SYNTHESIS OF 18-SUBSTITUTED STEROIDS. PART II (1). IMPROVEMENTS IN THE PREPARATION OF 18-HYDROXYPROGESTERONE

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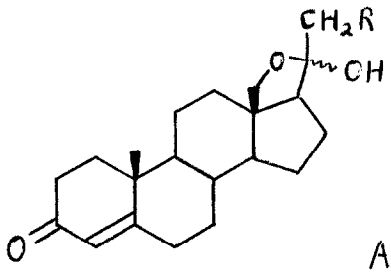
ABSTRACT

18-Hydroxyprogesterone is conveniently prepared from 3β-acetoxypregn-5-en-20β-ol by a modified route. 3β-Acetoxy-18-iodopregn-5-en-20-one, obtained by the hypoiodite-photolysis procedure and oxidation, is treated with methanolic silver acetate to give the 18,20-epoxy-20-methoxy derivative, which crystallises directly without need for chromatography. Hydrolysis of the 3-acetate, and a modified Oppenauer oxidation, gave 18-hydroxy-progesterone in 24% over-all yield.

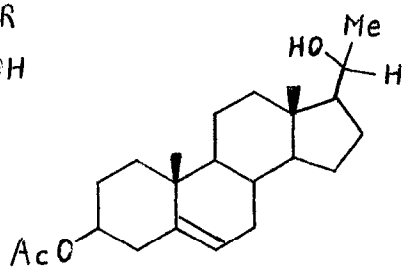
18-Hydroxyprogesterone, which exists in the hemiacetal form (I), is the key intermediate for the recently-described synthesis of 18-hydroxydeoxycorticosterone (II) (1,2,3,), an important hypertensive agent (4). In order to prepare 18-hydroxydeoxycorticosterone in considerable quantity, we required a more convenient synthetic route to 18-hydroxyprogesterone than those described in the literature (5-8), which involve tedious separation of mixtures of products. 3β-Acetoxypregn-5-ene-20β-ol (III), readily available from pregnenolone acetate, has been converted by the normal hypoiodite photolysis route (9) into

18-hydroxypregnenolone 3-acetate, obtained as the hemiacetal (IV), but the procedure required a lengthy chromatographic separation of the compound (IV) from several by-products.

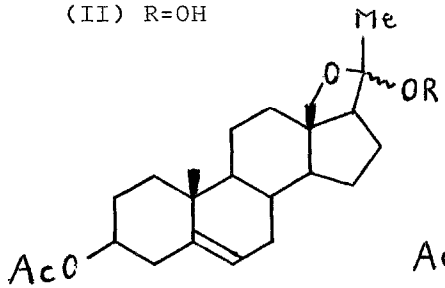
We, like other workers, had no difficulty with the hypoiodite reaction [$Pb(OAc)_4$-I_2-hν] and oxidation of the product to give crude 3β-acetoxy-18-iodopregn-5-en-20-one (V) (10). Purification of this iodo-ketone by direct crystallisation has been described recently (11), but was unsuccessful in our hands. The iodo-ketone (V) has previously been transformed into the hemiacetal (IV) by silver ion-assisted hydrolysis. We found, however, that methanolysis (AgOAc-MeOH) of the crude material containing the iodo-ketone is a much more satisfactory procedure, because the resulting 18,20-epoxy-20-methoxy derivative (VI) is sparingly soluble, and under careful control



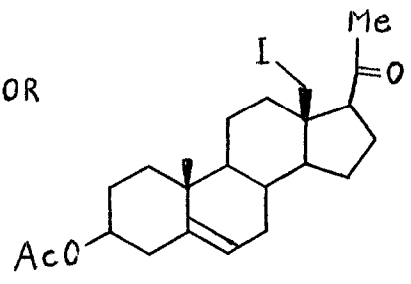
(I) R=H
(II) R=OH



(III)



(IV) R=H
(VI) R=Me



(V)

(see Experimental Section) will crystallize directly from the products of methanolysis in almost pure condition. The chromatographic stage is thereby circumvented.

Alkaline hydrolysis of the 3β-acetate (VI), followed by the Keana-Reich modification (12) of the Oppenauer oxidation, afforded 18-hydroxyprogesterone (I). The modification consists in employing N-methyl-4-piperidone as the hydrogen acceptor in place of the more usual cyclohexanone. The methylpiperidone and its reduction product are conveniently removed by washing with dilute acid, eliminating the need for steam distillation to remove residual cyclohexanone and cyclohexanol.

This procedure has given reproducible over-all yields of 24%, slightly exceeding the yields claimed for an alternative synthesis described very recently (13), which proceeds through 3β-acetoxy-20-hydroxypregn-5-en-18-oic acid 20,18-lactone, and an Oppenauer oxidation of the derived pregn-5-ene-3β,18,20-triol.

