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# PHOSPHORUS CONTAINING STEROIDS

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**Abstract**—The dimethyl steroidalphosphonates **8**, **9**, **10**, **11**, **12**, **13**, **25**, **27**, **33**, **34** and **35** were prepared and characterized. A configuration was assigned to the first five compounds listed, on the basis of the Cotton Effects exhibited by lactone **11**. The order of steps in the conversion of **26** to **27** was elucidated as **6** → **28** → **30** → **32** → **27**. Attempts to convert some of the compounds reported herein to 4-phosphasteroids were unsuccessful. The etherification of alcohols by dimethyl phosphite under acid catalysis was noted.

SYNTHETIC heterocyclic steroids, and steroids bearing hereoatom substituents, have been the subject of sustained interest for almost two decades. The list of pharmacological properties they exhibit is most impressive, though the extent of practical medical application to date has been relatively disappointing. Nevertheless, the search has continued unabated. Most of the heterocyclic derivatives studied have had O or N as the ring heteroatom, though a fair number of such sulfur compounds have also been prepared. No steroids containing a phosphorus heterocycle have, as yet, been reported, although a few bearing a P atom bonded directly to the carbon skeleton are known.[2–4]

Herein we report on the chemistry of a number of novel A-seco- and 4-oxo steroidal phosphonates, on the intermediates utilized in their synthesis, and on attempts to convert some of these to 4-phosphasteroids.

A-Seco-4-nor-5-oxo-cholestan-3-oic acid[5] (**2**), obtained by periodate-permanganate oxidation of $\Delta^4$-3-cholestanone (**1**), served as a convenient starting point for our first series. Its methyl ester[5] (**3**) was converted to the ketal **4*** whose reduction with LAH yielded **5**. Hydrolysis of the latter in boiling 80% aqueous acetic acid† resulted in A-seco-4-nor-3-acetoxy-5-cholestanone[6] (**6**).

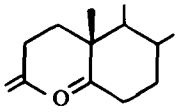
The attempted *base catalyzed* addition[7] of dimethyl phospite to the ketone group of **6** to yield A-seco-4-nor-3-acetoxy-5-dimethoxyphophinylcholestan-5-ol failed despite the variety of conditions explored (Experimental). We attribute this failure to an unfavourable equilibrium constant‡ for the addition. Indeed, the thermodynamic control of the reaction can be circumvented by the use of acid catalysis which converts the first formed hydroxyphosphonate irreversibly to secondary products. Thus, when **6** was heated (80°–90°) in dimethyl phosphite solution in the presence of a

* Notwithstanding the report[6] that the ketalization yields a mixture of products, the NMR of crude **4** obtained in this investigation showed it to be free of contaminants.

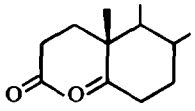
† The acetylation of the $C_3$—OH under these conditions deserves comment. We believe the acetylating species to be an acetylal formed on $C_4$ on acetolysis of the ketal.

‡ The rationalization of this unfavourable equilibrium as being due to steric hinderance at the position $\alpha$ to the carbonyl (Cf. Ref. 4) is incomplete. Thus it was found (see Experimental) that 2-methylcyclohexanone and 2-heptanone smoothly add dimethyl phospite under basic catalysis while methyl 6-oxoheptanoate, methyl A-seco-4-nor-5, 17-dioxoestran-3-oate[8] and **22** (*vide infra*) do not.

catalytic quantity of *p*-toluenesulfonic acid*, a neutral product bearing a dimethoxyphosphinyl group was obtained. However, its elemental analysis ($C_{28}H_{51}O_4P$) and spectral properties showed it to be 5-dimethoxyphosphinyl-4-oxa-cholestane (**8**) rather than the naïvely expected **7**. The IR (Experimental) had no bands in the O—H, C=O or C=C stretching regions, but did show strong absorptions attributable to the $(CH_3O)_2PO$ group. Its presence was corroborated by two doublets in the 60 MHz NMR spectrum ($\delta$ 3·72, d, $J_{PH}$ = 10·5 Hz 3H; $\delta$ 3·82, d, $J_{PH}$ = 10·5 Hz, 3H) indicating the diastereotopic nature of the two OMe groups. By elimination, the fourth oxygen must be in an ether linkage. Indeed the expected NMR signal ($\delta$ 4·08, m, 2H) assignable to a $\underline{CH_2}$—O—C group is found. Furthermore, the proposed structure, **8**, is confirmed by the mass spectrum. No molecular ion is observed, but the most abundant ion by far has *m/e* 373 corresponding to structure **a** and originates, predictably, from the $M^{+\cdot}$ by loss of $(CH_3O)_2PO$. The second most intense peak has a relative intensity of only 1·6% and is at *m/e* 357 (ion **a**–$CH_3$).



ion – **a**



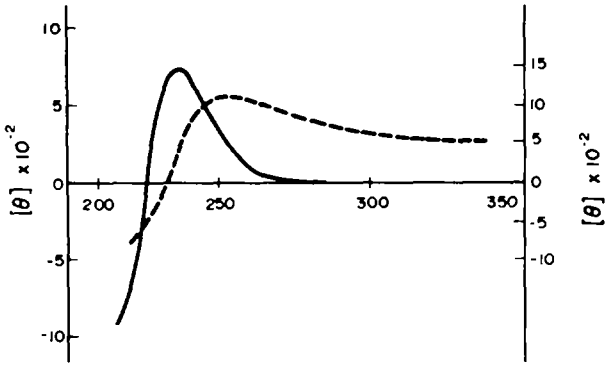
ion – **b**

Obviously, in the reaction of **6** deacetylation had occurred, freeing the $C_3OH$ for cyclization onto $C_5$. It is not known whether this cyclization precedes or follows attachment of the phosphono function. Reasonable mechanisms may be written for either alternative. The formation of the dimethyl phosphonate **8** is accompanied by that of varying amounts of the monomethyl ester **9** and the dibasic acid **10**. They are the result of hydrolysis and/or demethylation (i.e. Arbuzov reaction with dimethyl phosphite) or **8**. Both **9** and **10** were converted to **8** by diazomethane. Prolonged refluxing of **8** in dilute hydrochloric acid yielded **10**. The configuration of $C_5$ in **8**, **9**, and **10** is discussed below, in connection with **11**.

