101. *Synthetic Oestrogens related to Triphenylethylene. Part II.*

By Wadie Tadros.

2-Phenyl-1 : 1-di-*p*-hydroxyphenylethylene is readily obtained by heating compounds 3 and 7 (see Table) in a vacuum in presence of a trace of sulphuric acid or by refluxing their solutions in acetic acid in presence of sulphuric or hydrobromic acid. 2-*Bromo*-2-*phenyl*-1 : 1-*di*-*p*-*hydroxyphenylethylene* is readily obtained by refluxing a solution of 2-*bromo*-2-*phenyl*-1 : 1-*di*-p-iso*propoxyphenylethylene* in acetic acid in presence of sulphuric acid. This and its diacetate which can be readily obtained by bromination of 2-*phenyl*-1 : 1-*di*-p-*acetoxyphenylethylene* have been shown to be highly active oestrogenic compounds (Tadros and Robson, *Nature*, 1947, **160**, 20). Some new triphenylchloroethylenes were prepared by chlorinating their corresponding ethylenes. *Di*-p-*ethylthiophenylbenzylcarbinol* and *di*-p-n-*propylthiophenylbenzylcarbinol* are obtained by adding the appropriate ketone to the ethereal solution of benzylmagnesium chloride.

INJECTED subcutaneously in oily solution into ovariectomised mice, 2-*bromo*-2-*phenyl*-1 : 1-*di*-p-*hydroxyphenylethylene* has been found (Tadros and Robson, *loc. cit.*) to possess high oestrogenic activity; but the duration time, like that of diethylstilboestrol (Dodds, Golberg, Lawson, and Robinson, *Proc. Roy. Soc.*, 1939, **127**, *B*, 140), is not appreciably increased with increased dosage.

2-Bromo-2-phenyl-1 : 1-di-*p*-acetoxyphenylethylene (Tadros and Robson, *loc. cit.*) shows more prolonged action, and its minimal effective dose is lower. Some points of interest have been noted on the preparation of the 2-bromo-2-phenyl-1 : 1-di-*p*-hydroxyphenylethylene and 2-phenyl-1 : 1-di-*p*-hydroxyphenylethylene, the latter first prepared (Dodds *et al.*, *loc. cit.*) by demethylation of 2-phenyl-1 : 1-di-*p*-methoxyphenylethylene. Comment on the findings and a discussion of the mechanism of reaction or reactions involved are, however, deferred until work in progress has been completed.

Addition of *pp'*-disubstituted benzophenones to an ethereal solution of benzylmagnesium chloride, and decomposition of the products with aqueous ammonium chloride, give rise to the corresponding carbinols when the substituent is methoxy- (Koelsch, *J. Amer. Chem. Soc.*, 1932, **54**, 2487; cf. Orekhoff, *Bull. Soc. chim.*, 1919, **25**, 174) or ethoxy- (Tadros and Schönberg, *J.*, 1943, 394) (see Table). In the present communication it is shown (Table) that under the same experimental conditions the carbinols are similarly obtained when the substituent is benzyloxy-, ethylthio-, or *n*-propylthio-, whereas the corresponding triphenylethylenes are directly isolated when it is *n*-propoxy-, *iso*propoxy-, or allyloxy-.

Ketone.	Product.
pp'-Dimethoxybenzophenone.	Di-*p*-methoxyphenylbenzylcarbinol (1).
pp'-Diethoxybenzophenone.	Di-*p*-ethoxyphenylbenzylcarbinol (2).
pp'-*Dibenzyloxybenzophenone*.	*Di*-p-*benzyloxyphenylbenzylcarbinol* (3).
pp'-*Diethylthiobenzophenone*.	*Di*-p-*ethylthiophenylbenzylcarbinol* (4).
pp'-*Di*-n-*propylthiobenzophenone*.	*Di*-p-n-*propylthiophenylbenzylcarbinol* (5).
pp'-Di-*n*-propoxybenzophenone.	2-*Phenyl*-1 : 1-*di*-p-n-*propoxyphenylethylene* (6).
pp'-Di-*iso*propoxybenzophenone.	2-*Phenyl*-1 : 1-*di*-p-iso*propoxyphenylethylene* (7).
pp'-*Diallyloxybenzophenone*.	2-*Phenyl*-1 : 1-*di*-p-*allyloxyphenylethylene* (8).

