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2-HETERO-CHOLESTANES

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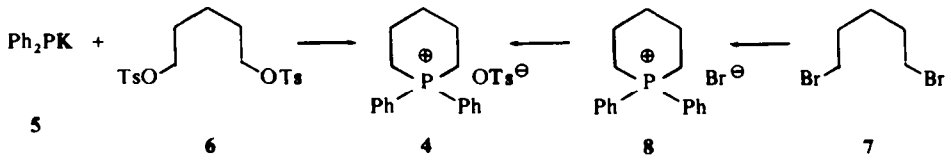
Abstract—2-oxa (**11**), 2-thia (**12**) and 2-aza (**19**), 5α-cholestanes were prepared from the sulfonic esters of A-seco-2-nor-5α-cholestan-1,3-diol (**9** and **10**). Although cyclopentamethylenediphenylphosphonium tosylate (**4**) could be obtained from pentan-α,ω-ditosyloxy (**6**) and Ph_2PK, attempts to prepare 3-phospha-cholestane (**16**) in a similar fashion from **9** or **10**, yielded only A-seco-2-nor 5α-cholestan-1-tosyloxy-3-diphenylphosphine (**17**).

ATTEMPTS have been made[1] to prepare a phospha-steroid from a suitable seco-steroid by linking the phosphorus moiety in two consecutive steps. A series of various phosphorus-containing steroids were obtained bearing an exocyclic dimethylphosphinyl group at C-5. However, in no case was the phosphorus atom an integral part of the steroidal skeleton. Here we modified our approach and attempted to apply known methods for the one step synthesis of phosphorinans,[2] from α,ω-dihalo-pentanes, to steroidal systems.

The hitherto unknown A-seco-2-nor-5α-cholestan-1,3-diol (**3**), which is easily obtained from cholest-2-en-3-one (**1**) via A-seco-2-nor-5α-cholestan-1,3-dioic acid (**2**), presented a suitable starting material for preparing the required A-seco-2-nor-cholestan-1,3-dihalide, which itself may also be utilized in the synthesis of other 2-hetero-cholestanes. Attempts to prepare the 1,3-seco-dibromide from **3** by methods cited in the literature, were unsuccessful.[3] The failure of some of the methods is certainly due to the neopentyl nature of the C-1 atom, although the feasibility of the above substitution by some of these methods is known.[3b,c,e,f]

It has been reported that the Arbuzov reaction is not limited to alkyl halides, but can also be performed with esters of sulfonic acids.[4] We therefore attempted the analogous preparation of cyclopentamethylendiphenylphosphonium tosylate (**4**) by reacting potassium diphenylphosphide[5] (**5**) with pentamethylenditosyloxy (**6**). This model reaction could be utilized with the steroid sulfonic esters and could thus avoid the preparation of the dibromo compound. Indeed, under similar conditions as employed for the reaction of α,ω-dibromopentane[6] (**7**), the expected phosphonium salt **4** was obtained from compound **6**. Compound **4** has a rather high m.p. (240–245°) and shows in the IR spectrum the characteristic absorptions of Ph-P (1440 cm^{-1}) and SO_2 (1160, 1365 cm^{-1}). Unequivocal evidence for its structure is the NMR data: six methylene protons (δ 1·60–2·10, m) appear together with the tosylate Me group (δ 2·26, s) (the latter value is shifted upfield by 0·15 ppm compared with the starting material **6**, Table 1). Four additional hydrogens α to the phosphorus atom resonate at δ 2·00–3·00 while in the aromatic region, apart from ten protons which belong to the two Ph groups (δ 7·4–8·1), an AA'BB' system of the tosylate appears (δ_A 7·05, δ_B 7·75). A significant feature of this system is the value $\delta_A - \delta_B = 0{\cdot}7$ ppm compared to the corresponding value of 0·4–0·45 ppm in other covalent bonded tosyloxy compounds

(Table 1). The above salt-cyclopentamethylendiphenylphosphonium tosylate, can also be obtained from the corresponding phosphonium bromide (**8**) by the exchange of the bromide with $OTs^{\ominus}$. Addition of an equimolar amount of *p*-TsOH to an aqueous solution of compound **8**, with removal of HBr, yielded **4**. Having achieved



the synthesis of this phosphorinanium salt from pentan-α,ω-ditosyloxy (**6**) on a large scale, it was necessary to scale down the method as is usually required in steroid work. This was done by using a dilute solution of Ph_2PK in a mixture of dioxan-THF, and determining its concentration by measuring the atomic absorption of potassium (see experimental).

