Secosteroids. Preparation of 5-Oxo-2,5-seco-A-dinorcholestan-2-amide

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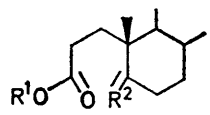
The preparation of the title compound and a number of other 2,5-seco-A-dinorcholestanes, and of some 3,5-seco-A-norcholestanes is described. Three heterocyclic steroids are mentioned; a 4-oxacholestene (6) and the 3-oxa- and 3-aza-A-norcholestan-2-ones (11) and (13), respectively. Two mixed ethoxyformic anhydrides (10) and (12) were made; the contrast in their activity towards nitrogen nucleophiles is discussed.

In connection with work involving a steroid as carrier molecule for biologically active functional groups, the amide (15) was required as a synthetic intermediate. We describe the preparation of this compound and items of interest met with in the course of this synthesis.

The keto-acid (1) was prepared by periodate–permanganate oxidation of cholest-4-en-3-one [1] and was converted into its methyl ester (2) with diazomethane.[2b,c]



(1) R^1 = H, R^2 = O
(2) R^1 = Me, R^2 = O
(3) R = Me, R = O·CH_2CH_2·O

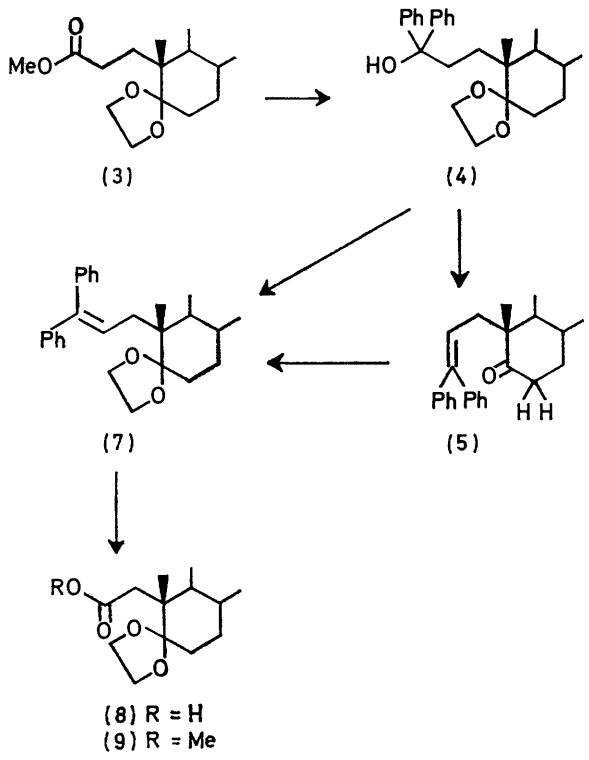
Conversion of the keto-ester into the ethylene acetal (3) [2a,c,d] proceeded cleanly, there being no evidence of an earlier reported [2c] contaminant, β-hydroxyethyl-3,5-seco-A-nor-5-oxocholestan-3-oate, an absence confirmed recently by Kashman and Sprecher.[2d]

In order to obtain the acid (8) a Barbier-Wieland degradation (Scheme 1) of the ester (3) was undertaken. Formation of the diphenylcarbinol (4) proceeded smoothly *via* the Grignard reaction between the ester (3) and phenylmagnesium bromide.[2a] In attempts to effect the second step of the degradation, several of the usual techniques were tried, the presence of the ethylene acetal group dictating non-acid conditions. Phosphoryl chloride in pyridine was ineffective even at 60°. Some measure of success was achieved using thionyl chloride at room temperature, although the ethylenedioxy-olefin (7) was accompanied by much larger quantities of the keto-olefin (5). Toluene-*p*-sulphonyl chloride in pyridine was completely ineffective, but in the same solvent, a satisfactory dehydration [(4) ⟶ (7)] was achieved in *ca.* 60% yield by use of the sterically less demanding methanesulphonyl chloride. Chromatography was the best way of obtaining pure material, and also enabled the isolation of another compound for which the oxacholestene structure (6) is proposed. The i.r. spectrum showed an absorption at 1670 cm^{-1} (C=C), but of an enhanced intensity compared with that in cholest-5-ene or cholesterol, indicating the direct attachment of an electronegative group to one of the carbon atoms. The n.m.r. spectrum showed a multiplet at τ 2·7 (10H, aromatic) and at τ 4·96 a vinyl proton doublet ($J_{6,7\beta}$ 5·0 Hz) in which each arm is broadened but not resolved further ($J_{6,7\alpha}$ *ca.* 0). The size of $J_{6,7\beta}$ is in the range expected for

[1] J. T. Edward, D. Holder, W. H. Lunn, and I. Puskas, *Canad. J. Chem.*, 1961, **39**, 599.