4-*iso*Propoxystilbene is also directly isolated after the addition of *p*-*iso*propoxybenzaldehyde to the same Grignard reagent and decomposition of the product with aqeuous ammonium chloride.

2-Phenyl-1 : 1-di-*p*-hydroxyphenylethylene is obtained by heating compound **3** or **7** (Table) in a vacuum in presence of one drop of 10 or 20% sulphuric acid, or by refluxing its solution in acetic acid in presence of sulphuric or hydrobromic acid. A red colour develops always on heating.

As a result of the cleavage of one ether linkage only, intermediary *cis*- and *trans*-derivatives would be formed.

2-Bromo-2-phenyl-1 : 1-di-*p*-hydroxyphenylethylene is readily obtained by refluxing a solution of 2-bromo-2-phenyl-1 : 1-di-*p*-isopropoxyphenylethylene in acetic acid in presence of sulphuric acid.

pp'-Diethylthiobenzophenone was prepared by the Friedel–Crafts reaction or by the method by which Schönberg (*Annalen*, 1923—24, **436**, 205) obtained *pp'*-dimethylthiobenzophenone. *pp'*-Diethylthiobenzophenone and *pp'*-di-*n*-propylthiobenzophenone have thus been obtained when thiophenetole or phenyl *n*-propyl sulphide was caused to react with oxalyl chloride in carbon disulphide by adding anhydrous aluminium chloride.

2-*Chloro*-2-*phenyl*-1 : 1-*di*-p-*ethoxyphenyl*-, -*di*-p-n-*propoxyphenyl*-, and *di*-p-iso*propoxy*-

phenyl-ethylene were prepared by adding slightly less than the requisite molar quantity of chlorine in acetic acid to a solution of the corresponding ethylenic compound in the same solvent. 2-Chloro-2-phenyl-1 : 1-di-*p*-ethoxyphenylethylene was also prepared by chlorinating the ethylenic compound with sulphuryl chloride in presence of a little benzoyl peroxide.

EXPERIMENTAL.

pp′-*Diallylbenzophenone*, prepared from *pp*′-dihydroxybenzophenone (30 g.) (Jones, *J.*, 1936, 1854), allyl iodide (60 g.), and alcoholic sodium ethoxide (6·4 g. of sodium added to 200 c.c. of absolute alcohol), separated from alcohol in colourless crystals, m. p. 128—130° (Found: C, 77·4; H, 6·1. $C_{19}H_{18}O_3$ requires C, 77·5; H, 6·1%).

pp′-*Dibenzyloxybenzophenone*, similarly prepared using equivalent quantity of benzyl bromide, separated from benzene or absolute alcohol in colourless crystals, m. p. 186—188° (Found: C, 81·7; H, 5·5. $C_{27}H_{22}O_3$ requires C, 82·2; H, 5·6%).

pp′-Diethoxybenzophenone, m. p. 130—131° (Jones, *loc. cit.*), was readily obtained by the Friedel–Crafts condensation of *p*-ethoxybenzoyl chloride (520 g.), phenetole (1 kg.), and aluminium chloride (800 g.) (yield *ca.* 80%).

pp′-*Diethylthiobenzophenone*. (*a*) Aluminium chloride (18 g.) was gradually added to an ice-cooled mixture of thiophenetole (32 g.) and *p*-ethylthiobenzoyl chloride (Donleavy and English, *J. Amer. Chem. Soc.*, 1940, **62**, 220) [from *p*-ethylthiobenzoic acid (14 g.) and phosphorus pentachloride (16·5 g.)]. The black mixture was subsequently heated on the water-bath for 20 minutes, decomposed with ice, and excess of thiophenetole steam distilled. The ketone separated from alcohol in pale greenish crystals which sintered at 113°, m. p. 117—118°.

