Aza Analogs of 5-(*p*-Fluorophenyl)salicylic Acid[1]

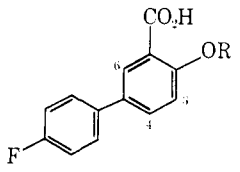
G. L. WALFORD,* H. JONES, AND T. Y. SHEN

Merck Sharp and Dohme Research Laboratories, Rahway, New Jersey 07065

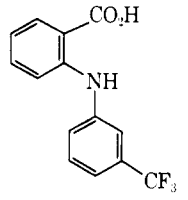
Received September 10, 1970

The chemical synthesis and biological activity of two aza isosteres of the antiinflammatory agent, flufenisal [acetyl-5-(*p*-fluorophenyl)salicylic acid], are described. 6-(*p*-Fluorophenyl)-3-hydroxypicolinic acid (**6**) was prepared by carbonation of 6-(*p*-fluorophenyl)-3-pyridinol; the latter compound was the ultimate product of a lengthy sequence of reactions, the necessity for which is discussed in relation to the general problem of the synthesis of 5-substituted 2-arylpyridines. 2-(*p*-Fluorophenyl)-5-hydroxyisonicotinic acid (**5**) was prepared *via* alkaline hypohalite treatment of 6-(*p*-fluorophenyl)cinchomeronimide, followed by diazotization of the resulting 5-amino-2-(*p*-fluorophenyl)isonicotinic acid. Compound **6** exhibited antiinflammatory and analgetic activity approaching that of flufenisal, while **5** exhibited no significant biological activity.

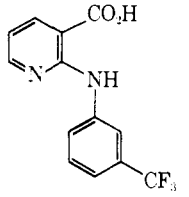
In an extensive evaluation of substituted salicylic acids in these laboratories several years ago, acetyl-5-(*p*-fluorophenyl)salicylic acid (flufenisal, **1a**) was found to be a more potent and less irritating, as well as longer-acting, antiinflammatory and analgetic agent than aspirin.[2] Although the aza isosteres of salicylic acid, the *o*-hydroxypyridinecarboxylic acids,[3] are generally less potent than salicylic acid itself, an aza analog of flufenamic acid (**2**), nifluril (**3**),[4] was introduced recently as an antiinflammatory agent comparable to **2** in potency but with different metabolic properties. Another isostere, triflocin (**4**), was unexpectedly found to possess an interesting degree of diuretic activity.[5] Thus, it was of interest to investigate the corresponding aza analogs of **1**.



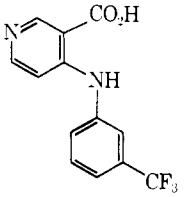
1a, R = Ac
b, R = H



2



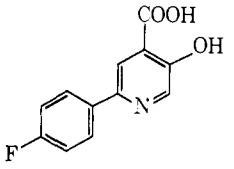
3



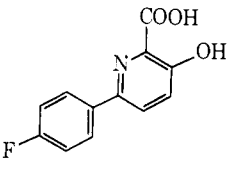
4

Keeping the stereochemistry of *p*-fluorophenyl para to the OH as in **1b**, there are 3 possible aza isosteres, with an N atom replacing C_3, C_4, and C_6, respectively.

Since the 3-aza isostere of **1b**, with the N adjacent to OH, is most likely to assume the 2[1*H*]-pyridone structure, our attention was directed to the synthesis of the 4-aza and 6-aza isosteres, 2-(*p*-fluorophenyl)-5-hydroxyisonicotinic acid (**5**) and 6-(*p*-fluorophenyl)-3-hydroxypicolinic acid (**6**), respectively.



5

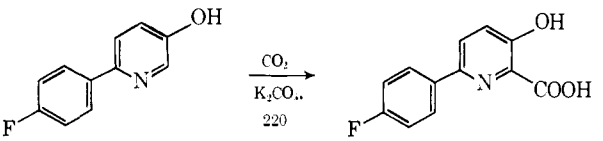


6

Chemistry.—Salicylic acid is readily prepared by the action of CO_2 on PhONa (Kolbe–Schmitt synthesis). The reaction has been extended to relatively few OH heterocyclic aromatic compounds, although 3-pyridinol has been carbonated successfully by both the Kolbe–Schmitt procedure and its Marassé modification.[6-8]

The course of the carbonation of 3-pyridinol is highly dependent on the reaction conditions employed, the products being 3-hydroxypicolinic acid, 5-hydroxypicolinic acid, or mixtures of both. Although there appears to be no reason for a marked difference in reactivity at the two ortho positions in 3-pyridinol, no 3-hydroxyisonicotinic acid has ever been isolated.

These considerations suggested that 6-(*p*-fluorophenyl)-3-hydroxypicolinic acid (**6**) should be formed exclusively on application of the Kolbe-Schmitt reaction to 6-(*p*-fluorophenyl)-3-pyridinol (**7**).



7 6

The preparation of the key intermediate **7** is outlined below.

3-Cyano-6-(*p*-fluorophenyl)-2[1*H*]-pyridone (**8**) was prepared by condensation of the Na salt of *p*-fluorobenzoylacetaldehyde with cyanoacetamide in the presence of piperidine acetate catalyst.[9-11] Chlorodehy-

(1) A preliminary account of this work was presented before the Division of Medicinal Chemistry (CIC) at the Joint Conference of the Chemical Institute of Canada and the American Chemical Society, Toronto, Canada, May 1970; Abstracts of Papers, MEDI 19 (1970).

(2) (a) J. Hannah, W. V. Ruyle, K. Kelly, A. Matzuk, W. J. Holtz, B. E. Witzel, C. A. Winter, R. H. Silber, and T. Y. Shen, *Clin. Pharmacol. Ther.*, **11**, 747 (1970); (b) S. Bloomfield, T. Barden, and R. Hille, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **29**, 686 (1970).

(3) (a) W. O. Foye, M. D. Baum, and D. A. Williams, *J. Pharm. Sci.*, **56**, 332 (1967). (b) W. O. Foye and J. M. Kauffman, *Chim. Ther.*, **2**, 462 (1967).

(4) C. Hoffmann and A. Faure, *Bull. Soc. Chim. Fr.*, 2316 (1966).

