of 0.64 g. (5 mmoles) of *p*-chloroaniline in 5 ml. of pyridine. After 30 min., the solvent was removed *in vacuo* and the residue crystallized from 55 ml. of water with the aid of Norit; yield, 0.90 g. (57%), m.p. 190–191°. Recrystallization from 50% ethanol gave white crystals, m.p. 196–198°; λ_{max}^{KBr} 2.93, 3.10, 6.70μ (NH), 5.65μ (C_4=O of hydantoin), 5.82μ (C_2=O of hydantoin), 7.55, 8.75μ (S → O of —SO_2N—), 11.95μ (*p*-disubstituted phenyl). For additional details and for other compounds prepared in the manner (Procedure B), see Table I.

DL-5-(*β-Phenylsulfamoylethyl*)*hydantoin* (IIIb, R_1 = C_6H_5, R_2 = H). *Procedure C.* To a stirred solution of 15.8 g. (0.17 mole) of aniline in 120 ml. of 95% ethanol was added portionwise 20.0 g. (0.088 mole) of DL-5-(*β*-chlorosulfonylethyl)hydantoin (IIb) over a period of 5 min. The reaction mixture was stirred for 90 min., then was allowed to stand overnight. The product was collected on a filter and washed with 40 ml. of 95% ethanol; yield, 20.7 g. (86%), m.p. 205–207°. For additional details, see Table I. Other compounds prepared by this method (Procedure C) are described in Table I. In some cases it was necessary to evaporate the ethanol and crystallize the product from water.

DL-5-[(*β-Carbamoylmethylsulfamoyl*)*ethyl*]*hydantoin* (IIIb, R_1 = CH_2CONH_2, R_2 = H). To a warm (56°) mixture of 0.90 g. (8.1 mmoles) of glycinamide hydrochloride in 8 ml. of dry *N,N*-dimethylformamide and 5 ml. of dry triethylamine was added with stirring a solution of 1.81 g. (8 mmoles) of DL-5-(*β*-chlorosulfonylethyl)hydantoin (IIb) in 5 ml. of *N,N*-dimethylformamide, the temperature rising to 71°. After being stirred for an additional 45 min., the heterogeneous mixture was allowed to stand for 20 hr. in a closed flask. The reaction mixture was processed as in Procedure A; yield, 1.05 g. (50%), m.p. 230–248° dec. Two recrystallizations from 95% ethanol gave white crystals with the same m.p.; λ_{max}^{KBr} 2.88, 2.99, 3.12μ (NH), 5.66μ (C_4=O of hydantoin), 5.80μ (C_2=O of hydantoin), 6.00μ (amide C=O), 7.55, 8.75μ (S → O of —SO_2N—).

Anal. Calcd. for $C_7H_{12}N_4O_5S$: C, 31.8; H, 4.57; N, 21.2. Found: C, 32.1; H, 4.50; N, 20.8.

DL-5-(*β-Azidosulfonylethyl*)*hydantoin.* To a stirred solution of 8.0 g. (0.035 mole) of DL-5-(*β*-chlorosulfonylethyl)hydantoin (IIb) in 125 ml. of 95% ethanol was added immediately a solution of 3.0 g. (0.046 mole) of sodium azide in 11 ml. of water. After the mixture was stirred for 1 hr., the precipitate was collected on a filter and washed with 75 ml. of 95% ethanol in portions, then with water; yield, 5.8 g., m.p. 123–128°. Recrystallization from 110 ml. of absolute ethanol gave 4.6 g. (56%) of white crystals, m.p. 131–133°; λ_{max}^{KBr} 4.59, 4.65μ (—N_3), 5.60μ (C_4=O of hydantoin), 5.75μ (C_2=O of hydantoin), 7.30, 8.57, 8.65μ (S → O of —SO_2N—).

Anal. Calcd. for $C_5H_7N_5O_4S$: C, 25.8; H, 3.02; N, 30.0; S, 13.8. Found: C, 26.2; H, 2.92; N, 29.8; S, 14.0.

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MENLO PARK, CALIF.

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

Bromination of Some 1,2,2-Triarylethylenes

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The synthesis of a number of new diversely substituted 1,2,2-triarylethylenes is described, and their bromination reactions are investigated. It is shown that in addition to normal substitution on the ethylene chain, nuclear bromination also can occur when reactive aryl or thienyl groups are present.