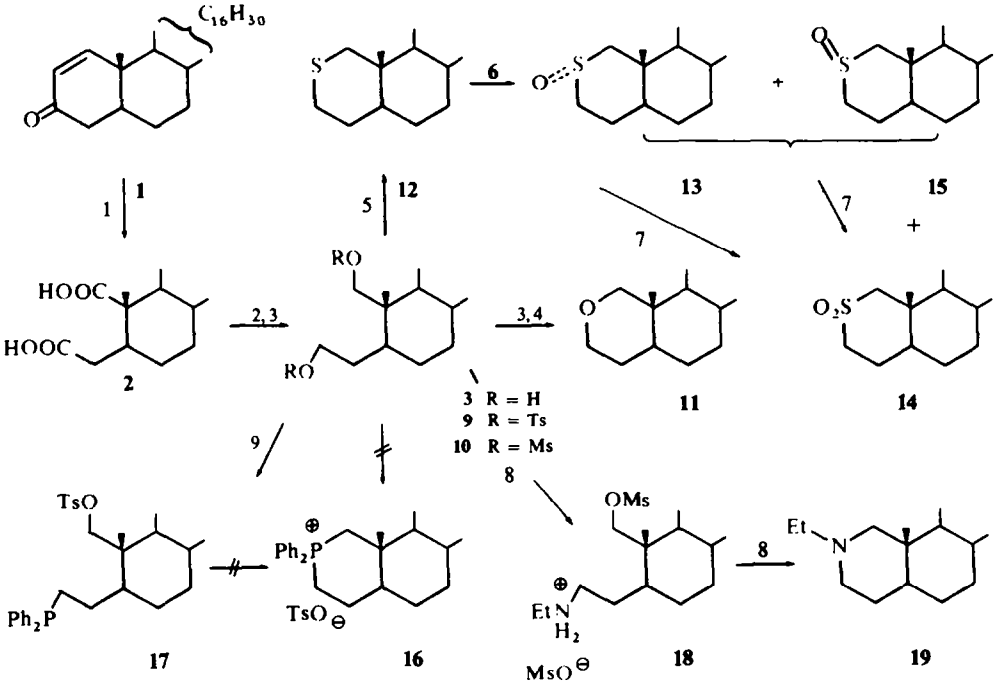
TABLE 1. THE AROMATIC PROTON SHIFTS (PPM, IN $CDCl_3$) OF *p*-TOLUENSULFONATE SYSTEMS

Compound	δ_A	δ_B	$\delta_A - \delta_B$	δ_{CH_3}
Pentan—1,5-ditosyloxy	7·33	7·73	0·40	2·41
Cyclopentamethylendiphenylphosphonium tosylate	7·05	7·75	0·70	2·26
A-seco-1,3-nor-5α-cholestan-1,3-ditosyloxy	7·79 7·77	7·37 7·35	0·42 0·42	2·44 2·44
A-seco-1,3-nor-5α-cholestan-1-tosyloxy-3-diphenylphosphine	7·71	7·31	0·40	2·40

Encouraged by the above results we prepared two sulfonic esters of **3**; A-seco-1,3-nor-5α-cholestan-1,3-ditosyloxy (**9**) and A-seco-1,3-nor-5α-cholestan-1,3-dimesyloxy (**10**), which are equivalent to **6**, as starting materials for preparing a phosphahetero-cyclic compound. These sulfonic esters, (**9**) and (**10**), were also employed in the synthesis of other hitherto unknown 2-hetero-cholestanes.

Treatment of A-nor-3,5-seco-5α-cholestan-3,5-diol with TsCl in pyridine at room temperature yields the cyclic ether, 4-oxa-5α-cholestane, as main product.[7a] The same ether can also be obtained by refluxing the 3,5-seco-ditosyloxy in acetone,[7b] and we expected the 1,3-seco-diol (**3**) to behave similarly. Indeed, under the same experimental conditions we obtained from **3**, in addition to compound **9**, the unknown 2-oxa-5α-cholestane (**11**). The ether (**11**) accompanied compound **9** even if the tosylation was carried out at −20°. In contrast, mesylation of **3** at −20° resulted in 1,3-seco-dimesyloxy (**10**) exclusively.

As 2-oxa-cholestane (**11**) was unknown, we undertook its investigation. This ether **11**, ($C_{26}H_{46}O$) exhibits typical IR absorptions of a cyclic ether (C—O 1083, 1097 cm^{-1}). In the NMR spectrum (Fig 1) the four low field protons α to the oxygen give rise to a peculiar pattern, from which the conformation of ring A can be postulated (vide infra), as a somewhat twisted chair. This distortion may originate from the



Reagents: 1. $KMnO_4$, $NaIO_4$; 2. $LiAlH_4$; 3. MsCl-Pyr. or TsCl-Pyr. 4. Acetone, Δ; 5. Na_2S-$9H_2O$; 6. *m*-chloroperbenzoic acid; 7. H_2O_2; 8. $EtNH_2$, Dioxane; Δ; 9. Ph_2PK

