Hydroxy-steroids. Part X.* The Preparation and Properties of A-Homo-5α-cholestan-4-one

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The formation of A-homo-5α-cholestan-4-one from 5α-cholestan-3-one and diazomethane (N. A. Nelson and R. N. Schut, *J. Amer. Chem. Soc.*, 1959, **81**, 6486) was re-investigated. Using pre-formed diazomethane in ether–methanol the reaction was very slow. However, in the presence of potassium hydroxide ring expansion occurred smoothly to give a mixture from which the A-homo-4-ketone was readily isolated.

It was confirmed that base-catalysed condensations occur at position 3 of the A-homo-ketone. The 3-bromo-derivative is dehydrobrominated to a mixture of the non-conjugated and conjugated ketones A-homo-5α-cholest-1- and -2-en-4-one, the former of which is the more stable.

RING expansion of 5α-cholestan-3-one by the Tiffeneau sequence afforded a product [1] shown by later work to be A-homo-5α-cholestan-4-one, and obtained more directly from cholestanone with diazomethane.[2] In this reaction an excess of *N*-nitrosomethylurea (5 mol.) was added to 5α-cholestan-3-one in ether–methanol containing potassium hydroxide (*i.e.*, *in situ* conditions, see below). Repetition of the experiment showed that no 5α-cholestan-3-one remained in the product: careful chromatography afforded the A-homo-4-ketone in 46% yield, and smaller amounts (*ca.* 2%) of A-homo-5α-cholestan-3-one and an A-dihomo-ketone, in agreement with Nelson and Schut.[2]

From related work [3] with α-decalones it seemed possible that the relative amounts of the products might be changed by treating 5α-cholestan-3-one with pre-formed diazomethane (*ex situ* conditions). When cholestanone and diazomethane (up to 4 mol.) were kept at 0° in ether–methanol for 5 hr., 95% of the ketone was unchanged. (The infrared procedure [2] for following the conversion to A-homo-compounds is usefully supplemented by gas–liquid chromatographic analysis.) Surprisingly, with a small amount of potassium hydroxide (*ca.* 2 mol.) present in the solution, but the conditions otherwise unchanged, reaction occurred smoothly. The product obtained using 4 mol. of diazomethane contained A-homoketones (75%), starting material (15%), and other substances (10%): from this the A-homo-4-ketone (I) was conveniently isolated, by crystallisation, in 42% yield. While hydroxylic solvents and Lewis acids are known to promote ketone–diazomethane reactions,[4] and bases to influence the relative proportions of the product,[3] we are not aware of cases in which the rates are increased markedly by strong alkalis. The effect is unlikely to arise from reaction between cholestanone and the base, since this leads to equilibration with the enolate anion which would be unreactive to the nucleophilic attack of diazomethane. It may be that a hydroxide–diazomethane interaction generates a species (*e.g.*, $^{-}CH_2$–N=N–OH) of high nucleophilicity, but there is no evidence to substantiate this suggestion.

The hydroxymethylene derivative of the A-homo-4-ketone was shown [2] to have formula (IV) by oxidising it to the 3,4-seco-A-homo-diacid (VII): the latter's structure was based on a synthesis from 5α-cholestan-3-one in which the first step, condensation with dimethyl oxalate, was considered to occur at position 2 (ref. 2).

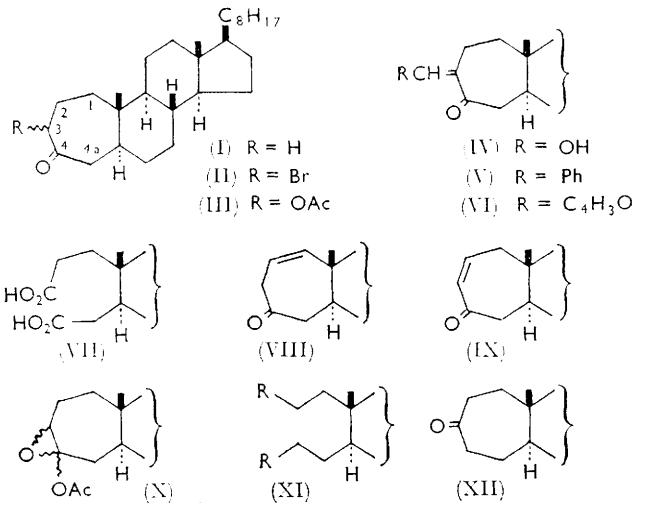
* Part IX, P. C. Cherry, W. R. T. Cottrell, G. D. Meakins, and E. E. Richards, *J. Chem. Soc.* (*C*), 1967, 181.