Following the above findings with **6**, we investigated the reaction of **3** with dimethyl phospite in the presence of acid. Higher temperatures (100–110°) and longer reaction periods were found necessary. Considerable quantities of starting material were recovered, and a mixture of products was obtained. Bicarbonate extraction and chromatography on silica permitted the isolation of three compounds, two crystalline and one oil. The IR spectrum of the principal product ($C_{28}H_{49}O_5P$; neutral; mp. 160°) indicated the absence of OH and olefinic groups but showed the usual bands for the $(CH_3O)_2PO$ grouping, and a CO stretching band at 1745 $cm^{-1}$ attributable to a 6-membered lactone ring. It was therefore assigned structure **11**. This assignment was supported by the NMR spectrum, which showed no lowfield absorptions other than the six protons of the dimethoxyphosphinyl group ($\delta$ 3·76, d, $J_{PH}$ = 10·5 Hz; $\delta$ 3·83, d, $J_{PH}$ = 10·5 Hz), and by the mass spectrum, which showed the molecular ion at *m/e* 496 (rel. int. 1%) and the base peak at *m/e* 387, corresponding to $[M-(CH_3O)_2PO]^+$, ion **b**. The further fragmentations of ion **b** involved the characteristic breakdown of

* The addition of p-toluenesulfonic acid was unnecessary if undistilled commercial (Fluka) dimethyl phospite was used. The acid catalysis may be necessary for the cyclization step only. Cholestanone gave 3-hydroxy-3-dimethoxyphosphinylcholestane on heating in purified dimethyl phosphite in the absence of either added acidic or basic catalyst (*cf* ref. 7).

the sidechain and ring D. Structure **11** was then confirmed by diborane ($NaBH_4$ + $BF_3$ *in situ*) reduction of the lactone to the ether, **8**. The action of methanolic HBr at 100° (sealed tube) on **11** reconverted it to **3**.




FIGS 1 and 2

The CD spectrum and ORD curve of **11** are shown in Figs 1 and 2, respectively. The former displays the presence of two bands, one of clearly non-Gaussian shape with a positive maximum at about 237 mμ and another with a negative maximum at ≤ 217 mμ. Such a double curve is characteristically obtained from the overlap of two bands with opposite sign separated by a few mμ.[9, 10] The two Cotton effects shown by the CD spectrum are merged in the ORD, yielding a curve (Fig 2) with a very broad peak around 252 mμ and a broad shallow trough around 220 mμ.

The appearance of two CD bands in the spectral region of the n→π* transition of certain δ-lactones has been previously noted[10, 15, 16] and convincingly explained on the basis of a conformational equilibrium between the boat (with $\lambda_{max} < 225$mμ) and half-chair (with $\lambda_{max} > 230$ mμ) forms.[11–14] We likewise interpret the CD spectrum of **11** as evidencing the existence of such a conformational equilibrium, which is displaced towards the half-chair form by the bulky dimethoxyphosphinyl group* on $C_5$†.[10, 15, 16] We thus conclude (Fig 1) that **11** with a half chair conformation of ring A exhibits a positive Cotton effect, while **11** in a boat conformation shows a negative one. These conclusions are compatible only with the assignment of a 5β configuration to **11**, as follows from the rules established by Klyne *et al.*,[17] by Wolf[15] and by Legrand and Bucourt,[18] relating the absolute chirality of δ-lactones with the sign of their Cotton effect.

The 5β configuration of **11** is further suggested by the close similarity of its ORD curve to that of 4-oxa-5β-cholestan-3-one and its marked dissimilarity to that of the 5α epimer.[17] Since the shape of these curves is greatly influenced by "background"

* In the absence of evidence to the contrary, we assume that the dimethoxyphosphinyl group does not affect the CD spectrum in an unpredictable manner.

† The two $C_5$ epimeric 4-oxacholestan-3-ones, which correspond to **11** with the $C_5$ substituent replaced by hydrogen, exist primarily in the boat form. They each show a dominant maximum below 225 mμ (pos. max. for 5α and neg. max for 5β) and only weak bands (of opposite sign respectively) at higher wavelength[15].

rotation, the similarity is in the customary manner, presumed, to be the result of identical $C_5$ configuration.

The diborane reduction of **11** to **8** indicates that compounds **8**, **9**, and **10** (as well as **12**, below) also have a 5β configuration.

The details of the mechanisms of formation of **8** and **11** are unknown. It is therefore not clear whether the formation of the 5β isomers is the result of kinetic or, as appears to us quite likely, thermodynamic control.

In the NMR spectrum, the $C_{19}$ Me group resonance of **11** appears at $\delta$ 1·20. Since the corresponding resonance of the 5β-H lactone is at $\delta$ 1·00,[19] the downfield shift of the $C_{19}$ hydrogens due to a 5β-dimethoxyphosphinyl group in this system is 0·20 ppm.

From among the acidic products of the reaction of **3**, we succeeded in isolating the crystalline phosphonic acid **12**. Its elemental analysis, spectral properties (Experimental), and conversion to **11** by diazomethane secure its structure. The appearance of the CO stretching band of **12** at 1730 $cm^{-1}$ lower than in **11** (both spectra in KBr), is presumably the result of H-bonding with the acidic hydrogens.

The third product, obtained as an oil in very low yield (<2%), accompanied **11** in the neutral fraction, and was separated from it by preparative TLC. Its mass spectrum ($M^{+\cdot}$, *m/e* 510), IR (neat; 1735, 1610, 1235, 1195, 1175, 1055, 1030, 825, 760 $cm^{-1}$), and NMR ($\delta$ 2·11, m, $-CH_2-COOCH_3$; $\delta$ 3·65, s, $COOCH_3$; $\delta$ 3·70, d, $J_{PH}$ = 10·5Hz, $(CH_3O)_2PO$; $\delta$ 6·81, d of m, $J_{cis\ PH}$ = 23Hz, PC=CH) establish the presence of the functional groups shown in **13** and support this proposed structure. Especially noteworthy is the fact that the protons of the two diastereotopic Me groups of the phosphonate substituent in **13** resonate at the same frequency, contrasting with the situation in **8** and **11**. This may be taken to confirm the larger distance between the dimethoxyphosphinyl group and an assymetric center in **13** than in **8** and **11**.