In the framework of a general investigation on potential chemical inhibitors of the secretions of the anterior pituitary,[1] 1,2,2-triarylethylenes were found to constitute an attractive group for the study of relationships between chemical structure and biological activity of this type.[2] The known fact that the introduction of further oxygen-containing radicals into the molecule of estradiol results in compounds with reduced estrogenic activity (*e.g.* estriol and 6-ketoestradiol) and which can act as antagonists of the mother-substance,[3] now suggested the study of 1,2,2-triarylethylenes derived from veratrole (those derived from anisole are known to be strong estrogens).[4]

1,2-Diphenyl-2-(3,4-dimethoxyphenyl)ethylene (I) was prepared by the reaction of benzylmagnesium chloride on 3,4-dimethoxybenzophenone and dehydration of the resulting tertiary carbinol by means of formic acid.[5] Bromination of this ethylene with one mole of bromine gave 1-bromo-1,2-diphenyl-2-(3,4-dimethoxyphenyl)ethylene (II); with two moles of bromine, nuclear bromination also occurred, the reaction product probably being 1-bromo-1,2-diphenyl-2-(6-bromo-3,4-dimethoxyphenyl)ethylene (III). This abnormal behavior is most likely due to the fact that in the molecule of the olefin (I), the position 6 in the veratryl radical is activated both by a *p*-methoxy group and by the *o*-styryl group; the influence of this latter group is in accord with the results of the theoretical computation of π-electron densities in the molecule of

(1) N. P. Buu-Hoï, *Acta Unio Intern. contra Cancrum*, **13**, 442 (1957).

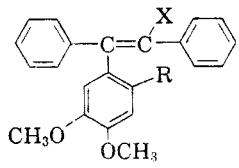
(2) N. P. Buu-Hoï, N. D. Xuong, and A. Beauvillain, *Experientia*, **13**, 20 (1957); *Bull. soc. chim. biol.*, **39**, 431 (1957); J. M. Gazave, N. P. Buu-Hoï, N. D. Xuong, and H. Clédière, *Bull. soc. chim. biol.*, **39**, 1343 (1957); N. P. Buu-Hoï, E. Lescot, and N. D. Xuong, *J. Org. Chem.*, **22**, 1057 (1957).

(3) *Cf.* C. Huggins and E. V. Jensen, *J. Exp. Med.*, **102**, 335, 347 (1955).

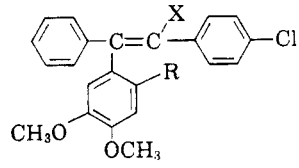
(4) *Cf.* J. M. Robson, A. Schönberg, and W. Tadros, *Nature*, **150**, 22 (1942); A. Lacassagne, N. P. Buu-Hoï, L. Corre, J. Lecocq, and R. Royer, *Experientia*, **2**, 70 (1946).

(5) N. P. Buu-Hoï, *Bull. soc. chim. France*, **13**, 117 (1946).

1,2,2-triphenylethylene.[6] The effect on halogenation of this double activation seems to be general, as



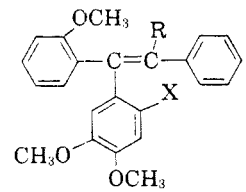
I; X = R = H
II; X = Br, R = H
III; X = R = Br



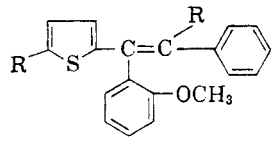
IV; X = R = H
V; X = Br, R = H
VI; X = R = Br

1-(4-chlorophenyl)-2-phenyl-2-(3,4-dimethoxyphenyl)ethylene (IV), prepared from 3,4-dimethoxybenzophenone and *p*-chlorobenzylmagnesium chloride, behaved in the same way, one mole of bromine giving 1-bromo-1-(4-chlorophenyl)-2-phenyl-2-(3,4-dimethoxyphenyl)ethylene (V), while with two moles, a dibromo compound (VI) was obtained.