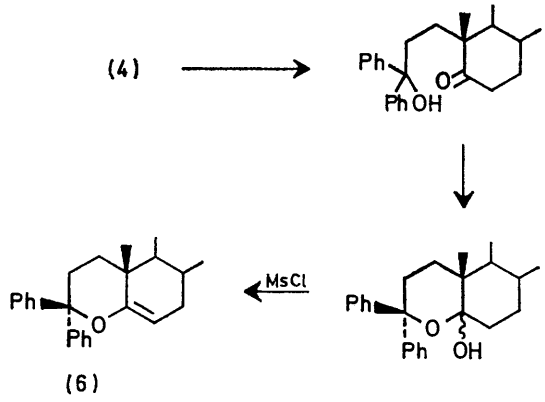
[2] (*a*) F. L. Weisenhorn, D. C. Remy, and T. L. Jacobs, *J. Amer. Chem. Soc.*, 1954, **76**, 552; (*b*) J. McKenna and A. Tulley, *J. Chem. Soc.*, 1960, 945; (*c*) W. J. Rodewald and J. Wicha, *Bull. Acad. polon. Sci. Ser. Sci. chim.*, 1963, **11**, 437; (*d*) Y. Kashman and M. Sprecher, *Tetrahedron*, 1971, **27**, 1331.

this type [3] of vicinal coupling. Traces of the keto-olefin (5) were isolated in repeat runs of this dehydration procedure, and, although this could be an intermediate



SCHEME 1

in the formation of compound (6), the latter is better explained by Scheme 2.



SCHEME 2

The last step in the degradation, the oxidative cleavage of the olefin (7) to the carboxylic acid (8), was accomplished in high yield (>90%) with sodium periodate and ruthenium dioxide in aqueous acetone.[4,5] Treatment of the acid so obtained with diazomethane afforded the ester (9); this reaction was slower than the corresponding esterification of the keto-acid, (1), presumably because of the greater extent of steric crowding at the carboxy-group in (7) due to the presence of the ethylenedioxy-group and also the shortening of the side chain bearing the carboxy-function.

It was expected that treatment of the ester (9) with ammonia would give the acetal of the required amide (15). This was not the case, however; an attempt to effect the reaction in liquid ammonia failed also, and refluxing with hydrazine hydrate produced no hydrazide. The ester (9) was saponified and the acid (8) was converted cleanly into the mixed anhydride (10) with ethyl chloroformate.[6] Treatment of the anhydride with ammonia gas gave (remarkably) only the acid (8), together with some ethyl carbamate. This is in marked contrast to the conversion of ethyl hydrogen bicyclo[2,2,2]octane-1,4-dicarboxylate into ethyl 4-carbamoylbicyclo[2,2,2]octane-1-carboxylate (87% yield of amide recorded [7]). A further demonstration of the lack of reactivity of the mixed anhydride (10) with nucleophiles occurred in the use of the Weinstock modification [8] of the Curtius reaction, where (in the present case) the anhydride, after initial treatment with sodium azide and subsequent heating in toluene, produced no isocyanate, only the acid (8).

