Tetrahedron Letters No.2, pp. 219-222, 1966. Pergamon Press Ltd.
Printed in Great Britain.

STEREOSPECIFIC CARBONYL-OLEFINATION ON 3-KETOSTEROIDS WITH PHOSPHONATE CARBANION

H. Kaneko and M. Okazaki

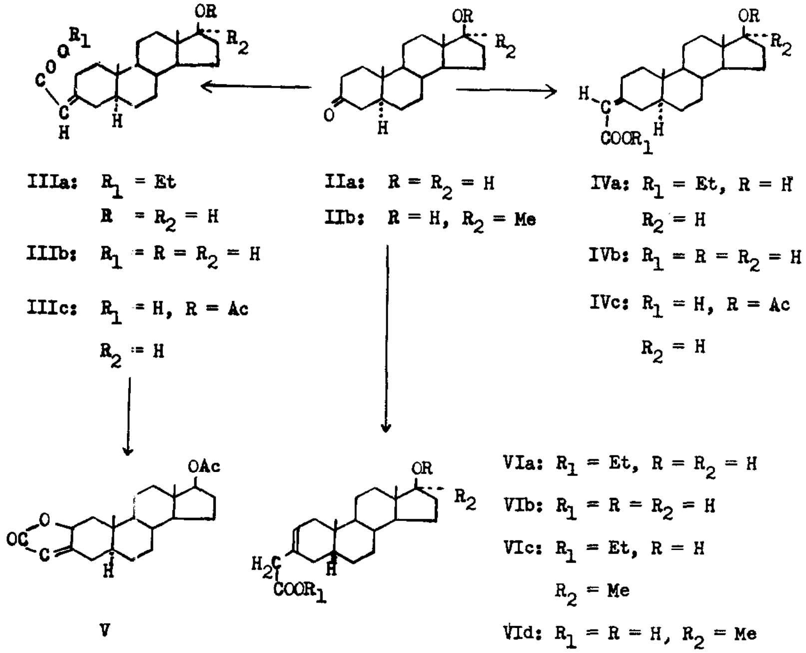
Research Laboratory, Dainippon Pharmaceutical Co., Ltd.

Fukushima-ku, Osaka, Japan

(Received 18 November 1965)

In an earlier publication (1), the Wittig reaction was assumed to be a stereo-unselective carbonyl olefination. Recently Bergelson and Shemyakin (2) have pointed out the possibility of controlling the steric course in the reaction by appropriate selection of the environmental conditions and the structure of the reactants. The olefination by means of the phosphonate carbanion modification of Wittig reaction, on the other hand, has been reported to furnish a great preponderance of trans olefin (3). There seems to be a considerable difference in stereospecificity between phosphonate carbanions and phosphorous ylids.

The stereochemistry of the Wittig reaction in the steroid field does not appear to have been studied (4, 5). We first explored the stereospecific olefination on steroid 3-ketones with phosphonate carbanion as outlined in the chart.



IIIa: R_1 = Et
R = R_2 = H
IIIb: R_1 = R = R_2 = H
IIIc: R_1 = H, R = Ac
R_2 = H

IIa: R = R_2 = H
IIb: R = H, R_2 = Me

IVa: R_1 = Et, R = H
R_2 = H
IVb: R_1 = R = R_2 = H
IVc: R_1 = H, R = Ac
R_2 = H

VIa: R_1 = Et, R = R_2 = H
VIb: R_1 = R = R_2 = H
VIc: R_1 = Et, R = H
R_2 = Me
VId: R_1 = R = H, R_2 = Me

The reaction of dihydrotestosterone (II a) with diethylethoxycarbonylmethylphosphonate (I) in an aprotic solvent e.g. glyme, dimethylformamide and benzene in the presence of NaH (equimol. to I) at room temperature exclusively afforded trans-3-ethoxycarbonylmethylene-5α-androstane-17β-ol(6)(III a ; m.p. 182-184°; λ_{max} 226 mμ (ε, 18,700); $[\alpha]_D$=+76°; 1700cm^{-1} (conjugated ester), 1642cm^{-1} (c=c); 4.35τ(c=c$\underline{H}$-)), whereas addition of t-BuoK as Lewis base to the reaction resulted in preponderance of the cis-isomer (IVa ; m.p. 82-84°; λ_{max} 226 mμ (ε, 15, 600); $[\alpha]_D$-57°; 1697cm^{-1} (conjugated ester), 1640cm^{-1} (c=c); 4.41τ(c=c$\underline{H}$-)).