The acid catalyzed reaction of the keto-acid **2** with dimethyl phosphite leads to the same products as the keto-ester **3**, apparently by way of **3**. In fact, **2** was found to be quantitatively converted to **3** after 1 hr under the reaction conditions.

Of the various steroidal derivatives described above, **13** is undoubtedly the most suited as an intermediate on the route to a 4-phosphasteroid. Unfortunately the very small quantities in which it was obtained precluded, to date, its use in the above role. Sundry attempts to convert **11** to **13**, failed, as did also other efforts to achieve ring A opening of lactone **11** or of ether **8** while preserving the phosphorus substituent. Some of these efforts developed novel chemistry which will be the subject of a subsequent report.

Our next goal was an intermediate of type **14** (see Scheme-2), and its synthesis was based on the known A-seco-5-oxocholest-3-yne (**17**)[20]. The latter was prepared from cholest-4-en-3-one (**15**) via 4,5-epoxycholestan-3-one (**16**) by the method of Eschenmoser.[21] Sodium borohydride reduction of the CO group in (**17**) gave a mixture of the epimeric alcohols **18** and **19** in the ratio of 5 : 1 respectively, which was separated by careful chromatography on silica. The major product (**18**) was expected to be the epimer with the equatorial OH,[19] and this was corroborated by its NMR spectrum ($C_5$-H axial, $\delta$ 3·47, d of d, $J$ = 10·2Hz and 4·5Hz). In contrast, isomer **19** with axial OH shows the equatorial $C_5$-H resonance as a narrow triplet at lower field ($\delta$ 3·57, t, $J$ = 3Hz) with equal coupling constants to both $C_6$ hydrogens.

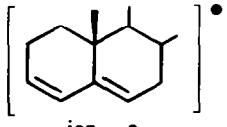
The hydroxyacetylenes **18** and **19** were converted to their respective acetates, **20** and **21**, and then to the methyl ketones **22** and **23** by the action of aqueous trifluoracetic acid in the presence of mercuric sulfate.

The reaction of **22** with dimethyl phosphite under base catalysis lead only to the recovery of starting material, whereas under acid catalysis a complex mixture (rather than **24**; compare with behaviour of **6**) was obtained. From this mixture only, a single chromatographically homogeneous material (**25**) could be isolated as an oil in low yield (< 10%) by preparative TLC. The following spectral data support the proposed structure **25**. The IR spectrum shows the absence of an OH but the presence of an aliphatic ester ($\nu_{max}$ 1735 $cm^{-1}$) and a phosphonate group ($\nu_{max}$ 1240, 1190 $cm^{-1}$). The NMR spectrum has characteristic absorptions at $\delta$ 2·02 (s, $CH_3COOC$), at $\delta$ 3·33, (s, $CH_3O$), at $\delta$ 3·76 (d, $J$ = 10·5Hz,$(CH_3O)_2(PO)$, and at $\delta$ 4·69 (double d, $J$ = 11 and 4Hz, $C_5$—H). Again, (*cf* **13** above) the resonance of the two Me groups of the phosphonate function at the same frequency is significant. Two epimers about $C_3$ of **25** are possible. We have no evidence on which to base an assignment of stereochemistry of our product, and indeed it may be a mixture of the two diastereomers.

The precursor of the 3-methoxy-3-dimethoxyphosphinyl ensemble in **25** is undoubtedly a 3-hydroxy-3-dimethoxyphosphinyl grouping. The formation of **25** therefore bears witness to the previously unknown efficacy of the reaction conditions as an etherification method. Indeed, control experiments showed that the acid catalyzed reaction of alcohols with dimethyl phosphite gives methyl ethers in good yields. The details and scope of this method will be reported elsewhere.

Another keto-steroid whose reaction with dimethyl phosphite was studied, was A-seco-3,5-cholestandione (**26**). This compound has been prepared previously[22] by the reaction of methylmagnesium iodide on 4-oxacholest-5-en-3-one, but was in the present instance obtained by the action of aqueous trifluoracetic acid and mercuric sulfate on **17**.

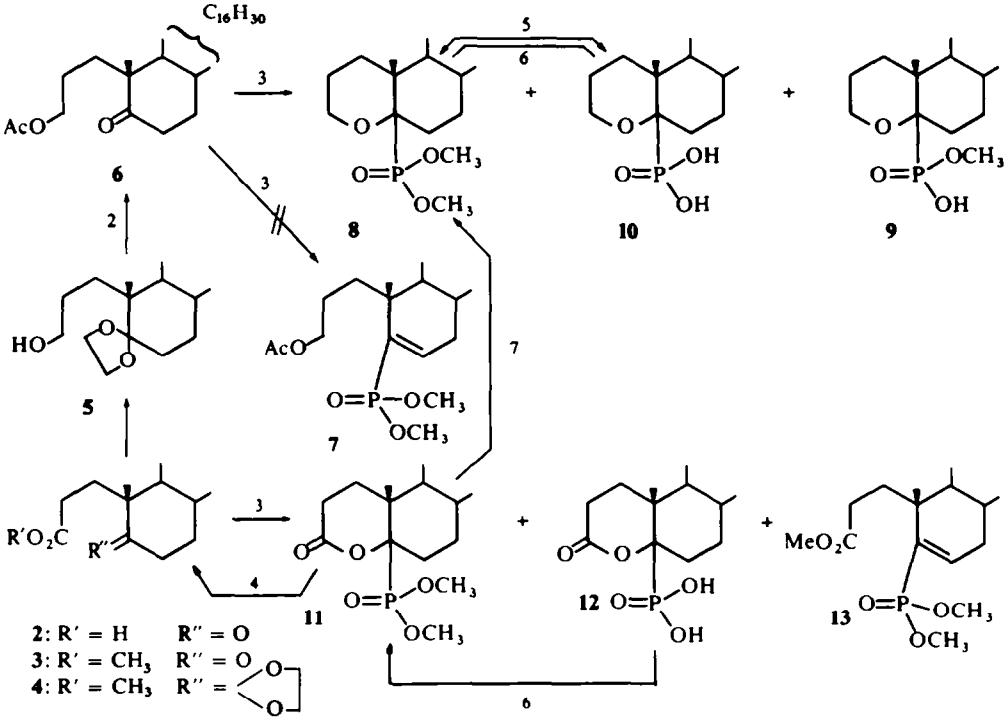
In keeping with the behaviour of **6** and **22**, **26** did not add a dimethoxyphosphinyl group under basic catalysis. Rather, recovered starting material was accompanied by smaller amounts of **15**, the product of an intramolecular aldol condensation and dehydration. Under acid catalysis on the other hand, the intramolecular aldol condensation was followed by dimethyl phosphite addition and dehydration, converting **26** to **27**. (For proof of the order of the last two steps, see below). The structure of **27** is securely based on its elemental analysis, spectral properties and chemical interconversions. Its UV spectrum has $\lambda_{max}^{EtOH}$ 251 mμ (ε,18,900) corresponding to a conjugated heteroannular diene*. The IR spectrum showed the usual bands of the $(CH_3O)_2PO$ group and two C—C double bonds ($\nu_{max}$ 1630, 1595 $cm^{-1}$) but was otherwise unexceptional. The NMR spectrum confirms the presence of the $(CH_3O)_2PO$ function by a doublet at $\delta$ 3·86 ($J$ = 10·5Hz,6H) and the diene function by two peaks in the