In the case of 1-phenyl-2-(2-methoxyphenyl)-2-(3,4-dimethoxyphenyl)ethylene (VII), prepared from benzylmagnesium chloride and 2′,3,4-trimethoxybenzophenone, the dibromination product (VIII) was already obtained with only one mole of bromine. The same observation was also made with 1-phenyl-2-(2-methoxyphenyl)-2-(2-thienyl)ethylene (IX), prepared from benzylmagnesium chloride and 2-(2-methoxybenzoyl)thiophene, which readily yielded 1-bromo-1-phenyl-2-(2-methoxyphenyl)-2-(5-bromo-2-thienyl)ethylene (X); the structure of this last compound was established by its formation in the monobromination of the ethylene prepared from 2-bromo-5-(2-methoxybenzoyl)thiophene. A similar instance of nuclear bromination of a thienyldiarylethylene had already been reported.[7]

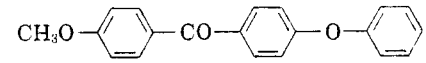


VII; R = X = H
VIII; R = X = Br

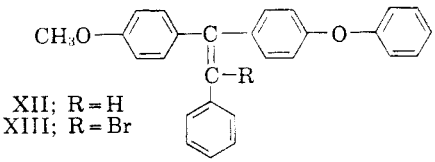


IX; R = H
X; R = Br

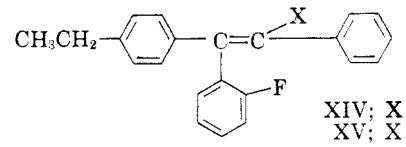
On the other hand, the presence of a phenoxyphenyl radical with a free *para*-position in the molecule of 1-phenyl-2-(4-methoxyphenyl)-2-(4-phenoxyphenyl)ethylene (XII) does not lead to dibromination; this ethylene, obtained from benzylmagnesium chloride and 4-methoxy-4′-phenoxybenzophenone (XI), gave the side-chain bromination product (XIII). Of course, when only unreactive aryl groups are present in the molecule of triarylethylene, only a monobromination product is to be expected, even when two moles of the halogen are used: thus, 1-phenyl-2-(4-ethylphenyl)-2-(2-fluorophenyl)ethylene (XIV), prepared from 4-ethyl-2′-fluorobenzophenone, afforded the normal monobromination product (XV).



XI



XII; R = H
XIII; R = Br



XIV; X = H
XV; X = Br

In biological tests, the monobromo compounds II, V, VIII, and XII showed some Allen-Doisy activity; the other ethylenes were either barely estrogenic or inactive, and are therefore being examined for inhibitory effects on the secretions of the anterior pituitary.

EXPERIMENTAL

1,2-Diphenyl-2-(3,4-dimethoxyphenyl)ethylene (I). 3,4-Dimethoxybenzophenone (40 g., b.p. 235°/20 mm.) was prepared by Friedel-Crafts condensation of 39 g. of benzoyl chloride with 34 g. of veratrole in the presence of 34 g. of aluminum chloride in carbon disulfide. To an ice-cooled Grignard solution prepared from 7.8 g. of benzyl chloride and 2 g. of magnesium shavings in 150 ml. of ether, 10 g. of the above ketone was added portionwise with stirring, and the mixture refluxed for 10 min. to complete the reaction. After decomposition with dilute sulfuric acid, the organic layer was separated, washed with water, dried over sodium sulfate, and the solvent removed. The crude tertiary carbinol was treated with 80 ml. of formic acid, and the mixture refluxed for 5 min. to complete the dehydration. After cooling, water was added, the ethylene obtained taken up in benzene, the benzene solution washed with water and dried over sodium sulfate, the solvent removed, and the residue vacuum-fractionated. The yield was 8.5 g. of a product, b.p. 277–278°/28 mm., which crystallized from ethanol in fine colorless prisms, m.p. 102°.

Anal. Calcd. for $C_{22}H_{20}O_2$: C, 83.5; H, 6.4. Found: C, 83.2; H, 6.1.

1-Bromo-1,2-diphenyl-2-(3,4-dimethoxyphenyl)ethylene (II). A solution of 1 g. of the foregoing ethylene in 15 ml. of pure anhydrous chloroform was treated dropwise with a chloroform solution of 0.49 g. of bromine. After decoloration of the solution, the solvent was distilled off, and the residue crystallized several times from ethanol. The yield was 0.8 g. of fine colorless needles, m.p. 105°. The side-chain position of the bromine in this compound was ascertained by the formation of 3,4-dimethoxybenzophenone on chromic oxidation.

Anal. Calcd. for $C_{22}H_{19}BrO_2$: C, 66.8; H, 4.8. Found: C, 67.0; H, 4.9.