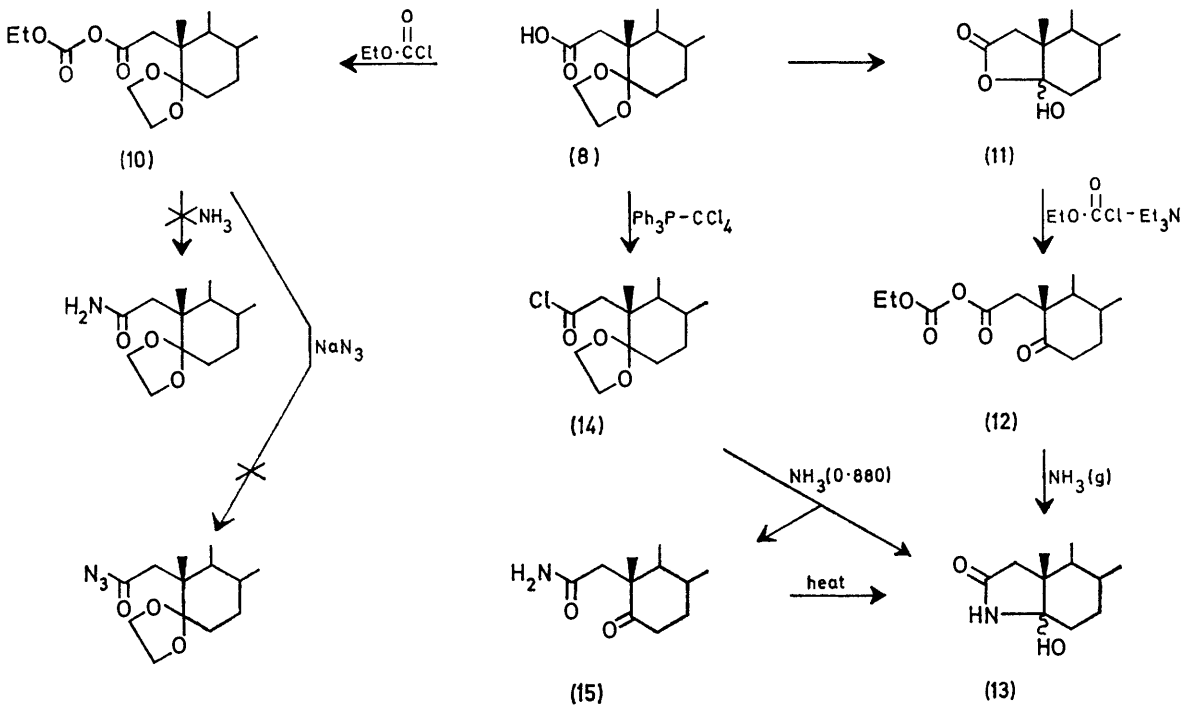
Originally, the ethylenedioxy-group at C-5 was utilised in order to protect the carbonyl group during the Grignard reaction. Its continued presence was desirable to reduce complicating side reactions typified by the formation of the oxacholestene (6). However, it now seemed that the lack of reactivity of both the ester (9) and the mixed anhydride (10) towards ammonia could be ascribed to a sterically hindered approach by the nucleophile to the carbonyl group. It was decided to hydrolyse the acetal group, prepare the mixed anhydride of the product, and treat this with ammonia. Treatment of the acetal (8) with perchloric acid in tetrahydrofuran [9] yielded not the desired keto-acid but the hydroxy-lactone (11), which, nevertheless, reacted with ethyl chloroformate and triethylamine to afford the mixed anhydride (12) (Scheme 3). This reaction involves attack by the triethylamine upon the hydrogen atom of the angular hydroxy-group, followed by ring opening to afford the carboxylate anion which reacts with the chloroformate ester in the usual way. Ammonia gas converted the anhydride (12) into a mixture, the major component of which was assigned the hydroxy-lactam structure (13) (see later). The i.r. spectrum of the crude product revealed the presence of a small quantity of keto-amide (15) which could not be purified.

We then attempted to prepare the acid chloride (14), to see whether this would react with ammonia to yield the required product. The need to avoid strongly acidic

[3] S. Sternhell, *Quart. Rev.*, 1969, **23**, 236.
[4] Y. Yanuka and S. Sarel, *Proc. Israel Chem. Soc.*, 1957, **6A**, 286.
[5] R. Pappo and A. Becker, *Bull. Res. Council Israel*, 1956, **5A**, 300.
[6] *Inter alia* R. L. Barnden, R. M. Evans, J. C. Hamlet, B. A. Hems, A. B. A. Jensen, M. E. Trevett, and G. B. Webb, *J. Chem. Soc.*, 1953, 3733; R. M. Evans and A. B. A. Jensen, *ibid.*, 1954, 4037.
[7] J. B. Roberts, W. T. Moreland, and W. Frazer, *J. Amer. Chem. Soc.*, 1953, **75**, 637.
[8] J. Weinstock, *J. Org. Chem.*, 1961, **26**, 3511.
[9] J. A. Zderic and D. C. Limon, *J. Amer. Chem. Soc.*, 1959, **81**, 4570.

conditions for the conversion (8) ⟶ (14) narrowed the choice of reagents. Reaction with thionyl chloride in dimethylformamide [10] afforded a multiplicity of products (t.l.c.), a result which was also obtained upon treating the

