Hypervalent Iodine in Organic Synthesis. A Novel Route to the Dihydroxyacetone Side-chain in the Pregnene Series

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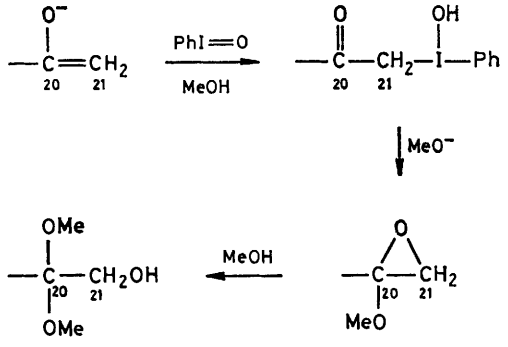
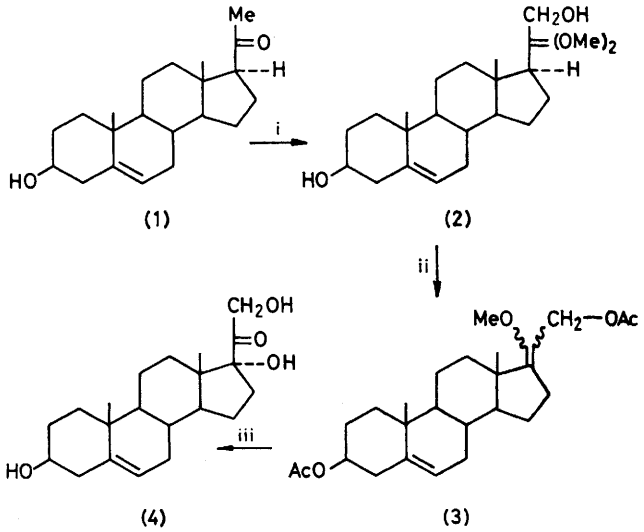
Summary Treatment of pregnenolone (**1**) with PhI=O and KOH in MeOH yields 3β,21-dihydroxypregn-5-en-20-one dimethyl acetal (**2**) from which a molecule of MeOH is lost to yield the C(17)–C(20) enol methyl ether (**3**) which may be epoxidized and hydrolysed to yield the C-17-dihydroxyacetone side-chain in the correct configuration as in 3β,17α,21-trihydroxypregn-5-en-20-one (**4**).

THE conversion of the C-17-acetyl side-chain present in pregnenes into the dihydroxyacetone side-chain of glucocorticoids is of central importance in the partial syntheses of these steroids and has been accomplished in various ways.[1] We report now a simple procedure for this transformation which leaves the 3β-hydroxy-Δ^5 system untouched. The reaction (**1**) → (**2**) is based upon our recently described dimethyl acetal acyloin synthesis which involves treatment of ketones with PhI=O and KOH in MeOH.[2] This proceeds *via* nucleophilic addition (Scheme 1) of the enolate anion to PhI=O and cleavage of the C–I^{III} bond occurs by addition of $^-$OMe to the carbonyl group followed by intramolecular displacement from the thus-formed tetrahedral intermediate to yield the epoxy-ether, which in turn adds a second molecule of MeOH. The yield of 3β,21-dihydroxypregn-5-en-20-one dimethyl acetal (**2**) was 67%.†



SCHEME 1



SCHEME 2. Reagents: i, PhI=O, KOH, MeOH; ii, Ac_2O, pyridine, then *p*-xylene, 138 °C; iii, *m*-$ClC_6H_4CO_3H$, 5 min, 0 °C, then OH^-.

† Acid hydrolysis of (**2**) yielded the C-20 ketone. The diacetate of (**2**) had m.p. 108—110 °C; 60 MHz Fourier transform ^1H n.m.r. spectra ($CDCl_3$): (**2**) δ 5·30 and 5·37 (6-H), 3·94 and 3·82 (21-H_2), 3·28 and 3·30 (OMe), 0·74 (18-H_3), and 1·00 (19-H_3); diacetate of (**2**), δ 5·33 and 5·39 (6-H), 2·08 (3-OAc), 2·02 (21-OAc), 4·22 (21-H_2), 1·01 (18-H_3), and 3·26 (OMe).

In order to form the C(17)–C(20) enol methyl ether (**3**) a molecule of MeOH is eliminated from the diacetate of (**2**) by refluxing in *p*-xylene with a catalytic amount of toluene-*p*-sulphonic acid to give the product in 80% yield (Scheme 2). Initially a mixture of *E*- and *Z*-isomers of the 20-methoxy-compound (**3**) is formed but a longer reaction time leads to a predominance of one isomer which on steric grounds is the *E*-isomer.[3]‡ Owing to the high reactivity of the enol methyl ether towards peroxy-acid, epoxidation with *m*-chloroperbenzoic acid occurs exclusively at the C(17)–C(20) double bond.[4] Without isolation, the product was hydrolysed with base to afford 3β,17α,21-trihydroxypregn-5-en-20-one (**4**)[5] in 60% yield.[6]

The obvious advantages of this sequence are that secondary hydroxy-groups and double bonds do not interfere. Since the 3β-hydroxy-Δ^5-system may be converted *via* Oppenauer oxidation into the 3-oxo-Δ^4-system, mineralocorticoids and the glucocorticoids may also be obtained by the above sequence.

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‡ The mixture of C-20-epimers of (**3**) had m.p. 90—96 °C; δ 5·38 (6-H), 4·63 (21-H_2), 3·51 (OMe), 2·09 (3-OAc), 2·02 (21-OAc), 0·97 (18-H_3), and 1·05 (19-H_3). Hydrolysis yielded the epimeric diols, m.p. 122—126 °C.

[1] For a review see E. P. Oliveto in 'Organic Reactions in Steroid Chemistry,' eds. J. Fried and J. A. Edwards, Van Nostrand Reinhold, New York, 1972, pp. 127—217.

[2] R. M. Moriarty and H. Hu, *J. Am. Chem. Soc.*, 1981, **103**, 686; R. M. Moriarty, H. Hu, and S. C. Gupta, *Tetrahedron Lett.*, 1981, **22**, 1283.

[3] This type of reaction has been reported by A. Serini and H. Köster, *Ber.*, 1938, **71**, 1766.

[4] Analogous epoxidation and hydrolysis have been carried out on C(17)–C(20) enol acetates in the pregnane series: T. H. Kritchevsky and T. F. Gallager, *J. Am. Chem. Soc.*, 1951, **73**, 184; H. V. Anderson, E. R. Garrett, F. H. Lincoln, Jr., A. H. Nathan, and J. H. Hogg, *ibid.*, 1954, **76**, 743; E. P. Oliveto and E. B. Hershberg, *ibid.*, p. 5167.

[5] K. Flory and M. Ehrenstein, *J. Org. Chem.*, 1954, **19**, 1331.

[6] H. A. F. Heinemann and W. Kreiser, in Ger. Offen., 2,665,104 (*Chem. Abstr.*, 1978, **89**, 129,802P) report that dehydroepiandrosterone may be converted into (**3**) by a five-step sequence which involves addition of the C-20 and C-21 carbon atoms to the C-17-oxo-precursor.