TABLE VII

COMPARISON OF YIELDS OF SCHIFF BASES

Schiff Bases	Yield, % Method 1[a]	Method 2[b]	References
N-Phenylbenzhydrylidenimine	81	71	(7)
N-p-Methoxyphenylbenzhydrylidenimine	78.5	56	(8)
N-*p*-Chlorophenylbenzhydrylidenimine	80	59	(9)
N-*α*-Naphthylbenzhydrylidenimine	74	66	(3)
N-Phenyl-9-florenylidenimine	75	56	(2)

[a] Modified method. [b] Reddelien's method, see refs. (2) and (3).

of a one-molar stock solution of lithium aluminum hydride (0.025 mole) diluted with 200 ml. of absolute ether was refluxed in a 1-liter, three-necked flask equipped with a dropping funnel, a mercury-sealed stirrer, and a reflux condenser. A solution of 13 g. (0.05 mole) of *N*-phenylbenzhydrylidenimine in 100 ml. of absolute ether was added dropwise at a rate to maintain gentle refluxing. The addition required 20 min. and the solution was refluxed for an additional 30 min. During this time, the yellow color of the solution gradually faded and finally became nearly colorless. The complex formed and the excess of hydride were decomposed by careful addition of water with cooling of the flask in an ice bath. Through the top of the condenser, enough ordinary ether was added to compensate for the amount which had been entrained by the evolved hydrogen. This was followed by the addition of 100 ml. of 20% sodium potassium tartrate and 40 ml. of 10% sodium hydroxide, which caused most of the precipitate to dissolve. The contents of the flask were then transferred to a separatory funnel and the ether layer separated. After the ether solution had been dried over sodium hydroxide pellets, the ether was evaporated, leaving an oily residue which was fractionally distilled. The material that distilled at 178–182° under 2 mm. pressure was collected as a pale yellow oil. For isolation of the product in crystalline form, the oily mass was dissolved in 125 ml. of boiling absolute ethanol and the hot solution filtered. The filtrate was allowed to cool slowly, and then chilled at 0° for 24 hr. The precipitate which crystallized was collected and washed twice with 5-ml. portions of cold ethanol. The filtrate and washings were evaporated to a volume about one half that of the original filtrate, and a second crop of crystals was obtained upon cooling. The crude product weighed 10.6 g., and melted at 54–56°. Two recrystallizations from absolute ethanol gave 10.1 g. (77.1%) of colorless crystals, melting at 57°. The melting point agrees with that previously described.[11–13]

Acetyl derivatives of N-arylbenzhydrylamines and related compounds (Table IV). One gram of the amine and a four- to fivefold excess of acetic anhydride were mixed and heated under gentle reflux for 15 to 30 min. After being cooled, the reaction mixture was poured into 30–40 moles of cold water. The aqueous mixture was then neutralized by careful addition of solid sodium carbonate. The mixture was cooled, and the insoluble acetamide was collected, washed, and dried in a vacuum desiccator. Recrystallization was effected from water-ethanol mixtures or from cyclohexane-benzene mixtures.

Phenylurea derivatives of N-arylbenzhydrylamines and related compounds (Table VI). A slight excess of phenyl isocyanate was added to a solution of 1 or 2 g. of the amine in 10–20 ml. of petroleum ether (b.p. 90–120°). If the amine was only slightly soluble, heating was necessary to bring it into solution. The mixture was boiled at a gentle reflux for about 5 min., and then allowed to cool. When the precipitate did not form even after the wall of the container had been rubbed, the heating was repeated, two times if necessary. The solid product was collected and extracted with 10–20 ml. of boiling petroleum ether (b.p. 90–120°), and the solution was filtered and cooled. If the phenylurea did not crystallize, the filtrate was concentrated. The crystals were collected, dried, and the melting point determined. If the latter was not sharp, petroleum ether (b.p. 60–120°) or 95% of ethanol was used for recrystallization.

Hydrochlorides of N-arylbenzhydrylamines and related compounds (Table VII). The hydrochlorides were prepared by dissolving one gram of the amine in 15–30 ml. of absolute ether and passing dry hydrogen chloride through this solution for 5 to 15 min. The precipitate which formed was collected and dried over phosphorus pentoxide. The amine hydrochlorides were recrystallized from an ether-ethanol mixture. All of the salts obtained were white, solid, and non-hygroscopic. The yields in all cases were over 95%.

