## 37. *Synthetic Oestrogens of the Triphenylethylene Series.*

By P. R. Carter and D. H. Hey.

Several new mono-, di- and tri-*p*-alkoxytriphenylbromoethylenes have been prepared as synthetic oestrogens by bromination of the corresponding diphenylbenzylcarbinols. The latter were obtained by means of Grignard reactions between (*a*) a benzophenone and a benzylmagnesium halide, (*b*) a phenylacetic ester and a phenylmagnesium halide, or (*c*) a deoxybenzoin and a phenylmagnesium halide. Some of the bromoethylenes exist in geometrically isomeric forms. An improved preparation of *p*-hydroxyphenylacetic acid is described.

The oestrogenic activity of triphenylethylene was first reported almost simultaneously and independently by Robson and Schönberg (*Nature*, 1937, **140**, 196) and by Dodds, Fitzgerald, and Lawson (*Nature*, 1937, **140**, 772). It was subsequently found that non-nuclear halogen substitution of triphenylethylene enhances the oestrogenic activity, and according to Robson, Schönberg, and Fahim (*Nature*, 1938, **142**, 292) chlorotriphenylethylene is some twenty times more active than the unsubstituted triphenylethylene. More recently Segaloff (*Endocrinology*, 1944, **34**, 335) has claimed that chlorotriphenylethylene is one hundred times more active than triphenylethylene. On the other hand nuclear halogen substitution at the *para* positions either destroys the oestrogenic activity completely or reduces it to very small proportions (Schönberg, Robson, Tadros, and Fahim, *J.*, 1940, 1327). Alkyl groups attached to the ethylenic carbon atom increase the oestrogenic activity in a similar manner to a halogen atom, but not to such a large extent (Davies and Elson, B.P. 549,353); the cyano-group is much less effective (Badger, Elson, Haddow, Hewett, and Robinson, *Proc. Roy. Soc.*, 1942, *B*, **130**, 255). Probably the most interesting members in this series of synthetic oestrogens are those containing one or more alkoxy-groups at the *para* position in the aromatic nuclei, and among these 2-bromo-1 : 1 : 2-tri-*p*-anisylethylene (B.P. 549,200, 559,374) and 2-bromo-2-phenyl-1 : 1-di-*p*-ethoxyphenylethylene or DBE (Robson and Schönberg, *Nature*, 1942, **150**, 22; Schönberg and Tadros, B.P. 563,811) have attracted most attention. The importance of the alkoxy-derivatives probably arises from the fact that one or more free phenolic groups are formed during the metabolic processes (Stroud, *Nature*, 1939, **144**, 245; 1940, **146**, 166). This is in keeping with the prolonged action which is characteristic of oestrogens of this type and differentiates them from synthetic oestrogens of the stilboestrol type (cf. Robson and Ansari, *J. Pharm. Exp. Ther.*, 1943, **79**, 340; Greene, *Brit. Med. J.*, 1946, i, 9; Way, *ibid.*, p. 10). With regard to the effect of alkoxy-groups on oestrogenic activity in the triphenylethylene series, Davies and Basford (B.P. 549,200 and 559,374) have claimed that 2-bromo-1 : 1 : 2-tri-*p*-anisylethylene is more active than 2-bromo-2-phenyl-1 : 1-di-*p*-anisylethylene, which, according to Schönberg, Robson, Tadros, and Fahim (*loc. cit.*), has the same activity as 2-bromo-2-phenyl-1 : 1-di-*p*-ethoxyphenylethylene. Further, Basford (B.P. 561,508) states that chlorotri-*p*-anisylethylene is ten times more active than chlorotriphenylethylene. This seems to indicate that in the triphenylethylene series, as with synthetic oestrogens of the stilboestrol type, the maximum activity requires substitution by hydroxy- or alkoxy-groups at the *para* positions in at least two benzene nuclei attached to different ethylenic carbon atoms. This indication is supported by the observation of Dodds, Golberg, Grünfeld, Lawson, Saffer, and Robinson (*Proc. Roy. Soc.*, 1944, *B*, **132**, 83) that 4 : 4′-dihydroxy-β-phenyl-α-ethylstilbene is not less than one-twelfth as active as stilboestrol, and would appear to be the most active derivative of triphenylethylene so far reported.

In order to obtain further information concerning the relationship between chemical constitution and intensity and duration of oestrogenic activity in the triphenylethylene series a number of new mono-, di-, and tri-*p*-alkoxy-bromotriphenylethylenes and one substituted chlorotriphenylethylene have been prepared. Although the corresponding free phenols might in general possess greater activity than the alkyl ethers, their effect is likely to be of shorter duration owing to rapid excretion and decomposition in the body. In this series of synthetic oestrogens duration of activity is of greater importance than high intrinsic activity provided the compound is sufficiently non-toxic for therapeutic doses to be administered with safety and without undesirable side-effects such as nausea and vomiting.

