A Two-step Synthesis of the Pregnane and Corticoid Side-chains

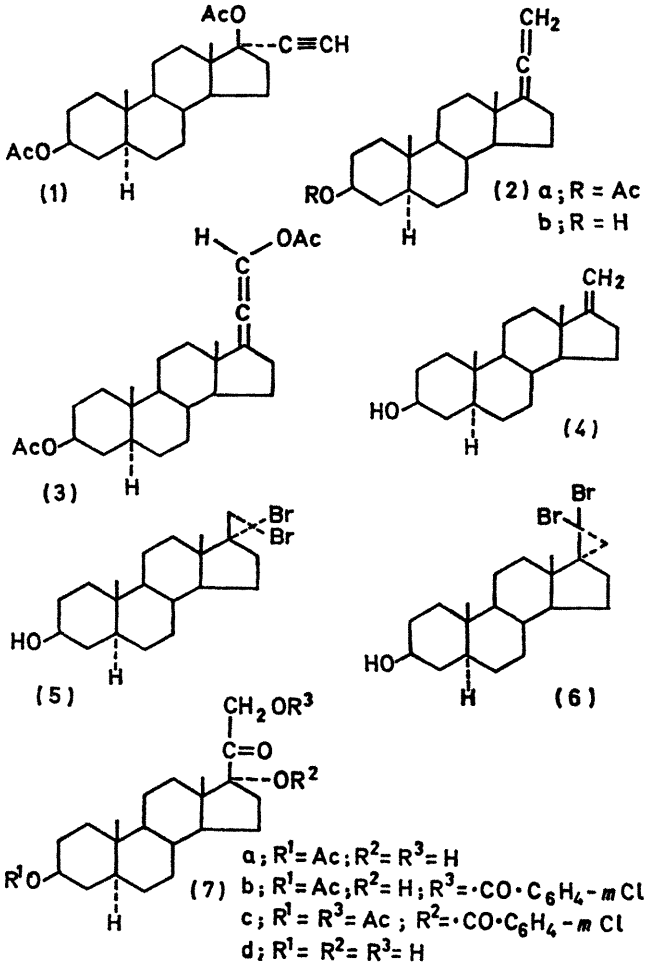
By M. BIOLLAZ,† W. HAEFLIGER,† E. VELARDE, P. CRABBÉ,* and J. H. FRIED
(*Research Laboratories, Syntex, S. A., Apartado Postal* 10–820, *Mexico* 10, *D. F., Mexico*)

Summary Zinc converts the 17α-ethynyl carbinol acetate (1) by a reductive process accompanied by rearrangement and elimination, into the allenyl steroid (2a), a useful intermediate for the preparation of the corticoid chain by osmylation, and of 17α-hydroxy-20-oxo-pregnanes by peracid oxidation.

AN important step in the total synthesis of steroids is the elaboration of the pregnane and the tri-oxygenated corticoid chains at position 17. We report novel procedures for the elaboration of 17-hydroxylated and 17,21-dihydroxylated pregnan-20-ones, either from 17α-ethynyl-3β,17β-dihydroxy-5α-androstane diacetate (1) or from its 17-keto-precursor, by means of the allene intermediates (2) and (3). It was expected that the allenes could be hydroxylated to give either 17α-hydroxy-20-keto- or 17α,21-dihydroxy-20-keto-steroids.

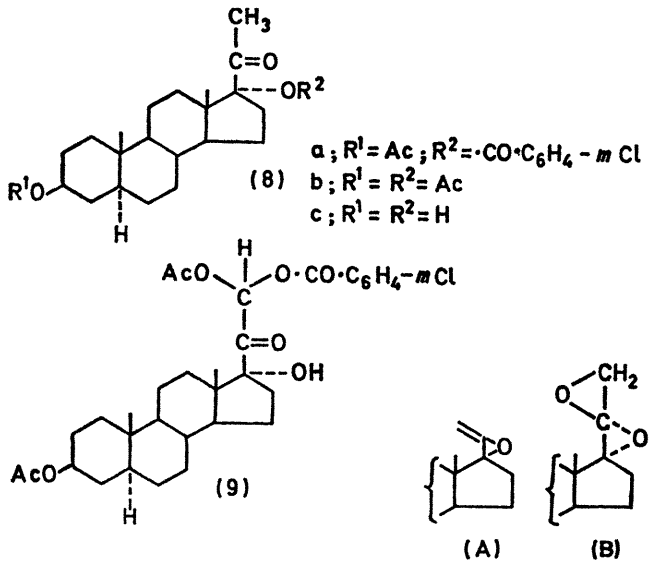
The allene (2a) m.p. 114—115°, $[\alpha]_D$ +35°, ν_{max} 1960 cm^{-1}, *m/e* 342(M^+) was prepared in 86% overall yield (with 6% of recovered starting material) from the ethynyl derivative (1) by reaction with zinc dust in refluxing anhydrous diglyme. This zinc reduction, accompanied by rearrangement and elimination, is reminiscent of the previously described allene synthesis from prop-2-ynyl alcohol derivatives.[1] Less efficient was the preparation of the allene (2b) *via* the 17-methylene-steroid (4),[2] by dibromocarbene addition[3] to afford a mixture of the *gem*-dibromo-adducts (5) m.p. 167—168°, δ 0·86 p.p.m. (18-H), and (6) m.p. 162—164°, δ 1·12 p.p.m. (18-H), followed by methyl-lithium fragmentation[4] to give the propadiene (2b) m.p. 126—127°, $[\alpha]_D$ + 32°, ν_{max} 1960 cm^{-1}, *m/e* 300 (M^+), in 56% yield. Reaction of (2a) with osmium tetroxide–pyridine in benzene, followed by cleavage of the osmate ester with sodium sulphite and potassium hydrogen carbonate afforded the desired 17α,21-dihydroxy-keto-steroid (7a) in 53% yield.

