786. *Derivatives of* 1 : 3- *and* 1 : 4-*Di-α-stilbenylbenzene and Other Complex Triarylethylenes.*

By Ng. Ph. Buu-Hoï, T. B. Loc, and Ng. D. Xuong.

The synthesis is reported of a number of highly conjugated derivatives of triphenylethylene derived from 1 : 3- and 1 : 4-di-α-stilbenylbenzene and α-(4-*m*-terphenylyl)stilbene, which had little or no œstrogenic activity; the diphenyl ether of hexœstrol, prepared from *p*-1-chloropropylphenyl phenyl ether with iron powder, was likewise inactive.

In investigations concerning the mechanism and site of fixation of œstrogenic molecules on cell proteins, derivatives of triphenylethylene having a large molecular encumbrance area were required for determination of their œstrogenic activity. Triphenylethylene, and especially its α-halogenated derivatives, possess pronounced œstrogenic properties,[1] and it is known that appropriate substitution with bulky radicals such as methoxy- or

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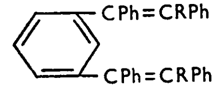
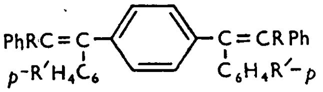
[1] Robson and Schönberg, *Nature*, 1937, **140**, 196; Robson, Schönberg, and Fahim, *Nature*, 1938, **142**, 292.

ethoxy-groups[2] can maintain or enhance this activity; similarly, 1-bromo-1-*p*-diphenylyl-1 : 2-diphenylethylene is œstrogenic, despite the considerable size of its molecule.[3] The present work reports the preparation of highly conjugated compounds derived from *m*- (I; R = H) and *p*-di-α-stilbenylbenzene (II; R = R′ = H), whose molecular structure comprises two triphenylethylene complexes.

(I)

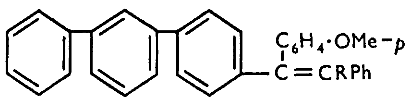


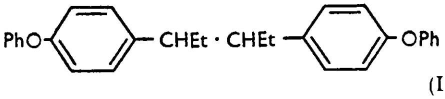


(II)

The reaction of 2 mol. of benzylmagnesium chloride with 1 mol. of *p*-dibenzoylbenzene (this diketone was prepared from terephthaloyl dichloride and benzene by a Friedel–Crafts reaction, according to Noelting and Kohn[4]) gave a tertiary diol, which was not isolated but was directly dehydrated by formic acid[5] to *p*-di-α-stilbenylbenzene, a hydrocarbon with the surprisingly low m. p. of 74°; halogenation of this compound with bromine (2 mol.) in acetic acid afforded *p*-di-(β-bromo-α-stilbenyl)benzene (II; R = Br, R′ = H). Friedel–Crafts reaction of terephthaloyl dichloride with anisole yielded *p*-di-*p*′-anisoylbenzene which with benzylmagnesium chloride gave *p*-di-(4-methoxy-α-stilbenyl)benzene (II; R = H, R′ = OMe); this underwent dichlorination to *p*-di-(β-chloro-4-methoxy-α-stilbenyl)benzene (II; R = Cl, R′ = OMe), and dibromination to *p*-di-(β-bromo-4-methoxy-α-stilbenyl)benzene (II; R = Br, R′ = OMe). In the *meta*-series, a similar sequence of reaction with *m*-dibenzoylbenzene (prepared by Friedel–Crafts condensation of *iso*phthaloyl dichloride with benzene and aluminium chloride[4]) afforded *m*-di-(β-bromo-α-stilbenyl)benzene (I; R = Br), *via* *m*-di-α-stilbenylbenzene. It is worth mention that *m*-dibenzoylbenzene, which Reindel and Siegel could not reduce by a Clemmensen reaction,[6] was readily converted into *m*-dibenzylbenzene by the Huang-Minlon[7] modification of the Wolff–Kishner reaction. A highly conjugated triarylethylene of another type was prepared from 4-*p*-anisoyl-*m*-terphenyl,[8] which was converted by benzylmagnesium chloride into 4-methoxy-α-(4-*m*-terphenylyl)stilbene (III; R = H), and this underwent monobromination of β-bromo-4-methoxy-α-(4-*m*-terphenylyl)stilbene (III; R = Br).

