4,4'-Dimethoxy-2,2'-dihalogeno-α, α'-dialkylstilbenes, Their Ultraviolet Absorption Spectra and Estrogenic Action

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(Received March 9, 1953)

The essential features of the molecular structure favorable for the development of a strong estrogenic activity are two groups carrying active hydrogen atoms or producing such in vivo, located at an optimum distance from each other, and an optimum thickness.(2) Diethylstilbestrol, 4-$HOC_6H_4CEt=CEtC_6H_4OH$-4', acquires its favorable molecular structure by virtue of the steric effect of the two ethyl groups at the α, α'-positions which force the benzene rings to rotate to a suitable extent. The smaller activity of 4,4'-dihydroxy-α, α'-dimethylstilbene (dimethylstilbestrol), 4-HO-$C_6H_4CMe=CMeC_6H_4OH$-4', is attributed to its thinner structure formed by the smaller steric effect of the methyl groups. It has been reported by Hudson and Walton(3) that 4,4'-dihydroxy-2,2',α,α'-tetramethylstilbene, 4,2-

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

(3) B. J. F. Hudson and E. Walton, *J. Chem. Soc.*, **1946**, 85.

Table 1

Estrogenic Activity of 4,4′-Dimethoxy-2,2′-dihalogeno-α,α′-dialkylstilbenes, $4,2\text{-}CH_3OXC_6H_3CR=CRC_6H_3XOCH_3\text{-}2',4'$.

	Substance	Melting point or Boiling point	Minimum active dose in mice
(I)	$R=CH_3$, $X=Cl$	[112—113°]	200 γ (5.9×10^{-7}mol.)
(II)	$R=CH_3$, $X=Br$	[117.5—119.5°]	200 γ (4.7× 〃)
(III)	$R=CH_3$, $X=I$	[159—160°]	500 γ (9.6× 〃)*
(IV)	$R=C_2H_5$, $X=Cl$, trans	[105.5—106.5°]	100 γ (2.7× 〃)
(V)	$R=C_2H_5$, $X=Br$, trans	[114.5—115°]	100 γ (2.2× 〃)
(VI)	$R=C_2H_5$, $X=I$, trans		200 γ (3.6× 〃)
(VII)	$R=C_2H_5$, $X=Cl$, cis	(88—89°/0.07 mm.)	1 mg.
(VIII)	$R=C_2H_5$, $X=Br$, cis	(87—89°/0.04 mm.)	1 mg.
(IX)	$R=C_2H_5$, $X=I$, cis	(108—110°/0.02 mm.)	1 mg.

* Active in 75 % animals.

Table 2

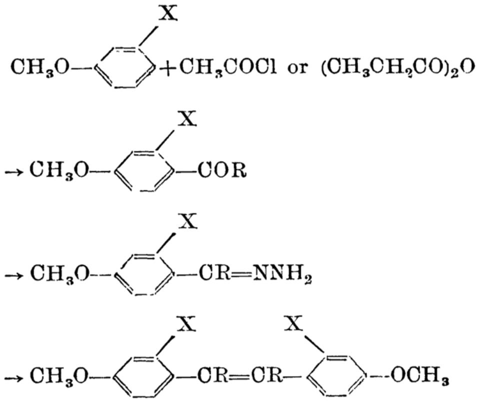
Absorption and Estrogenic Activity of 4,4′-Dimethoxy-α,α′-dialkylstilbenes, $4\text{-}CH_3OC_6H_4CR=CRC_6H_4OCH_3\text{-}4'$.

