

AN IMPROVED SYNTHESIS OF
6 β -HYDROXY-5 β -PREGNANE-3,20-DIONE.

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ABSTRACT

6 β -Hydroxy-5 β -pregnane-3,20-dione, formerly prepared by a hydroboration method, has been obtained in greatly improved yield by a simpler irradiation-hydrogenation procedure.

INTRODUCTION

6 β -Hydroxy-5 β -pregnane-3,20-dione is a key intermediate in the preparation of the 6,7-unsaturated derivative of 5 β -pregnane-3 α ,20 α -diol 3 α -glucuronide and hence of the corresponding [6,7-³H]-labelled steroid conjugate, which has been used in radioimmunoassay studies (1). It is also of potential use in the preparation of steroid haptens suitable for linking with protein via a 6 oxygen function in such studies.

During much of the early work carried out in our laboratories, it was prepared by the hydroboration method of Kirk and Leonard (2). These authors made no attempt to isolate the 6 β -hydroxy-dione but proceeded directly to 5 β -pregn-6-ene-3,20-dione. In our hands, the method gave variable results and, at best, only poor yields of the

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6-ene were obtained. The yields were improved somewhat by prior isolation of the 6 β -hydroxy-3,20-dione but still left much to be desired and we therefore sought an improved synthesis.

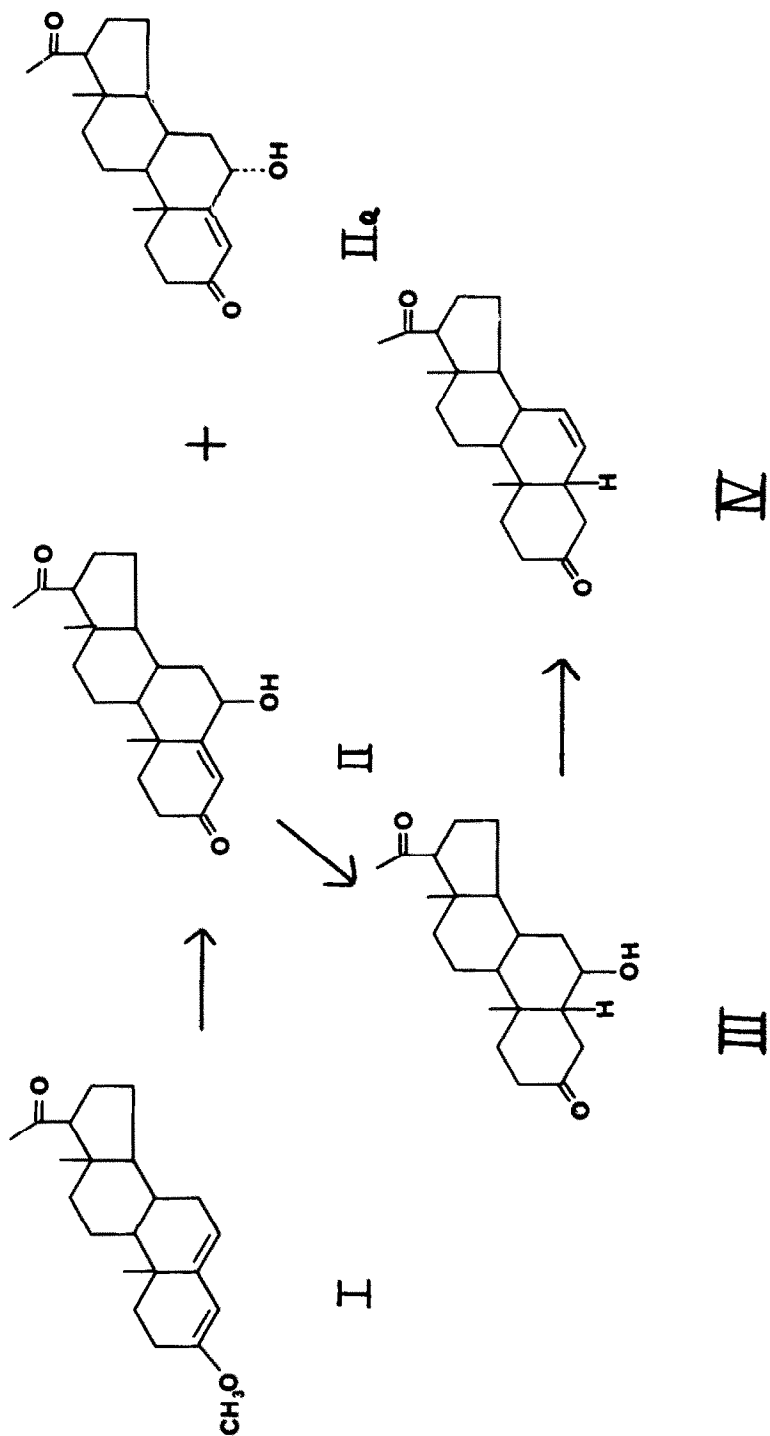
Gardi and Lusignani (3) have reported a simple route to 6 β -hydroxy steroidal Δ^4 -3-ketones by autoxidation of 3,5-dien-3-ol ethers and the reaction has been extended by Tsuji *et al.* (4) to the preparation of 6 α - and 6 β -hydroxy- and hemisuccinoxy-derivatives of some corticosteroids.

