Copenhaver,[5] was added over a 3-hr. period to 76.5 (1.1 moles) of hydroxylamine hydrochloride in 500 ml. water at 60–70°. Heating was continued for an additional hour at 60–70°. The mixture was distilled collecting water, alcohol, and isoxazole to a vapor temperature of 95°.

The distillate was added dropwise to a well stirred saturated solution of an excess of 183 g. cadmium chloride in 150 ml. water. The curdy precipitate that resulted was suction filtered, washed with a little cold water, and sucked as dry as possible. The precipitate was suspended in water and heated to boiling, distilling out a mixture of isoxazole and water. The distillate, which had separated into two phases, was extracted with ether. The ether extract was dried with $CaCl_2$ and distilled. After removal of the ether, there was obtained 49.3 g. (70%) of isoxazole boiling at 93–95°. Speroni and Pino[6] report the boiling point of isoxazole as b_{760} 94.8°.

(Note: A reference to a similar procedure appeared during the preparation of the manuscript.[7])

β-ethoxyacrylonitrile (II). Instead of preparing pure isoxazole for the preparation of β-ethoxyacrylonitrile, it was found advantageous to employ the aqueous alcoholic solution of isoxazole as described under the preparation of isoxazole. Thus, to 561 g. of aqueous alcoholic isoxazole containing 88.5 g. of isoxazole (1.285 moles), determined by alkaline hydrolysis or by isolation with cadmium chloride, was added 570 g. (3.7 moles) of technical diethyl sulfate. The mixture was chilled to 5° with stirring and 606 g. of 24.45% sodium hydroxide (3.7 moles) solution was added over a 4-hr. period, maintaining reaction temperature at 5–10° with the use of an ice bath. Stirring was continued for 2 hr. at 5–10° after the caustic addition. The mixture was slowly warmed up, removing ether and alcohol through a 1.5-ft. packed column. The column was removed and the product removed by steam distillation. The product phase was separated from the aqueous layer, dried with $CaCl_2$ and distilled at reduced pressure. There was obtained 114 g. of product boiling from 80–90° at 12 mm., d_{20}^{20} 0.9463, n_D^{20} 1.4531. Based on nitrogen analysis, the fraction consists of 78.9% β-ethoxyacrylonitrile and 21.1% of cyanoacetaldehyde acetal.

The mixture was heated to boiling at atmospheric pressure until the evolution of alcohol ceased. After removal of residual alcohol under reduced pressure, 108.2 g. β-ethoxyacrylonitrile boiling at 90–91° (19 mm.), d_{20}^{20} 0.9437, n_D^{20} 1.4545, M_D 27.86 (calcd. 27.97) was obtained. Final yield of β-ethoxyacrylonitrile, 86.9% on isoxazole employed. McElvain and Clarke[8] report the following constants for β-ethoxyacrylonitrile b_8 71–72°C, n_D^{25} 1.4520, d_4^{25} 0.945.

Anal. Calcd. for: C_5H_7NO: N, 14.42. Found: N, 14.15.

Cytosine (III). To a cooled solution of 23 g. of sodium (1 g.-atom) in 690 ml. dry butanol, was added 60 g. (1 mole) of dry urea and 97.0 g. (1.0 mole) of β-ethoxyacrylonitrile. The mixture was refluxed (112–115°) for 2 hr. and cooled to 20°. Sulfuric acid (128.0 g.) in 1250 ml. water was added and the mixture was stirred for 0.5 hr. The aqueous layer was separated from the butanol, heated to 80° and 2500 ml. alcohol was added. The mixture was chilled to 0° and the crude cytosine sulfate filtered off. The cytosine sulfate was added to 1 l. of H_2O and alkalized with concentrated ammonium hydroxide until the mixture was slightly alkaline to alkacid paper. The crude cytosine was filtered, added to 1 l. of water, and clarified with charcoal. On cooling there were obtained colorless plates of cytosine. Concentration of the mother liquor yielded an additional amount of cytosine. There was obtained a total of 48.5 g. of cytosine. Yield, 43.7% based on β-ethoxyacrylonitrile employed. Melting point 305° (browns), 319–323° (decomp.) The infrared spectrum of the compound obtained was identical with a known sample of cytosine[9].