	Substance	Melting point	λmax.(mμ)	εmax.$\times10^{-4}$	Minimum active dose in mice
(X)	$R=CH_3$	141.5—143°	247	2.85	100 γ (3.7×10^{-7}mol.)
(XI)	$R=C_2H_5$	121.5—123°	236	2.20	2.5 γ (0.084× 〃)

$HOMeC_6H_3CMe=CMeC_6H_3MeOH\text{-}2',4'$, is a strong estrogen. Then it comes out that the methyl groups at 2,2′-positions may coöperate with the methyl groups at α,α′-positions to produce a molecular structure favorable for estrogenic action. As the bromine atom possesses a van der Waals radius nearly equal to that of the methyl group, it might be expected that introduction of bromine atoms into the 2,2′-positions of the 4,4′-dihydroxy-α,α′-dimethylstilbene would give also a potent estrogen, although it has been indicated that the bromine atoms in 4,4′-dimethoxy-α,α′-dibromostilbene, $4\text{-}MeOC_6H_4CBr=CBrC_6H_4OMe\text{-}4'$, appear to have a smaller steric effect on the rotation of the benzene rings than that of the methyl groups in the corresponding α,α′-dimethyl compound.(4)

The present paper records the results of the investigations on the effect of introduction of two equal halogen atoms into the 2,2′-positions of 4,4′-dimethoxy-α,α′-dimethylstilbene and 4,4′-dimethoxy-α,α′-diethylstilbene (diethylstilbestrol dimethyl ether). The general principle of preparations, which are described in details in the Experimental Part, was as follows:

2-Halogeno-4-methoxy-acetophenone or -propiophenone, prepared from *m*-halogenoanisole and acetyl chloride or propionic anhydride, was transformed into the hydrazone. The hydrazone was oxidized to the diazomethane with yellow mercuric oxide. Treatment of the diazomethane with sulfur dioxide followed by decomposition of the resulting ring-sulfone gave the final product. Estrogenic potency was taken as an evidence for the structure of the product and as the basis for distinguishing the trans-form from the cis-form. Only the trans-form of each dimethyl compound was obtained, while in the cases of the diethyl compounds fractional distillation of the products gave geometrical isomerides.



($R=CH_3$ or C_2H_5; $X=Cl$, Br, or I)

The ultraviolet absorption curves of the trans-compounds are shown in Figs. 1 and 2. The absorption data of the parent compounds are given in Table 2. The trans-diiododiethyl compound (VI) was not obtained in a pure state and was not included in the

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(4) M. Ōki, This Bulletin, 26, 37 (1953).

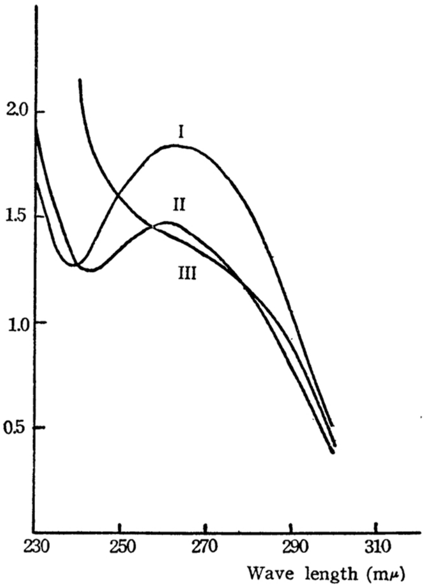

Fig. 1.—Ultraviolet absorption spectra of 4,4′-Dimethoxy-2,2′-dichloro-α,α′-dimethylstilbene ( ), 4,4′-Dimethoxy-2,2′-dibromo-α,α′-dimethylstilbene (II), and 4,4′-Dimethoxy-2,2′-diiodo-α,α′-dimethylstilbene(III)

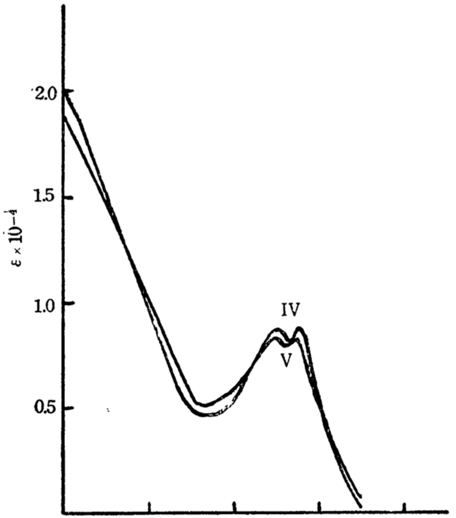

Fig. 2.—Ultraviolet absorption spetra of 4,4′-Dimethoxy-2,2′-dichloro-α,α′-diethylstilbene (IV) and 4,4′-Dimethoxy-2,2′-dibromo-α,α′-diethylstilbene (V).

