716. *Potential Chemical Pituitary Inhibitors of the Polyarylethylene Series.*

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A series of new 1 : 1-diarylethylenes and 1 : 1 : 2-triarylethylenes has been prepared for biological testing as potential pituitary inhibitors. The abnormal condensation to polyarylethylenes of acid chlorides with phenyl ethers, in the presence of aluminium chloride, was investigated, and is shown to be highly susceptible to constitutional factors and to experimental conditions. Certain other compounds are described.

Recent developments in the study of œstrogens have made it increasingly evident that their overall physiological and clinical activity cannot be accurately estimated solely by means of the Allen–Doisy test. For instance, stilbœstrol is frequently more valuable in clinical use than hexœstrol, which has a higher Allen–Doisy activity (Bishop, *Lancet*, 1948, ii, 764); also, successful treatments of stilbœstrol-resistant cancers of the prostate have also been reported with weaker œstrogens such as dienœstrol (Cox, *Brit. Med. J.*, 1946, ii, 191) or 1-bromo-1 : 2 : 2-triphenylethylene (Berger and Buu-Hoï, *Lancet*, 1947, ii, 173). Further, in animal physiology, œstriol has been found highly active in inducing œstrus in immature female mammals, although displaying a weak potency in the Allen–Doisy test (Meyer, Miller, and Cartland, *J. Biol. Chem.*, 1936, **112**, 597); and lumiœstrone, ineffective in spayed animals (Butenandt and Poschmann, *Ber.*, 1944, **77**, 392), produces prolonged œstrus in immature rats (Figge, *Endocrinology*, 1945, **36**, 178).

The present work deals with the synthesis of new derivatives of the 1 : 1-diarylethylene and 1 : 1 : 2-triarylethylene series. Several œstrogens have already been found in these series, in which the œstrogenic activity is extremely sensitive to constitutional factors (Robson and Schönberg, *Nature*, 1942, **150**, 22; Dodds *et al.*, *Proc. Roy. Soc.*, 1944, *B*, **132**, 83; Buu-Hoï *et al.*, *Compt. rend.*, 1944, **219**, 589; Lacassagne *et al.*, *Experientia*, 1946, **2**, 70; Buu-Hoï and Lecocq, *J.*, 1947, 641; Carter and Hey, *J.*, 1948, 150; Buu-Hoï and Royer, *J.*, 1948, 1078; Tadros *et al.*, *J.*, 1949, 439).

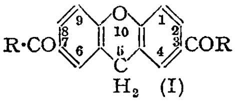
An interesting route to 1 : 1-diarylethylenes, $CRR'{:}CAr_2$ in which Ar contains alkyloxy-groups is the reaction of alkyl phenyl ethers with acid chlorides of the type $CHRR'{\cdot}COCl$ in the presence of aluminium chloride. This reaction was discovered by Gattermann (*Ber.*, 1889, **22**, 1130), who found that Friedel–Crafts condensation of propionyl chloride with anisole yielded 1 : 1-di-*p*-methoxyphenylpropene in addition to 4-methoxypropiophenone, the normal product. Later, it was extended by Skraup and Nieten (*Ber.*, 1924, **57**, 1300) to the preparation of 1 : 1-di-*p*-methoxyphenyl-*n*-butene, and its mechanism was studied by Mentzer and Xuong (*Compt. rend.*, 1946, **222**, 1004; XIth International Congress of Chemistry, London, 1947). This reaction has now been applied to a series of alkyl ethers of mono- and di-hydric phenols on the one hand, and to several acid chlorides on the other. Formation of 1 : 1-diarylethylenes was favoured by use of an excess of the phenyl ether, and hindered when the reaction was performed in certain solvents such as nitrobenzene, or involved highly reactive phenol ethers. A series of reactions effected without solvent, and affording several new 1 : 1-diarylethylenes, is given in Table 1*a* (p. 3742), where references are also given to other preparations by this method.