ion – c

* A calculation based on Woodward's rules for the UV of dienes shows that the increment due to the dimethoxyphosphinyl group in **27** is +18 mμ.

vinyl hydrogen region, one at $\delta$ 6·80 (d, $J_{PH}$ = 21Hz, 1H) and one at $\delta$ 5·75 (m, 1H). The former peak corresponds to the $C_4$-H, situated *cis* to the vinylphosphonate group, and the latter to the $C_6$—H. In the mass spectrum the molecular ion at *m/e* 476 is the most abundant, with the fragment ion **c**$[M-(CH_3O)_2PO]^+$, at *m/e* 367 having a rel. int. of only 20%. This contrasts sharply with our findings in the case of **8** and **11** where the $M^{+\cdot}$ peaks were not observed or were of negligible heights, while the peaks for ions **a** and **b**, both $[M-(CH_3O)_2PO]^+$, were the dominant ones in the spectra.

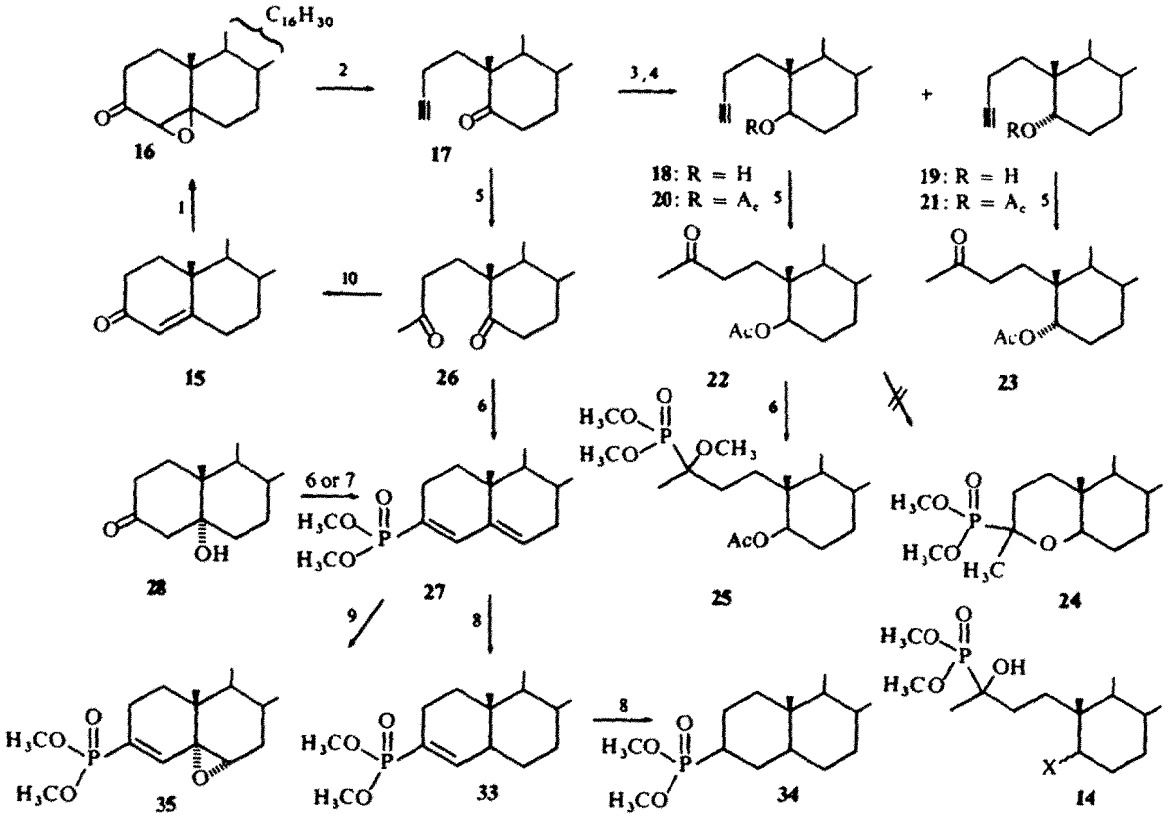



*Reagents*: 1. LAH; 2. 80% $CH_3CO_2H$; 3. $HOP(OCH_3)_2$, pTsOH; 4. HBr-$CH_3OH$; 5. HCl, $H_2O$-EtOH; 6. $CH_2N_2$; 7. $NaBH_4$, $BF_3$-eth., diglyme.

SCHEME 1

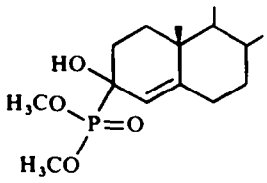
The differing behaviour is, however, easily comprehensible. The fragment ions **a** and **b** derived from **8** and **11** respectively, are stabilized cations, whereas **c** derived from **27** is formally a high energy vinyl carbonium ion.

