251. *Synthetic Oestrogens related to Triphenylethylene.*

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In view of the remarkable oestrogenic activity of triphenylchloroethylene, a number of new compounds related to triphenylethylene were synthesised. The physiological investigation of these compounds and of others already known showed that one of them, namely, αα-di-*p*-methoxyphenyl-β-phenylbromoethylene, was endowed with a much higher potency than triphenylchloroethylene.

4 : 4'-*Dimethoxystilbenediol diacetate* was obtained by reduction of anisil in presence of acetic acid.

TESTED on mice, triphenylchloroethylene has developed a remarkable oestrogenic activity (Robson, Schönberg, and Fahim, *Nature*, 1938, **142**, 292). The clinical application of the compound by Macpherson and Robertson (*Lancet*, 1939, 1362) has shown that it brings about uterine growth, proliferation of the endometrium, withdrawal bleeding, relief of menopausal symptoms, and inhibition of lactation. It can be safely administered as a local application, by injection or by the mouth.

Other derivatives of triphenylethylene have been investigated and a number of new compounds have been prepared, namely, *αα-di-*p*-bromophenyl-β-phenylethylene* (I), *αα-di-*p*-iodophenyl-β-phenylethylene* (II), *αα-di-*p*-chlorophenyl-β-phenylbromoethylene* (III), *αα-di-*p*-bromophenyl-β-phenylbromoethylene* (IV), and *αα-di-*p*-iodophenyl-β-phenylbromoethylene* (V).

Preliminary investigations on mice have shown that, of the new compounds, the last (V) only induced some oestrogenic activity when subcutaneously injected in a dose of 5 mg. (Robson). αα-Di-*p*-methoxyphenyl-β-phenylbromoethylene (VI) (Koelsch, *J. Amer. Chem. Soc.*, 1932, **54**, 2487), however, has been found to develop a very high oestrogenic activity, which considerably surpasses that of triphenylchloroethylene. The possibility that impurity in either substance might influence its oestrogenic activity was excluded by the fact that the two substances were recrystallised six times after their purity had been attested by the analytical data and yet their physiological activities remained unchanged.

The relative oestrogenic activities of αα-di-*p*-methoxyphenyl-β-phenylbromoethylene, triphenylchloroethylene, and stilboestrol are shown in the Table. The compounds were injected subcutaneously in solution in oil of sesame in groups of ovariectomised mice, and their activity measured according to methods previously described (Robson, Schönberg, and Fahim, *loc. cit.*; Robson, *Quart. J. Exper. Physiol.*, 1938, **28**, 195). The chief importance of the triphenylethylene compounds lies in the fact that they produce a prolonged action, though the threshold dose is comparatively high.

Substance.	Dose, μg.	Duration till intensity falls to half, days.	Proportion of mice showing full vaginal cornification.
αα-Di-*p*-methoxyphenyl-β-phenylbromoethylene	100	68	3/3
,, ,, ,,	20	9	10/10
,, ,, ,,	5	Only slight effect	0/5
Triphenylchloroethylene	100	12	11/15
,, ,, ...	50	No appreciable effect	0/10
Stilboestrol	500	16	10/10
,, ...	50	9	10/10

4 : 4′-*Dimethoxystilbenediol diacetate*, $[\text{OMe}\cdot\text{C}_6\text{H}_4\cdot\text{C(OAc)}:]_2$, was prepared by the reduction of anisil in presence of acetic acid in analogous manner to that adopted by Thiele (*Annalen*, 1899, **306**, 142) in the preparation of stilbenediol diacetate.

EXPERIMENTAL.

Di-p-*bromophenylbenzylcarbinol.*—To the Grignard reagent prepared from magnesium (2 g.), benzyl chloride (14 g.), and ether (60 c.c.), *pp*′-dibromobenzophenone (8 g.) was added and after 4 hours' stirring the solution was left overnight and then decomposed with cold aqueous ammonium chloride. Ether extracted the *carbinol*, which separated from petroleum (b. p. 100—110°) in colourless crystals, m. p. 163—164°. The yield was almost theoretical (Found: C, 56·1; H, 3·9; Br, 37·1. $C_{20}H_{16}OBr_2$ requires C, 55·6; H, 3·7; Br, 37·0%).

Di-p-*iodophenylbenzylcarbinol*, similarly prepared (magnesium 0·9 g., benzyl chloride 5 g., ether 40 c.c.; *pp*′-di-iodobenzophenone 10 g.) and crystallised, had m. p. 198—199°. The yield was almost theoretical (Found: C, 46·4; H, 3·3; I, 48·4. $C_{20}H_{16}OI_2$ requires C, 45·6; H, 3·1; I, 48·3%).