The autoxidation procedure, followed by catalytic hydrogenation of the purified unsaturated 6 β -hydroxy steroid, appeared to offer a satisfactory route to the required 6 β -hydroxy-5 β -pregnane-3,20-dione and such proved to be the case.

SYNTHESIS

The 3-enol methyl ether of progesterone (I) (5) in methanol was irradiated by means of a domestic fluorescent lamp until optimal conversion to 6 β -hydroxyprogesterone (II) (as indicated by TLC studies) had occurred. The crude product was chromatographed on Celite in the Bush B3 system (6) giving pure 6 β -hydroxyprogesterone in 38% yield. The slightly more polar 6 α -epimer (IIa) was obtained in much lower yield. Although the crude material showed only a single spot on TLC, crystallisation proved extremely difficult and gave only 1.15% yield of the pure substance.

Hydrogenation of the 6 β -epimer in pyridine employing palladium on calcium carbonate as catalyst (7) gave an



excellent yield of 6 β -hydroxy-5 β -pregnane-3,20-dione (III). This sample was identical in all respects with a sample prepared by the method of Kirk and Leonard (2) and fully characterized per se and by conversion, in 71.5% yield, to 5 β -pregn-6-ene-3,20-dione (IV). Its N.M.R. spectrum was identical with that reported recently by Bond et al. (8) who prepared the same compound by a similar hydroboration technique.

In the preparation of compound III by the hydroboration method, chromatography on alumina led to the isolation of the slightly more polar isomer: 6 α -hydroxy-5 α -pregnane-3,20-dione.

EXPERIMENTAL

Materials & Methods

Infrared spectra were obtained with a Perkin-Elmer Model 237 Grating Spectrophotometer for KBr discs. N.M.R. spectra were obtained for solutions in CDCl_3 at 100 MHz. Specific rotations are recorded for chloroform solutions and were determined with the ETL-NPL Automatic Polarimeter type 143A (Bendix Electronics Ltd.). Microanalyses were carried out by Dr F.B. Strauss, Oxford. Melting points were determined on a Kofler Micro Heating Stage and are corrected. Products were examined by TLC in benzene-ethanol (9:1) and by paper chromatography in Bush systems A, B2 and B3 (6).

6 α - & 6 β -Hydroxyprogesterone

The 3-enol methyl ether of progesterone (5) (400 mg) in ethanol (160 ml) was irradiated in a conical flask, 1 metre beneath two 40 watt fluorescent light tubes for seven days at room temperature (ca. 20°C). The total crude solid obtained, after rotary evaporation of the ethanol, was chromatographed on Celite (100 g) employing the Bush B3 system. 10 ml fractions were collected, nos. 78-101 giving the 6 β -hydroxy progesterone and nos. 128-153 the 6 α -hydroxy progesterone. Fractions 78-101 were pooled and rotary evaporated and the residues crystallised from acetone to give 6 β -hydroxy progesterone, 152 mg, m.p. 174-177°, identical in all respects with an authentic sample. Rotary evaporation of fractions 128-153 gave a glass. Crystallisation from acetone-petroleum ether gave 6 α -hydroxyprogesterone as slender prisms, 4.6 mg, m.p. 191-193°.