The influence of constitutional factors is shown in Table 2, which lists the results of standardised Friedel–Crafts reactions between propionyl chloride and various phenyl and thiophenyl ethers.

The abnormal Gattermann reaction can also be applied to the synthesis of symmetrically substituted 1 : 1 : 2-triarylethylenes (Mentzer and Xuong, *loc. cit.*; Xuong, Cagniant, and Mentzer, *Compt. rend.*, 1948, **226**, 1453), and was here used for the preparation of 1 : 1-di-(4-methoxy-2-methylphenyl)- and 1 : 1-di-(3-chloro-4-methoxyphenyl)-2-phenylethylene from phenylacetyl chloride and the methyl ethers of *o*-chlorophenol and *m*-cresol. Methyl or halogen groups were introduced in order to decrease the œstrogenic properties of these triarylethylenes. We have also prepared 1-*p*-*n*-propylphenyl- and 1-*p*-*n*-butylphenyl-1 : 2-

diphenylethylene by routine Grignard reactions of benzylmagnesium chloride on 4-*n*-propyl- and 4-*n*-butyl-benzophenone, and dehydration of the alcohols thus formed. Bromination of the four 1 : 1 : 2-triarylethylenes mentioned readily yielded the corresponding 1 : 1 : 2-triaryl-2-bromoethylenes. It is noteworthy that 1 : 1-di-*p*-methoxyphenyl-propene and -butene could also be converted by bromine into the corresponding 2-bromo-derivatives (cf. Gattermann, *loc. cit.*; Wieland, *Ber.*, 1910, **43**, 718; Lipp, *Ber.*, 1923, **56**, 569).

During this work it was observed that xanthen, which can be considered as a phenyl ether, underwent Friedel–Crafts reactions with acetyl and propionyl chloride to give 3 : 7-diacetyl- (I; R = Me) and 3 : 7-dipropionyl-xanthen (I; R = Et) as the main products, no corresponding ethylenic compounds being detected. Incidentally, a series of new ketones derived from *n*-propylbenzene was prepared (see Table 3).



(I)

The 1 : 1-diaryl- and 1 : 1 : 2-triaryl-ethylenes described, which are non-œstrogenic or only feebly so, are being tested for potential pituitary-inhibiting activity; results will be reported elsewhere.

EXPERIMENTAL

The solvent for recrystallisation was methanol, unless stated otherwise.

Abnormal Gattermann Reactions.—(a) *Without solvent.* To a solution of the redistilled acid chloride (1 mol.) in the phenyl ether (2·5—3 mol.) containing phosphorus oxychloride (*ca.* 1 c.c.), finely powdered aluminium chloride (1·5—2 mol.) was added in small portions with stirring.

TABLE 1*a*.

No.	Phenyl ether, H·Ar: Ar =	Acid chloride, CHRR′·COCl: R	R′	1 : 1-Diarylethylene, CRR′:CAr₂ M. p.*	B. p./mm.	Formula	Found, %: C	H	Reqd., %: C	H
1	C_6H_4·OMe	Me	Me	66°	*ca.* 215°/12	$C_{18}H_{20}O_2$	80·5	7·5	80·6	7·5
2	C_6H_4·OMe	H	Pr^i	—	220/13	$C_{19}H_{22}O_2$	80·6	7·5	80·9	7·8
3	C_6H_4·OEt	H	Et	75	240/12	$C_{20}H_{24}O_2$	81·0	8·1	81·1	8·1
4	C_6H_4·OEt	H	Pr^i	—	235/13	$C_{21}H_{26}O_2$	80·9	8·1	81·3	8·4
5	C_6H_4·OBu^n	H	Me	49	280—285/22	$C_{23}H_{30}O_2$	81·4	9·0	81·7	8·9
6	*o*-C_6H_3Me·OMe	H	Me	93 [a]	224—225/13	$C_{19}H_{22}O_2$	80·5	8·0	80·8	7·8
7	*m*-C_6H_3Me·OMe	H	Me	92 [b]	220/13	,,	80·4	7·6	,,	,,
8	*m*-C_6H_3Me·OEt	H	Me	—	238—240/13 [b]	$C_{21}H_{26}O_2$	81·0	8·6	81·3	8·4
9	*o*-$C_6H_3(OMe)_2$	H	Me	81 [b] †	265—268/12	—	—	—	—	—
10	*m*-$C_6H_3(OMe)_2$	H	Me	89	—	$C_{19}H_{22}O_4$	72·4	7·1	72·6	7·0

