38. *Triphenylethylenes and Related Compounds. Part IV.**

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New triphenylethylenes have been prepared and tested for œstrogenic activity.

The presence of a *p*-bromine atom in the phenyl group marked *, like that of chlorine (Tadros, Farahat, and Robson, *J.*, 1949, 439), confers œstrogenic activity on substances of type $(Hal\cdot C_6H_4)_2C{:}CBrPh^*$ (Hal = Cl or Br). Substitution of a methyl group for either of these atoms causes even greater increase in the activity. On the other hand, the œstrogenic activity is suppressed on introduction of a *p*-cyano-group into the benzene nuclei. The significance of these findings cannot be explained in advance of a study of the metabolism of these compounds.

The introduction of a halogen atom into the ethylenic linkage of the triphenylethylenes reported herewith was accompanied by increase in potency (see Robson, Schönberg, and Fahim, *Nature*, 1938, **142**, 292; also Tadros and Aziz, *J.*, 1951, 2553).

The time required for the œstrogenic activity to fall to half was measured by the method described by Robson (*Quart. J. Exp. Physiol.*, 1938, **28**, 195) with Shorr's method for staining (*Science*, 1940, **91**, 579). The compounds were dissolved in sesame oil, and the œstrogenic activity was examined on injection subcutaneously into a group of 5 ovariectomised mice of average weight 22 grams (see Table 1 for results).

The triphenylethylenes were obtained by addition of *pp'*-disubstituted benzophenones to an ethereal solution of benzyl-, 4-bromobenzyl- or 4-methylbenzyl-magnesium bromide (excess of magnesium should be used for the last compound), followed by decomposition with aqueous ammonium chloride, the alcohols or triphenylethylenes being formed. Dehydration of the alcohols gave the triphenylethylenes and these were then chlorinated

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or brominated. 4-Cyano- and 4 : 4′-dicyano-benzophenone and 2-*p*-cyanophenyl-1 : 1-diphenylethylene were prepared from the corresponding bromo-compounds by a method slightly modified from that used by Bance, Barber, and Woolman (*J.*, **1943**, 1) for the preparation of 4 : 4′-dicyanostilbene from 4 : 4′-dibromostilbene. 1 : 1-Di-*p*-ethoxyphenyl-2-*p*-nitrophenylethylene was obtained by Meerwein reaction from ββ-di-*p*-ethoxyphenylacrylic acid. ββ-Diphenylacrylic acids were prepared (*a*) by the method of Kharasch, Kane, and Brown (*J. Amer. Chem. Soc.*, 1942, **64**, 333) or (*b*) by hydrolysis of the ester obtained by Reformatsky reaction. Ethyl *p*-benzoylbenzimidate and *p*-amidinobenzophenone hydrochloride were also prepared but proved toxic.

TABLE 1. $(p\text{-X}\cdot C_6H_4)_2C\colon CY\cdot C_6H_4Z\text{-}p$.

X	Y	Z	Dose (mg.)	Time (days)	X	Y	Z	Dose (mg.)	Time (days)
Cl	H	Br	5	∞	Br	Cl	Br	1	11
Br	H	Br	5	∞				5	15
H,CO·CH$_2$Ph	H	H	5	∞	Br	Br	Br	1	7
CN	H	H	5	∞	Cl	Br	Me	5	>90
Cl	H	Me	5	∞	OEt	Br	Br	0·1	8
OEt	H	Br	1	<125				0·5	>130
Cl	Cl	Br	5	12	H	H	CN	1	Slight activity

EXPERIMENTAL

p-*Cyanobenzophenone*.—Freshly prepared, powdered cuprous cyanide (2·5 g.; previously dried at 110° for 36 hours) and *p*-bromobenzophenone (5 g.) were heated at 220° for 1 hour. Pyridine (2·5 c.c.) was then added and the mixture heated for further $\frac{1}{2}$ hour at the same temperature and then decomposed with concentrated hydrochloric acid (50 c.c.). The solid material was filtered off through glass wool, washed with concentrated hydrochloric acid (20 c.c.) and then water, sublimed, and crystallised from ethyl alcohol from which it separated in pale yellow crystals (2·1 g.), m. p. 107—108° (Found : C, 80·9; H, 4·1; N, 6·6. Calc. for $C_{14}H_9ON$: C, 81·2; H, 4·3; N, 6·8%).