(*b*) To a cooled (ice–salt) solution of thiophenetole (13 g.), and oxalyl chloride (6·4 g.) in carbon disulphide (50 c.c.), aluminium chloride (15 g.) was gradually added. The solution was left at room temperature for 3 hours and then heated at 35° for 1 hour. The carbon disulphide was poured off and the dark brown residue treated with ice. The *ketone* thus obtained separated from alcohol in pale greenish plates which sintered at 113°, m. p. 117—118° (Found: C, 67·8; H, 6·2; S, 20·6. $C_{17}H_{18}OS_2$ requires C, 67·6; H, 6·0; S, 21·2%).

pp′-*Di*-n-*propylthiobenzophenone*, similarly prepared as in (*b*) above (phenyl *n*-propyl sulphide, 15·2 g.; oxalyl chloride, 6·4 g.; carbon disulphide, 70 c.c.; anhydrous aluminium chloride, 15 g.) and crystallised, was obtained in colourless crystals which sintered at 62°, m. p. 65—66° (Found: C, 69·5; H, 6·7; S, 19·0. $C_{19}H_{22}OS_2$ requires C, 69·1; H, 6·7; S, 19·4%).

The following carbinols were prepared by adding the appropriate *pp*′-disubstituted benzophenone (0·5 mole) to the Grignard reagent prepared from magnesium (1 atom), benzyl chloride (1 mole), and ether (1800 c.c.), stirring for 4 hours, leaving overnight, then decomposing the products with aqueous ammonium chloride, extracting with ether or benzene–ether, and crystallising from petroleum (b. p. 100—110°) from which they separated in colourless crystals, the yields being almost theoretical. *Di*-p-*benzyloxyphenylbenzylcarbinol* lost consistency at 132°, and had m. p. 136° (Found: C, 84·1; H, 6·2. $C_{34}H_{30}O_3$ requires C, 84·0; H, 6·2%). *Di*-p-*ethylthiophenylbenzylcarbinol* had m. p. 94—96° (Found: C, 72·8; H, 6·5; S, 16·0. $C_{24}H_{26}OS_2$ requires C, 73·1; H, 6·6; S, 16·2%). *Di*-p-n-*propylthiophenylbenzylcarbinol* had m. p. 90—92° (Found: C, 73·8; H, 7·2; S, 15·4. $C_{26}H_{30}OS_2$ requires C, 74·0; H, 7·1; S, 15·2%).

The following ethylenes were isolated in colourless crystals and in almost theoretical yields on attempting the preparation of the corresponding carbinols as above; they were crystallised from alcohol: 2-*phenyl*-1 : 1-*di*-p-*allyloxyphenylethylene*, m. p. 71—73° (Found: C, 84·8; H, 6·7. $C_{26}H_{24}O_2$ requires C, 84·8; H, 6·5%); 2-*phenyl*-1 : 1-*di*-p-n-*propoxyphenylethylene*, m. p. 76—77° (when heated in vacuum in presence of 1 drop of 20% sulphuric acid, the compound distilled unchanged) (Found: C, 83·8; H, 7·7. $C_{26}H_{28}O_2$ requires C, 83·9; H, 7·5%); 2-*phenyl*-1 : 1-*di*-p-iso*propoxyphenylethylene*, m. p. 83—84° (Found: C, 83·7; H, 7·5. $C_{26}H_{28}O_2$ requires C, 83·9; H, 7·5%).

2-*Phenyl*-1 : 1-*di*-p-*benzyloxyphenylethylene* was obtained in almost theoretical yield by heating di-*p*-benzyloxyphenylbenzylcarbinol (5 g.) alone or in presence of 1 drop of 10% sulphuric acid in a vacuum in an oil-bath at 170—175° for about 10 minutes. On cooling, the substance solidified; it separated from alcohol in colourless crystals which sintered at 88°, m. p. 94° (Found: C, 86·7; H, 6·0. $C_{34}H_{28}O_2$ requires C, 87·2; H, 6·0%).