SCHEME 1

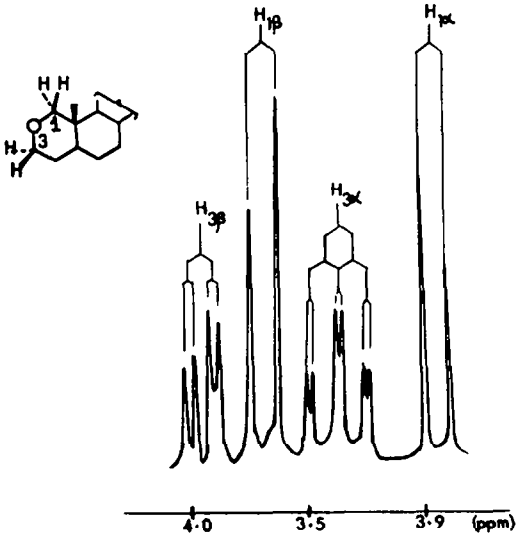
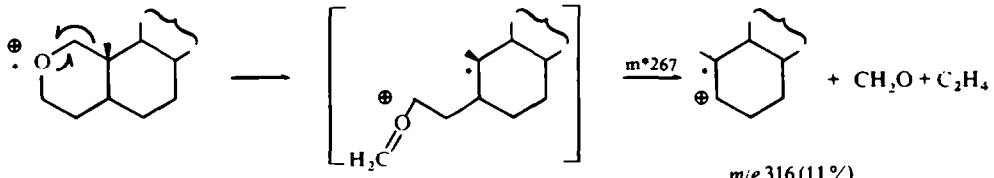


FIG 1. Part NMR spectrum of compound **11**

steric interaction between the Me group on C-10 and the axial H atom on C-4 (1,3-interaction). The deformation is such that the angle between C-3 β-H and C-4 α-H becomes *ca.* 90° and therefore their mutual coupling constant in the NMR spectrum is zero (see Fig. 1). The equatorial C-3β proton which absorbs at δ 3·92 is hence coupled only by the C-3 α-H (J = 11 Hz), and by C-4 β-H (J = 5 Hz) thus giving rise to a doublet. Irradiation of C-3 α-H at δ 3·35 removed the splitting of 11 Hz, in the double doublet and it became a broadened singlet. (The coupling constant of 5 Hz gives a calculated[8] angle (45°) which is in accord with the angle measured between C-3β-H and C-4β-H, using a Dreiding Model (40°)). The axial proton C-3α-H absorbs at a higher field (δ 3·35) and forms a double triplet, with coupling constants of 3 and 11 Hz. Irradiation of C-3β-H transformed the above double triplet into a double doublet with the same coupling constants (3 and 11 Hz) thereby indicating that $J_{H_{3\alpha},H_{4\beta}} = J_{H_{3\alpha},H_{3\beta}} = 11$ Hz and $J_{H_{3\alpha},H_{4\alpha}} = 3$ Hz. (The angles calculated from the above J values agree with the measured angles in the Dreiding model: 155° for the angle between C-3α-H and C-4β-H and 40° for that between C-3α-H and C-4α-H). The other two protons which resonate at the same low field region (Fig 1) are the C-1 protons, which form an AB quartet ($\delta_{H_{1\alpha}}$ 2·95, $\delta_{H_{1\alpha}}$ 3·69, $J_{H_{1\alpha},H_{1\beta}}$ = 11 Hz). The mass spectrum of **11** shows, in addition to the strong molecular ion peak at *m/e* 374 (90%), a characteristic peak at *m/e* 316 (11%) due to a cleavage of ring A. This loss of 58 m.u., which is accompanied by a metastable peak at *m/e* 267 can be explained by the following probable fragmentation:



m/e 374 (90%) *m/e* 316 (11%)

Similarly a loss of 58 m.u. is observed after fragmentations of the side chain-C_8H_{17}: (*m/e* 261 ([$M^{\oplus}$-113], 75%) → *m/e* 203 ([261–58], 13%) and ring D: (*m/e* 234 ([$M^{\oplus}$-140], 27%) → *m/e* 176 ([234–58], 25%), *m/e* 220 ([$M^{\oplus}$-154], 91%) → *m/e* 162 ([220–58], 28%); *m/e* 219 ([$M^{\oplus}$-155], 100%) → *m/e* 205 ([219–14], 14%) → *m/e* 147 ([205–58], 30%)).*

Having prepared the 1,3-seco-dimesyloxy (**10**) we were anxious to examine the possibility of two consecutive nucleophilic displacements on C-3 and C-1 to form a heterocyclic ring. Na_2S, which has minimal steric requirements, is known to react with ROMs,[9] and thus could produce 2-thia-cholestane, the second 2-heterosteroid in this series. Indeed, by refluxing **10** with Na_2S in acetone, the desired 2-thia-5α-cholestane (**12**) was obtained in good yield. This method is more convenient for preparing 2-thia-steroids than that for the synthesis of 2-thia-androstanes.[10] The