The bromo-*p*-alkoxytriphenylethylenes were prepared by the action of bromine on the corresponding substituted diphenylbenzylcarbinols in glacial acetic acid solution at room temperature. In one instance a chlorotriphenylethylene was prepared by the action of chlorine under similar conditions. This procedure is preferred to the bromination of the substituted triphenylethylenes formed from the carbinols by dehydration, since it eliminates one stage and the solid carbinols are more convenient for purification when working with small quantities.

The substituted diphenylbenzylcarbinols were prepared by the following three methods (R, R′, and R″ = *p*-O-Alkyl or H).

Method *A*. Reaction of a *p*-alkoxybenzophenone with a benzylmagnesium halide :

$$R{\cdot}C_6H_4{\cdot}CO{\cdot}C_6H_4{\cdot}R + Ph{\cdot}CH_2{\cdot}Mg{\cdot}Hal \longrightarrow (R{\cdot}C_6H_4)_2C(OH){\cdot}CH_2Ph$$

Method *B*. Reaction of a *p*-alkoxyphenylacetic ester with a *p*-alkoxyphenylmagnesium halide :

$$R{\cdot}C_6H_4{\cdot}CH_2{\cdot}CO_2Et + 2R'{\cdot}C_6H_4{\cdot}Mg{\cdot}Hal \longrightarrow (R'{\cdot}C_6H_4)_2C(OH){\cdot}CH_2{\cdot}C_6H_4{\cdot}R$$

Method *C*. Reaction of a *p*-alkoxy-deoxybenzoin with a *p*-alkoxyphenylmagnesium halide :

$$R{\cdot}C_6H_4{\cdot}CO{\cdot}CH_2{\cdot}C_6H_4{\cdot}R' + R''{\cdot}C_6H_4{\cdot}Mg{\cdot}Hal \longrightarrow \begin{matrix} R{\cdot}C_6H_4 \\ R''{\cdot}C_6H_4 \end{matrix}\!\!>\!C(OH){\cdot}CH_2{\cdot}C_6H_4{\cdot}R'$$

Method *C* provides two routes to the same carbinol by interchanging R and R″. In one case method *B* gave a substituted triphenylethylene, namely 2-*p*-ethoxyphenyl-1 : 1-di-*p*-*n*-propoxyphenylethylene, in place of the carbinol, but on repeating the Grignard reaction under milder conditions the expected carbinol was obtained in the normal manner. Method *A* had been applied to *para*-substituted benzophenones by Busignies (*Compt. rend.*, 1910, **151**, 516), Ley and Kirchner (*Z. anorg. Chem.*, 1928, **173**, 395), and Koelsch (*J. Amer. Chem. Soc.*, 1932, **54**, 2487), and after the completion of this work Basford reported further examples (B.P. 566,415). This method was also used by Schönberg and Tadros (*J.*, 1943, 394; B.P. 563,810). Attempts to extend the applicability of this reaction to the preparation of tri-*p*-alkoxy-diphenylbenzylcarbinols by the utilisation of a Grignard reagent from a *p*-alkoxybenzyl halide were unsuccessful. Method *B* has also been employed with unsubstituted ethyl phenylacetate by Koelsch (*loc. cit.*), who claimed that the method was applicable only to the preparation of di-substituted compounds. It has now been extended to include the preparation of tri-*p*-alkoxy-derivatives by the use of *p*-alkoxyphenylacetic esters. Method *C* has been used by Dodds, Golberg, Lawson, and Robinson (*Proc. Roy. Soc.*, 1939, *B*, **127**, 161) and by Davies (B.P. 549,200) and more recently by Basford (B.P. 566,415, 567,807). In all three methods it was found desirable to use excess of the Grignard reagent, two molecular proportions being used in the reactions with ketones (*A* and *C*), and three molecular proportions in the reactions with esters (*B*).

The *p*-alkoxyphenylacetic esters for use in Method *B* were prepared by alkylation of *p*-hydroxyphenylacetic acid, which has now been obtained in almost theoretical yield by diazotisation of *p*-aminophenylacetic acid. This represents a considerable improvement on the methods of Salkowski (*Ber.*, 1879, **12**, 1438) and Pschorr, Wolfes, and Buckow (*Ber.*, 1900, **33**, 171), and avoids the necessity of having recourse to the more involved methods of preparation due to Cain, Simonsen, and Smith (*J.*, 1913, **103**, 1036) and Kindler, Metzendorf, and Dschi-yin-Kwok (*Ber.*, 1943, **76**, 308).