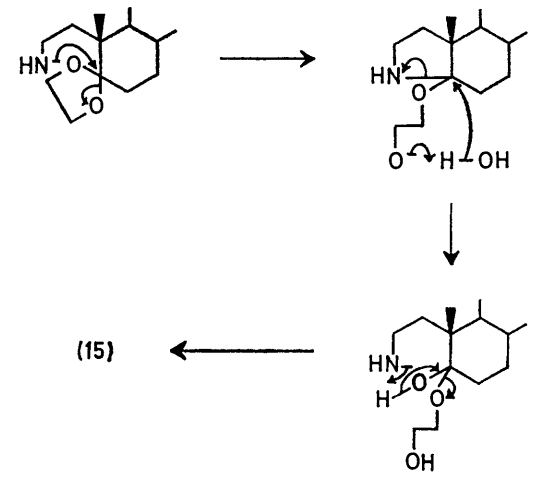
Structure (13) is suggested on the basis of the nature of the reactions in which it was formed and from i.r. and n.m.r. evidence. The n.m.r. spectrum ($CDCl_3$) shows signals at τ 2·12 (NH) and 5·23 (OH) (both exchangeable),



SCHEME 3

acid (8) with *NN'*-carbonyldi-imidazole.[11a,b] Lee has shown [12] that the acid chloride of 2,3-*O*-isopropylideneglyceric acid can be prepared in high yield by the action of triphenylphosphine in carbon tetrachloride upon the acid.[12] This reaction, when applied to the acid (8) afforded the acid chloride (14) in only about 30% yield, but in a manner that enabled simple chromatographic work-up. With conc. ammonia solution the acid chloride afforded in one instance the keto-amide (15) and, under slightly differing conditions, the hydroxy-lactam (13) encountered previously. To account for the last two compounds one must assume hydrolysis of the ethylenedioxy-group in alkaline solution, presumably with participation of the amide function. In support of this, the hydrolysis of methylthioacetaldehyde acetals occurs with great ease in 50% water–dioxan owing to participation by the sulphur atom.[13] Topping and Tutt have further shown that hydroxide ion-catalysed participation by an amide group occurs with exclusive attack by nitrogen.[14] In the present case the amide anion probably participates as shown in Scheme 4. This suggestion is reinforced by the isolation of the hydroxy-lactam (13). This is apparently the first example of base-catalysed amide participation in ethylene acetal hydrolysis.

and 7·85 (2H, broad unresolved s, CH_2·CO). I.r. absorptions appear at 3425 (OH), 3165 and 3067 (CO*NH*) and 1695 cm^{-1} (*C*ONH).



SCHEME 4

Although the keto-amide (15) was shown to be pure by t.l.c. it did not melt sharply. A sample was examined by t.l.c. after it had melted. The original spot had largely

[10] H. H. Bosshard, R. Mory, M. Schmid, and H. Zollinger, *Helv. Chim. Acta*, 1959, **42**, 1653.

[11] (*a*) H. A. Staab and K. Wendel, *Ber.* 1960, **93**, 2902; (*b*) H. A. Staab, K. Wendel, and A. P. Datta, *Annalen*, 1966, **694**, 78.

[12] J. B. Lee, *J. Amer. Chem. Soc.*, 1966, **88**, 3440.

[13] J. C. Speck, D. J. Rynbrandt, and I. H. Kochevar, *J. Amer. Chem. Soc.*, 1965, **87**, 4979.

[14] R. M. Topping and D. E. Tutt, *Chem. Comm.*, 1966, 698.

disappeared and a new spot corresponding to the hydroxy-lactam (13) was seen.

EXPERIMENTAL

N.m.r. data were obtained with a JEOL-JNM-4H-100 spectrometer at room temperature. I.r. spectra were recorded with a Perkin-Elmer Infracord 137. T.l.c. was performed with Merck silica gel G. Optical rotations were measured for solutions in chloroform.