* It is of interest to compare the mass spectrum of **11** with that of 4-oxa-5α-cholestane. In the latter, fragments due to cleavage of ring A are very weak. (For example, the peak at *m/e* 316 [$M^{\oplus}$-58] has a relative intensity of only 3%, as well as the peak resulting from cleavage of rings A and B: *m/e* 303 [$M^{\oplus}$-71], 20%). Contrary to compound **11**, cleavage of ring D resulted in strong peaks: *m/e* 234 [$M^{\oplus}$-140], 22%; *m/e* 220 [$M^{\oplus}$-154], 70% and *m/e* 219 | $M^{\oplus}$-155], 100%.

structure of **12** was corroborated by means of NMR, (where four hydrogens resonate together at δ 2·35–2·70),* mass spectrum (*m/e* 380, $M^{\oplus}$, 40%) and elemental analysis. Oxidation of **12** with *m*-chloroperbenzoic acid led to a mixture of three compounds, according to TLC and the appearance of three signals for the C-19-CH_3 in the NMR spectrum at δ 0·97, 1·16 and 1·27 ppm. Careful chromatography of the mixture on neutral alumina gave only two of the oxidation products. Comparison of their spectral data with the corresponding known oxidation products of 2-thia-androstane[11] indicated that the above eluted compounds were 2α-sulfoxide-5α-cholestane (**13**) and 2-sulfon-5α-cholestane (**14**). The production of **13** as the predominant sulfoxide isomer, is in accordance with the known fact that oxidation under these conditions yields mainly the equatorial isomer.[12]

Alternatively the sulfone **14** can be prepared directly from **12** or from a mixture of **13** and **15** by oxidation with excess H_2O_2. In the mass spectrum, the molecular ion of the 2α-sulfoxide (**13**) was the base peak (*m/e* 406, 100%), while the next in intensity was the fragment which appeared at *m/e* 390 (90%, m* 374).† The third fragment in intensity (*m/e* 375 [$M^{\oplus}$-CH_3], 50%) loses 48 m.u. (SO) yielding *m/e* 343 (5%, m* 301). The other typical fragmentations for sulfoxides result in low intensity peaks: *m/e* 357 [$M^{\oplus}$-HSO], (6%); *m/e* 329 [$M^{\oplus}$-CH_2CH_2SOH], (5%) and *m/e* 301 [$M^{\oplus}$-(CH_3 + $CH_2SOCH_2CH_2$)], (7%)—arising from the ring-A fragmentations. The more abundant ions are those formed by cleavages of the side chain: *m/e* 293 [$M^{\oplus}$-113), (33%) and this ion minus 16 m.u. (*m/e* 277, 15%). In the sulfone **14** the molecular ion *m/e* 422 (100%) is again the base peak as in the sulfoxide **13**. The appearance of *m/e* 356 [$M^{\oplus}$-H_2SO_2] (6%, m* 300·5) and *m/e* 330 [$M^{\oplus}$-$CH_2CH_2SO_2$] (3%), was further indication for the presence of a SO_2 group, while the following fragmentations were characteristic of the cholestane series: *m/e* 309 [$M^{\oplus}$-113], (8%); *m/e* 282 [$M^{\oplus}$-113], (8%); *m/e* 282 [$M^{\oplus}$-140], (18%) and *m/e* 267 [$M^{\oplus}$-155] (67%, m* 169·5).

