[Contribution from the Department of Organic Chemistry, Radium Institute, University of Paris]

FLUORINE-CONTAINING DIARYL- AND TRIARYL-ETHYLENES

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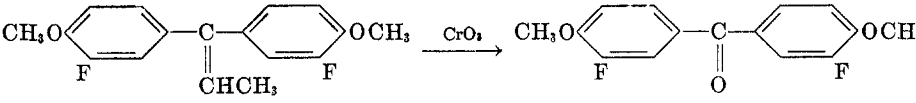
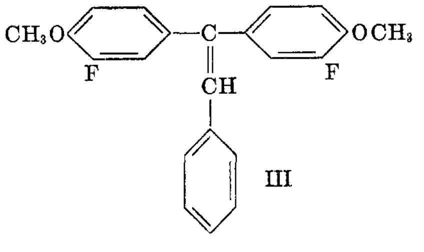
Several fluorinated aromatic compounds, such as 3-fluorotyrosine and 3-fluoro-4-hydroxyphenylacetic acid, have been used with success in the treatment of Graves-Basedow's disease (1); the estrogens have also been advocated for the treatment of this disease (2). It was therefore thought of interest to synthesize, for biological investigation, fluorine-containing estrogenic substances, of which the group of 1,1,2-triarylethylenes was especially considered in view of their well-known prolonged duration of action (3).

A convenient intermediate for such syntheses was 3,3′-difluoro-4,4′-dimethoxybenzophenone (II), readily prepared by the chromic acid oxidation of 1,1-di-(3-fluoro-4-methoxyphenyl)propene (I), which was obtained in considerable amount as a by-product in the Friedel-Crafts reaction of *o*-fluoroanisole with propionyl chloride; the formation of such symmetrical diarylethylenes is known to occur frequently when aluminum chloride is used as catalyst in the acylation of phenol ethers (4). The Grignard reaction of benzylmagnesium chloride on 3,3′-difluoro-4,4′-dimethoxybenzophenone afforded a tertiary alcohol, which was dehydrated with formic acid to 1,1-di-(3-fluoro-4-methoxyphenyl)-2-phenylethylene (III). Friedel-Crafts reaction of phenacetyl chloride on *o*-fluoroanisole in the presence of aluminum chloride in excess gave as a by-product the same ethylene. Treatment of this latter compound with chlorine or bromine led to 2-chloro- (IV) and 2-bromo-1,1-di-(3-fluoro-4-methoxyphenyl)-2-phenylethylene (V). 2-Chloro- (VII) and 2-bromo-1,1-di-(3-fluoro-4-ethoxyphenyl)-2-phenylethylene (VIII), two compounds related to the clinically employed, long-acting estrogen 2-bromo-1,1-di-(4-ethoxyphenyl)-2-phenylethylene (5), were prepared by a similar sequence of reactions, starting from 3,3′-difluoro-4,4′-diethoxybenzophenone; this latter ketone was prepared by demethylation of ketone II with pyridine hydrochloride, and ethylation of the 3,3′-difluoro-4,4′-dihydroxy-

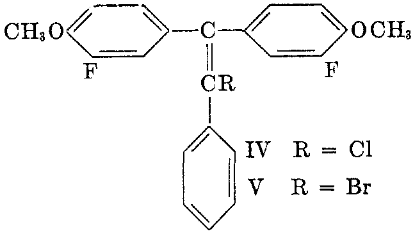


I

II



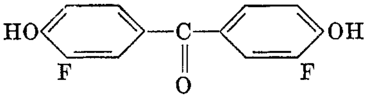
III



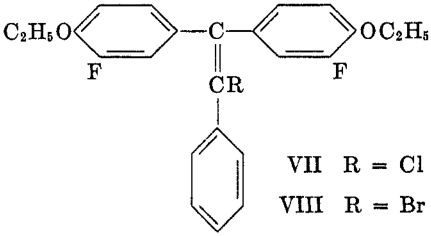
IV R = Cl

V R = Br

benzophenone (VI) thus obtained. Triarylethylenes bearing substituents on all three benzene nuclei were prepared from 3,3′-difluoro-4,4′-dimethoxybenzophenone and the Grignard reagents made from 4-methylbenzyl and 4-chloro-