BLOOMINGTON, IND.

(11) W. Schlenk, J. Appenrodt, H. Michael, and A. Thal, *Ber.*, **47**, 473 (1914).
(12) M. Busch and A. Rinck, *Ber.*, **38**, 1761 (1905).
(13) P. Grammaticakis, *Comp. rend.*, **210**, 716 (1940).

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

Some Nitrogen Derivatives of 1-Fluoronaphthalene

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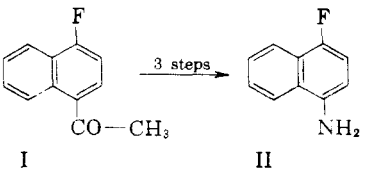
4-Fluoro-1-naphthylamine has been synthesized from 4-fluoro-1-acetonaphthone, and used for the preparation of a number of fluorinated *N,N'*-diarylthioureas of interest as potential antiviral agents. Various nitrogen-containing heterocyclic derivatives of 1-fluoronaphthalene have also been prepared from various 4-fluoro-1-acylnaphthalenes, for biological testing.

A number of aryl derivatives of thiourea bearing nuclear fluorine substituents, especially 4-chloro-4'-fluorothiocarbanilide, have been found to possess chemotherapeutic activity against influenza virus,[1] and these observations prompted the preparation of similar compounds derived from the 4-fluoro-1-naphthyl radical. 4-Fluoro-1-naphthylamine (II),



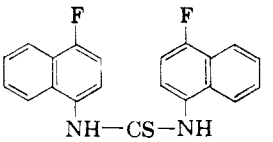
I II

(1) N. P. Buu-Hoï, P. Gley, N. D. Xuong, and A. Bouffanais, *Compt. rend.*, **238**, 2582 (1954); N.P. Buu-Hoï, P. Gley, A. Bouffanais, N. D. Xuong, and N. H. Nam, *Experientia*, **12**, 73 (1956).

required for these syntheses, was prepared free from isomers by a Beckmann rearrangement of the oxime of 4-fluoro-1-acetonaphthone (I);[2] this, treated with phosphorus pentachloride in ether, furnished 4-fluoro-1-acetonaphthalide, which was subsequently submitted to acid hydrolysis. Amine II has previously been obtained in another way,[3] and in a less pure state.

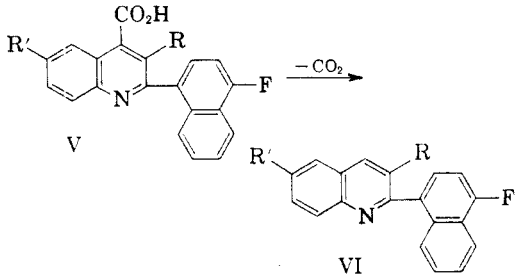
Condensation of 4-fluoro-1-naphthylamine with aryl isothiocyanates yielded various *N*-aryl-*N'*-(4-fluoro-1-naphthyl)thioureas (III), and *N,N'*-bis(4-fluoro-1-naphthyl)thiourea (IV) was obtained by reaction between carbon disulfide and amine II.

III



IV

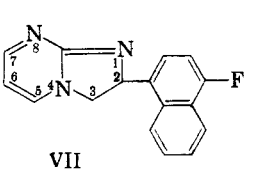
For the preparation of a number of nitrogen-containing heterocyclic compounds bearing a 1-fluoronaphthyl radical, various 4-fluoro-1-acylnaphthalenes were used as intermediates. In the quinoline series, Pfitzinger reaction[4] of isatin and its 5-bromo- and 5-chloro- derivative on the one hand, and 4-fluoro-1-acetonaphthone, 4-fluoro-1-propionaphthone, and 4-fluoro-1-phenacetonaphthone on the other hand, readily afforded the corresponding 2-(4-fluoro-1-naphthyl)cinchoninic acids (V), listed in Table I; these underwent thermal de-



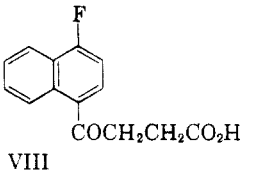
V VI

carboxylation to give the corresponding 2-(4-fluoro-1-naphthyl)quinolines (VI). Bromination of 4-fluoro-1-acetonaphthone yielded the liquid 4-fluoro-1-bromoacetonaphthone, along with the solid 4-fluoro-1-dibromoacetonaphthone.

