
COMMUNICATIONS TO THE EDITOR

ON THE CHEMICAL BEHAVIOR OF CAFESTEROL

Sir:

In view of the recent publication of Wettstein, *et al.* [*Helv. Chim. Acta*, **24**, 332E (1941)], which we have just received, it appears desirable to record some of our observations in this field. The existence of a benzenoid ring in cafesterol, as suggested by Slotta and Neisser [*Ber.*, **71**, 2342 (1938)], is highly improbable, since nitric acid oxidation of this compound gives neither benzene tetra- or dicarboxylic acid; from the reaction mixture was obtained only a non-acidic substance, apparently a nitro derivative, m. p. 220–230°. Cafesterol possesses a highly reactive conjugated double bond system in one ring, a fact shown by the formation of the maleic anhydride adduct (m. p. 185–192°), in benzene solution at room temperature or on *gentle* warming. Boiling such a solution promptly causes decomposition. In absolute alcoholic solution cafesterol takes up two moles of hydrogen in presence of palladized charcoal (20% Pd) giving a tetrahydro derivative, m. p. 153–155°, acetate 150–152°. Neither this tetrahydrocafesterol nor its acetate gives any coloration with concentrated hydrochloric acid, while cafesterol in alcoholic solution gives an intense blue to blue-green color reaction with this reagent (Slotta and Neisser). Contrary to the observations of Wettstein, *et al.*, and Slotta and Neisser, on treatment with sodium and alcohol (or amyl alcohol), cafesterol gives a new product, m. p. 153–156°, acetate 162–165°. Despite similar melting points, the difference of this product from cafesterol is shown by the fact that with concentrated hydrochloric acid, its alcoholic solution gives a purple coloration which *does not turn blue even on boiling*. Its acetate on the other hand gives a yellow to orange coloration with the same reagent. Sodium-alcohol treatment does not appear to affect the conjugated double bond system, because the acetate of the product gives a maleic anhydride adduct, m. p. 185°. The adduct gives no coloration with hydrochloric acid at room temperature.

A detailed report will be published at a later date.

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DERIVATIVES OF ESTRONE CONTAINING OXYGEN AT POSITION 16

Sir:

The interesting hypothesis, recently advanced by Marrian,¹ that 16-ketoestrone is an estrogen metabolite in the human, leads to the speculation that estriol (theelol) may be formed from estrone by the reduction of 16-ketoestrone. If such a reduction occurs, it is logical to assume that 16-hydroxyestrone may also lie on this metabolic pathway as an intermediate between the dione and glycol forms. In the reduction of 16-ketoestrone, two stereoisomeric 16-hydroxyestrones and four stereoisomeric estriols are theoretically possible. The question also arises whether or not a compound in this series may be regarded as an abnormal estrogen metabolite, which might conceivably play a role in the etiology of carcinoma of the uterus and of the mammary gland.

We have succeeded in preparing (i) the methyl ether of 16-ketoestrone, (ii) a compound believed to be one of the two epimeric 16-hydroxyestrones, and (iii) an estriol which is isomeric with the naturally-occurring theelol.

Estrone was converted to the 16-isonitroso derivative by the method of Litvan and Robinson,² and this derivative on reduction with zinc and acetic acid³ yielded a mixture of α -ketols, from which there was isolated in pure form a compound which is probably a 16-hydroxyestrone (m. p. 234–237°; $[\alpha]^{29.5D} - 102^\circ$ in ethanol). This compound was characterized by the following derivatives: oxime (m. p. 222.5–223°), monobenzoate (m. p. 241.5–243.5°), methyl ether (m. p. 174–177°), and oxime of the methyl ether (m. p. 175–177°).

Reduction of a similar α -ketol mixture with hydrogen and Adams catalyst yielded a mixture of estriols, one of the components of which proved to be an isomer of theelol. The isomer of estriol obtained has m. p. of 267–269° and $[\alpha]^{29.5D} + 88^\circ$ (in ethanol). A mixed melting point with theelol shows a depression of 10°. It gives a methyl ether melting at 141–142° and a triacetate melting at 152°.

(1) Marrian, *Bull. New York Acad. Med.*, **15**, 27 (1939).

(2) Litvan and Robinson, *J. Chem. Soc.*, 1997 (1938).

(3) Stodola, Kendall and McKenzie, *J. Org. Chem.*, **6**, 841 (1941).