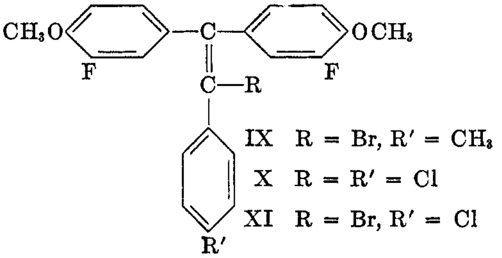
VI



VII R = Cl

VIII R = Br

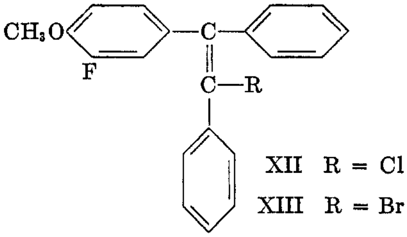
benzyl chloride; halogenation of the resulting ethylenes readily gave 2-bromo-1,1-di-(3-fluoro-4-methoxyphenyl)-2-*p*-tolyethylene (IX) on the one hand, and 2-chloro- (X) and 2-bromo-1,1-di-(3-fluoro-4-methoxyphenyl)-2-*p*-chlorophenylethylene (XI) on the other.



IX R = Br, R′ = CH₃

X R = R′ = Cl

XI R = Br, R′ = Cl



XII R = Cl

XIII R = Br

The triarylethylenes (XII) and (XIII) which bear only one fluorine atom and one methoxyl group, were obtained by halogenation of 1-(3-fluoro-4-methoxyphenyl)-1,2-diphenylethylene, prepared from 2-fluoro-4-phenacetylanisole with phenylmagnesium bromide.

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EXPERIMENTAL

1,1-Di-(3-fluoro-4-methoxyphenyl)propene (I). This substance was obtained most easily when the Friedel-Crafts reaction between *o*-fluoroanisole and propionyl chloride involved large quantities of the reagents. To a well-stirred, ice-cooled solution of 500 g. of *o*-fluoroanisole and 400 g. of propionyl chloride in 1000 ml. of dry carbon disulfide, 595 g. of aluminum chloride was added in small portions over three hours. The mixture was kept for five more hours then poured onto ice, and the organic layer was diluted with chloroform, washed with a dilute aqueous solution of sodium hydroxide, then with water, and dried over sodium sulfate. The residue from distillation of the solvents yielded on vacuum-fractionation 420 g. of *3-fluoro-4-methoxypropiophenone* (6) and 70 g. of *1,1-di-(3-fluoro-4-methoxyphenyl) propene,* b.p. 225–226°/16 mm., which crystallized from ethanol as shiny, colorless leaflets, m.p. 100°, giving a blood-red halochromation with sulfuric acid.

Anal. Calc'd for $C_{17}H_{16}F_2O_2$: C, 70.3; H, 5.5.

Found: C, 70.1; H, 5.5.

3,3′-Difluoro-4,4′-dimethoxybenzophenone (II). To a solution of 50 g. of the foregoing ethylene in 300 ml. of acetic acid, a solution of 45 g. of chromic acid in 500 ml. of acetic acid was added portionwise with stirring, whereby an exothermic reaction took place. After the reaction had subsided, the green solution was refluxed for a few minutes, and on cooling, was poured into water. The solid precipitate obtained was filtered off, washed with water, and recrystallized from ethanol. Yield: 32 g. of shiny needles, m.p. 160°, giving an orange-red halochromation with sulfuric acid.

Anal. Calc'd for $C_{15}H_{12}F_2O_3$: C, 64.7; H, 4.3.
Found: C, 64.5; H, 4.2.

3,3'-Difluoro-4,4'-dihydroxybenzophenone (VI). A mixture of 10 g. of the foregoing ketone and 40 g. of redistilled pyridine hydrochloride was gently refluxed for ten minutes; water was added on cooling, and the precipitate was filtered off, washed with water, and recrystallized from 20% aqueous acetic acid. Yield: 7.3 g. of shiny, colorless prisms, m.p. 190°, dissolving in aqueous alkalis with a yellow coloration.

