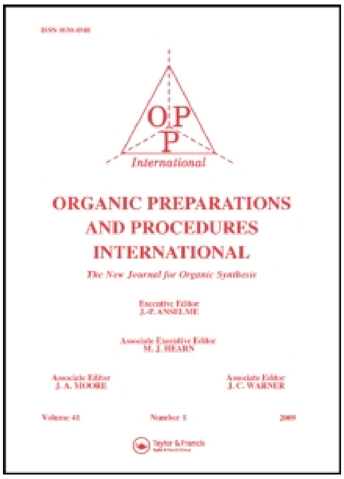

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A NEW SYNTHESIS OF Δ2-STEROIDS

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A NEW SYNTHESIS OF Δ2-STEROIDS

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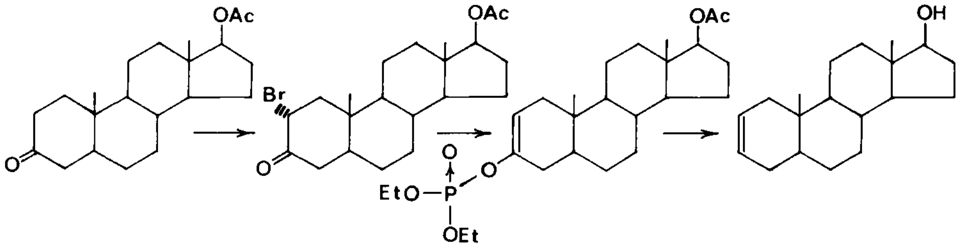
Δ2-Steroids have been prepared by dehydration of alcohols[1], eliminations of sulfonic esters[2], reduction of halohydrins[3] and of episulfides[4], Hofmann eliminations[5] and by dehydrohalogenation[6]. We now report a new method of preparation of Δ2-steroids which has been elaborated in this laboratory. The key intermediate is an enol diethyl phosphate which was reduced by sodium in liquid ammonia. According to Kenner and Williams[7] reduction of aryl diethyl phosphates under these conditions gave arenes.

Enol diethyl phosphates were conveniently prepared from α-bromoketones via a Perkow reaction and their reduction provides a new preparation of ethylenic compounds from ketones. This reaction may be general, although we did not study its scope in detail. It relies on the synthesis of the enol phosphate which is possible with α-bromocyclohexanones and α-bromoaliphatic ketones, but not with α-bromocyclopentanones[8].



Ireland and Pfister[9] had independently found that reduction (excess lithium/ethylamine/t-butylalcohol) of diethylenol phosphates gave the corresponding olefins in high yields and specificity. The desired phosphates were obtained by the action of diethylphosphorochloridate on enolate anions.

EXPERIMENTAL

5α-Androstan-17β-ol-3 one, 2α bromoacetate. To a 250 ml flask charged with 2 g (6 mmoles) of androstan-17β-ol-3-one acetate[10], dissolved in purified tetrahydrofuran[11] (30 ml), was added 2.26 g (6 mmoles) of phenyltrimethylammonium tribromide[12] and the solution stirred magnetically. After a few minutes, the orange solution became pale yellow and a white precipitate appeared. After 30 min., water was added until complete dissolution of the precipitate.* The solution was extracted with ether (4 x 20 ml) and the ethereal extracts dried over Na_2SO_4. Evaporation at room temperature under reduced pressure gave 2.3 g (95%)of the crude product which was recrystallized from a mixture of methanol-hexane** to yield 2.03 g (82 %) of white needles, m.p. 175-176°, lit.[13] mp 177-178° $[\alpha]_D^0 = +33°$ ($CHCl_3$, C = 1).

n m r ($CDCl_3$) :	49 cps (3H) 66 cps (3H)	Me 18 and 19	(two singlets)
	123 cps (3H)	Acetate	(singlet)

I.R. (CS_2) 1740 cm^{-1}

Anal. Calcd. for $C_{21}H_{31}BrO_3$: C 61.31, H 7.59, 0 11.66, Br 19.43

Found : C 61.43, H 7.55, 0 11.84, Br 19.22

Caution ! As triethylphosphite is toxic, this preparation should be carried out in a well-ventilated hood.

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* Alternatively, the desired product may be made to crystallize out by addition of excess water.

