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

FLUORINE-CONTAINING ANALOGS OF 4-HYDROXYPROPIOPHENONE

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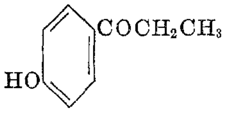
4-Hydroxypropiophenone (I), a product from the oxidative splitting of stilbestrol, with an extremely low degree of estrogenicity (1), has been found a valuable drug for checking the growth of lung metastases secondary to certain malignant tumors such as chorionepitheliomas (2) or nephroblastomas (3). It has also been found active in the control of experimental ovarian tumors in animals (4), and of various forms of Graves-Basedow's disease (5) and Riehl's melanosis in man (6). Such versatile activities might possibly be due to the incorporation of this atoxic molecule in the pattern of animal proteins of hormonal or enzymatic significance, competitively with aromatic amino acids or their metabolites. The same working hypothesis may be offered for explaining the therapeutic effects of various fluorine-containing aromatic compounds currently used against hyperthyreosis, such as 3-fluorotyrosine[1] (II) and 3-fluoro-4-hydroxyphenylacetic acid[2] (III). The ability of animal organisms to take up artificial substances in their proteins had already been experimentally demonstrated with several molecules such as the carcinogenic 4-dimethylaminoazobenzene (7) or the alkaloid mescalin, and confirmed by studies with radioactive tracers (8).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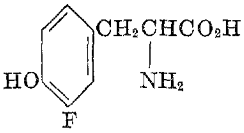
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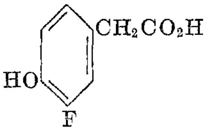
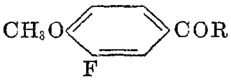
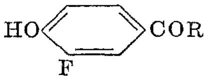

III

With a view to obtaining analogs of 4-hydroxypropiophenone[3] of greater therapeutic value and with even less estrogenic activity, several new fluorine-containing aromatic hydroxy ketones were prepared for biological investigation. *o*-Fluoroanisole readily underwent Friedel-Crafts acylations to give, not only the known 3-fluoro-4-methoxyacetophenone (9), but also 3-fluoro-4-methoxypropiophenone (V) and 3-fluoro-4-methoxy-*n*-butyrophenone (VI); demethylation to the corresponding hydroxy ketones (VII, VIII, and IX) was as readily



IV R = CH_2Br
V R = CH_2CH_3
VI R = $CH_2CH_2CH_3$



VII R = CH_3
VIII R = CH_2CH_3
IX R = $CH_2CH_2CH_3$

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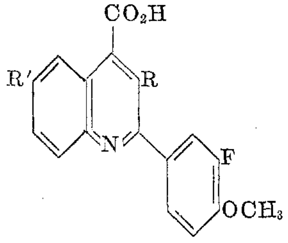
[1] Marketed in Germany by I. G. Farbenindustrie under the name "Pardinon."

[2] Marketed in Germany by Knoll A. G. under the name "Capacin."

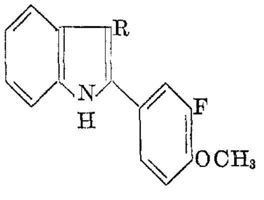
[3] Marketed in Europe by Laroche-Navarron Laboratories under the name "Frenantol."

effected with pyridine hydrochloride as for 4-hydroxypropiophenone itself (1). On the other hand, an attempt to demethylate 3-iodo-4-methoxypropiophenone was unsuccessful, and resulted in extensive dehalogenation.

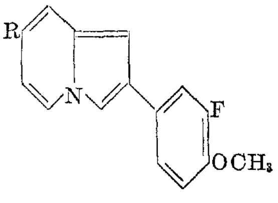
In the course of this research, a number of new nitrogen-containing fluoro compounds of potential biological interest were synthesized from the foregoing ketones. 2-(3′-Fluoro-4′-methoxyphenyl)cinchoninic acid (X) and its 3-methyl (XI) and 3-ethyl (XII) homologs were prepared from ketones IV, V, and VI and isatin by a Pfitzinger condensation; the same reaction, performed with 5-bromoisatin, yielded 6-bromo-2-(3′-fluoro-4′-methoxyphenyl)cinchoninic acid (XIII) and its 3-methyl (XIV) and 3-ethyl (XV) homologs in high yield; 6-methyl-2-(3′-fluoro-4′-methoxyphenyl)cinchoninic acid (XVI) and 6-chloro-3-methyl-2-(3′-fluoro-4′-methoxyphenyl)cinchoninic acid (XVII) were similarly obtained with 5-methyl- and 5-chloro-isatin. These compounds are halogenated derivatives of atophan, and are of biological interest as potential cirrhogenic agents for the liver. Thermal decarboxylation of these acids resulted in the corresponding quinoline bases.