Anal. Calc'd for $C_{13}H_8F_2O_3$: C, 62.4; H, 3.2.
Found: C, 62.1; H, 3.3.

Treatment of this ketone with diethyl sulfate and aqueous sodium hydroxide gave a quantitative yield of *3,3'-difluoro-4,4'-diethoxybenzophenone*, b.p. 240°/13 mm., crystallizing from ethanol as lustrous, colorless leaflets, m.p. 138°.

Anal. Calc'd for $C_{17}H_{16}F_2O_3$: C, 66.7; H, 5.2.
Found: C, 66.6; H, 5.3.

5,5'-Dibromo-3,3'-difluoro-4,4'-dihydroxybenzophenone. To a solution of 3 g. of 3,3'-difluoro-4,4'-dihydroxybenzophenone in 50% aqueous acetic acid, 3.9 g. of bromine dissolved in acetic acid was added portionwise with stirring. The precipitate obtained on dilution with water gave on recrystallization from 50% aqueous acetic acid shiny, sublimable prisms, m.p. 255°.

Anal. Calc'd for $C_{13}H_6Br_2F_2O_3$: C, 38.2; H, 1.5.
Found: C, 38.0; H, 1.6.

1,1'-Di-(3-fluoro-4-methoxyphenyl)-2-phenylethylene (III). (*a*) *By the Grignard reaction.* To a Grignard reagent made from 1.1 g. of magnesium and 5.5 g. of benzyl chloride in ether, a suspension of 10 g. of 3,3'-difluoro-4,4'-dimethoxybenzophenone in ether was added in small portions, and the mixture was refluxed for one hour on the water-bath. After decomposition with an ice-cooled 10% aqueous solution of sulfuric acid, the ethereal layer was washed with water, dried over sodium sulfate, and the solvent was removed. The crude tertiary carbinol was heated with 25 ml. of 99% formic acid for five minutes, and water was added; the ethylene formed was taken up in benzene, purified by vacuum fractionation, and recrystallized from ethanol. Yield: 4.8 g. of shiny, colorless prisms, m.p. 85°, b.p. 265–268°/15 mm., giving a deep red halochromation with sulfuric acid.

Anal. Calc'd for $C_{22}H_{18}F_2O_2$: C, 75.0; H, 5.1.
Found: C, 74.9; H, 5.1.

(b) *By the Friedel-Crafts reaction.* The same ethylene was obtained in 10% yield from *o*-fluoroanisole, phenacetyl chloride, and aluminum chloride in carbon disulfide as for the preparation of *1,1-di-*(3-fluoro-4-methoxyphenyl)propene.

2-Chloro-1,1-di-(3-fluoro-4-methoxyphenyl)-2-phenylethylene (IV). To a water-cooled solution of 1.5 g. of the foregoing ethylene in carbon tetrachloride, a solution of 0.36 g. of chlorine in 25 ml. of the same solvent was added dropwise with stirring; the residue from vacuum distillation of the solvent was recrystallized several times from ethanol, giving shiny, colorless prisms, m.p. 113°.

Anal. Calc'd for $C_{22}H_{17}ClF_2O_2$: C, 68.3; H, 4.4.
Found: C, 68.1; H, 4.5.

2-Bromo-1,1-di-(3-fluoro-4-methoxyphenyl)-2-phenylethylene (V). To a water-cooled solution of 2 g. of ethylene III in acetic acid, a solution of 1 g. of bromine in the same solvent was added dropwise with stirring; the precipitate obtained on dilution with water crystallized from ethanol as shiny, colorless needles, m.p. 122°.

Anal. Calc'd for $C_{22}H_{17}BrF_2O_2$: C, 61.3; H, 3.9.
Found: C, 61.0; H, 3.6.

1,1-Di-(3-fluoro-4-ethoxyphenyl)-2-phenylethylene was prepared as for the lower homolog, from 12 g. of 3,3′-difluoro-4,4′-diethoxybenzophenone and a Grignard reagent made from 1.1 g. of magnesium and 6 g. of benzyl chloride in ether. The yield, 6 g. of the ethylene, b.p. 272°/13 mm., crystallizing from ethanol as colorless needles, m.p. 91°, giving a deep red halochromation with sulfuric acid.