5,5-Ethylenedioxy-3,3-diphenyl-3,5-seco-A-norcholestan-3-ol (4).—Methyl 5,5-ethylenedioxy-3,5-seco-A-norcholestan-3-oate (3) (16·9 g) in dry ether (50 ml) was added, at room temperature, to a stirred solution of phenylmagnesium bromide [from bromobenzene (11·83 g) and magnesium (1·83 g)] in ether (50 ml). The mixture was then heated under reflux for 0·5 h ,cooled, and treated with water. The ether was decanted from inorganic solids. These were dissolved in dilute ammonium sulphate solution and extracted with ether. The combined ether solutions were dried ($MgSO_4$) and evaporated to leave a pale yellow syrup (21·4 g) which solidified upon treatment with ethanol, from which the *carbinol* (4) crystallised as needles (12·6 g). Chromatography on silica of the contents of the mother liquor (elution with 1 : 9 ether–benzene) afforded a further 1·6 g (total 14·2 g, 66%); m.p. 151° (Found: C, 81·8; H, 9·8. $C_{40}H_{58}O_3$ requires C, 81·9; H, 10·0%), $[\alpha]_D$ +34·3° (*c* 1·7).

Dehydration of the Carbinol (4) *with Thionyl Chloride.*—The carbinol (4) (8·8 g) in dry pyridine (270 ml) was treated with thionyl chloride (90 ml) in pyridine (180 ml) at −10° during 0·75 h. The mixture was then kept at 2° for 21 h, allowed to warm to room temperature, poured on ice, and extracted with ether. The ether layer was cautiously washed with dilute sulphuric acid followed by sodium hydrogen carbonate solution, and dried ($MgSO_4$). Removal of the ether yielded a brown gum which was largely (by i.r.) the keto-olefin (5). This was separated from the mixture by chromatography [1 : 1 petroleum (b.p. 40—60°)–benzene as eluant] and *3,3-diphenyl-3,5-seco-A-norcholest-2-en-5-one* was obtained as a non-crystallisable gum (1·8 g), pure by t.l.c. and n.m.r., $[\alpha]_D$ +98·5° (*c* 0·7); $\nu_{max.}$ (KBr) 1608 (C=C) and 1721 (C=O) cm^{-1}; τ ($CDCl_3$) 2·63 (5H, m, Ph), 2·78 (5H, s, Ph), 3·94 [1H, q, $(Ph)_2C:CH$, *J* 9·9 and 4·5 Hz], and 7·3 (2H, 2q, $C:CH\cdot CH_2\cdot$).

Conversion of the Ketone (5) *into the Acetal* (7).—The keto-olefin (5) (1·6 g) in benzene (75 ml) was heated under reflux with ethane-1,2-diol (1·1 g) and toluene-*p*-sulphonic acid (0·05 g) for 45 h. The cooled mixture was washed with dilute sodium carbonate solution several times, the solvent was removed azeotropically, and the resulting gum was triturated with chilled methanol to give a white solid which afforded *5,5-ethylenedioxy-3,3-diphenyl-3,5-seco-A-norcholest-2-ene* (7) as prisms (0·77 g, 45%), m.p. 101·5—102° (ethanol) (Found: C, 84·2; H, 9·7. $C_{40}H_{56}O_2$ requires C, 84·45; H, 9·9%), $[\alpha]_D$ +12·15° (*c* 1·8); $\nu_{max.}$ ($CHCl_3$) 1629 cm^{-1} (C=C); τ ($CDCl_3$) 2·80 (10H, m, 2 × Ph), 3·56 (1H, t, $C:CH\cdot$, *J* 7 Hz), 6·23br (4H, s, $O\cdot CH_2\cdot CH_2\cdot O$), and 7·25 (2H, 2q, $C:CH\cdot CH_2\cdot$).

Dehydration of 5,5-Ethylenedioxy-3,3-diphenyl-3,5-seco-A-norcholestan-3-ol (4) *with Methanesulphonyl Chloride.*—The carbinol (4) (1·0 g) in dry pyridine (5 ml) was heated at room temperature with mesyl chloride (2·0 g, 10-fold excess) and then, with stirring, warmed at 60° for 3 h; the reaction was followed by t.l.c. (benzene eluant). The mixture was cooled, poured into iced water (120 ml), and extracted with ether (2 × 50 ml). The extract was washed with water (2 × 30 ml), dried, and evaporated to give a gum, which after chromatography (benzene) yielded the olefinic acetal (7). Recrystallisation (ethanol) afforded a sample identical with that already described.