1-Bromo-1,2-diphenyl-2-(6-bromo-3,4-dimethoxyphenyl)ethylene (III). A similar operation, effected with 1 g. of

(6) N. P. Buu-Hoï, C. A. Coulson, P. and R. Daudel, M. Martin, and A. and B. Pullman, *Rev. Sci.*, **85**, 1041 (1947).

(7) N. P. Buu-Hoï, E. Lescot, and N. D. Xuong, *J. Org. Chem.*, **22**, 1057 (1957).

ethylene I and 1 g. of bromine in chloroform, afforded a compound which crystallized from ethanol in shiny colorless prisms, m.p. 138°, yield: 1.2 g.

Anal. Calcd. for $C_{22}H_{18}Br_2O_2$: C, 55.7; H, 3.8. Found: C, 55.3; H, 3.9.

1-(4-Chlorophenyl)-2-phenyl-2-(3,4-dimethoxyphenyl)-ethylene (IV). A Grignard solution, made from 9.5 g. of *p*-chlorobenzyl chloride and 2 g. of magnesium shavings in 150 ml. of ether, was treated with 10 g. of 3,4-dimethoxybenzophenone, and the reaction product worked up, as for ethylene III. The yield was 7.5 g. of a product, b.p. 285°/20 mm., crystallizing from ethanol in shiny colorless prisms, m.p. 119°.

Anal. Calcd. for $C_{22}H_{19}ClO_2$: C, 75.3; H, 5.5. Found: C, 75.5; H, 5.8.

1-Bromo-1-(4-chlorophenyl)-2-phenyl-2-(3,4-dimethoxyphenyl)ethylene (V). Monohalogenation of the foregoing ethylene (1 g.) in chloroform was best performed when a less than theoretical amount of bromine (0.3 g.) was used. The yield was 0.8 g. of a compound crystallizing from ethanol in fine colorless prisms, m.p. 124°. When the theoretical quantity of bromine was used, some of the dibrominated product was obtained.

Anal. Calcd. for $C_{22}H_{18}BrClO_2$: C, 61.5; H, 4.2. Found: C, 61.4; H, 4.2.

1-Bromo-1-(4-chlorophenyl)-2-phenyl-2-(6-bromo-3,4-dimethoxyphenyl)ethylene (VI), prepared by treating either the previous ethylene with 1 mole of bromine, or ethylene IV with 2 moles of bromine, in chloroform, crystallized from ethanol in shiny colorless prisms, m.p. 168°.

Anal. Calcd. for $C_{22}H_{17}Br_2ClO_2$: C, 51.9; H, 3.3. Found: C, 52.2; H, 3.3.

2',3,4-Trimethoxybenzophenone was prepared by Friedel-Crafts condensation of 11.5 g. of 2-methoxybenzoyl chloride and 10 g. of veratrole with 10 g. of aluminum chloride in 75 ml. of carbon disulfide, in the cold. The yield was 10 g. of a pale yellow, viscous oil, b.p. 243°/18 mm.

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.6; H, 5.9. Found: C, 70.7; H, 5.9.

1-Phenyl-2-(2-methoxyphenyl)-2-(3,4-dimethoxyphenyl)-ethylene (VII) was prepared from 10 g. of the foregoing ketone and a Grignard solution made from 6.8 g. of benzyl chloride and 1.3 g. of magnesium in 100 ml. of ether. The yield was 6 g. of a product, b.p. 268–270°/15 mm., crystallizing from methanol in fine colorless prisms, m.p. 136°.

Anal. Calcd. for $C_{23}H_{22}O_3$: C, 79.7; H, 6.4. Found: C, 79.8; H, 6.5.

1-Bromo-1-phenyl-2-(2-methoxyphenyl)-2-(6-bromo-3,4-dimethoxyphenyl)ethylene (VIII). This compound was the only product which could be isolated in the bromination of 1 g. of the foregoing ethylene and 0.46 g. (1 mole) of the halogen in chloroform. The yield was 0.6 g. of a compound crystallizing from acetic acid in fine colorless prisms, m.p. 155°.

Anal. Calcd. for $C_{23}H_{20}Br_2O_3$: C, 54.8; H, 4.0. Found: C, 54.9; H, 4.0.

2-(2-Methoxybenzoyl)thiophene, prepared in the usual way from 18.5 g. of 2-methoxybenzoyl chloride, 10 g. of thiophene, and 15.5 g. of aluminum chloride in 100 ml. of carbon disulfide, was a pale yellow, viscous oil, b.p. 208°/18 mm.; yield: 10 g.

