272. *Studies in the Sterol Group. Part XXVI. 7-Methylenecholesterol.*

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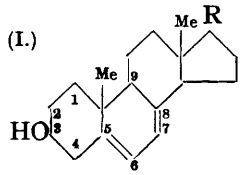
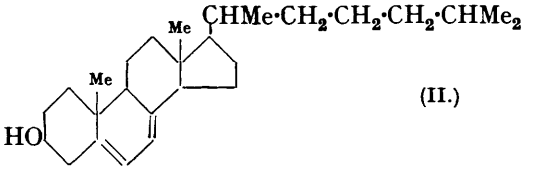
Ergosterol (I, R = $CHMe{\cdot}CH{:}CH{\cdot}CHMe{\cdot}CHMe_2$) and 22-dihydroergosterol (I, R = $CHMe{\cdot}CH_2{\cdot}CH_2{\cdot}CHMe{\cdot}CHMe_2$) (Windaus and Langer, *Annalen*, 1933, **508**, 105) are both converted into antirachitic products on irradiation with ultra-violet light. It is therefore justifiable to assume that the necessary condition to be fulfilled in order that a sterol should be a provitamin-*D* is that it shall contain a system of conjugated ethylenic linkages at C_5—C_6 and C_7—C_8. The initial object of this investigation was to prepare and examine sterols having this unsaturated grouping, such as 7-dehydrocholesterol (II). Windaus,

(I.)





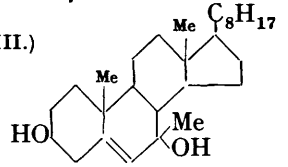
(II.)

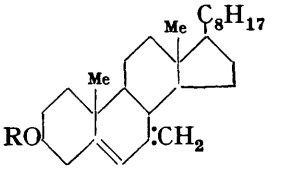
Lettré, and Schenck (*Annalen*, 1935, **520**, 98) have, however, anticipated us with a description of (II), which was found to give a highly antirachitic product on irradiation with ultra-violet light. We have consequently directed our attention to a study of an alternative method for the introduction of an unsaturated centre in cholesterol between C_7 and C_8.

Treatment of 7-ketocholesteryl acetate with 3 mols. of methylmagnesium iodide gives *7-hydroxy-7-methylcholesterol* (III), m. p. 165°, characterised by its *3-monobenzoate*, m. p. 175°, and its *3-monoacetate*, m. p. 164°. Sublimation of the monobenzoate in high vacuum gives *7-methylenecholesteryl benzoate* (IV; R = COPh), m. p. 141°, also obtained by dehydration of the diolmonobenzoate by means of *p*-toluenesulphonyl chloride and by the Darzens method (*Compt. rend.*, 1911, **152**, 1601). Hydrolysis of 7-methylenecholesteryl benzoate

gives 7-methylenecholesterol (IV; R = H), m. p. 85° (**3 : 5-*dinitrobenzoate***, m. p. 162°; ***acetate***, m. p. 62—64°), which shows a well-defined inflexion at 2360 A. (log ε = 4·3); its constitution was confirmed by ozonolysis, formaldehyde being obtained. As we anticipated, irradiated 7-methylenecholesterol is antirachitically inactive when fed to rats in daily doses of 4·7 γ.

(III.)





(IV.)

7-Methylenecholesterol can be isolated directly from the mother-liquors of (III), and also as sole product by the action of excess of methylmagnesium iodide on 7-ketocholesteryl acetate.

So far, all attempts partially to dehydrate the diol (III) have led to 7-methylenecholesterol and not to the required 7-dehydro-7-methylcholesterol.

Experimental.

7-Hydroxy-7-methylcholesterol.—A solution of 7-ketocholesteryl acetate (22·5 g.) in anisole (150 c.c.) was added slowly to a solution of methylmagnesium iodide (from 4·4 g. Mg) in ether (70 c.c.). After standing over-night, the solution was heated under reflux for 2 hours, decomposed with ice and ammonium chloride solution, and extracted with ether. The extract was distilled in steam, and the residual solid, isolated by means of ether, crystallised from acetone–methyl alcohol, from which ***7-hydroxy-7-methylcholesterol*** was obtained in plates which contain solvent of crystallisation. The anhydrous diol separates from benzene in long needles, m. p. 165°. With the antimony trichloride reagent it gives a transient deep purple coloration passing into royal blue; $[\alpha]_D^{20°}$ − 30° (*l* = 1, *c* = 2·7 in chloroform) (Found: C, 80·7; H, 11·7. $C_{28}H_{48}O_2$ requires C, 80·7; H, 11·6%).