(5) R. Z. Gussin, J. R. Cummings, E. H. Stokey, and M. A. Ronsberg, *J. Pharmacol. Exp. Ther.*, **167**, 194 (1969).

(6) H. Bojarska-Dahlig and T. Urbański, *Pr. Placowek Nauk-Badawcz. Ministerstwa Przemyslu Chem.*, 1 (1952); *Chem. Abstr.* **48**, 1337*i* (1954).

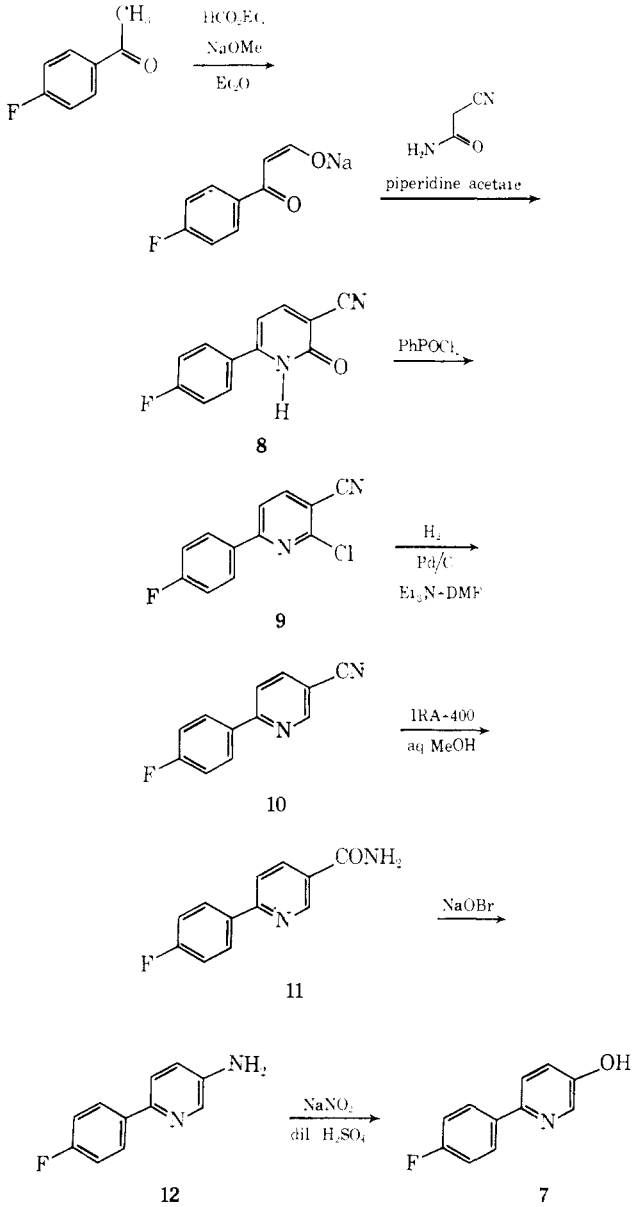
(7) H. Bojarska-Dahlig and T. Urbański, *Rocz. Chem.*, **26**, 158 (1952).

(8) O. Baine, G. F. Adamson, J. W. Barton, J. L. Fitch, D. R. Swayampati, and H. Jeskey, *J. Org. Chem.*, **19**, 510 (1954).

(9) *Cf.* R. P. Mariella, *J. Amer. Chem. Soc.*, **69**, 2670 (1947).

(10) *Cf.* (a) W. Gruber and K. Schlogl, *Monatsh. Chem.*, **81**, 83 (1950). (b) R. P. Mariella and R. Stansfield, *J. Amer. Chem. Soc.*, **73**, 1368 (1951).

(11) *Cf.* C. Barat, *J. Indian Chem. Soc.*, **8**, 801 (1931).



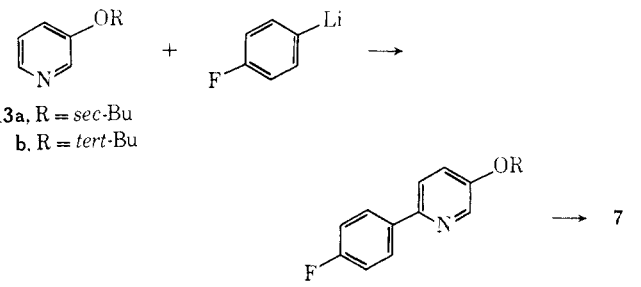
droxylation of **8** did not proceed well with $POCl_3$–PCl_5 at reflux; phenylphosphonic dichloride[12] provided an extremely useful alternative, however. With this reagent at 180°, 2-chloro-3-cyano-6-(*p*-fluorophenyl)pyridine (**9**) was obtained in excellent yield. Removal of the 2-chloro substituent by hydrogenolysis occurred smoothly in DMF in the presence of 1 equiv of Et_3N as acid scavenger; the more usual solvent for hydrogenolysis, EtOH, was ineffective in this reaction, quite probably because of the limited solubility of the substrate. Hydration of 6-(*p*-fluorophenyl)nicotinonitrile (**10**) was accomplished catalytically with the synthetic ion-exchange resin IRA-400 (OH^- form).[13] Conversion of 6-(*p*-fluorophenyl)nicotinamide (**11**) by the Hofmann reaction into 5-amino-2-(*p*-fluorophenyl)pyridine (**12**), and diazotization of **12** afforded the required 6-(*p*-fluorophenyl)-3-pyridinol (**7**).

This synthesis, although reasonably straightforward, is lengthy and time consuming, an apparently unavoidable circumstance. 6-Aryl-3-pyridinols such as **7** represent a heretofore unknown class of compounds for which a more direct method of synthesis is evidently not available. Classically, the preparation of arylpyridines has involved the use either of diazo or of organometallic compounds, and indeed, both methods immediately suggested appealingly short routes to **7**. Further investigation, however, soon uncovered serious limitations on the applicability of either method to the present synthesis.

Arylation with diazo compounds involves the reaction of an aryl compound with a diazo- or nitrosoacylaminopyridine[14,15] or conversely, of pyridine with an aryldiazo compound.[16] The former approach succeeds well with 3-aminopyridine and its derivatives, but is reported to fail entirely with derivatives of 2-aminopyridine due to difficulty in diazotizing the α-amino group or in nitrosating the *N*-acyl derivative. The latter approach has evidently never been investigated in the case of 3-substituted pyridines, but a complex mixture of products might be anticipated.