Certain of the above bromotriphenylethylenes, namely those which contain two different *p*-alkoxyphenyl groups attached to the same carbon atom, should exist in geometrically isomeric forms, but only in the case of 2-bromo-1-phenyl-1-*p*-anisyl-2-*p*-ethoxyphenylethylene was it possible to isolate both *cis*- and *trans*-forms. Inconclusive evidence was obtained of the existence of 2-bromo-1 : 2-diphenyl-1-*p*-ethoxyphenylethylene in geometrically isomeric forms, but the results were complicated by the existence of one of the forms in polymorphic modifications. 2-Bromo-2-phenyl-1 : 1-di-*p*-ethoxyphenylethylene also appears to exist in two polymorphic forms, and 2-bromo-2-phenyl-1-*p*-ethoxyphenyl-1-*p*-*n*-propoxyphenylethylene was probably obtained as a mixture of *cis*- and *trans*-isomerides. Doubtless both isomerides are formed together in most cases, but only the more insoluble or the more abundant form was obtained in the method of isolation which was not quantitative. Similar observations were recorded by Dodds, Golberg, Lawson, and Robinson (*loc. cit.*) in the case of 1-phenyl-1 : 2-di-*p*-anisylethylene. Koelsch (*loc. cit.*) had previously reported the isolation of both *cis*- and *trans*-forms of 2-bromo-1 : 2-diphenyl-1-*p*-chlorophenylethylene, and by converting them into indones had assigned probable constitutions to the two forms, although, as stated, the proof is not rigid.

At the time of the commencement of this work the only bromoalkoxytriphenylethylenes established were 2-bromo-1 : 2-diphenyl-1-*p*-anisylethylene and 2-bromo-2-phenyl-1 : 1-di-*p*-anisylethylene (Koelsch, *loc. cit.*), 2-bromo-2-phenyl-1 : 1-di-*p*-ethoxyphenylethylene (DBE) (Tadros and Schönberg, *loc. cit.*), and 2-bromo-1 : 1 : 2-tri-*p*-anisylethylene (B.P. 549,200). During the course of this investigation preparations of 2-bromo-2-phenyl-1-*p*-anisyl-2-*p*-ethoxyphenylethylene, 2-bromo-1-*p*-ethoxyphenyl-1 : 2-di-*p*-anisylethylene (B.P. 566,415), and 2-bromo-1-phenyl-1 : 2-di-*p*-ethoxyphenylethylene (B.P. 567,807) were reported. Later preparations of

2-bromo-2-phenyl-1 : 1-di-*p*-ethoxyphenylethylene and 2-bromo-1 : 1 : 2-tri-*p*-anisylethylene have also been reported in B.P. 567,807 and B.P. 559,374 respectively.

Tests carried out by Dr. J. M. Robson showed that many of the new compounds described in this paper possessed oestrogenic activity with a duration of action comparable with that previously associated with 2-bromo-2-phenyl-1 : 1-di-*p*-ethoxyphenylethylene. Full details will be published elsewhere.

## Experimental.

*Preparation of Ketones.*—*4 : 4′-Diethoxybenzophenone.* Ethyl iodide (100 g.) was added slowly to a boiling solution of 4 : 4′-dihydroxybenzophenone (66 g.), prepared as described by Baeyer and Burkhardt (*Annalen*, 1880, **202**, 126), and sodium (13·8 g.) in absolute alcohol (600 c.c.). Boiling under reflux was continued for 1 hour, after which a solution of sodium (6·9 g.) in alcohol (150 c.c.) and ethyl iodide (50 g.) were added in turn. The mixture was boiled under reflux for a further 3 hours until neutral. The alcohol was removed on the steam-bath and water was added to the residue. The solid 4 : 4′-diethoxybenzophenone (76·8 g.) was collected at the pump, washed with water, and dried at 60°. It had m. p. 131° in agreement with Staedel and Beck (*Annalen*, 1878, **194**, 330).

*Phenyl* p-*ethoxybenzyl ketone.* *p*-Ethoxyphenylacetic acid was prepared by ethylation of crude *p*-hydroxyphenylacetic acid, obtained from *p*-aminophenylacetic acid (20·2 g.) as described below. The resultant mixture of *p*-ethoxyphenylacetic acid and its ethyl ester was boiled under reflux for 2 hours with 2N-sodium hydroxide (200 c.c.), and acidification of the cooled solution gave crystalline *p*-ethoxyphenylacetic acid (21·2 g.), which was collected, washed with water, and dried (m. p. 84°). Crystallisation from dilute alcohol raised the m. p. to 88° as recorded by Salkowski (*Ber.*, 1879, **12**, 1440), who gave no analytical figures for the compound. A mixture of *p*-ethoxyphenylacetic acid (21·2 g.) and phosphorus trichloride (8·3 g.) was heated for 2 hours at 100°. Dry benzene (100 c.c.) was added to the warm acid chloride, and the solution was decanted and added to an ice-cold mixture of dry benzene (50 c.c.) and freshly ground aluminium chloride (19 g.) with mechanical stirring. The mixture was stirred over-night with ice-cooling and then for 8 hours with the addition of ice and concentrated hydrochloric acid. The product was extracted with ether–benzene, washed successively with aqueous sodium hydroxide and water, and dried ($Na_2SO_4$). After removal of the solvent on the steam-bath the residue was purified by chromatographic adsorption on alumina from benzene solution, and finally crystallised from benzene–alcohol. Phenyl *p*-ethoxybenzyl ketone (3·8 g.) was obtained in colourless prisms, m. p. 110°, in agreement with Tiffeneau, Orékhov, and Roger (*Bull. Soc. chim.*, 1931, **49**, 1763), who obtained the ketone by the deamination of 2-hydroxy-2-phenyl-2-*p*-ethoxyphenylethylamine.