pp′-*Dicyanobenzophenone*.—Similarly prepared (*pp*′-dibromobenzophenone, 50 g.; cuprous cyanide, 39·2 g.; pyridine, 10 c.c.), this separated from acetic acid in colourless crystals (19·5 g.), m. p. 162° alone or mixed with an authentic sample (Ashley, Barber, Ewins, Newbery, and Self, *J.*, 1942, 103).

ββ-*Di*-p-*ethoxyphenylacrylic Acid*.—(*a*) (cf. Kharasch, Kane, and Brown, *loc. cit.*) *as*-Di-*p*-ethoxyphenylethylene (2 g.) (Tadros and Aziz, *loc. cit.*) and oxalyl chloride (3·75 g.) were mixed and left at room temperature until no more hydrogen chloride was evolved (0·5 hour). The mixture was then refluxed on the water-bath for 45 minutes and excess of oxalyl chloride was distilled off under reduced pressure. The syrupy residue was decomposed with cold aqueous sodium carbonate, and after 3 hours the whole was boiled for 10 minutes with charcoal and filtered. The filtrate was acidified with concentrated hydrochloric acid. The precipitate was dissolved in aqueous sodium carbonate and filtered from tar. The filtrate was acidified, and the precipitated *acid* crystallised from benzene as pale yellow needles (1·2 g.), m. p. 134° (Found : C, 72·3; H, 6·3. $C_{19}H_{20}O_4$ requires C, 73·1; H, 6·4%).

(*b*) Hydrolysis of ethyl ββ-di-*p*-ethoxyphenylacrylate (*A*) with alcoholic sodium ethoxide (1·25 mol.) gave the same acid, m. p. and mixed m. p. 133°.

The *ethyl* ester (*A*), m. p. 59° [from light petroleum (b. p. 30—50°)] (Found : C, 73·9; H, 6·8. $C_{21}H_{24}O_4$ requires C, 74·1; H, 7·0%), was prepared in *ca.* 45% yield by a Reformatsky reaction from *pp*′-diethoxybenzophenone (10 g.) in benzene–toluene.

ββ-*Di*-(p-n-*propoxyphenyl*)*acrylic acid*, prepared according to method (*a*) and crystallised from benzene, had m. p. 128—129° (0·52 g. from 2 g.) (Found : C, 74·5; H, 7·0. $C_{21}H_{24}O_4$ requires C, 74·1; H, 7·0%).

Grignard Reactions.—The alcohols were prepared by adding the appropriate *pp*′-disubstituted benzophenone (1 mol.) to the Grignard reagent from magnesium (2 atoms), 4-bromobenzyl chloride (1·8 mol.), and dry ether (1800 c.c.). In the case of the cyano-compounds 1·25 mol. of benzyl chloride and 1·25 atoms of magnesium were used. It was found necessary, however, to use excess of 4-methylbenzyl bromide (10 mol.) and double the equivalent of magnesium (20 atoms). The solutions were stirred after the addition of the ketones for 4 hours, then left overnight, and the products were decomposed with aqueous ammonium chloride, extracted with ether or benzene–ether, and crystallised mainly from light petroleum (b. p. 40—60° or 60—80°) from which they separated in colourless or pale yellow crystals. Yields were about 40%.

During the preparation of 1-*p*-cyanophenyl-1 : 2-diphenylethanol, 1 : 2-diphenyl-1-*p*-phenylacetylphenylethanol was obtained. The latter was apparently formed by interaction of the cyano-alcohol first formed and excess of benzylmagnesium chloride.

