166. *Studies in the Sterol Group. Part XXII. 3-Chloro*allo*norcholanic Acid and its Epimeride.*

By T. Barr, I. M. Heilbron, and F. S. Spring.

In an attempt to define the position of the hydroxyl group in ergosterol, Heilbron, Samant, and Simpson (J., 1933, 1410) oxidised chloroergostane to a chloro*allo*norcholanic acid, m. p. 213° (methyl ester, m. p. 158—159°), which was not identical with the 3-chloro*allo*norcholanic acid, m. p. 232—234° (methyl ester, m. p. 176°), prepared by these authors by degradation of 3-chloro*allo*cholanic acid (Windaus and Hossfeld, *Z. physiol. Chem.*, 1925, **145**, 177). This result meant that either the hydroxyl group of ergosterol is not attached to C_3 or an epimerisation had occurred during the chlorination of either cholesterol or ergostanol.

Subsequently Fernholz and Chakravorty (*Ber.*, 1934, **67**, 2021) produced conclusive proof that the hydroxyl group of ergosterol is attached to C_3, a property possessed by all naturally occurring sterols and bile acids that have so far been examined in detail. It follows that the chloro*allo*norcholanic acid of Heilbron, Samant, and Simpson must be a 3-chloro*allo*norcholanic acid, differing from that prepared by degradation of the Windaus and Hossfeld 3-chloro*allo*cholanic acid solely in the orientation of the groups attached to C_3.

It is to be noted that two isomeric 3-chlorocholestanes exist, namely, α-cholestyl chloride, m. p. 115° (Windaus and Hossfeld, *loc. cit.*), and β-cholestyl chloride, m. p. 105° (Ruzicka, Goldberg, and Brüngger, *Helv. Chim. Acta*, 1934, **17**, 1389). Of these, the latter is probably the *trans-* and the α-isomeride the *cis*-form (Ruzicka, Wirz, and Meyer, *ibid.*, 1935, **18**, 998; the terms *cis-* and *trans-* refer here to the orientation of the chlorine atom with respect to the hydrogen atom attached to C_5).

Since the 3-chloro*allo*norcholanic acid of Heilbron, Samant, and Simpson was prepared from α-cholestyl chloride, we have repeated the degradation, employing β-cholestyl chloride. We find that the 3-chloro*allo*norcholanic acid so obtained is identical with that previously prepared from chloroergostane. Depending upon the value of the melting point characterisation of α- and β-cholestyl chlorides, this 3-chloro*allo*norcholanic acid obtained from chloroergostane and β-cholestyl chloride is the *trans-* and that from α-cholestyl chloride the *cis*-isomeride. It will be noted that this decision again agrees with the melting point rule.

Experimental.

(trans ?)-3-*Chloro*allo*cholanic acid* from β-cholestyl chloride has previously been described by Ruzicka, Goldberg, and Brüngger (*loc. cit.*), but, as these authors anticipated, their product (m. p. 186—188°) was not pure; furthermore, it was not analysed or characterised. By repeated crystallisation from ether–light petroleum (b. p. 40—60°) the pure acid was obtained in plates, m. p. 195—196° (Found: C, 72·1; H, 9·6; Cl, 9·4. $C_{24}H_{39}O_2Cl$ requires C, 72·3; H, 9·9; Cl, 9·0%).

Methyl (trans ?)-3-*chloro*allo*cholanate*, prepared from the acid by means of diazomethane, separated from ether–methyl alcohol in flat needles, m. p. 134—135° (Found: C, 73·6; H, 10·0; Cl, 9·0. $C_{25}H_{41}O_2Cl$ requires C, 73·4; H, 10·0; Cl, 8·7%).

Methyl (trans ?)-3-*Chloro*allo*norcholanate.*—An ethereal solution of methyl (*trans* ?)-3-chloro*allo*cholanate (1·2 g.) was added to a Grignard solution of magnesium (0·26 g.), bromobenzene (1·5 g.), and ether (100 c.c.), and the mixture heated under reflux for 4 hours. The ether was removed and the residue was heated on the steam-bath for a further 4 hours, decomposed with cold dilute sulphuric acid, and set aside over-night. The diphenylcarbinol was extracted with ether and isolated in the usual manner. It formed a pale yellow resin, which showed no tendency to crystallise from the common solvents and was therefore directly oxidised in glacial acetic acid solution (50 c.c.) with a solution of chromic anhydride (2·2 g.) in acetic acid (20 c.c. of 95%), added during 2 hours, and the heating was continued for a further 2 hours, mechanical stirring being applied throughout. After dilution with water the solution was extracted with ether, and the ethereal extract washed with water. On addition of potassium hydroxide solution (10%) the potassium salt of the 3-(*trans* ?)-chloro*allo*norcholanic acid was precipitated and isolated by centrifuging. The 3-(*trans* ?)-chloro*allo*norcholanic acid, obtained as an oil, was converted into its methyl ester with diazomethane, which after repeated crystallisation from ether–methyl alcohol separated in plates, m. p. 157—158°, giving no depression on admixture with methyl chloro*allo*norcholanate from chloroergostane (Found: C, 72·5; H, 9·34; Cl, 9·4. Calc. for $C_{24}H_{39}O_2Cl$: C, 72·9; H, 9·9; Cl, 9·0%). Hydrolysis of the ester was accompanied by partial removal of chlorine.

Our thanks are due to the Governors of the Royal Technical College, Glasgow, for a Scholarship which enabled one of us (T. B.) to participate in this investigation, also to Dr. K. M. Samant for help in the experimental section.

THE UNIVERSITY, MANCHESTER. [*Received, April 2nd*, 1936.]