

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

Synthesis of Two Fluorinated 1-Naphthylacetic Acids

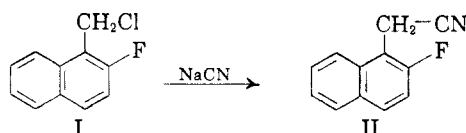
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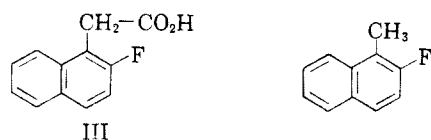
It is shown that 1- and 2-fluoronaphthalene readily undergo chloromethylation with paraformaldehyde and hydrochloric acid to give 4- and 2-fluoro-1-chloromethylnaphthalene respectively. These chloromethyl compounds served for the synthesis of 4- and 2-fluoro-1-naphthylacetic acid, compounds with biological interest as potential plant growth regulators. Friedel-Crafts cyclization of 2-fluoro-1-naphthylacetyl chloride afforded 3-fluoroacenaphthen-1-one, which was reduced to 3-fluoroacenaphthene.

As 1-naphthylacetic acid on the one hand, and several halogenated phenoxyacetic acids on the other hand, are powerful regulators of growth in plants, it was of interest to synthesize a number of still untested halogenated 1-naphthylacetic acids, especially the fluorine-containing ones.

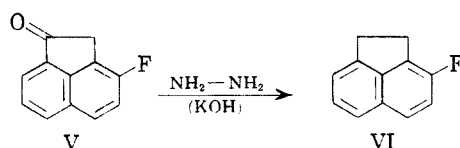
2-Fluoro-1-naphthylacetic acid (III) was prepared by hydrolysis of 2-fluoro-1-naphthylacetonitrile (II), itself obtained by reaction of sodium cyanide on 2-fluoro-1-chloromethylnaphthalene (I); chloromethylation of 2-fluoronaphthalene was effected in good yield, although experimental



conditions notably more drastic than with naphthalene were required. The constitution of the chloromethyl derivative (I), assumed on grounds of analogy with 2-methylnaphthalene which was chloromethylated in position 1,¹ was rigidly proven by the aluminum chloride-catalyzed cyclization of 2-fluoro-1-naphthylacetyl chloride to 3-



fluoroacenaphthene-1-one (V). Kishner-Wolff reduction of this ketone readily yielded 3-fluoroacenaphthene (VI), a compound also potentially



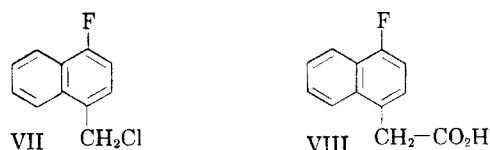
interesting in plant biology in view of the known mitoclastic activity of acenaphthene itself² and the growth-accelerating effects of certain substituted acenaphthenes on the roots of cereal seed-

(1) See N. P. Buu-Hoï and P. Cagniant, *Compt. rend.*, **214**, 315 (1942).

(2) P. and N. Gavaudan and T. F. Durand, *Compt. rend.*, **208**, 593 (1939).

lings.³ Of similar interest (in view of the polyploidogenic activity of 1-fluoro- and 1-methylnaphthalene⁴) is 2-fluoro-1-methylnaphthalene (IV), prepared by reduction of compound I with zinc powder in ethanol.

Chloromethylation of 1-fluoronaphthalene was also successfully performed, and 4-fluoro-1-chloromethylnaphthalene (VII) thus obtained was converted into 4-fluoro-1-naphthylacetic acid (VIII), *via* 4-fluoro-1-naphthylacetonitrile. In the present case, the structure of the chloromethyl derivative (VII) was not rigidly proven, but was assumed on the grounds of the known directing influence of the fluorine atom⁵ and because 1-methylnaphthalene is known to undergo chloromethylation in position 4.⁶ 4-Fluoro-1-naphthylacetonitrile readily



underwent alkali-catalyzed condensation with various aromatic aldehydes, to give a series of α -(4-fluoro-1-naphthyl)- β -arylacrylonitriles, listed in the Table. 2-Fluoro-1-naphthylacetonitrile failed to react in similar conditions.

Results of the plant tests will be published elsewhere.