The reaction of 4-fluoro-1-bromoacetonaphthone with 2-aminopyrimidine in ethanol resulted in 2-(4-fluoro-1-naphthyl)-8-azapyrimidazole (VII), following a reaction recently described by Buu-Hoï and Xuong,[5] and involving the tautomeric imino form of 2-aminopyrimidine. Compound VII bears



VII



VIII

a heterocyclic arrangement which resembles the purine nucleus, and is therefore of potential biological interest as a possible competitor of purines.

In the course of this work it was found that, contrary to what was expected, 4-fluoro-1-acetonaphthone and 4-fluoro-1-propionaphthone could not be reduced by the Kishner-Wolff method[6] to the corresponding fluoro hydrocarbons, and in both instances only high boiling products of unknown constitution were obtained; nor could β-(4-fluoro-1-naphthoyl)propionic acid (VIII), prepared in good yield by Friedel-Crafts succinoylation of 1-fluoronaphthalene, be satisfactorily reduced by the same method. This remarkable lability of the fluoro radical in these naphthalene derivatives is in contrast both with the stability of the chlorine group in similar reductions, and with the known possibility to reduce fluoro ketones in the benzene group.[7]

EXPERIMENTAL

4-Fluoro-1-acetonaphthone (I) and corresponding chalcones. The preparation of this ketone, b.p. 180–181°/30 mm., $n_D^{29.5}$ 1.6049, has already been reported.[2,8] The *piperonylidene derivative*, prepared by condensation of this ketone with piperonal in ethanol in the presence of aqueous sodium hydroxide, crystallized from ethanol in shiny yellowish prisms, m.p. 114°.

Anal. Calcd. for $C_{20}H_{13}FO_3$: C, 75.0; H, 4.1. Found: C, 75.1; H, 4.3.

The *2-methoxy-1-naphthylidene derivative*, similarly prepared from 2-methoxy-1-naphthaldehyde, crystallized from ethanol in pale yellow leaflets, m.p. 162°.

Anal. Calcd. for $C_{24}H_{17}FO_2$: C, 80.9; H, 4.8. Found: C, 80.6; H, 5.0.

4-Fluoro-1-propionaphthone. This ketone was prepared from 50 g. of 1-fluoronaphthalene, 35 g. of propionyl chloride, and 55 g. of aluminum chloride in 200 ml. of dry carbon disulfide, the mixture left for 24 hr., and then refluxed for 1 hr. on the water bath. After decomposition with ice and hydrochloric acid, the organic layer was washed with water and dried over sodium sulfate, the solvent was removed, and the residue was vacuum-fractionated. The yield was 56 g. of a pale yellow oil, b.p. 188°/18 mm., n_D^{32} 1.5895.

Anal. Calcd. for $C_{13}H_{11}FO$: C, 77.2; H, 5.4. Found: C, 77.3; H, 5.7.

4-Fluoro-1-phenacetonaphthone, prepared with phenacetyl chloride, crystallized from methanol in long colorless needles, m.p. 76°.

Anal. Calcd. for $C_{18}H_{13}FO$: C, 81.8; H, 4.9. Found: C, 82.0; H, 4.8.

Preparation of 4-fluoro-1-naphthylamine (II). *4-Fluoro-1-acetonaphthone oxime* (21 g.), prepared by refluxing for 12 hr. a solution of 28 g. of the ketone, 20 g. of hydroxylamine

(2) The structure of compound I had already been established by T. L. Jacobs, S. Winstein, J. W. Ralls, and J. H. Robson, *J. Org. Chem.*, **11**, 27 (1946).

(3) G. Schiemann, W. Gueffroy, and W. Winkelmueller, *Ann.*, **487**, 270 (1931).

(4) See N. P. Buu-Hoï, R. Royer, N. D. Xuong, and P. Jacquignon, *J. Org. Chem.*, **18**, 1209 (1953).

(5) N. P. Buu-Hoï and N. D. Xuong, *Compt. rend.*, **243**, 2090 (1956).