X R = R′ = H
XI R = CH_3, R′ = H
XII R = CH_2CH_3, R′ = H
XIII R = H, R′ = Br
XIV R = CH_3, R′ = Br
XV R = CH_2CH_3, R′ = Br
XVI R = H, R′ = CH_3
XVII R = CH_3, R′ = Cl



XVIII R = H
XIX R = CH_3
XX R = CH_2CH_3



XXI R = H
XXII R = CH_3

Indolization of the phenylhydrazones of 3-fluoro-4-methoxyacetophenone and its homologs (V) and (VI) readily gave 2-(3′-fluoro-4′-methoxyphenyl)indole (XVIII) and its 3-methyl (XIX) and 3-ethyl (XX) homologs respectively. 3-Fluoro-4-methoxy-ω-bromoacetophenone (IV) underwent a Tschitschibabin reaction with α-picoline and 2,4-lutidine (10) to give respectively 2-(3′-fluoro-4′-methoxyphenyl)pyrrocoline (XXI) and its 7-methyl homolog (XXII). 3-Fluoro-4-methoxyacetophenone was found to be a convenient intermediate for the preparation of 3-fluoro-4-methoxyaniline (11), by Beckmann rearrangement of its oxime.

EXPERIMENTAL[4]

Preparation of intermediates. An ice-cooled solution of 19 g. of *o*-fluoroanisole (prepared from *o*-anisidine by the Schiemann reaction) and 13 g. of acetyl chloride in 150 ml. of carbon disulfide, was treated with 22.5 g. of finely-powdered aluminum chloride in small portions with vigorous shaking. The mixture was kept 5 hours at room temperature, and decomposed with ice; the reaction product was taken up in chloroform, washed with a dilute aqueous solution of sodium hydroxide, then with water, and dried over sodium sulfate; the solvent was removed, and the residue vacuum-distilled. Yield, 23 g. (92%) of 3-fluoro-4-methoxyacetophenone, b.p. 147–148°/20 mm., crystallizing from ethanol in shiny colorless needles, m.p. 90° (lit. 92°). The corresponding *oxime* had b.p. 175°/15 mm., and formed from benzene shiny colorless prisms, m.p. 99°.

Anal. Calc'd for $C_9H_{10}FNO_2$: C, 59.0; H, 5.5.
Found: C, 58.8; H, 5.3.

The *2,4-dinitrophenylhydrazone* crystallized from acetic acid in red prisms, m.p. 256°; the *semicarbazone* formed shiny colorless prisms from ethanol, decomposing above 235°, and melting at 248°.

Preparation of 3-fluoro-4-methoxyaniline. To an ice-cooled solution of 9.5 g. of 3-fluoro-4-methoxyacetophenone oxime in anhydrous ether, 12 g. of finely powdered phosphorus pentachloride was added in small portions; the mixture was shaken for 30 minutes, and poured on ice. The ethereal layer was washed with water and dried over sodium sulfate; the solid obtained after removal of solvent was crystallized from benzene, giving 3-fluoro-4-methoxyacetanilide (11) as colorless prisms, m.p. 112°, in 90% yield. A mixture of 7 g. of this amide and 50 ml. of concentrated hydrochloric acid was refluxed for 30 minutes, and the resultant clear solution on cooling yielded a precipitate of *3-fluoro-4-methoxyaniline hydrochloride* as silky colorless needles; the free *base* (11) obtained by treatment with aqueous sodium hydroxide had b.p. 135°/18 mm., and crystallized from petroleum ether in colorless prisms, m.p. 83°. It was further characterized by its condensation product with 2,3-dichloro-1,4-naphthoquinone (12); *2-chloro-3-(3'-fluoro-4'-methoxyanilino)-1,4-naphthoquinone* crystallized from propanol as dark red needles, m.p. 251°.

Anal. Calc'd for $C_{17}H_{11}ClFNO_3$: N, 4.2. Found: N, 4.1.

3-Fluoro-4-hydroxyacetophenone (VII). A mixture of 7 g. of 3-fluoro-4-methoxyacetophenone and 20 g. of pyridine hydrochloride was refluxed for 15 minutes, and poured on ice; the solid obtained on standing was collected, washed with water, and crystallized from benzene. Yield, 5 g. of silky colorless needles, m.p. 125°, soluble in aqueous sodium hydroxide to give a yellow solution.