[1] M. W. Goldberg and H. Kirchensteiner, *Helv. Chim. Acta*, 1943, **26**, 288.

[2] N. A. Nelson and R. N. Schut, *J. Amer. Chem. Soc.*, 1959, **81**, 6486.

[3] C. D. Gutsche and H. H. Peter, *J. Amer. Chem. Soc.*, 1955, **77**, 5971.

[4] See, *inter alia*, H. O. House, E. J. Grubbs, and W. F. Gannon, *J. Amer. Chem. Soc.*, 1960, **82**, 4099.



Confirmation was provided in the present work by cyclising the seco-diacid to 5α-cholestan-3-one. (Condensation of A-homo-5α-cholestan-4-one at position 4a would have led to a 4,4a-seco-diacid and thence to 5α-cholestan-4-one.) Although oily products had been obtained in attempts to condense the homo-ketone (I) with benzaldehyde,[1] this reaction and that with furfuraldehyde afforded crystalline products, (V) and (VI), under controlled basic conditions.[5] Both compounds were ozonised to the 3,4-seco-diacid (VII).

Dehydrobromination of a monobromo-A-homo-4-ketone [now established to be the 3-derivative (II)] was reported to give an αβ-unsaturated ketone (not isolated), from which a dicarboxylic acid, $C_{27}H_{46}O_4$, was formed by oxidation.[1] In our work the dehydrobromination resulted in a 1 : 1 mixture of two unsaturated ketones absorbing at 1705 and 1670 cm.$^{-1}$. Spectroscopic examination of the non-conjugated ketone ($\bar{\nu}_{max.}$ 1705 cm.$^{-1}$) showed it to be A-homo-5α-cholest-1-en-4-one (VIII). This compound did not isomerise under acidic conditions, behaviour recalling that of A-homo-cholest-4a-en-3-one.[6] Although the conjugated ketone (IX) could not be fully purified it was shown to be isomerised, at least partially, to the non-conjugated isomer (VIII) by acid or base.

Reduction of A-homo-5α-cholestan-4-one (I) with lithium aluminium hydride or with sodium in propan-2-ol afforded one alcohol in fairly high yield. The enol-acetate, probably the Δ^3-compound, was converted to the epoxy-ester (X) which was rearranged by acid to the acetoxy-ketone (III). The spectroscopic data (see Experimental section) did not lead to configurational assignments at C-3 in compounds (II), (III), and (X).

An alternative route from 2,3-seco-5α-cholestane-2,3-dioic acid to A-homo-5α-cholestan-3-one (XII),[2] *via* the intermediates (XI; R = OH,[7] I, and CN), gave a somewhat higher overall yield (11%) than that involving a modified Arndt–Eistert sequence (8% yield).[2]

[5] D. J. Hampson, G. D. Meakins, and D. J. Morris, *J. Chem. Soc.* (*C*), 1966, 1277.

[6] W. S. Johnson, M. Neeman, S. P. Birkeland, and N. A. Fedoruk, *J. Amer. Chem. Soc.*, 1962, **84**, 989.