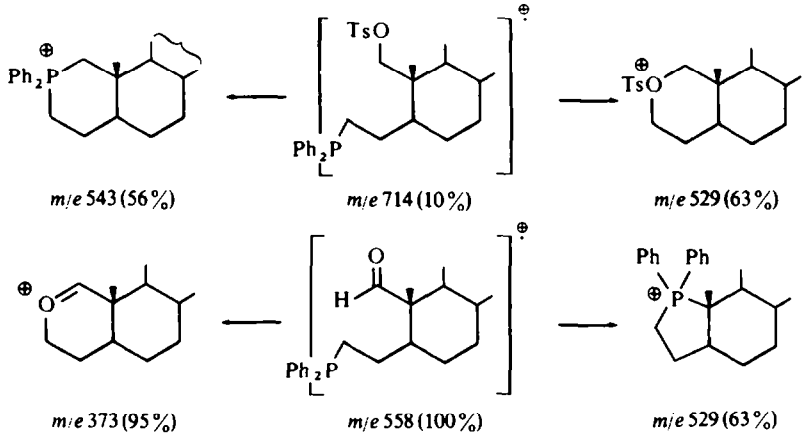
After preparing 2-hetero-cholestane from **9** and **10**, we examined the possibility of obtaining 2-diphenylphosphonium-5α-cholestane tosylate (**16**) by reacting 1.3-seco-ditosyloxy (**9**) with potassium diphenylphosphide (**5**) under the same experimental conditions used for preparing the phosphorinanonium salt (**4**). After prolonged refluxing of **9** with potassium diphenylphosphide (**5**) in dioxan-THF, an oily compound was isolated by chromatography. (The only other compound separated from the reaction mixture was *p*-TsOK). In the IR this oil shows the absorptions for Ph-P (1435) and SO_2 (1175, 1350 cm^{-1}). The NMR spectrum exhibits an AB quartet for the C-1 protons (δ_A 3·61, δ_B 3·75 and J_{AB} = 10 Hz), as in the starting material **9**, but the signals corresponding to the two C-3-protons are shifted upfield (δ 2·1–2·5, m). In the aromatic region, apart from the familiar AA'BB' system of one tosyloxy group (δ_A 7·31, δ_B 7·71) (Table 1), ten additional protons appear which belong to two Ph groups (δ 7·2–7·9, m). Although all the functional groups of the heterocyclic salt **16** seem to be present in the above oil, a more thorough examination of the NMR spectrum indicates the product is different. Had the heterocyclic salt been the structure in question, the two C-3 protons should have resonated at a higher field ($\delta \sim 3{\cdot}0$) as in **4** and **8** with the AA'BB' system of the aromatic ring of the tosylate group having a larger $\delta_A - \delta_B$ value (Table 1). On the basis of this data, we conclude that the product

* In contrast to the cyclic ether **11**, no conclusions regarding the conformation of ring A could be drawn.

† This loss of 16 m.u. is rather unusual and it can be attributed to the loss of an oxygen atom from the sulfoxide. This fragmentation, to our knowledge, has not been noted in the literature.

is not the heterocyclic phosphacholestane (**16**) but rather A-seco-2-nor-5α-cholestan-1-tosyloxy-3-diphenylphosphine (**17**). Further support for this is the fragmentation pattern of **17**, the molecular ion at *m/e* 714 (10%) is of low intensity while the base peak appears at *m/e* 558 (100%) (Scheme 2).

Particularly note the ion which appears at *m/e* 543 (56%) for which one of the proposed structures is the much desired 2-phospha-steroid structure. Apart from the ions shown in scheme 2, the peaks originating from the cleavage of the side chain and ring-D are also present: *m/e* 445 ([558–113], 40%), and *m/e* 403 ([558–155], 12%).



m/e 543 (56%) *m/e* 714 (10%) *m/e* 529 (63%)

m/e 373 (95%) *m/e* 558 (100%) *m/e* 529 (63%)

SCHEME 2*

Attempts to cyclize **17** to **16** by boiling under N_2 atm. in DMSO, DMF or HMPT were unsuccessful, possibly due to the strong interaction between the C-19-CH_3 and the Ph group on the phosphorus moiety in the transition state. Conceivably, this probable repulsion could be prevented by reacting[2] **9** or **10** with phosphorus reagents such as $PhPH_2$[14] and $PhPLi_2$[5,15]; however, in preliminary reactions using these reagents no phosphorus containing cholestane was obtained.

The final 2-hetero-steroid synthesized from **10** was the 2-aza-cholestane. 2-aza-steroids were previously prepared via Beckmann rearrangement and Schmidt reaction.[7a,13] However, reacting 1,3-seco-dimesyloxy (**10**) and $EtNH_2$ was found to be more convenient. After reaction (sealed tube, 80°), and evaporation of excess $EtNH_2$, two products were isolated. The first, which was obtained by adding ether to the reaction residue, was very hygroscopic salt like. Its NMR spectrum shows two sharp singlets which correspond to two different mesylate groups (δ 3.12 and δ 2·76). At δ 4·12 only two protons resonated (α-to the MsO) (*cf.* four in the starting material **10**), while a further four protons α-to the nitrogen, and the two acidic nitrogen protons, all absorb at δ 2·3–3·1. Thus, we conclude that the above salt is A-seco-2-nor-5α-cholestan-1-mesyloxy-3-(N-ethyl)-ammonium mesylate (**18**)-the aza analogue of **17**. Contrary to the phospha compound **17**, compound **18** could undergo ring closure to the aza heterocyclic compound **19**, namely N-Ethyl-2-aza-5α-cholestane. Compound **19** (second product isolated) has the molecular formula $C_{28}H_{51}N$. (elemental analysis and mass spectrum (*m/e* 401, $M^{\oplus}$, 40%)). (The only other peak

* Other structures are possible for the cyclic fragments.

which appears at high mass was $M^{\oplus}$-15 (40%)). The NMR spectrum of **19** is in full accord with its structure. It shows at high field, in addition to the skeleton Me's, a triplet at δ 1·03 (J = 7 Hz) (3H) attributed to the Me of the N–Et group, the methylene of which appears at δ 2·35 (q, J = 7 Hz). The four other ring protons α to the nitrogen are divided into two groups: δ 2·7–3·0 being the equatorial protons and δ 1·80–2·50 the axial ones.

