Anal. Calcd for $C_{15}H_{20}N_2$: C, 78.90; H, 8.83. Found: C, 79.15; H, 9.09.

2-*N*-Benzoyl-1-adamantanaminopyridine. This was obtained (84%) by benzoylation of the above amine in benzene: mp 210–212° (EtOH); ir (KBr) 1670 cm^{-1} (CO); *m/e* (rel intensity) 333 (9, M^+), 135 (100).

Anal. Calcd for $C_{22}H_{24}N_2O$: C, 79.48; H, 7.28. Found: C, 79.33; H, 7.53.

Acknowledgments. Part of this work was carried out during the tenure (by G. M. S.) of a University of Saskatchewan Teaching Fellowship (1967). The rest was supported by a grant from the National Institutes of Health (GM 16626), whom we thank. Pyridine 1-oxides were a gift from Reilly Tar and Chemical Co., to whom we are also grateful. We also wish to thank Dr. Elizabeth M. Smith for carrying out some of the experiments described herein.

Registry No.—Pyridine 1-oxide, 694-59-7; benzenediazonium tetrafluoroborate, 369-57-3; 2-*N*-acetylanilinopyridine, 51263-25-3; *N*-phenylbenzimidoyl chloride, 4903-36-0; 2-*N*-benzoylanilinopyridine, 20107-78-2; *N*-phenylbenzonitrilium hexachloroantimonate, 51293-24-4; 2-*N*-benzoyl-*p*-toluidinopyridine, 51263-26-4; *N*-*p*-tolylbenzimidoyl chloride, 15999-95-8; 2-*p*-toluidinopyridine, 51263-27-5; 2-*N*-benzoyl-*p*-anisidinopyridine, 51263-28-6; 2-*N*-benzoyl-*p*-chloroanilinopyridine, 51263-29-7; 2-*N*-benzoylbenzylaminopyridine, 24244-29-9; 2-*N*-benzoylcyclohexylaminopyridine, 51263-30-0; *p*-nitroanilinopyridine, 24068-29-9; *N*-*p*-nitrophenylbenzimidoyl chloride, 34918-79-1; 2-*N*-benzoyl-*p*-nitroanilinopyridine, 51263-31-1; caprolactam, 105-60-2; *N*-2-pyridylcaprolactam, 51263-32-2; *N*-2-pyridylcaprolactam picrate, 51263-33-3; *N*-2-pyridylsaccharin, 51263-34-4; saccharin pseudochloride, 567-19-1; *N*-2-pyridyl-*o*-carbethoxybenzenesulfonamide, 51263-35-5; 3-*N*,*N*-dimethylaminopseudosaccharin, 22716-43-4; *N*-benzoyl-*p*-toluidine, 582-78-5; 2-*N*-benzoylanilino-4-picoline, 51263-36-6; 4-picoline 1-oxide, 1003-67-4; 2-anilino-4-picoline, 19933-06-3; *N*-benzoyl-1-adamantanamine, 19026-84-7; thionyl chloride, 7719-09-7; *N*-1-adamantylacetonitrilium bromopentachloroantimonate, 51263-54-8; *N*-1-adamantylbenzonitrilium bromopentachloroantimonate, 51263-56-0; 2-(1-adamantanamino)pyridine, 22947-50-8; 2-fluoropyridine, 372-48-5; 1-adamantanamine, 768-94-5; 2-*N*-benzoyl-1-adamantanaminopyridine, 51263-37-7.

