4, 4'-Dimethoxy-α, α'-dihalogeno-stilbenes: Estrogenic Halogen Derivatives of the Stilbestrol Series

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It has been postulated by the author and Y. Urushibara[(1)] that the development of a strong estrogenic activity requires not only the presence of two active hydrogen atoms or any groups capable of producing such in vivo at the optimum distance from each other[(2)] but also an optimum thickness of the molecule. Diethylstilbestrol acquires its favorable molecular thickness through the steric effect of the two ethyl groups at the α, α'-positions which force the benzene rings to rotate to a moderate extent. The substitution of lower or higher alkyl groups for the ethyl groups reduces the estrogenic activity and, as far as the molecular thickness is concerned, it is attributed to the deviation of the rotation of the benzene rings and consequently the molecular thickness from the optimum. The rotation of the benzene rings and its extent were deduced from the absorption spectra on

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(1) M. Ōki and Y. Urushibara, This Bulletin, **25**, 109 (1952).

(2) F. W. Schueler, *Science*, **103**, 221 (1946)

the assumption that the deterioration in the light absorption is associated with the loss in conjugation caused by the rotation of the benzene rings from the coplanar structure, although nothing can be said as to the direction of the rotation.(3)

It has been proved that the groups carrying or producing the active hydrogen atoms need not be the hydroxyl or the alkoxy groups. Namely, thio-analogs of diethylstilbestrol dimethyl ether, $CH_3SC_6H_4C(C_2H_5)=C(C_2H_5)-C_6H_4SCH_3$ and $CH_3OC_6H_4C(C_2H_5)=C(C_2H_5)-C_6H_4SCH_3$, were found potent estrogens as reported by the author.(4) On the other hand, no fundamental change in the physiological properties is caused by the replacement of the ethyl groups of diethylstilbestrol by other groups capable of exerting a similar steric effect. Thus, 1,2-bis-(*p*-methoxyphenyl)-1,2-bis-(methylthio)-ethylene, $CH_3OC_6H_4C(SCH_3)=C(SCH_3)C_6H_4OCH_3$, has been found a strong estrogen as reported from this laboratory.(5)

In this paper the author presents the results of the studies on 4,4′-dimethoxy-*α*,*α*′-dihalogenostilbenes. Dodds et al.(6) prepared already the dichloro-compound and found 1,000 international units per gram. The present author prepared the same substance by a different method and synthesized other symmetrical and unsymmetrical dihalogeno-compounds. The methods of preparation of these substances are described in the Experimental Part. The absorption data and the estrogenic activity are shown in Table 1. In Table 2 the absorption data of dialkylstilbestrols and some reference substances are given for comparison.

Table 1

Absorption Data and Estrogenic Activity of 4,4′-Dimethoxy-*α*,*α*′-dihalogeno-stilbenes, $CH_3OC_6H_4CX=CX'C_6H_4OCH_3$

	X	X′	λmax. (mμ)	εmax. ×10^{-4}	Minimum active dose in mice
(I)	Cl	Cl	282 .	2.87	200γ(6.5×10^{-7}mol.)
(II)	Br	Br	263	2.53	300γ(7.5 〃)
(III)	I	I	235	2.24	inactive at 800γ(16 〃)
(IV)	Cl	I	227 267	1.22 1.27	100γ(2.5 〃)
(V)	Br	I	234 261	1.72 1.58	>600γ(13 〃)

Table 2

$CH_3OC_6H_4CR=CRC_6H_4OCH_3$ (1)		λmax. (mμ)	εmax. ×10^{-4}
(VI)	R=H	230 305 326	1.27 3.47 3.37
(VII)	$R=CH_3$	247	2.85
(VIII)	$R=C_2H_5$	236	2.20
(IX)	$R=C_3H_7$	235	1.81
(X)	*p*-Cresol methyl ether	224 277 286	0.66 0.14 0.13
(XI)	*p*-Methoxy-benzyl chloride	227 272	1.17 0.25