(6) Using the Huang-Minlon technique [*J. Am. Chem. Soc.*, **68**, 2487 (1946)].

(7) N. P. Buu-Hoï, N. Hoán, and N. D. Xuong, *Rec. trav. chim.*, **71**, 285 (1952).

(8) N. P. Buu-Hoï, N. D. Xuong, and R. Rips, *J. Org. Chem.*, **22**, 193 (1957).

TABLE I

2-(4-FLUORO-1-NAPHTHYL)CINCHONINIC ACIDS (V)

Substituents	Formula	M.P., °C.	Analyses			
			Calcd.		Found	
			C	H	C	H
R = R′ = H	$C_{20}H_{12}FNO_2$	260	75.7	3.8	75.4	3.6
R = H; R′ = Cl	$C_{20}H_{11}ClFNO_2$	294	68.3	3.1	68.2	3.2
R = H; R′ = Br	$C_{20}H_{11}BrFNO_2$	>310	60.6	2.8	60.3	2.7
R = CH_3; R′ = H	$C_{21}H_{14}FNO_2$	306	76.2	4.2	75.9	4.1
R = CH_3; R′ = Cl	$C_{21}H_{13}ClFNO_2$	295	68.9	3.6	68.6	3.5
R = CH_3; R′ = Br	$C_{21}H_{13}BrFNO_2$	293	61.5	3.2	61.3	3.0

hydrochloride, and 18 g. of sodium hydroxide in aqueous ethanol, crystallized from ethanol in fine colorless prisms, m.p. 119°.

Anal. Calcd. for $C_{12}H_{10}FNO$: N, 6.9. Found: N, 7.0.

The Beckmann rearrangement was effected by shaking a solution of 21 g. of the foregoing oxime in anhydrous ether with 30 g. of finely powdered phosphorus pentachloride. After treatment with water and evaporation of the ether, the crude *4-fluoro-1-acetonaphthalide* was directly hydrolyzed by refluxing its solution in ethanol for two hours with hydrochloric acid; after evaporation of the solvent, and basification with aqueous sodium hydroxide, the *4-fluoro-1-naphthylamine* obtained was taken up in ether and purified by vacuum-distillation. The yield was 14 g. of a product, b.p. 165°/15 mm., crystallizing from petroleum ether in colorless prisms, m.p. 57–58°.

Anal. Calcd. for $C_{10}H_8FN$: C, 74.5; H, 5.0. Found: C, 74.6; H, 5.3.

N,N′-Bis(4-fluoro-1-naphthyl)thiourea (IV). Prepared by refluxing a solution of the foregoing amine (2 moles) in ethanol with carbon disulfide (1.5 moles) in the presence of a small amount of sulfur, this compound crystallized from ethanol in shiny colorless prisms, m.p. 219°.

Anal. Calcd. for $C_{21}H_{14}F_2N_2S$: C, 69.3; H, 3.9. Found: C, 69.0; H, 3.7.

N-p-Fluorophenyl-N′-(4-fluoro-1-naphthyl)-thiourea. To a warm solution of 4-fluoro-1-naphthylamine (1 mole) in the minimum of ethanol, *p*-fluorophenyl isothiocyanate[9] (1 mole) was added with stirring, and the mixture was left to cool. The solid precipitate, obtained in almost quantitative yield, crystallized from ethanol in shiny colorless prisms, m.p. 184°.

Anal. Calcd. for $C_{17}H_{12}F_2N_2S$: C, 65.0; H, 3.8. Found: C, 64.7; H, 4.0.

N-p-Chlorophenyl-N′-(4-fluoro-1-naphthyl)-thiourea. Similarly prepared from *p*-chlorophenyl isothiocyanate, this thiourea crystallized from ethanol in colorless needles, m.p. 215°.

Anal. Calcd. for $C_{17}H_{12}ClFN_2S$: C, 61.8; H, 3.7. Found: C, 61.5; H, 3.8.

N-p-Bromophenyl-N′-(4-fluoro-1-naphthyl)thiourea. Prepared from *p*-bromophenyl isothiocyanate, this compound crystallized from ethanol in colorless needles, m.p. 219°.