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Direct Acylamination of 3-Substituted Pyridine 1-Oxides. Directive Effect of the Substituent[1a]

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Received January 2, 1974

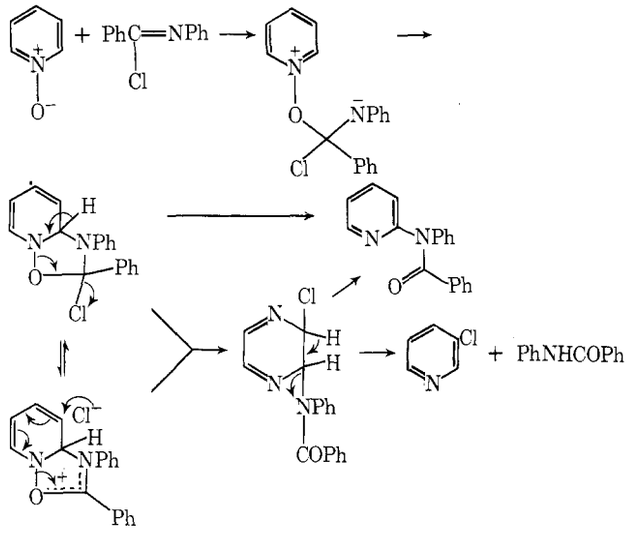
The effect of a 3 substituent upon the orientation of the entering group in the direct acylamination of pyridine 1-oxides with *N*-phenylbenzimidoyl chloride has been studied, and a possible explanation of the results is proposed. In the case of electron-attracting substituents (CN, CO_2Me) the formation of substantial amounts of 5-chloro derivative complicates the interpretation. With a 3-mesylamino substituent it is the 6-chloro compound that is formed as a by-product, and the intermediate 2-acylaminated product cyclizes to 2,3-diphenyl-3*H*-imidazo[4,5-*b*]pyridine.

The direct acylamination of pyridine 1-oxides by imidoyl chlorides or nitrilium salts has been reported.[1b] The main by-products formed were 3-chloropyridine and benzanilide (from *N*-phenylbenzimidoyl chloride), and the

Table I
Authentic New 2-Anilinopyridines (7) and 2-*N*-Benzoylanilinopyridines (3 and 4)

Compd	Yield, %	Mp, °C	Molecular formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
7, R = 3-Me	52	123–125	$C_{12}H_{12}N_2$	78.26	6.52	78.33	6.72
7, R = 5-Me	61	114–116	$C_{12}H_{12}N_2$	78.26	6.52	78.16	6.42
3a	63	122–123	$C_{19}H_{16}N_2O$	79.16	5.56	79.20	5.81
4a	80	104–105	$C_{19}H_{16}N_2O$	79.16	5.56	79.21	5.74
7, R = 3-CO_2Me	80	Oil, picrate mp 192–194 (EtOH)	$C_{13}H_{12}N_2O_2 \cdot C_6H_3N_3O_7$	49.89	3.28	49.86	3.48
7, R = 5-CO_2Me	40	119–120	$C_{13}H_{12}N_2O_2$	68.42	5.25	68.15	5.18
4b	77	116–117	$C_{20}H_{16}N_2O_3$	72.29	4.82	72.11	4.97
7, R = 3-F	9	69–70	$C_{11}H_9FN_2$	70.21	4.79	70.02	4.94
7, R = 5-F	42	99–100	$C_{11}H_9FN_2$	70.21	4.79	70.05	4.94
3d	65	123.5–124.5	$C_{18}H_{13}FN_2O$	73.97	4.54	74.00	4.63
4d	70	142–144	$C_{18}H_{13}FN_2O$	73.97	4.54	73.99	4.59
7, R = 3-OMe	45	Oil, picrate mp 190–192 (EtOH)	$C_{12}H_{12}N_2O \cdot C_6H_3N_3O_7$	50.35	3.50	50.44	3.60
3f	40	177–178	$C_{19}H_{16}N_2O_2$	75.00	5.26	75.08	5.38