Anal. Calcd. for $C_4H_5N_3O$: N, 37.82. Found: N, 37.1.

WEST HAVERSTRAW, N. Y.

(5) U.S. Patent **2,527,533** (Gen. Aniline & Film Corp., Oct. 31, 1950).

(6) G. Speroni and P. Pino, *Proc. XIth Intern. Congr. Pure and Applied Chem. (London)* **2**, 311 (1947).

(7) R. Justoni and R. Pessina, *Gazz. chim. ital.*, **85**, 34–40 (1955). [*Chem. Abstr.* **50**, 4127d.]

(8) S. McElvain and R. Clarke, *J. Am. Chem. Soc.*, **69**, 2657 (1947).

(9) Private communication, Dr. J. S. Fox, Sloan-Kettering Institute for Cancer Research.

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

New Fluorine-containing Aromatics as Potential Carcinostats

NG. PH. BUU-HOÏ, N. D. XUONG, AND R. RIPS

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A large number of fluorine-containing aromatic acids, nitriles, and ketones have been synthesized from various fluoro aromatics for biological testing as potential carcinostatic agents.

3-Fluorotyrosine (Pardinon) has been found to inhibit the initiation and development of various tumors in animals, such as grafts of Jensen sarcomas in rats and tumors induced in mice through injection or painting with 3,4-benzpyrene.[1] Further, the same compound and 3-fluoro-4-hydroxyphenylacetic acid (Capacin) have found therapeutic use against hyperthyreosis.[2] Both these biological effects have recently been accounted for on the grounds of an antagonism toward aromatic acids and their metabolites.[3] With this in mind, a large number of new compounds more or less related to that type of molecular structure have now been prepared for biological investigation for possible carcinostatic activity and inhibitory effects on the pituitary secretions.

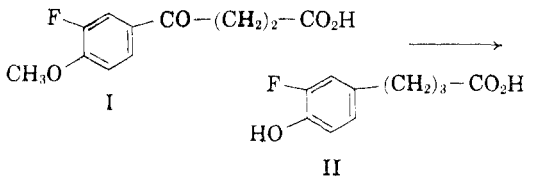
o-Fluoroanisole readily underwent Friedel-Crafts succinoylation to β-(3-fluoro-4-methoxybenzoyl)-

(1) May and Litzka, *Zeitschr. Krebsforsch.*, **48**, 376 (1939).

(2) May, *Die Basedowsche Krankheit, Jod und Fluor*, Editio Cantor (Aulendorf), 1950.

(3) Buu-Hoï, Symposium on Chemotherapy of Cancer (Oslo, 1956); *Acta Unio Intern. contra Cancrum*, in press.

propionic acid (I); demethylation occurred during an attempt to reduce this compound by the Huang-Minlon modification of the Kishner-Wolff method,[4] γ-(3-fluoro-4-hydroxyphenyl)butyric acid (II), a higher homolog of Capacin, being obtained. γ-

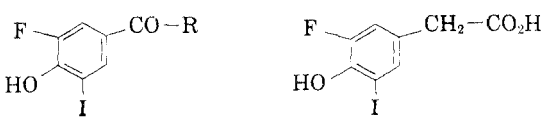


I II

(3-Fluoro-4-methoxyphenyl)butyric acid, prepared by methylation, was readily cyclized to give 6-fluoro-7-methoxy-1-keto-1,2,3,4-tetra-hydronaphthalene (III); this ketone, which readily gave 2-arylidene compounds with aromatic aldehydes, yielded on treatment with pyridine hydrochloride the demethylated compound (IV). This

III IV; R = H
V; R = I

latter substance could also be prepared in low yield by Friedel-Crafts cyclization of the chloride of acid II, and gave with iodine 6-fluoro-8-iodo-7-hydroxy-1-keto-1,2,3,4-tetrahydronaphthalene (V). Other hydroxy ketones containing both fluorine and iodine included 3-fluoro-5-iodo-4-hydroxy-caprophenone (VI), -*n*-decanophenone (VII), -benzophenone (VIII), and -phenacetophenone (IX), which, similarly, were prepared by halogenation of the fluoro ketones with iodone in the presence of mercuric oxide.[5] These various ketones were synthesized in view of the recorded pituitary-inhibitory activity of the similarly built *n*-butyl 3,5-diiodo-4-hydroxybenzoate;[6] the same



