{20}$ +150.3° (acetone), +129° (chloroform). v. Euw, Lardon and Reichstein (10) prepared this substance from bisnordesoxycholic acid and reported m.p. 182–184°, $[\alpha]_D^{18}$ +147.5° (acetone).

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

Found: C, 73.37; H, 9.39.

Pregnan-11β-ol-3,20-dione (Vc). A solution of 10 g. of pregnane-3α,11β-diol-20-one (Va) in 350 cc. of toluene and 55 cc. of cyclohexanone was dried by distilling out a small amount, 2.5 g. of distilled aluminum isopropoxide in 10 cc. of toluene was added and the mixture was refluxed for 45 minutes. After removing the volatile components by steam-distillation, the residue was extracted with ethyl acetate, washed well with water, dried, and evaporated. One crystallization from hexane-ethyl acetate yielded 5.1 g. (52%) of dione Vc with m.p. 170–172°. Reoxidation of the mother liquors furnished an additional 1.3 g. (13%) of equal purity. Further recrystallization raised the m.p. to 174–176° (Kofler), $[\alpha]_D^{20}$ +124.7°, the infrared spectrum (chloroform) showed a free hydroxyl band as well as a carbonyl band at 1702 cm.$^{-1}$

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

Found: C, 75.70; H, 9.87.

4-Bromopregnan-11β-ol-3,20-dione (VI). A solution of 2.0 g. of the diketone Vc in 10 cc. of C.P. glacial acetic acid was treated dropwise with 0.48 g. of bromine in 5 cc. of acetic acid. Decolorization was complete within 2 minutes, whereupon ice-water was added, the product was extracted with chloroform, washed with dilute bicarbonate solution and water, dried, and evaporated. Crystallization from ether afforded 1.3 g. (52%) of the 4-bromo derivative with m.p. 183–185°, $[\alpha]_D^{20}$ +122.4°. The combined mother liquors were debrominated with zinc and acetic acid, whereupon 0.58 g. (29%) of the starting material (Vc) was recovered.

Anal. Calc'd for $C_{21}H_{31}BrO_3$: C, 61.31; H, 7.60.

Found: C, 60.80; H, 7.48.

Δ^4-Pregnen-3,20-dione-11β-ol (11β-hydroxyprogesterone) (VII). To 1.9 g. of the above bromo derivative in 80 cc. of glacial acetic acid was added a solution of 1.2 g. of semicarbazide hydrochloride and 1.3 g. of anhydrous sodium acetate in 10 cc. of 80% acetic acid and the mixture was kept for 2 hours at 75° in an atmosphere of nitrogen. At the end of this period, 10 cc. of distilled pyruvic acid, 20 cc. of water, and 3 g. of anhydrous sodium acetate were added, the mixture heated for 2 hours at 70° and then left at room temperature overnight. After pouring into 500 cc. of 8% sodium hydroxide solution, the product was extracted with ether, washed well with alkali, dried, and concentrated to a small volume; 0.56 g. (37%) of colorless crystals with m.p. 170–175° crystallized upon chilling in an ice-bath. Two recrystallizations from ether led to the analytical sample with m.p. 186–188°, $[\alpha]_D^{20}$ +217° (acetone), ultraviolet absorption maximum at 242 mμ (log ε 4.26), infrared spectrum (chloroform) with free hydroxyl band as well as carbonyl bands at 1700 (20-ketone) and 1658 cm.$^{-1}$ (Δ^4-3-ketone). Reichstein and Fuchs (2) reported m.p. 187–188°, $[\alpha]_D^{17}$ +222.5° ±4° (acetone) for a specimen prepared from corticosterone. A mixture melting point determination, kindly performed by Prof. T. Reichstein of the University of Basle, further confirmed the identity of the two specimens.

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

Found: C, 76.68; H, 9.37.

SUMMARY

A new synthesis of Δ^4-pregnene-3,20-dione-11β-ol (11β-hydroxyprogesterone) (VII) from the readily available pregnan-3α-ol-11,20-dione acetate (III) is

described. Selective lithium aluminum hydride reduction of the 11-keto group was accomplished by protecting the C-20 carbonyl function by means of ketal formation and the resulting pregnane-3α,11β-diol-20-one (Va) was submitted to Oppenauer oxidation yielding pregnane-3,20-dione-11β-ol (Vc). Monobromination at C-4 and dehydrobromination with semicarbazide led to the desired 11β-hydroxyprogesterone (VII).

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