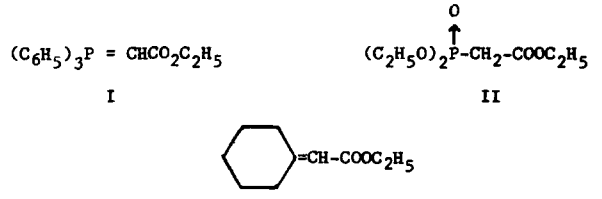
Tetrahedron Letters No. 15, pp. 959-963, 1963. Pergamon Press Ltd.
Printed in Great Britain.

STEROIDS I. INTRODUCTION OF THE CORTICAL SIDE CHAIN USING PHOSPHONATE CARBANIONS

by Ajay K. Bose and Robert T. Dahill, Jr.
Department of Chemistry and Chemical Engineering
Stevens Institute of Technology, Hoboken, New Jersey, U.S.A.

(Received 20 March 1963)

With the intention of introducing the cortical side chain at different sites on the steroid nucleus, we have been interested in the preparation of unsaturated steroid esters. The Wittig reaction failed to take place between cholestan-3-one and the phosphorane I (1). Following the appearance of the report (2) that the triethyl phosphonoacetate (II) reacts under mild conditions with cyclohexanone to give ethyl cyclohexylidineacetate (III) in high yield, we studied the reaction of II with various steroid ketones. We wish to report here on the marked selectivity that II shows in its reactions.



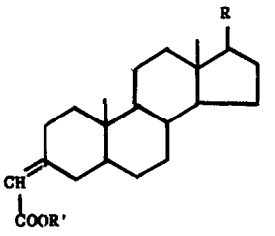
I II

III

The reaction of cholestan-3-one with an excess of II in N,N-dimethylformamide in the presence of sodium ethoxide (equimolar to I) at room temperature afforded ethyl cholestanylidene acetate (3) (IV), m.p. 84-85°, in 94% yield. On the basis of N.M.R. spectra it was established that only one isomer was formed in this reaction. It is interesting to note that on hydrolysis IV gives the same acid as was obtained by Milas and Priesling (4) from cholestan-3-one and ethoxy-

acetylene.

Dihydrotestosterone and II gave a nearly theoretical yield of the α,β -unsaturated ester V, m.p. 177-178°. Coprostan-3-one also underwent facile reaction with II to yield a liquid ester (VI) which was hydrolyzed to the acid VII, m.p. 162-163°.



IV R=C_8H_{17} ; R'=C_2H_5 ; 5α-H

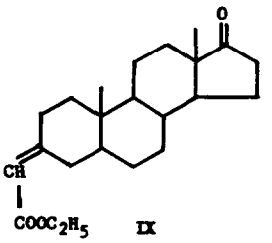
V R=OH ; R'=C_2H_5 ; 5α-H

VI R=C_8H_{17} ; R'=C_2H_5 ; 5β-H

VII R=C_8H_{17} ; R'=H ; 5β-H

$(C_6H_5)_3P = CH_2$

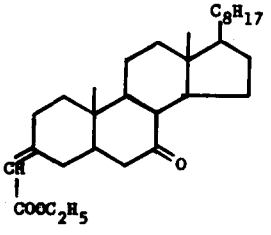
VIII



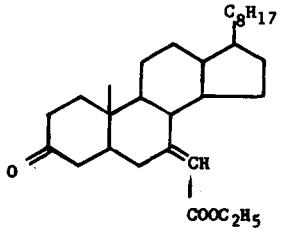
IX

In their study of the Wittig reaction of various steroid ketones with the phosphorane VIII, Sondheimer and Mechoulam (5) were able to introduce a methylene group at various positions--such as C_3, C_7, C_{12}, C_{17} and C_{20}--in 30-80% yield. In contrast to the phosphorane VIII, the phosphonate II proved to be very selective. Thus, estrone methyl ether and dehydroepiandrosterone acetate completely failed to react with the phosphonate II. When androstane-3,17-dione was treated with an excess of II, reaction took place selectively with the 3-keto group leading to the formation in 62% yield of the unsaturated ketoester IX. m.p. 156-157°, which was stereochemically homogeneous on the basis of its N.M.R. spectrum. Even such apparently unhindered ketones as 3β-acetoxycholestane-6-one and 3β-acetoxycholestan-7-one were unreactive