absorption measurement. The dimethyl compounds and the diethyl compounds, respectively, showed absorption maxima at the same wave lengths irrespective of the kinds of halogen atoms at 2,2′-positions, although the diiodo-dimethyl compound (III) gave no maximum but a shoulder. Provided that the observed absorptions are those depending on the conjugation of the system comprising the benzene rings and the central ethylenic linkage, this may suggest that the halogen atoms at 2,2′-positions in any of the substances examined have little steric influence on the rotation degree of the benzene rings, because it would be less plausible to consider alternatively that they had definite and equal influence in spite of their different bulks. Then it may be said that the alkyl groups at α,α′-positions alone determine the rotation degree of the benzene rings, and the 2,2′-dihalogeno-compounds retain the structures of the parent compounds except the halogen atoms present in place of the hydrogen atoms at 2,2′-positions.

However, it remains unexplained why the bathochromic effect of the halogen substitution is greater in the diethyl compounds than in the dimethyl compounds. The observed absorptions of the dimethyl compounds and those of the diethyl compounds might not correspond to each other, because they appear characteristically different both in the shapes and in the extinction coefficients.

The minimum active doses were determined by the vaginal smear test with ovariectomized mice, substances in camellia oil being injected subcutaneously in two portions. The results given in Table 1 indicate that the diethyl compounds are stronger than the corresponding dimethyl compounds, and, either in the diethyl or in the dimethyl series, the dichloro-compound and the dibromo-compound have nearly the same potency, while the diiodo-compound a weaker potency. The liquid isomerides of the diethyl compounds showed very weak activities, indicating that they were cis-forms. The activities of the parent compounds are given in Table 2 with the absorption data. Comparison of the activities of the dihalogeno-derivatives with those of the parent compounds shows that the halogen substitution at 2,2′-positions reduced the activity, slightly in the dimethyl series, while profoundly in the diethyl series. The reduction of the activity was probably caused, at least partly, by the fattening of the molecules by the halogen atoms, and it is quite natural to suppose that the sharp peak of activity peculiar to the optimum structure of diethylstilbestrol may be very sensitive even to a slight deformation of the structure.

Experimental Part

4-Methoxy-2-chloroacetophenone.—To a mixture of 14.3 g. of 3-chloroanisole, prepared from 3-methoxybenzenediazonium chloride and cuprous chloride,(5) and 16.0 g. of anhydrous aluminum chloride in 30 c.c. of carbon disulfide, 7.9 g. of acetyl chloride were gradually added with good stirring and cooling. The reaction mixture was left to stand for 30 minutes at room temperature and then gently boiled for 30 minutes. The upper carbon disulfide layer was decanted off. After treated with ice and hydrochloric acid (20 c.c.), the mixture was extracted with benzene. The benzene solution was washed with 10% aqueous sodium hydroxide and then with water, dried over calcium chloride, and distilled under a reduced pressure. 4-Methoxy-2-chloroacetophenone distilled over at 139–141° (10 mm.) and solidified on cooling. Recrystallization from petroleum ether gave colorless needles melting at 26–27°. Yield 11.5 g. (62% of the theory). Found: Cl, 19.15. Calculated for $C_9H_9O_2Cl$: Cl, 19.20%.

The 2, 4-dinitrophenylhydrazone was obtained in yellowish orange needles melting at 181–183°, when recrystallized from ethyl acetate. Found: N, 15.58; Cl, 9.56. Calculated for $C_{15}H_{13}O_5N_4Cl$: N, 15.36; Cl, 9.72%.

