A Simple Construction of the Hydroxy-ketone Side Chain of Corticosteroids from 17-Oxo-steroids *via* Nitro-olefins

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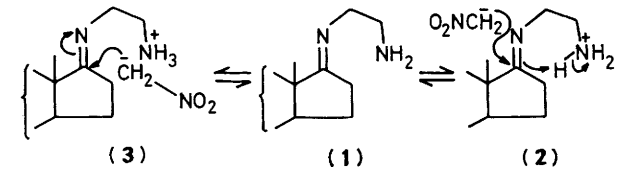
17-Oxo-steroids, in the presence of catalytic amounts of ethylenediamine, react smoothly with nitromethane to give the corresponding nitro-olefins; these are easily transformed into 21-hydroxy-20-oxo-corticosteroids with or without a double bond at position 16.

We have reported recently a convenient method for the synthesis of the corticosteroid side chain starting with the readily available 17-oxo-steroids.[1] In complementary studies, we have now developed a simple, high-yielding synthesis of 21-hydroxy-20-oxo-steroids with or without a double bond at the strategically important 16(17)-position.

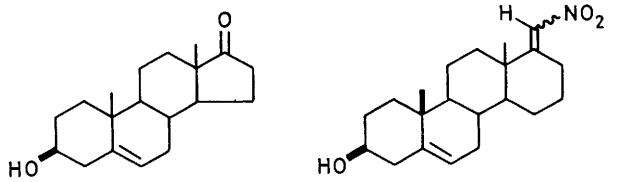
Unlike aldehydes, aliphatic and alicyclic ketones do not usually give good yields of nitro-olefins when condensed with nitromethane.[2,3] Primary amines are often used as catalysts[2] but are not effective for steroidal 17-ketones. We conceived that ethylenediamine, or a close congener, might prove effective for reasons which are suggested by the equilibria between (**1**), (**2**), and (**3**). The acidity of nitromethane is such that the intermediate (**1**) is certainly protonated as in (**2**) and (**3**). The NH_3^+ function might serve to aid the addition by transfer of a proton as in (**2**) and/or orient favourably the attacking anion as in (**3**).

Heating 3β-hydroxyandrost-5-en-17-one (**4**) with 1% w/w of ethylenediamine in nitromethane (50—60 h) gave the desired nitro-olefin (**5**) in 95% yield {m.p. 118—122 °C; $[\alpha]_D$ −88° ($CHCl_3$)}. Such a condensation appears to be without precedent in the literature. Trimethylenediamine and tetramethylenediamine also catalysed the reaction but less effectively.

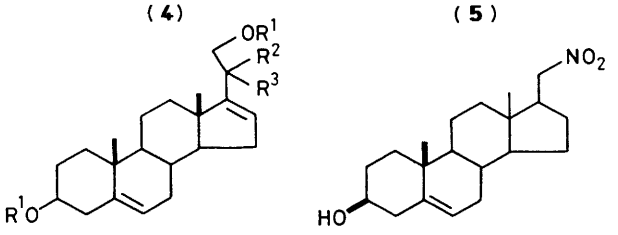
Treatment of the nitro-olefin (**5**) with aqueous formaldehyde (dioxan, triethylamine), keeping the temperature below 10 °C, gave the diol (**6**) in 91% yield after chromatography {diacetate (**7**), m.p. 155—163 °C; $[\alpha]_D$ −52° ($CHCl_3$)}. However, conducting the reaction in propan-2-ol (0.1 M; triethylamine, 10 equiv.; 40% aqueous formaldehyde, 13 equiv.; room temp.; 30—40 min) and dilution of the reaction mixture with water produced the diol (**6**) quantitatively. It was collected easily by filtration. Reduction of the nitro-group to give the corresponding oxime (**8**) was achieved by very brief expos-



(3) (1) (2)

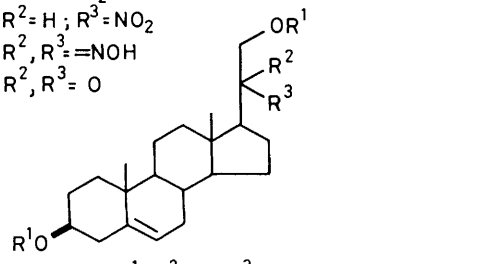


(4) (5)



(6) $R^1 = R^2 = H$; $R^3 = NO_2$
(7) R^1 = Ac ; $R^2 = H$; $R^3 = NO_2$
(8) R^1 = Ac ; R^2, R^3 = =NOH
(9) R^1 = Ac ; R^2, R^3 = O

(10)



(11) $R^1 = R^2 = H$; $R^3 = NO_2$
(12) R^1 = Ac ; $R^2 = H$; $R^3 = NO_2$
(13) R^1 = Ac ; R^2, R^3 = =NOH
(14) R^1 = Ac ; R^2, R^3 = O

ure of the diacetate (7) to aqueous chromium(II) chloride.[4] Treatment with aqueous titanium trichloride[5] gave the known 21-acetoxy-20-ketone derivative (9) in an overall yield of 80% from the starting 17-ketone (4). Such enones are immediate precursors to the important 16-substituted corticosteroids[6] (*e.g.* triamcinolone).

Sodium borohydride reduction of the nitro-olefin (5) gave the saturated nitro-derivative (10) which on treatment with formaldehyde furnished the diol (11) {diacetate (12), m.p. 187—195 °C; $[\alpha]_D$ −22 ° ($CHCl_3$)} in a quantitative overall yield.

The 20-oxo-derivative (14) was obtained in 75% yield by exposing briefly the diacetate (12) to aqueous chromium(II) chloride and hydrolysing the crude oxime (13) with acetic acid–aqueous sodium nitrite. 17-Deoxy-corticosteroids possess mineralocorticoid activity[6] and are synthetic precursors of aldosterone[7] and cardenolides.[8,9]

Although several methods for the elaboration of 17-oxo-steroids into corticosteroids have been published,[1,10] this approach has the advantage of simplicity, cheapness of reagents, and high overall yields. Furthermore, nitro-olefins are unusually versatile intermediates[2,11,12] and can provide access to a large variety of analogues and new steroidal derivatives.

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