THE ALKOXIDE-CATALYZED DECONJUGATION OF ESTRA-4, 9-DIEN-3-ONES

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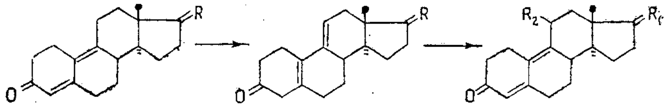
Δ^4-3-Ketosteroids are rapidly deconjugated by the action of potassium tert-butoxide in tert-butanol to form Δ^5-3-ketosteroids [1]. $\Delta^{1,4}$- and $\Delta^{4,6}$-3-ketosteroids are stable under these conditions [1] but can be isomerized into $\Delta^{1,5}$- and $\Delta^{5,7}$-3-ketosteroids, respectively, under more severe alkaline conditions [2]. A similar isomerization in the estra-4, 9-dien-3-one series (I, II) represents the optimum route to the estra-5(10), 9(11)-dien-3-ones (III, IV), which are important intermediates in the synthesis of the 11β-hydroxyestra-4, 9-dien-3-ones (VI, VII) and the estra-4, 9, 11-trien-3-ones [3]. The latter, as is well known, possess a very high anabolic activity [4].



I R = OH, H
II R = O

III R = OH, H
IV R = O

V R_1 = O; R_2 = O_2H
VI R_1 = OH,H; R_2 = OH
VII R_1 = O; R_2 = OH

We have carried out the deconjugation of the ketones I and II even with a 0.9 M solution of potassium tert-butoxide in tert-butanol by prolonged action (16 hr, 20° C). In the case of the hydroxy ketone I, the crude product obtained by subsequent acidification with acetic acid was chromatographed on SiO_2, and the first portions of the chloroform eluate furnished the hydroxy ketone III with a yield of 82%, mp 111–115° C. An analytical sample had mp 110–113° C [ether–ethyl acetate (9 : 1)]. Literature data: mp 111–118° C [5]. IR spectra, cm^{-1}: 3270 (OH), 1718 (CO), 1608 ($C{=}O{-}C{=}CH$). The following eluates gave a mixture of substances (12%, oil) consisting mainly of the hydroxy ketone I.

In the analogous transformation of the diketone II, the diketone IV was not purified because of its extreme capacity for autoxidation to the hydroperoxide V. The latter compound is also unstable and is converted on standing into the hydroxy diketone VII. Consequently, the diketone IV was oxidized in an atmosphere of oxygen in an ethanolic solution containing triethylamine and trimethyl phosphite for 5 hr [6]. The resulting mixture of substances was chromatographed on Al_2O_3: the first portions of eluate gave a 9.5% yield of estrone with mp 253–256° C (ethanol–water) identical (mixed melting point, R_f, IR spectrum) with an authentic sample, and the later portions gave the hydroxy diketone VII with a yield of 59%, mp 168–170° C. An analytical sample had mp 175–178° C (ethyl acetate). Literature data: mp 178–179° C [3]. IR spectrum cm^{-1}: 3550, 3418 (OH), 1730 (CO), 1660 ($O{=}C{-}CH{=}C{-}C{=}C$), 1620, 1592 ($CH{=}C{-}C{=}C$).

The fact that aromatization does in fact take place in the process of alkaline deconjugation was shown by the isolation of estrone in the same yield from the mixture of the products of the treatment of the diketone II with the alkoxide. In the case of the hydroxy ketone I, aromatization was less pronounced and the content of estradiol in the reaction mixture did not exceed 1%, according to GLC.

In tests for anabolic activity by Herschberger's method [7], the hydroxy diketone VII and the dihydroxy ketone VI obtained similarly possessed 20% of the anabolic and androgenic effect of testosterone propionate.

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