[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, RADIUM INSTITUTE, UNIVERSITY OF PARIS]

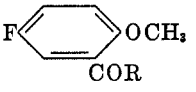
SOME SYNTHESES FROM *p*-FLUOROANISOLE

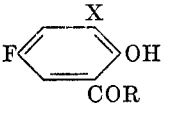
NG. PH. BUU-HOÏ, DENISE LAVIT, AND NG. D. XUONG

Received April 21, 1954

The chemistry of fluorine-containing organic compounds has frequently been studied with a view to preparing substances of possible medicinal interest (1). In particular, *o*-fluoroanisole was recently investigated by Minor and Vanderwerf (2) and by Buu-Hoï, Xuong, and Lavit (3). The present work is an extension of this line of research to *p*-fluoroanisole, which is readily available by a Schiemann reaction (4), and which proved a convenient intermediate for many syntheses.

Whereas Suter, Lawson, and Smith (5) reported the failure of *p*-fluorophenetole to give the expected ketones in Friedel-Crafts reactions, *p*-fluoroanisole has now been found to give readily 5-fluoro-2-methoxyacetophenone (I), 5-fluoro-2-methoxypropiophenone (II), 5-fluoro-2-methoxybenzophenone (III), and 4-fluoro-2-phenacetylanisole (IV). More conveniently and with better yields





I R = CH_3
II R = C_2H_5
III R = C_6H_5
IV R = $CH_2C_6H_5$
V R = CH_2Br

VI X = Cl, R = CH_3
VII X = Br, R = CH_3
VIII X = Br, R = C_2H_5
IX X = Cl, R = $CH_2C_6H_5$
X X = Br, R = $CH_2C_6H_5$

than by the Fries reaction used by Suter, Lawson, and Smith, and more recently by Kindler and Oelschläger (6), 4-fluoro-2-acylphenols were obtained by demethylation of these ketones with pyridine hydrochloride (7); it is noteworthy that this reagent failed to demethylate *p*-fluoroanisole itself. Phenolic ketones bearing two kinds of halogens were prepared by chlorination or bromination of the fluorohydroxy ketones obtained above (Table I). In these halogenations, no displacement of a fluorine atom by another halogen was observed, while *p*-fluorophenetole is known to give 2,4-dibromophenetole on bromination (5).

5-Fluoro-2-methoxyacetophenone is likewise a convenient intermediate for various preparations. Oxidation with sodium hypobromite gave 5-fluoro-2-methoxybenzoic acid, previously synthesized by Suter and Weston (8) and Gilman, Langham, and Moore (9) by more complicated methods; demethylation of this acid with hydrobromic acid gave 5-fluorosalicylic acid, from which 5-fluorosalicylhydrazide (XI) was prepared in view of the tuberculostatic activity of its chloro analog (10). 5-Fluoro-2-methoxyaniline (XII) was readily accessible through Beckmann rearrangement of the oxime of 5-fluoro-2-methoxyacetophenone; Corse and Ingraham (11) had prepared this amine from 4-fluoro-2-nitrophenol, but described only its hydrochloride.