4-Methoxy-2-bromoacetophenone.—Obtained in the same way as 4-methoxy-2-chloroacetophenone by using 18.7 g. of 3-bromoanisole, prepared from 3-methoxybenzenediazonium bromide and cuprous bromide.(6) 4-Methoxy-2-bromoacetophenone distilled at 149–151° (8 mm.) or 163–166° (15 mm.). It solidified on cooling in a refrigerator to large prisms melting below the room temperature (23°). Yield 13.5 g. (59% of the theory). Found: Br, 34.72. Calculated for $C_9H_9O_2Br$: Br, 34.89%.

The 2, 4-dinitrophenylhydrazone was obtained in reddish yellow needles melting at 193–194°, when recrystallized from ethyl acetate. Found: N, 13.67; Br, 19.76. Calculated for $C_{15}H_{13}O_5N_4Br$: N, 13.69; Br, 19.53%.

4-Methoxy-2-iodoacetophenone.—Synthesized in the same way as described for 4-methoxy-2-chloroacetophenone from 23.4 g. of 3-iodoanisole, prepared by the decomposition of 3-methoxybenzenediazonium chloride in an acidic potassium iodide solution.(7) 4-Methoxy-2-iodoacetophenone distilled at 168—170° (9.5 mm.) or 158—159° (6 mm.) and was recrystallized from petroleum ether. Colorless needles melting at 68—70°. Yield 15.8 g. (55% of the theory). Found: I, 45.52. Calculated for $C_9H_9O_2I$: I, 45.97%.

The 2, 4-dinitrophenylhydrazone was prepared as usual and recrystallized from ethyl acetate. Red needles melting at 108.5—109°. Found: N, 12.40; I, 27.87. Calculated for $C_{15}H_{13}O_5N_4I$: N, 12.28; I, 27.82%.

4-Methoxy-2-chloropropiophenone.—A mixture of 14.3 g. of 3-chloroanisole and 30.0 g. of anhydrous aluminum chloride in 50 c.c. of carbon disulfide was treated with 10.5 g. of propionic anhydride analogously as in the preparation of its lower homolog. 4-Methoxy-2-chloropropiophenone distilled at 152–153° (12 mm.). Yield 12.2 g. (61% of the theory). Found: Cl, 18.02. Calculated for $C_{10}H_{11}O_2Cl$: Cl, 17.85%.

The 2, 4-dinitrophenylhydrazone was prepared as usual and recrystallized from ethyl acetate-alcohol. Orange leaflets melting at 168–169°. Found: N, 15.55; Cl, 9.50. Calculated for $C_{16}H_{15}O_5N_4Cl$: N, 15.45; Cl, 9.77%.

4-Methoxy-2-bromopropiophenone.—Prepared in the same way as 4-methoxy-2-chloropropiophenone, 18.7 g. of 3-bromoanisole being used instead of 3-chloroanisole. 4-Methoxy-2-bromopropiophenone distilled at 146–147° (6 mm.). Yield 15.7 g. (65% of the theory). Found: Br, 32.94. Calculated for $C_{10}H_{11}O_2Br$: Br, 32.88%.

The 2, 4-dinitrophenylhydrazone was prepared as usual and recrystallized from ethyl acetate-alcohol. Orange leaflets melting at 154–155°. Found: N, 13.51; Br, 19.68. Calculated for $C_{16}H_{15}O_5N_4Br$: N, 13.76; Br, 19.62%.

4-Methoxy-2-iodopropiophenone.—Prepared in the same way from 23.4 g. of 3-iodoanisole. 4-Methoxy-2-iodopropiophenone distilled at 158–162° (6 mm.) and solidified on cooling. Recrystallization from petroleum ether gave colorless plates melting at 61–63°. Yield 17.3 g. (58% of the theory). Found: I, 43.86. Calculated for $C_{10}H_{11}O_2I$: I, 43.75%.