Scheme I



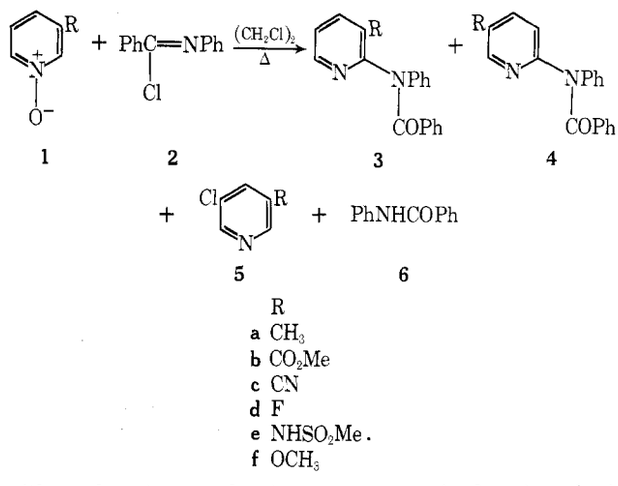
mechanism outlined in Scheme I was proposed to explain the formation of the products.

In seeking to examine the scope of this novel acylamination we have extended the reaction to 3-substituted pyridine 1-oxides. 3-Substituted 2-anilinopyridines are of potential pharmaceutical interest. Several 2-anilinonicotinic acid derivatives are reported to exhibit analgesic,[2,3] antiinflammatory,[2,3] antiphlogistic,[4] and antineoplastic[5] properties. Likewise, 6-anilinonicotinic acid derivatives and 6-anilino-3-nitro- and 6-anilino-3-aminopyridines have been found to have antineoplastic,[5] antiinflammatory,[3] and antiphlogistic[6] properties. Such compounds have been available in the past only through multistep synthetic schemes. The above one-step procedure could make available conveniently and economically a variety of substituted derivatives of these useful compounds.

We now report a quantitative study of the effect of a 3 substituent upon orientation in the intramolecular acylamination using *N*-phenylbenzimidoyl chloride. Attack can take place either at the 2 or the 6 position to give **3** and **4**, respectively, and in most cases both isomers were formed, at least initially (Scheme II).

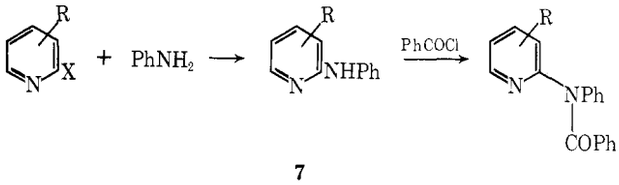
Quantitative analyses were performed using gas chromatography of the reaction mixtures following a minimum amount of manipulation and contact with the atmosphere. The products were resolved by preparative chromatography and characterized by their spectral properties and by comparison (melting point, ir, retention times)

Scheme II



R
a CH_3
b CO_2Me
c CN
d F
e $NHSO_2Me$.
f OCH_3

with authentic samples in most cases. Authentic substituted anilinopyridines were prepared from aniline and the appropriately substituted 2-chloro- or 2-bromopyridine, followed by benzoylation. The properties of new com-



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pounds so prepared are summarized in Table I. This comparison with authentic samples was made necessary because in some instances the nmr spectra of the products did not allow unambiguous assignments of orientation. Thus, H_6 in **4f** consisted of a narrow triplet of unevenly spaced lines (para H–H coupling with C_3 H[7]) at δ 8.38 while the signal for H_6 in **3f** was a barely resolved doublet of doublets at δ 8.34 with the coupling between H_6 and H_5 (4 Hz) being almost the same as that between H_6 and H_4 (3 Hz). In 2-chloro-3-methoxypyridine as well, the ortho coupling constant is smaller than expected (4 Hz) while the meta one is larger (3 Hz). Again, H_6 in **4d** appeared as a broad doublet which, on scale expansion, turned out to be a multiplet, probably arising by the further splitting of the expected doublet of doublets (coupling with H_4 and with F) by H_3. On the other hand, both 2-bromo-5-fluoropyridine and 2-anilino-5-fluoropyridine exhibited only a doublet (J = 3 Hz) for H_6 with no evidence of H–F cou-