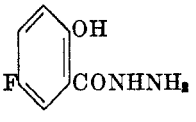
TABLE I

NEW FLUORO KETONES PREPARED FROM *p*-FLUOROANISOLE

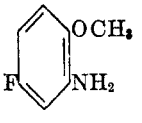
Substance	Formula	m.p., °C.	Analyses			
			Calc'd		Found	
			C	H	C	H
5-Fluoro-2-methoxybenzophenone[a]	$C_{14}H_{11}FO_2$	80	73.0	4.8	73.2	5.1
5-Fluoro-2-hydroxybenzophenone[b]	$C_{13}H_9FO_2$	77	72.2	4.2	72.0	4.2
4-Fluoro-2-phenacetylanisole[c]	$C_{15}H_{13}FO_2$	55	73.8	5.3	73.7	5.2
4-Fluoro-2-phenacetylphenol	$C_{14}H_{11}FO_2$	84	73.0	4.8	73.0	4.9
5-Fluoro-2-methoxy-ω-bromoacetophenone[d]	$C_9H_8BrFO_2$	79	43.7	3.2	43.4	3.2
3-Chloro-5-fluoro-2-hydroxyacetophenone	$C_8H_6ClFO_2$	84	50.9	3.2	50.7	3.1
3-Bromo-5-fluoro-2-hydroxyacetophenone	$C_8H_6BrFO_2$	97	41.2	2.6	41.0	2.9
3-Bromo-5-fluoro-2-hydroxypropiophenone	$C_9H_8BrFO_2$	85	43.7	3.2	43.4	3.0
6-Chloro-4-fluoro-2-phenacetylphenol	$C_{14}H_{10}ClFO_2$	122	63.5	3.8	63.3	3.8
6-Bromo-4-fluoro-2-phenacetylphenol	$C_{14}H_{10}BrFO_2$	130	54.4	3.2	54.3	3.1

[a] B.p. 186–192°/15 mm. [b] All the hydroxyketones crystallized from aqueous acetic acid as shiny, yellowish prisms, giving yellow alkaline solutions. Chlorination and bromination were performed in aqueous acetic acid medium. [c] B.p. 204–205°/18 mm.; recrystallized from ethanol. [d] Crystallized from ligroin as shiny, colorless needles.

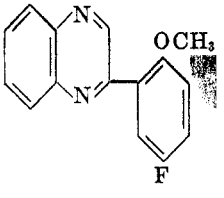
In the field of heterocyclics, reaction of ω-bromo-5-fluoro-2-methoxyacetophenone (V) with *o*-phenylenediamine (12) resulted in 2-(5-fluoro-2-methoxyphenyl)quinoxaline (XIII); from the same ω-bromo ketone and 2-methyl- and



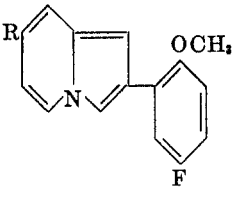
XI



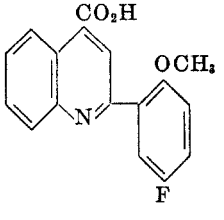
XII



XIII

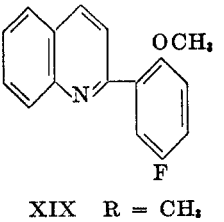


XIV R = H
XV R = CH_3



XVI R = H
XVII R = CH_3
XVIII R = C_6H_5

→



XIX R = CH_3
XX R = C_6H_5

2,4-dimethyl-pyridine, 2-(5-fluoro-2-methoxyphenyl)pyrrocoline (XIV) and 7-methyl-2-(5-fluoro-2-methoxyphenyl)pyrrocoline (XV) were prepared by the Tschitschibabin reaction (13). The Pfitzinger condensation of isatin with ketones I, II, and IV gave 2-(5-fluoro-2-methoxyphenyl)cinchoninic acid (XVI) and its 3-methyl (XVII) and 3-phenyl (XVIII) derivative, which are analogs of atophan. Thermal decarboxylation of the two latter acids afforded 3-methyl- (XIX) and 3-phenyl-2-(5-fluoro-2-methoxyphenyl)quinoline (XX).

EXPERIMENTAL

5-Fluoro-2-methoxyacetophenone (I). To an ice-cooled solution of 50 g. of *p*-fluoroanisole and 34 g. of acetyl chloride in 200 ml. of dry carbon disulfide, 58 g. of finely powdered aluminum chloride was added portionwise with stirring. The mixture was kept for five hours, then poured on ice-cooled dilute hydrochloric acid, and chloroform was added; the organic layer was washed with water, then several times with an aqueous solution of sodium hydroxide, to remove the phenolic by-products. After drying over sodium sulfate and removal of solvent, the residue was vacuum-fractionated, giving 36 g. of *5-fluoro-2-methoxyacetophenone*, b.p. 128°/15 mm., n_D^{23} 1.5220, which solidified to a colorless crystalline mass, melting at about 23°.