(III)





(IV)

A derivative of hexœstrol with large *para*-substituents is *meso*-3 : 4-di-(*p*-phenoxyphenyl)hexane (IV), which was readily prepared by bimolecular dehalogenation of *p*-1-chloropropylphenyl phenyl ether by means of iron powder in water.[9]

In biological tests, *m*- and *p*-di-α-stilbenylbenzene and their dibromo-derivatives, as well as compound (IV), showed no œstrogenic activity at a dose of 0·1 mg. in the Allen–Doisy test in castrated rats; at a dose of 1 mg., however, compound (III; R = Br, R′ = H) produced incomplete œstrus.

EXPERIMENTAL

m-*Di-α-stilbenylbenzene* (I; R = H).—To a water-cooled solution of benzylmagnesium chloride (17·8 g.) in anhydrous ether (100 c.c.), *m*-dibenzoylbenzene (m. p. 100°; 8 g., in ether) was added in small portions, and the mixture then refluxed for 30 min. on the water-bath.

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[2] Robson, Schönberg, and Tadros, *Nature*, 1942, **150**, 22; Dodds, Goldberg, Grünfeld, Lawson, Saffer, and Robinson, *Proc. Roy. Soc.*, 1944, **132**, *B*, 83.

[3] Lacassagne, Buu-Hoï, Corre, Lecocq, and Royer, *Experientia*, 1946, **2**, 70.

[4] Noelting and Kohn, *Ber.*, 1886, **19**, 147; Ador, *Ber.*, 1880, **13**, 320.

[5] For general procedure see Buu-Hoï, *Bull. Soc. chim. France*, 1946, **13**, 115.

[6] Reindel and Siegel, *Ber.*, 1923, **56**, 1554.

[7] Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487.

[8] Buu-Hoï and Royer, *J. Org. Chem.*, 1951, **16**, 320.

[9] Buu-Hoï and Hoán, *J. Org. Chem.*, 1949, **14**, 1023.

After cooling, and decomposition with cold dilute aqueous sulphuric acid, the product was taken up in benzene, the benzene solution washed with water and dried (Na_2SO_4), the solvent removed, and the crude tertiary diol dehydrated by 5 minutes' refluxing with pure formic acid (5 parts). After dilution with water, the dehydration product was taken up in benzene, washed with water, and dried (Na_2SO_4), the solvent removed, and the residue distilled *in vacuo.* m-*Di-α-stilbenylbenzene,* b. p. 257—259°/0·6 mm., crystallised as colourless needles (5 g.), m. p. 57°, from methanol (Found: C, 93·8; H, 6·2. $C_{34}H_{26}$ requires C, 94·0; H, 6·0%).

m-*Di-(β-bromo-α-stilbenyl)benzene* (I; R = Br).—To a water-cooled solution of the foregoing diethylene (1 g.) in acetic acid (40 c.c.), bromine (0·7 g.; in acetic acid) was added in small portions with stirring, and the mixture obtained was warmed on the water-bath for 15 min. The precipitate obtained on dilution with water was taken up in benzene, washed with dilute aqueous alkali, then with water, and dried (Na_2SO_4), and the solvent evaporated. The residue crystallised as colourless prisms (0·7 g.), m. p. 84°, from light petroleum (Found: C, 68·6; H, 3·9. $C_{34}H_{24}Br_2$ requires C, 68·9; H, 4·1%).

m-*Dibenzylbenzene.*—A mixture of *m*-dibenzoylbenzene (4 g.), 95% hydrazine hydrate (10 g.), and diethylene glycol (50 c.c.) was heated at 120° for 10 min. to allow formation of the dihydrazone, then cooled, and potassium hydroxide (10 g.) was added; the mixture was then refluxed for 30 min. with removal of water. After cooling, water was added, the reduction product taken up in benzene, washed with dilute hydrochloric acid, then with water, and dried, the solvent removed, and the residue distilled *in vacuo.* *m*-Dibenzylbenzene was a colourless oil, b. p. 223—224°/13 mm., $n_D^{18.5}$ 1·6038; a sample prepared by Friedel–Crafts reactions [10] boiled at 230°/14 mm.

p-*Di-α-stilbenylbenzene* (II; R = R′ = H).—To a solution of benzylmagnesium chloride (29 g., 4 mol.) in anhydrous ether (150 c.c.), *p*-dibenzoylbenzene, m. p. 160° (14 g., 1 mol.) in suspension in ether (100 c.c.) was added in small portions, and the mixture then refluxed for 30 min. on the water-bath. The product was worked up as for the *m*-isomer. Distillation *in vacuo* gave the *diethylene,* b. p. 280—281°/0·9 mm., needles (7 g.), m. p. 74° (from ethanol) (Found: C, 93·7; H, 6·2%).