Anal. Calc'd for $C_8H_7FO_2$: C, 62.3; H, 4.5.
Found: C, 62.2; H, 4.5.

The corresponding *semicarbazone* crystallized from benzene in shiny colorless prisms, decomposing above 220°, m.p. 237°.

Anal. Calc'd for $C_9H_{10}FN_3O_2$: N, 19.9. Found: N, 19.7.

The *2,4-dinitrophenylhydrazone* formed red needles, m.p. 299°, from acetic acid.

3-Fluoro-4-methoxypropiophenone (V). To an ice-cooled, well-stirred mixture of 100 g. of *o*-fluoroanisole, 280 g. of finely powdered aluminum chloride, and 300 ml. of carbon disulfide, 90 g. of propionic anhydride was added dropwise; the reaction mixture was kept overnight at room temperature, and treated in the usual way. Yield, 85 g. of a ketone, b.p. 160–162°/15 mm., crystallizing from methanol in silky colorless leaflets, m.p. 86°.

Anal. Calc'd for $C_{10}H_{11}FO_2$: C, 65.9; H, 6.0.
Found: C, 65.8; H, 6.0.

Its *oxime* had b.p. 219–220°/18 mm., and formed long shiny needles, m.p. 84°, from methanol.

Anal. Calc'd for $C_{10}H_{12}FNO_2$: N, 7.1. Found: N, 7.0.

The *semicarbazone* crystallized from ethanol in shiny, colorless prisms, m.p. 216°; the

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[4] The biological properties of the substances described in this work are being investigated in this Institute under Professor A. Lacassagne.

2,4-dinitrophenylhydrazone separated from acetic acid as shiny red prisms, m.p. 212°, and the *thiosemicarbazone* formed shiny colorless needles, m.p. 187°, from ethanol.

3-Fluoro-4-hydroxypropiophenone (VIII) was prepared from the ketone V and pyridine hydrochloride as for the lower homolog; it crystallized as silky colorless needles, m.p. 109–110°, from water.[5]

Anal. Calc'd for $C_9H_9FO_2$: C, 64.3; H, 5.4.

Found: C, 64.1; H, 5.3.

The corresponding *2,4-dinitrophenylhydrazone* formed slender, dark red prisms, m.p. 260–261°, from acetic acid.

Anal. Calc'd for $C_{15}H_{13}FN_4O_5$: N, 16.1. Found: N, 15.8.

3-Iodo-4-methoxypropiophenone was prepared in 75% yield from *o*-iodoanisole, aluminum chloride, and propionic anhydride in carbon disulfide as for the corresponding fluoro ketone; it crystallized as silky colorless needles, m.p. 95°, b.p. about 170°/2 mm., from ethanol.

Anal. Calc'd for $C_{10}H_{11}IO_2$: C, 41.4; H, 3.8.

Found: C, 41.6; H, 4.0.

The corresponding *semicarbazone* crystallized as lustrous colorless leaflets, m.p. 219–220°, from ethanol.

Anal. Calc'd for $C_{11}H_{14}IN_3O_2$: N, 12.1. Found: N, 12.3.

Attempts to demethylate this ketone with pyridine hydrochloride or hydrobromic acid resulted in the liberation of iodine and the formation of untractable resins.

3-Fluoro-4-methoxy-n-butyrophenone (VI) was prepared in 90% yield from 29 g. of *o*-fluoroanisole, 27 g. of *n*-butyryl chloride, and 35 g. of aluminum chloride in 200 ml. of carbon disulfide; it had b.p. 161–162°/16 mm., and crystallized from petroleum ehter (b.p. 60–80°) as silky colorless needles, m.p. 55°.

Anal. Calc'd for $C_{11}H_{13}FO_2$: C, 67.3; H, 6.6.

Found: C, 67.2; H, 6.8.

The corresponding *semicarbazone* formed shiny colorless needles, decomposing above 187° and melting at 208°, from ethanol; the *2,4-dinitrophenylhydrazone* crystallized as shiny red needles, m.p. 188°, from a mixture of ethanol and benzene.

Anal. Calc'd for $C_{17}H_{17}FN_4O_5$: N, 14.9. Found: N, 14.6.

3-Fluoro-4-hydroxy-n-butyrophenone (IX). A mixture of 3 g. of ketone VI and 10 g. of pyridine hydrochloride was refluxed until a homogeneous solution was obtained, then for a further five minutes; the reaction product was poured on ice, and the precipitate was collected, washed with water, and crystallized from cyclohexane. Yield, 20 g. of silky colorless needles, m.p. 90°.