γ_{\max} 3525, 1704, 1658 and 1610 cm^{-1} . Found C, 76.18; H, 9.11%. Calc. for $\text{C}_{21}\text{H}_{30}\text{O}_3$: C, 76.32; H, 9.15%. Balant and Ehrenstein (9) reported m.p. 192-193°.

6 β -Hydroxy-5 β -pregnane-3,20-dione (III)

(a) Purified 6 β -hydroxyprogesterone, 100 mg, m.p. 174-177°, in redistilled pyridine (12 ml) was hydrogenated using a palladium (10%) on calcium carbonate (100 mg) catalyst. The catalyst was removed by filtration and the filtrate evaporated. Crystallisation from acetone-hexane gave crude 6 β -hydroxy-5 β -pregnane-3,20-dione (82.6 mg) as prismatic needles, m.p. 171-176°. Purification by further crystallisation from acetone-hexane and then methanol-water gave the pure material, 42.2 mg, m.p. 176-178, $[\alpha]_D + 94.2^\circ$.

γ_{KBr} 3450, 1700(sh), 1690 and 1222 cm^{-1} ; τ [CDCl₃] 9.33 (18-H₃), 8.79 (19-H₃), 7.90 (21-H₃) and 6.30 [width 6Hz] (equatorial 6 α -H). Found: C, 75.90; H, 9.63%. Calc. for $\text{C}_{21}\text{H}_{32}\text{O}_3$: C, 75.86; H, 9.73%. Bond *et al.* (8) reported m.p. 186-189°, τ [CDCl₃] 9.32, 8.82, 7.88 and 6.32.

(b) Crude 3,3,20,20-bisethylenedioxy-5 β -pregnan-6 β -ol (8.4 g), prepared by the method of Kirk and Leonard (2), in 70% acetic acid (84 ml) was left to stand overnight at room temperature. The reaction mixture was poured into water and the products were extracted with ether (800 ml). Rotary evaporation to 80 ml gave a crystalline product (700 mg, m.p. 182-195°) which was filtered off and discarded. The filtrate was evaporated to dryness to give a partially crystalline residue (6.1 g). Chromatography on neutral alumina by the gradient elution method of Kellie and Wade (10) gave crude 6 β -hydroxy-5 β -pregnane-3,20-dione, 1.73 g, m.p. 158-161°. Recrystallisation from acetone-hexane gave the pure material, 265 mg, m.p. 177-178°. Continuation of the gradient elution chromatography gave 0.43 g, m.p. 210-215° of a compound which was slightly more polar than 6 β -hydroxy-5 β -pregnane-3,20-dione. Recrystallisation of this compound from acetone gave 6 α -hydroxy-5 α -pregnane-3,20-dione as hexagonal prisms, 184 mg, m.p. 216-217°, $[\alpha]_D + 98.5^\circ$. This compound was unchanged by the dehydration procedure employed to convert compound III to compound IV.

γ_{KBr} 3580, 1710, 1695 and 1040 cm^{-1} ; τ [CDCl₃] 9.38 (18-H₃), 8.99 (19-H₃), 7.90 (21-H₃) and 6.50 (broad-axial 6 β -H). Found: C, 76.15; H, 9.65. Calc. for $\text{C}_{21}\text{H}_{32}\text{O}_3$: C, 75.86; H, 9.73%.

5 β -Pregn-6-ene-3,20-dione (IV)

6 β -Hydroxy-5 β -pregnane-3,20-dione, 50 mg, m.p. 171-176°, in pyridine (0.5 ml) was chilled thoroughly in an ice-salt bath and treated dropwise whilst stirring with phosphorus oxychloride (0.06 ml). After overnight storage at room temperature the mixture was again chilled and treated with crushed ice followed by iced water. The solid, separated by filtration was dried and purified from acetone-hexane to give 5 β -pregn-6-ene-3,20-dione

as flat needles, 33.8 mg, m.p. 152-153°, $[\alpha]_D + 146.3^\circ$.
 $\gamma_{\text{max}}^{\text{KBr}}$ 3020, 1660(sh), 1720 and 1704 cm^{-1} . [Kirk and Leonard
 (2) reported m.p. 152-154°, $\gamma_{\text{max}}^{\text{nujol}}$ 3010, 1662 (cis-olefin),
 1717 and 1704 cm^{-1}].

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