p-*Di-(β-bromo-α-stilbenyl)benzene* (II; R = Br, R′ = H).—To a solution of the foregoing diethylene (4·3 g.) in acetic acid (50 c.c.), bromine (3·2 g.) in acetic acid was added in small portions, and the mixture worked up in the usual way; the *dibromo-compound* crystallised as prisms (4·9 g.), m. p. 206°, from acetic acid (Found: C, 68·9; H, 4·4%).

p-*Di*-p′-*anisoylbenzene.*—To a solution of terephthaloyl dichloride (20 g.) and anisole (22 g.) in anhydrous carbon disulphide (150 c.c.), finely powdered aluminium chloride (26 g.) was added portionwise with stirring, and the mixture left for 24 hr. at room temperature. After decomposition with water, the solid precipitate was filtered off and recrystallised from *o*-dichlorobenzene, giving prisms (10 g.), m. p. 239° (Found: C, 76·3; H, 5·3. $C_{22}H_{18}O_4$ requires C, 76·3; H, 5·2%).

p-*Di-(4-methoxy-α-stilbenyl)benzene* (II; R = H, R′ = OMe).—The foregoing ketone (9 g.), treated in the usual way with benzylmagnesium chloride (15 g.) in ether (150 c.c.), afforded a *diethylene,* b. p. 312°/0·2 mm., prisms (5 g.), m. p. 129° (from methanol) (Found: C, 87·2; H, 6·3. $C_{36}H_{30}O_2$ requires C, 87·5; H, 6·1%).

p-*Di-(β-bromo-4-methoxy-α-stilbenyl)benzene* (II; R = Br, R′ = OMe).—Prepared from the foregoing diethylene (5 g.) and bromine (3 g.) in acetic acid, this *dibromo-compound* crystallised as prisms (5 g.), m. p. 224°, from acetic acid (Found: C, 66·1; H, 4·3. $C_{36}H_{28}O_2Br_2$ requires C, 66·3; H, 4·3%). p-*Di-(β-chloro-4-methoxy-α-stilbenyl)benzene* (II; R = Cl, R′ = OMe), similarly prepared with chlorine (1·5 g.) in chloroform, formed needles (4 g.), m. p. 178°, from acetic acid (Found: C, 76·9; H, 5·2. $C_{36}H_{28}O_2Cl_2$ requires C, 76·7; H, 5·0.

4-*Methoxy-α-(4-*m*-terphenylyl)stilbene* (III; R = H).—A solution of benzylmagnesium chloride (7 g.) in anhydrous ether (80 c.c.) was treated with 4-*p*′-anisoyl-*m*-terphenyl (7 g., prepared according to Buu-Hoï and Royer [8]) in the usual way; the *ethylene* (5 g.), b. p. 287—289°/0·6 mm., crystallised as needles, m. p. 77°, from ethanol (Found: C, 90·3; H, 6·1. $C_{33}H_{26}O$ requires C, 90·4; H, 5·9%). β-*Bromo-4-methoxy-α-(4-*m*-terphenylyl)stilbene* (III; R = Br), prepared from the foregoing ethylene (1·8 g.) with bromine (0·8 g.) in acetic acid, formed colourless needles (1·6 g.), m. p. 119°, from ethanol (Found: C, 76·5; H, 5·0. $C_{33}H_{25}OBr$ requires C, 76·6; H, 4·8%).

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[10] Rabzewitsch and Subkowski, *Chem. Zentr.*, 1915, I, 836; Zonew, *ibid.*, 1923, I, 1497.

meso-3 : 4-*Di*-(p-*phenoxyphenyl*)*hexane* (IV).—An ice-cooled solution of phenyl *p*-propenylphenyl ether (5 g.) in ligroin was saturated with hydrogen chloride, and the solution of crude *p*-1-chloropropylphenyl phenyl ether thus obtained was added portionwise to a suspension of iron powder (10 g.) in water at 98°. The mixture was then refluxed for 15 min., and, after cooling, more ligroin was added. The organic layer was collected, washed with dilute aqueous sodium hydroxide, then with water, dried (Na_2SO_4), and evaporated. The oily residue gave, on prolonged standing in the refrigerator, a small quantity of a solid, which was recrystallised from ethanol, yielding the *product* (IV) as prisms (0·5 g.), m. p. 142° (Found: C, 84·9; H, 7·2. $C_{30}H_{30}O_2$ requires C, 85·3; H, 7·3%).

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