Alternatively, exposure of the propadienyl-steroid (2a) to *m*-chloroperbenzoic acid (2 equiv) provided (7b) m.p. 160—161°, $[\alpha]_D$ + 61°, λ_{max} 232, 282, and 291 nm (ε 9600, 1010, and 960), in 16% yield, and the pregnane derivative (8a) m.p. 245—246°, $[\alpha]_D$ −15°, λ_{max} 234, 284, and 292 nm (ε 9750, 1200 and 1040), in 29% yield.[5] When the allene (2a) was allowed to react with *m*-chloroperbenzoic acid (4 equiv) in chloroform solution buffered with disodium hydrogen phosphate, only the 17α-chlorobenzoate (8a) was isolated, in 34% yield. Similarly, reaction of (2a) with an excess of peracetic acid furnished only the acetoxy-pregnane (8b), in 20% yield, with recovery of 30% starting material. Mild base hydrolysis of (8a) or (8b) furnished the known diol (8c), thus establish-ing their structure and stereochemistry.



The above results suggest the formation of a 17,20-allene oxide intermediate (A), since only this species appears to be a reasonable precursor for (8a) and (8b). In addition it appears that the allene oxide (A) reacts with peracid at a rate

† Syntex Postdoctorate Fellows.



which is at least competitive with hydrolysis, to afford the dioxaspiro[2,2]pentane (B). The reactivity of (A) can be attributed to the $+M$ effect of the epoxide oxygen atom increasing the nucleophilicity of the 20,21-double bond.[6] The species (B), which was not isolated, is an attractive precursor to (7b). The isolation of a highly substituted dioxaspiropentane has been reported.[6,7]

A further alternate uses the acetoxy-allene (3) m.p. 172—173°, $[\alpha]_D$ +29°, ν_{max} 1975 and 1745 cm^{-1}, *m/e* 400 (M^+), prepared by silver-catalysed rearrangement[8] of the 17β-acetoxy-ethynyl carbinol (1). Reaction of (3) with *m*-chloroperbenzoic acid in the presence of disodium hydrogen phosphate and *m*-chlorobenzoic acid in chloroform solution, gives a mixture containing 36% of the corticoid 17-ester (7c) m.p. 230°, $[\alpha]_D$ +66°, λ_{max} 234, 284, and 292 nm (ϵ 9550, 1150, and 1200), and 34% of the corresponding 21-aldehyde diester (9) m.p. 208°, $[\alpha]_D$ +20°, λ_{max} 234, 284, and 292 nm (ϵ 9550, 1150 and 1110), δ 2·17 (21-OAc) and 7·49 p.p.m. (21-H), in addition to 15% of recovered (3). The corticoid (7c) results presumably from opening of the 17,20-mono-epoxide, whereas (9) is generated from the di-epoxide.

The β-configuration of the side-chain at position 17 in (7b) and (7c) was established by mild alkaline hydrolysis, yielding in all cases the known triol (7d).

(*Received, August 3rd, 1971; Com. 1346.*)

[1] *Cf.* J. S. Cowie, P. D. Landor, and S. R. Landor, *Chem. Comm.*, 1969, 541.
[2] F. Sondheimer and R. Mechoulam, *J. Amer. Chem. Soc.*, 1957, **79**, 5029.
[3] W. von E. Doering and A. K. Hoffmann, *J. Amer. Chem. Soc.*, 1954, **76**, 6162.
[4] L. Skattebøl, *Acta Chem. Scand.*, 1963, **17**, 1683; W. R. Moore and H. R. Ward, *J. Org. Chem.*, 1962, **27**, 4179; L. Skattebøl, *ibid.*, 1966, **31**, 2789
[5] J. K. Crandall and W. H. Machleder, *Tetrahedron Letters*, 1966, 6037; *J. Amer. Chem. Soc.*, 1968, **90**, 7292.
[6] J. K. Crandall, W. H. Machleder, and M. J. Thomas, *J. Amer. Chem. Soc.*, 1968, **90**, 7346.
[7] R. L. Camp and F. D. Greene, *J. Amer. Chem. Soc.*, 1968, **90**, 7349; D. B. Sclove, J. F. Pazos, R. L. Camp and F. D. Greene, *ibid.*, 1970, **92**, 7488; W. P. Reeves and G.G. Stroebel, *Tetrahedron Letters*, 1971, 2945.
[8] W. R. Benn, *J. Org. Chem.*, 1968, **33**, 3113; P. Crabbé, M. Biollaz, H. Caprio, A. Failli, P. Rona, E. Velarde, and J. H. Fried, in preparation.