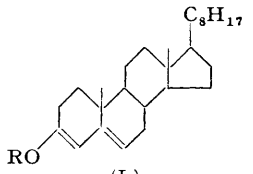
476. *A Conversion of Cholest-4-en-3-one into Cholesterol.*

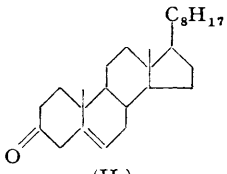
By Arthur J. Birch.

The enol-acetate (I; R = Ac) of cholest-4-en-3-one (III) reacts with potassium amide in liquid ammonia, followed by water, to give chiefly cholest-5-en-3-one (II).

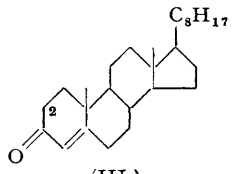
The equilibrium between a βγ- and the corresponding αβ-unsaturated ketone, *e.g.*, cholest-5-en-3-one (II) and cholest-4-en-3-one (III), is rapidly established in the presence of acidic or alkaline catalysts, and is usually greatly in favour of the αβ-unsaturated isomer. The conversion of the αβ- into the βγ-isomer can then be accomplished only by indirect means. Cholest-4-en-3-one



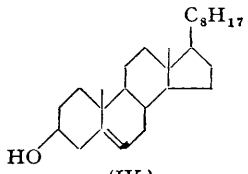
(I.)



(II.)



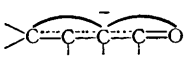
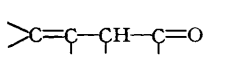
(III.)



(IV.)

(III) has been converted into cholesterol (IV) by Reich and Lardon (*Helv. Chim. Acta*, 1946, **29**, 671),* but the process is rather laborious. A desirable step in such a conversion would be the direct preparation of the unconjugated ketone (II) from the conjugated ketone (III).

It has been pointed out (Birch, *J.*, 1950, 1551) that a mesomeric anion of the type (V) may be expected to add a proton to give a high proportion of the unconjugated ketone (VI)

(V.)   (VI.)

if the addition takes place under conditions where it is irreversible. This expectation depends on the fact that the product is then determined by a reaction rate rather than by an equilibrium position. In effect, the high energy of the anion is used in part to convert the conjugated isomer into the unconjugated isomer of higher energy level. The conditions are fulfilled when the proton source is a much stronger acid than the ketone formed (pK about 20), but not acidic enough to bring about the acid-catalysed equilibrium. Water is therefore a suitable proton-donor, and to it can be added a weak acid like ammonium chloride to remove the alkali formed in the reaction.

If the conjugated ketone is to be used as the source of the anion, it must enolise in such a way as to provide eventually the oxygen atom at the end of the charged system. There appeared to be some possibility that cholest-4-en-3-one would provide the desired salt (I; R = K), since the enol-acetate is known to be 3-acetoxycholesta-3 : 5-diene (I; R = Ac) (Westphal, *Ber.*, 1937, **70**, 2128; Inhoffen, *Ber.*, 1936, **69**, 2144). However, some experiments kindly carried out by Dr. S. Sunner showed that the starting ketone (III) was recovered after treatment with potassium amide in liquid ammonia, followed by water. Under these conditions enolisation therefore proceeds most rapidly by the loss of a proton from the 2-position. The desired enolate (I; R = K) was eventually obtained from 3-acetoxycholesta-3 : 5-diene (I; R = Ac) by the action of potassium amide in ammonia, and gave rise as expected to cholest-5-en-3-one (II).

While this work was in progress it was reported by Shoppee and Summers (*J.*, 1950, 687) that cholest-5-en-3-one (II) is reduced by lithium aluminium hydride to yield principally cholesterol (IV). This work has been confirmed on the ketone obtained by the present method. The isomerisation and reduction reactions in conjunction thus make possible the introduction into the steroid ring B of the 5-double bond characteristic of cholesterol and many other sterols, together with the production of the 3-hydroxyl group in the natural steric configuration. The 4-unsaturated ketones can be obtained from the saturated ketones having the ring junction A–B in either the *cis*- or the *trans*-configuration (Rosenkranz, Kaufman, Pataki, and Djerassi, *J. Amer. Chem. Soc.*, 1950, **72**, 1046).

An immediate application of the reactions would be the preparation of radioactive cholesterol from radioactive cholestenone (Turner, *J. Amer. Chem. Soc.*, 1950, **72**, 579).

* [*Added, June 18th*, 1950.] After this paper had been submitted for publication, Dauben and Eastham (*J. Amer. Chem. Soc.*, 1950, **72**, 2305) described the direct production of cholesterol by reduction of the enol-acetate of cholestenone. This process probably follows the route here described, without the isolation of the intermediate βγ-unsaturated ketone.

Experimental.

Cholest-5-en-3-one from Cholest-4-en-3-one.—3-Acetoxycholesta-3 : 5-diene (Westphal, *loc. cit.*) (1·20 g.) was dissolved in pure ether (10 c.c.) and stirred into potassium amide (from the metal, 1·0 g.) in liquid ammonia (100 c.c.). After 1 hour, the suspension was poured cautiously into a solution of ammonium chloride (10 g.) in water (150 c.c.). The product was extracted as rapidly as possible with 4 successive portions of ether (50 c.c.), the combined extract washed 3 times with water (100 c.c.), a small piece of solid carbon dioxide added to neutralise any remaining ammonia, and the solution again washed with water and dried (Na_2SO_4). The residue left by evaporation of the ether was crystallised from methanol–acetone (1 : 1). The crude cholest-5-en-3-one so obtained formed colourless needles (0·6 g.), m. p. 110—115°. The gummy substance in the mother-liquor seemed to consist principally of a mixture of cholest-4- and -5-en-3-one, because passage through a column of alumina in benzene solution (conditions known to cause isomerisation of the latter ketone to the former) gave cholest-4-en-3-one (0·19 g.), m. p. 80°. Several crystallisations of the crude cholest-5-en-3-one from acetone–methanol were necessary to give material, $[\alpha]_D$ −2°, m. p. 125° with slight preliminary sintering, undepressed by an authentic specimen, m. p. 126°. Westphal (*loc. cit.*) gives m. p. 127°, with preliminary softening, $[\alpha]_D$ −4·2°. Attempts to chromatograph the crude product on neutral alumina (washed with acetic acid and reactivated at 280—300°; cf., however, Shoppee and Summers, *loc. cit.*, who succeeded in carrying out the process with a differently prepared alumina) resulted in quantitative isomerisation to cholest-4-en-3-one, m. p. 80°.

Reduction of Cholest-5-en-3-one to Cholesterol.—The crude ketone, m. p. 110—115° (200 mg.), was added to lithium aluminium hydride (100 mg.) in ether (10 c.c.). After an hour, the mixture was worked up in the known manner, and the product crystallised from methanol as needles (150 mg.), m. p. 135—140°. Two more crystallisations from methanol gave pure cholesterol as flat needles, m. p. 148°, undepressed by an authentic specimen. It was further identified by formation of the acetate, m. p. 115°, undepressed by an authentic specimen, and of a precipitate with alcoholic digitonin.

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