5,5-Ethylenedioxy-2,5-seco-A-dinorcholestan-2-oic Acid (8).—To a stirred solution of the acetal (7) (1·0 g) in acetone (100 ml) was added sodium periodate (1·38 g) in water (15 ml), giving a slight turbidity. Ruthenium dioxide (*ca.* 50—75 mg) was added and after a few minutes a grey-green solid started to precipitate. The reaction was followed by t.l.c. (benzene) and was generally complete in 1—1·5 h.* Water (400 ml) was added and the mixture was extracted with chloroform (3 × 150 ml). The extract was washed with water (2 × 100 ml), filtered twice through Celite, and evaporated at room temperature *in vacuo*. Crystallisation from methanol (charcoal) yielded the *acid* (8) as needles (0·72 g, 94%), m.p. 191—191·5° (Found: C, 74·8; H, 10·4. $C_{27}H_{46}O_4$ requires C, 74·6; H, 10·7%), $[\alpha]_D$ +34·3° (*c* 1·7); $\nu_{max.}$ (KBr) 1698 (C=O) and 2667 (CO_2H) cm^{-1}; τ ($CDCl_3$) 6·06br (4H, s, $O\cdot CH_2\cdot CH_2\cdot O$) and 7·70 (2H, q, $O:C\cdot CH_2\cdot$, J_{gem} *ca.* 13 Hz).

Methyl 5,5-Ethylenedioxy-2,5-seco-A-dinorcholestan-2-oate (9).—Treatment of the acid (8) (2·2 g) with diazomethane in ether gave, upon work up, a yellow semi-solid mass. Chromatography (1 : 4 ether–benzene) afforded a colourless glass (2·2 g) which when kept in ammonia (*d* 0·880)–ethanol deposited the *ester* (9) as plates (Found: C, 74·8; H, 10·4. $C_{28}H_{48}O_4$ requires C, 74·95; H, 10·8%), $[\alpha]_D$ +28·2° (*c* 1·1); $\nu_{max.}$ (KBr) 1730 cm^{-1} (C=O); τ ($CDCl_3$) 6·1 (4H, m, $O\cdot CH_2\cdot CH_2\cdot O$), 6·4 (3H, s, OMe), and 7·74 (2H, q, $O:C\cdot CH_2\cdot$, J_{gem} 14 Hz).

The ester could be saponified by heating with 25% ethanolic potassium hydroxide under reflux for 2·5 h, cooling, pouring into water, and acidifying with acetic acid. Yields, after crystallisation from ethyl acetate–methanol, were 85—90%.

5-Hydroxy-A-nor-3-oxacholstan-2-one (11).—The acid (8) (0·20 g) in tetrahydrofuran (4 ml) was treated with *ca.* 3N-perchloric acid (1·0 ml) and kept at room temperature for 48 h. Water was added; the white precipitate afforded the *hydroxy-lactone* (11) as needles (0·13 g, 72%), m.p. 165—165·5° (from methanol) (Found: C, 76·6; H, 10·6. $C_{25}H_{42}O_3$ requires C, 76·9; H, 10·8%), $[\alpha]_D$ +35° (*c* 1·1); $\nu_{max.}$ (KBr) 1767 ($O:C\cdot O\cdot$) and 3344 ($O\cdot C\cdot OH$) cm^{-1}; τ ($CDCl_3$) 7·45 (2H, q, $O:C\cdot CH_2\cdot$, J_{gem} 16 Hz).

Ethoxyformic 5,5-Ethylenedioxy-2,5-seco-A-dinorcholestan-2-oic Anhydride (10).—The acid (8) (0·44 g) in dry chloroform (3 ml) was treated at 0° with dry triethylamine (0·1 g) and ethyl chloroformate (0·11 g). The solution was stirred at 0° for 0·25 h; t.l.c. (1 : 4 ether–benzene) then indicated the reaction to be complete. After being washed twice with iced water and dried ($MgSO_4$) the solution was evaporated at *ca.* 10° to afford the anhydride (10) as a gum, $[\alpha]_D$ +8·6° (*c* 0·2); $\nu_{max.}$ (neat) 1087, 1757, 1789, and 1812 cm^{-1}; τ ($CDCl_3$) 5·72 (2H, q, $CH_3\cdot CH_2\cdot O\cdot$, *J* 7·5 Hz), 6·06 (4H, m, $O\cdot CH_2\cdot CH_2\cdot O$), 7·65 (2H, t, $O:C\cdot CH_2\cdot$, J_{gem} 15 Hz), and 8·66 (3H, t, $CH_3\cdot CH_2\cdot O$).

