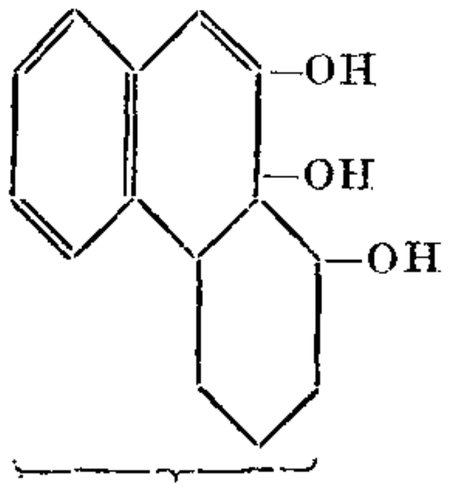
Chemistry of the Œstrogenic Hormones.

THE presence of an active substance in ovarian extracts which produces symptoms typical of normal œstrus in ovariectomised animals was first clearly demonstrated by Marshall and Joly in 1906. It was shown to be fat-like in its solubility and to be highly thermostable. Allen and Doisy in 1923 developed a rapid method for the quantitative assay of the hormone and in 1927 Ascheim and Zondek showed its presence in the urine of pregnant women. Shortly afterwards four different groups of workers, Doisy *et al*, Butenandt, Dingemanse, Laqueur *et al*, and Marrian, isolated independently the crystalline œstrogenic substance from the urine of pregnant women. In an article on the "Recent Progress in the chemistry of the œstrus producing hormone" in *Science Progress* (**28**, 69, 1933) Dr. Marrian discusses the several formulæ suggested for the substance. The work of the different authors mentioned clearly showed the presence of two chemically distinct œstrogenic substances in human pregnancy urine, a hydroxyketone of the formula $C_{18}H_{22}O_2$ and a triol, $C_{18}H_{24}O_3$. Butenandt and Hildebrandt in 1931 converted the triol into the hydroxyketone by dehydration *in vacuo* with potassium bisulphate. Since water was eliminated from the two non-acidic hydroxyl groups of the former, it was assumed that these two hydroxyl groups were attached to adjacent carbon atoms.

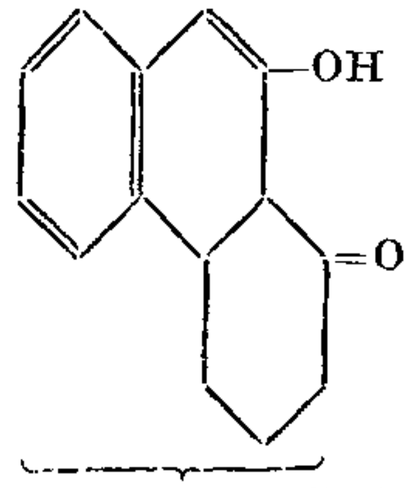
In 1932, Butenandt and Stormer separated two isomers of the hydroxyketone. A number of œstrogenic substances have been since isolated from the urine of mares. It seems likely that there are many closely allied œstrogenic substances yet to be discovered in human and mares' urine.

The work of Butenandt, Thayer, Levin and Doisy showed that besides three aromatic double bonds in the molecule of ketohydroxyœstrin there was another non-aromatic one. Marrian and co-workers showed later that the evidence on which the fourth double bond was postulated was untenable and that there were only three aromatic double bonds in the ketohydroxyœstrin molecule. This was confirmed by Butenandt by hydrogenation experiments.

On the former evidence of four double bonds the following formulæ were suggested for trihydroxyœstrin (I) and for ketohydroxyœstrin (II)

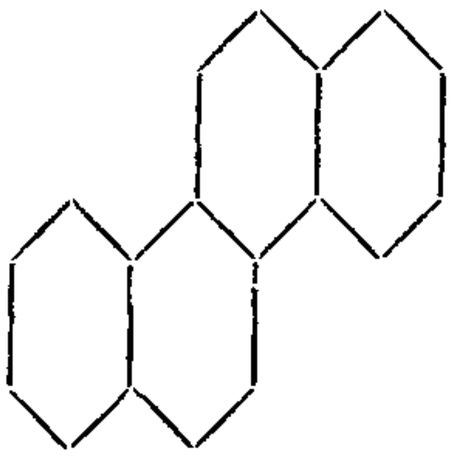


I

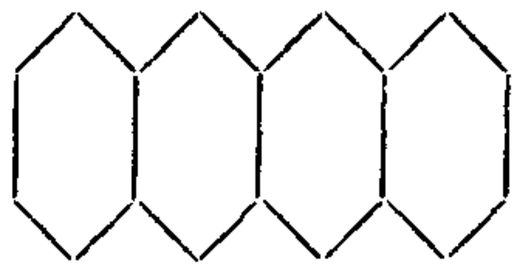


II

But when it was definitely shown that there were only three double bonds, the most probable carbon skeletons were the chrysene (III) or the naphthacene (IV) types.