The 2,4-dinitrophenylhydrazone was prepared as usual. Recrystallization from ethyl acetate gave orange-yellow needles melting at 161-162°. Found: N, 12.78; I, 28.23. Calculated for $C_{16}H_{15}O_5N_4I$: N, 12.56; I, 27.94%.

4-Methoxy-2-chloroacetophenone-hydrazone.—A solution of 4-methoxy-2-chloroacetophenone (5.0 g.) and hydrazine hydrate (1.6 g.) in hot propyl alcohol (5 c.c.) was refluxed for 5 hours on an oil bath. Crystals separating on cooling were collected and recrystallized from alcohol. Colorless needles melting at 138–139°. Yield 0.2 g. (4% of the theory). Found: N, 14.22; Cl, 18.09. Calculated for $C_9H_{11}ON_2Cl$: N, 14.10; Cl, 17.85%. On standing it decomposed probably to an azine.

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(5) F. Leverdin and F. Eckhard, *Ber.*, **32**, 2626 (1899).

(6) Cf. H. R. Snyder and Z. Wicks, Jr., "Organic Syntheses", Vol. 24, p. 22.

(7) A. Baeyer and V. Villiger, *Ber.*, **35**, 3026 (1902).

All the ketones described above gave poor yields of hydrazones even when heated with hydrazine hydrate in ethanol for 5 hours.

4, 4′-Dimethoxy-2, 2′-dichloro-α, α′-dimethylstilbene (I).—A suspension of 3.0 g. of the above hydrazone and 5.5 g. of yellow mercuric oxide in 30 c.c. of petroleum ether was shaken for 8 hours at 12–16°. The resulting red solution containing the diazomethane was filtered from solids. To the filtrate cooled in ice-water, a rapid stream of sulfur dioxide was passed until the color disappeared. The solvent was distilled off from the reaction mixture and the remainder was heated at 160–200° to complete the decomposition. The oil solidified on cooling and was purified by chromatographical separation followed by recrystallization from benzene-petroleum ether. Pale yellow needles melting at 112–113°. Yield 0.4 g. (16% of the theory). Found: Cl, 21.32. Calculated for $C_{18}H_{18}O_2Cl_2$: Cl, 21.03%.

4-Methoxy-2-bromoacetophenone-hydrazone.—Treatment of the ketone (13.5 g.) with hydrazine hydrate (3.5 g.) in propyl alcohol gave difficultly crystallizable hydrazone, which was directly used in the next reaction. On long standing at a cool place it solidified and was recrystallized from alcohol. Colorless needles melting at 88–90°. Found: N, 11.60; Br, 32.98. Calculated for $C_9H_{11}ON_2Br$: N, 11.48; Br, 32.74%.

4, 4′-Dimethoxy-2, 2′-dibromo-α, α′-dimethylstilbene (II).—A suspension of the above crude hydrazone and yellow mercuric oxide in petroleum ether was treated in an analogous way as described for the dichloro-compound (I). Recrystallization from benzene-petroleum ether gave 4, 4′-dimethoxy-2, 2′-dibromo-α, α′-dimethylstilbene in pale yellow needles melting at 117.5–119.5°. Yield 0.3 g. (3% of the theory). Found: Br, 37.73. Calculated for $C_{18}H_{18}O_2Br_2$: Br, 37.51%.

4-Methoxy-2-iodoacetophenone-hydrazone.—Prepared in the same way. The crystalline product obtained in colorless needles melting at 158–160° after recrystallization from benzene-petroleum ether was not the expected hydrazone. The major part of the product was an oil and used in the next step without purification.

4, 4′-Dimethoxy-2, 2′-diiodo-α, α′-dimethylstilbene (III).—Prepared from the above crude hydrazone in the same way as the dichloro-compound (I). Chromatographical separation followed by recrystallization from benzene-alcohol or ethyl acetate gave pale yellow plates melting at 159–160°. Yield 0.03 g. from 3.0 g. of the crude hydrazone (1% of the theory). Found: I, 49.12. Calculated for $C_{18}H_{18}O_2I_2$: I, 48.80%.