Arylation of pyridine with organometallic compounds, particularly LiAr, provides 2-arylpyridines exclusively.[17,18] Similarly, arylation of a 2- or 4-substituted pyridine with 1 mole of LiAr can lead to the formation of only a single product. On the other hand, arylation of a 3-substituted pyridine may lead to one of two possible products, the 2-aryl-3-substituted pyridine or the 2-aryl-5-substituted pyridine, or to a mixture of both. Although contradictory observations concerning the orientation of addition of ArLi compounds to 3-substituted pyridines have appeared,[19–25] the best evidence would seem to indicate that the product which usually predominates is the 2-aryl-3-substituted pyridine, and not the corresponding 2,5 isomer.

It is possible, however, that the 3 substituent may exert a steric effect upon the orientation of the entering aryl group.[21,23] A bulky 3-pyridinol ether, such as 3-*sec*-butoxypyridine (**13a**) or 3-*tert*-butoxypyridine (**13b**), for example, might be arylated preferentially at C_6.



13a, R = *sec*-Bu
b, R = *tert*-Bu

In order to test this hypothesis, *p*-FC_6H_4Li was prepared at −70° by reaction of *n*-BuLi with *p*-FC_6H_4Br.

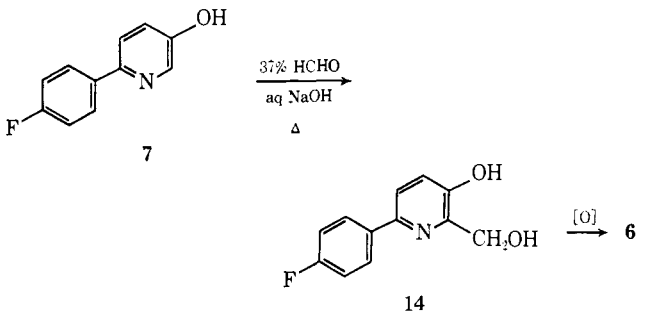
(12) M. M. Robison, *J. Amer. Chem. Soc.*, **80**, 5481 (1958).
(13) *Cf.* A. Galat, *ibid.*, **70**, 3945 (1948).
(14) H. Rapoport, M. Look, and G. J. Kelly, *ibid.*, **74**, 6293 (1952).
(15) W. J. Adams, D. H. Hey, P. Mamalis, and R. E. Parker, *J. Chem. Soc.*, 3181 (1949).
(16) W. E. Bachmann and R. A. Hoffman, *Org. React.*, **2**, 224 (1944).
(17) K. Ziegler and H. Zeiser, *Ber.*, **63**, 1847 (1930).
(18) J. C. W. Evans and C. F. H. Allen, "Organic Syntheses," Coll. Vol. II, Wiley, New York, N. Y., 1943, p 517.
(19) A. D. Miller, C. Osuch, N. N. Goldberg, and R. Levine, *J. Amer. Chem. Soc.*, **78**, 674 (1956).
(20) R. H. Wiley, C. H. Jarboe, P. X. Callahan, and N. J. Nielsen, *J. Org. Chem.*, **23**, 780 (1958).
(21) R. A. Abramovitch, G. C. Seng, and A. D. Notation, *Can. J. Chem.*, **38**, 761 (1960).
(22) R. A. Abramovitch, G. C. Seng, and A. D. Notation, *ibid.*, **38**, 1445 (1960).
(23) R. A. Abramovitch, K. S. Ahmed, and C. A. Giam, *ibid.*, **40**, 213 (1962).
(24) R. A. Abramovitch and C. S. Giam, *ibid.*, **41**, 3127 (1963).
(25) R. A. Abramovitch and C. S. Giam, *ibid.*, **42**, 1627 (1964).

Unfortunately, under conditions at which it was stable (*ca.* −50°), *p*-FC_6H_4Li did not react with 3-*sec*-butoxypyridine; as a preparative method for the required 6-*p*-fluorophenyl-3-pyridinol (**7**), then, this approach was of no value.

On the other hand, the more stable PhLi could be added to the alkoxypyridines **13** at room temp. Work-up with H_2O afforded mixtures of the corresponding 3- and 5-alkoxy-2-phenyl-1,2-dihydropyridines, from which the respective alkoxyphenylpyridines were obtained either by air oxidation on distillation or by passing in O_2.

Interestingly, the product of the addition of PhLi to 3-*tert*-butoxypyridine (**13b**) was shown to contain a large preponderance (4:1) of 3-*tert*-butoxy-2-phenylpyridine over the 5,2 isomer. By contrast, in accordance with the anticipated steric effect of a bulky 3-substituent, addition of PhLi to 3-*tert*-butylpyridine is reported[23] to give a product containing 95.5% of 5-*tert*-butyl-2-phenylpyridine.

As anticipated, carbonation of pyridinol **7** by means of the Marassé modification of the Kolbe–Schmitt reaction afforded 6-(*p*-fluorophenyl)-3-hydroxypicolinic acid (**6**). Furthermore, hydroxymethylation of pyridinol **7** could be effected readily by treatment with alkaline aq CH_2O; oxidation of the product **14** either directly,[26] or subsequent to protection of the phenolic