*p*-Ethoxyphenyl benzyl ketone, m. p. 103°, was prepared in 45% yield from phenylacetic acid, phosphorus trichloride, aluminium chloride, and phenetole in carbon disulphide solution by the method of Tiffeneau, Orékhov, and Roger (*loc. cit.*). When stannic chloride was used in place of aluminium chloride, as recommended by Wilds and Biggerstaff (*J. Amer. Chem. Soc.*, 1945, **67**, 789), the yield was increased to 71%.

*Phenyl* p-n-*propoxybenzyl ketone* was prepared from *p*-*n*-propoxyphenylacetic acid (15·3 g.), phosphorus trichloride (5·5 g.), aluminium chloride (12 g.), and benzene (150 c.c.) as described above for the preparation of phenyl *p*-ethoxybenzyl ketone. It was obtained in colourless plates (3·5 g.), m. p. 92° (Found: C, 80·3; H, 7·2. $C_{17}H_{18}O_2$ requires C, 80·3; H, 7·1%). p-n-*Propoxyphenylacetic acid* was prepared from ethyl *p*-*n*-propoxyphenylacetate (15 g.), obtained as described below, by hydrolysis with boiling 2N-sodium hydroxide (50 c.c.) for 2 hours. After filtration with charcoal, the filtrate was acidified with concentrated hydrochloric acid and extracted with ether. The residue, obtained on removal of the ether, was crystallised from aqueous alcohol and gave the acid (11 g.) in colourless plates, m. p. 91° (Found: C, 68·7; H, 7·4. $C_{11}H_{14}O_3$ requires C, 68·1; H, 7·2%).

*Preparation of Esters.*—*Ethyl* p-*ethoxyphenylacetate.* A solution of *p*-aminophenylacetic acid (30·2 g.), prepared as described by Robertson (*Org. Synth.*, Coll. Vol. I, 52), in a mixture of concentrated sulphuric acid (40 c.c.) and water (320 c.c.) was cooled in a freezing mixture and a solution of sodium nitrite (14 g.) in water (40 c.c.) was added dropwise with stirring during 10 minutes at 2—3°. After a further 10 minutes the clear pale yellow solution of the diazonium salt, kept at 0°, was added during ½ hour in 10—20 c.c. portions to a refluxing mixture of concentrated sulphuric acid (40 c.c.) and water (320 c.c.). The resulting clear pale yellow solution containing no tar was cooled, saturated with sodium sulphate, and extracted with ether. Removal of the ether from the dried ($Na_2SO_4$) extract left the crude hydroxy-acid (30·4 g.) as a brownish solid, m. p. *ca.* 140°. Crystallisation from water gave pure *p*-hydroxyphenylacetic acid, m. p. 148°, in agreement with Salkowski (*loc. cit.*), who prepared it by a similar procedure but gave no yield, and with Pschorr, Wolfes, and Buckow (*loc. cit.*), who claimed only a 50% yield. Ethyl iodide (66 g.) was added to a boiling solution of the crude *p*-hydroxyphenylacetic acid (30·4 g.) in absolute alcohol (400 c.c.) containing sodium (9·2 g.), and after 2 hours' boiling under reflux a solution of sodium (4·6 g.) in absolute alcohol (100 c.c.), followed by a further quantity of ethyl iodide (33 g.), was added. The mixture was boiled for a further 3 hours until neutral, after which the bulk of the alcohol was removed on the steam-bath. Excess of ice-cold dilute hydrochloric acid was added to the residue, which was then extracted with ether. The extract was washed successively with aqueous sodium hydrogen sulphite and water, and after drying ($Na_2SO_4$) the ether and remainder of the alcohol were distilled off on the water-bath, finally under reduced pressure, leaving a mixture of solid *p*-ethoxyphenylacetic acid containing a little ethyl *p*-ethoxyphenylacetate. This crude mixture was boiled under reflux for 3 hours with absolute ethyl alcohol (200 c.c.) containing concentrated sulphuric acid (8 c.c.). The cold mixture was diluted with water and extracted with ether, and the extract was washed successively with aqueous sodium carbonate and water and dried ($Na_2SO_4$). The ether and alcohol were removed on the steam-bath, and distillation of the residue under reduced pressure gave *ethyl* p-*ethoxyphenylacetate* (33·4 g.) as a very pale yellow oil, b. p. 130°/3 mm., 148°/7 mm. (Found: C, 69·2; H, 7·8. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·7%).

