[CONTRIBUTION FROM THE RADIUM INSTITUTE OF THE UNIVERSITY OF PARIS]

1,2,2-Triarylethylenes Containing *o*- and *m*-Substituents

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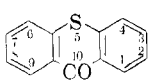
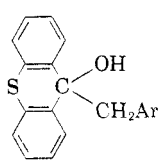
A number of new 1,2,2-triarylethylenes bearing substituents in the *ortho* and *meta* positions have been synthesized from thiaxanthone and from *o*- and *m*-substituted benzophenones. The bromination of these ethylenes has been investigated, and the products thus obtained are being tested as potential inhibitors of the secretions of the anterior pituitary.

Many derivatives of 1,2,2-triphenylethylene show more or less pronounced estrogenic activity,[1] or possess other interesting biological properties, such as inhibition of the secretions of the anterior pituitary,[2] or antagonistic action towards mammary gland hypertrophy induced by more potent estrogens.[3] As these various activities are not necessarily present in the same degree in any one triarylethylene, it was hoped that substitution in the *ortho* and *meta* positions, known to be unfavorable to estrogenic activity, would result in compounds useful for their other biological properties. The present work records the synthesis of a number of *o*- and *m*-substituted 1,2,2-triarylethylenes.

One of the intermediates used was thiaxanthone (I), which was condensed with the Grignard reagents from benzyl chloride and several of its substitution products. The tertiary thiaxanthydrols of general formula II obtained readily underwent dehydration to give the ethylenes of general formula

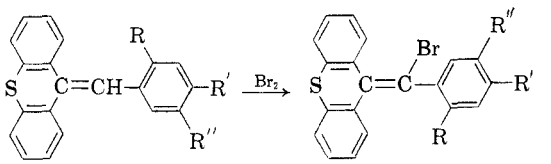


I



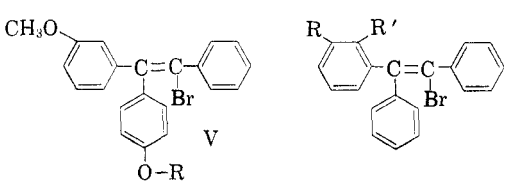
II

III. In this series, 10-benzalthiaxanthene and 10-(4-chlorobenzal)thiaxanthene have already been described in the literature;[4] 10-(2-chlorobenzal)-, 10-(2,4-dichlorobenzal)-, 10-(3,4-dichlorobenzal)-, and 10-(2,5-dimethylbenzal)-thiaxanthene are new compounds. As is the case with 10-arylidenexanthenes,[5] bromination of these 10-arylidenethiaxanthenes resulted in substitution on the ethylene bond, with formation of a series of 10-(ω-bromoarylidene)thiaxanthenes (IV), in excellent yield.



III IV

It is known that in the 1,2,2-triphenylethylene group, the presence of alkyloxy groups in *para* positions results in potent estrogens, as is the case of 1-bromo-1-phenyl-2,2-bis(*p*-ethoxyphenyl)-ethylene,[6] which has found clinical application. The synthesis of similar compounds in which one alkyloxy group has been shifted to a *meta* position has now been performed, starting from *m*-methoxybenzoic acid, whose chloride underwent Friedel-Crafts reactions with anisole and phenetole to give 3,4′-dimethoxybenzophenone and 3-methoxy-4′-ethoxybenzophenone respectively; interaction of the substituted benzophenones with benzylmagnesium chloride, and dehydration of the tertiary alcohols obtained, yielded the corresponding liquid ethylenes which underwent bromination to the well-crystallized 1-bromo-1-phenyl-2-(*m*-methoxyphenyl)-2-(*p*-methoxyphenyl)ethylene (V; R = CH_3) and 1-bromo-1-phenyl-2-(*m*-methoxyphenyl)-2-(*p*-ethoxyphenyl)ethylene (V; R = C_2H_5). In view of the interesting biological properties found in many fluorine-containing molecules,[7] 2- and 3-fluorobenzophenone were condensed with benzylmagnesium chloride to give 1,2-diphenyl-2-(2-fluorophenyl)- and 1,2-diphenyl-2-(3-fluorophenyl)ethyl-



V

VI; R = H, R′ = F
VII; R = F, R′ = H

(1) J. M. Robson and A. Schönberg, *Nature*, **140**, 196 (1937); J. M. Robson, A. Schönberg, and W. Tadros, *Nature*, **150**, 22 (1942); A. Lacassagne *et al.*, *Experientia*, **2**, 70 (1946); *Bull. soc. chim. biol.*, **29**, 1087 (1947); **30**, 674 (1948); **32**, 255 (1950).

