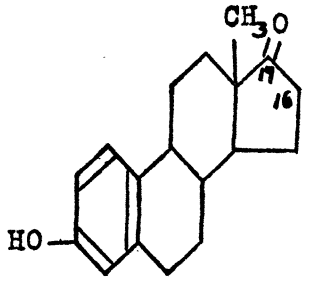
DISCUSSION

THE CHEMICAL TRANSFORMATION OF ESTRONE TO ESTRIOL (THEELOL)

THEELOL was first obtained in 1930 from human pregnancy urine by Marrian[1] and by Doisy.[2] Browne[3] later isolated it from human placenta. Theelol is the principal estrogenic hormone not only in human pregnancy urine but in human placenta as well. Endo-

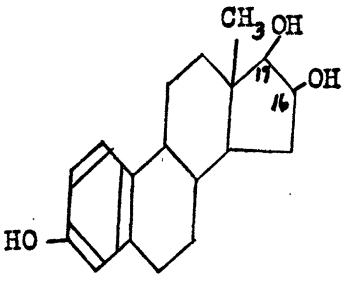


I

crinologists have generally held that theelol (II) arises biologically from the metabolism of estrone (I). That such a conversion can take place is now known with certainty as a result of the recent research of Pearlman and Pincus.[4]

Theelol differs from all other naturally occurring estrogens in possessing a functional group at steroid position 16. Peculiarly, this hormone is found only in the human species. On assay in the intact, immature, female rat it exhibits biological activity[5] much greater than that of its own precursor, estrone. These facts have led to the speculation that the physiological role of theelol may be qualitatively different from that of the other estrogens.

Abnormal estrogen metabolism has long been suspected in the etiology of carcinoma of the genital organs. Three years ago one of us (M.N.H.) commenced work on this problem with the view[6, 7, 8] that such an abnormal metabolism should be sought for generally in the transformation of estrone to theelol and particularly in the formation of an isomeric estriol possessing the unchanged estrone nucleus but



II

differing from theelol in the spatial arrangement of the carbinols at positions 16 and 17. It was in pursuance of this research that the isomeric estriol, isoestriol-A, was prepared.[6, 7] In attempting to make other stereoisomeric estriols of this class the present authors have obtained a small amount of a compound which has proved identical with theelol, the naturally occurring estriol.

We, therefore, wish to report the transformation of estrone to theelol by application of methods of pure organic chemistry. After a seven-step synthesis we obtained a low yield of pure theelol. It crystallized from aqueous methanol in very tiny needles which melted at 268.5–270° (unc.). An authentic sample of theelol kindly supplied by Dr. D. W. MacCorquodale, of the Abbott Laboratories, melted at 268.5–269.5° (unc.). A mixed melting point performed with authentic theelol and our estriol showed no depression. A microanalysis[9] of synthetic estriol gave: C 74.80, 74.76; H 8.46, 8.51 (calculated: C 74.97; H 8.39). There was no depression of the melting point of theelol-3-methyl ether-16,17-diacetate after admixture with the synthetic 3-methyl ether-16,17-diacetate.

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5 J. M. Curtis and E. A. Doisy, *Jour. Biol. Chem.*, 91: 647, 1931.
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8 The reasons for this hypothesis would be out of place in this communication. It is interesting to note that Hirschmann (*Jour. Biol. Chem.*, 150: 363, 1943) has recently isolated from the urine of a patient with adrenocortical carcinoma a Δ^5-androstenetriol-3(β),16,17—a steroid of the androgen series closely comparable to theelol in the estrogen series.

9 Performed by Dr. E. W. D. Huffman, Denver.

ON THE INHIBITION OF UREASE BY PENICILLIN[1]

IN a recent announcement, Turner, Heath and Magasanik[2] reported that urease is inhibited by penicillin preparations. The authors suggested the *in vitro* inhibition of the enzyme as a basis for the assay of penicillin. We have repeated their experiments using urease (Squibb) solutions of 0.1 and 0.5 per

1 Contribution from Research Laboratories, Merck and Company, Inc., Rahway, N. J.
2 J. C. Turner, F. K. Heath and B. Magasanik, *Nature*, 152: 326, 1943.