100. *Synthetic Oestrogens related to Triphenylethylene. Part I.*

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A number of triphenylethylenes have been synthesised and tested for oestrogenic activity. Injected subcutaneously in doses of 5 mg., the new compounds 4, 5, and 6 (see Table) showed oestrogenic activity in contrast to the corresponding compounds with no halogen in the phenyl group, which are inactive in this dose. The time required for the oestrogenic activity of the new compounds 8 and 10 (see Table) to fall to half after subcutaneous injection in solution in olive oil in 100 μg. doses into ovariectomised mice is, however, shorter than that of the corresponding compounds with a phenyl group only on the ethylenic 2-carbon atom.

A NUMBER of new triphenylethylene derivatives have been prepared with the object of extending a systematic study of the effect of different substituents in the benzene nuclei on the oestrogenic activity.

By addition of different *pp'*-disubstituted benzophenones to an ethereal solution of *p*-chlorobenzylmagnesium chloride (it was not found necessary to filter this solution in the present investigation; contrast Kharasch and Weinhouse, *J. Org. Chem.*, 1936—37, **1**, 209), and decomposition of the product with aqueous ammonium chloride, the corresponding carbinols are obtained. Dehydration of the carbinols gives the triphenylethylenes, and these on bromination readily yield the corresponding triphenylbromoethylenes.

The time required for the oestrogenic activity to fall to half was measured by the method described by Robson (*Quart. J. Exp. Physiol.*, 1938, **28**, 195). The compounds were dissolved in olive oil and the oestrogenic activity was examined on injection subcutaneously and on administration orally by a stomach tube into groups of 5 ovariectomised mice (see Table). Average weight of the mice was 20—25 g.

Time required for oestrogenic activity to fall to half.

No.	Substance.	Dose (μ g.).	Time (days).
1	1 : 1-*Diphenyl*-2-p-*bromophenylethylene*	1000	2
2	2-Bromo-1 : 1-diphenyl-2-*p*-bromophenylethylene	1000	56
3	2-*Bromo*-1 : 1-*diphenyl*-2-p-*chlorophenylethylene*	100	11
4	*Bromotri*-p-*chlorophenylethylene*	5000	5
5	2-*Bromo*-2-p-*chlorophenyl*-1 : 1-*di*-p-*bromophenylethylene*	5000	10
6	2-*Bromo*-2-p-*chlorophenyl*-1 : 1-*di*-p-*iodophenylethylene*	5000	10
7	2-p-*Chlorophenyl*-1 : 1-*di*-p-*methoxyphenylethylene*	1000	3
8	2-*Bromo*-2-p-*chlorophenyl*-1 : 1-*di*-p-*methoxyphenylethylene*	100	5
	,, ,, ,, ,,	10 *	slight
	,, ,, ,, ,,	100 *	12
9	2-p-*Chlorophenyl*-1 : 1-*di*-p-*ethoxyphenylethylene*	1000	slight
10	2-*Bromo*-2-p-*chlorophenyl*-1 : 1-*di*-p-*ethoxyphenylethylene*	100	3
	,, ,, ,, ,,	10 *	3
	,, ,, ,, ,,	100 *	16
11	2-Bromo-2-phenyl-1 : 1-di-*p*-ethoxyphenylethylene (D.B.E.)	10 *	7
	,, ,, ,, ,,	50 *	21
	,, ,, ,, ,,	500 *	38

* Compounds in solution in olive oil administered orally by a stomach tube into groups of 5 ovariectomised mice. In all other cases compounds in solution in olive oil were injected subcutaneously into groups of 5 ovariectomised mice.

It is interesting to note that when injected subcutaneously in oily solution in doses of 5 mg. into groups of 5 ovariectomised mice, the compounds 4, 5, and 6 in which the three para-positions are occupied by a halogen possess oestrogenic activity, whereas the corresponding derivatives, 2-bromo-2-phenyl-1 : 1-di-*p*-chloro-bromo-, and -iodo-phenylethylene, with only the phenyl group on the ethylenic 2-carbon atom show little or no oestrogenic activity (Schönberg, Robson, Tadros, and Fahim, *J.*, 1940, 1327). The time required for the oestrogenic activity of the new compounds 8 and 10 to fall to half is, however, shorter than that of the corresponding compounds without the chlorine in the phenyl group [Schönberg, *et al.*, *loc. cit.*; Robson, Schönberg, and Tadros, *Nature*, 1942, **150**, 22 (the name of the third author was inadvertently omitted in this publication); Tadros and Schönberg, *J.*, 1943, 394], the latter of which is especially interesting as it exerts prolonged activity when administered orally. It is also remarkable that compounds 8 and 10 show more prolonged action when administered orally than when injected subcutaneously in doses of 100 μg.

