The Reaction of *m*-Chloroperbenzoic Acid with 3-Acetoxy-steroidal 3,5-Dienes

By D. N. KIRK* and JENNIFER M. WILES

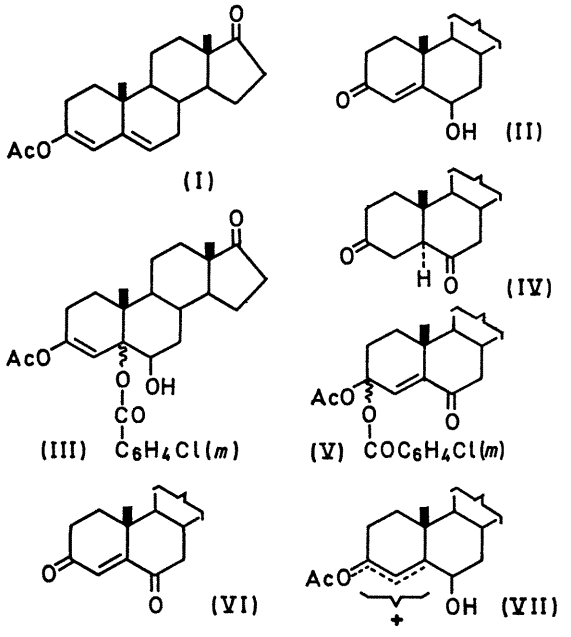
(*Medical Research Council Steroid Reference Collection, Chemistry Department, Westfield College, Hampstead, London, N.W.3*)

Summary *m*-Chloroperbenzoic acid and 3-acetoxyandrosta-3,5-dien-17-one form a 1 : 1 addition compound (III) in non-polar solvents, or 6β-hydroxyandrost-4-ene-3,17-dione (II) in aqueous solvents.

ENOL ACETATES (*cf.* I) or enol ethers of steroidal 4-en-3-ones are reported to give the corresponding 6β-hydroxy-4-en-3-ones (II) on reaction with peroxy-acids.[1] Yields, however, are generally low, and in our experience, not reproducible under the conditions described.

3-Acetoxyandrosta-3,5-dien-17-one (I) reacts rapidly with *m*-chloroperbenzoic acid in solvents of low polarity (benzene, carbon tetrachloride, dichloromethane, *etc.*). Examination of the reacting solution by t.l.c., n.m.r., and $[\alpha]_D$, showed that little, if any, of the 6β-hydroxy-steroid (II) was produced, but instead a less polar product running as a single spot (t.l.c.). Rapid washing of the solution with sodium hydrogen carbonate solution removed excess of peroxy-acid and any *m*-chlorobenzoic acid, leaving in solution a rather unstable compound showing i.r. and n.m.r. characteristics of both the steroid and the aromatic acid.

We formulate the product as (III), resulting from an unprecedented addition of OH and $O{\cdot}CO{\cdot}C_6H_4Cl$ groups, derived from the peroxy-acid, on to the 5,6-double bond of the enol acetate. This structure is based upon the following spectral details: i.r.: 3600 cm^{-1} (O–H); 1760 and 1210 cm^{-1} (enol acetate); 1740 cm^{-1} (17-ketone); 1730 and 1260 cm^{-1} (*m*-chlorobenzoate); n.m.r.: τ 2·4 (aromatic protons), 3·8 (s, 4-H), 5·64 (t, 6α-H), 7·94 (s, acetate), 8·75 (s, 10-CH_3), 9·10 (s, 13-CH_3). The mass spectrum showed peaks derived from both the steroid and the *m*-chlorobenzoate moieties. The molecular ion (M^+ 500/502) was barely discernible, but strong peaks at *m/e* 440/442 may represent the elimination of a molecule of acetic acid from the molecular ion.



The following chemical evidence supports the structure (III). The compound could not be crystallised; it was stable for a few days, at most, at low temperature in non-polar solvents, but gradually broke down to a complex mixture containing traces of the 6β-hydroxy-4-en-3-one (II), 5α-androstane-3,6,17-trione (IV), and numerous unidentified products. Polar solvents, moist air, or chromatographic absorbents accelerated this decomposition, although the compound survived brief contact with silica gel t.l.c. plates. The solution in pyridine was stable over short periods, permitting acetylation of the secondary 6β-hydroxy-group by acetic anhydride. The amorphous 3,6-diacetate retained the i.r. and n.m.r. features of the enol acetate and *m*-chlorobenzoate groups, and gave, on mild hydrolysis, 6β-acetoxyandrost-4-ene-3,17-dione. Oxidation of the addition compound (III) with chromium trioxide–pyridine gave the 6-ketone, ν_{max} 1715 cm^{-1}. The absence of any u.v. absorption in the range 220—280 nm, except that due to the *m*-chlorobenzoate group, excluded the alternative 4-en-6-one conjugated structure (V), which could have arisen *via* initial "1,4-addition" of the peroxy-acid to the enol acetate, and might have been reconcilable with the spectral data quoted above. The 6-ketone readily decomposed in polar solvents to give androst-4-en-3,6,17-trione (VI).

Other steroidal 3-acetoxy-3,5-dienes (*e.g.* the enol acetate of cholest-4-en-3-one) gave similar addition products with *m*-chloroperbenzoic acid, indicated by the n.m.r. spectra of reacting solutions. In the absence of a 17-oxo-group, however, the addition compounds were too unstable to be isolated: 6β-hydroxy-4-en-3-ones were obtained, although in low and erratic yields. However, the latter compounds were formed in good yields (up to 90%) if the reaction of any of these enol acetates with peroxy-acid was carried out in *aqueous* dioxan.

We interpret the effect of solvent character in terms of alternative reactions available to an intermediate mesomeric cation (VII) resulting from donation of "HO^+" to the enol acetate. Water apparently effects direct hydrolysis of the cation to give the 6-hydroxy-4-en-3-one, whereas, in non-polar solvents, the *m*-chlorobenzoate anion is the most nucleophilic species present, and attacks C-5.

From analysis of n.m.r. spectra and other features we consider the 5β-configuration likely for compound (III). This evidence, with other properties of the addition compound, and the mechanisms of these, and related reactions, will be discussed fully in our definitive paper.

(*Received, March 11th*, 1970; *Com.* 350.)

[1] J. Romo, G. Rosenkranz, C. Djerassi, and F. Sondheimer, *J. Org. Chem.*, 1954, **19**, 1509; J. P. Dusza, J. P. Joseph, and S. Bernstein, *ibid.*, 1963, **28**, 92.