731. *Triphenylethylenes. Part III.**

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A number of triphenylethylene derivatives possessing the dimethylamino-group in the *para*-position of the two phenyl groups on the same ethylenic carbon atom have been synthesised. Two of them showed œstrogenic activity in contrast to the corresponding halogen compounds. Other derivatives also showed œstrogenic activity. Introduction of a halogen atom at the ethylenic linkage did not increase the potency, in contrast to previously tested triphenylethylenes. The quaternary ammonium compounds and stilbenes possessing *p*-dimethylamino-groups were inactive.

In continued study of the effect of substituents on the œstrogenic activity, a number of triphenylethylene derivatives possessing *p*-dimethylamino-groups have been prepared and tested.

1 : 1-Bis-*p*-dimethylaminophenyl-2-phenylethylene was obtained by the dehydration of 1 : 1-bis-*p*-dimethylaminophenyl-2-phenylethanol. The latter was obtained by heating Michler's ketone, toluene, and metallic sodium (Rodd and Linch, *J.*, 1927, 2179), or by addition of Michler's ketone to an ethereal solution of excess of benzylmagnesium chloride (Madelung and Volker, *J. pr. Chem.*, 1927, **115**, 24; Rodd and Linch, *loc. cit.*). The di-*p*-chloro- and di-*p*-bromo-triphenylethylenes were similarly obtained. 4 : 4'-Di*cyclo*hexyloxy- and 4-dimethylamino-4'-methoxy-benzophenone with benzylmagnesium chloride gave the corresponding alcohols, and the methoxy-compound was dehydrated to the ethylene.

Triphenylbromoethylenes containing dimethylamino-groups were obtained by bromination of the corresponding ethylenes and, in view of the result obtained on testing their œstrogenic activity, their structure was confirmed by ozonolysis.

4-Bromo-4'-dimethylaminostilbene (Haddow, Harris, Kon, and Roe, *Proc. Roy. Soc.*, 1948, *A*, **241**, 147) was prepared by reduction of 4-bromo-4'-nitrostilbene, followed by methylation and decomposition of the quaternary product. Haddow *et al.* (*loc. cit.*) noted that this stilbene could not be obtained by condensation of *p*-bromobenzylmagnesium bromide and *p*-dimethylaminobenzaldehyde. We obtained it by the dehydration of the corresponding alcohol which we prepared in almost quantitative yield by use of an excess of Grignard reagent. The alcohol was dehydrated by phosphoric oxide in hot anhydrous benzene or when heated alone at 155—160°.

The time required for the œstrogenic activity to fall to half was measured as described by Robson (*Quart. J. Exp. Physiol.*, 1938, **28**, 195) with Shorr's method of staining (*Science*, 1940, **91**, 579). The compounds were dissolved in sesame oil and examined by injection subcutaneously into 20—25-g. mice. The œstrogenic table shows that: (*a*) Whereas the stilbenes (8) and (9) have no œstrogenic activity, the triphenylethylenes possessed considerable activity at the same dose (Haddow *et al.*, *loc. cit.*, stated that aminostilbenes, including compound 8, appeared to have no œstrogenic activity but the dose was not reported; Baker, *J. Amer. Chem. Soc.*, 1943, **65**, 572, reported that the amino-analogue of hexœstrol—3 : 4-bis-*p*-aminophenylhexane—was inactive in both the *meso*- and the racemic form), (*b*) In contrast to the inactivity of triphenylethylenes or their bromo-derivatives containing *p*-halogen atoms in the two phenyl groups on the same ethylenic carbon atom (Schönberg, Robson, Tadros, and Fahim, *J.*, 1940, 1327), the corresponding dimethylamino-compounds are active. (*c*) Whereas the introduction of the halogen atom at the ethylene double bond in many triphenylethylenes was accompanied by considerable increase in œstrogenic activity (see Tadros and Aziz, *J.*, 1951, 2553) the introduction of bromine as in compounds (5—7) did not appreciably increase the potency. (*d*) Comparison of compounds (4) with 1 : 1-di-p-methoxyphenyl-2-phenylethylene (Schönberg *et al.*, *loc. cit.*) showed that the replacement of the methoxy- by the dimethylamino-group decreased the potency.