Adequate discussion of the above findings is impossible before a study of the metabolism of these compounds is carried out. It has been found (Stroud, *J. Endocrinol.*, 1940, **2**, 55) that stilbene, diphenyl ether, diphenylmethane, and diphenylhexadiene undergo metabolic conversion in female rabbits, giving rise to phenolic compounds, with more potent oestrogenic activity than the corresponding mother substances, in which the hydroxyl group or groups are in the *p*-positions. It would therefore be important to study the metabolic products of the various triphenylethylenes with halogens in the *p*-positions and to correlate with their oestrogenic activity the extent to which they may be hydroxylated in the body.

The increase in potency on introducing a halogen atom into the ethylenic linkage of the triphenylethylene shown by triphenylchloroethylene (Robson, Schönberg, and Fahim, *Nature*, 1938, **142**, 292), triphenylbromoethylene, and triphenyliodoethylene (Robson, Schönberg, and Fahim, unpublished) has also been observed with the triphenylethylene derivatives tested in the present investigation.

1 : 1-Diphenyl-2-*p*-bromophenylethylene * (compound 1) was prepared by the dehydration of diphenyl-*p*-bromobenzylcarbinol (Koelsch, *J. Amer. Chem. Soc.*, 1936, **58**, 1328). On bromination, 2-bromo-1 : 1-diphenyl-2-*p*-bromophenylethylene,* m. p. 114—115°, was readily obtained. The latter, m. p. 109—110°, was obtained (Koelsch, *loc. cit.*) by direct bromination of the carbinol, the product being purified by distillation under reduced pressure followed by recrystallisation from acetic acid.

Experimental.

Diphenyl-p-*chlorobenzylcarbinol* (Kharasch and Weinhouse, *loc. cit.*).—To the Grignard reagent prepared from magnesium (2·85 g.), *p*-chlorobenzyl chloride (20 g.), and ether (100 c.c.), benzophenone (12 g.) was added; after two 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. 116°. The yield of this and the 12 following compounds were almost theoretical (Found : C, 77·8; H, 5·6; Cl, 11·4. Calc. for $C_{20}H_{17}OCl$: C, 77·8; H, 5·5; Cl, 11·5%).

Di-p-*chlorophenyl*-p-*chlorobenzylcarbinol*, similarly prepared (magnesium 2 g., *p*-chlorobenzyl chloride 14 g., ether 100 c.c.; *pp'*-dichlorobenzophenone 10 g.), was obtained in colourless crystals, m. p. 100—102° (Found : C, 63·6; H, 4·0; Cl, 28·1. $C_{20}H_{15}OCl_3$ requires C, 63·6; H, 4·0; Cl, 28·2%).

Di-p-*bromophenyl*-p-*chlorobenzylcarbinol*, similarly prepared (magnesium 1·7 g., *p*-chlorobenzyl chloride 12 g., ether 100 c.c.; *pp'*-dibromobenzophenone 10 g.), was obtained in almost colourless crystals, m. p. 126—128° (Found : C, 52·1; H, 3·4; Cl, 7·6; Br, 34·4. $C_{20}H_{15}OClBr_2$ requires C, 51·4; H, 3·2; Cl, 7·6; Br, 34·3%).

Di-p-*iodophenyl*-p-*chlorobenzylcarbinol*, similarly prepared (magnesium 0·7 g., *p*-chlorobenzyl chloride 5 g., ether 50 c.c.; *pp'*-di-iodobenzophenone 5 g.), was obtained in pale straw-yellow or colourless crystals, sintering at 155°, m. p. 164° (Found : C, 43·3; H, 2·7; Cl, 6·3; I, 44·9. $C_{20}H_{15}OClI_2$ requires C, 42·8; H, 2·7; Cl, 6·3; I, 45·3%).

Di-p-*methoxyphenyl*-p-*chlorobenzylcarbinol*, similarly prepared (magnesium 2 g., *p*-chlorobenzyl chloride 14 g., ether 100 c.c.; *pp'*-dimethoxybenzophenone 10 g.), was obtained in colourless crystals, m. p. 116—117° (Found : C, 71·7; H, 5·7; Cl, 9·8. $C_{22}H_{21}O_3Cl$ requires C, 71·6; H, 5·7; Cl, 9·6%).