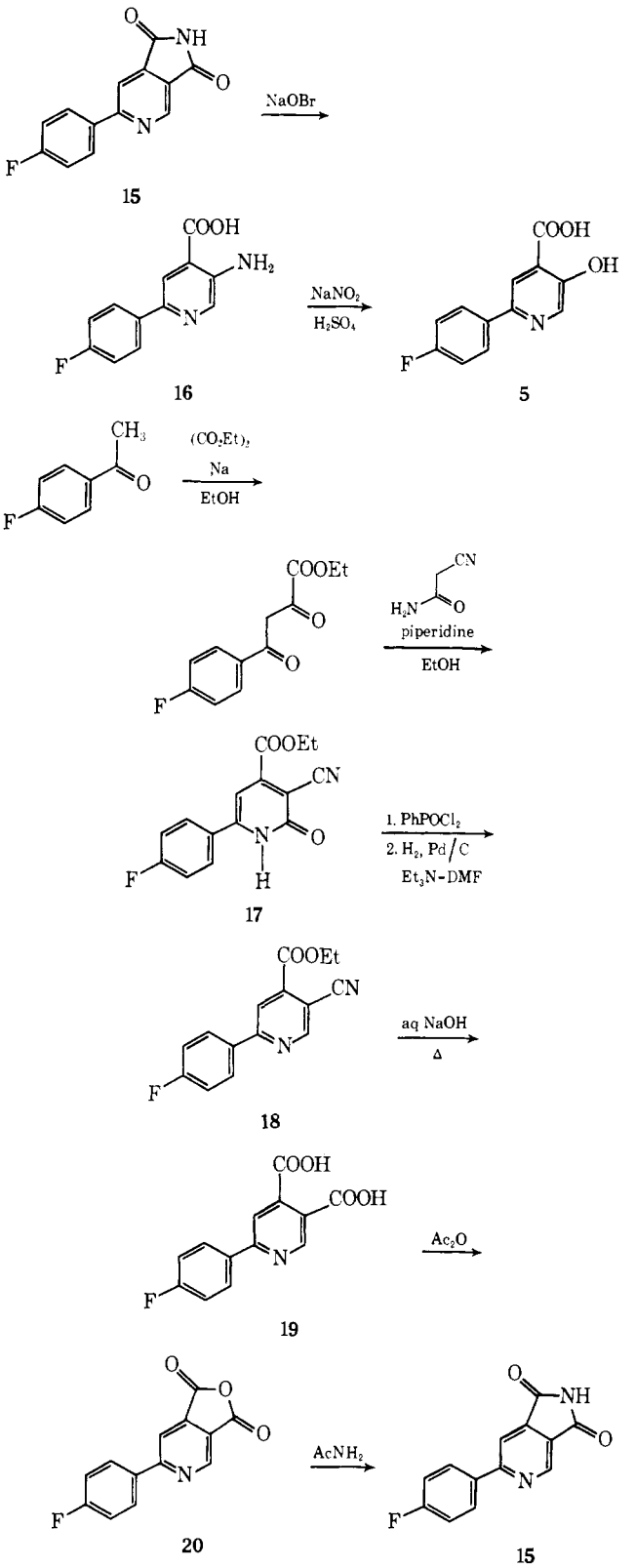
OH,[27] provides an alternative route to **6**.

Although not available from 3-pyridinol *via* the Kolbe–Schmitt reaction, 3-hydroxyisonicotinic acid is a known compound, its synthesis having been achieved through alkaline hypohalite treatment of cinchomeronimide, followed by diazotization of the resulting 3-aminoisonicotinic acid.[28–31] A similar reaction sequence was applied successfully to the synthesis of 2-(*p*-fluorophenyl)-5-hydroxyisonicotinic acid (**5**).

The possibility that application of the Hofmann reaction to 6-(*p*-fluorophenyl)cinchomeronimide (**15**) might lead to 4-amino-6-(*p*-fluorophenyl)nicotinic acid rather than 5-amino-2-(*p*-fluorophenyl)isonicotinic acid (**16**) was ruled out on the basis of the spectral properties of **16** and its diazotization product **5** which are entirely compatible with the structures depicted.

6-(*p*-Fluorophenyl)cinchomeronimide (**15**) was prepared as outlined below.

Condensation of ethyl *p*-fluorobenzoylpyruvate with cyanoacetamide in the presence of piperidine afforded



4-carboethoxy-3-cyano-6-(*p*-fluorophenyl)-2[1*H*]-pyridone (**17**).[32] Chlorodehydroxylation followed by hydrogenolysis using the reaction conditions described previously gave 4-carboethoxy-3-cyano-6-(*p*-fluorophenyl)pyridine (**18**) which, on alkaline hydrolysis, was converted into 6-(*p*-fluorophenyl)cinchomeronic acid

(26) *Cf.* T. Urbański, *J. Chem. Soc.*, 1104 (1946).
(27) *Cf.* J. T. Sheehan, *J. Org. Chem.*, **31**, 636 (1966).
(28) S. Gabriel and J. Colman, *Ber.*, **35**, 2831 (1902).
(29) H. H. Fox, *J. Org. Chem.*, **17**, 547 (1952).
(30) H. H. Fox and J. T. Gibas, *ibid.*, **17**, 1653 (1952).
(31) K. C. Blanchard, E. H. Dearborn, L. C. Lasagna, and E. L. Buhle, *Bull. Johns Hopkins Hosp.*, **91**, 330 (1952).
(32) *Cf.* D. Liebermann, N. Rist, F. Grumbach, S. Clas, M. Moyeux, and A. Rouaix, *Bull. Soc. Chim. Fr.*, 687 (1958).

(**19**). The corresponding imide (**15**) was then prepared *via* the anhydride (**20**).[33]

Biological Activity.—The antiinflammatory activity of **5** and **6** as measured by the carrageenin-induced foot-edema assay in rats[34] is summarized in Table I. The

TABLE I
ANTIINFLAMMATORY ACTIVITY IN THE CARRAGEENIN EDEMA ASSAY

Compound	Dose, mg/kg	Foot-vol inhibition, %
5	10	10
	30	14
6	10	27
	30	43
	90	74
Flufenisal (1a)	10	38
	30	44
	90	68
Aspirin	30	25
	90	37
	270	74

corresponding activities of aspirin and flufenisal (**1a**) are listed for comparison. Obviously, the 6-aza isostere **6**, with a potency approaching that of **1a**, is much more active than the 4-aza isostere **5**.

In the yeast-induced hyperesthesia test,[35] **6** was somewhat comparable to aspirin in elevating the threshold of the inflamed foot in the rat, with an effective dose of *ca.* 120 mg/kg. At this dose level, **5** showed marginal analgesia only.

Unlike triflocin (**4**), **6** exhibited no significant diuretic activity. In common with many salicylates,[36] **6** showed marginal hypoglycemic activity in the adrenalectomized rat.

Experimental Section

Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Mr. R. N. Boos and his associates; where analyses are indicated only by symbols of the elements, the analytical results obtained for those elements were within ±0.4% of the theoretical values.