*Ethyl* p-n-*propoxyphenylacetate.* Crude *p*-hydroxyphenylacetic acid (30·4 g.), prepared as described above, was boiled under reflux for 2 hours with absolute ethyl alcohol (150 c.c.) containing concentrated sulphuric acid (6 c.c.). After removal of the bulk of the alcohol on the steam-bath the cooled residue was treated with water and extracted with ether. The extract was washed with aqueous sodium carbonate and with water, and dried ($Na_2SO_4$). Distillation of the ether and removal of the alcohol under reduced pressure gave crude ethyl *p*-hydroxyphenylacetate (31·25 g.), which was added to a solution of sodium (3·45 g.) in absolute alcohol (100 c.c.). *n*-Propyl bromide (18·5 g.) was added to the boiling solution under reflux, and after 2 hours a further addition of sodium (1·75 g.) in absolute alcohol (50 c.c.) followed by *n*-propyl bromide (10 g.) was made. After a further 2 hours' boiling under reflux the bulk of the alcohol was removed on the steam-bath and ice–water was added to the cold residue, which was extracted with ether. After the extract had been washed with aqueous sodium hydroxide and with water, and dried ($Na_2SO_4$), the ether was removed; distillation of the residue under reduced pressure gave *ethyl* p-n-*propoxyphenylacetate* (26 g.) as a pale yellow oil, b. p. 160°/6 mm. (Found: C, 70·25; H, 7·8. $C_{13}H_{18}O_3$ requires C, 70·3; H, 8·1%).

*Methyl* p-*anisylacetate.* To a boiling solution of crude *p*-hydroxyphenylacetic acid, prepared as described above from *p*-aminophenylacetic acid (30·2 g.), dissolved in a solution of sodium (9·2 g.) in absolute alcohol (400 c.c.), was added methyl iodide (60 g.). Boiling under reflux was continued for 2 hours, after which a further solution of sodium (4·6 g.) in absolute alcohol (100 c.c.) followed by methyl iodide (30 g.) were added. After a further two hours' boiling under reflux the bulk of the alcohol was removed on the steam-bath and the cooled residue treated with ice–water and dilute acid and extracted with ether. The extract was washed successively with aqueous sodium hydrogen sulphite, water, 2N-sodium hydroxide, and water, and finally dried ($NaSO_4$). Removal of the ether and distillation of the residue under reduced pressure gave methyl *p*-anisylacetate (14·7 g.) as a very pale yellow oil, b. p. 141—142°/16 mm. Pschorr, Wolfes, and Buckow (*loc. cit.*) give b. p. 155—157°/23 mm. for the ester prepared from *p*-hydroxyphenylacetic acid, methyl iodide, and potassium hydroxide in methyl alcohol at 100°.

*Ethyl* p-*anisylacetate.* The sodium hydroxide washings from the preparation of methyl *p*-anisylacetate were acidified and extracted with ether. After the extract had been washed with aqueous sodium hydrogen sulphite and with water and dried ($Na_2SO_4$), the ether was removed and the residual *p*-anisylacetic acid was boiled under reflux for 3 hours with ethyl alcohol (100 c.c.) containing concentrated sulphuric acid (4 c.c.). After removal of the bulk of the alcohol on the steam-bath the cooled residue was treated with water and extracted with ether. The extract was washed with aqueous sodium hydroxide and with water and dried ($Na_2SO_4$). Removal of the ether, followed by distillation under reduced pressure, gave ethyl *p*-anisylacetate (6·5 g.) as a very pale yellow oil, b. p. 138—140°/7 mm. Cain, Simonsen, and Smith (*loc. cit.*) give b. p. 138—140°/7 mm. for the ester prepared by oxidation of *p*-anisylpyruvic acid followed by esterification.

*Preparation of* p-*Alkoxyphenyl Bromides.*—*p*-Bromophenetole was prepared by the bromination of phenetole in carbon disulphide, as described by Michaelis (*Ber.*, 1894, **27**, 258), whereas *p*-bromoanisole was prepared in similar manner but in carbon tetrachloride solution (cf. Michaelis and Weitz, *Ber.*, 1887, **20**, 49). In both reactions yields of 90% were obtained. Phenyl *n*-propyl ether was prepared by the addition of *n*-propyl bromide (123 g.) to a boiling solution of phenol (94 g.) in absolute ethyl alcohol (1000 c.c.) containing sodium (23 g.). After 2 hours a further quantity of sodium (11·5 g.) in alcohol (500 c.c.) was added, followed by more *n*-propyl bromide (62 g.). After two hours' boiling under reflux the alcohol was removed and the residue treated with water and extracted with ether. Removal of the ether from the dried extract left phenyl *n*-propyl ether, which was collected as a colourless oil (100 g.) at 190° (cf. Cahours, *Bull. Soc. chim.*, 1874, **21**, 78). Bromine (118 g.) was added dropwise to a stirred solution of the ether (100 g.) in carbon disulphide (300 c.c.) at 0°. The resulting pale yellow solution was washed with water and with aqueous sodium thiosulphate. After removal of the solvent the *p*-bromophenyl *n*-propyl ether (152 g.) was collected as a pale yellow oil at 128°/24 mm. (Found: C, 50·6; H, 5·5. Calc. for $C_9H_{11}OBr$: C, 50·2; H, 5·2%). Bradfield and Jones (*J.*, 1931, 2903) reported this compound but gave no experimental details.