αα-Di-p-*bromophenyl*-β-*phenylethylene.*—A solution of di-*p*-bromophenylbenzylcarbinol (2 g.) in glacial acetic acid (20 c.c.) and concentrated sulphuric acid (1·5 c.c.) was refluxed for an hour and cooled, and the precipitate washed with a little glacial acetic acid and recrystallised from methyl alcohol or absolute ethyl alcohol. The *compound* was obtained in colourless crystals, m. p. 133—134°, in almost theoretical yield (Found: C, 58·5; H, 3·4; Br, 38·3. $C_{20}H_{14}Br_2$ requires C, 58·0; H, 3·4; Br, 38·6%).

αα-Di-p-*iodophenyl*-β-*phenylethylene*, similarly prepared from di-*p*-iodophenylbenzylcarbinol (2·4 g.), glacial acetic acid (75 c.c.), and concentrated sulphuric acid (5 c.c.) (3 hours' heating) and crystallised, had m. p. 155—156°. The yield was almost theoretical (Found: C, 47·6; H, 2·9; I, 49·5. $C_{20}H_{14}I_2$ requires C, 47·2; H, 2·8; I, 50·0%).

αα-Di-p-*chlorophenyl*-β-*phenylbromoethylene.*—To a glacial acetic acid solution of αα-di-*p*-chlorophenyl-β-phenylethylene (Alexander and Fuson, *J. Amer. Chem. Soc.*, 1936, **58**, 1745), a slight excess of bromine was added. The solution was boiled for an hour and cooled, and the crystalline precipitate recrystallised from methyl alcohol, absolute ethyl alcohol or glacial acetic acid; m. p. 156—157° (Found: C, 59·3; H, 3·3; Cl, 17·0; Br, 19·2. $C_{20}H_{13}Cl_2Br$ requires C, 59·4; H, 3·2; Cl, 17·6; Br, 19·8%).

αα-Di-p-*bromophenyl*-β-*phenylbromoethylene*, similarly prepared and crystallised, formed very pale yellow crystals, m. p. 164—165° (Found: C, 49·0; H, 2·8; Br, 48·3. $C_{20}H_{13}Br_3$ requires C, 48·7; H, 2·7; Br, 48·7%).

αα-Di-p-*iodophenyl*-β-*phenylbromoethylene*, also prepared in the same way, formed colourless needles, m. p. 173—174° (Found: C, 41·3; H, 2·2; Br, 13·6; I, 43·2. $C_{20}H_{13}BrI_2$ requires C, 40·9; H, 2·2; Br, 13·6; I, 43·3%).

αα-Di-*p*-methoxyphenyl-β-phenylbromoethylene was very soluble in benzene, petroleum (b. p. 100—110°), and ether, fairly readily soluble in methyl alcohol and absolute ethyl alcohol. When it was treated with concentrated sulphuric acid, a red colour developed (Found: C, 66·7; H, 4·9; Br, 20·3. Calc. for $C_{22}H_{19}O_2Br$: C, 66·9; H, 4·9; Br, 20·3%).

Triphenylchloroethylene (H. A. FAHIM).—Triphenylvinyl alcohol (1 mol.) was heated with phosphorus pentachloride (1·5 mols.) for 1 hour at 140—150° (*Bull. Acad. roy. Belg.*, 1897, **34**, 67). The product was cooled, decomposed with a little water, and extracted with ether. The ethereal solution was washed with a dilute alkaline solution and the ether was then distilled off. Triphenylchloroethylene was insoluble in water, soluble in ethyl alcohol and light petroleum (b. p. 30—50°), and freely soluble in chloroform, benzene, ether and acetone. Crystallised from ethyl alcohol, it had m. p. 117°.

4 : 4′-*Dimethoxystilbenediol Diacetate* (H. A. FAHIM).—A solution of anisil (25 g.) in acetic anhydride (200 c.c.) was treated with a mixture of glacial acetic acid (60 c.c.) and concen-

trated sulphuric acid (30 c.c.). To the vigorously stirred solution, zinc dust (40 g.) was gradually added during 1 hour, the temperature being kept at about 40°. The product, after cooling, was poured into water and extracted with ether. The *diacetate* separated from ethyl alcohol in colourless crystals, m. p. 163—164°, freely soluble in chloroform, acetone, and benzene (Found: C, 67·3; H, 5·5. $C_{20}H_{20}O_6$ requires C, 67·4; H, 5·6%). It gave with cold concentrated sulphuric acid a reddish-brown colour, which turned bluish-green.

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