1,2-Bis-(*p*-methoxyphenyl)-1-(methylthio)-butane, 1,2-Bis-(*p*-methoxyphenyl)-1-(methylthio)-2-methoxy-ethane, and 1,2-Bis-(*p*-methoxyphenyl)-1,2-bis-(methylthio)-ethylene. Estrogenic Sulfur Analogs of Hexestrol Dimethyl Ether and of Diethylstilbestrol Dimethyl Ether

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The syntheses of some estrogenic analogs of hexestrol have already been reported from this laboratory.(1)(2) In the present paper the syntheses of further analogs of hexestrol dimethyl ether and of diethylstilbestrol dimethyl ether are described.

1,2-Bis-(*p*-methoxyphenyl)-1-(methylthio)-butane, $CH_3OC_6H_4CH(SCH_3)CH(C_2H_5)C_6H_4OCH_3$.—1,2-Bis-(*p*-methoxyphenyl)-butanol-(1), $CH_3OC_6H_4CHOHCH(C_2H_5)C_6H_4OCH_3$, m. p. 100-103°, was prepared by the reduction of the corresponding ketone, α-ethyldesoxyanisoin, with sodium amalgam in alcoholic solution.(3) The substituted butanol (1.0 g.) and methyl mercaptan (2 cc.) were dissolved in glacial acetic acid (30 cc.) and dry hydrogen chloride was passed into the solution for an hour, methyl mercaptan (1 cc.) being added every fifteen minutes. After the addition of a small amount of zinc chloride, the mixture was left to stand overnight under a stopper. The crystalline deposits were collected and recrystallized from ethyl acetate. 1,2-Bis-(*p*-methoxyphenyl)-1-(methylthio)-butane (0.55 g.) was obtained in colorless prisms melting at 152.5-154.5° and soluble with difficulty in alcohol.

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(1) Y. Urushibara and M. Ōki, This Bulletin, **23**, 35 (1950).

(2) Y. Urushibara and T Takahashi, *ibid.*, **23**, 53 (1950).

(3) T. Takahashi, read before the annual meeting of the Chemical Society of Japan on April 2, 1950.

Yield: 49% of the theory. Found: S, 9.95%; molecular weight, 329. Calculated for $C_{19}H_{24}O_2S$: S, 10.13%; molecular weight, 316.

1, 2-Bis-(*p*-methoxyphenyl)-1-(methylthio)-2-methoxy-ethane, $CH_3OC_6H_4CH(SCH_3)CH(OCH_3)C_6H_4OCH_3$.—Anisoin methyl ether, $CH_3OC_6H_4CH(OCH_3)COC_6H_4OCH_3$, prepared by the action of methyl iodide and silver oxide on anisoin was reduced to hydranisoin methyl ether, $CH_3OC_6H_4CH(OCH_3)CHOHC_6H_4OCH_3$, with sodium amalgam.(4) The hydranisoin methyl ether (1.0 g.) was treated with methyl mercaptan and hydrogen chloride in the same way as described above. The product was recrystallized from ethyl acetate or alcohol. 1,2-Bis(*p*-methoxyphenyl)-1-(methylthio)-2-methoxy-ethane was obtained in colorless prisms melting at 190-191°, soluble in glacial acetic acid and in ethyl acetate, and soluble with difficulty in alcohol and in acetone. Yield: 55% of the theory (0.6 g.). Found: S, 10.25%; molecular weight, 305. Calculated for $C_{18}H_{22}O_3S$: S, 10.07%; molecular weight, 318.

Attempted preparation of anisoin methyl ether from α-bromodesoxyanisoin, $CH_3OC_6H_4CHBrCOC_6H_4OCH_3$, failed. The latter compound was prepared by the bromination of desoxyanisoin in direct sun light. α-Bromodesoxyanisoin melts at 101-103° with decomposition. Found: Br, 23.83%. Calculated for $C_{16}H_{15}O_3Br$: Br, 23.84%. It gave anisoin by the action of either sodium methoxide or sodium ethoxide.

1,2-Bis-(*p*-methoxyphenyl)-1,2-bis-(methylthio)-ethylene, $CH_3OC_6H_4C(SCH_3)=C(SCH_3)C_6H_4OCH_3$.—Anisoin (0.6 g.) was dissolved in glacial acetic acid (30 cc.). Methyl mercaptan (1 cc.) was added to the solution and dry hydrogen chloride was passed for an hour, while methyl mercaptan (0.5 cc.) was added every fifteen minutes. After the addition of a small amount of zinc chloride, the mixture was left to stand overnight. Deposited crystals were collected and recrystallized from ethyl acetate. 1,2-Bis-(*p*-methoxyphenyl)-1,2-bis-(methylthio)-ethylene was obtained in colorless prisms melting at 194-196° and soluble with difficulty in alcohol. Analysis gave the required result. Found: C, 65.65; H, 6.19; S, 19.12%; molecular weight, 337. Calculated for $C_{18}H_{20}O_2S_2$: C, 65.02; H, 6.06; S, 19.29%; molecular weight, 332. $C_{18}H_{22}O_2S_2$ would require H, 6.72%. The absorption spectrum of this substance gave a maximum at 235 mμ coinciding with the maximum given by diethylstilbestrol dimethyl ether, showing the presence of a similar dimethoxy-stilbene structure. Furthermore, it was different from the saturated 1,2-bis-(*p*-methoxyphenyl)-1,2-bis-(methylthio)-ethane, which was newly synthesized. The corresponding free phenol and its diacetate had already been synthesized.(1) The dimethyl ether was prepared from hydranisoin and from isohydranisoin as follows:

To obtain hydranisoin and isohydranison anisil was reduced with sodium amalgam in alcoholic solution. The two stereoisomeric products were separated by taking advantage of their different solubilities in ether and recrystallized from alcohol. Hydranisoin, $CH_3OC_6H_4CHOHCHOHC_6H_4OCH_3$, was treated with methyl mercaptan and hydrogen chloride in the same way as described above. Recrystallized from acetic acid, 1,2-bis-(*p*-methoxyphenyl)-1,2-bis-(methylthio)-ethane, $CH_3OC_6H_4CH(SCH_3)CH(SCH_3)C_6H_4OCH_3$, was obtained in colorless prisms melting at 188-190°. Found: S, 19.10%; molecular weight, 335. Calculated for $C_{18}H_{22}O_2S_2$: S, 19.17%; molecular weight, 334. Isohydranisoin, treated similarly, gave a viscous oil and a small amount of the same substance as obtained from hydranisoin. The oily product could not be purified.

Estrogenic Activities.—Since attempted demethylation to free phenols with thiophenol(5) was successful with neither of the hexestrol dimethyl ether analogs described above, the dimethyl ethers were tested on their physiological activities. The minimum doses to produce full estrus in ovariectomized mice by subcutaneous injection in two portions in oil solution were found as follows: 1,2-bis-(*p*-methoxyphenyl)-1-(methylthio)-butane 100 γ, 1,2-bis-(*p*-methoxyphenyl)-1-(methylthio)-2-methoxy ethane 100 γ, 1,2-bis-(*p*-methoxyphenyl)-1,2-bis-(methylthio)-ethylene 10 γ.

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(4) I. Moodie, *J. Chem. Soc.*, **1907**, 543.

(5) *Cf.* G. K. Hughes and E. O. P. Thompson, *Nature*, **164**, 365 (1949).