We have shown that 3-seco-sulfonic esters like compounds **9** and **10** can be used for the preparation of 2-hetero-cholestanes, with the exception of the 2-phospha compound. A possible preparation of this steroid would be to react the esters with the less bulky and more reactive alkyl phosphine derivatives. This will be the subject of a subsequent report.

EXPERIMENTAL

M.ps were taken on a "Uni-melt". Thomas and Hoover Capillary apparatus and uncorrected. IR spectra were recorded on a Perkin–Elmer Infracord 337 and UV spectra on a Perkin–Elmer 137 UV spectrophotometer. NMR spectra (5–10% solutions, $CDCl_3$, TMS as internal standard) on a Varian HA-100 spectrometer. Chemical shifts are quoted in units of δ and coupling constants (J) in Hz. Mass spectra were taken with an Atlas CH_4 instrument and a Hitachi Perkin–Elmer RMU 6, (direct introduction at 70 ev, electron current 20 μA). Optical rotations were determined on a Perkin–Elmer 141 automatic polarimeter in $CHCl_3$. Atomic absorptions were measured on Perkin–Elmer 290. Unless otherwise stated, column chromatography was carried out on silica gel (7734-Merck), and TLC on silica gel-G (7731-Merck).

A-seco-2-nor-5α-cholestan-1.3-dioic acid (**2**). Treatment of 5α-cholest-1-en-3-one (**1**) (20 gr) with $KMnO_4$–$NaIO_4$, under the same conditions as described for the preparation of A-seco-4-nor-5-oxa-cholestan-3-oic acid,[14] yielded compound **2** (20 gr, 90%) m.p. 228–230° (ether–petrol ether, lit.[15] 227°–230°).

A-seco-2-nor-5α-cholestan-1.3-diol (**3**). The dimethyl ester of compound **2** (20 gr) prepared quantitatively by addition of CH_2N_2 to its solution in ether, was added to a stirred solution of $LiAlH_4$ (6 gr) in ether (200 ml). After 24 hr reflux, excess hydride was destroyed by addition of EtOAc to the cold solution. The complex was decomposed by adding saturated Na_2SO_4 aq and the precipitate filtered. The dried ($MgSO_4$) ethereal solution was evaporated to yield **3** m.p. 165° (EtOH, 12 gr 71%). $[\alpha]_D^{25}$ 0° ($CHCl_3$, c, 0·1). ν_{max}^{KBr} 3250 (O—H), 1035 (C—O) cm^{-1}. NMR 3·44 (s, 1-H); 3·5–3·86 (m, 3-H); 0·65 (s, 18-H); 1·54 (s, 19-H). Mass spectra *m/e* 390 ($M^{\oplus}$-H, 3%); *m/e* 388 (3%); *m/e* 374 ($M^{\oplus}$-H_2O, 10%); *m/e* 361 ($M^{\oplus}$-CH_2OH, 100%; *m/e* 343 (361-H_2O, m* 326·5, 14%); *m/e* 317 (361-CH_3CHO, m* 378·9%); *m/e* 315 (361–46, 5%). (Found: C, 79·28; H, 12·30; $C_{26}H_{48}O_2$ requires: C, 79·53; H, 12·32%).

Potassium diphenylphosphide (**5**). A solution of this reagent was prepared in dioxan from Ph_3P and K under N_2.[5] After 24 hr, the deep red solution was filtered under N_2 and concentration of Ph_2PK in the clear filtrate determined by measuring the atomic absorption of K in a H_2O diluted solution. Calibration solutions were made from PhP(O)(OH)(OK) and PhP(O)(OH)$_2$ in the above solvents. The atomic absorption method was used in all reactions of **5**.

Pentamethylenditosyloxy (**6**). To a cold solution (0°) of pentan-1,5-diol (10 gr) in dry pyridine (100 ml), freshly recrystallized TsCl (75 gr) was added. After 24 hr at −20° the mixture was poured into stirred ice water (400 gr). A white precipitate was collected by vacuum filtration, washed several times with water and dried to give **6** (off-white crystalline solid) (36 gr, 90%). ν_{max}^{KBr} 1190 (C—O), 1270, 1350 (SO_2) cm^{-1}. λ_{max}^{EtOH} 228 (log ε 4·6), 250 (log ε 3·3), 260 (log ε 3·4), 263 (log ε 3·45), 268 (log ε 3·3), 272 (log ε 3·28). NMR 1·5 (m, 2-H, 3-H and 4-H); 5·5 (t, J = 5·5, 1-H and 5-H); 7·33 and 7·73 (AA'BB' system, aromatic protons).