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* Part II, *J.*, 1949, 442.

When injected subcutaneously in solution in saline at the dose of 2 mg., the quaternary ammonium chloride from compound (1) led to death of the mice within 15 minutes. On administration in saline solution at the doses of 5 mg. orally by stomach tube, this salt was inactive. The loss of œstrogenic activity on conversion into the quaternary salt compares with that when aminostilbenes showing growth-inhibitory and carcinogenic properties were converted into their quaternary ammonium salts (Haddow *et al.*, *loc. cit.*).

Time required for œstrogenic activity to fall to half.

No.	Compound	Dose (mg.)	Time (days)
1	1 : 1-Bis-*p*-dimethylaminophenyl-2-phenylethylene	5	15
2	2-*p*-Chlorophenyl-1 : 1-bis-*p*-dimethylaminophenylethylene	5	15
3	2-*p*-Bromophenyl-1 : 1-bis-*p*-dimethylaminophenylethylene	5	16
4	2-*p*′-Dimethylaminophenyl-2-*p*-methoxyphenyl-1-phenylethylene	0·2	5
5	2-Bromo-1 : 1-bis-*p*-dimethylaminophenyl-2-phenylethylene	5	19
6	2-Bromo-2-*p*-chlorophenyl-1 : 1-bis-*p*-dimethylaminophenylethylene	5	18
7	2-Bromo-2-*p*-bromophenyl-1 : 1-bis-*p*-dimethylaminophenylethylene	5	17
8	4-Bromo-4′-dimethylaminostilbene	5	Inactive
9	4 : 4′-Bisdimethylaminostilbene *	5	Inactive

* Tadros and Ekladious, unpublished.

The triphenylethylene bases are not toxic at doses of 5 mg. and are being tested for chemotherapeutic (*e.g.*, antitubercular) activity in collaboration with Professor S. El Kholy (Ibrahim Pasha University).

EXPERIMENTAL

M. p.s are uncorrected. Microanalysis was carried out by Drs. Weiler and Strauss of Oxford.

1 : 1-*Bis*-p-cyclo*hexyloxyphenyl*-2-*phenylethanol*.—To the Grignard reagent from benzyl chloride (3·8 g.), ether (100 c.c.), and magnesium (0·7 g.), 4 : 4′-di*cyclo*hexyloxybenzophenone (2 g.) (Tadros and Latif, *J.*, 1949, 3337) in benzene (10 c.c.) was added and the mixture was refluxed for 3 hours and then decomposed with aqueous ammonium chloride. Ether extracted the *alcohol* which separated from ethanol in colourless crystals, m. p. 112° (70%) (Found : C, 81·4; H, 8·1. $C_{32}H_{38}O_3$ requires C, 81·7; H, 8·2%).

1-p-*Dimethylaminophenyl*-1-p-*methoxyphenyl*-2-*phenylethanol*, similarly prepared, had m. p. 169° (yield 70%) (Found: C, 79·6; H, 7·6; N, 4·2. $C_{23}H_{25}O_2N$ requires C, 79·5; H, 7·2; N, 4·0%).

1-p-*Dimethylaminophenyl*-1-p-*methoxyphenyl*-2-*phenylethylene*.—The corresponding alcohol was dehydrated by heating it under reflux for 1 hour with 2N-hydrochloric acid. The product was cooled, neutralised with sodium carbonate, and filtered off (almost quantitative yield). The *ethylene* separated from methyl alcohol–acetone in pale yellow crystals, m. p. 162—163° (Found : C, 83·4; H, 7·2; N, 4·6. $C_{23}H_{23}ON$ requires C, 83·8; H, 7·0; N, 4·3%).