2-*Phenyl*-1 : 1-*di*-p-*hydroxyphenylethylene*. (*a*) A solution of either 2-phenyl-1 : 1-di-*p*-*iso*propoxyphenylethylene (5 g.) or di-*p*-benzyloxyphenylbenzylcarbinol (7 g.) in glacial acetic (49 c.c.), water (1 c.c.), and concentrated sulphuric acid (2 c.c.) was refluxed on a sand-bath, the former for 3 hours and the latter for 10 minutes. The red solutions were then diluted with cold water and left in the ice-chest overnight. The precipitate was dissolved in 2—3% sodium hydroxide solution. The violet alkaline solution was either filtered or extracted with benzene–ether, and the phenolic compound was precipitated in the usual manner. It separated from benzene in almost colourless crystals (yield *ca.* 60—70%) (Found: C, 83·3; H, 5·5. Calc. for $C_{20}H_{16}O_2$: C, 83·3; H, 5·6%).

(*b*) A solution of di-*p*-benzyloxyphenylbenzylcarbinol (5 g.) in glacial acetic acid (50 c.c.), and hydrobromic acid (*d* 1·49; 10 c.c.) was refluxed on a sand-bath for 1 hour. The red solution was then diluted with water, made slightly alkaline, and extracted with ether. This extract contained benzyl bromide, b. p. 196°. The violet alkaline solution was treated as above, and 2-phenyl-1 : 1-di-*p*-hydroxyphenylethylene, m. p. 178°, was isolated in *ca.* 60% yield.

(*c*) 2-Phenyl-1 : 1-di-*p*-*iso*propoxyphenylethylene (10 g.), to which a drop of 20% sulphuric acid was added, was heated in a vacuum in an oil-bath at 220—230° for about 5 minutes. A pink colour developed with rise of temperature, but subsequently faded. The substance was then dissolved in aqueous sodium hydroxide and treated as above, and the above phenolic compound, m. p. 178°, was obtained.

(*d*) On heating di-*p*-benzyloxyphenylcarbinol (5 g.) in presence of 1 drop of 10% sulphuric acid in a vacuum at 190° for about 10 minutes, and then cooling, the substance set into a glassy mass from which the above compound, m. p. 178°, was extracted with 1% aqueous sodium hydroxide. The carbinol became rose-coloured when heated, but turned bluish-green at 220—230°; the products will be investigated.

2-*Phenyl*-1 : 1-*di*-p-*acetoxyphenylethylene*. A solution of 2-phenyl-1 : 1-di-*p*-hydroxyphenylethylene (2·5 g.) in acetic anhydride (25 c.c.) was refluxed on a sand-bath for 1 hour. The solution was diluted with cold water and left overnight in the ice-chest. The semi-solid *product* separated from methyl alcohol in colourless crystals, m. p. 84° (yield almost theoretical) (Found : C, 77·4; H, 5·4. $C_{24}H_{20}O_4$ requires C, 77·4; H, 5·4%).

2-*Phenyl*-1 : 1-*di*-p-*propionyloxyphenylethylene*, similarly prepared using propionic anhydride and refluxing for 2 hours, separated from ether–petroleum (b. p. 50—60°) or methyl alcohol in colourless crystals which sintered at 62°, m. p. 65—66° (yield *ca.* 90%) (Found : C, 78·1; H, 6·1. $C_{26}H_{24}O_4$ requires C, 78·0; H, 6·0%).

4-*isoPropoxystilbene*. On adding *p*-*iso*propoxybenzaldehyde to an ethereal solution of benzylmagnesium chloride and treating the product as above, a colourless crystalline substance, m. p. 115—116°, separated from alcohol. Repeated fractional recrystallisation of the material gave the same substance, m. p. 115—116°. The substance was either the *cis*- or the *trans*-form of 4-iso*propoxystilbene* (Found : C, 85·1; H, 7·5. $C_{17}H_{18}O$ requires C, 85·7; H, 7·6%).

2-*Chloro*-2-*phenyl*-1 : 1-*di*-p-*ethoxyphenylethylene*. (*a*) Sulphuryl chloride (8 g.) was added to a solution of 2-phenyl-1 : 1-di-*p*-ethoxyphenylethylene (15 g.) in glacial acetic acid (60 c.c.) containing benzoyl peroxide (0·06 g.). The vigorous reaction was controlled by dipping the flask in cold water. After ½ hour on a bath at 70—75°, the solution was diluted with water, and the precipitate recrystallised from alcohol from which it separated in colourless crystals, m. p. 86—88° (Found : C, 75·5; H, 6·1; Cl, 9·2. $C_{24}H_{23}O_2Cl$ requires C, 76·1; H, 6·1; Cl, 9·4%).