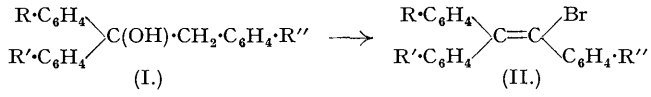
*Preparation of Carbinols. General Methods.—Method* A. The Grignard reagent, prepared from freshly distilled benzyl chloride (0·5 mol.) and magnesium (0·5 mol.) in dry ether (400 c.c.), was treated, with ice-cooling and stirring, with the benzophenone (0·25 mol.). After boiling under reflux for 2 hours and standing over-night, the mixture was added to a mixture of crushed ice (2 kg.) and ammonium chloride (200 g.). The carbinol which separated was filtered off, washed with water and a little ether, and dried and/or extracted with ether and the ethereal layer was separated, dried ($Na_2SO_4$), and evaporated. The carbinols were crystallised from light petroleum (b. p. 60—80°) and were usually obtained in the form of colourless needles in good yield.

*Method* B. The Grignard reagent, prepared from magnesium (1·0 mol.), freshly distilled bromo-compound (1·0 mol.), and ether (625 c.c.), was treated, with ice-cooling and stirring, with a solution of the phenylacetic ester (0·33 mol.) in ether (275 c.c.) added dropwise. After being heated under reflux for 2 hours and left over-night the mixture was poured on crushed ice (2 kg.) and ammonium chloride (250 g.), and the carbinol was isolated in yields varying from 40 to 70% (calculated on ester) as described above under Method *A*. In one instance this procedure led to the ethylene and not the carbinol, but repetition of the reaction without heating under reflux gave the carbinol in the normal manner (see later).

*Method* C. The Grignard reagent, prepared from magnesium (0·5 mol.), the bromo-compound (0·5 mol.), and ether (500 c.c.), was treated, with ice-cooling and stirring, with a solution of the deoxybenzoin (0·25 mol.) in ether (500 c.c.) added dropwise. After boiling under reflux for two hours, the mixture was cooled and poured on a mixture of crushed ice and ammonium chloride. The carbinol was extracted with ether or benzene. After the extract had been dried and the solvent removed, the residual carbinol crystallised from light petroleum (b. p. 60—80°). Yields varied from 40 to 60% calculated on the deoxybenzoin.

*Preparation of Bromoethylenes. General Method.*—A solution of bromine (1·6 g., 0·01 mol.) in glacial

*Carbinols and Bromoethylenes* (R, R′, and R″ = *p*-*O*-Alkyl or H).



(I.) (II.)