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

Found: C, 64.3; H, 5.5.

5-Fluoro-2-hydroxyacetophenone. (*a*). The yellow alkaline solutions from the above-mentioned operation gave on acidification with hydrochloric acid 2 g. of *5-fluoro-2-hydroxyacetophenone*, crystallizing from ligroin as yellowish prisms, m.p. 57°; lit. (5), m.p. 56–56.5°.

(*b*). A mixture of 70 g. of redistilled pyridine hydrochloride and 25 g. of 5-fluoro-2-methoxyacetophenone was gently refluxed for 15 minutes until homogeneous; water was added after cooling, and the reaction product taken up in chloroform, washed with water, and dried over sodium sulfate. After removal of solvent and vacuum-distillation of the residue, 17 g. of the *hydroxy ketone*, b.p. 103–104°/13 mm., was obtained.

5-Fluoro-2-methoxypropiophenone (II) was prepared as for the lower homolog, except that the reaction mixture was kept overnight at room temperature before decomposition; this *ketone* was a colorless oil, b.p. 132°/13 mm., n_D^{23} 1.5175.

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

Found: C, 65.8; H, 6.0.

Demethylation of 5 g. of this ketone with 15 g. of pyridine hydrochloride gave 3.5 g. of *5-fluoro-2-hydroxypropiophenone*, b.p. 111–112°/13 mm., which crystallized from ligroin as colorless prisms, m.p. 32°; lit. (5), m.p. 30.5°.

5-Fluorosalicylic acid. 5-Fluoro-2-methoxyacetophenone (20 g.) was shaken for 20 minutes with a solution of sodium hypobromite made from 20 ml. of bromine and 38.7 g. of sodium hydroxide in 250 ml. of iced water. The reaction was completed by a brief heating at 60°, the oxidizing agent in excess was destroyed with sodium hydrogen sulfite, and the neutral impurities were removed by ether extraction. The precipitate obtained on acidification with hydrochloric acid gave on recrystallization from benzene 12 g. of *5-fluoro-2-methoxybenzoic acid*, m.p. 89°. A solution of 5 g. of this acid in 50 g. of acetic acid was refluxed for five hours with 50 g. of 40% hydrobromic acid; addition of water after cooling gave a precipitate of 4 g. of *5-fluorosalicylic acid*, crystallizing from water as long, colorless needles, m.p. 180°, subliming above 150°; lit. (8), m.p. 178.5–179.5°. *Ethyl 5-fluorosalicylate* was a colorless oil, b.p. 110°/16 mm., n_D^{22} 1.5070, with an aromatic odor.

Anal. Calc'd for $C_9H_9FO_3$: C, 58.7; H, 4.9.

Found: C, 58.5; H, 4.9.

5-Fluoro-2-acetoxybenzoic acid (5-fluoroaspirin), prepared by refluxing for 15 minutes a solution of 1 g. of 5-fluorosalicylic acid in 5 ml. of acetyl chloride, crystallized from benzene as shiny, colorless needles, m.p. 138°; Suter and Weston (8) prepared this compound with acetic anhydride and sulfuric acid, and gave m.p. 130–131°.

5-Fluorosalicylhydrazide (XI). A solution of 1.5 g. of ethyl 5-fluorosalicylate and 0.5 g. of 95% hydrazine hydrate in ethanol was refluxed for 20 hours; the precipitate obtained on cooling crystallized from ethanol as shiny, colorless, sublimable prisms, m.p. 197°.

Anal. Calc'd for $C_7H_7FN_2O_2$: N, 16.5. Found: N, 16.4.

Salicylaldehyde 5-fluorosalicylhydrazone crystallized from ethanol as fine yellowish prisms, m.p. 309–310° (sublimation above 300°).

Anal. Calc'd for $C_{14}H_{11}FN_2O_3$: N, 10.2. Found: N, 9.9.

Preparation of 5-fluoro-2-methoxyaniline (XII). *5-Fluoro-2-methoxyacetophenone oxime* crystallized from aqueous methanol as colorless needles, m.p. 125°.