The conversion of **26** to **27** proceeds via the sequence **26** → **28** → **30** → **27**, as is shown by the following findings. The reaction of independently prepared **28** with dimethyl phosphite under acid catalysis gave **27** in good yield, while basic catalysis produced a mixture of **30** and **32**, identified by NMR. Chromatography of this mixture on acidic silica gel converted it to **27**. The alternative, or possibly parallel, sequence **26** → **28** → **15** (or **31**) → **29** → **27** was eliminated by showing that neither **15** nor **31** yield **27** under the reaction conditions used (though **31** is isomerized to **15**).




*Reagents*: 1. $H_2O_2$, $OH^{\ominus}$; 2. $TsNHNH_2$; 3. $NaBH_4$; 4. $Ac_2O$-Pyr. 5. $H_2O$-$CH_3CO_2Hg^+$; 6. $HOP(OCH_3)_2$, p-TsoH, $\Delta$; 7. $HOP(OCH_3)_2$, NaH; 8. $H_2$, Pd-C; 9. *m*-chloroperbenzoic acid, $CH_2Cl_2$. 10. Base, or $Al_2O_3$ column.

SCHEME 2

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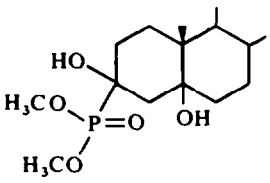


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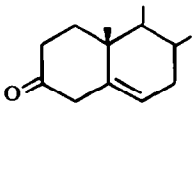


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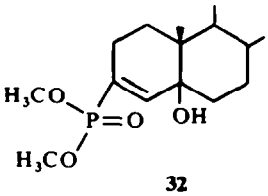


32

The catalytic hydrogenation of **27** over platinum proceeds in two separable stages. After 2 hr essentially only the 5,6-double bond is saturated. The reaction is only stereoselective, yielding mainly 3-dimethoxyphosphinyl-5α-cholest-3-ene(**33**)[4] accompanied by small amounts of the 5β isomer. The two isomers are distinguishable by their NMR spectra. The $C_{19}$ Me group of **33** absorbs at $\delta$ 0·74 and its $C_4$ hydrogen at $\delta$ 6·43 (d, $J_{PH}$ = 21·5Hz) while the 5β isomer shows the corresponding absorptions at $\delta$ 0·69 and at $\delta$ 6·50 (d, $J_{PH}$ = 21·5Hz). Continuation of the catalytic hydrogenation for 24 hr results in the production of a mixture of fully saturated isomers. Repeated recrystallization from methanol permits the isolation of pure 3β-dimethoxyphosphinyl-5α-cholestane(**34**), identical in all respects with the compound reported in the literature.[4]

In the reaction of **27** with the *m*-chloroperbenzoic acid it is the 5,6-double bond, remote from the phosphonate substituent, which is attacked, and a mixture of the 5,6α-(**35**) and 5,6β-(**36**) epoxides is obtained. We succeeded in purifying only the major component, presumably the 5,6α isomer, whose NMR spectrum showed the $C_6$—$H_4$ (epoxide H) resonance at $\delta$ 3·10 (d, $J$ = 2·5Hz) and the $C_4$—H (vinyl H) resonance shifted upfield to $\delta$ 5·88 (d, $J_{PH}$ = 21·5Hz). The corresponding values for the minor component, to which we assign the 5,6β configuration are $C_6$—H, at $\delta$ 3·10 (broad s) and $C_4$—H at $\delta$ 6·17 (d, $J_{PH}$ = 21·5Hz). Attempts to further convert compounds prepared in Scheme 2 to 4-phosphasteroids were unsuccessful.

## EXPERIMENTAL

M.ps were taken on a Unimelt Thomas and Hoover's Capillary m.p. apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer Infracord model 337 spectrophotometer, UV spectra were recorded on a Perkin–Elmer 137 UV spectrophotometer. NMR spectra were taken on a Varian HA-100 spectrometer on 5–10%, solns in $CDCl_3$ containing TMS as an internal standard, chemical shifts are quoted in units of $\delta$. Mass spectra were taken with a Hitachi Perkin–Elmer RMU 6 instrument, the samples being introduced directly into the ion source through a vacuum-lock, electron energy 70 ev, electron current 20μA. CD and ORD spectra were taken on a Cary 60 spectropolarimeter in MeOH soln. Optical Rotations were determined on Perkin–Elmer Model 141 automatic polarimeter in $CHCl_3$ soln. Unless stated otherwise, column chromatography was carried out on silica gel (7734-Merck) and TLC on silica gel-G (7731-Merck).

*Attempted base catalytic addition of dimethylphosphite to various ketones.* Each one of the tested ketones underwent the reaction with dimethylphosphite (Fluka) by dissolving the compound in the reagent only or in soln of benzene, and addition of NaH, NaOMe or $NEt_3$ at room temp or 60°–80°, then leaving the mixture aside for 24–48 hr. After which the mixture was poured into water, extracted with ether, then washed several times with water, 5% $NaHCO_3$, dried ($Na_2SO_4$) and the solvent removed under vacuum.

*Methyl A-seco-4-nor-5,17-dioxoestran-3-oate.* Methyl A-seco-4-nor-17-hydroxy-5-oxo-estran-3-oate[8] (100 mg) was oxidised with Jones reagent for 2 hr at 0–5°. Following work up, the corresponding ketone

(50 mg) was obtained as an oil; $\nu_{max}^{CHCl_3}$ 1740, 1710, 1240, 1195, 1165, 1080, 1040 $cm^{-1}$; NMR 0·95 (s, 18-H); 3·63 (s, $CO_2CH_3$). (Found: M⁺306; $C_{18}H_{26}O_4$ requires: M⁺306).

*2-Hydroxy-2-dimethylphosphinylheptane.* A mixture of 2-heptanone (4 gr) and dimethylphosphite (4·5 gr) to which a catalylic amount of NaH had been added, was left at r.t. overnight. The crude adduct was dissolved in ether, and the etheral solution washed several times with water then dried ($Na_2SO_4$) and evaporated. The crude oil was distilled at low-pressure, b.p. 115°–120°/1mm. The product (3 gr) solidified after distillation m.p. 35°–40°; $\nu_{max}^{neat}$ 3300, 2920, 1470, 1370, 1230, 1180, 1050, 950, 870, 830, 780 $cm^{-1}$; NMR 0·86 (t, $J$ = 7Hz, $CH_3-CH_2-$), 1·30 (s, $(-CH_2-)_n$), 1·46 (s, $CH_3-C<$), 3·40 (broad s, OH), 3·77 (d, $J$ = 10·5Hz, $P(OCH_3)_2$). (Found: C, 48·19; H, 9·36; P, 13·52; $C_9H_{21}PO_4$ requires: C, 48·21; H, 9·44; P, 13·81%).