Anal. Calc'd for $C_{24}H_{22}F_2O_2$: C, 75.8; H, 5.8.
Found: C, 75.5; H, 5.8.

2-Chloro-1,1-di-(3-fluoro-4-ethoxyphenyl)-2-phenylethylene (VII) was crystallized several times from ethanol; it formed shiny, colorless prisms, m.p. 88°.

Anal. Calc'd for $C_{24}H_{21}ClF_2O_2$: C, 69.5; H, 5.1.
Found: C, 69.6; H, 5.4.

2-Bromo-1,1-di-(3-fluoro-4-ethoxyphenyl)-2-phenylethylene (VIII) was crystallized several times from ethanol; it formed colorless prisms, m.p. 86°.

Anal. Calc'd for $C_{24}H_{21}BrF_2O_2$: C, 62.7; H, 4.6.
Found: C, 62.5; H, 4.5.

1,1-Di-(3-fluoro-4-methoxyphenyl)-2-p-chlorophenylethylene was prepared in the usual way from 9 g. of ketone II and a Grignard reagent made from 0.9 g. of magnesium and 6.3 g. of *p*-chlorobenzyl chloride; yield: 5.5 g. of an ethylene, b.p. 285°/13 mm., crystallizing from ethanol as shiny, colorless prisms, m.p. 90°, giving a blood-red solution with sulfuric acid.

Anal. Calc'd for $C_{22}H_{17}ClF_2O_2$: C, 68.3; H, 4.4.
Found: C, 68.5; H, 4.2.

2-Chloro-1,1-di-(3-fluoro-4-methoxyphenyl)-2-p-chlorophenylethylene (X) was crystallized from ethanol as shiny, colorless prisms, m.p. 141°.

Anal. Calc'd for $C_{22}H_{16}Cl_2F_2O_2$: C, 62.7; H, 3.8.
Found: C, 62.4; H, 3.7.

2-Bromo-1,1-di-(3-fluoro-4-methoxyphenyl)-2-p-chlorophenylethylene (XI) was crystallized from ethanol as shiny prisms, m.p. 135°.

Anal. Calc'd for $C_{22}H_{16}BrClF_2O_2$: C, 56.7; H, 3.4.
Found: C, 56.3; H, 3.5.

2-Bromo-1,1-di-(3-fluoro-4-methoxyphenyl-2-p-tolylethylene (IX) was obtained from the bromination of the ethylene prepared from 10 g. of ketone II and a Grignard reagent made from 1 g. of magnesium and 6.1 g. of *p*-methylbenzyl chloride; it crystallized from ethanol as colorless prisms, m.p. 119°.

Anal. Calc'd for $C_{23}H_{19}BrF_2O_2$: C, 62.0; H, 4.3.
Found: C, 61.7; H, 4.1.

2-Chloro-1-(3-fluoro-4-methoxyphenyl)-1,2-diphenylethylene (XII). 1-(3-Fluoro-4-methoxyphenyl)-1,2-diphenylethylene (8 g.) was prepared from 10 g. of 2-fluoro-4-phenacetylanisole (7) and a Grignard reagent made from 1.2 g. of magnesium, and 7.7 g. of bromobenzene in ether; yield: 8 g. of an ethylene, b.p. 245–255°/13 mm. Two g. of this crude ethylene gave on treatment with 0.5 g. of chlorine in carbon tetrachloride, compound XII, which crystallized from ethanol as shiny, colorless needles, m.p. 123°, giving a brown-yellow color with sulfuric acid.

Anal. Calc'd for $C_{21}H_{16}ClFO$: C, 74.4; H, 4.7.
Found: C, 74.2; H, 4.9.

2-Bromo-1-(3-fluoro-4-methoxyphenyl)-1,2-diphenylethylene (XIII) crystallized from ethanol as colorless prisms, m.p. 121°.

Anal. Calc'd for $C_{21}H_{16}BrFO$: C, 65.8; H, 4.2.
Found: C, 65.5; H, 4.2.

SUMMARY

1. A large number of triarylethylenes containing fluorine have been prepared for biological examination as potential pituitary inhibitors.

2. Several derivatives of *o*-fluorophenol were synthesized in the course of this investigation.

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