Table II
Products Formed on Acylamination of 3-R-Pyridine 1-Oxide with *N*-Phenylbenzimidoyl Chloride

R	Yield, % 3	4	5	6
CH_3	6.8	82.3	5	12.3
CO_2CH_3	Trace	53.2[a]	36.6	40.1
CN	33.4	19.8	30.6	36.7
F	25.9	55.9		10
$NHSO_2CH_3$	39[b]	36.5	10[c]	26.5
OCH_3	76.2	18.9	Trace	4.2

[a] 2-Anilino-5-carbomethoxypyridine was also isolated. [b] The product isolated was 2,3-diphenyl-3*H*-imidazo[4,5-*b*]-pyridine. [c] The product isolated was 2-chloro-5-(*N*-methanesulfonamido)pyridine.

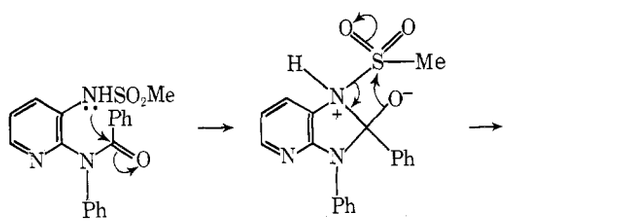
pling. This is in marked contrast to the known ortho H–F coupling constants (6.2–10.1 Hz) in fluorobenzene[8] derivatives. The expected meta coupling between H_3 and the fluorine atom ($J_{3,F}$ = 3.5 Hz) was observed in 2-anilino-5-fluoropyridine; this is smaller than in fluorobenzenes ($J_{m\text{-}H,F}$ = 6.2–8.3 Hz)[8] and 2-fluoropyridine.[9]

The products **3c** and **4c** from 3-cyanopyridine 1-oxide were characterized on the basis of their spectral and analytical data, and by their hydrolysis to either the 2- or the 6-anilinonicotinic esters, identical with authentic samples.

The quantitative (glc analysis except for R = $NHSO_2CH_3$) results of the acylaminations are summarized in Table II.

No 5-chloro-3-fluoropyridine (**5**, R = F) was detected in the run with 3-fluoropyridine 1-oxide. From the limited experience to date, it appears that the highest yields of **5** are obtained with **1** (R = H)[1] and with *N*-oxides bearing electron-withdrawing substituents at C_3. Some unexpected products were obtained with **1** (R = $NHSO_2Me$). The halogenated product proved to be 2-chloro-5-(*N*-methanesulfonamido)pyridine (**8**) rather than the corresponding β-chlorinated derivative. Its formation can be rationalized as in Scheme III.

Also, no 2-(*N*-benzoylanilino)-3-(*N*-methanesulfonamido)pyridine (**3e**) was isolated; instead, 2,3-diphenyl-3*H*-imidazo[4,5-*b*]pyridine (**9**) was formed, undoubtedly from **3e**, perhaps as follows.



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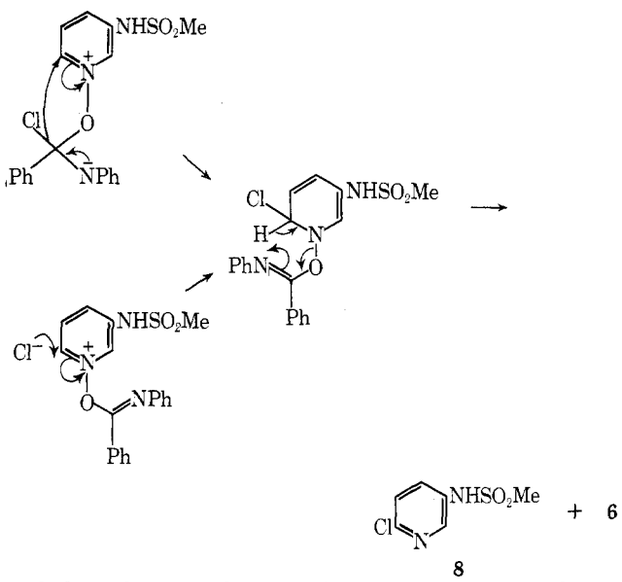
A similar compound, dipyrido[1,2-*a*:3′,2′-*d*]imidazole, was isolated from the reaction of 3-acetamidopyridine 1-oxide with 2-bromopyridine[10] and is probably formed from *N*-(3-acetamido-2-pyridyl)-2-pyridone.