*Dimethyl-1-hydroxy-2-methylcyclohexylphosphonate.* The compound was obtained from 2-methylcyclohexane following the same procedure described above, m.p. 116°–117°; $\nu_{max}^{KBr}$ 3270, 2910–2830, 1220, 1030 $cm^{-1}$; NMR 1·03(d, $J$ = 7Hz, $CH_3$—), 2·85 (d, $J_{PH}$ = 4Hz, OH), 3·75 (d, $J$ = 11Hz, $P(OCH_3)_2$). (Found: C, 48·64; H, 8·62; H, 8·62; P, 13·74; $C_9H_{17}O_4P$ required: C, 48·64; H, 8·62; P, 13·94%).

*Compounds* **8**, **9** *and* **10**. Compound **6** (1 gr) suspended in dimethylphosphite (5 ml) in the presence of a trace of p-TsOH was heated under $N_2$ atm in an oil bath at 80°–90° for 24–48 hr, (the reaction was stopped when according to the IR spectrum, most of the starting material reacted). Alternatively, *p*-toluensulfonic acid was omitted and undistilled dimethylphosphite was used. The crude product was dissolved in ether, the etheral soln washed several times with water then extracted with a 5%-$NaHCO_3$ aq and washed once again with water. Following evaporation of solvent, the dried residue was chromatographed on a silica gel column yielding **8** (400 mg) m.p. 116–117° (hexane); $[\alpha]_{546}$ + 44°; $[\alpha]_{365}$ + 112° ($CHCl_3$, C, 0·36); $\nu_{max}^{KBr}$ 1230, 1200, 1180, 1060, 1025, 820, 760 $cm^{-1}$; NMR 0·65 (s, 18-H), 1·10 (s, 19-H), 3·27 and 3·82 (two d, both $J_{PH}$ = 10·5Hz, $P(OCH_3)_2$), 4·08 (m, 3-H). (Found: C, 70·03; H, 10·72, P, 6·2; $C_{28}H_{51}O_4P$ requires: C, 69·65; H, 10·65; P, 6·4%).

Etheral extraction of the acidified bicarbonate soln yielded a mixture of **9** and **10** in varying percentages; **9** m.p. 214° $[\alpha]_{589}$ + 34°; $[\alpha]_{546}$ + 44°; $[\alpha]_{365}$ + 127° (c, 0·2); $\nu_{max}^{KBr}$ 3500–2400, 1220, 1210, 1175, 1050, 970, 790 775 $cm^{-1}$; NMR 0·65 (s, 18-H); 1·12 (s, 19-H); 3·74 (d, $J$ = 10·5Hz, $P(OCH_3)_2$); 4·08 (m, 3-H). Found: C, 69·57; H, 10·68; P, 6·7; $C_{27}H_{49}O_4P$ requires: C, 69·20; H, 10·54; P, 6·6%). Compound **10** is an amorphous substance decomposing above 220°, $\nu_{max}^{KBr}$ 3700–2100, 1180, 1070, 1020, 990, 920, 860 $cm^{-1}$; NMR 0·66 (s, 18-H); 1·14 (s, 19-H); 3·92 (m, 3-H).

Additional of etheral $CH_2N_2$ soln to **9** or **10** which were dissolved in MeOH-ether (1:9), yielded quantitatively **8**.

*Hydrolysis of compound* **8**. Compound **8** (100 mg) in 2%-ethanolic-HCl (15 ml) was refluxed for 48 hr (after 24 hr 1 ml of HCl-conc was added). Following workup compound **10** (30 mg) was obtained.

*Compounds* **11**, **12** *and* **13**. Compound **2** or **3** (1 gr) suspended in dimethylphosphite (5 ml) was heated, under $N_2$ atm at 100–110° in the presence of catalytic amounts of *p*-TsOH, for 24–48 hr (till the absorption at 1700 $cm^{-1}$, in the IR spectrum, almost disappeared). After work up as described for compound **6**, the crude material was chromatographed. Elution with petrol-ether; $CHCl_3$ (3:1) gave unreacted methylester **3** (400 mg), further elution with petrol-ether; $CHCl_3$ (2:1) yielded **11** (200 mg) m.p. 160° (hexane); $[\alpha]_{589}$ + 34°; $[\alpha]_{546}$ + 42°; $[\alpha]_{365}$ + 99° (c, 0·12); $\nu_{max}^{KBr}$ 1745, 1238, 1190, 1178, 1150, 1055, 1025, 980, 820, 775, 750 $cm^{-1}$; NMR 0·66 (s, 18-H); 1·20 (d, $J$ = 0·7Hz, 19-H); 2·52 (m, 2-H); 3·76 d and 3·83 d ($J$ = 10·5Hz ($P(OCH_3)_2$). (Found: M⁺496 C, 67·50; H, 10·07; P, 6·1; $C_{28}H_{49}O_5P$ requires: M⁺496·6 C, 67·71; H, 9·94 P, 6·2%); CD $[\theta]_{270}$ O; $[\theta]_{237}$ + 798; $[\theta]_{226}$ O; $[\theta]_{218}$ − 1020 (MeOH); ORD $[\phi]_{280}$ + 850°; $[\phi]_{252}$ + 1190°; $[\phi]_{232}$ O°; $[\phi]_{220}$ − 930° (MeOH, *c*, 0·037).

The third compound which was eluted with the same eluent was compound **13** (50 mg), an oil which could not be crystallized; $\nu_{max}^{neat}$ 1735, 1610, 1235, 1195, 1175, 1055, 1030, 825, 760 $cm^{-1}$; NMR 0·68 (s, 18-H); 1·16 (s, 19-H); 2·11 (m, 2-H); 3·65 (s, $CO_2CH_3$); 3·70 (d, $J$ = 10·5 Hz; $P(OCH_3)_2$) and 6·81 (d of m, $J_{PH}$ = 23 Hz, $>C=CH-$). (Found: M⁺510; $C_{29}H_{51}O_5P$ requires: M⁺510).

