LETTERS TO THE EDITORS

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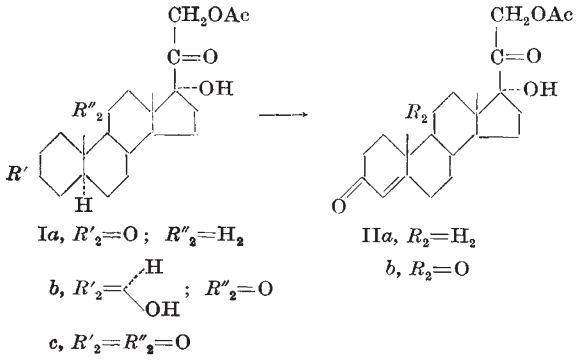
Cortical Hormones from *allo*Steroids: Synthesis of Cortisone from Reichstein's Compound *D*

Cortisone acetate (II*b*) has so far only been synthesized[1] from bile acids which possess the 'normal' configuration at C-5 (rings *A*/*B cis*). Since the potentially most abundant sources, such as the steroidal sapogenins, belong to the *allo* series (rings *A*/*B trans*) or are readily convertible to the latter, it is important to accomplish the transformation of an *allo*steroid to cortisone. We have recently described[2] a method for the conversion of 3-keto-*allo*steroids into Δ^4-3-ketones, which involved dibromination to a 2,4-dibromo derivative, treatment of the latter with sodium iodide in acetone solution to yield a 2-iodo-Δ^4-3-ketone and subsequent de-iodination with chromous chloride, collidine or zinc. This procedure was applied successfully in the androstane, etio*allo*cholanic acid and *allo*pregnane series. The usefulness of this method for the important 17,21-dihydroxy-20-keto steroids remained to be demonstrated.



I*a*, R'_2=O; R''_2=H_2

b, R'_2=H, OH; R''_2=O

c, R'_2=R''_2=O

II*a*, R_2=H_2

b, R_2=O

Fleisher and Kendall[3] have recently shown that adrenal corticosteroids possessing the 20-keto-21-acetoxy grouping are readily brominated in position 21. Since such a reaction may seriously complicate the synthesis of 2,4-dibromo derivatives of 3-keto-*allo*steroids possessing the 17,21-dihydroxy-20-keto side-chain, we have examined the sodium iodide method[2] in the case of *allo*pregnane-3,20-dione-17α,21-diol 21-acetate (I*a*)[4]. The ketone I*a* was treated at 16° in chloroform – acetic acid solution with two moles of bromine, a small amount of anhydrous hydrogen bromide in acetic acid was added to facilitate the rearrangement of the presumable[5] initial 2,2-dibromo compound to the 2,4-isomer, and after twenty hours the chloroform solution was washed free of acid and evaporated to dryness *in vacuo*. The crude 2,4-dibromo derivative was not crystallized, but was refluxed immediately with an excess of sodium iodide in acetone solution for twenty hours. After concentrating, extracting with ether, washing with thiosulphate solution and evaporating to dryness, the residue was refluxed for half an hour in dioxane solution with 5 per cent sodium bisulphite solution. This latter de-iodination procedure proved particularly suitable for adrenal hormones of type II. Dilution with water, filtration and recrystallization from acetone afforded Δ^4-pregnene-3,20-dione-17α,21-diol 21-acetate (II*a*) (Reichstein's compound *S* acetate) of melting point 233–235° (all melting points are uncorrected), $[\alpha]_D^{20}$ + 109° (acetone), ultra-violet absorption maximum (95 per cent ethanol) at 240 mμ (log ε, 4·36). This represents the third synthesis of Reichstein's compound *S* from readily available pregnane derivatives[6].

The synthesis of *allo*pregnane-3β,17α,21-triol-11,20-dione 21-acetate (I*b*) (Reichstein's compound *D* monoacetate) was recently accomplished in this laboratory[7] from *allo*pregnane-11,20-dione-3β-ol, which in turn was obtained from a number of steroidal sapogenins. I*b* had a melting point of 235–237°, $[\alpha]_D^{20}$ + 66° (acetone) (calc. for $C_{23}H_{34}O_6$: C, 67·95; H, 8·43; found: C, 68·22; H, 8·73), and was correlated with Reichstein's compound *D*[8] via the 3,21-diacetate (m.p. 220°)[9]. Oxidation of I*b* with N-bromoacetamide in pyridine solution afforded *allo*pregnane-3,11,20-trione-17α,21-diol 21-acetate (I*c*), of melting point 235–237°, $[\alpha]_D^{20}$ + 78° (acetone), + 89° (chloroform) (calc. for $C_{23}H_{32}O_6$: C, 68·29; H, 7·98; found: C, 68·13; H, 7·63). Dibromination in acetic acid solution (without chloroform), as described above for I*a*, followed by dilution with water, produced a solid dibromo derivative (m.p. 150–153° (dec.); calc. for $C_{23}H_{30}O_6Br_2$: Br, 28·42; found: Br, 28·67) which without purification was carried through the sodium iodide and sodium bisulphite steps as described above. Passage of the final product through a short column of ethyl acetate-washed alumina and two recrystallizations from acetone of the benzene–ether eluates yielded colourless needles of Δ^4-pregnene-3,11,20-trione-17α,21-diol 21-acetate (II*b*) (cortisone acetate), of melting point 236–238°, $[\alpha]_D^{20}$ + 181° (acetone), ultra-violet absorption maximum at 238 mμ (log ε, 4·35). The infra-red spectrum (chloroform) was identical with that of an authentic specimen.

While the overall yield in the conversion of the ketones I*a* and I*c* to the adrenal hormones II was somewhat lower than observed earlier[2] in the androstane series, the present results clearly demonstrate the feasibility of synthesizing cortisone and other adrenal hormones from *allo*steroids of plant origin.

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