478. *Steroids. Part III.** 3-*Methyl*-A-*norcholest*-3(5)-*ene*.

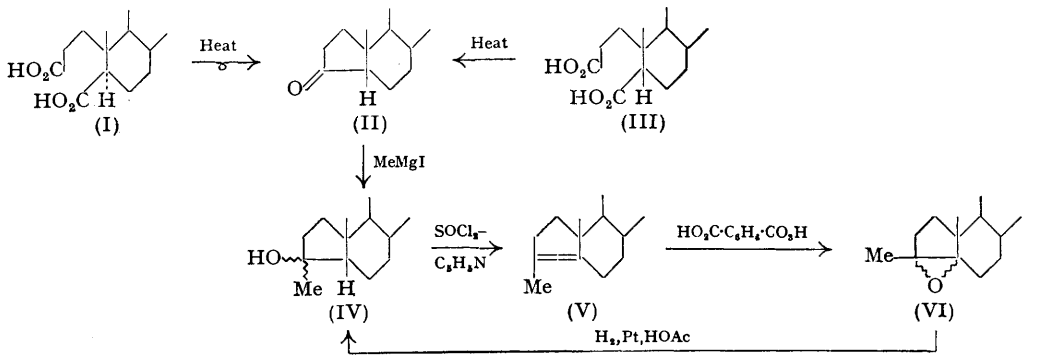
By C. W. Shoppee and G. H. R. Summers.

The partial synthesis of this hydrocarbon is described.

It has been shown (Schmid and Kägi, *Helv. Chim. Acta*, 1950, **33**, 1582) that the saturated hydrocarbon 3 : 5-*cyclo*cholestane is converted by treatment with hydrogen chloride in boiling acetic acid into an isomeric unsaturated hydrocarbon, m. p. 65°, $[\alpha]_D$ +58°. It was suggested that the reaction involved fission of the $C_{(4)}$–$C_{(5)}$ bond and that the product was 3-methyl-A-norcholest-3(5)-ene † (V). This structure was supported by conversion through the ozonide into a diketone (cf. Heard and Ziegler *J. Amer. Chem. Soc.*, 1951, **73**, 4046), which by Wolff–Kishner reduction gave cholest-3-ene, cholest-4-ene, and the corresponding tricyclic hydrocarbon.

We have obtained the hydrocarbon (V) by partial synthesis from the pyroketone (II) obtained by pyrolysis of either 3 : 4-*seco*-5α-cholestane-3 : 4-dicarboxylic acid † (I) or 3 : 4-*seco*-5β-cholestane-3 : 4-dicarboxylic acid (III).

Cholesterol was oxidised to 3 : 4-*seco*cholest-5-ene-3 : 4-dicarboxylic acid (Diels' acid), which was converted into the αβ-unsaturated pyroketone; hydrogenation of this in the presence of palladium gave the saturated pyroketone (II) (cf. Windaus, *Ber.*, 1912, **45**, 1316; 1919, **52**, 170). By treatment with methylmagnesium iodide, the ketone (II) yielded a crystalline alcohol (IV), which may be identical with the difficultly crystallisable alcohol, m. p. 55°, $[\alpha]_D$ +30°, obtained by Schmid and Kägi by catalytic hydrogenation of the epoxide (VI). Dehydration of the alcohol with thionyl chloride–pyridine at 20° furnished 3-methyl-A-norcholest-3(5)-ene (V), double m. p. 59° and 62°, $[\alpha]_D$ +54°. This did not give a depression with a genuine specimen, m. p. 63°, kindly supplied by Professor Schmid through the good offices of Professor P. Karrer; it gave a yellow colour with tetranitromethane and a positive Liebermann–Burchard reaction (red ⟶ green), and was characterised by conversion into the beautifully crystalline, extremely stable ozonide, m. p. 114°, and into the epoxide (VI), m. p. 98°, $[\alpha]_D$ +35°. These derivatives gave no depression of the m. p. when mixed with specimens prepared by the procedure of Schmid and Kägi; we are most grateful to Professor Schmid of the University of Zurich for carrying out the mixed melting point determination on the ozonide.