Anal. Calc'd for $C_9H_{10}FNO_2$: C, 59.0; H, 5.5.
Found: C, 58.8; H, 5.6.

To an ice-cooled suspension of 8.5 g. of this oxime in dry ether, 10 g. of phosphorus pentachloride was added portionwise with stirring. The mixture was shaken for 20 minutes more, and the solution thus obtained was poured on ice, and the organic layer washed with water and dried over sodium sulfate; *5-fluoro-2-methoxyacetanilide*, obtained in 95% yield on evaporation of the solvent, crystallized from cyclohexane as shiny, colorless prisms, m.p. 102°.

Anal. Calc'd for $C_9H_{10}FNO_2$: C, 59.0; H, 5.5.
Found: C, 58.9; H, 5.5.

This amide was converted into *5-fluoro-2-methoxyaniline hydrochloride* by heating for 30 minutes with hydrochloric acid, and basification gave *5-fluoro-2-methoxyaniline* as a pale yellow oil, b.p. 113°/15 mm., n_D^{22} 1.5450.

Anal. Calc'd for C_7H_8FNO: C, 59.6; H, 5.7.
Found: C, 59.6; H, 5.6.

Condensation of this amine with equimolecular amounts of 2,3-dichloro-1,4-naphthoquinone in ethanol (14) yielded *2-(5-fluoro-2-methoxyanilino)-3-chloro-1,4-naphthoquinone*, crystallizing from methanol as brown-red needles, m.p. 173°.

Anal. Calc'd for $C_{17}H_{11}ClFNO_3$: C, 61.5; H, 3.3.
Found: C, 61.2; H, 3.1.

2-(5-Fluoro-2-methoxyphenyl)quinoxaline (XIII). A solution of 1 g. of ω-bromo-5-fluoro-2-methoxyacetophenone and 0.45 g. of *o*-phenylenediamine in 20 ml. of ethanol was refluxed for two hours with some sodium acetate. The precipitate obtained on cooling crystallized from methanol as shiny, pale yellow needles (0.7 g.), m.p. 117°.

Anal. Calc'd for $C_{15}H_{11}FN_2O$: N, 11.0. Found: N, 10.8.

2-(5-Fluoro-2-methoxyphenyl)pyrrocoline (XIV). A solution of 1.5 g. of ω-bromo-5-fluoro-2-methoxyacetophenone and 0.6 g. of α-picoline in 10 ml. of ethanol was heated at 60° for 30 minutes; addition of ether gave a precipitate of the quaternary picolinium compound, which was dissolved in an aqueous solution of sodium hydrogen carbonate. A brief boiling of the solution produced the precipitation of an oil, which solidified on cooling; crystallization from methanol gave a 70% yield of lustrous, colorless leaflets, m.p. 56°.

Anal. Calc'd for $C_{15}H_{12}FNO$: C, 74.7; H, 5.0.
Found: C, 74.4; H, 5.1.

7-Methyl-2-(5-fluoro-2-methoxyphenyl)pyrrocoline (XV) was similarly prepared with 2,4-lutidine; it crystallized from methanol as shiny, colorless leaflets, m.p. 74°.

Anal. Calc'd for $C_{16}H_{14}FNO$: C, 75.3; H, 5.5.
Found: C, 75.4; H, 5.5.

2-(5-Fluoro-2-methoxyphenyl)cinchoninic acid (XVI). A solution of 2 g. of 5-fluoro-2-methoxyacetophenone, 2 g. of isatin, and 2 g. of potassium hydroxide in 15 ml. of ethanol was refluxed for 24 hours. Water was added after cooling, the neutral impurities were removed by ether extraction, and the aqueous solution was acidified with acetic acid. The precipitate was crystallized from ethanol, giving 2.8 g. of yellow needles, m.p. 200–202°.

Anal. Calc'd for $C_{17}H_{12}FNO_3$: C, 68.7; H, 4.0.
Found: C, 68.6; H, 4.1.