Cyclopentamethylenediphenylphosphonium tosylate (**4**). (a) To a boiling, stirred solution of **6** (5 gr) in dioxan (50 ml) under N_2, a solution of the phosphide **5** (3·2 gr) in dioxan (85 ml) was added dropwise. After reflux for 24 hr, the precipitate of *p*-KOTs was separated by centrifugation, washed with $CHCl_3$ and centrifuged again. The combined liquid phase was dried and evaporated to yield **4** (2 gr, 40%), m.p. 240–245 (EtOH–ether). ν_{max}^{KBr} 1440 (Ph-P), 1180, 1365 (SO_2) 1160 (C—O) cm^{-1}. NMR Heterocyclic ring: 1·86 and 2·08 (m, 3-H, 4-H and 5-H), 3·16 (m, 2-H and 6-H), tosylate protons: 7·1 and 7·8 (AA'BB' system) 7·62 (m, $\underline{Ph}_2$-P).

(b) A similar experiment, (smaller scale) carried out with **6** (1 gr) and Ph_2PK (0·61 gr) in dioxan (17 ml) gave **4** (0·35 gr, 35%).

(c) Addition of an equimolar amount of p-TsOH (0·5 m/mole) to the cyclic phosphonium bromide[6] (**8**) (0·5 m/mole) in water (5 ml) and repeated evaporation from water until all the HBr was expelled yielded **4** (50 mg).

2-oxa-5α-cholestane (**11**). To 1,3-seco-diol (**3**) in pyridine (5 ml) at 0°, recrystallized *p*-TsCl (petrol ether, 1 gr) was added. After 24 hr at −20° the solution was added to crushed ice (50 gr); and ether extracted (3 × 150 ml). The organic layer, which was washed with HCl (1:4) and water to pH 7, dried ($MgSO_4$) and evaporated at room temperature, yielded **9** (90%). ν_{max}^{neat} 1170 (C—O), 1183, 1360 (SO_2) cm^{-1}. NMR 0·57 (s, 18-H); 1·59 (s, 19-H); 3·92 (s, 1-H); 4·12 (m, 3-H); 7·35 and 7·77 (AA'BB' system, aromatic ring protons). The above crude 1,3-seco-ditosyloxy (**9**) was refluxed in acetone (50 ml). After 24 hr the solution was evaporated, ether (200 ml) was added and the resultant ethereal solution washed with bicarbonate and H_2O to pH 7. The dried ethereal solution ($MgSO_4$) was evaporated and the crude residue chromatographed on alumina (neutral, act. II) yielding **11**, m.p. 107–108° (Petrol–ether). $[\alpha]_D^{25}$ 15° ($CHCl_3$, c, 0·09). ν_{max}^{KBr} 1083, 1097 (C—O). NMR 0·66 (s, 18-H); 0·96 (s, 19-H); 2·95 and 3·69 (AB quartet, J_{AB} = 11, 1-H); 3·35 (dt, J = 3, 11, 3α-H); 3·92 (dd, J = 5, 11; 3β-H). (Found: M⊕ 374, $C_{26}H_{46}O$, requires M⊕ 374).

2-thia-5α-cholestane (**12**). Na_2S nonahydrate (7·5 gr) was added to 1,3-seco-dimesyloxy (**10**) in EtOH (100 ml). The latter was prepared in the same manner described for 1,3-seco-ditosyloxy (**9**) from 1,3-seco-diol (**3**) (1·25 gr) using MsCl (1 ml). After reflux for 48 hr EtOH was evaporated and the residue extracted with ether (3 × 100 ml). The organic layer which was washed with water to pH 7, dried ($MgSO_4$) and evaporated, yielded **12** (600 mg) m.p. 98–100° (EtOH–ether) $[\alpha]_D^{25}$ 100° ($CHCl_3$, c: 0·06). NMR 0·67 (s, 18-H); 1·05 (s, 19-H); 2·5 (m, 1-H and 3-H). (Found: C, 79·70; H, 11·79; S, 8·3; $C_{26}H_{46}S$ requires: C, 79·97; H, 11·87; S, 8·19%).