(2) *Cf.* N. P. Buu-Hoï, N. D. Xuong, and A. Beauvillain, *Experientia*, **13**, 20 (1957).

(3) *Cf.* N. P. Buu-Hoï, International Symposium on Chemotherapy of Cancer (Oslo, 1956); to be published in *Acta Unio Intern. contra Cancrum.*

(4) E. Bergmann, *et al.*, *Bull. soc. chim. France*, 262 (1952).

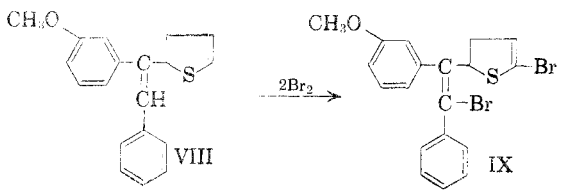
(5) Cf. N. P. Buu-Hoï and N. D. Xuong, *J. Org. Chem.*, **16**, 1633 (1951).

(6) R. Greene, *Brit. Med. J.*, **1**, 9 (1946).

(7) *Cf.* N. P. Buu-Hoï, L. Corre-Hurst, and N. D. Xuong, *Bull. soc. chim. biol.*, **37**, 867 (1955); N. P. Buu-Hoï, D. Lavit, and N. D. Xuong, *J. Org. Chem.*, **19**, 1617 (1954).

ene, and these compounds underwent bromination to form the bromo derivatives VI and VII.

In the group of thiophene analogs of triarylethylene, an interesting case is that of compound VIII, prepared from 2-(*m*-methoxybenzoyl)thiophene, whose bromination afforded, not the expected monobrominated derivative, but a dibromo compound of formula IX. The structure of this latter product was determined by an independent synthesis from 2-bromo-5-(*m*-methoxybenzoyl)-thiophene, thus proving that one bromine atom had entered the heterocyclic nucleus.[8]



All the ethylenes prepared are very weak estrogens or are inactive in this respect, and are currently being tested for inhibitory activity towards the secretions of the anterior pituitary.

EXPERIMENTAL

Preparation of 10-arylidenethiaxanthenes. To a water-cooled solution in anhydrous ether of a Grignard reagent prepared from magnesium shavings (1.2 g.-atoms) and benzyl chloride or one of its substitution derivatives (1.1 moles), thiaxanthone[9] (1 mole, suspended in ether) was added in small portions, and the mixture refluxed for 30 min. on a bath. After cooling, and decomposition with an ice-cooled dilute aqueous solution of sulfuric acid, the ether solution of the appropriate tertiary alcohol (II) was washed with water, the solvent removed, and the residue dehydrated by refluxing for 5 min. with pure formic acid (3 parts). After dilution with water the dehydration product was taken up in benzene, the benzene solution washed with water and dried over calcium chloride, the solvent removed, and the residue vacuum-fractionated. The yields of 10-arylidenethiaxanthenes thus obtained ranged from 70 to 80%. *10-(2-Chlorobenzal)thiaxanthene* (III; R = Cl, R′ = R″ = H), thus prepared from *o*-chlorobenzyl chloride, boiled at 275–285°/20 mm., and crystallized from acetic acid in fine, yellowish needles, m.p. 121°.

Anal. Calcd. for $C_{20}H_{13}ClS$: C, 74.9; H, 4.1. Found: C, 74.7; H, 3.8.

10-(2,4-Dichlorobenzal)thiaxanthene (III; R = R′ = Cl, R″ = H), b.p. 295–305°/20 mm., prepared with 2,4-dichlorobenzyl chloride, crystallized from acetic acid in pale yellow prisms, m.p. 128°.