Although the bromine atom possesses a van der Waals radius comparable with that of the methyl group, the absorption spectrum of the dibromo-compound (II) appears to show that the steric effect on the rotation of the benzene rings is smaller than that of the methyl group, provided that the bathochromic effect of the halogen atoms is such as shown by the absorption spectra of *p*-cresol methyl ether (X) and of *p*-methoxybenzyl chloride (XI). And, on the same assumption, it can be said that in the diiodo-compound (III) the steric effect is greater than in the dipropyl compound (IX). The spectra of the unsymmetrical dihalogeno-compounds (IV and V) show two maxima attributable to two halves of their molecules. If it can be assumed that each half has a structure with a benzene ring which rotates in the same manner as it does in the symmetrical compound corresponding to the double of it, then it can be concluded that the hypsochromic effect of the unsymmetry is slight in the bromo-iodo-compound (V), while it is greater in the chloro-iodo-compound (IV).

The physiological activity was examined by the vaginal smear test with ovariectomized mice, substances in oil solution being subcutaneously injected in two portions. Among the symmetrical dihalogeno-compounds the dichloro-compound (I) showed the greatest activity, although only slightly more active than the dibromo-compound (II). If it is taken as significant, then it is deduced that there is another favorable thickness, to which the dichloro-compound is nearer than the dibromo-compound. H. Suzuki(7) estimated the angle of the rotation of the benzene rings in *α*,*α*′-dimethylstilbene as 60 or 56°. As the same rotation angle should be valid for the 4,4′-dimethoxy-*α*,*α*′-dimethylstilbene (VII), the angle of the rotation of the benzene rings in the dibromo-compound (II) must be smaller than this value and still smaller in the dichloro-compound (I), while naturally greater in diethylstilbestrol (VIII), but the angle peculiar to diethylstilbestrol is far surpassed in the diiodo-compound (III).

By the molecular thickness the author means the molecular dimension in the direction perpendicular to the plane of the central ethylene grouping, and, as far as the domains of the benzene rings are concerned, the thickness is complementary with the width. If the thickness and the width are interchangeable for the purpose

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(3) Cf. G. A. Jeffrey, H. P. Koch, and S. C. Nyburg, *J. Chem. Soc.* **1948**, 1118 ; C. H. Carlisle and D. Crowfoot, ibid.,. **1941**, 6.

(4) M. Ōki, This Bulletin, **25**, 112 (1952).

(5) Y. Urushibara, M. Ōki and R. Ikeda, ibid., **25**, 66 (1952).

(6) E. C. Dodds, L. Golberg, E. I. Grünfeld, W. Lawson, C. M. Saffer, Jr. and R, Robinson, *Proc. Roy. Soc.*, **B 132**, 83 (1944).

(7) H. Suzuki, This Bulletin, **25**, 145 (1952).

of attaining the optimum molecular shape, then there can be two favorable structures, unless the angle of the rotation is 45°. Then it comes out that none of the symmetrical dihalogeno-compounds correspond to the favorable structure of diethylstilbestrol but the dichloro-compound (I) is near to the other favorable structure which does not exist in the dialkylstilbestrols.

The chloro-iodo-compound (IV), being the most active of the present series, reminds the author of methyl-propyl-stilbestrol, which is as active as diethylstilbestrol. As it is probable that the steric effect of the chlorine atom is smaller than that of the methyl group while the iodine atom exerts a greater effect than the propyl group, as mentioned above, then, regarding the molecular thickness, the chloro-iodo-compound is more unbalanced than the methyl-propyl-stilbestrol; but their potency may probably be explained on the same grounds,

The direction of the rotation of the benzene rings being left in ambiguity, it is impossible to visualize a definite figure of the molecular structure. Moreover, the animal test may not offer a reliable basis for a quantitative discussion, and no information is available as to the physiological effect of the halogen atoms themselves. Hence, the considerations presented in this paper cannot claim more than only a reserved significance.