When the anhydride (10) was treated with ammonia according to the method of Roberts and his co-workers [7] or with sodium azide (Weinstock's modification of the Curtius

* The time for reaction varied widely for batches of the oxide provided by different manufacturers. In the worst case no reaction occurred at all; oxide obtained from Koch–Light proved the most satisfactory.

reaction [8]) the only steroidal material isolated was the acid (8).

Ethoxyformic 5-Oxo-2,5-seco-A-dinorcholestan-2-oic Anhydride (12).—The hydroxy-lactone (11) (0·066 g) in chloroform (3 ml) was similarly treated with triethylamine (0·1 g) and ethyl chloroformate (0·028 g) to give the anhydride (12) as an oil, $[\alpha]_D$ +33·9° (*c* 0·8), $\nu_{max.}$ (neat) 1721 (C=O), and 1767 and 1818 (O:C·O·C:O) cm^{-1}; τ ($CDCl_3$) 5·75 (2H, q, $CH_3{\cdot}CH_2{\cdot}O{\cdot}$, *J* 7·0 Hz) and 7·44 (2H, q, $O{:}C{\cdot}CH_2{\cdot}$, J_{gem} 16 Hz).

Treatment of the Anhydride (12) *with Ammonia.*—Through a solution of the anhydride (12) in chloroform was bubbled ammonia at −5 to −10° for 3 h. After removal of the chloroform and ammonia *in vacuo* the residue was treated with boiling chloroform, which gave a white solid (ammonium chloride) and a solution which was washed with water and dried ($MgSO_4$). Removal of the solvent and treatment with ether afforded a white solid which crystallised from acetone as prism clusters, m.p. 188—189° (for spectral details, see Discussion section).

5,5-Ethylenedioxy-2,5-seco-A-dinorcholestan-2-oyl Chloride (14).—The acid (8) (1·3 g) in carbon tetrachloride (dry; 50 ml) was treated with triphenylphosphine (0·86 g, 1·05 mol. equiv.) and the mixture was stirred at room temperature for 6 days. The solvent was removed at 15° *in vacuo*. The i.r. spectrum of the crude solid indicated that *ca.* 10—15% of the acid was unchanged. Column chromatography with 1 : 2 : 3 acetone–ethyl acetate–cyclohexane (*cf.* ref. 15) gave triphenylphosphine followed by a two-component mixture. Chromatography of this mixture with 1 : 5 : 10 : 29 acetic acid–ethyl acetate–acetone–cyclohexane as eluant produced unchanged acid (8) (0·02 g) and the *acid chloride* (14) as a white solid (0·45 g), m.p. 119·5—120·5° (from n-hexane), $[\alpha]_D$ +42·8° (*c* 1·4); $\nu_{max.}$ (KBr) 1770 (C=O) and 914 (COCl) cm^{-1}; τ ($CDCl_3$) 6·31 (4H, s, $O{\cdot}CH_2{\cdot}CH_2{\cdot}O$) and 7·54 (2H, q, $O{:}C{\cdot}CH_2{\cdot}$, J_{gem} 16 Hz).

Treatment of the Acid Chloride (14) *with Ammonia.*—Compound (14) (0·38 g) was stirred with ammonia (*d* 0·880, 25 ml) at room temperature for 6 days. The solution was diluted with water and the mixture evaporated at 35—40°. Final drying was achieved by successive azeotropic treatments with chloroform. The solid obtained crystallised from ethanol to afford *5-oxo-2,5-seco-A-dinorcholestan-2-amide* (15) as needles (Found: C, 76·7; H, 10·8; N, 3·4. $C_{25}H_{43}NO_2$ requires C, 77·1; H, 11·1; N, 3·6%), $[\alpha]_D$ +55·7° (*c* 0·6); $\nu_{max.}$ (KBr) 1645, 1669, and 3333 cm^{-1}.

In a repeat experiment with 10 ml of ammonia solution for only 3 days the main product after initial work-up was 5-hydroxy-A-nor-3-azacholestan-2-one (13), m.p. 189° (prism clusters from acetone). The mother liquor contained a small quantity of the keto-amide (15).

We thank Mr. A. C. Thomas for microanalyses, Mrs. E. A. Allenby for help with the preparation of some of the early intermediates, and Mrs. R. A. Chittenden and Mrs. C. E. Dean for determining the n.m.r. spectra.

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[15] A. Lamotte, A. Francina, and J.-C. Merlin, Coloq. Internationaux du Centre Nationale de la Recherche Scientifique No. 182, Chimie Organique du Phosphore, Paris, 19—24 Mai, 1967.