3-Cyano-6-(*p*-fluorophenyl)-2[1*H*]-pyridone (8). A.—To a well-stirred, ice-cold suspension of NaOMe (39.1 g, 0.725 mole) in anhyd Et_2O (600 ml) was added dropwise a mixt of *p*-fluoroacetophenone (100 g, 0.725 mole) and ethyl formate (53.7 g, 0.725 mole). When the addition was complete (*ca.* 3 hr), the ice bath was removed, and the reaction mixt was stirred overnight at room temp.

B.—The above thick, Et_2O suspension of the Na salt of *p*-fluorobenzoylacetaldehyde was extd with H_2O (400 ml). The aq phase was sepd, and to it was added cyanoacetamide (61.0 g, 0.725 mole) and a soln prepd from AcOH (10 ml), H_2O (25 ml), and sufficient piperidine to give an alkaline reaction. The resulting aq reaction mixt was heated under reflux for 2 hr, acidified with AcOH, and chilled thoroughly. The ppt of 3-cyano-6-(*p*-fluorophenyl)-2[1*H*]-pyridone was collected by filtration, washed thoroughly by slurrying with H_2O and EtOH, and dried. The recovery of crude product suitable for further chemical modification was 100 g (65%). Recrystn of a small quantity of crude **8** from EtOH afforded an anal. sample as very fine, pale yellow needles, mp 304–307°. *Anal.* ($C_{12}H_7FN_2O$) C, H, N.

2-Chloro-3-cyano-6-(*p*-fluorophenyl)pyridine (9).—A mixt of **8** (42.8 g, 0.20 mole) and $PhPOCl_2$ (78 g, 0.40 mole) was heated at 180° with exclusion of moisture for 4 hr. On cooling, the mixt was treated with ice-H_2O (500 ml), and the resulting suspension was rendered slightly alk by addn of concd NH_4OH. The solid was collected by filtration and washed thoroughly with H_2O and EtOH. The recovery of **9**, mp 174–176°, suitable for further chemical transformation, was 42.4 g (91%).

For purposes of characterization, a small sample was recrystd from EtOH (decolorizing C) affording colorless needles, mp 175–176°. *Anal.* ($C_{12}H_6ClFN_2$) C, H, N.

6-(*p*-Fluorophenyl)nicotinonitrile (10).—Compound **9** (42.4 g, 0.18 mole) was hydrogenolyzed in DMF (270 ml) in the presence of Et_3N (18.4 g, 0.18 mole) and 10% Pd/C (4.2 g) at room temp and under an H_2 pressure of 2.8 kg/cm². When 1 equiv of H_2 had been consumed, the reaction was stopped and the mixt was filtered. Dilution of the filtrate with H_2O (*ca.* 500 ml) afforded a solid grey ppt which was collected by filtration, washed thoroughly with H_2O, and dried overnight *in vacuo* at 50°. The crude solid (35.5 g) was treated with concd HCl (150 ml) at room temp, and the resulting mixt was filtered to remove considerable dark, acid-insol material. The pale yellow filtrate was cooled in an ice bath and rendered strongly alk by the addn of aq NaOH. The pptd creamy-white, amorphous solid was collected by filtration, washed thoroughly with H_2O, and dried *in vacuo* at 50°. Crystn of the crude product (18.0 g) from EtOH (350 ml) afforded **10** (15.1 g, 42%), mp 143–147°, of suitable purity for further chemical transformation. Recrystn of a small quantity from EtOH afforded an anal. sample as colorless needles, mp 146–148°. *Anal.* ($C_{12}H_7FN_2$) C, H, N.

6-(*p*-Fluorophenyl)nicotinamide (11).—The commercial synthetic ion-exchange resin, Amberline IRA-400 (30 g), was stirred with aq 5% NaOH (150 ml) for 10 min at room temp. The resin was then collected by filtration and washed to neutrality with distd H_2O. Finally, the resin was washed thoroughly with MeOH.

Compd **10** (15.1 g, 0.076 mole) was dissolved with warming in a mixt of MeOH (240 ml) and H_2O (60 ml). To this soln was added the resin prepared above, and the mixt was heated under reflux, with vigorous stirring, for 4 hr. The hot mixt was filtered, and the collected resin was washed thoroughly with hot MeOH to redissolve product which had begun to separate. The combined filtrate and washings were concd on the steam bath to a final vol of *ca.* 300 ml, and then chilled thoroughly, yielding **11** (11.4 g, 70%) as colorless needles, mp 233–234°. *Anal.* ($C_{12}H_9FN_2O$) C, H, N.

5-Amino-2-(*p*-fluorophenyl)pyridine (12).—To an ice-cold soln of NaOH (12.8 g, 0.32 mole) in H_2O (150 ml), Br_2 (10.2 g, 0.064 mole) was added dropwise. Ice cooling of the resulting soln was contd while a thick paste, prepd by thoroughly grinding **11** (11.4 g, 0.053 mole) with a little H_2O, was added portionwise, with stirring, during 30 min. The mixt was then stirred at 0° for an addnl 30 min, during which time virtually complete soln of the added solid occurred.

The ice bath was not replenished, the soln being allowed to warm gradually to room temp during the next 2 hr. Finally, it was warmed gradually to 80° in an oil bath, and then maintained at that temp for 1 hr. As the reaction temp was increased, the color of the soln darkened, and a chocolate-brown solid began to sep. The mixt was chilled thoroughly, and the brown solid was collected by filtration, washed thoroughly with H_2O, and dried *in vacuo* at 35–40°; the recovery was 6.7 g. Extn of the combined aq mother liquor and washings with Et_2O (3 × 150 ml), followed by drying ($MgSO_4$) of the combined Et_2O exts and evapn under reduced pressure, gave an addnl 0.6 g of crude product.

The total crude solid (7.3 g) was extd thoroughly with Et_2O, the soln filtered from Et_2O-insol material, and the filtrate concd and treated with hexane to incipient crystn. Compd **12** (4.9 g, 49%) was recovered as stout, brownish needles, mp 101–105°, suitable for further chemical transformation. Recrystn of a small portion of this material from Et_2O-hexane with decolorizing C provided a sample suitable for microanalysis as fine, colorless needles, mp 104–105°. *Anal.* ($C_{11}H_9FN_2$) C, H, N.