Etheral extraction of the acidified bicarbonate soln yielded, after evaporation, **12** m.p. 239° (hexane); $[\alpha]_{589}$ + 30°; $[\alpha]_{546}$ + 38°; $[\alpha]_{365}$ + 109° (*c*, 0·07); $\nu_{max}^{KBr}$ 3600–2100, 1730, 1260, 1230, 1180, 1150, 1045, 980 $cm^{-1}$; NMR 0·66 (s, 18-H) and 1·20 (s, 19-H). (Found: C, 66·68; H, 9·75; P, 6·7; $C_{26}H_{45}O_5P$ requires: C, 66·64; H, 9·48; P, 6·6%).

*Conversion of compound* **11** *to compound* **8**. To a soln of **9** (100 mg) and $NaBH_4$ (100 mg) in diglyme (2 ml),

$BF_3$-etherate (0·7 ml) was added. After 2 hr most of the solvent was removed under reduced pressure, MeOH (5 ml) was added and the soln was refluxed for 1 hr. After evaporation of solvent, the residue was dissolved in ether, washed with water, $NaHCO_3$, then dried and the ether evaporated. Upon chromatography, elution with petrol-ether; $CHCl_3$ (8:2) **8** (50 mg) was obtained.

*Conversion of compound* **11** *to compound* **3**. Compound **11** (200 mg) in a saturated soln of HBr in MeOH (5 ml), was heated in a sealed tube at 100° for 24 hr. The cooled soln was poured into water, then extracted with ether. The combined ethereal soln was washed with 5%-$NaHCO_3$, $H_2O$, dried ($Na_2SO_4$), and evaporated leaving a residue which was then chromatographed on a neutral $Al_2O_3$-column yielding, upon elution with light pet-$CHCl_3$ (7:3) **3** (50 mg).

*5α and 5β-4-Oxa-cholestan-3-ones*. The two lactones were prepared from **2** by $NaBH_4$ reduction:[19] NMR 0·66 (s, 18-H); 0·93 (s, 19-H) and 3·94 (dd, $J$ = 5; 10·5 Hz, 5α-H) for the 5α isomer and 0·66 (s, 18-H); 1·00 (s, 19-H) an 4·12 (t, $J$ = 3Hz, 5β-H) for the 5β isomer.

*Compounds* **18** *and* **19**. Compound **17** was obtained according to Eschenmoser's method,[21] from **16**. $NaBH_4$ (250 mg) was added over a period of 5 min to a methanolic soln (0–5°; 40 ml) of **17** (2 gr), and stirred for 2 hr. The excess reagent was destroyed with a few drops of AcOH, most of the solvent was removed under vacuum and then ether was added. The soln was washed with water, dried ($Na_2SO_4$) and evaporated. Chromatography on silica gel (elution with light pet-$CHCl_3$ 1:1) gave the two epimeric alcohols: **18** (800 mg) was an oil $\nu_{max}^{CHCl_3}$ 3450, 3280, 2105 $cm^{-1}$; NMR 0·64 (s, 18-H); 0·83 (s, 19-H); 1·93 (t, $J$=2·5 Hz) and 2·10 m ($-CH_2-C\equiv CH$); 3·47 (dd, $J$ = 4·5, 10·2 Hz, 5-H). (Found $M^{\oplus}$386; $C_{27}H_{46}O$ requires: $M^{\oplus}$386). Compound **19** (160 mg) m.p. 91–3° (hexane). $[\alpha]_{589}$ + 32°; $[\alpha]_{546}$ + 39°; $[\alpha]_{365}$ + 107° (*c*, 0·24), $\nu_{max}^{CHCl_3}$ 3450, 3280, 2105 $cm^{-1}$; NMR 0·64 (s, 18-H); 0·85 (s, 19-H); 2·18 (doublet. $J$ = 2·5; 7 Hz) and 1·94 (t, $J$ = 2·5 Hz) ($-CH_2-C\equiv CH$); 3·57 (t, $J$ = 3 Hz, 5-H). (Found: C, 83·95; H, 12·05; $M^{\oplus}$386: $C_{27}H_{46}O$ requires: C, 83·87; H, 11·99%; $M^{\oplus}$386).

*Compounds* **20** *and* **21**. The acetates were prepared by the usual method of treating the alcohols with $Ac_2O$ in pyridine. Compound **20** m.p. 73°–75°, $\nu_{max}^{KBr}$ 3280, 2105, 1730, 1250 $cm^{-1}$; NMR 0·64 (s, 18-H); 0·82 (s, 19-H); 1·92 (t, $J$ = 2·5, $\equiv CH$); 2·03 (s, $OCOCH_3$) and 4·64 (dd, $J$ = 11; 4 Hz, 5-H). (Found: C, 81·35; H, 11·37; $M^{\oplus}$428; $C_{29}H_{48}O_2$ requires: C, 81·25; H, 11·29%, $M^{\oplus}$428). Compound **21** m.p. 139° (hexane); $[\alpha]_{589}$ + 52°; $[\alpha]_{546}$ + 62°; $[\alpha]_{365}$ + 163° (*c*, 0·17). $\nu_{max}^{CHCl_3}$ 3280, 2105, 1730, 1250 $cm^{-1}$; NMR 0·64 (s, 18-H); 0·95 (s, 19-H); 1·92 (t, $J$ = 2·2 Hz) and 2·08 m ($-CH_2-C\equiv CH$); 2·05 (s, $OCOCH_3$) and 4·66 (t, $J$ = 3 Hz, 5-H). (Found: C, 80·97; H, 11·40; $M^{\oplus}$428).