Di-p-*ethoxyphenyl*-p-*chlorobenzylcarbinol*, similarly prepared (magnesium 2 g., *p*-chlorobenzyl chloride 14 g., ether 100 c.c.; *pp'*-diethoxybenzophenone 10 g.), was obtained in colourless crystals m. p. 108° (Found : C, 72·8; H, 6·4. $C_{24}H_{25}O_3Cl$ requires C, 72·6; H, 6·3%).

1 : 1-*Diphenyl*-2-p-*chlorophenylethylene*.—This *compound* was obtained by vacuum distillation of diphenyl-*p*-chlorobenzylcarbinol (10 g.) in presence of one drop of 20% sulphuric acid. The oily distillate which solidified on cooling separated from alcohol in colourless crystals, m. p. 76—77° (Found : C, 82·7; H, 5·3; Cl, 12·3. $C_{20}H_{15}Cl$ requires C, 82·6; H, 5·2; Cl, 12·2%).

Tri-p-*chlorophenylethylene*.—A solution of di-*p*-chlorophenyl-*p*-chlorobenzylcarbinol (3 g.) in glacial acetic (20 c.c.) and concentrated sulphuric acid (1 c.c.) was refluxed for an hour, then poured into cold water, left overnight, and the precipitate filtered off and washed with water. The *compound* separated

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from ethyl alcohol in colourless crystals, m. p. 90—91° (Found : C, 66·8; H, 3·9; Cl, 29·7. $C_{20}H_{13}Cl_3$ requires C, 66·8; H, 3·6; Cl, 29·6%).

2-p-*Chlorophenyl*-1 : 1-*di*-p-*bromophenylethylene*, similarly prepared from di-*p*-bromophenyl-*p*-chlorobenzylcarbinol, separated from ethyl alcohol in colourless crystals, m. p. 84° (Found : C, 53·7; H, 3·0; Cl, 7·9; Br, 35·8. $C_{20}H_{13}ClBr_2$ requires C, 53·5; H, 2·9; Cl, 7·9; Br, 35·7%).

2-p-*Chlorophenyl*-1 : 1-*di*-p-*iodophenylethylene*, similarly prepared from di-*p*-iodophenyl-*p*-chlorobenzylcarbinol (4 g.), glacial acetic acid (60 c.c.), and conc. sulphuric acid (2·5 c.c.) (3 hours' heating), crystallised from acetic acid or petroleum (b. p. 50—60°) in colourless crystals, m. p. 102—103° (Found: C, 44·4; H, 2·5; Cl, 6·5; I, 46·7. $C_{20}H_{13}ClI_2$ requires C, 44·2; H, 2·4; Cl, 6·5; I, 46·8%).

1 : 1-*Diphenyl*-2-p-*bromophenylethylene* was similarly prepared from diphenyl-*p*-bromobenzylcarbinol (Koelsch, *loc. cit.*) (2 g.), glacial acetic acid (15 c.c.), and concentrated sulphuric acid (0·2 c.c.) (45 minutes heating). On adding the concentrated sulphuric acid to the carbinol in acetic acid, a green colour developed, which changed gradually on heating to bluish-green. The compound separated from ethyl alcohol in colourless crystals, m. p. 77° (Found : C, 71·8; H, 4·6; Br, 23·3. $C_{20}H_{15}Br$ requires C, 71·6; H, 4·5; Br, 23·9%).

2-p-*Chlorophenyl*-1 : 1-*di*-p-*methoxyphenylethylene*.—(*a*) A solution of di-*p*-methoxyphenyl-*p*-chlorobenzylcarbinol (3 g.) in glacial acetic acid (20 c.c.) and concentrated sulphuric acid (1 c.c.) was refluxed for 45 minutes and then treated as above. The *compound* separated from ethyl alcohol in colourless crystals, m. p. 91°. On addition of the sulphuric acid to the carbinol in glacial acetic acid, a dark violet colour developed. (*b*) The ethylenic compound was also obtained from the carbinol (5 g.) by vacuum distillation in presence of one drop of 20% sulphuric acid. On heating, a greenish-blue colour developed, changing gradually to blue, and before distillation the colour became very pale brown. The compound separated from ethyl alcohol in colourless crystals, m. p. 91° (Found : C, 75·3; H, 5·5. $C_{22}H_{19}O_2Cl$ requires C, 75·3; H, 5·4%).

