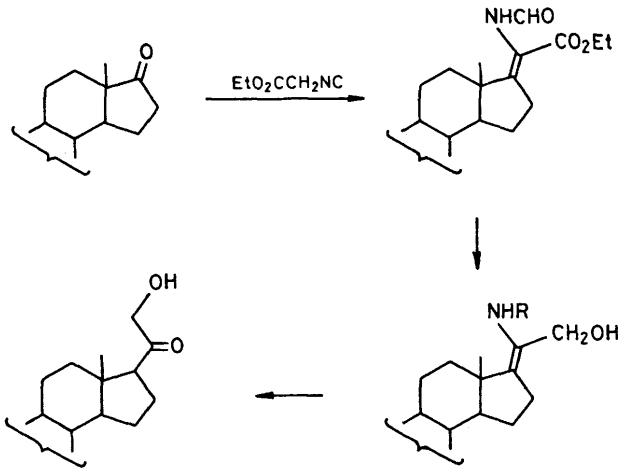
Simple Route for Elaboration of the Hydroxy-ketone and Dihydroxy-acetone Side-chains of Corticosteroids from 17-Oxo-steroids

By LUCIEN NÉDÉLEC,* VESPERTO TORELLI, and MICHEL HARDY
(*Centre de Recherches, Roussel-Uclaf*, 93230 *Romainville, France*)

Summary α-Formylaminoacrylic esters, produced by the condensation of ethyl isocyanoacetate with 17-oxo-steroids, have been reduced selectively to give the corresponding alcohols; the latter gave, in high yield, the hydroxyacetyl side-chain on acidic hydrolysis or the dihydroxy-acetone side-chain after appropriate oxidation and hydrolysis.

As part of a search for new anti-mineral corticoids we have prepared a series of 19-nordeoxycorticosteroids.[1] Since the most suitable starting materials for these compounds were the 17-oxo-19-nor steroids, we were interested in developing an efficient and simple method for the introduction of a 17β-(hydroxy-ketone) side-chain.

The recent publication of Neef *et al.*[2] concerning the synthesis of the corticoid side-chain from 17-oxo-steroids prompted us to report our results using isocyanoacetate esters to give alkoxycarbonyl-formylamino-methylenes from aldehydes and ketones. Although this reaction has often been applied,[3] it does not seem to have been used in the steroid field for the introduction of the required side chain, as in the steps shown in Scheme 1.[4,5]



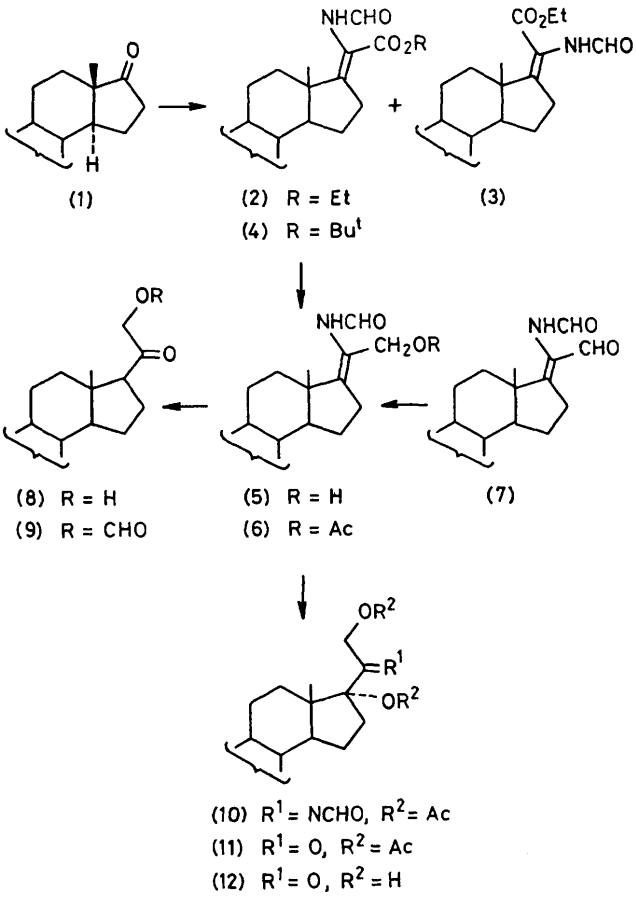
SCHEME 1

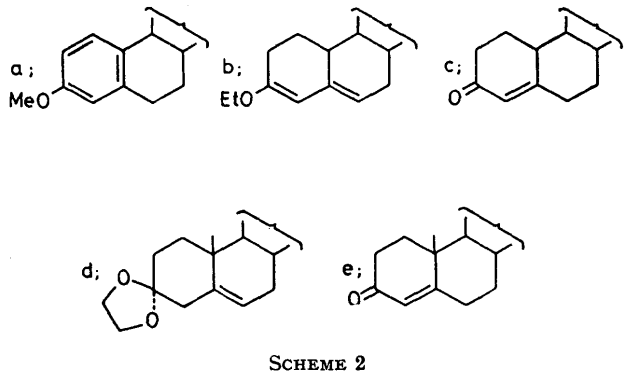
We have observed that condensation of the ketone (**1a**) with ethyl isocyanoacetate (1·5 mol) and potassium t-butoxide proceeded rapidly at room temperature in tetrahydrofuran (THF) to give 90% of the compound previously described by Schöllkopf and Hantke[5] as being the *E*-isomer (**3a**), but which is in fact (see below) the *Z*-isomer (**2a**) (Scheme 2), m.p. 161—162 °C; ^{1}H n.m.r. ($CDCl_3$) δ 0·98 (split s, C-18), 1·30 (split t, $MeCH_2O$), 4·21 (split q, $MeCH_2O$), and 8·02 and 8·27 (together 1 H, 2 × d, J 12 and 2 Hz, NCHO of the rotamers). From the mother-liquors we obtained the t-butyl ester (**4a**) (1·5%), m.p. 176 °C and the more polar *E*-isomer (**3a**) (3·5%), m.p. 195 °C; ^{1}H n.m.r. ($CDCl_3$) δ 1·10 (s, C-18), 1·33 (t, $MeCH_2O$), 4·28 (q, $MeCH_2O$), and 8·10 and 8·17 (together 1 H, 2 × d, J 12 and 2 Hz, NCHO of the rotamers).