6-(*p*-Fluorophenyl)-3-pyridinol (7).—Compd **12** (4.7 g, 0.025 mole) was dissolved with gentle warming in 2 *N* H_2SO_4 (85 ml). The soln was cooled in an ice bath, while $NaNO_2$ (1.9 g, 0.0275 mole) was added portionwise with stirring. When the addn was complete, the ice bath was not replenished, and the soln was allowed to warm to room temp, with continued stirring, during the next hour, then on the steam bath until evolution of N_2 ceased

(33) *Cf.* C. M. Atkinson and B. N. Biddle, *J. Chem. Soc. C*, 2053 (1966).
(34) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962).
(35) C. A. Winter and L. Flataker, *J. Pharmacol. Exp. Ther.*, **150**, 165 (1956).
(36) V. Fang, W. O. Foye, S. M. Robinson, and H. J. Jenkins, *J. Pharm. Sci.*, **57**, 2111 (1968).

(*ca.* 15 min), and then was filtered by gravity, while still warm, from a little, dark, insol material. The filtrate was cooled in ice while its pH was adjusted to about 6 by the addn of dil aq NaOH. Compd **7** (4.4 g, 93%) sepd as a creamy white solid which was collected by filtration, washed with H_2O, and air-dried, mp 143–147°. Recrystn from the min quantity of C_6H_6 gave fine, colorless needles (3.5 g), mp 145–147°. An addnl recrystn from C_6H_6 afforded an anal. sample, mp 147–147.5°. *Anal.* ($C_{11}H_8FNO$) C, H, N.

6-(*p*-Fluorophenyl)-3-hydroxypicolinic Acid (6).—Compd **7** (380 mg, 2.0 mmoles) and anhyd K_2CO_3 (1.9 g, excess) were mixed intimately by grinding together in a mortar. The mixt was dried overnight *in vacuo* at 60°, and then was heated for 10 hr at 220° under a CO_2 pressure of 70.3 kg/cm². The mixt was taken up in H_2O (20 ml), and the resulting suspension was digested for a short time on the steam bath. Upon cooling, the suspended brown solid was collected by filtration, washed thoroughly with H_2O, and dried in air; the recovery was 415 mg.

The crude solid was digested for a short time on the steam bath with dil aq NaOH (2.5 *N* NaOH (4 ml) dild with H_2O to *ca.* 25 ml). Dark, insol material was removed by filtration, and the filtrate was then cooled in ice and acidified strongly with concd HCl. The pale yellow, amorphous ppt of crude **6** was collected by filtration, washed thoroughly with H_2O, and dried; the recovery of crude product, mp 155–160°, was 200 mg (47%). Final purification was effected by sublimation *in vacuo* at 100°. A 160-mg sample afforded 130 mg of pure **6** as very fine, colorless needles; mp 161–163°; τ (DMSO) 0.21 [broad singlet (2)], 1.83 [doublet of doublets (2), J = 9.0 cps and J = 5.5 cps], 1.87 [doublet (1), J = 9.0 cps], 2.47 [doublet (1), J = 9.0 cps], 2.70 [triplet (2), J = 9.0 cps] ppm. *Anal.* ($C_{12}H_8FNO_3$) C, H, N, F.

6-(*p*-Fluorophenyl)-3-hydroxy-2-hydroxymethylpyridine (14).—A soln of **7** (946 mg, 5.0 mmoles) in 2.5 *N* NaOH (2.2 ml, 5.5 mmoles) and 37% HCHO (1.4 ml, *ca.* 15 mmoles) was heated under reflux for 1.5 hr. Upon cooling, the soln was treated with AcOH (0.5 ml), affording a viscous oil which was induced to solidify by vigorous rubbing with a spatula. The solid was collected by filtration, washed thoroughly with H_2O, and dried. The yield of crude **14**, mp 166–170°, was quantitative (1.10 g). Crystn from EtOH provided an anal. sample, mp 170–172°. *Anal.* ($C_{12}H_{10}FNO_2$) C, H, N.

3-*sec*-Butoxypyridine (13a); 3-*tert*-Butoxypyridine (13b).—The general procedure developed by Fürst and Dietz[37] for the prepn of 3-alkoxypyridines was employed. 3-*sec*-Butoxypyridine was recovered in 14% yield by fractional distn of the crude reaction mixt *in vacuo*, bp 78–79° (2 mm). With 3-*tert*-butoxypyridine, the yield was lower (3%), bp 90–94° (4 mm).

***p*-Fluorophenyllithium.**[38]—A soln of 2.25 *N* *n*-BuLi in hexane (100 ml, 0.225 mole) was added with stirring under Ar to a soln of *p*-FC_6H_4Br (35.0 g, 0.2 mole) in Et_2O (200 ml) at −70° to −80°. The mixt was stirred for 10 min at this temp. A syringe sample of known volume was removed *via* an injection port, and added immediately to an equimolar quantity of Ph_2CO in Et_2O. Subsequently, the sample reaction mixt was extd with 5% HCl, and the Et_2O phase sepd, dried ($MgSO_4$), and evapd *in vacuo* to give *p*-fluorophenyldiphenylcarbinol (89% based on Ph_2CO), mp 120–121° (*lit.*[39] 121–122°), yielding a chloride, mp 90–91° (*lit.*[39] 91–92°).

The Et_2O soln of *p*-FC_6H_4Li was thus quantitatively standardized based on these figures. It was kept in the dark at −70° and normally used immediately.

***p*-FC_6H_4Li and 3-*sec*-Butoxypyridine.**—A soln of 3-*sec*-butoxypyridine (21.0 g, 0.139 mole) in Et_2O (50 ml) was run into a freshly prepared soln of *p*-FC_6H_4Li in hexane-Et_2O (300 ml, 0.178 mole) at −70° with stirring under Ar. A sample aliquot was removed and the free base isolated using basic washing. The residue was identified as essentially pure unreacted starting material by vpc and ir spectrum.

The reaction was run at −40° with the same result. At 0°, the *p*-FC_6H_4Li decompd rapidly.

