A Facile Synthesis of Deoxycorticosterone using the Controlled Alkaline Hydrolysis of 21-Bromo-20-ketopregnenes

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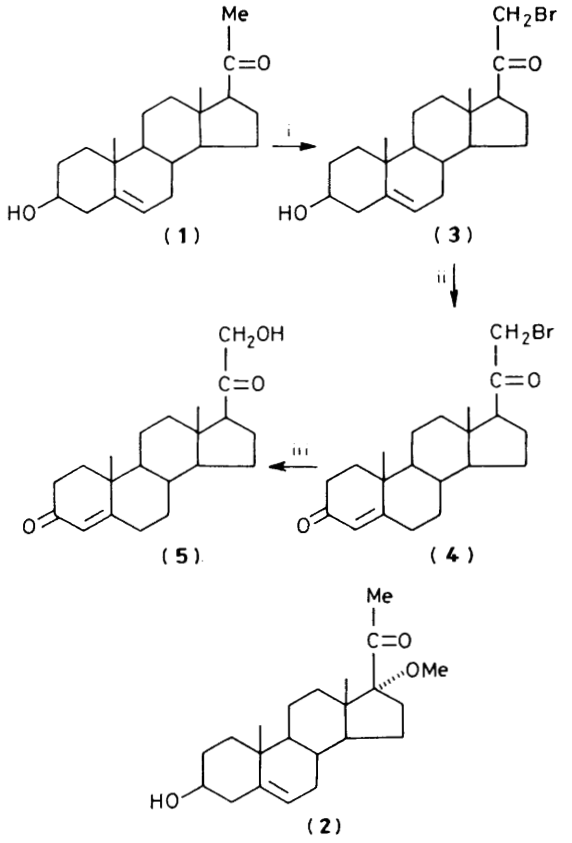
A novel synthesis of deoxycorticosterone (**5**) has been accomplished using the controlled alkaline hydrolysis of 21-bromopregn-4-ene-3,20-dione (**4**), obtained by the direct bromination of 3β-hydroxypregn-5-en-20-one (**1**) with $CuBr_2$ in the presence of pyridine, followed by oxidation with 2.67 M CrO_3 and subsequent acid-treatment.

Introduction of the 21-oxygen function into the 17β-acetyl side-chain of pregnenes is of central importance in the partial synthesis of corticoids. Probably the most widely used method for this synthesis involves the halogenation of 20-ketopregnenes, followed by displacement of 21-halides by acetate.[1] From observations on the bromination of 3β-hydroxypregn-5-en-20-one (**1**) with common reagents (*e.g.*, Br_2[1] or $CuBr_2$[2]), it has been considered impossible to obtain the 21-bromide (**3**) from the 20-ketone (**1**) directly. Moreover, efficient displacement of the bromo-group of a 21-bromo-20-ketone by a hydroxy-group has not been achieved probably owing to the Favorskii rearrangement[3] involved in the reaction and the sensitivity of the product, 21-hydroxy-20-ketone, to basic reagents. We now report a novel synthesis of deoxycorticosterone (**5**) which involves the direct bromination at C-21 of the 20-ketone (**1**) and the subsequent alkaline hydrolysis of the 21-bromide (**3**) under the controlled conditions[4] which we recently discovered and utilized in the synthesis of 16α-hydroxy-17-keto- and 2α-hydroxy-3-keto-steroids.

Treatment of 20-ketopregnene (**1**) with $CuBr_2$ (3 mol. equiv.,[4e] dry MeOH, reflux, 24 h) gave 3β-hydroxy-17α-methoxypregn-5-en-20-one (**2**) as reported[2] but with an improved yield (65%). In contrast, when the 20-ketone (**1**) was treated with the brominating agent as above but in the presence of pyridine (3 equiv.), instead of producing a higher yield of the methoxide (**2**) analogous to the results of Sollman and Dodson,[5] the 21-bromide (**3**) [m.p. 156—158 °C (lit.[6] m.p. 159—159.5 °C); ^{1}H n.m.r. δ ($CDCl_3$) 0.67 (3H, s, 3 × 18-H), 1.62 (3H, s, 3 × 19-H), 3.50 (1H, m, 3α-H), 3.92 (2H, s, 2 × 21-H), 5.38 (1H, m, 6-H); ν_{max} (KBr) 1719 cm^{-1}; m/z 394 and 396 (M^+)], was obtained regioselectively in 71% yield without the formation of the methoxide (**2**). This is the first direct bromination at C-21 of the 20-ketone (**1**) without affecting the integrity of the isolated double bond at C-5. This is a surprising result, in view of the usual reaction pathway of bromination with $CuBr_2$[2] or Br_2,[1] and can be explained by the base functioning analogously to CaO[7] and probably promoting enolization, in the Hofmann sense, toward C-21.

The completion of a 21-hydroxy-20-one side-chain was accomplished by the use of an interesting reaction, the controlled alkaline hydrolysis[4] of the corresponding 21-bromo-20-one. When the bromoketone (**4**) [m.p. 184—185 °C (lit.[6] m.p.



Scheme 1. *Reagents:* i, $CuBr_2$, pyridine, MeOH; ii, 2.67 M CrO_3, acetone and then toluene-*p*-sulphonic acid, acetone; iii, NaOH and aqueous DMF or K_2CO_3 and aqueous acetone.

190—191 °C); ^{1}H n.m.r. δ ($CDCl_3$) 0.70 (3H, s, 3 × 18-H), 1.18 (3H, s, 3 × 19-H), 3.90 (2H, s, 2 × 21-H), 5.73 (1H, s, 4-H), ν_{max} (KBr) 1718, 1660 cm^{-1}], obtained by oxidation of the bromide (**3**) with 2.67 M CrO_3 and subsequent treatment with toluene-*p*-sulphonic acid, was treated with NaOH [1.2 equiv., 67% aqueous dimethylformamide (DMF),[4e] room temp., 30 min] or K_2CO_3[4c] (1 mol. equiv., 60% aqueous acetone, reflux, 1 h), deoxycorticosterone (**5**), m.p. 139—140 °C (lit.[8] 141—142 °C), was obtained in 85—95% yield. The ketol (**5**) was identical with the natural product in every respect and the overall yield, without purification and isolation of intermediates, was *ca.* 55%.

The obvious advantages of this sequence are that the 3β-hydroxy-5-ene system does not interfere with the reaction and a 21-bromo-20-ketone can be converted directly into the corresponding 21-hydroxide. 11-Deoxycortisol having a dihydroxyacetone side-chain has also been efficiently obtained (70%) by the controlled alkaline hydrolysis of 21-bromo-17α-hydroxypregn-4-ene-3,20-dione.

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