EXPERIMENTAL

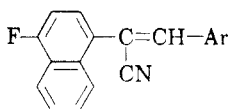
Chloromethylation of 2-fluoronaphthalene. A mixture of 58 g. of 2-fluoronaphthalene, 22 g. of paraformaldehyde, 52 ml. of acetic acid, 73 ml. of hydrochloric acid, and 33 ml. of phosphoric acid was heated for 12 hr. at 80–85° with stirring, hydrogen chloride being added at frequent intervals. After cooling and dilution with water, the solid product obtained was taken up in benzene, and the benzene solution washed, and dried over sodium sulfate. The solvent was then removed, and the residue vacuum-fractionated to yield 50

(3) R. Garrigues, N. P. Buu-Hoï, and P. Cagniant, *Compt. rend.*, **234**, 553 (1952).

(4) M. Simonet and M. Guinochet, *Compt. rend. Soc. biol.*, **132**, 455 (1939).

(5) See N. P. Buu-Hoï and P. Jacquignon, *J. Chem. Soc.*, 4173 (1952); N. P. Buu-Hoï and N. D. Xuong, *J. Chem. Soc.*, 386 (1953).

(6) G. Darzens and G. Levy, *Compt. rend.*, **202**, 73 (1936).

α -(4-FLUORO-1-NAPHTHYL)- β -ARYLACRYLONITRILES

Aryl group	Formula	M.P., °C.	Color with H ₂ SO ₄	Analyses	
				Calcd. N	Found N
<i>p</i> -Fluorophenyl	C ₁₉ H ₁₁ F ₂ N	170	Pale yellow	4.8	4.5
<i>p</i> -Methoxyphenyl	C ₂₀ H ₁₄ FNO	170	Green	4.6	4.5
3,4-Dimethoxyphenyl	C ₂₁ H ₁₆ FNO ₂	182	Green	4.2	4.0
3,4-Dioxymethylenephenyl	C ₂₀ H ₁₂ FNO ₂	180	Greenish brown	4.4	4.2
2-Thienyl	C ₁₇ H ₁₀ FNS	162	Deep green	5.0	4.9

g. of a product boiling at 150–151°/15 mm., and crystallizing from petroleum ether in colorless needles, m.p. 63°.

Anal. Calcd. for C₁₁H₈ClF: C, 67.9; H, 4.1. Found: C, 67.7; H, 3.9.

2-Fluoro-1-naphthylacetonitrile (II). A solution of 38.8 g. of 2-fluoro-1-chloromethylnaphthalene and 12 g. of sodium cyanide in 100 ml. of ethanol and 50 ml. of water was refluxed for 6 hr. The ethanol was distilled off, the reaction product taken up in ether, and the ether solution washed with water and dried over sodium sulfate. The solvent was then removed, and the residue vacuum-fractionated to yield 21 g. of a nitrile, b.p. 189–190°/17 mm., crystallizing from ethanol in silky colorless prisms, m.p. 82°.

Anal. Calcd. for C₁₂H₉FN: N, 7.6. Found: N, 7.3.

2-Fluoro-1-naphthylacetic acid (III). A mixture of 50 g. of the foregoing nitrile and 225 ml. of a 20% solution of potassium hydroxide in ethanol was refluxed for 6 hr. The ethanol was distilled off, and water was added to the residue; the aqueous solution was treated with ether to remove the neutral impurities, then acidified with dilute hydrochloric acid. The yield was 45 g. of an acid, crystallizing from aqueous ethanol in colorless needles, m.p. 154°.

Anal. Calcd. for C₁₂H₉FO₂: C, 70.6; H, 4.4. Found: C, 70.9; H, 4.7.

The corresponding *acid chloride*, prepared with thionyl chloride, was a pale yellow oil, b.p. 142–143°/1 mm., n_D^{25} 1.5986.

Anal. Calcd. for C₁₂H₉OClF: Cl, 16.0. Found: Cl, 15.6.

Reaction of this chloride with ice cooled, concentrated aqueous ammonia afforded *2-fluoro-1-naphthylacetamide*, crystallizing from aqueous ethanol in fine colorless prisms, m.p. 185°.

Anal. Calcd. for C₁₂H₁₀FNO: N, 6.9. Found: N, 6.8.

3-Fluoroacenaphthen-1-one (V). To a water cooled solution of 23 g. of 2-fluoro-1-naphthylacetyl chloride in 100 ml. of dry nitrobenzene, 16 g. of finely powdered aluminum chloride was added portionwise with stirring, and the mixture left overnight at room temperature. After decomposition with water, the nitrobenzene was distilled off with steam, and the residue was taken up in ether. The ethereal solution was washed first with 5% aqueous sodium hydroxide, then with water, and dried over sodium sulfate. The solvent was then removed, and the residue vacuum-fractionated. The portion boiling at 166–168°/1 mm., was recrystallized from ethanol, giving 2 g. of shiny colorless prisms, m.p. 155°.