2-Sulfoxide-5α-cholestane (**13**). A solution of *m*-chloroperbenzoic acid (0·25 gr) in CH_2Cl_2 (5 ml) was slowly added to a solution of 2-thia-cholestane (**12**) (0·5 gr) in CH_2Cl_2 (5 ml) at 5°. After stirring for 17 hr at 5° and 7 hr at room temperature, 100 ml of ether were added. The organic layer was washed with bicarbonate, until negative to KI, and H_2O to pH 7, dried ($MgSO_4$) and evaporated. In the NMR spectrum of the crude residue three C-19-Me corresponding to **13**, **14**, **15** resonated at three different frequencies (δ 0·97, 1·16 and 1·27 respectively). From chromatogrpahy on alumina (neutral, act. II), only **13** and the corresponding 2-sulfone (**14**) (see below) were eluted by $CHCl_3$: Petrol–ether (1:1) but not **15**. The sulfoxide **13** m.p. 160° (EtOH–Petrol ether), $[\alpha]_D^{25}$ 19° ($CHCl_3$, c, 0·09) ν_{max}^{KBr} 1038 (SO equatorial). NMR 0·65 (s, 18-H); 0·97 (s, 19-H); 3·36 and 3·56 (AB quartet, J_{AB} = 6, 1-H) and 3·45 (m, 3-H). (Found: M⊕ 406, $C_{26}H_{46}OS$, requires M⊕ 406).

2-sulfon-5α-cholestane (**14**). H_2O_2 (30%, 2 ml) was added to a solution of 2-thia-cholestane (**12**) (60 mg) in AcOH (40 ml) at 5°. After 48 hr, ether (250 ml) was added and the resultant solution washed with $FeSO_4$ aq until negative to KI, with bicarbonate and H_2O to pH 7. The dried ether ($MgSO_4$) yielded **14** upon evaporation, (45 mg, 70%) m.p. 210° (EtOH). $[\alpha]_D^{25}$ 22° ($CHCl_3$, c, 0·07). ν_{max}^{KBr} 1105, 1130, 1305 cm^{-1} (SO_2). NMR 0·68 (s, 18-H); 1·16 (s, 19-H); 2·62 and 3·09 (AB quartet, J_{AB} = 6, 1-H); 2·8–3·1 (m, 3-H). (Found: M⊕ 422, $C_{26}H_{46}O_2S$, requires M⊕ 422).

A-seco-2-nor-5α-cholestane-1-tosyloxy-3-diphenylphosphine (**17**). Following the same procedure used for compound **4**. Ph_2PK (**5**) ($3·6 \times 10^{-3}$ mole) was added dropwise to a boiling solution of 1,3-seco-ditosyloxy (**9**) (2·5 gr), $3·5 \times 10^{-3}$ m) in dioxan: THF (1:1, 200 ml) with stirring under N_2. The phosphorus reagent lost its deep red colour and a white precipitate of *p*-KOTs was formed. After the addition was completed the solution was refluxed for 5 hr and the precipitate separated by centrifuge. Solution evaporated at reduced pressure and residue chromatographed. Elution with $CHCl_3$ yielded **17** (0·8 gr, 32%), ν_{max}^{neat} 1185, 1350 (SO_2), 1175 (C—O), 1435 cm^{-1} (Ph-P). NMR 0·56 (s, 18-H); 0·53 (s, 19-H); 3·61 and 3·75 (AB quartet, J_{AB} = 10, 1-H); 2·3 (m, 3-H); 7·2–7·9 (m, $\underline{Ph_2}$-P); 7·31 and 7·71 (AA'BB' system, tosylate protons). (Found: M⊕ 714, $C_{45}H_{63}O_3PS$ requires M⊕ 714).

A-seco-2-nor-5α-cholestan-1-mesyloxy-3-(N-ethyl) ammonium mesylate (**18**) *and N-ethyl-2-aza-5α-cholestane* (**19**). A sealed glass tube, containing 1,3-seco-dimesyloxy (**10**) (0·5 gr) and $EtNH_2$ (3 ml) in dioxan (5 ml) was heated at 80° for 24 hr. Addition of ether (50 ml) to the residue precipitated out compound **18** as an hygroscopic white crystalline solid (210 mg) m.p. 156–157° ($CHCl_3$, sealed capillary). NMR 0·66 (s, 18-H); 0·72 (s, 19-H); 4·12 (m, 1-H); 2·9–3·3 (3-H, $CH_3C\underline{H}_2—N\underline{H}_2$); 2·76 and 3·12 (two singlets of the two Ms groups).

Ether solution from above was extracted with HCl (1:4, 3 × 20 ml) the acidic solution basified with NaOH, and extracted with ether (3 × 50 ml). The organic layer, after drying (K_2CO_3) and removal of solvent, yielded **19** (200 mg, 55%), m.p. 58° (acetone). $[\alpha]_D^{25°}$ −29° ($CHCl_3$, c, 0·04) NMR 0·65 (s, 18-H, 0·92 (s, 19-H). (Found: C, 83·41; H, 12·75; N, 3·35; $C_{28}H_{51}N$ requires: C, 83·72; H, 12·80; N, 3·49%). **19**

was also obtained by refluxing **18** (50 mg) in dry dioxan (25 ml) in the presence of K_2CO_3 (0·25 gr). The hot solution was filtered added to ether, (100 ml). and treated as above, yielding **19** (20 mg).

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