Experimental Part

4, 4'-Dimethoxy-α, α'-dichlorostilbene (I).—To a suspension of 472 mg. of 4,4'-dimethoxytolane, prepared by the oxidation of anisil dihydrazone with yellow mercuric oxide,⁽⁸⁾ in acetic acid (5 c.c.), 5 c.c. of an acetic acid solution containing 142 mg. of chlorine was gradually added with good cooling and shaking. The reaction mixture was left to stand for 2 hours at room temperature and then the crystals were collected and recrystallized from alcohol containing a little acetone. The mother liquor from the reaction mixture gave a more crop. Yield, 347 mg. Colorless prisms melting at 163–164°. Found: Cl, 23.08; Calculated for $C_{16}H_{14}O_2Cl_2$: Cl, 22,94%. Dodds et al. (6) give m.p. 170°.

4, 4'-Dimethoxy-α, α'-dibromostilbene (II).—This substance was already prepared by H. Wiechell(9) who gave m.p. 197°. The present author prepared this compound by adding an equivalent amount (320 mg.) of bromine to a suspension of 4, 4'-dimethoxytolane (472 mg.) in acetic acid. Recrystallization of the product from acetone or ethyl acetate gave colorless prisms melting at 198°. Yield, 552 mg. Found: Br, 40.32; Calculated for $C_{16}H_{14}O_2Br_2$: Br, 40.08%.

4, 4'-Dimethoxy-α, α'-diiodostilbene (III).—To a suspension of 472 mg. of 4, 4'-dimethoxytolane in 5 c.c. of acetic acid, 15 c.c. of an acetic acid solution containing 508 mg. of iodine was added and the reaction mixture was left to stand for 72 hours at room temperature, when the brown color of iodine almost disappeared. The crystalline deposits were collected and carefully recrystallized from acetic acid. The substance was obtained in colorless prisms hardly soluble in most organic solvents and decomposing at 173° with evolution of iodine vapor. Yield, 847 mg. Found: I, 52.04; Calculated for $C_{16}H_{14}O_2I_2$: I, 51.58%.

4, 4'-Dimethoxy-α-chloro-α'-iodostilbene (IV)—Prepared from 472 mg. of 4, 4'-dimethoxytolane and 325 mg. of iodine monochloride in freshly distilled acetic acid in the same way as the dichloro-compound. Recrystallization of the product from acetone gave colorless prisms melting at 176–177°. Yield, 615 mg. Found: Cl, 9.16; I, 31.84; Calculated for $C_{16}H_{14}O_2ClI$: Cl, 8.85; I, 31.68%.

4, 4'-Dimethoxy-α-bromo-α'-iodostilbene (V).—Prepared from 4, 4'-dimethoxytolane and equivalent iodine monobromide in an analogous way. Recrystallization of the product from a large quantity of ethyl acetate gave colorless prisms melting at 207° with decomposition. 472 mg. of 4, 4'-dimethoxystilbene gave 708 mg. of the product. Found: Br, 18.03; I, 28.68; Calculated for $C_{16}H_{14}O_2BrI$: Br, 17.73; I, 28.29%.

Ultraviolet absorption spectra.—They were recorded with a Beckman Model DU photoelectric quartz spectrophotometer. Substances were dissolved in 95% ethanol. The concentrations are given in Table 3. The thickness of the solutions was 5 mm.

Table 3

Substances	Concentration
p-Methoxy-benzyl chloride	7.03×10^{-5}mol./l.
I	2.33 〃
II	4.10 〃
III	4.29 〃
IV	3.03 〃
V	2.12 〃

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(8) W. Schlenk and E. Bergmann, *Ann.*, **463**, 82 (1928).

(9) H. Wiechell, *Ann.*, **279**, 339 (1894).