Anal. Calcd. for C₁₂H₇FO: C, 77.4; H, 3.8. Found: C, 77.7; H, 3.9.

The corresponding *semicarbazone* crystallized from ethanol in fine colorless prisms, m.p. 236°.

3-Fluoroacenaphthene (VI). Reduction of 1 g. of ketone V with 1 g. of 95% hydrazine hydrate and 1 g. of potassium hydroxide in diethylene glycol⁷ afforded 0.6 g. of a product, crystallizing from ethanol in silky colorless needles, m.p. 98°.

Anal. Calcd. for C₁₂H₉F: C, 83.7; H, 5.2. Found: C, 83.5; H, 5.4.

The corresponding *picrate* crystallized from ethanol in silky orange needles, m.p. 136°.

Anal. Calcd. for C₁₃H₁₂FN₃O₇: C, 53.9; H, 3.0. Found: C, 53.5; H, 3.2.

2-Fluoro-1-methylnaphthalene (IV). Into a warm suspension of 20 g. of 2-fluoro-1-chloromethylnaphthalene in 100 ml. of 80% aqueous ethanol, 25 g. of zinc powder was stirred portionwise, and the mixture refluxed on a water bath for one hour. After cooling, the zinc in excess was filtered off and washed with ethanol, the ethanol was distilled off from the filtrate, and the residue taken up in benzene. The benzene solution was washed with water and dried over sodium sulfate, the solvent was removed, and the residue vacuum-fractionated. The portion, b.p. 122–128°/18 mm., was redistilled, yielding 11 g. of the reduction product, a colorless liquid, b.p. 241°, or 126–128°/20 mm.

Anal. Calcd. for C₁₁H₉F: C, 82.5; H, 5.6. Found: C, 82.2; H, 5.8.

The corresponding *picrate* crystallized from ethanol in silky yellow needles, m.p. 101°.

As a by-product of the above reduction, some α,β -di(2-fluoro-1-naphthyl)ethane could be isolated. It crystallized from ethanol in colorless needles (1 g.), m.p. 167°.

Anal. Calcd. for C₂₂H₁₆F₂: C, 83.0; H, 5.0. Found: C, 82.8; H, 4.9.

4-Fluoro-1-chloromethylnaphthalene (VII). The chloromethylation of 50 g. of 1-fluoronaphthalene was performed as for the 2-fluoro isomer. The yield was 45 g. of *4-fluoro-1-chloromethylnaphthalene*, b.p. 157–158°/18 mm., crystallizing from ethanol in silky colorless prisms, m.p. 56°. Like its isomer, this compound possesses pronounced skin irritating and lachrymatory properties.

Anal. Calcd. for C₁₁H₈ClF: C, 67.9; H, 4.1. Found: C, 67.9; H, 3.9.

4-Fluoro-1-naphthylacetonitrile. This compound, prepared by refluxing the foregoing chloromethyl derivative for 24 hr. with a slight excess of sodium cyanide in acetone, crystallized from ethanol in silky colorless needles, m.p. 87°.

Anal. Calcd. for C₁₂H₉FN: N, 7.6. Found: N, 7.5.

4-Fluoro-1-naphthylacetic acid (VIII). Prepared by alkaline hydrolysis of the foregoing nitrile, this acid crystallized from aqueous ethanol in shiny colorless needles, m.p. 162°.

Anal. Calcd. for C₁₂H₉FO₂: C, 70.6; H, 4.4. Found: C, 70.8; H, 4.5.

The corresponding *acid chloride*, prepared with thionyl chloride, was a pale yellow oil, b.p. 127–129°/0.5 mm., n_D^{25} 1.6043, which could not be cyclized to 5-fluoroacenaphthen-1-one by means of aluminum chloride in nitrobenzene.

Preparation of 1-(4-fluoro-1-naphthyl)-2-arylacrylonitriles. A solution of equimolar amounts of 4-fluoro-1-naphthylacetonitrile and the appropriate aromatic or heterocyclic aldehyde in warm ethanol was shaken with a few drops of 25% aqueous sodium hydroxide, and the precipitate obtained on cooling was recrystallized from ethanol.

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(7) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).