* Where a m. p. is not given, the substance was a liquid.

† Prepared by another method by Haworth, Mavin, and Sheldrick (*J.*, 1934, 1423).

[a] Yield, 55%. [b] Yield, 50%.

Analogous compounds have been prepared from anisole and/or phenetole and lower aliphatic acid chlorides and/or mono- or di-chloroacetyl chloride by Gattermann (*Ber.*, 1889, **22**, 1132), Weill (*Bull. Soc. chim.*, 1931, **49**, 1811), Wiechell (*Annalen*, 1894, **279**, 338), Fritsch and Feldmann (*ibid.*, 1899, **308**, 78), and Brand (*Ber.*, 1913, **46**, 2942).

TABLE 1*b*.

No.	Phenones, CHRR′·COAr M. p.	B. p./mm.	Derivative, and m. p.
1	—	280°/760	Semicarbazone, 208°
2	—	178/13	,, 210
3	42°	168/12	(See Klages, *Ber.*, 1904, **37**, 4001)
4	—	178/12	Semicarbazone, 192
6	42	—	Oxime, 99 (see *idem*, *ibid.*, p. 3991)
7	—	—	,, 95 ,, ,,

The mixture was kept for 72 hours at room temperature and decomposed with cold dilute hydrochloric acid, the organic layer taken up in ether, and the ethereal solution washed with a 5% aqueous sodium hydroxide, then with water, and dried (Na_2SO_4). After removal of the solvent, the residue was fractionated in a vacuum. The ethylene fraction boiled at least 40° higher than the normal ketonic reaction product; in most cases, it could be recrystallised from ethanol or ligroin, and the colourless solid obtained gave with sulphuric acid deep halochromic colours, ranging from orange-red to deep violet. The 1 : 1-*diarylethylenes* are recorded in

Table 1*a*. The reactions giving rise to them are numbered, and these numbers are used in Table 1*b* to denote the corresponding, usually predominating, ketonic products.

(b) *With solvent.* A solution of the acid chloride (1·1 mol.) and the phenyl ether (1 mol.) in pure benzene or nitrobenzene (4 parts) was treated with aluminium chloride (1·5 mol.) as above; after 18 hours at room temperature, the mixture was decomposd with ice and hydrochloric acid, the solvent removed by steam-distillation, and the residue treated in the usual way. The results are recorded in Table 2.

TABLE 2. *Yields of reaction with propionyl chloride.*

Phenyl ether	Solvent *	Yield of 1 : 1-diarylethylene, % †	Phenyl ether	Solvent *	Yield of 1 : 1-diarylethylene, % †
Anisole	B	60—70	Methyl thymyl ether	N	0
Anisole	N	30—40	*p*-Xylyl 2-methyl ether	B	0
Phenetole	B	30—40	,, ,,	B	0
n-Butoxybenzene	B	30—40	1-Methoxynaphthalene	N	0
Diphenyl ether	B	20—25	2-Methoxynaphthalene	N	0
Thioanisole	N	20—25	Veratrole	N	0
Methyl thymyl ether	B	0	1 : 3-Dimethoxybenzene	N	0

* B = Benzene. N = nitrobenzene.

† Under the experimental conditions used, yields below 10% could not be determined with accuracy, and the zero values are nominal. The yields were calculated with reference to the ether.