The ***monoacetate***, prepared by refluxing the diol (1·0 g.) with acetic anhydride (5 c.c.) for 5 minutes, separates from acetone in needles, m. p. 164°, $[\alpha]_D^{20°}$ − 35·1° (*l* = 1, *c* = 3·6 in chloroform) (Found: C, 78·7; H, 10·9. $C_{30}H_{50}O_3$ requires C, 78·5; H, 11·0%). The ***monobenzoate***, prepared by the action of benzoyl chloride (1·3 mol.) on the diol (1 mol.) in excess pyridine at room temperature for 18 hours, crystallises from acetone in needles, m. p. 175°, $[\alpha]_D^{20°}$ − 6·75° (*l* = 1, *c* = 4·2 in chloroform) (Found: C, 80·7; H, 10·35. $C_{35}H_{52}O_3$ requires C, 80·7; H, 10·1%).

7-Methylenecholesteryl Benzoate.—A solution of 7-ketocholesteryl acetate (43 g.) in anisole (200 c.c.) was added slowly to methylmagnesium iodide (from 20 g. Mg) in ether (500 c.c.), after which the mixture was refluxed for 6 hours, decomposed with dilute hydrochloric acid and ice, and extracted with ether. The extract was washed successively with sodium bisulphite solution, sodium carbonate solution, and water, and after removal of the ether, distilled in steam. The product, isolated by means of ether, was a pale yellow oil (40 g.) which could not be induced to crystallise; it was converted into its benzoyl derivative by treatment with benzoyl chloride and pyridine. After standing for 2 days at room temperature, the solution was poured into water, and the heavy oil removed and triturated successively with methyl alcohol and acetone, whereupon it gradually solidified. Repeated crystallisation of the crude benzoate from ethyl acetate gave ***7-methylenecholesteryl benzoate*** as long needles, m. p. 141°, $[\alpha]_D^{20°}$ − 122° (*l* = 1, *c* = 3·2 in chloroform) (Found: C, 83·6; H, 10·2. $C_{35}H_{50}O_2$ requires C, 83·6; H, 10·0%).

7-Methylenecholesterol.—A solution of the benzoate (1 g.) in benzene (10 c.c.) was added dropwise to boiling 1% alcoholic potash (80 c.c.) over a period of 30 minutes. The product, isolated by means of ether, was repeatedly crystallised from aqueous acetone, from which it separated in clusters of fine needles, m. p. 85°, which hold solvent of crystallisation tenaciously; $[\alpha]_D^{20°}$ − 191° (*l* = 1, *c* = 2·7 in chloroform). With the antimony trichloride reagent it gives the same coloration as 7-hydroxy-7-methylcholesterol.

The **3 : 5-*dinitrobenzoate*** separates from methyl alcohol–acetone in pale yellow needles, m. p. 162°, $[\alpha]_D^{20°}$ − 105° (*l* = 1, *c* = 1·3 in chloroform) (Found: C, 70·9; H, 8·1; N, 4·9. $C_{35}H_{48}O_6N_2$ requires C, 70·9; H, 8·2; N, 4·7%). The ***acetate***, prepared by means of acetic anhydride and pyridine, separates from methyl alcohol–ether as prisms, m. p. 62—64°, $[\alpha]_D^{20°}$ − 178° (*l* = 1, *c* = 3·73 in chloroform) (Found: C, 82·1; H, 11·1. $C_{30}H_{48}O_2$ requires C, 81·75; H, 11·0%).

Ozonolysis of 7-Methylenecholesterol.—A solution of 7-methylenecholesterol (2·6 g.) in carefully purified chloroform (50 c.c.) was treated with a slow stream of ozonised oxygen for 4 hours, the issuing gases being washed with water. The subsequent procedure for the detection and estimation of the formaldehyde produced was as described by Clemo and Macdonald (J., 1935, 1294), the weight of dimedon derivative being 240 mg. (11·2%), m. p. 185—186°.

Dehydration of 7-Hydroxy-7-methylenecholesteryl Benzoate.—(*a*) The benzoate was heated in a retort at 180° and 1×10^{-3} mm. After 24 hours the sublimed solid was crystallised from acetone, from which it separated in needles, m. p. 141°, either alone or in admixture with 7-methylenecholesteryl benzoate.

(*b*) A solution of the benzoate (1 g.) in ether (50 c.c.) and pyridine (1 c.c.) was treated with thionyl chloride (0·2 g.) in ether, the whole being stirred at — 15° for 1 hour. After standing over-night at room temperature, the mixture was washed successively with dilute hydrochloric acid and water. Removal of the solvent, followed by crystallisation of the residue, gave 7-methylenecholesteryl benzoate as needles from acetone, m. p. 141°.

(*c*) A solution of the benzoate (0·5 g.) and *p*-toluenesulphonyl chloride (0·5 g.) in pyridine (5 c.c.) was heated on the steam-bath for 30 minutes. The product, isolated by means of ether, followed by crystallisation from acetone, was identified as 7-methylenecholesteryl benzoate.

The analyses were carried out in this Department by Mr. W. F. Boston.

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