The following were isolated in yellowish-green crystals (*ca.* 60%) from benzene–light petroleum (b. p. 40—60°), on attempting the preparation of the corresponding alcohols as above : 2-p-*chlorophenyl*-, m. p. 154° (Found : C, 76·1; H, 6·4; N, 7·7; Cl, 9·9. $C_{24}H_{25}N_2Cl$ requires C, 76·5; H, 6·6; N, 7·4; Cl, 9·5%), and 2-p-*bromophenyl*-1 : 1-*bis*-p-*dimethylaminophenylethylene*, m. p. 159° (Found : C, 68·4; H, 5·8; N, 6·2; Br, 17·9. $C_{24}H_{25}N_2Br$ requires C, 68·4; H, 5·9; N, 6·6; Br, 18·3%).

Triphenylbromoethylenes.—An ice-cold solution of bromine (1 mol.) in the minimum amount of benzene was added all at once to a cooled benzene solution of the ethylene (1 mol.). A dark brown material separated immediately. The reaction mixture was shaken with 10% sodium hydroxide solution and extracted with more benzene (yield almost theoretical). Thus were obtained 1-*bromo*-2 : 2-*bis*-p-*dimethylaminophenyl*-1-*phenylethylene*, yellow, m. p. 185—186° (from benzene–alcohol) (Found : Br, 18·9. $C_{24}H_{25}N_2Br$ requires Br, 19·0%), 1-*bromo*-1-p-*chlorophenyl*-, yellow, m. p. 158—160° (from benzene–methyl alcohol) (Found: Hal, 24·8. $C_{24}H_{24}N_2BrCl$ requires Hal, 25·4%), and 1-*bromo*-1-p-*bromophenyl*-2 : 2-*bis*-p-*dimethylaminophenylethylene*, greenish-yellow, sinters at 170°, m. p. 177° (from acetone–methyl alcohol) (Found : Br, 31·8. $C_{24}H_{24}N_2Br_2$ requires Br, 32·0%).

Ozonolysis. A stream of dry ozonised oxygen (3%) was passed through a cold solution of the bromoethylene in carbon tetrachloride until the reaction was almost complete. The solution was shaken with water (removed hydrogen bromide) and evaporated and the residue was treated with 10% sodium hydroxide solution and filtered. The filtrate was acidified and the precipitated acid crystallised from alcohol. The alkali-insoluble material crystallised from dilute alcohol. 1-Bromo-2 : 2-bis-*p*-dimethylaminophenyl-1-phenylethylene gave benzoic acid, m. p. and mixed m. p. 120°, and Michler's ketone, m. p. and mixed m. p. 173°. 1-Bromo-1-*p*-bromophenyl-2 : 2-bis-*p*-dimethylaminophenylethylene gave *p*-bromobenzoic acid, m. p. and mixed m. p. 249—250°, and Michler's ketone. 1-Bromo-1-*p*-chlorophenyl-2 : 2-bis-*p*-dimethylaminophenylethylene gave *p*-chlorobenzoic acid, m. p. and mixed m. p. 234—235°, and Michler's ketone.

Quaternary Ammonium Salts.—The *salts* listed in the Table were prepared in the usual way. All are soluble in water and alcohol, but completely insoluble in ether, benzene, or acetone. The chlorides, bromides, and iodides are hygroscopic and retain solvent of crystallisation (particularly alcohol) which can only be removed by heating at 100°/vac. for a considerable time over phosphoric oxide or calcium chloride. They were generally crystallised from ethanol or methanol, with or without acetone or ether.

