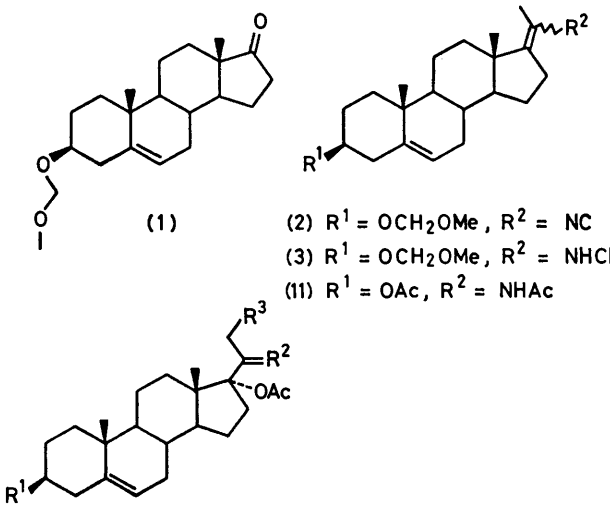
Efficient Synthesis of the Corticosteroid Side-chain from 17-Ketones

By DEREK H. R. BARTON, WILLIAM B. MOTHERWELL, and SAMIR Z. ZARD*
(*Institut de Chimie des Substances Naturelles, C.N.R.S., 91190 Gif-sur-Yvette, France*)

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.

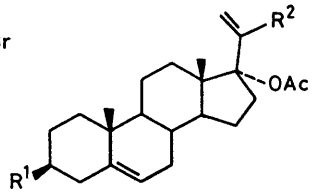
Our previous work[9] on the acetoxylation of pregnenolone derivatives led us to consider that an ene-formamide of type (A) (see the Scheme) could serve as a key intermediate. Diethyl α-isocyanoethyl phosphonate (b.p. 82—84 °C/0·5 mmHg) was prepared by formylation and dehydration[10] of diethyl α-aminoethyl phosphonate[11] 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 Ac_2O, room temperature) to give compound (**5**) {m.p. 148—151 °C, $[\alpha]_D$ — 133° ($CHCl_3$)}. The overall yield from compound (**2**) was practically quantitative. Further acetoxylation with lead tetra-acetate in benzene was unsuccesful 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, CH_2Cl_2, 0 °C], acid hydrolysis to give compound (**8**), and acetylation to give compound (**9**) [m.p. 157—159 °C, $[\alpha]_D$ — 25° ($CHCl_3$)]. Displacement of the bromine with acetate anion (AcOK, dimethylformamide, N_2, 80 °C) afforded the known (**10**).[9]



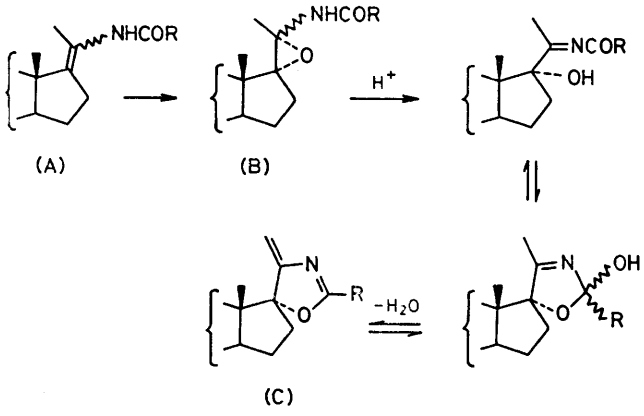
(1)

(2) R^1 = OCH_2OMe, R^2 = NC
(3) R^1 = OCH_2OMe, R^2 = NHCHO
(11) R^1 = OAc, R^2 = NHAc

(4) R^1 = OCH_2OMe, R^2 = NCHO, R^3 = H
(7) R^1 = OCH_2OMe, R^2 = NCHO, R^3 = Br
(8) R^1 = OH, R^2 = O, R^3 = Br
(9) R^1 = OAc, R^2 = O, R^3 = Br
(10) R^1 = R^3 = OAc, R^2 = O



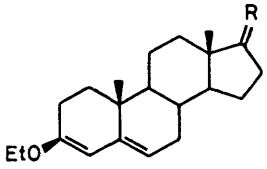
(5) R^1 = OCH_2OMe, R^2 = NHCHO
(6) R^1 = OCH_2OMe, R^2 = N=C=O



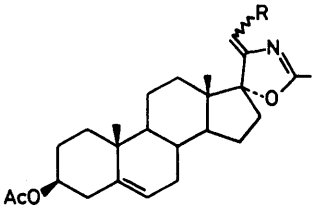
SCHEME

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.