** Utilisation of chlorined solvents often gives dirty products coming probably from secondary reactions

Androst-2-ene-3, diethylphosphate 17β-acetate. A mixture of 25-30 ml of freshly distilled triethylphosphite and 2 g (4.8 mmoles) of 5α-androstan-17β -ol-3 one, 2α-bromo-acetate in a 50 ml round-bottomed flask was refluxed (158°- 160°C) for 3 hrs and then distilled under reduced pressure to remove the ethyl bromide and the excess triethylphosphite. The pale yellow residue crystallized on standing overnight in an ice-box. The precipitate (1.6-1.8 g, ∿76 %) was filtered, washed with 50 ml of pentane and the mother liquor concentrated under reduced pressure to yield a second crop (0.2-0.4 g). The combined product[14] on recrystallization from a mixture of pentane-methylene chloride, gave 1.9-2.0 g (∿87%) of white plates, mp 90°-91°, $[\alpha]_D^{20} = +38° \pm 1°$ ($CHCl_3$ C = 1).

n.m.r. ($CDCl_3$) :	48 cps	(6H)	CH_3 18 and 19 (singlet)
	123 cps	(3H)	(singlet) acetate
	250 cps	(4H)	(Two overlapping quartets) $(CH_3\text{-}\underline{CH_2}\text{-}O)_2$
	80 cps	(6H)	(Two overlapping triplets) $(\underline{CH_3}\text{-}CH_2\text{-}O)_2$
	325 cps	(1H)	H of double bond) (singlet)

I.R. (CS_2) 1745 cm^{-1}, 1690 cm^{-1}, 1250 cm^{-1}, 1160 cm^{-1}, 1050 cm^{-1}

Anal. Calcd. for $C_{25}H_{41}O_6P$: C 64.08, H 8.82, P. 6.61
Found : C 63.90, H 9.03, P. 6.74

Androst-2-en-17β-ol. A dry 250 ml three-necked round-bottomed flask was fitted with a mechanical stirrer, an ammonia inlet tube and a Dry-Ice condenser equipped with a drying tube. It was then cooled in a Dry-Ice and acetone bath and the condenser was filled with the same mixture. Ammonia gas, after being passed through a flask containing pellets of KOH was condensed in the reaction vessel until about 100 ml were obtained. The ammonia inlet was then replaced with a stopper. Then 2.5 g of lithium[15] were introduced over 30 min. A blue, stable solution was thus obtained. A solution of 3 g of the crude enol phosphate in 25 ml of dry tetrahydrofuran[11] and 25 ml of dry t-butylalcohol[16] was then introduced by a dropping funnel over 30 min. The cooled mixture was stirred for 3 hrs. Methanol was then added dropwise until complete decoloration. The condenser and the cooling bath were removed and the ammonia allowed to evaporate overnight (in the hood). The white solid residue was triturated in 250 ml of ether, washed with a saturated solution of sodium bicarbonate (3 x 30 ml), with 20 ml of sodium hydroxyde 1 N and with distilled water (3 x 30 ml). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to give a solid 1.5 g (85 %). Recrystallization from methanol yielded 1.1. g (64 %) of androst-2-en-17β-ol, mp 163° - 164° $[\alpha]_D^{20}$ = + 57°± 4° ($CHCl_3$) (C = 1).

n m r ($CDCl_3$) : 44-45 cps (6H) Me 18 and 19
215 cps (1H) C - 17
333 cps (2H) H of double bond

I.R. (CS_2) 3020 cm^{-1}, 1660 cm^{-1}, 3600 cm^{-1}

Anal. Calcd. for $C_{19}H_{30}O$: C 83.15, H 11.02, O 5.83
Found : C 82.95, H 11.31, O 6.39

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10. Androstan-17β-ol-3-one acetate is prepared by refluxing

commercial dihydrotestosterone in an excess of acetic anhydride during 2 hours; yield: 95%.

11. The tetrahydrofuran is dried on KOH, then refluxed on Na under nitrogen and distilled.

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14. The crude product may be used directly in the next step. For example, the crude product of the Perkow reaction on cholestanone gives, after elimination of the excess triethylphosphite, an oil which can be reduced without further purification. Δ^2-cholestene is thus obtained in 64% yield from 2α bromo-cholestan-3-one.

15. A greater excess of lithium does not change the overall yield. The metal is hammered into thin foil and the pieces washed free of oil with petroleum ether and cut with scissors into chips.

16. The t-butyl alcohol is refluxed on Na and under nitrogen then distilled.

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