Anal. Calc'd for $C_{10}H_{11}FO_2$: C, 65.9; H, 6.0.

Found: C, 65.6; H, 6.1.

The corresponding *2,4-dinitrophenylhydrazone* separated from benzene as red needles, m.p. 222°; the *semicarbazone* formed colorless needles, m.p. 196°, from a mixture of ethanol and benzene.

Anal. Calc'd for $C_{11}H_{14}FN_3O_2$: N, 17.6. Found: N, 17.4.

2-(3'Fluoro-4'-methoxyphenyl)indole (XVIII). A mixture of 3 g. of 3-fluoro-4-methoxyacetophenone and 3 g. of phenylhydrazine was heated at 120–130° until evolution of water had ceased; 5 g. of finely powdered fused zinc chloride was added, and the mixture heated until a vigorous reaction set up. After five minutes' further heating at 170–180°, aqueous acetic acid was added, and the indole formed was taken up in benzene; after recrystallization from ethanol, it formed shiny colorless needles, m.p. 187°.

Anal. Calc'd for $C_{15}H_{12}FNO$: C, 74.7; H, 5.0.

Found: C, 74.5; H, 5.2.

3-Methyl-2-(3'-fluoro-4'-methoxyphenyl)indole (XIX). A solution of 3 g. of the crude phenylhydrazone of 3-fluoro-4-methoxypropiophenone (prepared as for the lower homolog) in acetic acid saturated with hydrogen chloride was refluxed for two minutes, and poured

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[5] This substance lowered the basal metabolic rate in some patients suffering from Graves-Basedow's disease (Private communication from Prof. M. Perrault, Paris).

into water; the indole formed was taken up in benzene, washed with water, dried over sodium sulfate, and purified by vacuum-distillation. Yield, 2 g. of an indole, b.p. 242–244°/20 mm., crystallizing as shiny colorless prisms, m.p. 122°, from methanol.

Anal. Calc'd for $C_{16}H_{14}FNO$: C, 75.3; H, 5.5.
Found: C, 75.1; H, 5.8.

3-Ethyl-2-(3'-fluoro-4'-methoxyphenyl)indole (XX) was similarly prepared from the phenylhydrazone of ketone VI; it crystallized as shiny, colorless prisms, m.p. 113°, from methanol.

Anal. Calc'd for $C_{17}H_{16}FNO$: C, 75.8; H, 5.9.
Found: C, 75.6; H, 5.8.

2-(3'-Fluoro-4'-methoxyphenyl)cinchoninic acid (X). A solution of 2 g. of ketone IV, 1.5 g. of isatin, and 1.7 g. of potassium hydroxide (in 2 ml. of water) in 12 ml. of ethanol was refluxed for 12 hours. The reaction product was diluted with water, the neutral impurities were removed by ether extraction, and the aqueous layer was acidified with acetic acid. Recrystallization of the precipitate from ethanol yielded 2.5 g. of colorless needles, m.p. 232°.

Anal. Calc'd for $C_{17}H_{12}FNO_3$: C, 68.7; H, 4.0.
Found: C, 68.5; H, 4.2.

2-(3'-Fluoro-4'-methoxyphenyl)quinoline, obtained by heating the foregoing acid above its melting point and vacuum-distilling the residue, formed colorless prisms, m.p. 105°, from methanol; the *picrate* separated from ethanol as yellow needles, m.p. 190°.

Anal. Calc'd for $C_{16}H_{12}FNO$: N, 5.5. Found: N, 5.6.

6-Bromo-2-(3'-fluoro-4'-methoxyphenyl)cinchoninic acid (XIII) was obtained in 90% yield from ketone IV and 5-bromoisatin; it formed pale yellow needles, m.p. > 355°, from a mixture of ethanol and benzene.

Anal. Calc'd for $C_{17}H_{11}BrFNO_3$: C, 54.3; H, 2.9.
Found: C, 54.0; H, 3.1.

The corresponding *6-bromo-2-(3'-fluoro-4'-methoxyphenyl)quinoline* crystallized as colorless needles, m.p. 186°, from ethanol.

Anal. Calc'd for $C_{16}H_{11}BrFNO$: N, 4.2. Found: N, 4.1.

3-Methyl-2-(3'-fluoro-4'-methoxyphenyl)cinchoninic acid (XI) formed pale yellow needles, m.p. 312°, from ethanol.