EXPERIMENTAL

M.p.s were determined on a Reichert melting point microscope, and are uncorrected. T.l.c. was performed on Merck silica gel HF 254. Cyclohexane was distilled over calcium hydride, and acetone from potassium permanganate. Anhydrous methanol was distilled from magnesium methoxide.

3β-Acetoxy-18,20-epoxy-20-methoxypregn-5-ene (VI).

3β-Acetoxypregn-5-en-20β-ol (III) (24g) in anhydrous cyclohexane (3600ml) was treated with lead tetra-acetate (72g) and iodine (9.5g), then stirred magnetically and heated under reflux while being irradiated from below with two 500 w. tungsten lamps. When the iodine colour had been discharged (ca. 50 min.) the mixture was cooled to room temperature and filtered. The filtrate was washed with sodium thiosulphate solution and water, dried (K_2CO_3), and the solvent was removed under reduced pressure from a water-bath below 35°C.

The residual yellow oil, in acetone (300 ml), was cooled in ice and stirred during the dropwise addition of Jones' chromic acid reagent (ca. 14 ml) until the orange colour persisted. Sodium acetate (300g) in water (700ml) was then added, and the product was extracted with benzene (3 x 300ml). The benzene was washed with saturated sodium chloride solution, dried (K_2CO_3), and taken to dryness under reduced pressure, from a water bath at ca. 35°C.

The crude iodo-ketone, in anhydrous methanol (1300ml), was treated with silver acetate (25g), then stirred and heated under reflux for 2 hr. The cooled mixture was filtered, and the solids on the filter were washed with methanol, which was added to the filtrate.

The methanolic solution was then concentrated to a volume of 750 ml. by distillation under atmospheric pressure. Black silver salts which precipitated during the distillation were removed by a further filtration. The solution was then set aside to crystallize at 0°C overnight, giving the 20-methoxy compound (VI) (8.2g), m.p. 171.5-175°, ν_{max} (KBr) 1738, 1392, 1252, 1089, 1045, 912, 875, and 832 cm^{-1}; τ($CDCl_3$) 9.06 (s, 10β-Me), 8.66 (s, 21-H_3), 7.99 (s, AcO), 6.82 (s, OMe), 6.53, 6.33 (dd, J=9Hz, 18-H_2), 5.4 (m, W ca. 30Hz, 3α-H), 4.63 (m, W=10Hz, 6-H). This material was free from any significant contamination by other steroids (t.l.c., n.m.r.) and contained only traces of silver salts. The latter could be removed if necessary by dissolution in ether, filtration, and evaporation of the ether. This further purification is unnecessary if the material is to be processed further as described below. The methanol mother-liquors contained recoverable pregnenolone acetate, and by-products.

The degree of concentration of the methanol solution (32-35 ml per gram of steroid) was found to be critical in order to optimise the yield while preventing co-crystallisation of the pregnenolone acetate from the crude mixture. The 20-methoxy-compound (VI) and

pregnenolone acetate have identical chromatographic mobility (t.l.c.); the presence of the latter as a contaminant may be detected qualitatively by i.r. spectroscopy (carbonyl absorption at 1705 cm^{-1}) or semi-quantitatively by n.m.r. spectroscopy, from comparison of the integrated intensities of the methoxy proton signal at τ ca. 6.82, and the 21-methyl proton signal (of pregnenolone acetate) at τ ca. 7.85 ($CDCl_3$).

18,20-Epoxy-20-methoxypregn-5-en-3β-ol.

The 3-acetate (8.2 g) in methanol (600 ml) was treated with methanolic sodium hydroxide (4.5%; 30 ml) and heated under reflux for 30 min. The solution was then concentrated under reduced pressure, cooled and diluted with ether. The ether was washed with water until the washings were neutral (all washings were re-extracted with ether before being rejected), and the ethereal solution was dried (K_2CO_3) and evaporated under reduced pressure to give the 3β-ol (7.22 g), m.p. 139-143° [lit. (14) m.p. 145-146°] which was essentially pure (t.l.c.).

Modified Oppenauer oxidation.

The 3β-ol (7.2 g from above) in dry toluene (120 ml) was treated with freshly redistilled N-methyl-4-piperidone (25 ml). The solution was heated under dry nitrogen until 25 ml of toluene had distilled, then aluminium isopropoxide (2M-solution in toluene; 35 ml) was added, and the mixture was heated under reflux in nitrogen for 1 hr. After cooling, the mixture was diluted with ether (400 ml), and washed with 5% sulphuric acid (500 ml), which was re-extracted with ether (150 and 100 ml) before being rejected. The combined ethereal solutions were washed with water, dried (K_2CO_3) and evaporated. The residue crystallised from acetone to give 18-hydroxyprogesterone (I) (4.62 g), m.p. 154-156° [lit. (5) m.p. 159-160°], identical in all respects with an authentic sample. Concentration of the acetone mother-liquor gave a further 0.85 g, m.p. 139-144°, which recrystallised from acetone to give 0.7 g, m.p. 153-155°. Total yield: 5.3 g (24% over-all).

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