The main product from the reaction (5) of propionyl chloride upon *n*-butoxybenzene was 4-n-*butoxypropiophenone*, a pale yellow oil, b. p. 199—200°/32 mm., solidifying to large shiny colourless plates, m. p. 29° (Found: C, 75·6; H, 8·7. $C_{13}H_{18}O_2$ requires C, 75·7; H, 8 7%); it was characterised by formation of a phenylhydrazone, which was converted by hydrogen chloride in acetic acid into 2-p-n-*butoxyphenyl*-3-*methylindole*, fine shiny colourless prisms, m. p. 98°, giving an orange colour with sulphuric acid (Found: C, 81·5; H, 7·3. $C_{19}H_{21}ON$ requires C, 81·7; H, 7·5%); the same ketone (5 g.) yielded with isatin (4·8 g.) and potassium hydroxide (5 g.) in ethanol medium (24 hours' refluxing) 2-p-n-*butoxyphenyl*-3-*methylcinchoninic acid*, crystallising from acetic acid as fine yellowish prisms, m. p. 275° (Found: N, 4·2. $C_{21}H_{21}O_3N$ requires N, 4·1%); a similar Pfitzinger reaction performed with 5-bromoisatin yielded 6-*bromo*-2-p-n-*butoxyphenyl*-3-*methylcinchoninic acid*, forming from toluene yellowish microcrystals, m. p. 299—300° (Found: N, 3·2. $C_{21}H_{20}O_3NBr$ requires N, 3·4%), which could be decarboxylated by heat to 6-*bromo*-2-p-n-*butoxyphenyl*-3-*methylquinoline*, shiny colourless leaflets, m. p. 133° (from ethanol) (Found: C, 64·6; H, 5·2. $C_{20}H_{20}ONBr$ requires C, 64·9; H, 5·4%), the picrate of which formed from ethanol silky yellow needles, m. p. 194°.

Oxidation of 1 : 1-*Di*-p-n-*butoxyphenylpropene*.—This ethylene (7 g.), treated with chromic acid (3 g.) in acetic acid, gave 4 : 4′-*di*-n-*butoxybenzophenone*, crystallising as large shiny colourless leaflets, m. p. 121° (Found: C, 77·0; H, 8·0. $C_{21}H_{26}O_3$ requires C, 77 3; H, 8·0%).

4 : 4′-*Diphenoxybenzophenone*. 1 : 1-Di-*p*-phenoxyphenylpropene was obtained from diphenyl ether (60 g.), propionyl chloride (30 g.), and aluminium chloride (45 g.) in benzene, as a thick yellow oil (25 g.), b. p. *ca*. 328—330°/19 mm.; it (7·5 g.) was characterised by oxidation with chromic acid (3 g.) to the *benzophenone*, crystallising from benzene as silky colourless needles, m. p. 139° (Found: C, 81·7; H, 5·2. $C_{25}H_{18}O_3$ requires C, 81·9; H, 4·9%).

Diacylations of Xanthen.—The xanthen was prepared from xanthone by the modified Wolff–Kishner method (Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **67**, 2487). A solution of xanthen (18 g.) and acetyl chloride (8 g.) in carbon disulphide (20 c.c.) was treated with aluminium chloride (14 g.), and the mixture worked up in the usual way. After distillation *in vacuo*, the portion, b. p. >250°/15 mm. (3 g.), yielded on recrystallisation 3 : 7-*diacetylxanthen* as shiny, colourless leaflets, m. p. 168°, giving a yellow colour with sulphuric acid (Found: C, 77·0; H, 5·4. $C_{17}H_{14}O_3$ requires C, 76·7; H, 5·3%). 3 : 7-*Dipropionylxanthen* prepared similarly, formed long, silky, colourless needles, m. p. 155° (Found: C, 77·3; H, 6·3. $C_{19}H_{18}O_3$ requires C, 77·5; H, 6·1%). Both ketones gave positive Pfitzinger reactions, and formed high-melting disemicarbazones.