(*b*) A solution of chlorine (0·9 g.) in acetic acid (35 c.c.) was added to a solution of 2-phenyl-1 : 1-di-*p*-ethoxyphenylethylene (5 g.) in the same solvent (20 c.c.). The solution was refluxed on a sand-bath for 2 hours. It was then diluted with water, and the precipitate recrystallised from methyl alcohol from which it separated in colourless crystals, m. p. 86—88°.

The following chloro- and bromo-ethylenes were prepared by adding a solution of slightly less than the requisite molar quantity of the halogen [as in (*b*) above] in acetic acid to the ethylene dissolved in the same solvent. The solutions were subsequently diluted with water, and the precipitates dissolved in alcohol. The alcoholic solutions were refluxed on the water-bath for 1—1½ hours. On cooling, the halogen derivatives separated in colourless crystals. 2-*Chloro*-2-*phenyl*-1 : 1-*di*-p-n-*propoxyphenylethylene* sintered at 99°, m. p. 102° (Found : C, 77·0; H, 6·9; Cl, 9·0. $C_{26}H_{27}O_2Cl$ requires C, 76·8; H, 6·6; Cl, 8·7%). 2-*Chloro*-2-*phenyl*-1 : 1-*di*-p-iso*propoxyphenylethylene* sintered at 102°, m. p. 106° (Found : C, 76·6; H, 7·1; Cl, 9·2. $C_{26}H_{27}O_2Cl$ requires C, 76·8; H, 6·6; Cl, 8·7%). 2-*Bromo*-2-*phenyl*-1 : 1-*di*-p-n-*propoxyphenylethylene* had m. p. 101° (Found : C, 69·4; H, 6·1; Br, 18·1. $C_{26}H_{27}O_2Br$ requires C, 69·2; H, 6·0; Br, 17·7%). 2-*Bromo*-2-*phenyl*-1 : 1-*di*-p-iso*propoxyphenylethylene* had m. p. 119—120° (Found : C, 69·6; H, 6·2; Br, 17·5. $C_{26}H_{27}O_2Br$ requires C, 69·2; H, 6·0; Br, 17·7%).

2-*Bromo*-2-*phenyl*-1 : 1-*di*-p-*acetoxyphenylethylene*. A solution of bromine (0·43 g.) in acetic acid (5 c.c.) was added to a solution of 2-phenyl-1 : 1-di-*p*-acetoxyphenylethylene (1 g.) in the same solvent (15 c.c.). Acetic anhydride (5 c.c.) was added and the mixture refluxed on the sand-bath for 45 minutes. The *bromo*-compound which was precipitated on dilution with iced water separated from methyl alcohol in colourless crystals, m. p. 157—159° (Found : C, 63·6; H, 4·3; Br, 18·0. $C_{24}H_{19}O_4Br$ requires C, 63·9; H, 4·2; Br, 17·7%).

2-*Bromo*-2-*phenyl*-1 : 1-*di*-p-*hydroxyphenylethylene*. To a solution of 2-bromo-2-phenyl-1 : 1-di-*p*-*iso*propoxyphenylethylene (2 g.) in glacial acetic acid (19·6 c.c.) and water (0·4 c.c.) was added concentrated sulphuric acid (0·8 c.c.), and the mixture was refluxed for 1 hour. A rosy red colour which developed on heating gradually changed to red. The solution was then diluted with water and made slightly alkaline. The violet alkaline solution was either filtered or extracted with ether–benzene, and the phenolic compound was precipitated in the usual manner; it separated from benzene in very pale yellow crystals, m. p. 205—207° (Found : C, 65·9; H, 4·3; Br, 22·0. $C_{20}H_{15}O_2Br$ requires C, 65·4; H, 4·1; Br, 21·8%).

I am grateful to Professor E. E. Turner, F.R.S., for offering facilities to carry out chemical work in the Chemistry Department, Bedford College, University of London, during my stay in England.

FACULTY OF SCIENCE, FOUAD I UNIVERSITY,
CAIRO, EGYPT.

[*Received, August* 25*th*, 1947.]