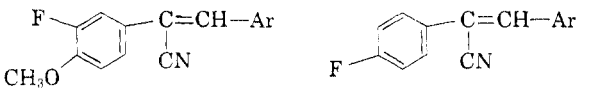
I I

VI; R = n-C_5H_{11}
VII; R = n-C_9H_{19}
VIII; R = C_6H_5
IX; R = CH_2—C_6H_5

(X)

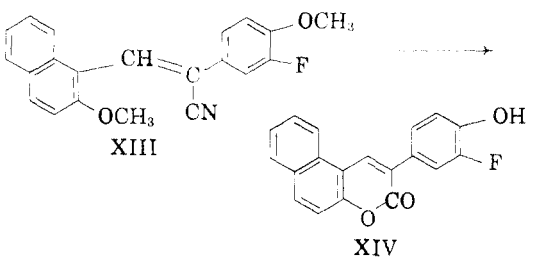
method was used for the preparation of 3-fluoro-5-iodo-4-hydroxyphenylacetic acid (X).

Numerous fluorine-containing stilbene nitriles, listed in Table I, were prepared in excellent yields by the alkali-catalyzed condensation of 3-fluoro-4-methoxybenzyl cyanide[7] with various aromatic aldehydes, and their demethylation afforded the corresponding hydroxystilbene nitriles. In the case



XI XII

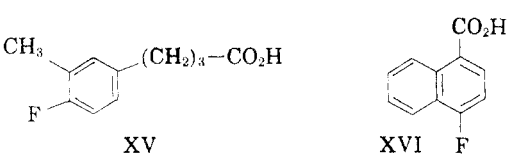
of 1-(3-fluoro-4-methoxyphenyl)-2-(2-methoxy-1-naphthyl)-acrylonitrile (XIII), demethylation resulted in the formation of 3-(3-fluoro-4-hydroxyphenyl)-5,6-benzocoumarin (XIV), in accordance with a recently described[8] coumarin synthesis. Nonoxygenated fluoro nitriles (XII), listed



XIII XIV

in Table II, were obtained by condensing aromatic aldehydes with *p*-fluorobenzyl cyanide in the presence of alkalies. The other nitriles recorded in the same table were obtained in similar manner by condensation of *p*-fluorobenzaldehyde with various arylacetonitriles.

Schöller and Gehrke[9] found that in slices of Jensen sarcoma, glycolysis was inhibited by sodium 4-fluorobenzoate, while the rate of respiration was increased. In view of this interesting property, several new fluorine-containing aromatic acids have now been prepared. *o*-Fluorotoluene was succinoylated to β-(4-fluoro-3-methylbenzoyl)propionic acid, which underwent Kishner-Wolff reduction to γ-(4-fluoro-3-methylphenyl)butyric acid (XV); 4-fluoro-1-naphthoic acid (XVI) was ob-



XV XVI

tained by sodium hypobromite oxidation of 4-fluoro-1-acetonaphthone. In view of the known inhibiting action of ethylenic ketones on certain enzymes, fluorine-containing chalcones were prepared by condensation of 4-fluoro-1-acetonaphthone and similar ketones with various aldehydes, and are listed in Table III, along with chalcones derived from 4-fluorobenzaldehyde; as expected from other similar cases,[10] the latter aldehyde condensed with cyclopentanone and cyclohexanone to give exclusively 2,5-*bis*(4-fluorobenzal)cyclo-

(4) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2478 (1946).
(5) See Buu-Hoï, Xuong, and Lavit, *J. Chem. Soc.*, 1034 (1954).
(6) Barker, Dirks, Garlick, and Klitgaard, *Proc. Soc. Exper. Biol. Med.*, **78**, 840 (1951).
(7) Kraft, *Ber.*, **84**, 150 (1951).
(8) Buu-Hoï *et al.*, *J. Chem. Soc.*, 2307 (1951); *J. Org. Chem.*, **19**, 1391, 1548 (1954).
(9) Schöller and Gehrke, *Klin. Wochenschr.*, 1129 (1930).
(10) Vorländer and Hobohm, *Ber.*, **29**, 1840 (1896).