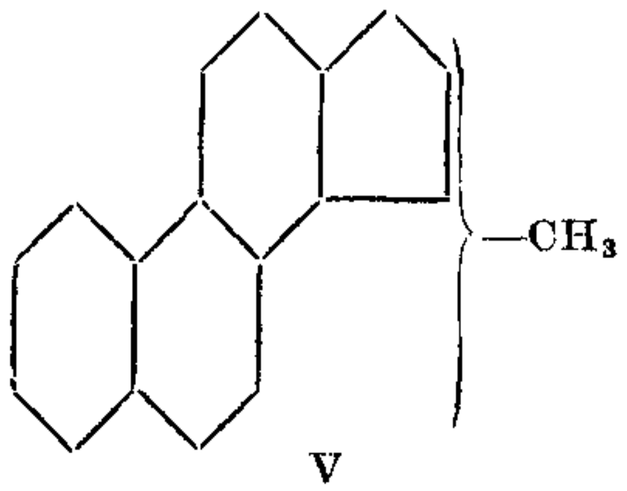


III

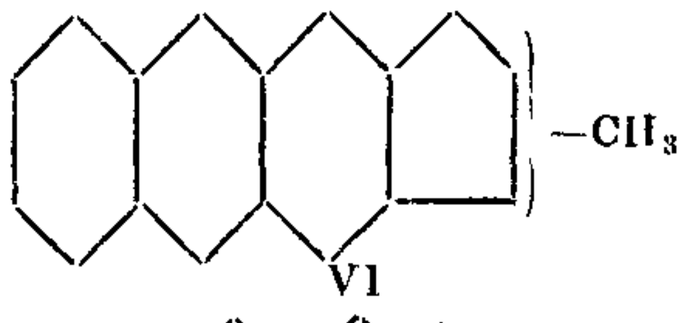


IV

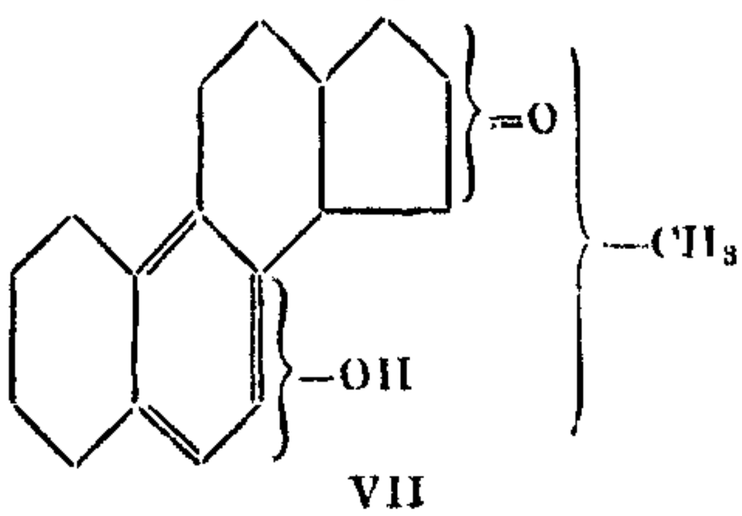
The results of Marrian and Haslewood in 1932, later confirmed by MaCorquodale, Thayer and Doisy in 1933, could be interpreted better on the basis of a five-membered ring than a six membered one. Therefore the most probable skeletons are V and VI