4-Methoxy-2-chloropropiophenone-hydrazone.—Prepared in the same way as the acetophenone-hydrazones. The oily hydrazone was used without purification.

4, 4′-Dimethoxy-2, 2′-dichloro-α, α′-diethylstilbene (IV) (VII).—Prepared in the same way as the corresponding dimethyl compound (I). Five hours' shaking was sufficient for oxidation. Distillation of the product gave a pale yellow oil boiling at 125–145° (0.5 mm.) and another yellow viscous oil boiling at 210–220° (0.5 mm.). Redistillation of the former gave a colorless oil boiling at 88–89° (0.07 mm.). Found: Cl, 19.52. Calculated for $C_{20}H_{22}O_2Cl_2$: Cl, 19.41%. The latter fraction solidified on standing at a cool place for a long time and was recrystallized from alcohol. Colorless prisms melting at 105.5–106.5°. Found: Cl, 19.53. Calculated for $C_{20}H_{22}O_2Cl_2$: Cl, 19.41%. Yield 0.8 g. of the liquid compound and 1.5 g. of the solid isomeride from 10.0 g. of the starting ketone (25% of the theory).

The estrogenic activities showed that the liquid compound was the cis-form and the solid the trans-form. The same holds good for other diethyl compounds described below.

4-Methoxy-2-bromopropiophenone-hydrazone.—Obtained as an oily substance and used without purification.

4, 4′-Dimethoxy-2, 2′-dibromo-α, α′-diethylstilbene (V) (VIII).—Prepared from the above crude hydrazone. Distillation of the product gave a pale yellow oil boiling at 135–140° (0.3 mm.) and a yellow viscous oil boiling at 190–205° (0.25 mm.). The former was refined to a colorless oil boiling at 87–89° (0.04 mm.). Found: Br, 35.02. Calculated for $C_{20}H_{22}O_2Br_2$: Br, 35.19%. The higher boiling fraction solidified on standing at a cool place for a long time and was recrystallized from alcohol. Colorless prisms melting at 114.5–115°. Found: Br, 35.23. Calculated for $C_{20}H_{22}O_2Br_2$: Br, 35.19%. Yield 1.2 g. of the liquid cis-isomeride and 1.7 g. of the solid trans-isomeride from 10.0 g. of the starting ketone (31% of the theory).

4-Methoxy-2-iodopropiophenone-hydrazone.—Obtained as an oily substance and used without purification.

4, 4′-Dimethoxy-2, 2′-diiodo-α, α′-diethylstilbene (VI) (IX).—Synthesized from the above hydrazone. Distillation of the product gave a yellow oil boiling at 65–120° (0.03 mm.)

and a residue. The distillate was refined to a colorless oil boiling at 108–110°(0.02 mm.). Found: I, 46.58. Calculated for $C_{20}H_{22}O_2I_2$: I, 46.74%. The residue did neither distil even at 200°(0.0005 mm.) nor solidify. It was fractionated through an alumina column in benzene solution and the solvent was evaporated in vacuo. A heavy viscous oil. Found: I, 45.82. Calculated for $C_{20}H_{22}O_2I_2$: I, 46.74%. Yield 1.3 g. of the cis-isomeride and 2.0 g. of the trans-isomeride from 10.0 g. of the starting ketone (33% of the theory).

Ultraviolet absorption spectra. — They were recorded with a Beckman Model DU photoelectric quarz spectrophotometer in 95% ethanol. The length of solutions was 5 mm. and the concentrations were 0.02 to 0.05 millimol per litre.

The author wishes to thank Professor Y. Urushibara for his kind guidance. Thanks are also due to Mr. F. Ueno of the Teikoku Hormone Manufacturing Co., Ltd., Kawasaki, for the bio-assays and to the Ministry of Education for the Grant in Aid for Fundamental Scientific Research.

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