EXPERIMENTAL

For general directions and details of g.l.c. see Part IV.[8]

Reactions between 5α-Cholestan-3-one and Diazomethane.—(*a*) In situ *conditions*.[2] *N*-Nitrosomethylurea (18 g.) was added at 0° to a stirred solution of 5α-cholestan-3-one (13·2 g.) in dry ether (500 ml.)–methanol (850 ml.) containing potassium hydroxide (28 g.), and the mixture stirred at 0° for 5 hr. 10% Hydrochloric acid (300 ml.) was added, the mixture filtered, and the organic layer worked up to give material (11·5 g.) shown by g.l.c. to be free of 5α-cholestan-3-one. Adsorption on alumina (1000 g., grade H) and elution with light petroleum–benzene (17 : 3) gave A-dihomo-5α-cholestanone [210 mg., m. p. 110—112°, after crystallisation from methanol; $\bar{\nu}_{max.}$ 1699 and 1320 cm.$^{-1}$ (lit.,[2] m. p. 111·5—112°; $\bar{\nu}_{max.}$ 1698 and 1320 cm.$^{-1}$)] and then A-homo-5α-cholestan-3-one (XII) {195 mg., m. p. 82—83°, after two crystallisations from methanol, $[\alpha]_D$ +50° (*c* 0·8); $\bar{\nu}_{max.}$ 1708, 1334, and 1315 cm.$^{-1}$ (lit.[2], m. p. 85—85·5°; $\bar{\nu}_{max.}$ 1703, 1333, and 1315 cm.$^{-1}$)}. Light petroleum–benzene (3 : 1) afforded A-homo-5α-cholestan-4-one (I) (6·3 g.), m. p. 87—88° (from methanol), $[\alpha]_D$ +31° (*c* 1·1); $\bar{\nu}_{max.}$ 1704 and 1334 cm.$^{-1}$ (lit.,[2] m. p. 87—88°; $\bar{\nu}_{max.}$ 1704 and 1333 cm.$^{-1}$, and [1] m. p. 85—87°, $[\alpha]_D$ +50°).

(*b*) Ex situ *conditions without potassium hydroxide*. Solutions of 5α-cholestan-3-one (1·6 g.) in ether (40 ml.)–methanol (60 ml.) and diazomethane [4 mol., prepared (80% yield) from *N*-nitrosomethylurea (2·1 g.)] in ether (40 ml.) were mixed and kept at 0° for 5 hr. The product, shown by g.l.c. to be 95% 5α-cholestan-3-one (retention time 31 min.) and *ca.* 5% A-homo-5α-cholestan-4-one (retention time 44 min.), was chromatographed as above to give 5α-cholestan-3-one [eluted with light petroleum–benzene (4 : 1), 1·2 g., m. p. 126—127°, after crystallisation from acetone–methanol], identified by infrared examination.

(*c*) Ex situ *conditions with potassium hydroxide*. Experiment (*b*) was repeated, but with potassium hydroxide (0·4 g.) present in the cholestanone solution before mixing with the ethereal diazomethane. The g.l.c. trace of the product showed peaks after 31 min. (15%, 5α-cholestan-3-one), 33 min. (broad, *ca.* 10% of unidentified material), and 44 min. (75%, A-homo-5α-cholestan-4-one). Two crystallisations from ethanol afforded the A-homo-ketone (I) (0·69 g.), m. p. and mixed m. p. 86—88°.

Compounds (IV)—(VII).—The conditions used in condensing A-homo-5α-cholestan-4-one (I) with ethyl formate and with furfuraldehyde were similar to those described with 5α-cholestan-3-one in ref. 5. The 3-hydroxymethylene derivative (IV) (91% yield) had m. p. 99—100°, $[\alpha]_D$ +13° (*c* 0·6); $\bar{\nu}_{max.}$ 1640 and 1585 cm.$^{-1}$; $\lambda_{max.}$ 278 mμ (ε 7100) (lit.,[2] m. p. 100·5—103°, $\bar{\nu}_{max.}$ 1640 and 1585 cm.$^{-1}$). *3-Furfurylidene-A-homo-5α-cholestan-4-one* (VI) (48% yield) had m. p. 114—118° (from ethanol–methanol), $[\alpha]_D$ −97° (*c* 0·8) (Found: C, 82·6; H, 10·2. $C_{33}H_{50}O_2$ requires C, 82·8; H, 10·5%); $\bar{\nu}_{max.}$ 1680 cm.$^{-1}$; $\lambda_{max.}$ 321 mμ (ε 20,900).