V

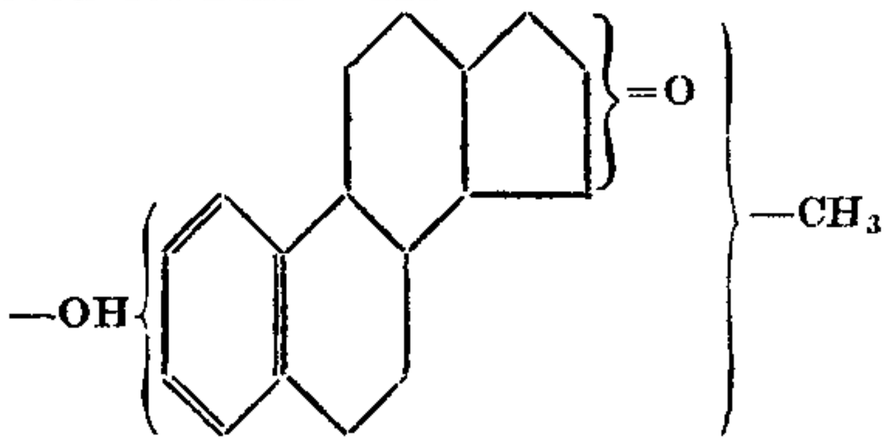


VI



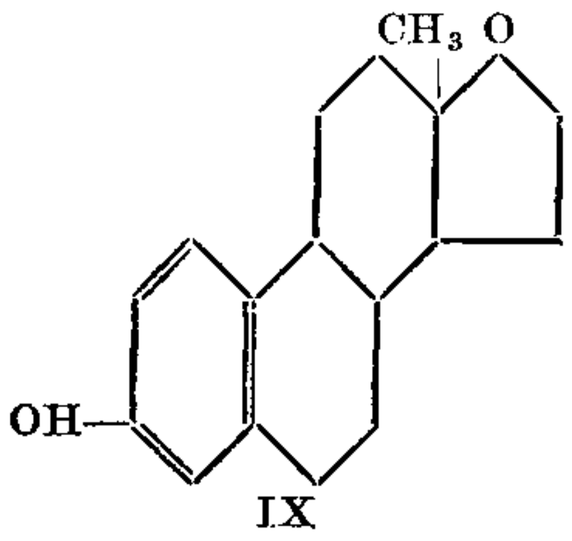
VII

The former authors preferred the skeleton V and postulated VII and VIII as alternatives for ketohydroxyœstrin. Later surface film work by Danielle *et al* clearly supported formula VIII.



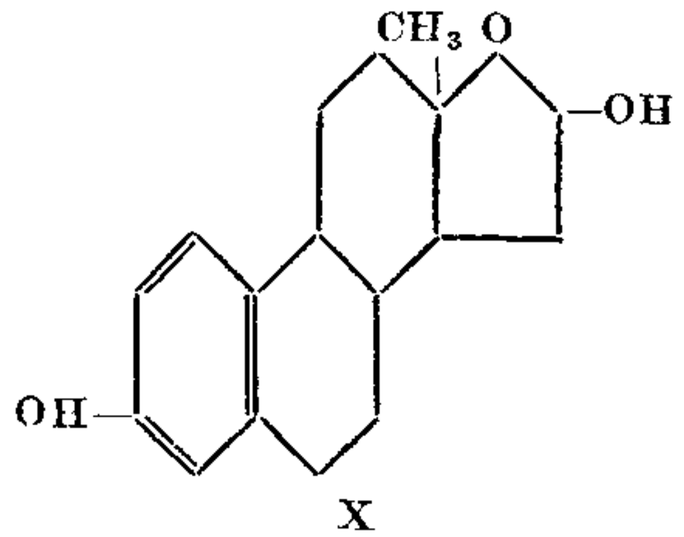
VIII

Simultaneous work on the constitution of sterols and bile acids by Rosenheim and King in 1932 suggested that a modified formula of the type of the chrysene skeleton III would explain the chemical and physical behaviour of the sterols and bile acids better than the old Wieland-Windaus formula. These views were adopted by Wieland and Windaus. This new formula for the sterols suggested the probable relation of the œstrins to the sterols and thus formula VII appeared much more probable. In fact, Butenandt went so far as to suggest IX and X



IX

for ketohydroxy and trihydroxyœstrin respectively. His arguments were criticised by Marrian as speculative but the most recent brilliant researches of Butenandt have proved that œstrins are chemically related to sterols.



X

One of the most remarkable recent developments in this subject is the synthetic work of Cook and Dodds who have produced a large number of œstrogenic substances. Among them are (1) 9 : 10-dihydroxy-9 : 10-di-n-butyl-9 : 10-dihydro-1 : 2 : 5 : 6 dibenzanthracene, (2) 1-keto-1 : 2 : 3 : 4-tetrahydrophenanthrene, (3) 5 : 6-cyclopenteno-1 : 2-benzanthracene, (4) 1 : 2-benzpyrene in descending order of potency. Two of these, *viz.*, 1 : 2 benzpyrene and 5 : 6-cyclopenteno-1 : 2-benzanthracene are also powerful carcinogenic agents. These results have opened a wide field of study. The fact that "the cell prolification which characterises the œstrus state is in some respects reminiscent of the early stages of malignant growth," as stated by Cook and Dodds, suggests that considerable light may be thrown on the whole problem of malignant growths. In view of the established relationship between the œstrins and the sterol group, it will be interesting to hear the results of Cook and Dodds investigations on the carcinogenic activity of 1 : 2-cyclopentenophenanthrene which may be regarded as the basic aromatic hydrocarbon of both the œstrins and sterols.