The ethylenes were obtained either directly or by dehydration of the alcohol. The alcohol (1 g.) was heated in acetic acid (20 c.c.) containing acetyl chloride (20 c.c.) or concentrated sulphuric acid (0·5 c.c.), or was distilled in a vacuum in presence of one drop of 20% sulphuric acid. The solutions were poured into aqueous sodium carbonate, and the precipitated ethylenes were recrystallised from alcohol from which they separated in colourless crystals. For the *products* see Table 2.

TABLE 2.

Compound				Found, %:				Required, %:		
			M. p.	C	H	Hal or N	Formula	C	H	Hal or N
			Alcohols, $p\text{-X}\cdot C_6H_4\cdot CH_2\cdot C(C_6H_4Y\text{-}p)(C_6H_4Z\text{-}p)\cdot OH$.							
X	Y	Z								
H	CN	H	103—104°	84·3	5·6	4·6	$C_{21}H_{17}ON$	84·3	5·7	4·7
H	$CO\cdot CH_2Ph$	H	144	85·4	6·2	—	$C_{28}H_{24}O_2$	85·7	6·1	—
H	CN	CN	194—195	80·9	5·2	8·4	$C_{22}H_{16}ON_2$	81·5	5·0	8·4
Br	Cl	Cl	109	57·7	3·5	35·5	$C_{20}H_{15}OCl_2Br$	56·9	3·6	35·8
Br	OEt	OEt	93	65·6	5·3	18·0	$C_{24}H_{25}O_3Br$	65·3	5·7	18·1
Me	Cl	Cl	120 *	70·6	5·3	19·4	$C_{21}H_{18}OCl_2$	70·6	5·0	19·9
			Ethylenes, $p\text{-X}\cdot C_6H_4\cdot CH{:}C(C_6H_4Y\text{-}p)\cdot C_6H_4Z\text{-}p$.							
X	Y	Z								
H	CN	H	138—139	89·9	5·0	5·1	$C_{21}H_{15}N$	89·7	5·3	5·0
H	CN	CN	151	85·9	4·8	8·8	$C_{22}H_{14}N_2$	86·3	4·6	9·1
H	$CO\cdot CH_2Ph$	H	110—111	90·2	5·7	—	$C_{28}H_{22}O$	89·9	5·9	—
Br	Cl	Cl	118	59·3	3·1	38·1	$C_{20}H_{13}Cl_2Br$	59·4	3·2	37·4
Br	Br	Br	101	48·7	2·8	48·4	$C_{20}H_{13}Br_3$	48·7	2·6	48·7
Br	OMe	OMe	107	67·1	4·8	19·5	$C_{22}H_{19}O_2Br$	66·9	4·8	20·2
Br	OEt	OEt	110	68·5	5·4	18·7	$C_{24}H_{23}O_2Br$	68·1	5·4	18·9
Me	Cl	Cl	94	73·8	4·7	21·6	$C_{21}H_{16}Cl_2$	74·3	4·7	20·9
			Halogenoethylenes, $p\text{-X}\cdot C_6H_4\cdot CHal{:}C(C_6H_4Y\text{-}p)_2$.							
X	Y	Hal								
Br	Cl	Cl	170—171	54·6	3·0	42·8	$C_{20}H_{12}Cl_3Br$	54·8	2·8	42·4
Br	Br	Cl	189	45·5	2·4	51·8	$C_{20}H_{12}ClBr_3$	45·5	2·3	52·1
Br	Cl	Br	174	50·0	2·6	48·4	$C_{20}H_{12}Cl_2Br_2$	49·7	2·5	47·8
Br	Br	Br	183 †	42·0	2·1	55·7	$C_{12}H_{12}Br_4$	41·9	2·1	55·9
Br	OMe	Br	114	55·7	4·0	34·1	$C_{22}H_{18}O_2Br_2$	55·7	3·8	33·7
Br	OEt	Br	99	57·3	4·4	32·0	$C_{24}H_{22}O_2Br_2$	57·3	4·4	31·9
Me	Cl	Br	158	60·5	3·6	35·5	$C_{21}H_{15}Cl_2Br$	60·3	3·6	36·1

* Contaminating 4 : 4′-dimethyldibenzyl should be removed, before recrystallisation, by steam-distillation. † This compound, m. p. 184—185°, was obtained (Buckles, Hansman, and Wheeler, *J. Amer. Chem. Soc.*, 1950, **72**, 2494) by bromination of solid triphenylethylene and bromoethylene with bromine vapour.