Anal. Calcd. for $C_{17}H_{12}BrFN_2S$: C, 54.5; H, 3.2. Found: C, 54.4; H, 3.2.

N-p-Chlorophenyl-N′-(4-fluoro-1-naphthyl)urea. Prepared from 4-fluoro-1-naphthylamine (1 mole) and *p*-chlorophenyl isocyanate in benzene, this compound crystallized from that solvent in shiny colorless prisms, m.p. 280°.

Anal. Calcd. for $C_{17}H_{12}ClFN_2O$: C, 64.9; H, 3.8. Found: C, 64.6; H, 3.6.

Bromination of 4-fluoro-1-acetonaphthone. To a solution of 18 g. of ketone I in 30 ml. of dry chloroform, 16 g. of bromine (dissolved in 15 ml. of chloroform) was added portionwise with stirring, and the mixture was warmed at 50° for one hour on the water bath. After cooling, water was added, the chloroform layer was dried over sodium sulfate, and the solvent was distilled. The oily residue deposited 2 g. of *dibromo-4-fluoro-1-acetonaphthone*, which crystallized from ethanol in shiny colorless prisms, m.p. 83°.

Anal. Calcd. for $C_{12}H_7Br_2FO$: C, 41.6; H, 2.0. Found: C, 41.8; H, 2.2.

The residual yellow oil, consisting mainly of the crude 4-fluoro-1-bromoacetonaphthone, was directly used for the following syntheses.

2-(4-Fluoro-1-naphthyl)-8-azapyrimidazole (VII). A solution of 2 g. of 4-fluoro-1-bromoacetonaphthone and 1 g. of 2-aminopyrimidine in ethanol was refluxed for 12 hr. After evaporation of the solvent, the residue was basified with aqueous sodium carbonate, and the solid obtained was recrystallized from ethanol, giving colorless needles, m.p. 158°.

Anal. Calcd. for $C_{16}H_{10}FN_3$: C, 73.0; H, 3.8. Found: C, 72.9; H, 3.8.

β-(4-Fluoro-1-naphthoyl)propionic acid (VIII). To a solution of 200 g. of 1-fluoronaphthalene and 137 g. of succinic anhydride in 800 ml. of nitrobenzene, 200 g. of finely powdered aluminum chloride was added in portions with stirring, and the mixture was left for 24 hr. at room temperature. After decomposition with dilute hydrochloric acid, the nitrobenzene was removed by steam distillation; after cooling, the keto acid obtained was purified *via* the sodium salt, and recrystallized from benzene to yield 100 g. of fine colorless prisms, m.p. 135°.

Anal. Calcd. for $C_{14}H_{11}FO_3$: C, 68.3; H, 4.5. Found: C, 68.5; H, 4.8.

Pfitzinger reactions. These were effected by refluxing for 24 hr. a solution of isatin or one of its 5-halogenated derivatives (1 mole), the ketone (1 mole), and potassium hydroxide (3 moles) in ethanol (in sufficient quantity to make a 15% solution of potassium hydroxide). After evaporation of the ethanol, water was added, the neutral impurities removed by ether extraction, and the *cinchoninic acid* precipitated with acetic acid. Recrystallization was from ethanol or acetic acid, and the yields ranged from 60 to 80%. All the cinchoninic acids, which are listed in Table I, crystallized in yellowish prisms.

2-(4-Fluoro-1-naphthyl)quinoline (VI, R = R′ = H). Prepared by heating the corresponding cinchonic acid above its melting point, this base crystallized from ethanol in shiny colorless needles, m.p. 79°.

Anal. Calcd. for $C_{19}H_{12}FN$: N, 5.1. Found: N, 4.8.

The corresponding *picrate* crystallized from benzene in yellow prisms, m.p. 234°.

6-Chloro-2-(4-fluoro-1-napthyl)quinoline (VI, R = H, R′ = Cl). This quinoline crystallized from ethanol in fine colorless prisms, m.p. 132°.

Anal. Calcd. for $C_{19}H_{11}ClFN$: N, 4.6. Found: N, 4.5.

The compounds described in this paper are currently undergoing biological tests, and results will be published at a later date.

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(9) N. P. Buu-Hoï, N. D. Xuong, and N. H. Nam, *J. Chem. Soc.*, 1573 (1955).