TABLE I

1-SUBSTITUTED 2-(*p*-FLUOROPHENYL)ACRYLONITRILES

Substituent	Formula	M.P.	Analyses			
			Calcd.		Found	
			C	H	C	H
2-Chlorophenyl-	$C_{15}H_9ClFN$	128°	69.9	3.5	69.9	3.3
3-Chlorophenyl-	$C_{15}H_9ClFN$	148	69.9	3.5	69.9	3.6
4-Chlorophenyl-	$C_{15}H_9ClFN$	127	69.9	3.5	70.1	3.6
4-Bromophenyl-	$C_{15}H_9BrFN$	114	59.6	3.0	59.3	3.1
4-Fluorophenyl-	$C_{15}H_9F_2N$	169	74.7	3.7	74.7	3.5
2,4-Dichlorophenyl-	$C_{15}H_8Cl_2FN$	142	61.6	2.7	61.3	2.7
Phenyl-	$C_{15}H_{10}FN$	111	80.7	4.5	80.6	4.6
4-Isopropylphenyl-	$C_{18}H_{16}FN$	116	81.5	6.0	81.7	6.2
2-SUBSTITUTED 1-(*p*-FLUOROPHENYL)ACRYLONITRILES (XII)						
2-Chlorophenyl-	$C_{15}H_9ClFN$	124	69.9	3.5	69.8	3.3
3-Chlorophenyl-	$C_{15}H_9ClFN$	107	69.9	3.5	69.9	3.6
4-Chlorophenyl-	$C_{15}H_9ClFN$	112	69.9	3.5	69.7	3.6
2-Bromophenyl-	$C_{15}H_9BrFN$	125	59.6	3.0	59.3	3.0
3-Bromophenyl-	$C_{15}H_9BrFN$	122	59.6	3.0	59.5	3.2
3,4-Dichlorophenyl-	$C_{15}H_8Cl_2FN$	155	61.6	2.7	61.3	2.8
4-Isopropylphenyl-	$C_{18}H_{16}FN$	99	81.5	6.0	81.7	5.9
1-Naphthyl-	$C_{19}H_{12}FN$	127	83.5	4.4	83.6	4.6
4-Dimethylaminophenyl-	$C_{17}H_{15}FN_2$	178	76.7	5.6	76.9	5.8

TABLE II

2-SUBSTITUTED 1-(3-FLUORO-4-METHOXYPHENYL)ACRYLONITRILES (XI)[a]

Substituent	Formula	M.P.	Analyses			
			Calcd.		Found	
			C	H	C	H
Phenyl	$C_{16}H_{12}FNO$	133°	75.9	4.7	75.6	4.5
2-Furyl	$C_{14}H_{10}FNO_2$	111	69.1	4.1	69.0	4.3
4-Fluorophenyl	$C_{16}H_{11}F_2NO$	181	70.8	4.1	70.5	4.1
2-Chlorophenyl	$C_{16}H_{11}ClFNO$	147	66.8	3.8	66.6	3.8
4-Chlorophenyl	$C_{16}H_{11}ClFNO$	145	66.8	3.8	66.7	3.8
3,4-Dichlorophenyl	$C_{16}H_{10}Cl_2FNO$	183	59.6	3.1	59.5	3.0
4-Isopropylphenyl	$C_{19}H_{18}FNO$	129	77.3	6.1	77.2	6.0
1-Naphthyl	$C_{20}H_{14}FNO$	130	79.2	4.9	79.0	5.1
4-Dimethylaminophenyl	$C_{18}H_{17}FN_2O$	148	73.0	5.7	73.1	5.6
3,4-Dimethoxyphenyl	$C_{18}H_{16}FNO_3$	147	69.0	5.1	68.8	5.2
3,4-Methylenedioxyphenyl	$C_{17}H_{12}FNO_3$	192	68.7	4.0	68.8	4.2
2-Methoxy-1-naphthyl	$C_{21}H_{16}FNO_2$	177	75.7	4.8	75.3	4.7

[a] Prepared by adding a few drops of 25% aqueous sodium hydroxide to a stirred, warm solution of equimolar amounts of 3-fluoro-4-methoxybenzyl cyanide and the appropriate aromatic or heterocyclic aldehyde, and leaving the mixture overnight at room temperature; the precipitate obtained was washed with water and recrystallized from ethanol.