4-n-*Butylbenzophenone*.—A solution of *n*-butylbenzene (30 g.; prepared from bromobenzene, *n*-butyl bromide, and sodium) and benzoyl chloride (40 g.) in carbon disulphide (100 c.c.) was treated with aluminium chloride (40 g.) without cooling, and the mixture kept for 12 hours; the *phenone* (50 g.), a pale yellow fluid oil, had b. p. 214—215°/15 mm., n_D^{20} 1·5729 (Found: C, 85·3; H, 7·4. $C_{17}H_{18}O$ requires C, 85·6; H, 7·6%); the *oxime* formed colourless prisms, m. p. 102° (Found: N, 5·4. $C_{17}H_{19}ON$ requires N, 5·5%). 4-n-*Propylbenzophenone*, prepared in the same way, was a similar oil, b. p. 200—201°/15 mm., n_D^{22} 1·5831 (Found: C, 85·6; H, 7·2. $C_{16}H_{16}O$ requires C, 85·7; H, 7·1%).

1-p-n-*Butylphenyl*-1 : 2-*diphenylethylene*.—The foregoing butylbenzophenone (24 g.) was added to a cooled Grignard reagent made from benzyl chloride (32 g.) and magnesium (3·5 g.) in ether; the mixture was refluxed for 15 minutes, and worked up in the usual way, the carbinol obtained being dehydrated with 92% formic acid. The *ethylene* formed a pale yellow viscous oil (20 g.), b. p. 262—264°/16 mm., n_D^{20} 1·6264 (Found: C, 92·1; H, 7·7. $C_{24}H_{24}$ requires C, 92·3; H, 7·7%). A cooled solution of this compound (21 g.) in acetic acid (120 c.c.), treated with bromine (10 g. dissolved in acetic acid), yielded 1-*bromo*-2-p-n-*butylphenyl*-1 : 2-*diphenylethylene*, crystallising from acetic acid as colourless leaflets, m. p. 112° (Found: C, 73·5; H, 6·2. $C_{24}H_{23}Br$ requires C, 73·7; H, 5·9%).

1 : 2-*Diphenyl*-1-p-n-*propylphenylethylene*.—Prepared from 4-*n*-propylbenzophenone (34 g.) and benzyl chloride, this *compound* formed a pale yellow viscous oil (32 g.), b. p. 256—257°/16 mm. (Found: C, 92·4; H, 7·6. $C_{23}H_{22}$ requires C, 92·6; H, 7·4%); on treatment in acetic acid solution with bromine (11·3 g.), it (21 g.) yielded 1-*bromo*-1 : 2-*diphenyl*-2-p-n-*propylphenylethylene*, crystallising from acetic acid as shiny colourless leaflets, m. p. 116° (Found: C, 73·1; H, 5·8. $C_{23}H_{21}Br$ requires C, 73·2; H, 5·6%).

TABLE 3.