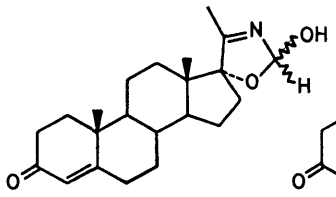
Indeed, in a model study, epoxidation of compound (**11**)[9] (*m*-chloroperbenzoic acid, CH_2Cl_2, 0 °C) followed by reflux



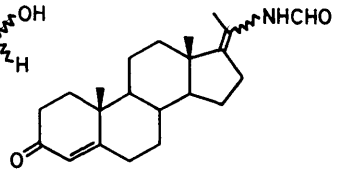
(12) R = O
(13) R = C(Me)NC



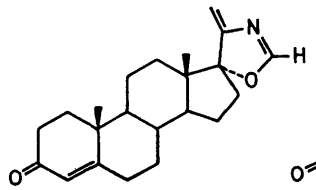
(14) R = H
(15) R = Br



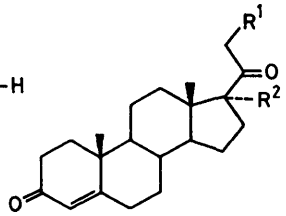
(16)



(17)



(18)



(19) R^1 = Br, R^2 = OCHO
(20) R^1 = OAc, R^2 = OCHO
(21) R^1 = Br, R^2 = OH
(22) R^1 = OAc, R^2 = OH

of the reaction mixture afforded compound (**14**) {m.p. 178—180 °C, $[\alpha]_D$ + 92° ($CHCl_3$); 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 (CH_2Cl_2, 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° ($CHCl_3$)} 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° ($CHCl_3$)}. It was found preferable to hydrolyse the aldehyde (**19**) to give (**21**) first ($KHCO_3$, MeOH, H_2O) 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. 17α-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.)

[1] W. J. Marsheck, S. Kraychy, and R. D. Muir, *Appl. Microbiol.*, 1972, **23**, 72.
[2] M. G. Wovcha, F. J. Antosz, J. C. Knight, L. A. Komineck, and T. R. Pyke, *Biochim. Biophys. Acta*, 1978, **539**, 308.
[3] M. Nagasawa, H. Hashiba, N. Watanabe, M. Bae, G. Tamura, and K. Arima, *Agric. Biol. Chem.*, 1970, **34**, 801.
[4] M. Nagasawa, M. Bae, G. Tamura, and K. Arima, *Agric. Biol. Chem.*, 1969, **33**, 1644.
[5] C. J. Sih, S. S. Lee, Y. Y. Tsong, K. C. Wang, and F. N. Chang, *J. Am. Chem. Soc.*, 1965, **87**, 2765.
[6] V. Van Rheenan and K. P. Shephard, *J. Org. Chem.*, 1979, **44**, 1582.
[7] H. Hofmeister, K. Annen, H. Laurent, and R. Wiechert, *Chem. Ber.*, 1978, **111**, 3086.
[8] G. Neef, U. Eder, A. Seeger, and R. Wiechert, *Chem. Ber.*, 1980, **113**, 1184.
[9] D. H. R. Barton, R. B. Boar, J. F. McGhie, and M. Robinson, *J. Chem. Soc., Perkin Trans.* 1, 1975, 1242.
[10] U. Schöllkopf, R. Schröder, and D. Stafforst, *Liebigs Ann. Chem.*, 1974, 44.
[11] M. E. Chalmers and G. M. Kosolapoff, *J. Am. Chem. Soc.*, 1953, **75**, 5278.
[12] P. L. Julian, E. Meyer, W. Karpel, and I. Ryden Waller, *J. Am. Chem. Soc.*, 1950, **72**, 5145.
[13] U. Schöllkopf and K. Hantke, *Chem. Ber.*, 1976, **109**, 3964.