TABLE III

CHALCONES[a] DERIVED FROM *p*-FLUOROBENZALDEHYDE

	Formula	M.P.	Analyses			
			Calcd.		Found	
			C	H	C	H
6-(4-Fluorocinnamoyl)tetralin	$C_{19}H_{17}FO$	75°	81.4	6.1	81.3	6.3
2-(4-Fluorocinnamoyl)naphthalene	$C_{19}H_{13}FO$	144	82.6	4.7	82.8	4.6
1-(4-Fluorocinnamoyl)-4-fluoronaphthalene	$C_{19}H_{12}F_2O$	83	77.6	4.1	77.5	4.3
(4-Fluorocinnamoyl)-3,4-dichlorobenzene	$C_{15}H_9Cl_2FO$	143	61.0	3.1	61.2	3.2
(4-Fluorocinnamoyl)-3,4-dimethylbenzene	$C_{17}H_{15}FO$	112	80.3	5.9	80.7	6.2
(4-Fluorocinnamoyl)-4-fluoro-3-methylbenzene	$C_{16}H_{12}F_2O$	124	74.4	4.7	74.2	4.6
(4-Fluorocinnamoyl)-2,4-dimethoxybenzene	$C_{17}H_{15}FO_3$	98	71.3	5.3	71.0	5.5
2-(4-Fluorobenzal)benzosuberone	$C_{18}H_{15}FO$	96	81.2	5.6	81.0	5.5
1-(4-Chlorocinnamoyl)-4-fluoronaphthalene	$C_{19}H_{12}ClFO$	112	73.4	3.9	73.4	4.0
1-(2,4-Dichlorocinnamoyl)-4-fluoronaphthalene	$C_{19}H_{11}Cl_2FO$	132	66.1	3.2	66.0	3.5
1-(4-Dimethylaminocinnamoyl)-4-fluoronaphthalene	$C_{21}H_{18}FNO$	140	79.0	5.6	78.7	5.8
2,6-bis(4-Fluorobenzal)cyclohexanone	$C_{20}H_{16}F_2O$	157	77.4	5.2	77.1	5.2
2,6-bis(4-Fuorobenzal)cyclopentanone	$C_{19}H_{14}F_2O$	244	77.0	4.7	76.8	4.8

[a] Prepared by shaking for some minutes a solution in ethanol of equimolar amounts of the appropriate ketone and *p*-fluorobenzaldehyde, with a few drops of 25% aqueous sodium hydroxide; recrystallization was effected from ethanol, except for the two last compounds, which were recrystallized from a mixture of ethanol and benzene.

pentanone and 2,6-*bis*(4-fluorobenzal)cyclohexanone, respectively.

EXPERIMENTAL

Succinoylation of o-fluoroanisole. To an ice-cooled solution of 30 g. of succinic anhydride and 31.5 g. of *o*-fluoroanisole in 200 ml. of nitrobenzene, 50 g. of finely powdered aluminum chloride was added in small portions with stirring; the reaction mixture was left at room temperature for 24 hr., then treated with ice and dilute hydrochloric acid. After removal of the nitrobenzene by steam-distillation, the residue was recrystallized from dilute aqueous acetic acid, giving a 96% yield of *β-(3-fluoro-4-methoxybenzoyl)-propionic acid* (I) in the form of shiny colorless prisms, m.p. 170–171°.

Anal. Calcd. for $C_{11}H_{11}FO_4$: C, 58.4; H, 4.9. Found: C, 58.1; H, 5.2.

γ-(3-Fluoro-4-hydroxyphenyl)butyric acid (II). A solution of 70 g. of the foregoing acid and 25 ml. of 98% hydrazine hydrate in 400 ml. of diethylene glycol was heated for 5 min. to allow the hydrazone to form; 64 g. of potassium hydroxide was then added, and the mixture refluxed for 4 hr. with removal of water. Most of the diethylene glycol was distilled off in a vacuum, and the residue was diluted with water and acidified with hydrochloric acid. The reaction product was taken up in ether, the ethereal solution dried over sodium sulfate, and the solvent distilled off. Crystallization of the residue from water gave a 75% yield of large colorless platelets, m.p. 107–108°.

