

Efficient Synthesis of the Corticosteroid Side-chain from 17-Ketones

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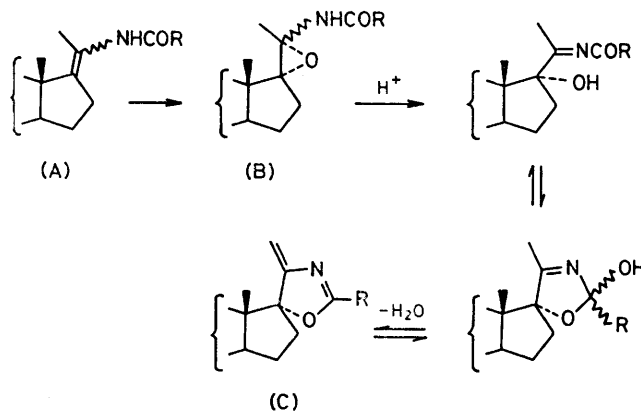
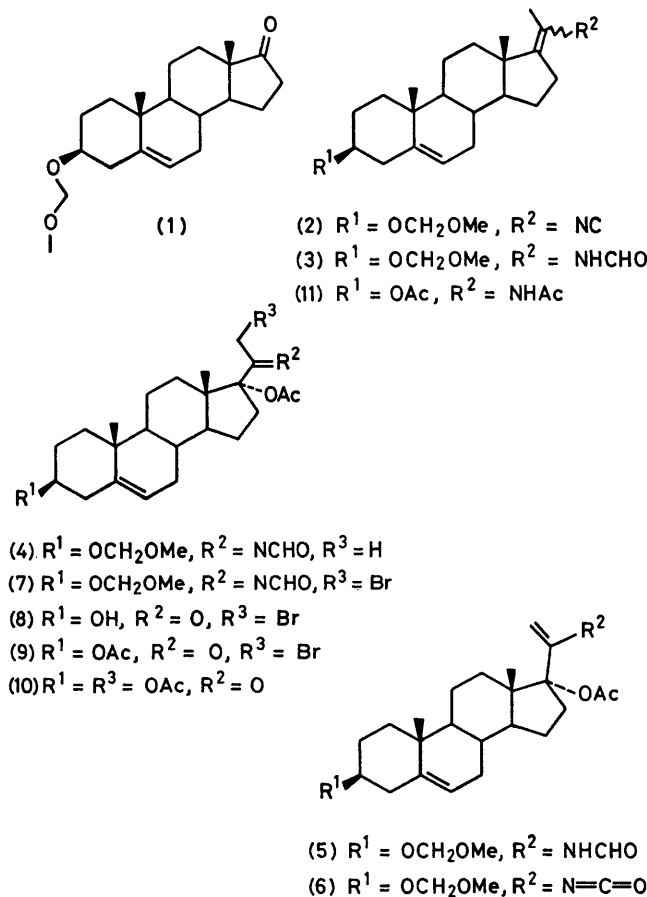
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Summary Steroidal 17-ketones react smoothly with diethyl α -isocyanoethyl phosphonate to give, after suitable oxidative and hydrolytic reactions, the dihydroxy-acetone side-chain of corticosteroids in high yield.

THE availability of 17-oxo-steroids by biodegradation of side-chain-saturated sterols has made them ideal starting materials for corticosteroid synthesis.¹⁻⁸ We describe herein a short and efficient method for producing the dihydroxy-acetone side-chain from 17-oxo-steroids.

Our previous work⁹ on the acetoxylation of pregnenolone derivatives led us to consider that an ene-formamide of type (A) (see the Scheme) could serve as a key intermediate. Diethyl α -isocyanoethyl phosphonate (b.p. 82–84 °C/0.5 mmHg) was prepared by formylation and dehydration¹⁰ of diethyl α -aminoethyl phosphonate¹¹ in 80% overall yield. Condensation of the ketone (1) with this reagent (KH,