*Compounds* **22** *and* **23**. To compound **20** (500 mg) in $CF_3CO_2H$ (2 ml), water (0·5 ml) containing a trace of $HgSO_4$ was slowly added. After 1 hr at r.t. more water was added and the compound was extracted with ether, washed with 5%-$NaHCO_3$ soln, water, dried ($Na_2SO_4$) and the solvent was removed. The residue was chromatographed on a florisil column yielding **22** (250 mg) which solidified, m.p. 125°–135°, $[\alpha]_{589}$ − 3°; $[\alpha]_{546}$ − 3°; $[\alpha]_{365}$ − 1°; ($CHCl_3$, c, 0·27) $\nu_{max}^{neat}$ 1715, 1450, 1370, 1250 $cm^{-1}$; NMR 0·64 (s, 18-H); 0·93 (s, 19-H); 2·02 (s, $OCOCH_3$); 2·10 (s, $-COCH_3$); 2·28 (m, 2-H) and 4·66 (dd, $J$ = 4, 11 Hz, 5-H). (Found: $M^{\oplus}$446; $C_{29}H_{50}O_3$ requires: $M^{\oplus}$446). Compound **23** was obtained by the same method of preparation used for **22** by hydration of **21**, m.p. 150° (acetone-hexane); $[\alpha]_{589}$ + 49°; $[\alpha]_{546}$ + 58°; $[\alpha]_{365}$ + 145° (*c*, 0·22) $\nu_{max}^{KBr}$ 1720, 1450, 1370, 1250 $cm^{-1}$; NMR 0·66 (s, 18-H); 0·87 (s, 19-H); 2·02 (s, $OCOCH_3$); 2·09 (s. $COCH_3$) and 4·68 (t. $J$ = 3 Hz, 5-H). (Found: $M^{\oplus}$446; C, 80·15; H, 11·32; $C_{29}H_{50}O_3$ requires C, 80·77; H, 11·28%, $M^{\oplus}$446).

*Compound* **25**. Compound **22** (250 mg) in dimethylphosphite (2 ml) in the presence of catalytic amounts of *p*-TsOH, was heated at 80–90° overnight under $N_2$ atm. The workup of the mixture was as described above, it was chromatographed on preparative TLC plates. Compound **25** (25 mg) was an oil which could not to be crystallized; NMR 0·65 (s, 18-H); 0·94 (s, 19-H); 2·02 (s, $OCOCH_3$); 3·33 (s, $OCH_3$); 3·76 (d, $J$ = 10·5 Hz, $P(OCH_3)_2$) and 4·69 (dd, $J$ = 4; 11 Hz, 5-H); $\nu_{max}^{CHCl_3}$ 1730, 1250, 1190, 1090, 1050, 1030 $cm^{-1}$. (Found: $M^{\oplus}$461; $C_{32}H_{59}PO_6$-$P(O)(OMe)_2$ requires: $M^{\oplus}$461.

*Compound* **26**. Compound **26** was obtained from **17**, by the method described above for **22** and **23**. The compound was an oil with the spectral data as found in the lit.[12]

*Compound* **27**. (a) Compound **26** (1 gr) suspended in dimethylphosphite (10 ml) in the presence of catalytic amounts of *p*-TsOH was heated overnight on an oil bath at 100–110° under $N_2$ atm. Following workup as described above **27** m.p. 134°–136° (hexane); $[\alpha]_{589}$ − 86°; $[\alpha]_{546}$ − 105°; $[\alpha]_{365}$ − 375° ($CHCl_3$, c, 0·34) was obtained, $\nu_{max}^{KBr}$ 1630, 1595, 1255, 1180, 1070, 1010, 845, 820, 790, 750 $cm^{-1}$; NMR 0·70 (s, 18-H); 0·91 (s, 19-H); 3·68 (d, $J$ = 10·5 Hz, $P(OCH_3)_2$); 6·80 (d, $J$ = 21 Hz, 4-H) and 5·75 (m, 6-H). (Found: C, 72·99; H, 13·29; P, 6·25; $M^{\oplus}$476; $C_{29}H_{49}O_3P$ requires: C, 73·07; H, 13·63; P, 6·49%, $M^{\oplus}$476).

(b) Compound **28** under the same conditions as described for **26** yielded **27**.

(c) To **28** (200 mg) dissolved in dimethylphosphite (10 ml) a trace of NaH was added and the mixture was left at r.t. overnight. After workup, a mixture of **30** and **32** was obtained as indicated by its NMR specturm which shows two doublets at 3·70 and 3·75 ($J$ = 10·5 Hz; $P(OCH_3)_2$ and 5·86 (d, $J$ = 22 Hz, 4-H). Prolonged chromatography on a silicagel column yielded **27** (50 mg).

*Compound* **33**. Compound **27** (100 mg) in abs EtOH (10 ml) was hydrogenated over 10% $PtO_2$ on charcoal at atmospheric pressure and r.t. for 2 hr. The product obtained following the workup was an inseparable mixture of the dihydro derivatives of **21**; NMR 0·66 (s, 18-H; and 6·43 (d, $J$ = 21·5 Hz, 4-H) for the 5α-isomer, and 0·66 (s, 18-H); 0·69 (s, 19-H) and 6·50 (d, $J$ = 21·5 Hz, 4-H) for the 5α-isomer.

*Compound* **34**. Lengthening the hydrogenation time of **27** to 24 hr yielded the saturated phosphonate **34** m.p. 108° (several crystallizations from MeOH). (Lit.[4] 108°–11°); NMR 0·65 (s, 18-H) 0·80 (s, 19-H) and 3·74 (d, $J$ = 11 Hz, $P(OCH_3)_2$). (Found: $M^{\oplus}$480, $C_{29}H_{53}O_3P$ requires: $M^{\oplus}$480).

*Epoxidation of* **27**. Compound **27** (200 mg) was epoxidised with *m*-chloroperbenzaic acid (200 mg) in $CH_2Cl_2$ (20 ml) for 24 hr at 4° and then 6 hr at r.t. The crude product following the usual workup was chromatographed on a silicagel column. Elution with light petrol-$CHCl_3$ (2:8) yielded mainly **35** (100 mg) m.p. 132°–133° (after several crystallizations from hexane), $[\alpha]_{589}$ − 40°; $[\alpha]_{546}$ − 47°; $[\alpha]_{365}$ − 115° (*c*, 0·08); $\nu_{max}^{KBr}$ 1630, 1250, 1180, 1060, 1020, 830 $cm^{-1}$; NMR 6·15 (s, 18-H); 0·95 (s, 19-H); 3·70 (d, $J$ = 11 Hz, $P(OCH_3)_2$); 5·88 (d, $J$ = 21·5 Hz, 4-H) and 3·10 (d, 2·5 Hz, 6-H). (Found: C, 70·33; H, 10·00; P, 6·15; $C_{29}H_{49}O_4P$ requires: C, 70·68; H, 10·25; P, 6·28%).

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