Anal. Calcd. for $C_{10}H_{11}FO_3$: C, 60.6; H, 5.6. Found: C, 60.5; H, 5.8.

Methylation of the foregoing acid with dimethyl sulfate (2 moles) and aqueous sodium hydroxide (2 moles), followed by alkaline hydrolysis of the methyl ester thus obtained, afforded in 98% yield γ-(3-fluoro-4-methoxyphenyl)-butyric acid, which crystallized from a mixture of petroleum ether and benzene in colorless needles, m.p. 62–63°.

Anal. Calcd. for $C_{11}H_{13}FO_3$: C, 62.3; H, 6.1. Found: C, 62.0; H, 6.1.

6-Fluoro-7-methoxy-1-keto-1,2,3,4-tetrahydronaphthalene (III). Fifteen grams of γ-(3-fluoro-4-methoxyphenyl)butyric acid was converted with thionyl chloride into the corresponding acid chloride, which was dissolved in 100 ml. of nitrobenzene; to this ice-cooled solution, 13 g. of aluminum chloride was added in small portions with stirring, and the mixture left 3 hr. at room temperature. After decomposition with ice and hydrochloric acid, and removal of the nitrobenzene by steam-distillation, the residue was taken up in ether, the ethereal solution washed with dilute aqueous sodium hydroxide, then with water, dried over sodium sulfate, and the solvent distilled off. Yield: 7 g. of ketone III, crystallizing from methanol in colorless prisms, m.p. 95°.

Anal. Calcd. for $C_{11}H_{11}FO_2$: C, 68.0; H, 5.7. Found: C, 68.2; H, 5.6.

The semicarbazone crystallized from ethanol in silky colorless needles, m.p. 216–217°.

Anal. Calcd. for $C_{12}H_{14}FN_3O_2$: N, 16.7. Found: N, 16.6.

2-(p-Fluorbenzal)-6-fluoro-7-methoxy-1-keto-1,2,3,4-tetrahydronaphthalene. A solution of the foregoing ketone (1 mole) and *p*-fluorobenzaldehyde (1 mole) in ethanol was shaken for some minutes with a few drops of a 20% aqueous solution of sodium hydroxide; the precipitate formed was collected, washed with water, and recrystallized from ethanol, giving silky colorless needles, m.p. 132°, in almost theoretical yield.

Anal. Calcd. for $C_{18}H_{14}F_2O_2$: C, 72.0; H, 4.7. Found: C, 71.9; H, 4.5.

2-(p-Chlorobenzal)-6-fluoro-7-methoxy-1-keto-1,2,3,4-tetrahydronaphthalene, similarly prepared with *p*-chlorobenzaldehyde, crystallized from ethanol in lustrous colorless leaflets, m.p. 136°.

Anal. Calcd. for $C_{18}H_{14}ClFO_2$: C, 68.2; H, 4.4. Found: C, 68.0; H, 4.4.

6-Fluoro-7-hydroxy-1-keto-1,2,3,4-tetrahydronaphthalene (IV). (a) A mixture of 2 g. of the tetralone (III) and 6 g. of pyridine hydrochloride was gently refluxed for 15 min., and water added after cooling; the precipitate crystallized from aqueous methanol in colorless tablets, m.p. 186–187°. Yield: 1 g. (b) The same product was obtained in poor yield by treating acid III with thionyl chloride, and cyclizing the crude acid chloride thus obtained by aluminum chloride in nitrobenzene solution in the usual way.

Anal. Calcd. for $C_{10}H_9FO_2$: C, 66.7; H, 5.0. Found: C, 67.0; H, 5.0.

6-Fluoro-8-iodo-7-hydroxy-1-keto-1,2,3,4-tetrahydronaphthalene (V). To a solution of 4.5 g. of the foregoing ketone in 50 ml. of ethanol, 6 g. of yellow mercuric oxide was added; 1 g. of iodine in ethanol was then shaken in portion-wise. After filtration and concentration of the filtrate, the reaction product was precipitated with water, and recrystallized from that solvent, giving 4 g. of fine gray-tinged prisms, m.p. 150°.