Benzaldehyde (0·45 g., distilled before use) in ethanol (5 ml.) was added to the A-homo-ketone (I) (1·2 g.) in 0·1N-ethanolic potassium hydroxide (100 ml.), and the stoppered mixture kept at 20° for 12 hr. The material isolated with ether was chromatographed on silica gel (70 g.). Elution with light petroleum–benzene gave *3-benzylidene-A-homo-5α-cholestan-4-one* (V) (0·64 g.), m. p.

[7] C. W. Shoppee and J. C. P. Sly, *J. Chem. Soc.*, 1958, 3458.

[8] G. M. L. Cragg, C. W. Davey, D. N. Hall, G. D. Meakins, (Mrs.) E. E. Ritchards, and T. L. Whateley, *J. Chem. Soc.* (*C*), 1966, 1266.

141—144° (from acetone–methanol), $[\alpha]_D$ −119° (*c* 0·5) (Found: C, 85·4; H, 10·8. $C_{35}H_{52}O$ requires C, 86·0; H, 10·7%); $\bar{\nu}_{max.}$ 1685 cm.$^{-1}$; $\lambda_{max.}$ 286 mμ (ε 17,400). This compound (0·6 g.) was treated with ozone as in ref. 5, and the product heated at 100°/15 mm. for 24 hr. to remove benzoic acid. Crystallisation of the residue from ether–pentane afforded 3,4-seco-A-homo-5α-cholestane-3,4-dioic acid (VII) (0·35 g.), m. p. 227—230°, $[\alpha]_D$ −19° (*c* 0·6); $\bar{\nu}_{max.}$ 1700 cm.$^{-1}$ (lit.,[2] m. p. 234—235°).

Acid (VII) was also obtained (51% yield) by ozonolysis of the furfurylidene derivative (VI), and (78% yield, conditions of ref. 5) by oxidising the hydroxymethylene compound (IV) with alkaline hydrogen peroxide. Pyrolysis at 350—370°/0·1 mm. of an intimate mixture of this acid (1 g.) and barium carbonate (2·5 g.) gave a distillate (0·45 g.) shown by g.l.c. to contain 70% 5α-cholestan-3-one (retention time 30·5 min.) and 30% of two compounds with retention times 39 and 47 min. Chromatography on alumina (40 g., grade H) afforded 5α-cholestan-3-one {eluted with light petroleum–benzene (4 : 1), 0·29 g., m. p. 128—129° (from acetone–methanol), $[\alpha]_D$ +40° (*c* 0·5)}, identified further by infrared examination. A mixture of this ketone and 5α-cholestan-4-one showed g.l.c. peaks whose retention times differed by 2 min.

3ξ-*Bromo*-A-*homo*-5α-*cholestan*-4-*one* (II).— The homoketone (I) (1·2 g.) in acetic acid (40 ml.) containing 48% hydrogen bromide in acetic acid (0·2 ml.), was treated with bromine (0·51 g.) in acetic acid (2 ml.). After 4 hr. at 20° the mixture was worked up and the product chromatographed on silica gel (60 g.). Light petroleum–benzene (9 : 1) gave the bromo-ketone (0·85 g.), m. p. 110—111°, $[\alpha]_D$ +13° (*c* 0·7) (Found: C, 69·6; H, 9·4; Br, 16·6. Calc. for $C_{28}H_{47}BrO$: C, 70·0; H, 9·8; Br, 16·7%) (lit.,[1] m. p. 113—115°, no rotation recorded); $\bar{\nu}_{max.}$ 1714 cm.$^{-1}$; R.D. (MeOH, *c* 0·1), [M] +680° (320 mμ) and −1200° (290 mμ), *a* +19.