1 : 1-*Di*-p-*ethoxyphenyl*-2-p-*nitrophenylethylene*.—To a solution of ββ-di-*p*-ethoxyphenylacrylic acid (4 g.) in acetone (100 c.c.) at 5°, a solution of diazotised *p*-nitroaniline (from 1·8 g. of *p*-nitroaniline), solid sodium acetate (3·5 g.), and aqueous cupric chloride (1 g. in 10 c.c. of water) were added. The temperature was allowed to rise alowly. Reaction started at 25° with evolution of gas which subsided after 20 minutes. The mixture was heated at 35° for 1 hour, then steam-distilled, and the semi-solid residue was taken up with benzene, washed with alkali, and then water, and evaporated. The residue was fractionally crystallised from alcohol from which *as*-di-*p*-ethoxyphenylethylene (1·55 g.), m. p. and mixed m. p. 142°, separated first. The mother-liquor was concentrated and the *triphenylethylene* separated thereafter in colourless crystals (0·72 g.), m. p. 88° (Found: C, 73·8; H, 6·1; N, 4·0. $C_{24}H_{23}O_4N$ requires C, 74·0; H, 5·9; N, 3·6%).

2-p-*Cyanophenyl*-1 : 1-*diphenylethylene*, prepared from 2-*p*-bromophenyl-1 : 1-diphenylethylene (Tadros, Farahat, and Robson, *loc. cit.*) by cuprous cyanide, etc., separated from alcohol in pale yellow crystals, m. p. 107—109° (Found: N, 4·3. $C_{21}H_{15}N$ requires N, 5·0%).

Ethyl p-*Benzoylbenzimidate*.—Powdered *p*-cyanobenzophenone (5 g.) was suspended in dry benzene (200 c.c.) and absolute alcohol (1 g.); the solution was saturated with hydrogen chloride at $-5°$ and left for 10 days at room temperature. Light petroleum (b. p. 60—70° 250 c.c.) was added, and the crystalline product which separated out on cooling in ice was filtered off (yield, 2·3 g.). This proved on analysis to be a mixture of the base and its hydrochloride and was treated with aqueous sodium carbonate; the *ester*, washed with distilled water and crystallised from benzene, had m. p. 164° (Found: C, 75·4; H, 5·9; N, 5·6. $C_{16}H_{15}O_2N$ requires C, 75·9; H, 6·0; N, 5·5%).

p-*Amidinobenzophenone Hydrochloride*.—A solution of ammonia (1 g.) in absolute alcohol (12 c.c.) was added to a solution of the crude foregoing hydrochloride (1·5 g.) in the same solvent (50 c.c.) and the mixture was kept at room temperature with occasional shaking for 3 hours; the solution was filtered and freed from alcohol, and the residue fractionally crystallised from benzene whereby unchanged ester (0·35 g.), m. p. and mixed m. p. with an authentic sample 163°, separated. The material recovered from the benzene mother-liquor was dissolved in methyl alcohol (2 c.c.), the solution was filtered, and dry ether (10 c.c.) was added. The crude *amidine hydrochloride* (0·72 g.) was further crystallised from dry benzene from which it separated in colourless crystals, m. p. 196° (1 mol. of methyl alcohol of crystallisation was not removed in vacuum-desiccator over $CaCl_2$) (Found: C, 61·9; H, 5·4; N, 9·7; Cl, 12·5. $C_{14}H_{13}ON_2Cl,CH_3\cdot OH$ requires C, 61·5; H, 5·7; N, 9·6; Cl, 12·1%).

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