Anal. Calcd. for $C_{12}H_{10}O_2S$: C, 66.1; H, 4.6. Found: C, 66.4; H, 4.7.

1-Phenyl-2-(2-methoxyphenyl)-2-(2-thienyl)ethylene (IX), prepared from 10 g. of the foregoing ketone and a Grignard solution made from 10 g. of benzyl chloride and 1.5 g. of magnesium in 100 ml. of ether, b.p. 258°/20 mm. (5 g.), crystallized from methanol in fine colorless prisms, m.p. 70–71°.

Anal. Calcd. for $C_{19}H_{16}OS$: C, 78.1; H, 5.5. Found: C, 78.1; H, 5.6.

Bromination of this ethylene with 2 moles of bromine in chloroform solution gave a 75% yield of the compound X, which crystallized from acetic acid in fine, yellowish prisms, m.p. 90°; the same compound was formed in 30% yield when one mole of the halogen was used. This derivative was identical with a product isolated in very poor yield from the reaction of 1 mole of bromine on the crude oily ethylene prepared from benzylmagnesium chloride and 5-bromo-2-(2-methoxybenzoyl)thiophene.

Anal. Calcd. for $C_{19}H_{14}Br_2SO$: C, 50.7; H, 3.1. Found: C, 50.5; H, 3.2.

4-Methoxy-4'-phenoxybenzophenone (XI). This ketone (27 g.), prepared by Friedel-Crafts condensation of 18 g. of anisoyl chloride with 18 g. of diphenyl oxide and 15 g. of aluminum chloride in carbon disulfide, crystallized from ethanol in fine colorless prisms, m.p. 120°.

Anal. Calcd. for $C_{20}H_{16}O_3$: C, 78.9; H, 5.3. Found: C, 79.2; H, 5.5.

1-Phenyl-2-(4-methoxyphenyl)-2-(4-phenoxyphenyl)ethylene (XII). Prepared from 10.8 g. of the foregoing ketone and a solution of 8 g. of benzylmagnesium chloride in 150 ml. of ether, this olefin (7 g.) was a pale yellow viscous oil, b.p. 309–311°/18 mm.

Anal. Calcd. for $C_{27}H_{22}O_2$: C, 85.7; H, 5.9. Found: C, 86.0; H, 5.9.

1-Bromo-1-phenyl-2-(4-methoxyphenyl)-2-(4-phenoxyphenyl)ethylene (XIII), prepared from 1 g. of the foregoing ethylene and 0.42 g. of bromine in chloroform, crystallized from ethanol in shiny colorless prisms, m.p. 96°; yield: 1 g.

Anal. Calcd. for $C_{27}H_{21}BrO_2$: C, 70.9; H, 4.6. Found: C, 71.2; H, 4.9.

4-Ethyl-2'-fluorobenzophenone. To a solution of 11 g. of ethylbenzene and 16 g. of *o*-fluorobenzoyl chloride in 50 ml. of carbon disulfide, 15 g. of aluminum chloride was added in small portions, and the mixture left overnight at room temperature, then refluxed for 30 min. on the water bath. After the usual treatment, the ketone was obtained as a pale yellow oil, b.p. 210°/25 mm., n_D^{20} 1.5711.

Anal. Calcd. for $C_{15}H_{13}FO$: C, 78.9; H, 5.7. Found: C, 79.2; H, 6.0.

1-Phenyl-2-(4-ethylphenyl)-2-(2-fluorophenyl)ethylene (XIV). Prepared from 8 g. of the above ketone and a solution of 10 g. of benzylmagnesium chloride in 100 ml. of ether, this olefin (9 g.) crystallized from petroleum ether (b.p. 40–60°) in colorless prisms, m.p. 57°.

Anal. Calcd. for $C_{22}H_{19}F$: C, 87.4; H, 6.2. Found: C, 87.5; H, 6.2.

Bromination of this ethylene in chloroform, whether one or two moles of bromine were used, yielded *1-bromo-1-phenyl-2-(4-ethylphenyl)-2-(2-fluorophenyl)ethylene* (XV), crystallizing from acetic acid in fine colorless prisms, m.p. 107°.

Anal. Calcd. for $C_{22}H_{18}BrF$: C, 69.2; H, 4.7. Found: C, 69.0; H, 4.7.

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