PhLi and 3-*sec*-Butoxypyridine.—A soln of 3-*sec*-butoxypyridine (20.4 g, 0.135 mole) in Et_2O (25 ml) was added with stirring under Ar to PhLi (2.24 *M* in C_6H_6-Et_2O, 70:30, 72.33 g, 0.161 mole) in Et_2O (75 ml), at such a rate that the Et_2O slowly refluxed. The mixt was refluxed for another 2 hr after the addn was complete. A probe was removed and worked up by the addn of H_2O. Vpc on 3% SE 30 on Chromosorb W, 3 mm × 3.1 m column, showed two main peaks plus a smaller one in the ratio 4:4:1. The total reaction mixt was then worked up similarly to give an oil (27.0 g). Distn of the crude oil served to oxidize the alkoxyphenyldihydropyridines present; bubbling through air or O_2 also had the same effect. An nmr spectrum in the aromatic region indicated that the product was a mixt of unchanged starting material together with 3- and 5-*sec*-butoxy-2-phenylpyridine (4:1). Fractional distn followed by prep vpc on similar columns to those described, provided samples of both Ph-substituted isomers: *m/e* 226; τ($CDCl_3$) for 3-*sec*-butoxy-2-phenylpyridine, 1.75 [doublet of doublets (1), J = 4.2 cps and J = 2.0 cps], 2.07 [multiplet (2)], 2.73 [multiplet (5)], 5.76 [multiplet (1)], 8.3 [multiplet (2)], 8.73 [multiplet (3)], 9.07 [triplet (3)] ppm; τ ($CDCl_3$) for 5-*sec*-butoxy-2-phenylpyridine, 1.94 [doublet (1), J = 2.0 cps], 2.1 [multiplet (2)], 2.73 [multiplet (5)] ppm, the remaining peaks due to the *sec*-BuO moiety as above.

4-Carboethoxy-3-cyano-6-(*p*-fluorophenyl)-2[1*H*]-pyridone (17). A. Ethyl *p*-Fluorobenzoylpyruvate.—Na (3.5 g, 0.15 g-atom) was dissolved in abs EtOH(200 ml). The soln was kept in an ice-salt bath, while a soln of diethyl oxalate (21.9 g, 0.15 mole) and *p*-fluoroacetophenone (20.7 g, 0.15 mole) in abs EtOH (100 ml) was added dropwise, with stirring, at such a rate that the reaction temp did not exceed 5°. As the addn progressed, addnl EtOH (total vol, 200 ml) was added to the reaction mixt at intervals to facilitate stirring. When the addn was complete, the ice bath was not replenished, and the mixt was stirred overnight at room temp. It was again cooled in ice, while being rendered strongly acidic with 20% H_2SO_4. Insol salts were removed by filtration, and the filtrate was dild with H_2O (500 ml) and extd with C_6H_6 (2 × 250 ml). The combined org exts were washed with aq 10% $NaHCO_3$ and with H_2O, dried ($MgSO_4$), and filtered, and the filtrate was evapd under reduced pressure to give a brown oily residue. Trituration of the oil with petr ether served to induce crystn. The crystals were collected by filtration, and washed thoroughly by slurrying with petr ether to remove colored impurities. The ethyl *p*-fluorobenzoylpyruvate so obtained was of suitable quality for further chemical transformation; the recovery was 17.3 g (49%), mp 47–49°. Recrystn from petr ether-C_6H_6 (10:1 v/v) afforded an anal. sample as practically colorless needles, mp 48–49.5°. *Anal.* ($C_{12}H_{11}FO_4$) C, H.

B. 4-Carboethoxy-3-cyano-6-(*p*-fluorophenyl)-2[1*H*]-pyridone.—Ethyl *p*-fluorobenzoylpyruvate (11.9 g, 0.05 mole) and cyanoacetamide (4.2 g, 0.05 mole) were dissolved with gentle warming in abs EtOH (60 ml). The soln was maintained at 60° in an oil bath while piperidine (1.6 ml) was added dropwise, with stirring, during 15 min. A mildly exothermic reaction ensued, the internal temp rising to *ca.* 70°; within a few min, a yellow cryst solid began to sep. When the addn of piperidine was complete, the mixt was stirred for 1 hr longer at 65–70°. After thorough chilling of the mixt, the yellow solid was collected by filtration and washed with EtOH. The yield of **17**, mp 255–257°, was 8.2 g (57%). Recrystn from aq AcOH provided a sample suitable for microanal., mp 256–257°. *Anal.* ($C_{15}H_{11}FN_2O_3$) C, H, N.

4-Carboethoxy-2-chloro-3-cyano-6-(*p*-fluorophenyl)pyridine.—Chlorodehydroxylation of 4-carboethoxy-3-cyano-6-(*p*-fluorophenyl)-2[1*H*]-pyridone (28.6 g, 0.10 mole) with $PhPOCl_2$ (39.0 g, 0.20 mole) as described previously for the prepn of **9** afforded the product (28.5 g, 94%) as stout, pale yellow needles, mp 148–150°. An anal. sample was prepared by recrystn from EtOH; pale yellow needles, mp 150–151°. *Anal.* ($C_{15}H_{10}ClFN_2O_2$) C, H, N.

4-Carboethoxy-3-cyano-6-(*p*-fluorophenyl)pyridine (18).—Hydrogenolysis of 4-carboethoxy-2-chloro-3-cyano-6-(*p*-fluorophenyl)pyridine (28.5 g, 0.094 mole) was carried out as described previously for the prepn of **10**. Extn of the crude product with concd HCl (75 ml), followed by filtration, and treatment of the filtrate with aq NaOH until strongly alk provided **18** (23.0 g, 90%) of sufficient purity for further chemical transformation, mp 135–137°. A small sample was crystd from aq EtOH affording fine, colorless needles, mp 136–137°. *Anal.* ($C_{15}H_{11}FN_2O_2$) C, H, N.