		Found, %					Required, %			
Salt [a]	M. p.[b]	C	H	N	Hal.		C	H	N	Hal.
1 : 1-*Bis*-p-*dimethylaminophenyl-2-phenylethylene salts.*										
A	220°	55·0	4·3	13·3	—	$C_{38}H_{36}O_{14}N_8$	55·1	4·3	13·5	—
B	204—205	69·9	6·9	6·9	15·6	$C_{26}H_{32}N_2Cl_2$	70·4	7·2	6·3	16·0
C	176—177	58·4	6·0	4·7	31·0	$C_{26}H_{32}N_2Br_2$	58·6	6·0	5·3	30·1
D [c]	198—200	50·1	5·5	4·5	40·5	$C_{26}H_{32}N_2I_2$	49·8	5·1	4·5	40·6
E	266	54·6	5·8	5·1	12·3	$C_{26}H_{32}O_8N_2Cl_2$	54·6	5·6	4·9	12·4
2-p-*Chlorophenyl*-1 : 1-*bis*-p-*dimethylaminophenylethylene salts.*										
A	187	52·6	4·0	13·1	4·0	$C_{38}H_{35}O_{14}N_8Cl$	52·9	4·1	13·0	4·1
B	163—164	65·1	6·5	5·8	22·1	$C_{26}H_{31}N_2Cl_3$	65·3	6·5	5·9	22·3
C	174—176	54·9	5·3	4·9	34·2	$C_{26}H_{31}N_2Br_2Cl$	55·1	5·5	4·9	34·5
D	220	47·0	4·5	4·1	43·5	$C_{26}H_{31}N_2ClI_2$	47·2	4·7	4·2	43·9
E	268	51·4	5·2	4·7	17·6	$C_{26}H_{31}O_8N_2Cl_3$	51·5	5·1	4·6	17·5
2-p-*Bromophenyl*-1 : 1-*bis*-p-*dimethylaminophenylethylene salts.*										
A	189—190	50·6	4·0	12·5	8·5	$C_{38}H_{35}O_{14}N_8Br$	50·3	3·9	12·3	8·8
B	180—182	59·5	5·8	5·4	28·5	$C_{26}H_{31}N_2Cl_2Br$	59·7	5·9	5·4	28·8
C	193	51·0	4·8	4·8	38·9	$C_{26}H_{31}N_2Br_3$	51·1	5·1	4·6	39·5
D	224	44·5	4·5	3·8	47·6	$C_{26}H_{31}N_2BrI_2$	44·2	4·4	4·0	47·4
E	286	48·4	4·6	4·2	22·9	$C_{26}H_{31}O_8N_2Cl_2Br$	48·0	4·8	4·3	23·2

[a] A, Picrate; B, chloride; C, bromide; D, iodide; E, perchlorate. [b] With decomp. (except for picrates). [c] Kehlstadt (*Helv. Chim. Acta*, 1944, **27**, 683) gave m. p. 195°.

Decomposition of Quaternary Salts.—The salt (5 g.) and methanolic sodium methoxide (2·5 atomic equivs. of sodium in 20 c.c. of methanol) was heated for 4 hours on the water-bath. Methyl alcohol was distilled off and the residue treated with concentrated hydrochloric acid (1 : 1), whereby a clear solution was obtained. The bases, precipitated by sodium hydroxide, crystallised from alcohol and were proved by their m. p.s and mixed m. p.s to be the tertiary bases.

2-p-*Bromophenyl*-1-p-*dimethylaminophenylethanol.*—To a Grignard reagent, prepared from *p*-bromobenzyl bromide (40 g.), magnesium (4·8 g.), and dry ether (350 c.c.), *p*-dimethylaminobenzaldehyde (6 g.) was added and the solution stirred for 2 hours, left overnight, and then decomposed with aqueous ammonium chloride. Ether extracted the alcohol and the ethereal solution was washed with 18% hydrochloric acid. The acid solution was diluted, filtered, and made alkaline with aqueous ammonia. The *alcohol* separated from ethanol in pale yellow crystals which sintered at 114° and melted at 117° (yield, almost 100%) (Found: C, 60·8; H, 5·6; N, 4·2; Br, 25·1. $C_{16}H_{18}ONBr$ requires C, 60·0; H, 5·6; N, 4·4; Br, 25·0%).

4-*Bromo*-4'-*dimethylaminostilbene.*—(*a*) A mixture of the foregoing alcohol (2 g.), phosphoric oxide (2 g.), and benzene (50 c.c.) was refluxed for 2 hours. After cooling, the solution was filtered. The residue was decomposed with water and the stilbene was filtered off. It separated from benzene and had m. p. 231—232° (yield, almost 100%) (Found: C, 63·5; H, 5·0; N, 4·4; Br, 26·2. Calc. for $C_{16}H_{16}NBr$: C, 63·5; H, 5·3; N, 4·6; Br, 26·5%).

(*b*) When the alcohol (2 g.) was heated, water was evolved at 155° and the material solidified within 1 minute at 155—160°, to give the stilbene.

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