3-Methyl-2-(5-fluoro-2-methoxyphenyl)cinchoninic acid (XVII) was obtained in 85%

yield from ketone II; it crystallized from ethanol as colorless needles, m.p. 326°, sublimable above 295°.

Anal. Calc'd for $C_{18}H_{14}FNO_3$: C, 69.5; H, 4.5.
Found: C, 69.2; H, 4.5.

3-Methyl-2-(5-fluoro-2-methoxyphenyl)quinoline (XIX) was prepared by heating the foregoing acid above its melting point, and distilling the residue in a vacuum; it crystallized from ligroin as colorless prisms, m.p. 89°.

Anal. Calc'd for $C_{17}H_{14}FNO$: N, 5.2. Found: N, 5.1.

The corresponding *picrate* crystallized from ethanol as deep yellow prisms, m.p. 185°.

3-Phenyl-2-(5-fluoro-2-methoxyphenyl)cinchoninic acid (XVIII) was prepared in almost theoretical yield from 2 g. of ketone IV, 1.3 g.of isatin, and 1.4 g. of potassium hydroxide in ethanol; it crystallized from ethanol as colorless prisms, m.p. 298°.

Anal. Calc'd for $C_{23}H_{16}FNO_3$: C, 74.0; H, 4.3.
Found: C, 73.9; H, 4.5.

3-Phenyl-2-(5-fluoro-2-methoxyphenyl)quinoline (XX) crystallized from ethanol as shiny, colorless prisms, m.p. 139°.

Anal. Calc'd for $C_{22}H_{16}FNO$: C, 80.2; H, 4.9.
Found: C, 80.0; H, 4.8.

SUMMARY

1. *p*-Fluoroanisole has been found to be a convenient intermediate for the synthesis of several fluoro compounds hitherto difficult to prepare.

2. A large number of new fluoro compounds, including ketones and heterocycles of potential biological interest, have been described.

PARIS V^e^, FRANCE

REFERENCES

(1) See SCHIEMANN, *Die organischen Fluorverbindungen*, Steinkopf (Frankfurt), 1950; MAY, *Die Basedowsche Krankheit, Jod und Fluor*, Editio Cantor (Aulendorf), 1950; NIEMANN, *et al.*, *J. Am. Chem. Soc.*, **62**, 350 (1940); **63**, 2204 (1941); BUU-HOÏ AND JACQAIGNON, *J. Chem. Soc.*, 4173 (1952); BUU-HOÏ, XUONG, AND LAVIT, *J. Chem. Soc.*, 1034 (1954).
(2) MINOR AND VANDERWERF, *J. Org. Chem.*, **17**, 1425 (1952).
(3) BUU-HOÏ, XUONG AND LAVIT, *J. Org. Chem.*, **18**, 910 (1953).
(4) BALZ AND SCHIEMANN, *Ber.*, **60**, 1188 (1927).
(5) SUTER, LAWSON, AND SMITH, *J. Amer. Chem. Soc.*, **61**, 161 (1939).
(6) KINDLER AND OELSCHLÄGER, *Ber.*, **87**, 194 (1954).
(7) BUU-HOÏ, *Rec. trav. chim.*, **68**, 795 (1949).
(8) SUTER AND WESTON, *J. Am. Chem. Soc.*, **61**, 2317 (1939).
(9) GILMAN, LANGHAM, AND MOORE, *J. Am. Chem. Soc.*, **62**, 2327 (1940).
(10) BUU-HOÏ, XUONG, NAM, AND BINON, *Compt. rend.*, **235**, 329 (1952).
(11) CORSE AND INGRAHAM, *J. Org. Chem.*, **16**, 1345 (1951).
(12) HINSBERG, *Ann.*, **292**, 246 (1896); BUU-HOÏ AND KHÔI, *Bull. soc. chim.*, **17**, 753 (1950).
(13) TSCHITSCHIBABIN, *Ber.*, **60**, 1607 (1927).
(14) See BUU-HOÏ, ROYER, AND ECKERT, *Rec. trav. chim.*, **71**, 1059 (1952).