Anal. Calc'd for $C_{18}H_{14}FNO_3$: C, 69.5; H, 4.5.
Found: C, 69.3; H, 4.6.

6-Bromo-3-methyl-2-(3'-fluoro-4'-methoxyphenyl)cinchoninic acid (XIV) crystallized as pale yellow needles, m.p. 315°, from a mixture of ethanol and benzene.

Anal. Calc'd for $C_{18}H_{13}BrFNO_3$: C, 55.4; H, 3.3.
Found: C, 55.2; H, 3.6.

6-Bromo-3-methyl-2-(3'-fluoro-4'-methoxyphenyl)quinoline formed shiny, pale yellow prisms, m.p. 136°, from methanol (*picrate*, m.p. 187°).

Anal. Calc'd for $C_{17}H_{13}BrFNO$: N, 4.0. Found: N, 3.8.

3-Ethyl-2-(3'-fluoro-4'-methoxyphenyl)cinchoninic acid (XII) crystallized as colorless needles, m.p. 267°, from a mixture of ethanol and benzene.

Anal. Calc'd for $C_{19}H_{16}FNO_3$: C, 70.2; H, 4.9.
Found: C, 70.0; H, 5.0.

6-Bromo-3-ethyl-2-(3'-fluoro-4'-methoxyphenyl)cinchoninic acid (XV) formed pale yellow prisms, m.p. 296°, from a mixture of ethanol and benzene.

Anal. Calc'd for $C_{19}H_{15}BrFNO_3$: C, 56.4; H, 3.7.
Found: C, 56.5; H, 4.0.

6-Bromo-3-ethyl-2-(3'-fluoro-4'-methoxyphenyl) quinoline crystallized from ethanol in silky colorless prisms, m.p. 125°; its *picrate* had m.p. 181°.

Anal. Calc'd for $C_{18}H_{15}BrFNO$: N, 3.9. Found: N, 4.0.

6-Methyl-2-(3'-fluoro-4'-methoxyphenyl)cinchoninic acid (XVI) formed pale yellow prisms from ethanol, m.p. 248–249°.

Anal. Calc'd for $C_{18}H_{14}FNO_3$: C, 69.5; H, 4.5.
Found: C, 69.4; H, 4.4.

6-Chloro-3-methyl-2-(3'-fluoro-4'-methoxyphenyl)cinchoninic acid (XVII) formed silky colorless needles, m.p. 328° from benzene.

Anal. Calc'd for $C_{18}H_{13}ClFNO_3$: C, 62.5; H, 3.8.
Found: C, 62.2; H, 4.0.

3-Fluoro-4-methoxy-ω-bromoacetophenone (IV). To a cooled solution of 7 g. of 3-fluoro-4-methoxyacetophenone in chloroform, 7 g. of bromine (in chloroform solution) was added in small portions with stirring; the reaction product was washed with an aqueous solution of sodium hydrogen carbonate, dried over sodium sulfate, and the solvent distilled off. The residue crystallized from cyclohexane in colorless prisms, m.p. 76°; yield, 96%.

Anal. Calc'd for $C_9H_8BrFO_2$: C, 43.7; H, 3.2.
Found: C, 43.7; H, 3.5.

2-(3'-Fluoro-4'-methoxyphenyl)pyrrocoline (XXI). A solution of 2 g. of the foregoing ω-bromo ketone and 2 g. of α-picoline in 15 ml. of ethanol was heated at 70° for 15 minutes, and the solvent was removed by vacuum distillation. An aqueous solution of the crystalline quaternary picolinium compound thus obtained was boiled for five minutes with 5 g. of sodium hydrogen carbonate; the pyrrocoline which separated in theoretical yield formed lustrous colorless leaflets, m.p. 197°, from benzene.

Anal. Calc'd for $C_{15}H_{12}FNO$: C, 74.7; H, 5.0.
Found: C, 74.6; H, 5.0.

7-Methyl-2-(3'-fluoro-4'-methoxyphenyl)pyrrocoline (XXII) was similarly prepared from 2,4-lutidine; it formed lustrous colorless leaflets, m.p. 209°, from ethanol.

Anal. Calc'd for $C_{16}H_{14}FNO$: C, 75.3; H, 5.5.
Found: C, 75.1; H, 5.6.

SUMMARY

1. Several fluorine-containing analogs of 4-hydroxypropiophenone have been prepared for testing as potential inhibitors of the growth of cancer metastases.

2. In the course of this research, a number of fluorinated indoles, quinolines, and pyrrocolines have been synthesized.

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