This bromo-ketone (710 mg.) in dry dimethylformamide (20 ml.) was heated under reflux with lithium bromide (3 g.) and lithium carbonate (3 g.) under nitrogen for 5 hr. The product, isolated with ether and shown by g.l.c. to be a 1 : 1 mixture [$\bar{\nu}_{max.}$ 1708 and 1670 cm.$^{-1}$, $\lambda_{max.}$ 229 mμ (ε 4000)], was chromatographed on neutral alumina (50 g.). Elution with light petroleum–benzene (13 : 7) gave A-*homo*-5α-*cholest*-1-*en*-4-*one* (VIII) (110 mg.), m. p. 94—95° (from acetone–methanol), $[\alpha]_D$ +31° (*c* 0·7) (Found: C, 84·5; H, 11·7. $C_{28}H_{46}O$ requires C, 84·35; H, 11·6%); $\bar{\nu}_{max.}$ 1705 and 758 (*cis*-CH=CH–) cm.$^{-1}$; no maximum between 200 and 250 mμ. The intensity of the infrared peak at 1705 cm. was not changed by treating the compound (50 mg.) in ethanol (25 ml.) with 2N-sulphuric acid (1 ml.) at 20°.

Light petroleum–benzene (3 : 2) eluted an oil (IX), $\bar{\nu}_{max.}$ 1670 cm.$^{-1}$, $\lambda_{max.}$ 229 mμ (ε *ca.* 9000). After treatment of this product with sulphuric acid (as above) or with 2N-potassium hydroxide (1 ml.), there was no selective absorption at 229 mμ, and the ratio of the intensities of the infrared bands at 1705 and 1670 cm.$^{-1}$ was approx. 4 : 1.

Further Reactions of A-*Homo*-5α-*cholestan*-4-*one* (I).— Reduction of the homoketone with lithium aluminium hydride and with sodium in propan-2-ol under standard conditions gave, in yields of 69 and 73%, respectively, A-*homo*-5α-*cholestan*-4ξ-*ol*, m. p. 112—114°, $[\alpha]_D$ +23° (*c* 0·5) (Found: C, 83·75; H, 12·6. $C_{28}H_{50}O$ requires C, 83·5; H, 12·5%); $\bar{\nu}_{max.}$ 3620 cm.$^{-1}$.

A solution of the homoketone (1·5 g.) in isopropenyl acetate (12 ml.) containing concentrated sulphuric acid (2 drops) was heated under reflux for 1 hr., then concentrated to a volume of *ca.* 9 ml. The mixture was warmed with fused sodium acetate (0·4 g.) and chloroform (10 ml.), filtered, evaporated at 20°/10 mm., and the residue chromatographed on silica gel (80 g.). Light petroleum–benzene (9 : 1) eluted 4-*acetoxy*-A-*homo*-5α-*cholest*-3-*ene* (1·2 g.), m. p. 91—94° (from ethyl acetate–methanol), $[\alpha]_D$ +20° (*c* 0·7) (Found: C, 81·5; H, 11·2. $C_{30}H_{50}O_2$ requires C, 81·4; H, 11·4%); $\bar{\nu}_{max.}$ 1752 cm.$^{-1}$. Treatment of this compound (1 g.) in benzene (40 ml.) with 0·1M-perbenzoic acid in benzene (60 ml.) at 20° for 36 hr. afforded the *epoxy-ester* (X) (0·66 g.), m. p. 109—111° (from methanol), $[\alpha]_D$ +22° (*c* 0·6) (Found: C, 78·7; H, 11·1. $C_{30}H_{50}O_3$ requires C, 78·55; H, 11·0%); $\bar{\nu}_{max.}$ 1770 and 1760 cm.$^{-1}$. The epoxy-ester (0·62 g.) in glacial acetic acid (80 ml.) was mixed at 20° with acetic acid (10 ml.) containing 60% perchloric acid (1 ml.). Isolation with ether after 20 min. gave material showing hydroxyl absorption in the infrared spectrum. This was kept with pyridine (12 ml.)–acetic anhydride (12 ml.) for 12 hr., worked up, and chromatographed on silica gel (40 g.). Benzene eluted the *acetoxy-ketone* (III) (0·18 g.), m. p. 112—116°, $[\alpha]_D$ +26° (*c* 0·9) (Found: C, 78·3; H, 11·2. $C_{30}H_{50}O_3$ requires C, 78·55; H, 11·0%); $\bar{\nu}_{max.}$ 1748 and 1728 cm.$^{-1}$; R.D. (MeOH, *c* 0·1), [M] −530° (302·5 mμ) and +1300° (270 mμ), *a* −18.