Anal. Calcd. for $C_{10}H_8FIO_2$: C, 39.2; H, 2.6. Found: C, 38.8; H, 2.5.

Iodination of fluorohydroxy ketones. The same procedure as above was used for the preparation of the following ketones:

3-Fluoro-5-iodo-4-hydroxycaprophenone (VI), which crystallized from aqueous ethanol in lustrous colorless leaflets, m.p. 102°.

Anal. Calcd. for $C_{12}H_{14}FIO_2$: C, 42.9; H, 4.2. Found: C, 42.6; H, 4.2.

3-Fluoro-5-iodo-4-decanophenone (VII), which crystallized from petroleum ether in fine colorless needles, m.p. 73°.

Anal. Calcd. for $C_{16}H_{22}FIO_2$: C, 48.9; H, 5.6. Found: C, 49.0; H, 5.6.

3-Fluoro-5-iodo-4-benzophenone (VIII), fine yellowish prisms from ethanol, m.p. 178°.

Anal. Calcd. for $C_{13}H_8FIO_2$: C, 45.6; H, 2.3. Found: C, 45.3; H, 2.1.

3-Fluoro-5-iodo-4-phenacetophenone (IX), fine yellowish prisms from ethanol, m.p. 172°.

Anal. Calcd. for $C_{14}H_{10}FIO_2$: C, 47.2; H, 2.8. Found: C, 47.0; H, 2.8.

3-Fluoro-5-iodo-4-hydroxyphenylacetic acid (X). Similarly prepared from 3-fluoro-4-hydroxyphenylacetic acid, this compound crystallized from water in shiny colorless leaflets, m.p. 164°.

Anal. Calcd. for $C_8H_6FIO_3$: C, 32.4; H, 2.0. Found: C, 32.1; H, 2.1.

3-(3-Fluoro-4-hydroxyphenyl)-5,6-benzocoumarin (XIV). A mixture of 1 g. of acrylonitrile XIII and 6 g. of redistilled pyridine hydrochloride was refluxed for 30 min., and dilute hydrochloric acid added after cooling. After 5 more minutes' refluxing for hydrolyzing the iminocoumarin formed, the precipitate obtained was washed with water and recrystallized from a mixture of ethanol and benzene, giving pale yellow needles, m.p. 255°.

Anal. Calcd. for $C_{19}H_{11}FO_3$: C, 74.5; H, 3.6. Found: C, 74.1; H, 3.5.

A similar technique applied to other methoxy acrylonitriles listed in Table I gave the following hydroxy compounds:

1-Phenyl-2-(3-fluoro-4-hydroxyphenyl)acrylonitrile, crystallizing from aqueous ethanol in fine colorless prisms, m.p. 184°.

Anal. Calcd. for $C_{15}H_{10}FNO$: C, 75.3; H, 4.2. Found: C, 75.0; H, 4.0.

1-(2-Chlorophenyl)-2-(3-fluoro-4-hydroxyphenyl)acrylonitrile, fine colorless prisms from aqueous ethanol, m.p. 171°.

Anal. Calcd. for $C_{15}H_9ClFNO$: C, 65.8; H, 3.3. Found: C, 65.6; H, 3.1.

1-(1-Naphthyl)-2-(3-fluoro-4-hydroxyphenyl)acrylonitrile, fine yellowish prisms from aqueous ethanol, m.p. 193°.

Anal. Calcd. for $C_{19}H_{12}FNO$: C, 78.9; H, 4.2. Found: C, 78.6; H, 4.1.

β-(4-Fluoro-3-methylbenzoyl)propionic acid. A mixture of 55 g. of *o*-fluorotoluene, 50 g. of succinic anhydride, and 75 g. of finely powdered aluminum chloride in 150 ml. of carbon disulfide was refluxed for 4 hr. on the water bath, and then left overnight at room temperature. After decomposition with ice and hydrochloric acid and evaporation of the solvent, the reaction product was taken up in ether, the etheral solution washed with water and dried over sodium sulfate, and the solvent distilled off. Crystallization of the solid residue from benzene gave 30 g. of colorless prisms, m.p. 119°. The position of the fluorine atom in this compound is assumed from analogy with the acylations.[11]

Anal. Calcd. for $C_{11}H_{11}FO_3$: C, 62.9; H, 5.3. Found: C, 63.2; H, 5.2.