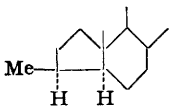


Schmid and Kägi (*loc. cit.*) describe two saturated hydrocarbons, obtained by catalytic hydrogenation of 3-methyl-A-norcholest-3(5)-ene (V); it seems possible to deduce their respective configurations from their molecular rotations. The *trans*-A/B-steroid hydrocarbons are all less dextrotatory than their *cis*-A/B-isomerides; this is also true for A-nor-5α-cholestane ($[M]_D$ +90°) and A-nor-5β-cholestane ($[M]_D$ +118°) (Lettré, *Z. physiol. Chem.*, 1933, **221**, 73). It is known that methyl groups attached to the terminal rings of the steroid nucleus make approximately the same rotational contribution as hydrogen atoms (cf. Klyne, *Chem. and Ind.*, 1952, 172), and this point is illustrated in

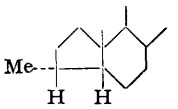
* Part II, *J.*, 1952, 1790.

† For nomenclature see *J.*, 1951, 3534.

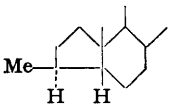
the present context by 3-methyl-A-norcholest-3(5)-ene (V; $[M]_D$ +215°) and its 3-nor-homologue, m. p. 80°, $[M]_D$ +200° (Lettré, *loc. cit.*; Grasshoff, *Z. physiol. Chem.*, 1934, **223**, 249). Since catalytic hydrogenation of (V) will involve *cis*-addition (cf. Linstead, Doering, Davis, Levine, and Whetstone, *J. Amer. Chem. Soc.*, 1942, **64**, 1985) it is suggested that the saturated hydrocarbon, m. p. 112°, is 3β-methyl-A-nor-5α-cholestane (VII; $[M]_D$ +101°) and that the liquid isomeride is 3α-methyl-A-nor-5β-cholestane (VIII; $[M]_D$ +160°).



(VII)



(VIII)



(IX)

A third isomeride, m. p. 44°, $[\alpha]_D$ +54°, obtained by hydrogenation of 3 : 5-*cyclo*cholestane by Schmid and Kägi, must belong to the *cis*-A-nor/B-series and may be 3β-methyl-A-nor-5β-cholestane (IX).

Experimental

M. p.s were determined thermo-electrically on a Kofler block (limit of error ±2°). Solvents for chromatographic operations were rigorously purified and dried and, unless stated otherwise, aluminium oxide (Spence type H, activity ~II) was used. For drying of ethereal extracts, brief treatment with anhydrous sodium sulphate was used.

3 : 4-seco*Cholest-5-ene*-3 : 4-*dicarboxylic Acid*.—This acid was satisfactorily prepared only by a modification of Diels and Abderhalden's method (*Ber.*, 1903, **36**, 3177). Potassium hypobromite solution was prepared by adding well-cooled bromine (32 g.) to vigorously stirred aqueous potassium hydroxide (17 g. in 375 c.c.) cooled externally by solid carbon dioxide–methanol. Finely powdered commercial cholesterol (25 g.) was added to this solution and the mixture shaken vigorously for 20 hours. Heat was generated during the reaction, and the yellow alkaline solution developed a thick froth. The solution was filtered from a sludge of unchanged cholesterol, and the filtrate, after cooling (ice–salt), acidified with 4N-sulphuric acid. The precipitate, a white semisolid mass, was filtered (on hardened filter-paper), and washed repeatedly with water. The product was warmed with glacial acetic acid and filtered off, and the granular material crystallised from aqueous dioxan, giving the dicarboxylic acid in fine needles, m. p. 296—298° (lit., 297°). The dimethyl ester, prepared by means of diazomethane, crystallised from methanol in needles, m. p. 68—70° (lit., 69°).