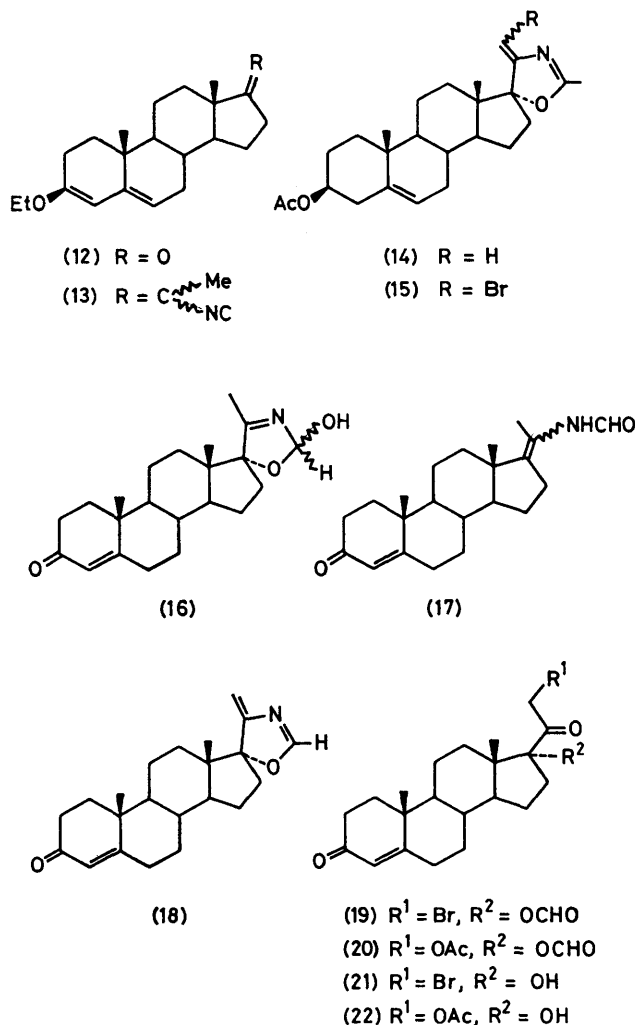
1,2-dimethoxyethane, 0 °C) gave the isocyanide (2) in 90% yield as a mixture of geometrical isomers. On exposure to formic acid (EtOAc, room temperature), the aldehyde (3) was formed. Without purification, compound (3) was oxidized with lead tetra-acetate (benzene, 0 °C) and the product (4) immediately rearranged in formic acid (EtOAc, trace Ac₂O, room temperature) to give compound (5) {m.p. 148–151 °C, $[\alpha]_D - 133^\circ$ (CHCl₃)}. The overall yield from compound (2) was practically quantitative. Further acetoxylation with lead tetra-acetate in benzene was unsuccessful under a variety of conditions. Addition of pyridine resulted in the formation of a compound whose spectroscopic properties are in accord with the isocyanate (6) [ν_{\max} 2250, 1740, and 1615 cm⁻¹; δ_H : 5.25 (1 H), 4.95 (1 H, s), 4.80 (1 H, s), 4.50 (2 H, s), 3.25 (3 H, s), 2.05 (3 H, s), 1.00 (3 H, s), and 0.70 (3 H, s); m/e 443 (M^+)]. The construction of the side chain could, however, be completed by a sequence involving selective bromination to the bromide (7) [pyridinium bromide perbromide (1 equiv.), pyridine, CH₂Cl₂, 0 °C], acid hydrolysis to give compound (8), and acetylation to give compound (9) [m.p. 157–159 °C, $[\alpha]_D - 25^\circ$ (CHCl₃)]. Displacement of the bromine with acetate anion (AcOK, dimethylformamide, N₂, 80 °C) afforded the known (10).⁹



SCHEME

Nevertheless, an alternative method which avoided the use of lead tetra-acetate was desirable. We envisaged that an epoxide of type (B), formed by epoxidation of (A), would rearrange on treatment with an acid to give a structure of type (C) (Scheme) which possesses all the necessary features for simple transformation into the dihydroxy-acetone side-chain.

Indeed, in a model study, epoxidation of compound (11)⁹ (*m*-chloroperbenzoic acid, CH₂Cl₂, 0 °C) followed by reflux



of the reaction mixture afforded compound (14) {m.p. 178—180 °C, $[\alpha]_D + 92^\circ$ (CHCl₃); ν_{\max} 1737 and 1620 cm⁻¹}. Bromination gave compound (15), acid hydrolysis gave compound (9), and acetate displacement gave the ketone (10)⁹ in high overall yield.

In an analogous manner the ketone (12) gave (13) in 92% yield, again as a mixture of geometrical isomers. Hydrolysis to compound (17) followed by epoxidation and rearrangement (CH₂Cl₂, 40 °C, 6 h) afforded an oil whose spectral properties agreed with structure (16). Addition of toluene and azeotropic removal of water gave the labile intermediate (18) which was brominated and hydrolysed *in situ* to give (19) {m.p. 192—194 °C, $[\alpha]_D + 96^\circ$ (CHCl₃)} in 60—70% yield from the isocyanide (13) without isolation of the intermediates. Acetate displacement (AcOK, acetone) afforded compound (20) in 70% yield {m.p. 227—233 °C, $[\alpha]_D + 78^\circ$ (CHCl₃)}. It was found preferable to hydrolyse the aldehyde (19) to give (21) first (KHCO₃, MeOH, H₂O) and then displace with acetate. The known (22)¹² was thus obtained in > 90% yield from compound (19).

This flexible scheme provides several useful intermediates. Pregnenolone and progesterone can be prepared in one step from compounds (1) and (12) by simple hydrolysis of the reaction mixture after condensation with diethyl α -isocyanoethyl phosphonate. 17 α -Hydroxyprogesterone was obtained in 88% yield from compound (17) by hydrolysis and saponification of the reaction mixture after the epoxidation of compound (11).

Although the condensation of ethyl isocyanoacetate with oestrone methyl ether was reported by Schöllkopf and Hantke,¹³ no further transformations were subsequently described in the literature.

(Received, 9th April 1981; Com. 418.)

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