γ-(4-Fluoro-3-methylphenyl)butyric acid (XV). Prepared as for acid II, this compound crystallized from water in shiny colorless tablets, m.p. 64–65°.

Anal. Calcd. for $C_{11}H_{13}FO_2$: C, 67.3; H, 6.6. Found: C 67.0; H, 6.6.

4-Fluoro-1-acetonaphthone. Obtained in 70% yield from 48 g. of 1-fluoronaphthalene, 28 g. acetyl chloride, and 70 g. of aluminum chloride in carbon disulfide as in the case of β-(4-fluoro-3-methylbenzoyl)propionic acid; the ketone was a pale yellow oil, b.p. 288°, n_D^{20} 1.6071.

Anal. Calcd. for $C_{12}H_9FO$: C, 76.6; H, 4.8. Found: C, 76.5; H, 4.6.

4-Fluoro-1-naphthoic acid (XV). Fifteen grams of the foregoing ketone was shaken with an aqueous solution of sodium hypobromite (prepared from 13 ml. of bromine and 26 g. of sodium hydroxide) for 2 hr. at room temperature, the neutral impurities were removed by water-extraction, and the aqueous solution was treated with sodium bisulfite, then acidified with hydrochloric acid. The precipitate, obtained in 70% yield, crystallized from benzene in fine, colorless, sublimable needles, m.p. 226°.

Anal. Calcd. for $C_{11}H_7FO_2$: C, 69.5; H, 3.7. Found: C, 69.2; H, 3.4.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF GEORGIA]

Addition of Mercaptoacetic Acid to Terpenes and Related Compounds

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The reaction of mercaptoacetic acid with *d*- and *l*-limonenes, dipentene, α-pinene, β-pinene, camphene, myrcene, anethole, oleic acid, and allyl chloride was studied. Ultraviolet light and peroxides generally accelerate the reactions and evidence is presented that atmospheric oxygen is sufficient to induce a rapid reaction with *d*-limonene. A different adduct to *d*-limonene was obtained in the presence of sulfuric acid. The products were characterized as *S*-benzylthiuronium salts.

In view of the sparsity of solid derivatives of terpenes, the action of mercaptoacetic acid on several representatives of this class of compounds was studied. Although the adducts were expected to be liquids, the carboxyl groups of the adducts should furnish a point for preparing solid derivatives, such as *S*-benzylthiuronium salts.

As ordinarily carried out, the addition of mercaptans, including mercaptoacetic acid, to unsaturated compounds is generally presumed to be a radical-type reaction. Kharasch, Read, and Mayo[2] have observed that the addition of mercaptoacetic acid to styrene and isobutylene is definitely peroxide-catalyzed and that no reaction occurs in the presence of 5 mole percent of hydroquinone. However, Hoog and Eichwald[3] found that mercaptoacetic acid adds to many "peroxide-free" olefins without ultraviolet light.

Vincent and Etzel[4] have reported the use of the mercaptoacetic acid adducts to limonene, pinene, and camphene as milling aids for butadiene-styrene copolymers. Isobornyl carboxymethyl sulfide was prepared at 95° in the presence of *p*-toluenesulfonic acid from camphene and mercaptoacetic acid. The products were not characterized.

During the course of the present work, it was observed that mercaptoacetic acid does add vigorously to *d*-limonene which had been freed of peroxides by distillation, treatment with ferrous salts or absorption of the peroxides on alumina. The products are the same as those obtained in the presence of peroxides and reaction is inhibited by hydroquinone. It appears, therefore, that atmospheric oxygen is sufficient to induce radical-type reactions in this example.

Under appropriate conditions, either a 2:1 or 1:1 adduct to *d*-limonene may be obtained. The 2:1 adduct, as well as the *S*-benzylthiuronium salt isolated from it, retained optical activity. Thus, the addition to at least one of the double bonds occurs contrary to Markownikoff's rule, as ionic addition to both double bonds would afford a symmetrical molecule.

Cunneen[5] has previously reported the "normal" addition of mercaptoacetic acid to l-methylcyclohexene in the presence of sulfuric acid. Under similar conditions a reaction of mercaptoacetic

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