Anal. Calcd. for $C_{20}H_{12}Cl_2S$: C, 67.7; H, 3.4. Found: C, 67.4; H, 3.5.

The isomeric *10-(3,4-dichlorobenzal)thiaxanthene* (III; R = H, R′ = R″ = Cl), b.p. 280–290°/16 mm., prepared with 3,4-dichlorobenzyl chloride, crystallized from acetic acid in shiny, yellowish prisms, m.p. 134°.

Anal. Calcd. for $C_{20}H_{12}Cl_2S$: C, 67.7; H, 3.4. Found: C, 68.0; H, 3.3.

10-(2,5-Dimethylbenzal)thiaxanthene (III; R = R″ = CH_3, R′ = H), b.p. 285–288°/25 mm., prepared with 2,5-dimethylbenzyl chloride, crystallized from ethanol in pale yellow prisms, m.p. 111°.

Anal. Calcd. for $C_{22}H_{18}S$: C, 83.8; H, 5.9. Found: C, 84.0; H, 5.8.

Bromination of 10-arylidenethiaxanthenes. To a solution of 1 g. of 9-(4-chlorobenzal)thiaxanthene[4] in 20 ml. of dry chloroform, 1.5 g. of bromine (in chloroform solution) was added in small portions, and, after decoloration, the solvent was distilled off. The residue was crystallized twice from acetic acid, giving 1.2 g. of *10-(ω-bromo-4-chlorobenzal)-thiaxanthene* (IV; R = R″ = H, R′ = Cl), as fine colorless prisms, m.p. 147°.

Anal. Calcd. for $C_{20}H_{12}BrClS$: C, 60.3; H, 3.0. Found: C, 60.2; H, 3.1.

The following compounds were similarly prepared:

(*a*) *10-(ω-Bromo-2-chlorobenzal)thiaxanthene* (IV; R = Cl, R′ = R″ = H), shiny colorless prisms, m.p. 157°.

Anal. Calcd. for $C_{20}H_{12}BrClS$: C, 60.3; H, 3.0. Found: C, 60.0; H, 3.1.

(*b*) *10-(ω-Bromo-2,4-dichlorobenzal)thiaxanthene* (IV; R = R′ = Cl, R″ = H), fine colorless prisms, m.p. 141°.

Anal. Calcd. for $C_{20}H_{11}BrCl_2S$: C, 55.4; H, 2.5. Found: C, 55.7; H, 2.6.

(*c*) *10-(ω-Bromo-3,4-dichlorobenzal)thiaxanthene* (IV; R = H, R′ = R″ = Cl), shiny, colorless prisms, m.p. 181°.

Anal. Calcd. for $C_{20}H_{11}BrCl_2S$: C, 55.4; H, 2.5. Found: C, 55.7; H, 2.8.

(*d*) *10-(ω-Bromo-2,5-dimethylbenzal)thiaxanthene* (IV; R = R″ = CH_3, R′ = H), fine, colorless prisms, m.p. 136°.

Anal. Calcd. for $C_{22}H_{17}BrS$: C, 67.2; H, 4.3. Found: C, 66.9; H, 4.6.

3,4′-Dimethoxybenzophenone. Aluminum chloride (28 g.) was added, in small portions to an ice-cooled solution of 20 g. of anisole and 31 g. of *m*-methoxybenzoyl chloride in 150 ml. of dry carbon disulfide; after 8 hr. at room temperature, followed by the usual treatment, 42 g. of product, b.p. 240–241°/15 mm., n_D^{27} 1.6099, was obtained, which solidified and crystallized from ethanol in colorless prisms, m.p. 60°.

Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.4; H, 5.8. Found: C, 74.3; H, 6.0.

The same procedure, applied to 22 g. of phenetole, yielded 34 g. of *3-methoxy-4′-ethoxybenzophenone*, b.p. 248–250°/15 mm., n_D^{27} 1.5979, which crystallized from ethanol in fine, colorless prisms, m.p. 51°.

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 75.1; H, 6.3. Found: C, 75.0; H, 6.3.

