1,2-Bis-(*p*-hydroxyphenyl)-1,2-dialkoxy-ethanes, Estrogenic Oxygen Analogs of Hexestrol[1]

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E. C. Dodds, L. Goldberg, W. Lawson, and R. Robinson[2] pointed out a close structural resemblance of diethyl-stilbestrol, HOC_6H_4-$C(C_2H_5)=C(C_2H_5)C_6H_4OH$, just then prepared by them, to estrone or estradiol. Hexestrol, $HOC_6H_4CH(C_2H_5)CH(C_2H_5)C_6H_4OH$, another strong synthetic estrogen, is expected to bear a much closer structural resemblance to the natural estrogens, because it is a meso-form and the groups around carbon atoms 8 and 9 of the natural estrogens are arranged also in a "meso-form". This has been demonstrated by X-ray investigations.[3] The stereoisomerides, *d*-, *l*-, and racemic forms, of hexestrol have been reported to possess very weak potencies.[3]

The structural resemblance causing the development of similar physiological properties may be given by the union of two principal features, namely, a resemblance in the shapes of the molecular skeletons and the presence of the same functional groups at the corresponding positions of the similar-shaped skeletons. As for the skeleton, the replacement of the members constituting it with different atoms or groups may cause no radical change in the physiological action, unless the shape is altered significantly and unless an appearance of a new physiological action is associated with the replacement. Thus, the authors are interested in possible estrogenic activity of hexestrol analogs in which oxygen atom or the imino-group replaces one or both of the methylene groups or nitrogen atom one or both of the central methine groups.

One of such compounds is 1,2-bis-(*p*-hydroxyphenyl)-1,2-dimethoxy-ethane, HOC_6H_4-$CH(OCH_3)CH(OCH_3)C_6H_4OH$. It was already prepared by Th. Zincke and S. Münch.[4] They described a higher and a lower melting stereoisomerides without determining their configurations. The present authors presumed the higher melting compound to be the meso-form, and prepared it by the following improved method:

Bromine was added to diacetoxy-stilbene, $CH_3COOC_6H_4CH=CHC_6H_4OCOCH_3$, obtained by the acetylation of dihydroxy-stilbene, HO-$C_6H_4CH=CHC_6H_4OH$, and the resulting dibromide, $CH_3COOC_6H_4CHBrCHBrC_6H_4OCOCH_3$, was treated with an excess of sodium methoxide in methanol at room temperature. After left to stand overnight, the reaction mixture was poured into water, and acidified with hydrochloric acid. The precipitated substance was recrystallized from dilute methanol. The product thus obtained showed the melting point 220–222°, while Zincke and Münch gave 219–221°.

The minimum dose to produce typical oestrus in ovariectomized mice by subcutaneous injections in two portions in oil solution was found 0.5 gamma, and showed 5 percent activity of hexestrol evaluated by the same method.

(1) Preliminary note was published in the *Chemistry and Chemical Industry* (*Kagaku to Kogyo*), **2**, No. 2, 34 (1949).

(2) *Nature*, **141**, 247 (1938).

(3) C. H. Carlisle and D. Crowfoot, *J. Chem. Soc.*, **1941**, 6; also cf. U. v. Solmssen, *Chem. Rev.*, **37**, 481 (1945).

(4) *Ann.*, **335**, 157 (1904).

Considering that the simple dihydroxy-dibenzyl, $HOC_6H_4CH_2CH_2C_6H_4OH$, shows only a very weak activity, the minimum active dose being as much as 100 mg. in rats, the two methoxy groups proved really quite effective in imitating the molecular shape of hexestrol, and thus it has been indicated that the methylene groups in the ethyl groups of hexestrol can be replaced with oxygen atoms without causing any fundamental change in the physiological properties. Further, the strong activity has demonstrated that the configuration of the compound used is in fact a meso-form.

The corresponding diethoxy-compound, 1,2-bis-(*p*-hydroxyphenyl)-1,2-diethoxy-ethane, $HOC_6H_4CH(OC_2H_5)CH(OC_2H_5)C_6H_4OH$, was newly synthesized by a similar method using sodium ethoxide in ethanol instead of sodium methoxide in methanol. It forms colorless needles when recrystallized from dilute ethanol, melts at 212.5–214.5°, and shows similar solubilities in various solvents to the methoxy-compound. As expected, it showed a far smaller potency than the methoxy-compound, the minimum active dose being 10 gammas.

A nitrogen analog of hexestrol dimethyl ether, ethyl-*p*-methoxyphenyl-(1-*p*-methoxyphenyl-propyl)-amine, $CH_3OC_6H_4N(C_2H_5)CH(C_2H_5)C_6H_4OCH_3$, m.p. 63.5°, has been prepared. It developed incomplete but distinct durable oestrus. A more detailed account will soon appear.[5] In this connection, it may be added that J. B. Niederl and M. I. Dexter[6] have found blood-pressure lowering, but no oestrus producing, action in 1,2-bis-(*p*-hydroxyphenyl)-1,2-di-(methylamino)-ethane, $HOC_6H_4CH(NHCH_3)CH(NHCH_3)C_6H_4OH$. In the present authors' opinion, however, it must be determined whether the compound is really a meso-form or not before concluding estrogenic inactivity of the nitrogen analog of hexestrol represented by the above formula.

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(5) A preliminary note was presented by Y. Nomura at the annual meeting of the Chemical Society of Japan on April 3, 1949.

(6) *J. Am. Chem. Soc.*, **70**, 3071 (1948).