Synthesis of 18,21-Dihydroxypregn-4-ene-3,20-dione ('18-Hydroxy-Deoxycorticosterone')

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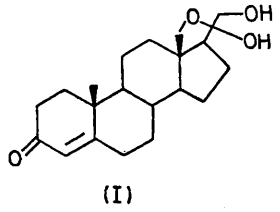
Summary An 18-hydroxypregnan-20-one, in the 20-hemiacetal form (II), reacts with lead tetra-acetate or with sources of electrophilic bromine to introduce acetoxy- or bromo-substituents, respectively, at C-21: alkaline hydrolysis then gives the 21-hydroxy-derivative in good overall yield.

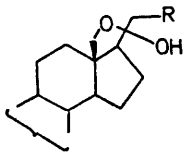
RECENT evidence suggests that the title compound (18-hydroxy-DOC), which exists in the 20-hemiacetal form (I), is an important hypertensive agent,[1] but extensive biological studies have been hampered by inadequate supplies, and by the lack of a practical synthesis. The only reported methods[2,3] afforded very poor yields. We report the transformation of 18-hydroxyprogesterone 20-hemiacetal (IIa) into (I) in two steps, with an overall yield exceeding 70%, as well as an alternative route from the 3β-hydroxy-Δ^5-analogue (IIb).

The hemiacetal (IIa) has been prepared from 3,3-ethylene-

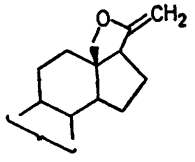
dioxy-20β-hydroxypregn-5-ene by the well-known hypoiodite photolysis route. We had little difficulty in adapting the published procedures[4] for the preparation of the corresponding 3-ethylene acetal derivative (IIc), or of 18-hydroxypregnenolone 3-acetate 20-hemiacetal (IId).



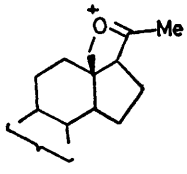
(I)



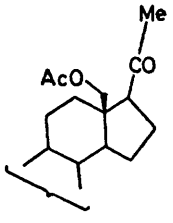
(II) R=H
(VI) R=OAc
(VII) R=OH
(VIII) R=Br



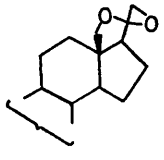
(III)



(V)



(IV)



(IX)

(a) 3-oxo-Δ^4 series.
(b) 3β-hydroxy-Δ^5 series.
(c) 3,3-ethylenedioxy-Δ^5 series.
(d) 3β-acetoxy-Δ^5 series.

The major problem to be overcome lay in the introduction of the 21-hydroxy-group. Attempts to prepare a vinyl ether (III) by dehydration of the hemiacetal (IIa)[2] were unrewarding: treatment of crude reaction products with osmium tetroxide or a peroxy-acid gave no evidence of C-21 oxygenation. Application to the 18-acetoxypregnan-20-ones (IV) of a wide variety of established procedures[5] for the introduction of oxygen or halogen functions at C-21 was similarly without success; the 18-acetoxy-group exerts a profound effect on the chemistry of the pregnan-20-one side-chain. Details of these experiments will be reported elsewhere.

Success came with the discovery that the oxonium ion (V), the key intermediate in the very rapid acid-catalysed conversion of the hemiacetal into a 20-alkoxy derivative,[6] is apparently in equilibrium with the vinyl ether (III) in acidic media, even though (III) could neither be isolated nor detected directly in solution. Dissolution of the hemiacetal (IId) in chloroform containing CH_3CO_2D resulted in rapid and virtually complete replacement of the C-21 hydrogen atoms by deuterium (n.m.r.). Furthermore, the reaction could be reversed by treating the labelled material with ordinary acetic acid.

Realizing that the vinyl ether (III), once formed, should react rapidly *in situ* with any available electrophile, we found that the hemiacetal (IIa) is rapidly converted by lead tetra-acetate in acetic acid into the 21-acetoxy-derivative (VIa). Alkaline hydrolysis then afforded 18-hydroxy-DOC (I) in excellent overall yield. Similar acetoxylation of the hemiacetal (IIb) in the 3β-hydroxy-Δ^5-series gave the acetate (VIb), which gave the free triol (VIIb) on alkaline hydrolysis. Oxidation of the 21-monoacetate (VIb) (Jones' reagent in acetone) produced the corresponding 3-ketone, which afforded 18-hydroxy-DOC (I) on alkaline hydrolysis.

As an alternative route to C-21 substituted derivatives, the hemiacetal (IIa) was treated with an equimolar amount of $PhMe_3N^+Br_3^-$ [7] in anhydrous tetrahydrofuran, giving the 21-bromo-hemiacetal (VIIIa), characterized from its n.m.r. and i.r. spectra, as the major product. Detection of chromatographically more mobile products showed that competing reactions occurred, probably owing to the presence of the αβ-unsaturated ketone system, for under similar conditions the hemiacetal (IId) gave the 21-bromo-derivative (VIIId) as the sole product.

Alkaline hydrolysis in aqueous dioxan converted the bromo-hemiacetals (VIIIa) and (VIIId) into 18-hydroxy-DOC (I) and its 3β-hydroxy-Δ^5-analogue (VIIb), respectively. When methanol was employed as the solvent for alkaline hydrolysis of (VIIId), a mixture of the triol (VIIb) and its 20-methoxy derivative was formed, suggesting that the hydrolysis takes place *via* a transient 20,21-epoxy-intermediate (IX): the 20-methoxy-derivative would result from methanolysis of the epoxide (IX) by cleavage of the more reactive C(20)–O bond. Methanolic alkali converted the crude bromo-hemiacetal (VIIIa) into a complex mixture of products, pointing to the presence of contaminants with bromine at positions other than C-21.

N-Bromosuccinimide could be used as an alternative source of bromine for the C-21 bromination of (IId).

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