It is noteworthy that the *cis*-isomer (IVa) was also obtained from a mixed solution of IIa and BF_3-etherate (as Lewis acid) when treated with I in the presence of NaH. The *cis*-*trans* ratio in the product was determined by gas chromatography.

A decision between the structures IIIa and IVa for *trans* and *cis* isomers was not possible on the basis of I.R. and N. M. R. spectra. On hydrolysis with methanolic KOH, IIIa and IVa gave 3-ylideneacetic acids (IIIb and IVb), respectively. *Trans* configuration of IIIa as shown in the chart was proved by the fact that the acetate of IIIb (IIIc ; m.p. 227-9°; $1730cm^{-1}$ (17-OAc), $1680cm^{-1}$ (-COOH) and $1633cm^{-1}$ (c=c)) was converted to the γ-lactone (V; m.p. 186-8°; λ max 217 mμ (14,400); $1750cm^{-1}$ (α,β-unsaturated γ-lactone), $1729cm^{-1}$ (17-OAc) and $1643cm^{-1}$ (c=c)) on treatment with SeO_2 in acetic anhydride at room temperature, whereas the acetate IVc (m.p. 157-60°; $1730cm^{-1}$ (OAc), $1678cm^{-1}$ (-COOH) and $1633cm^{-1}$ (c=c)) did not form a lactone on similar treatment.

It is further interesting to note that the reaction of IIa with I in monoglyme in the presence of NaH (two moles to I) at 80° afforded Δ^2-androstene-3-yl-acetate (VIa ; m.p. 95-8°; p-nitrobenzoate; m.p. 154-156°; $1720cm^{-1}$ (unconjugated ester); 7.07τ(singlet,-CH_2-) and 4.55τ (multiplet, C-2 proton)) in quantitative yield, which on hydrolysis with methanolic KOH yielded Δ^2-androstene-3-yl-acetic acid (VIb; m.p. 228-30°; $1698cm^{-1}$ (-COOH)). Using a similar reaction, 17α-methyl derivatives (VIc and VId) were also obtained from 17α-methyldihydrotestosterone (IIb).

Since exo-conjugated ester IIIa or IVa was not isomerized to VIa by treatment with acid (7), alkali or NaH in boiling solution, double bond migration from α,β-exo to β,γ-endo apparently does not occur during the course of the Wittig reaction, although the reaction may proceed via an alternative mechanism.

Acknowledgment — We wish to thank Dr. S. Ose, Dr. H. Takamatsu and Dr. S. Umemoto for their interest and many helpful discussions throughout the course of this work.

References

1. (a) S. Trippett, Advances in Organic Chemistry Vol.1, p83, N.Y. (1960).
   (b) U. Schoellkopf, Angew. Chem., **71**, 260 (1959).
2. L. D. Bergelson and M. M. Shemyakin, Pure & Appl. Chem. **9**, 271 (1964); Tetrahedron **19**, 149 (1963); Angew. Chem., **76**, 113 (1964).
3. (a) D. H. Wadsworth, O. E. Shupp, E. J. Seus and J. A. Ford, J.Org.Chem., **30**, 680 (1965).
   (b) L. Horner, H. Hoffmann, H. Whippel and G. Klabre, Chem. Ber., **92**, 2499 (1959).
4. A. K. Bose and R. T. Dahill, J.Org.Chem., **30**, 505 (1965).
5. G. Drefahl, K. Ponsold and H. Schick, Chem.Ber., **98**, 604 (1965).
6. 3-Ethoxycarbonylmethylene-5α-androstene-17β-ol reported by A.K. Bose et.al (4), having m.p. 178-180°; $[\alpha]_D$ + 59; λmax 226 mμ (ε, 16, 100), might be impure IIIa contaminated by trace amounts of the cis isomer.
7. K. Irmscher, M. G. Kraft and K. Brueckner, J.Med.Chem., **7**, 345 (1964).