6-(*p*-Fluorophenyl)cinchomeronic Acid (19).—A suspension of **18** (23.0 g, 0.085 mole) in aq NaOH (17.0 g (0.425 mole) of NaOH in 120 ml of H_2O) was heated under reflux with stirring. The suspended solid dissolved slowly; NH_3 was evolved. Refluxing was continued until evolution of NH_3 could no longer be detected (*ca.* 5 hr). The soln was allowed to cool, and then was filtered by

(37) H. Fürst and H. J. Dietz, *J. Prakt. Chem.*, **4**, 147 (1956).
(38) H. Gilman and R. D. Gorsich, *J. Amer. Chem. Soc.*, **77**, 3919 (1955).
(39) S. T. Bowden and T. F. Watkins, *J. Chem. Soc.*, 1249 (1940).

gravity from a little, suspended, dark solid. The filtrate was cooled in ice, and acidified to congo red with dil HNO_3. The ppt of **19** was collected by filtration, washed thoroughly with H_2O, and dried *in vacuo* at 50°. The crude product (16.7 g, 75%) was suitable for use without further purification. Recrystn of a small sample from aq HCOOH afforded an anal. sample, mp 241–243° dec. *Anal.* ($C_{13}H_8FNO_4$) C, H, N.

6-(*p*-Fluorophenyl)cinchomeronimide (15). A. 6-(*p*-Fluorophenyl)cinchomeronic Anhydride (20).—A mixt of **19** (16.2 g, 0.062 mole) and Ac_2O (100 ml) was heated in an oil bath at 85–90° for 5 hr with exclusion of moisture. The suspended diacid dissolved slowly during the first hour. Thorough chilling of the soln afforded crude **20** as a yellow cryst ppt which was collected by filtration and used immediately for conversion into the imide; the yield was quantitative.

B. 6-(*p*-Fluorophenyl)cinchomeronimide.—The collected crude anhydride was mixed with $AcNH_2$ (18.5 g, 0.31 mole), Ac_2O (5 ml) was added, and the mixt was heated in an oil bath at 125–130°, with stirring, for 6 hr. The reaction mixt was allowed to cool, and the ppt was collected by filtration, washed, first with a little AcOH, and then thoroughly with H_2O, and dried in air. The recovery of brown solid, mp 253–256°, suitable for further chemical transformation, was 7.1 g (47%). The crude product could be recrystd with the aid of decolorizing C from Me_2CO providing pure material as a pale yellow, microcryst solid, mp 255–256°. *Anal.* ($C_{13}H_7FN_2O_2$) C, H, N.

5-Amino-2-(*p*-fluorophenyl)isonicotinic Acid (16).—6-(*p*-Fluorophenyl)cinchomeronimide (4.8 g, 0.02 mole) was added in small portions to a well-stirred, ice-cold soln of Br_2 (3.5 g, 0.022 mole) in aq NaOH (4.8 g (0.12 mole) of NaOH in 50 ml of H_2O). When the addn was complete, the mixt was stirred for 1 hr at 0°, and then for 1 hr at 70–80°. The resulting dark soln was cooled in ice, and rendered strongly acidic with concd HCl giving a brown, gelatinous ppt. It was collected by filtration, washed thoroughly with H_2O, and then suspended in boiling MeOH (250 ml). Sufficient DMF was then added to the MeOH suspension to effect complete soln. After filtration, the hot soln was treated with H_2O to incipient crystn and chilled thoroughly. The product **16** (3.7 g, 80%) was obtained as a high-melting (dec >300°), straw-colored, cryst solid suitable for chemical transformation. On recrystn from MeOH-DMF-H_2O, 2 crystn modifications could be obtained. One of these, fine, straw-colored needles, decompn endotherm at 338° (DTA at 20°/min in air), was hygroscopic. After being dried *in vacuo* at 40–45° overnight, a sample analyzed for 0.7 mole of H_2O. In addition to the decompn endotherm at 338°, the DTA analysis exhibited a broad endotherm at *ca.* 160° corresponding to loss of solvent. A tga analysis (110° under dry N_2) indicated a loss on drying of 4.9%; on exposure to the atm at room temp, the dried sample regained weight rapidly. *Anal.* ($C_{12}H_9FN_2O_2 \cdot 0.7H_2O$) C, H, N, LOD.

The second cryst modification, a golden-yellow, microcryst solid, decompn endotherm at 335° (DTA at 20°/min in air), was a stable, nonhygroscopic form: τ (DMSO) 1.63 [singlet (1)], 1.98 [singlet (1)], 2.02 [doublet of doublets (2), J = 5.5 cps and J = 9.0 cps], 2.76 [triplet (2), J = 9.0 cps] ppm. *Anal.* ($C_{12}H_9FN_2O_2$) C, H, N, F.

2-(*p*-Fluorophenyl)-5-hydroxyisonicotinic Acid (5).—5-Amino-2-(*p*-fluorophenyl)isonicotinic acid (930 mg, 4.0 mmoles) was dissolved with gentle warming in a mixt of concd H_2SO_4 (4 ml) and H_2O (4 ml). The soln was cooled in an ice bath, and stirred vigorously while being dild slowly with addnl H_2O (10 ml). Stirring and cooling of the resulting finely divided suspension were contd as an ice-cold soln of $NaNO_2$ (300 mg, 4.4 mmoles) in H_2O (12 ml) was added dropwise. The color of the reaction mixt deepened and the suspended solid appeared to dissolve momentarily; a solid ppt rapidly formed again, however. When the addn was complete, the ice bath was not replenished, and the mixt was allowed to warm to room temp, with contd stirring, during the next hour. It was warmed on the steam bath; N_2 was evolved, and the suspended solid dissolved rapidly. When N_2 evoln had ceased, the soln was cooled, affording crude **5** (750 mg, 81%) as a dark brown ppt. The solid was collected by filtration, washed thoroughly with H_2O, and dried *in vacuo*. Purification of the crude product was effected by sublimation at 210–220° *in vacuo* (0.5–1.0 mm). The pale yellow sublimate exhibited a decompn endotherm at 312° (DTA at 20°/min under N_2): τ (DMSO) *ca.* 1.23 [broad singlet (2)], 1.53 [singlet (1)], 1.91 [singlet (1)], 1.95 [doublet of doublets (2), J = 5.5 cps and J = 9.0 cps], 2.72 [triplet (2), J = 9.0 cps] ppm. *Anal.* ($C_{12}H_8FNO_3$) C, H, N, F.

Acknowledgment.—The authors wish to thank several of their colleagues who supplied pharmacological data: Dr. C. G. Van Arman and Mr. E. A. Risley for the antiinflammatory assays, Mr. L. Flataker for the analgetic assays, Dr. L. Sherman Watson for the diuretic assay, and Dr. M. S. Glitzer for the hypoglycemic assay.