When the ester (**2a**) was reduced with $LiAlH_4$ (THF, 0 °C), the main product was the alcohol (**5a**), m.p. 191 °C. A small amount of the intermediate aldehyde (**7a**) was also isolated, m.p. 224 °C. The latter was reduced by addition of KBH_4 and water to the reaction mixture. Under these conditions, the alcohol (**5a**) was obtained in good yield (90%) from the ester (**2a**).

The selective reduction of the formamide esters (**2**) is another example of the protection of a functional group (the formamide) by anion formation whilst $LiAlH_4$ reduces another functional group (the ester), not so protected.[6]

Acid hydrolysis of the ene-amide (**5a**) (MeOH, 5N HCl, room temp.) afforded the hydroxy-ketone (**8a**) in quantitative yield, m.p 130—131 °C. The reaction proceeds through the





SCHEME 2

N → O transposition of the formyl group, as was proved by the isolation of the intermediate formate (**9a**), m.p. 126 °C. Thus, without any separation of the alcohol (**5a**) and the other possible intermediates, the β-(hydroxy-ketone) side-chain can be introduced in two steps [(**1**) → (**2**) → (**8**)], starting from a 17-ketone, with up to 80% yield.

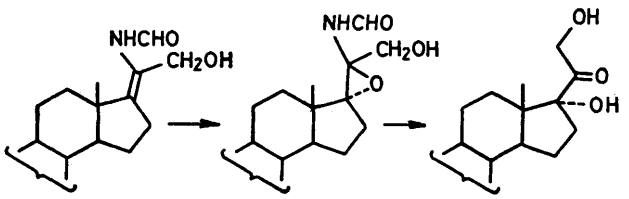
Similarly, treatment of the ketone (**1b**)[7] with ethyl isocyanoacetate under the same conditions as for compound (**1a**) gave mainly the *Z*-isomer (**2b**) (88%), m.p. 165 °C. In addition, small amounts of the t-butyl ester (**4b**) (3%), m.p. 159 °C, and the *E*-isomer (**3b**) (4%), m.p. 214 °C, were also isolated. Reduction of the ester (**2b**) followed by acidic hydrolysis of the resultant alcohol (**5b**) gave the 19-nor-

cortexone (**8c**) with an overall yield of 72%. Under less drastic conditions (AcOH, H_2O, room temperature), the enolic ether was selectively cleaved to give 85% of the ethylenic ketone (**5c**), m.p. 210 °C; $[\alpha]_D^{20} + 72°$ (1%, $CHCl_3$).

The *Z*-configuration of (**5c**) at C-20 was unambiguously determined by *X*-ray analysis.[8] This result allows the *Z*-configuration to be attributed to the ene-amido-compound (**2b**) and to the other corresponding derivatives (**2**) for which the C-18 methyl signals appear to be upfield compared with the *E*-isomers (**3**).

The ene-amides (**5**) can be considered as key intermediates to the corticoid side-chain following, for example, the route depicted in Scheme 3. However, treatment of the alcohol (**5a**) with different peracids under various conditions failed to give the expected epoxide and only gave the oestrone methyl ether (**1a**) with consumption of two moles of peracid.

Finally, the introduction of the oxygenated function at C-17 has been achieved by treatment of the acetate (**6a**), m.p. 125 °C, with lead tetra-acetate following a method previously described for a comparable 21-deoxy-derivative.[9] The resultant formylimine (**10a**), m.p. 135 °C was converted, in acidic medium, into the oxo-diacetate (**11a**), m.p. 162 °C, which easily gave the dihydroxy-acetone (**12a**) on saponification (KOH, MeOH, room temperature).



SCHEME 3

Following the same general procedure we have synthesized the cortexolone (**12e**) from the 3-acetal derivative (**1d**)[10] of androstenedione, which is a starting material easily available by biodegradation of sterols.[11] Thus, treatment of the acetal (**1d**) with ethyl isocyanoacetate followed by the reduction of the ester (**2d**) yielded *ca.* 80% of the alcohol (**5d**), m.p. 242 °C, which was transformed into the corresponding acetate (**6d**), m.p. 216 °C. Subsequent treatment of the latter derivative with $Pb(OAc)_4$ gave the diacetate (**10d**) (80%) and, after hydrolysis, the cortexolone diacetate (**11e**),[12] which was directly saponified to give the cortexolone (**12e**), m.p. 215 °C (80%).

(*Received, 9th April*, 1981; *Com.* 419.)

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