Ketone	M. p.	B. p./mm.	Formula	Found, %: C	Found, %: H	Reqd., %: C	Reqd., %: H
2-*p*-*n*-Propylbenzoylfuran [a]	*	202°/25	$C_{14}H_{14}O_2$	78·2	6·7	78·5	6·5
4-Ethyl-4′-*n*-propylbenzophenone [a]	*	235/20	$C_{18}H_{20}O$	85·5	8·1	85·7	7·9
4-Methyl-4′-*n*-propylbenzophenone [a]	*	225/20	$C_{17}H_{18}O$	85·5	7·7	85·7	7·6
4 : 4′-Di-*n*-propylbenzophenone [b] ...	*	230/18	$C_{19}H_{22}O$	85·6	8·5	85·7	8·3
2-*p*-*n*-Propylbenzoylthiophen [a]	*	195/20	$C_{14}H_{14}OS$	72·8	6·4	73·0	6·1
4-Chloro-4′-*n*-propylbenzophenone [a]	78°	228/20	$C_{16}H_{15}OCl$	74·1	5·8	74·2	5·8
4-Bromo-4′-*n*-propylbenzophenone [a]	92	233/18	$C_{16}H_{15}OBr$	63·1	5·0	63·4	5·0
4-*p*-*n*-Propylbenzoyldiphenyl [b]	104	270/15	$C_{22}H_{20}O$	87·8	6·9	88·0	6·7
2-*p*-*n*-Propylbenzoylfluorene [b]	108	*ca.* 280/10	$C_{23}H_{20}O$	88·6	6·3	88·5	6·4
3-*p*-*n*-Propylbenzoylindole [c]	186	—	$C_{18}H_{17}ON$	81·9	6·6	82·1	6·5
2-Methyl-3-*p*-*n*-propylbenzoyl-indole [c]	172	—	$C_{19}H_{19}ON$	82·0	6	82·3	6·9

* Denotes liquid.

[a] Prepared from *n*-propylbenzene and the corresponding acid chloride. [b] Prepared from *p*-*n*-propylbenzoyl chloride (liquid, b. p. 143°/20 mm.) and the corresponding hydrocarbon. [c] Prepared from *p*-*n*-propylbenzoyl chloride and the corresponding indole by Oddo's method (*Gazzetta*, 1910, **40**, II, 353; 1911, **41**, I, 237; 1913, **43**, II, 210).

1-*Bromo*-2 : 2-*di*-(3-*chloro*-4-*methoxyphenyl*)-1-*phenylethylene*.—To a mixture of *o*-chloroanisole (54 g.), phenylacetyl chloride (24 g.), and phosphorus oxychloride (0·5 c.c.), aluminium chloride (32 g.) was added in small portions; the mixture was kept overnight at room temperature, then heated at 60° on a water-bath for 4 hours. After the usual treatment, 1 : 1-di-(3-chloro-4-methoxyphenyl)-2-phenylethylene (11 g.) was obtained as colourless needles, m. p. 106° (cf. Hoán and Buu-Hoï, *Compt. rend.*, 1947, **224**, 1228). Bromination (0·32 g. of bromine) of this compound (0·75 g.) in acetic acid (10 c.c.) gave 1-*bromo*-2 : 2-*di*-(3-*chloro*-4-*methoxyphenyl*)-1-*phenylethylene* (0·6 g.), crystallising as fine yellowish prisms, m. p. 96° (Found: C, 56·7; H, 3·5. $C_{22}H_{17}O_2BrCl_2$ requires C, 56·9; H, 3·7%).

1-*Bromo*-2 : 2-*di*-(4-*methoxy*-2-*methylphenyl*)-1-*phenylethylene*.—1 : 1-*Di*-(4-*methoxy*-2-*methylphenyl*)-2-*phenylethylene* was obtained from methyl *m*-tolyl ether (65 g.), phenylacetyl chloride (39 g.), and aluminium chloride (50 g.) in the presence of iodine (0·5 g.); it formed from ethanol fine yellowish needles (22 g.), m. p. 78°, b. p. 260°/12 mm. (Found: C, 83·5; H, 7·0. $C_{24}H_{24}O_2$ requires C, 83·7; H, 7·0%); its bromination yielded 1-*bromo*-2 : 2-*di*-(4-*methoxy*-2-*methylphenyl*)-1-*phenylethylene*, crystallising as fine colourless prisms, m. p. 119° (Found: C, 68·0; H, 5·5; Br, 19·6. $C_{24}H_{23}O_2Br$ requires C, 68·1; H, 5·4; Br, 18·9%).

Certain new *ketones* derived from *n*-propylbenzene are recorded in Table 3.

We thank Miss Patricia F. Boshell, M.A. (Oxon.), for assistance.

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[*Received, June 3rd*, 1952.]