A-*Norcholest-5-en-3-one*.—The foregoing dicarboxylic acid (6 g.) was refluxed with acetic anhydride (10 c.c.) for 4 hours. The residual brown oil was slowly distilled during 3 hours at 0·1—0·05 mm. and an oily distillate collected at 270—320°. This product was dissolved in ether, washed with 2N-sodium hydrogen carbonate solution and water, and dried, and recovered by evaporation. The resulting oil failed to crystallise from any solvent. It was therefore refluxed with methanol (300 c.c.) for 1 hour, and the supernatant clear liquid decanted from tarry matter, cooled, and treated with hydroxylamine sulphate (5 g.) and crystalline sodium acetate (9 g.) in water (25 c.c.). This solution was refluxed for an hour and then the methanol was partly removed under reduced pressure. The insoluble oxime was filtered off, washed with water, dried on porous porcelain, and crystallised from pentane, to give A-norcholest-5-en-3-one oxime in plates, m. p. 176° (lit., 176°). The oxime was decomposed by refluxing ethanolic sulphuric acid (3 hours), the solution neutralised with ammonia, and the solvent removed under reduced pressure. The residual oil was extracted with ether, and the ethereal extract purified in the usual way; evaporation gave an oil (2·1 g.), which was further purified by filtration of a pentane solution through a column of aluminium oxide. A-Norcholest-5-en-3-one was obtained as needles from methanol–acetone, m. p. 95—96° (lit., 96°), giving a yellow colour with tetranitromethane–chloroform.

A-*Nor*-5β-*cholestan*-3-*one* (II).—A-Norcholest-5-en-3-one (1·8 g.) in 1 : 1 ether–acetic acid (40 c.c.) was shaken at room temperature in an atmosphere of hydrogen in the presence of palladium oxide (350 mg.). The theoretical uptake of hydrogen was attained within 0·75 hour and the hydrogenation then stopped. After removal of the catalyst the solution was evaporated to dryness under reduced pressure, and the residual oil extracted with ether. The ethereal extract was washed successively with 2N-hydrochloric acid, water, 2N-sodium hydrogen carbonate, and water, dried, and evaporated, to give an oil (1·42 g.). This was chromatographed in pentane and on aluminium oxide (62 g.), prepared in pentane; A-norcholestan-3-one was

isolated by elution with pentane–benzene (9 : 1 and 4 : 1). Recrystallised from methanol it formed needles, m. p. 74° (lit., 73—74°), and gave no colour with tetranitromethane–chloroform.

3-*Methyl*-A-*norcholest*-3(5)-*ene* (V).—A Grignard reagent from magnesium (0·81 g.), methyl iodide (0·9 c.c.), and dry ether (8 c.c.) was cooled to 0° and a solution of A-norcholestan-3-one (1·4 g.) in dry ether (20 c.c.) added during 0·25 hour. The mixture was heated under reflux for 0·25 hour kept for 1 hour, and then poured on crushed ice and ammonium chloride. The ethereal solution, after being washed with water, was dried and evaporated, to give a colourless oil (0·95 g.). This failed to crystallise but partly solidified from pentane solution, to yield hygroscopic crystals, m. p. 46—56°.

This product, in anhydrous pyridine (5 c.c.), was treated at 0° with redistilled thionyl chloride (0·5 c.c.). The solution became dark red and after 0·5 hour was allowed to acquire room temperature (18—20°). The pyridine was removed at 10 mm., and the residue taken up in ether, and purified in the usual way. The resultant oil (0·54 g.) was chromatographed in pentane on aluminium oxide (15 g.), prepared in pentane; 3-methyl-A-norcholest-3(5)-ene was isolated by elution with pentane (6 × 25 c.c.) as an oil, which solidified and then crystallised from methanol–acetone as prisms, m. p. 62° after partial transformation into thin needles at 59—60°; the melt solidified on slight cooling and remelted at 60—61°. A mixture with a specimen, m. p. 63° (after partial transformation into needles at 60—61°), supplied by Professor Schmid, melted at 62—63°. The hydrocarbon had $[\alpha]_D$ +54°±3° (*c*, 1·280 in chloroform), and gave a positive Liebermann–Burchard reaction (red ⟶ brown ⟶ green) and a yellow colour with tetranitromethane in chloroform. The epoxide, obtained by use of permonophthalic acid, after repeated crystallisation from ether–methanol had m. p. 97—98°, $[\alpha]_D$ +35°±3° (*c*, 0·656 in chloroform), and gave no depression when mixed with Professor Schmid's specimen. The ozonide, crystallised from ether–methanol, formed prismatic needles, m. p. 111—114°, undepressed when mixed with Professor Schmid's preparation; the mixture melted at 113·5—116·5°, and after resolidification melted at 113—117°.

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