| | | | | | | Analysis. Found, %. | | Calc, %. | | | | Analysis. Found, %. | | Calc, %. | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| R. | R′. | R″. | Carbinol (I). | M. p. | Prep. | C. | H. | C. | H. | Bromoethylene (II). | M. p. | C. | H. | C. | H. |
| H | H | MeO | $C_{21}H_{20}O_2$ | 142° | *B* | 82·5 | 6·4 | 82·9 | 6·6 | $C_{21}H_{17}OBr$ | 130° | 68·6 | 4·8 | 69·0 | 4·7 |
| H | EtO | H | $C_{22}H_{22}O_2$‡ § | 86—87 | *C* | 82·85 | 7·0 | 83·0 | 6·9 | $C_{22}H_{19}OBr$ ‡ | 83—84 | 69·4 | 5·1 | 69·7 | 5·0 |
| | | | | | | | | | | $C_{22}H_{19}OBr$ | 92 | 69·2 | 5·0 | 69·7 | 5·0 |
| | | | | | | | | | | $C_{22}H_{19}OBr$ | 111 | 69·3 | 5·1 | 69·7 | 5·0 |
| H | H | EtO | $C_{22}H_{22}O_2$ | 97·5 | *B* | 82·7 | 6·8 | 83·0 | 6·9 | $C_{22}H_{19}OBr$ | 95 | 69·8 | 5·0 | 69·7 | 5·0 |
| MeO | MeO | MeO | $C_{23}H_{24}O_4$ † | 129 | *B* | 75·9 | 6·5 | 75·8 | 6·5 | $C_{23}H_{21}O_3Br$ † | 120 | 64·9 | 4·9 | 64·9 | 5·1 |
| H | MeO | EtO | $C_{23}H_{24}O_3$ ‖ | 89 | *C* | 79·3 | 6·9 | 79·3 | 6·9 | $C_{23}H_{21}O_2Br$ | 106 | 67·6 | 5·0 | 67·5 | 5·1 |
| | | | | | | | | | | $C_{23}H_{21}O_2Br$ | 153 | 67·9 | 5·4 | 67·5 | 5·1 |
| H | *n*-PrO | H | $C_{23}H_{24}O_2$ § | 84 | *C* | 82·8 | 6·9 | 83·1 | 7·2 | $C_{23}H_{21}OBr$ | 118 | 69·9 | 5·5 | 70·2 | 5·3 |
| H | H | *n*-PrO | $C_{23}H_{24}O_2$ | 71 | *B* | 83·0 | 7·4 | 83·1 | 7·2 | $C_{23}H_{21}OBr$ | 92 | 70·3 | 5·3 | 70·2 | 5·3 |
| MeO | MeO | EtO | $C_{24}H_{26}O_4$ | 116 | *B* | 76·1 | 7·0 | 76·2 | 6·9 | $C_{24}H_{23}O_3Br$ | 76 | 65·6 | 5·5 | 65·6 | 5·2 |
| EtO | EtO | H | $C_{24}H_{26}O_3$ * | 124 | *A*, *B* | — | — | — | — | $C_{24}H_{23}O_2Br$ * | 97 | — | — | — | — |
| | | | | | | | | | | $C_{24}H_{23}O_2Br$ | 87 | — | — | — | — |
| H | MeO | *n*-PrO | $C_{24}H_{26}O_3$ ** | 107 | *C* | 79·5 | 7·05 | 79·5 | 7·2 | $C_{24}H_{23}O_2Br$ | 85 | 68·2 | 5·4 | 68·1 | 5·4 |
| EtO | EtO | MeO | $C_{25}H_{28}O_4$ | 107 | *B* | 76·3 | 7·2 | 76·5 | 7·1 | $C_{25}H_{25}O_3Br$ | 81 | 65·7 | 5·4 | 66·2 | 5·5 |
| EtO | *n*-PrO | H | $C_{25}H_{28}O_3$ ¶ | 105 | *C* | 80·1 | 6·9 | 79·8 | 7·45 | $C_{25}H_{25}O_2Br$ | *ca.* 70 | 66·2 | 5·4 | 68·6 | 5·7 |
| H | *n*-PrO | EtO | $C_{25}H_{28}O_3$ ‖ | 86 | *C* | 79·5 | 7·3 | 79·8 | 7·45 | $C_{25}H_{25}O_2Br$ | 71 | 68·1 | 5·6 | 68·6 | 5·7 |
| EtO | EtO | EtO | $C_{26}H_{30}O_4$ | 116 | *B* | 77·1 | 7·4 | 76·9 | 7·4 | $C_{26}H_{27}O_3Br$ | 81—82 | 66·6 | 6·0 | 66·8 | 5·8 |
| *n*-PrO | *n*-PrO | EtO | $C_{28}H_{34}O_4$ | 85 | *B* | 76·8 | 7·8 | 77·4 | 7·8 | $C_{28}H_{31}O_3Br$ | 86 | 68·2 | 6·3 | 67·9 | 6·3 |

* Previously prepared by Tadros and Schönberg (*J.*, 1943, 394) by Method *A*.
† Previously prepared by Davies (B.P. 549,200).
‡ Prepared by Dr. W. H. Hook.
§ Prepared from deoxybenzoin.
‖ Prepared from phenyl *p*-ethoxybenzyl ketone.
¶ Prepared from *p*-ethoxyphenyl benzyl ketone.
** Prepared from phenyl *p*-*n*-propoxybenzyl ketone.

acetic acid (16 c.c.) was added to a solution or suspension of the carbinol (0·01 mol.) in the same solvent (30 c.c.). The temperature was maintained below 20°. After two hours' stirring at room temperature the bulk of the acetic acid was removed under reduced pressure on the water-bath, and the residual bromoethylene was filtered off and recrystallised from absolute alcohol or light petroleum (b. p. 80—100°). Alternatively, the bromo-compound was thrown out of solution, usually as an oil, by the addition of water to the solution in glacial acetic acid. Many carbinols and bromoethylenes were purified by chromatographic adsorption on activated alumina, from solution in either light petroleum (b. p. 80—100°) or a mixture of that solvent with 10% v/v of benzene, followed by elution with the same solvent. In this manner it was frequently found possible to isolate the products in pure crystalline form from a crude product in the form of a brown viscous oil. The pure bromoethylenes were usually obtained as very pale yellow or almost colourless needles or prisms.

The carbinols and bromoethylenes prepared in this way are listed in the Table.