toward II. The reaction of cholestane-3,17-dione with II afforded an unsaturated ketoester (X), m.p. 99-100° (dec.), in good yield. A decision between the alternative structures X and XI did not seem feasible on the basis of I.R. and N.M.R. spectra. The physical measurement that promised to distinguish between X and XI appeared to be optical rotatory dispersion. Cholestan-3-one has been reported to give a strong positive Cotton effect curve while a moderately strong negative Cotton effect curve is given by 3β-acetoxycholestan-7-one (6). For the unsaturated ester IV, we have found the rotatory dispersion curve to be a positive plain curve. One can therefore expect a negative Cotton effect for X and a positive Cotton effect for XI, respectively. The O.R.D. of the unsaturated ketoester actually showed a weak negative Cotton effect which indicated the structure X to be correct.



X

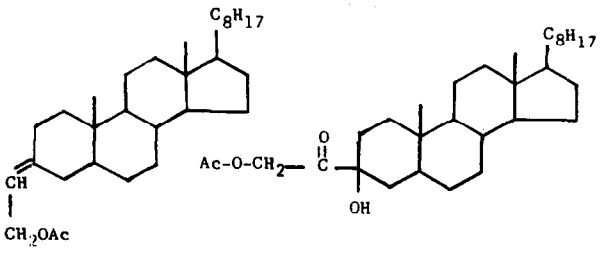


XI

The unsaturated ester IV was reduced with lithium aluminum hydride and acetylated to give the intermediate XII. Oxidation by the method described by Nathan, Magerlein and Hogg (7) converted XII in 30% yield into XIII, m.p. 168-169°, which is a steroid with a cortical side chain at C_3. Using similar reactions, VI was converted to XIV, m.p. 144-145°, the 5β-analog of XIII.

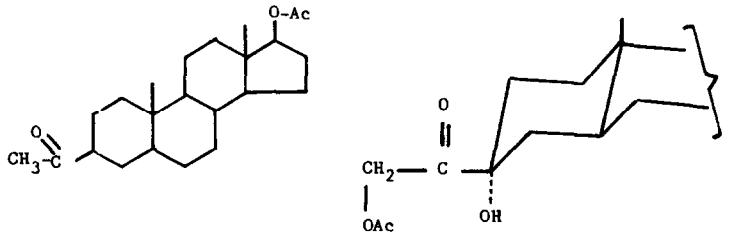
Dvolaitzky, Kagan and Jacques (8) have reported that 3β-acetyl-17β-acetoxy-5α-androstane (XV) gives a positive Cotton effect curve

$[\alpha]_{305}$ + 322° (peak) . Since compound XIII also shows a positive Cotton effect $[\alpha]_{307}$ + 195° (peak) , we are assigning the 3β-configuration to the α-acetoxyacetyl side chain (stereoformula XVI).



XII

XIII 5α-H
XIV 5β-H



XV

XVI

It is interesting to note that during the oxidation of XII, the bulkier substituent at C_3 assumes the more stable equatorial conformation, but the catalytic hydrogenation of IV leads to a nearly equal mixture of 3α- and 3β- derivatives.

Further work with steroid ketones and diverse phosphonate esters is in progress.

We are thankful to The Upjohn Company for generous gifts of steroids and to E. Rzucidlo (9) for the O.R.D. spectra. This work was supported in part by a grant (CA-05079) from the National Cancer Institute of the U. S. Public Health Service.

REFERENCES

(1) Similar results have been reported for other cyclohexanone systems, for example, see G. Fodor and I. Tömösközi, Tetrahedron Letters 579 (1961); S. Trippett and D. M. Walker, J. Chem. Soc. 1266 (1961).

(2) W. S. Wadsworth and W. D. Emmons, J. Am. Chem. Soc. 83, 1733 (1961).

(3) All new compounds were characterized by satisfactory elemental analysis and by I.R., U.V., and N.M.R. spectra.

(4) N. A. Milas and C. P. Priesling, J. Am. Chem. Soc. 80, 2189 (1958).

(5) F. Sondheimer and R. Mechoulam, J. Am. Chem. Soc. 79, 5029 (1957).

(6) C. Djerassi and W. Closson, J. Am. Chem. Soc. 78, 3761 (1956).

(7) A. H. Nathan, B. J. Magerlein and J. A. Hogg, J. Org. Chem., 24, 1517 (1959).

(8) M. Dvolaitzky, H. B. Kagan and I. Jacques, Bull. soc. chim. France 598 (1961).

(9) National Science Foundation Undergraduate Research Participant.