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STEROIDS. IV. THE WITTIG REACTION WITH CYCLIC α-HALOKETONES (1)

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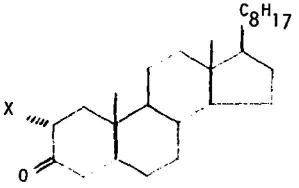
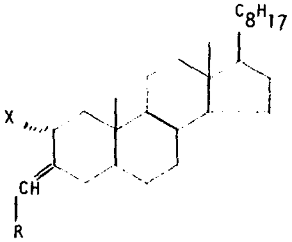
It has been reported (2) that acyclic α-bromoketones react with the phosphorane I to produce α,β-unsaturated γ-ketoesters of type II.

$$\underset{}{RCOCH_2Br} + \underset{\text{I}}{(C_6H_5)_3P{=}CHCO_2CH_3} \longrightarrow \underset{\text{II}}{RCOCH{=}CHCO_2CH_3}$$

We have found that the reaction of I with 2α-halocholestane-3-ones takes a different course (3,4). The ketones III, IV and V react with I in refluxing benzene in the absence of any condensing agent to afford the unsaturated haloesters VI, VII and VIII, respectively.

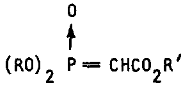


III, X = Cl
IV, X = Br
V, X = F



VI, X = Cl, R = CO_2CH_3
VII, X = Br, R = CO_2CH_3
VIII, X = F, R = CO_2CH_3
X, X = Cl, R = CN
XI, X = Br, R = CN

In each case only one product of unknown geometry around the double bond could be isolated. The configuration of the halogen atom in VI, VII and VIII was deduced to be equatorial on the basis of the NMR spectra from an examination of the spin-spin coupling pattern. After this phase of the work was completed, we became aware of a report (5) that some acyclic α-haloketone yield conjugated esters when allowed to react with the carbanion of a phosphonate ester (IX) under basic conditions.



$(RO)_2\overset{O}{\overset{\uparrow}{P}}{=}CHCO_2R'$

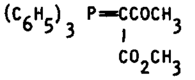
IX

$(C_6H_5)_3 P{=}CHR$

XII R = CN

XIII R = COC_6H_5

XIV R = $COCH_3$

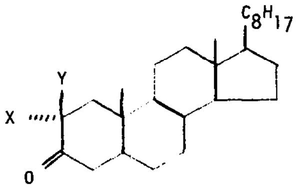


$(C_6H_5)_3 P{=}\underset{CO_2CH_3}{\underset{|}{C}}COCH_3$

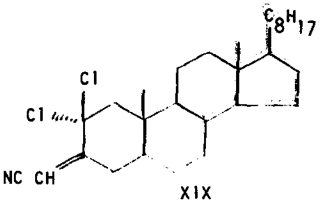
XV

We have extended our studies to the reaction of cyclic α-haloketones with other resonance-stabilized phosphoranes (6). The ketones III and IV react in boiling benzene with cyanomethylenetriphenylphosphorane (XII) to afford the conjugated nitriles X and XI, respectively. However, the resonance-stabilized ylides XIII, XIV and XV failed to undergo the Wittig reaction with the ketones III and IV under similar reaction conditions.

The phosphorane XII and 2,2-dichlorocholestane-3-one (XVI) produced the conjugated nitrile XIX in 44% yield but the ylide I did not react with XVI. The dihaloketones XVII, XVIII and 2α,4α-dibromocholestane-3-one failed to react with either I or XII.



XVI, X = Y = Cl
XVII,X = Cl; Y = Br
XVIII,X = Y = Br



XIX

It has been stated that electron-withdrawing substituents activate a carbonyl group for the Wittig reaction (7). The observation that cholestane-3-one does not react with I or XII but 2α-halocholestane-3-ones do, is in accord with this view; nevertheless, a decisive factor appears to be steric in nature, involving both the carbonyl moiety and the ylide. The lack of activity of the acyl phosphoranes may also be due in part to their tendency to exist in the betaine form.

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