LETTER

1, 2-Bis-(*p*-hydroxyphenyl)-1, 2-bis-(methylthio)-ethane, An Estrogenic Sulfur Analog of Hexestrol[1]

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In the programme of the survey of the possible estrogenic activity of hexestrol and stilbestrol analogs in which the members constituting the molecular skeletons of the well-established synthetic estrogens are replaced with other atoms or groups without altering the molecular shapes significantly, the discovery of a potent estrogen in 1, 2-bis-(*p*-hydroxyphenyl)-1, 2-dimethoxy-ethane, $HOC_6H_4CH(OCH_3)$-$CH(OCH_3)C_6H_4OH$, an oxygen analog of hexestrol,[2] has naturally allured the authors to the synthesis of the corresponding sulfur analog, namely, 1, 2-bis-(*p*-hydroxyphenyl)-1, 2-bis-(methylthio)-ethane, $HOC_6H_4CH(SCH_3)$ $CH(SCH_3)C_6H_4OH$.

The dibromide, m. p. 213-4°, from diacetoxystilbene was heated with methylthio-magnesium iodide, prepared by digesting sulfur with a Grignard reagent of methyl magnesium iodide or by passing methyl mercaptan into a Grignard reagent of ethyl magnesium iodide. The products were recrystallized from ethyl acetate. 1,2-Bis-(*p*-acetoxyphenyl)-1,2-bis-(methylthio)-ethane, $CH_3COOC_6H_4CH(SCH_3)CH(SCH_3)$-$C_6H_4OCOCH_3$, was obtained in poor yields (10% or less of the theory) from the less soluble fractions. It melts at 118-9°, is soluble in methanol, acetone, acetic acid, and ethyl acetate, difficultly soluble in benzene and in chloroform, and almost insoluble in petroleum ether. Found: S, 16.86%; molecular weight, 374. Calculated for $C_{20}H_{22}O_4S_2$: S, 16.43%; molecular weight, 390.

The authors owe a more successful synthesis of 1, 2-bis-(*p*-hydroxyphenyl)-1, 2-bis-(methylthio)-ethane to I. W. Ruderman and E. M. Fettes[3] who have recorded a new preparation of thio-ethers. *p,p'*-Dihydroxy-hydrobenzoin (1.5 g.), $HOC_6H_4CHOHCHOHC_6H_4OH$, m. p. 219°, prepared by reducing *p*-hydroxy-benzaldehyde with sodium amalgam, was suspended in glacial acetic acid (75 cc.), methyl mercaptan (4 cc.) was added, and dry hydrogen chloride was passed into the mixture for two hours while methyl mercaptan (1 cc.) was added every quarter to make up for possible losses. The mixture was left to stand under a stopper for a couple of days. The crystalline deposits, and the crystals resulting in two or three days from the oil precipitated on pouring the mother liquor into water, were recrystallized from methanol-water. The substance thus obtained forms colorless needles, and on heating it melts at 193.5-5°, solidifies instantly, and then decomposes gradually and totally at 255°. Such a melting behaviour was not affected by recrystallization from pure methanol, acetone-water, or glacial acetic acid. Yield, 1.2 g. (65% of the theory). Found: S, 21.17%; molecular weight, 310. Calculated for $C_{16}H_{18}$-O_2S_2: S, 20.93%; molecular weight, 306. The compound is easily soluble in methanol, acetone, and ether, sparingly soluble in benzene and in chloroform, almost insoluble in petroleum ether, and slightly soluble in boiling water. It precipitated a crystalline addition compound with mercuric chloride in saturated aqueous solution. Such a behaviour unlike a mercaptol

(1) A brief account was read by T. Takahashi before the annual meeting of the Chemical Society of Japan in Kyoto on April 2, 1950.

(2) Y. Urushibara and T. Takahashi, this Bulletin, **23**, No. 2 (1950), in press.

(3) *J. Am. Chem. Soc.*, **71**, 2264 (1949)

excludes a structure of the mercaptol of dihydroxy-desoxybenzoin, $HOC_6H_4CH_2COC_6H_4OH$, which might result from the dihydroxyhydrobenzoin. Further, acetylation with acetic anhydride and pyridine gave the same diacetate as obtained from diacetoxystilbene dibromide and methylthio-magnesium iodide.

In vagina smear test with ovariectomized mice 20 gammas of the free phenolic substance injected subcutaneously in two portions in oil solution produced oestrus in 67 percent, and 40 gammas in 100 percent, of the animals.

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