2-(3-Methoxybenzoyl)thiophene. Prepared from 20 g. of thiophene, 37.3 g. of *m*-methoxybenzoyl chloride, and 31 g. of aluminum chloride in 150 ml. of carbon disulfide (the reaction mixture was worked up after 3 hr.), this *ketone* was a yellow, viscous oil, b.p. 210–212°/24 mm., yield: 30 g.

Anal. Calcd. for $C_{12}H_{10}O_2S$: C, 66.1; H, 4.6. Found: C, 66.0; H, 4.5.

1-Bromo-1-phenyl-2-(m-methoxyphenyl)-2-(p-methoxyphenyl)ethylene (V; R = CH_3). To an ethereal solution of a Grignard reagent prepared from 15 g. of benzyl chloride and 1.8 g. of magnesium shavings, 15 g. of 3,4′-dimethoxybenzophenone (in ether solution) was added in small portions, with cooling, and the mixture was then refluxed for 1 hr. After the usual treatment and dehydration of the crude tertiary carbinol with formic acid, 18 g. of the *ethylene* was obtained as a viscous yellow oil, b.p. 286–288°/30 mm., which was dissolved in 35 ml. of chloroform, and treated directly with 11 g. of bromine. After evaporation of the solvent, the residue was recrystallized twice from ethanol, giving 15 g. of the *bromo compound* as fine, colorless prisms, m.p. 132–133°.

Anal. Calcd. for $C_{22}H_{19}BrO$: C, 66.9; H, 4.9. Found: C, 67.0; H, 4.8.

1-Bromo-1-phenyl-2-(m-methoxyphenyl)-2-(p-ethoxyphenyl)-ethylene (V; R = C_2H_5). The *ethylene* obtained from 3-methoxy-4′-ethoxybenzophenone (15 g.) and benzylmagnesium chloride was a viscous, yellow oil (17 g.), b.p. 270–273°/20 mm.; treatment with 7.5 g. of bromine in chloroform afforded the *bromo compound*, which crystallized from acetic acid in fine, colorless needles, m.p. 136°; yield: 16 g.

(8) For other instances, see N. H. Nam, N. P. Buu-Hoï, and N. D. Xuong, *J. Chem. Soc.*, 1690 (1954).

(9) K. Ziegler, *Ber.*, **23**, 2471 (1890).

Anal. Calcd. for $C_{23}H_{21}BrO_2$: C, 67.5; H, 5.2. Found: C, 67.8; H, 5.1.

1-Bromo-1-phenyl-2-(m-methoxyphenyl)-2-(5-bromo-2-thienyl)ethylene (IX). The *ethylene* obtained from 2-(*m*-methoxybenzoyl)thiophene (15 g.) and benzylmagnesium chloride was a pale yellow, viscous oil (24 g.), b.p. 251–252°/20 mm.; treatment of this substance with 24 g. of bromine (in chloroform) yielded 25 g. of the *dibromo compound*, which crystallized from acetic acid in cream-colored needles, m.p. 94°.

Anal. Calcd. for $C_{19}H_{14}Br_2OS$: C, 50.7; H, 3.2. Found: C, 50.6; H, 3.1.

This compound was found to be identical with the monobromination product of the ethylene prepared from 5-bromo-2-(*m*-methoxybenzoyl)thiophene and benzylmagnesium chloride.

m-Fluorobenzophenone. To a solution of 30 g. of benzene and 12.5 g. of *m*-fluorobenzoyl chloride in 50 ml. of dry carbon disulfide, 15 g. of aluminum chloride was added in small portions with stirring, and the mixture left for 8 hrs. at room temperature, then refluxed for 1 hr. The usual treatment afforded 12 g. of *m-fluorobenzophenone*, which crystallized from ligroin as lustrous, colorless leaflets, m.p. 55°; the corresponding 2,4-dinitrophenylhydrazone crystallized from acetic acid in orange-yellow needles, m.p. 260°.