2-*Chloro*-1 : 1-*di*-p-*anisyl*-2-p-*ethoxyphenylethylene*.—Chlorine (225 c.c.) was delivered slowly from a graduated aspirator into a solution of di-*p*-methoxyphenyl-*p*-ethoxybenzylcarbinol (3·78 g.) in glacial acetic acid (30 c.c.) at room temperature. After several hours the product was precipitated as an oil by dilution with water. The oil was extracted with light petroleum (b. p. 80—100°), dried, and purified by chromatographic adsorption on alumina. 2-*Chloro*-1 : 1-*di*-p-*anisyl*-2-p-*ethoxyphenylethylene* (1·7 g.) crystallised from absolute ethyl alcohol in colourless prisms, m. p. 82° (Found: C, 72·4; H, 5·7. $C_{24}H_{23}O_3Cl$ requires C, 73·0; H, 5·8%).

2-p-*Ethoxyphenyl*-1 : 1-*di*-n-*propoxyphenylethylene*.—A solution of ethyl *p*-ethoxyphenylacetate (7 g.) in dry ether (50 c.c.) was added to the Grignard reagent prepared in the usual manner from *p*-bromo-*n*-propoxybenzene (21·5 g.) and magnesium (2·43 g.) in dry ether (125 c.c.) with ice-cooling and stirring. The mixture was boiled under reflux for 2 hours, cooled, poured on ice and ammonium chloride, and extracted with ether. Evaporation of the dried extract left an oily residue which was purified by chromatographic adsorption on alumina from light petroleum (b. p. 80—100°). Crystallisation from light petroleum (b. p. 40—60°) gave 2-p-*ethoxyphenyl*-1 : 1-*di*-n-*propoxyphenylethylene* in colourless needles, m. p. 76° (Found: C, 81·0; H, 7·5. $C_{26}H_{32}O_3$ requires C, 80·8; H, 7·7%). When the above preparation was repeated without boiling under reflux *di*-p-n-*propoxyphenyl*-p-*ethoxybenzylcarbinol*, m. p. 85° (see Table), was isolated in the normal manner. In this instance the bromoethylene was prepared by the bromination of the ethylene, and not the carbinol, using the same general procedure in glacial acetic acid solution.

*Isomeric and Polymorphic Forms*.—2-*Bromo*-1 : 2-*diphenyl*-1-p-*ethoxyphenylethylene*. (By Dr. W. H. Hook.) When prepared from the carbinol by the general method the bromoethylene separated from the acetic acid solution on standing over-night in transparent plates, m. p. 91—92°, which on recrystallisation from ethyl alcohol gave colourless prisms, m. p. 83—84°. After fusion and slow cooling the melting-point was raised to 91—92° again. The two forms melting at 91—92° and 83—84° are regarded as polymorphic modifications. On irradiation in solution in ethyl alcohol with ultra-violet light for 3 days, followed by slow evaporation, colourless plates, m. p. 111°, were obtained. All three forms gave correct analytical figures for $C_{22}H_{19}OBr$ (see Table). The preparation of a bromination product of 1 : 2-diphenyl-1-*p*-ethoxyphenylethylene has been reported by Busignies (*loc. cit.*), who gave m. p. 73°. This product may have been a mixture of isomeric or polymorphic forms, although it is significant that the 1 : 2-diphenyl-1-*p*-ethoxyphenylethylene from which it was obtained had m. p. 93°, whereas Ley and Kirchner (*loc. cit.*) gave m. p. 76° for this compound.

2-*Bromo*-1-*phenyl*-1-p-*anisyl*-2-p-*ethoxyphenylethylene*.—When prepared from the carbinol by the general method and isolated immediately by dilution with water and recrystallisation from absolute ethyl alcohol the bromoethylene was obtained in colourless needles m. p. 106°. In another preparation the brominated carbinol was allowed to stand for 12 weeks in the glacial acetic acid solution in a corked flask. During this period the bromoethylene separated slowly in long colourless needles, which after recrystallisation from absolute ethyl alcohol melted at 153°. Both forms gave correct analytical figures for $C_{23}H_{21}O_2Br$ (see Table).

2-*Bromo*-2-*phenyl*-1 : 1-*di*-p-*ethoxyphenylethylene*.—This compound separates from dilute solution in light petroleum (b. p. 80—100°) in very pale yellow prisms, m. p. 97°, but on rapid crystallisation from concentrated solutions long colourless needles, m. p. 87°, are obtained.

2-*Bromo*-2-*phenyl*-1-p-*ethoxyphenyl*-1-p-n-*propoxyphenylethylene*.—This compound (m. p. *ca.* 70°) could not be further purified to give a product with a sharp melting point, and is probably a mixture of *cis*- and *trans*-isomerides.

The authors' thanks are accorded to Dr. W. H. Hook for the preparation of 2-bromo-1 : 2-diphenyl-1-*p*-ethoxyphenylethylene and the examination of its properties, and to Dr. J. M. Robson for carrying out the physiological tests.

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