the product was oxidized by the Oppenauer method. Chromatographic purification of the resulting impure keto-ester, followed by several crystallizations, then furnished pure methyl *d*-3-keto-$\Delta^{4,9(11),16}$-etiocholatrienate, m.p. 188–191°, $[\alpha]_D$ + 182° ±5° ($CHCl_3$). This keto-ester has been obtained by the degradation of Compound F[1], and had m.p. 187–191°, $[\alpha]_D$ +177 ±5° ($CHCl_3$); mixed m.p. showed no depression.

Hydrogenation of the *d*-keto-ester with platinum in acetic acid, and oxidation of the resulting saturated product with chromium trioxide in acetic acid, gave a mixture from which methyl 3-ketoetio*allo*cholanate (I), m.p. 177–180°, was isolated after chromatography and crystallization. An authentic sample of (I)[3,4] had m.p. 178–180°, and there was no depression in m.p. on admixture. The infrared spectra of the two samples were also identical.

The saturated keto-ester (I) has previously been converted to the Δ^4-compound,[4] which we have now hydrolyzed to the free acid, 3-keto-Δ^4-etiocholenic acid, m.p. 240–243°. In view of the conversion of the latter to desoxycorticosterone,[5] and progesterone,[6] this reaction sequence constitutes a total synthesis of these hormones.

Alkaline hydrolysis of the keto-ester (I) has given us the corresponding acid, 3-ketoetioallocholanic acid, m.p. 256–259°, which has previously been transformed into methyl 3-α-acetoxyetiallocholanate.[7] This compound has been converted to androsterone,[8] which in turn has been transformed *via* androstanedione[9] into androstenedione,[10] and thence into testosterone.[11] The conversion of progesterone to androstanedione has also been described,[12] and this constitutes another route to testosterone.

(3) Steiger and Reichstein, *Helv. Chim. Acta*, **20**, 1040 (1937).

(4) Djerassi and Scholz, THIS JOURNAL, **69**, 2404 (1947).

(5) Wilds and Shunk, *ibid.*, **70**, 2427 (1948).

(6) Riegel and Pront, *J. Org. Chem.*, **13**, 933 (1948); Reichstein and Fuchs, *Helv. Chim. Acta*, **23**, 684 (1940).

(7) Plattner and Fürst, *ibid.*, **26**, 2266 (1943).

(8) Dalmer, v. Werder, Honigmann and Heyns, *Ber.*, **68**, 1814 (1935).

(9) Butenandt and Tscherning, *Z. physiol. Chem.*, **229**, 185 (1934).

(10) Djerassi and Scholz, *J. Org. Chem.*, **13**, 697 (1948); Rosenkranz, Mancera, Gatica and Djerassi, THIS JOURNAL, **72**, 4077 (1950).

(11) *Inter al.*, Miescher and Fischer, *Helv. Chim. Acta*, **22**, 158 (1939).

(12) Marker, Kamm, Jones and Oakwood, THIS JOURNAL, **59**, 614 (1937).

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THE TOTAL SYNTHESIS OF CHOLESTEROL

Sir:

Cholesterol is the characteristic sterol of higher animals. It was isolated from gall stones by Conradi in 1775 and thus was the first member of the steroid family to be discovered. However it was not until 1932 that its correct structure (apart from stereochemical refinements) was proposed, mainly due to the brilliant researches of Windaus dating from 1903, and to those of Wieland dating from 1912. We now wish to record the total synthesis of cholesterol.

Methyl 3-ketoetio*allo*cholanate (I) has been obtained previously by total synthesis.[1] In view of conversions already described,[2] essentially the only remaining stage in a synthetic route from (I) to cholesterol is the homologation of 3-β-acetoxy*nor*-Δ^5-cholenic acid to 3-β-acetoxy-Δ^5-cholenic acid. The rather cumbersome nature of this scheme however led us to employ a more direct approach. Reduction of (I) with sodium borohydride in ethanol gave crude methyl 3-β-hydroxyetio*allo*cholanate, purified through the digitonide. The pure ester, m.p. 168–170° (undepressed on admixture with an authentic sample), was hydrolyzed to the corresponding hydroxy-acid, m.p. 249–251°, which was then acetylated. Treatment with thionyl chloride gave the acid chloride, m.p. 134–136°, which with excess cadmium-methyl yielded crude 3-β-acetoxy*allo*pregnanone-20, m.p. 139–144°. The latter reacted with excess isohexylmagnesium bromide,[3] and the gummy product, containing 20-hydroxycholestanol-3 and probably the C-20 epimer, was dehydrated (at C-20) and acetylated (at C-3) by boiling with acetic acid and then with acetic acid–acetic anhydride.[3] The reaction mixture was hydrogenated in the presence of a platinum catalyst. Chromatographic purification of the saturated material gave crude cholestanol-3 acetate, which on crystallization readily yielded the pure ester, m.p. 109–110°,[4] undepressed on admixture with an authentic sample (m.p. 110°). The infrared spectra of the two samples were also identical. Alkaline hydrolysis of the synthetic acetate furnished cholestanol-3, m. p. 142–142.5°,[4] undepressed on admixture with an authentic specimen (m.p. 142–143°). Cholestanol-3 has already been oxidized to cholestanone-3,[5] which in turn has been converted *via* Δ^4-cholestenone-3[6] into cholesterol[8]; the total synthesis of the latter is therefore complete.

Cholesterol has previously been converted into a number of other compounds of interest, the most important of which perhaps is vitamin D_3.

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(1) Woodward, Sondheimer and Taub, THIS JOURNAL, **73**, 3547 (1951).

(2) Djerassi and Scholz, *ibid.*, **69**, 2404 (1947); Reich and Lardon, *Helv. Chim. Acta*, **29**, 671 (1946); Butenandt and Schmidt-Thomé, *Ber.*, **71**, 1487 (1938); Steiger and Reichstein, *Helv. Chim. Acta*, **20**, 1164 (1937); MacPhillamy and Scholz, *J. Biol. Chem.*, **178**, 37 (1949); Ruzicka, Plattner and Pataki, *Helv. Chim. Acta*, **25**, 425 (1942); Plattner and Pataki, *ibid.*, **26**, 1241 (1943); Kuwada and Yogo, *J. Pharm. Soc. (Japan)*, **57**, 963 (1937); Riegel and Kaye, THIS JOURNAL, **66**, 723 (1944).

(3) *Cf.* Butenandt and Cobler, *Z. physiol. Chem.*, **234**, 218 (1935).

(4) These m.p's. were taken in a capillary. All others were taken on a Kofler micro hot-stage.

(5) *Inter al.* Bruce, *Organic Syntheses*, Coll. Vol. II, 139 (1943).

(6) Butenandt and Wolff, *Ber.*, **68**, 2091 (1935); Ruzicka, Plattner and Aeschbacher, *Helv. Chim. Acta*, **21**, 866 (1938). This transformation could probably be more conveniently carried out by use of the general method for converting *allo*steroids to Δ^4-3-ketosteroids recently developed (Ref. 7).

(7) Rosenkranz, Mancera, Gatica and Djerassi, THIS JOURNAL, **72**, 4077 (1950).

(8) Reich and Lardon, *Helv. Chim. Acta*, **29**, 671 (1946); Dauben and Eastham, THIS JOURNAL, **72**, 2305 (1950); Birch, *J. Chem. Soc.*, 2325 (1950).