2-p-*Chlorophenyl*-1 : 1-*di*-p-*ethoxyphenylethylene* was obtained from di-*p*-ethoxyphenyl-*p*-chlorobenzylcarbinol (10 g.) by vacuum distillation in presence of one drop of 20% sulphuric acid. The same display in colour as in (*b*) above took place. The compound separated from ethyl alcohol in colourless crystals, m. p. 76° (Found : C, 76·2; H, 6·3; Cl, 9·7. $C_{24}H_{23}O_2Cl$ requires C, 76·1; H, 6·1; Cl, 9·4%).

2-*Bromo*-1 : 1-*diphenyl*-2-p-*chlorophenylethylene*.—A solution of bromine (0·6 g.) in glacial acetic acid (10 c.c.) was added to a solution of 1 : 1-diphenyl-2-*p*-chlorophenylethylene (1·1 g.) in the same solvent (10 c.c.). The solution was refluxed for an hour and then cooled, and the crystalline precipitate recrystallised from ethyl alcohol from which the *compound* separated in straw-yellow crystals, m. p. 114—115° (Found : C, 64·6; H, 3·9; Cl, 9·6; Br, 21·6. $C_{20}H_{14}ClBr$ requires C, 65·0; H, 3·8; Cl, 9·6; Br, 21·7%).

Bromotri-p-*chlorophenylethylene*, similarly prepared (bromine 0·9 g., in acetic acid 10 c.c.; tri-*p*-chlorophenylethylene 2 g. in acetic acid 20 c.c.), formed colourless crystals, m. p. 166° (Found : C, 54·8; H, 2·9; Cl, 24·4; Br, 18·3. $C_{20}H_{12}Cl_3Br$ requires C, 54·7; H, 2·7; Cl, 24·3; Br, 18·2%).

2-*Bromo*-2-p-*chlorophenyl*-1 : 1-*di*-p-*bromophenylethylene*, similarly prepared (0·8 g. bromine in 10 c.c. glacial acetic acid; 2-*p*-chlorophenyl-1 : 1-di-*p*-bromophenylethylene 2 g., in acetic acid 10 c.c.), formed almost colourless crystals, m. p. 168° (Found : C, 46·0; H, 2·4; Cl, 6·7; Br, 45·5. $C_{20}H_{12}ClBr_3$ requires C, 45·5; H, 2·3; Cl, 6·7; Br, 45·5%).

2-*Bromo*-2-p-*chlorophenyl*-1 : 1-*di*-p-*iodophenylethylene* was similarly prepared (bromine 0·5 g. in acetic acid 10 c.c.; 2-*p*-chlorophenyl-1 : 1-di-*p*-iodophenylethylene 1·75 g. in acetic acid 20 c.c.); it separated from acetic acid in straw-yellow crystals, m. p. 158—160° (Found : C, 39·3; H, 2·0; 5·45 mg. gave 7·38 mg. of silver halide. $C_{20}H_{12}ClBrI_2$ requires C, 38·6; H, 1·9%; 7·19 mg. of silver halide).

2-*Bromo*-2-p-*chlorophenyl*-1 : 1-*di*-p-*methoxyphenylethylene*, similarly prepared (bromine 0·8 g. in acetic acid 10 c.c.; 2-*p*-chlorophenyl-1 : 1-di-*p*-methoxyphenylethylene 2 g. in acetic acid 10 c.c.), recrystallised from ethyl alcohol in colourless crystals, m. p. 112° (Found : C, 61·5; H, 4·3; Cl, 8·4; Br, 18·9. $C_{22}H_{18}O_2ClBr$ requires C, 61·5; H, 4·2; Cl, 8·3; Br, 18·6%).

2-*Bromo*-2-p-*chlorophenyl*-1 : 1-*di*-p-*ethoxyphenylethylene*, similarly prepared, was obtained in colourless crystals, m. p. 98° (Found: C, 63·0; H, 4·9; Cl, 7·8; Br, 17·7. $C_{24}H_{22}O_2ClBr$ requires C, 63·0; H, 4·8; Cl, 7·8; Br, 17·5%).

2-Bromo-1 : 1-diphenyl-2-*p*-bromophenylethylene, similarly prepared (0·22 g. bromine in 5 c.c. acetic acid; 1 : 1-diphenyl-2-*p*-bromophenylethylene 0·5 g. in acetic acid 15 c.c.), was obtained in very pale straw-coloured crystals, m. p. 114—115° (Koelsch, *loc. cit.*, gave m. p. 109—110°) (Found: Br, 38·4. Calc. for $C_{20}H_{14}Br_2$: Br, 38·4%).

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