Anal. Calcd. for $C_{13}H_9FO$: C, 78.1; H, 4.5. Found: C, 77.9; H, 4.5.

o-Fluorobenzophenone. Similarly prepared from *o*-fluorobenzoyl chloride, this *ketone* is a pale yellow oil, b.p. 190°/29 mm., n_D^{22} 1.5898, which formed a 2,4-dinitrophenylhydrazone, m.p. 220°.

Anal. Calcd. for $C_{13}H_9FO$: C, 78.1; H, 4.5. Found: C, 77.8; H, 4.6.

The starting material for this synthesis, *o*-fluorobenzoyl chloride, was characterized by its condensation product with *p*-phenylenediamine in pyridine medium; *1,4-bis(o-fluorobenzoylamino)benzene* crystallized from acetic acid in shiny colorless prisms, m.p. 273°.

Anal. Calcd. for $C_{20}H_{14}F_2N_2O_2$: N, 8.0. Found: N, 7.9.

1,2-Diphenyl-2-(m-fluorophenyl)ethylene. Prepared from 10 g. of *m*-fluorobenzophenone and benzylmagnesium chloride (10 g.) in ether, this compound, b.p .229–230°/16 mm., n_D^{22} 1.6502, crystallized from ethanol in shiny colorless prisms, m.p. 55°; yield: 10 g.

Anal. Calcd. for $C_{20}H_{15}F$: C, 87.7; H, 5.5. Found: C, 87.6; H, 5.7.

1-Bromo-1,2-diphenyl-2-(m-fluorophenyl)ethylene (VII), prepared by treating 11 g. of the above ethylene with 6.4 g. of bromine in chloroform medium, crystallized from ethanol in shiny, colorless needles, m.p. 97°.

Anal. Calcd. for $C_{20}H_{14}BrF$: C, 68.1; H, 4.0. Found: C, 68.1; H, 4.3.

1,2-Diphenyl-2-(o-fluorophenyl)ethylene. This compound crystallized from ethanol as lustrous, colorless leaflets, m.p. 73°. Yield: 10 g.

Anal. Calcd. for $C_{20}H_{15}F$: C, 87.7; H, 5.5. Found: C, 88.0; H, 5.3.

Bromination of the foregoing compound yielded *1-bromo-1,2-diphenyl-2-(o-fluorophenyl)ethylene* (VI), which crystallized from ethanol in shiny, colorless prisms, m.p. 100°.

Anal. Calcd. for $C_{20}H_{14}BrF$: C, 68.1; H, 4.0. Found: C, 68.4; H, 4.0.

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[CONTRIBUTION FROM THE COLLEGE OF ENGINEERING, RUTGERS UNIVERSITY]

Matrix-Formed Adsorbing Polymers

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A method is described wherein the pore volume of dry silica gel particles is filled with a low viscosity, catalyzed epoxide prepolymer, this being subsequently polymerized. Following polymerization the siliceous matrix material is removed from the solid polymer by solution in aqueous hydrofluoric acid. The porous, resinous particles thus produced exhibited a capacity for adsorbing water vapor and for complexing copper, zinc, and hydrogen ion.

Conventional ion-exchanging polymers, in the usual particulate form, impose a permeability requirement on the polymer structure. This requirement, coupled with the needed inclusion of specific chemical groups for ion-exchange activity, has placed definite limitations on such compositions. The method described here provides an alternative route to securing the required permeability through casting of the polymer in a microcapillary form at the time of polymerization.

In the work described here silica gel particles were employed as a parent, matrix substance. Silica gel particles having a pore volume of 0.80 ml./g. were saturated with the required volume of the epoxide prepolymer, catalyzed with diethylene triamine. Following completion of the polymerization the silica gel matrix was removed by solution in a 27% hydrofluoric acid solution and washed thoroughly with distilled water. Detailed experimental procedure is given below.

The resinous particles thus prepared have been termed "gel replicas."

The water vapor adsorption measured for the material prepared above, and determined after drying the washed particles for two hours at 85–90° C., is given in Table I. A bulk polymerized material, of

TABLE I

WATER VAPOR ADSORPTION OF GEL-REPLICAS

Relative Humidity, 25°C., %	Adsorbed Water, gm. water/g. gel replica
100	0.48
81	0.26
51	0.069