Route to A-*Homo*-5α-*cholestan*-3-*one* (XII).—Reduction of 2,3-seco-5α-cholestane-2,3-dioic acid [5,9] with an excess of lithium aluminium hydride gave the 2,3-diol (XI; R = OH) (79%), m. p. 157·5—159°, $[\alpha]_D$ +7° (*c* 0·8) (lit.,[7] m. p. 155—156°, $[\alpha]_D$ +5·2°). This diol (3·2 g.) was dissolved at 20° in a solution of 88% phosphoric acid (28 ml.) containing phosphoric oxide (13 g.), potassium iodide (20 g.) was added, and the mixture stirred at 120° for 7 hr. Isolation with ether gave 2,3-*di-iodo*-2,3-*seco*-5α-*cholestane* (XI; R = I) (4·7 g.), m. p. 89—90° (from methanol), $[\alpha]_D$ −28° (*c* 1·1) (Found: C, 52·3; H, 7·5; I, 40·15. $C_{27}H_{48}I_2$ requires C, 51·95; H, 7·7; I, 40·6%). A solution of compound (5·9 g.) and potassium cyanide (8 g.) in dimethyl sulphoxide (200 ml.) was stirred at 80° for 3 hr. Standard working up was followed by chromatography on neutral alumina (500 g.). Light petroleum–benzene (1 : 1) eluted 2,3-*dicyano*-2,3-*seco*-5α-*cholestane* (XI; R = CN) (3·7 g.), m. p. 92—93° (from ethanol), $[\alpha]_D$ −9° (*c* 1·1) (Found: C, 81·4; H, 11·4; N, 6·6. $C_{29}H_{48}N_2$ requires C, 81·8; H, 11·4; N, 6·6%); $\bar{\nu}_{max.}$ 2250 cm.$^{-1}$.

The dicyanide (2 g.) was heated under reflux for 7 hr. under nitrogen with a solution of sodium hydroxide (15 g.) in water (10 ml.)–ethyleneglycol (60 ml.). Cooling, washing with ether, acidification with 2N-sulphuric acid, and extraction with ether afforded 3,4-*seco*-A-*dihomo*-5α-*cholestane*-3,4-*dioic acid* (XI; R = CO_2H) (1·2 g.), m. p. 229—231°, $[\alpha]_D$ −17° (*c* 1·1) (Found: C, 74·8; H, 10·8. $C_{29}H_{50}O_4$ requires C, 75·3; H, 10·9%); $\bar{\nu}_{max.}$ 1710 cm.$^{-1}$. Pyrolysis at 350—370°/0·1 mm. of an intimate mixture of this acid (1 g.) and barium carbonate (2·4 g.) gave a distillate which was chromatographed on alumina (40 g.). Light petroleum–benzene (4 : 1) afforded A-homo-5α-cholestan-3-one (XII) (0·26 g.), m. p. 82—83°, identified by comparison (mixed m. p., infrared spectra) with authentic material.

We thank Professor W. Klyne for the R.D. examinations, and the S.R.C. for a grant (to D. J. M.).

[6/1216 *Received, September 27th,* 1966]

[9] H. Heymann and L. F. Fieser, *Helv. Chim. Acta*, 1952, **35**, 631.