Both electronic and steric effects have to be taken into account in any explanation of the influence of the 3 substituent upon orientation in the intramolecular cyclization. Approach of the α position by the nucleophile cannot be made from a direction perpendicular to the ring because of the geometric limitations enforced by the intramolecular mode of attack, so that one might expect steric

Scheme III



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and through-space electronic interactions between the nucleophile approaching C_2 and a substituent at C_3 to be larger than if approach by the nucleophile were initially perpendicular to the ring.

The effects of the three electron-donating substituents studied (CH_3, OMe, $NHSO_2Me$) are in agreement with predictions made on the basis of straightforward electronic and steric concepts. By virtue of its inductive and steric effect one would expect a 3-methyl group to deactivate C_2 more than C_6, this influence not being compensated by the weak hyperconjugative effect which would be expected to deactivate C_6 more than C_2. In intermolecular nucleophilic attacks by strong nucleophiles (RLi or $NaNH_2$) these effects are overshadowed by strong ion-dipole or London-type attractive forces between the approaching nucleophile and the 3-Me group.[11] In intramolecular nucleophilic substitutions, however, this is not the case and attack takes place predominantly at C_6, as for instance in the Emmert reaction.[12] In the present acylaminations, the inductive and steric effects of the methyl group direct substitution mainly to C_6 (Table II). The methoxyl group, on the other hand, is smaller than methyl[13] and its mesomeric effect is stronger than its inductive effect ($\sigma^n_{p\text{-MeO}}$ = −0.175). Mesomeric effects are known[14] to be more effective at the para than at the ortho positions (*p*-quinonoid contributing structure more stable than *o*-quinonoid ones). On that basis then, it would be predicted that a 3-methoxy substituent would deactivate C_6 more than C_2, and indeed this appears to be the case (Table II). A similar argument can be made concerning the methanesulfonamido group, though its size relative to methyl has not been determined; it would be anticipated that its electron-donating mesomeric effect would be less than that of the methoxyl group while its inductive (and field) effect should be greater. It is not surprising, therefore, that this group leads to only a slight preference for attack at C_2 over C_6.

The situtation with the three overall electron-withdrawing substituents studied (CN, CO_2CH_3, F) is not as clear-cut. The steric requirements of the linear nitrile group are small. It has been shown previously that nucleophilic attack at C_2 in 3-cyanopyridinium salts[15] or at the C_2 proton in 3-cyanopyridine methiodide[16] is faster than the corresponding attack at C_6. This is now also seen to be the case in the acylamination. The steric effect of the carbomethoxyl group is much larger, which could account for the predominant attack at C_6 in this case. A similar re-

versal was observed in the alkaline ferricyanide oxidation of 3-cyano- and 3-carbomethoxypyridinium salts.[15b] A major problem in the interpretation of these latter isomer ratios is the formation of substantial amounts of the 5-chloro derivatives (**5b** and **5c**) in these reactions, since it is not known whether they arise intra- or intermolecularly by the attack of chloride selectively at C_3 or C_5 of the 1,2-dihydropyridine intermediate (Scheme I). Further discussion of these is therefore not warranted until more is known about the mechanism of chlorination. The orientation with the 3-fluoropyridine derivative is difficult to rationalize simply. A fluorine substituent is electron withdrawing in the ground state (σ_p^n = +0.062), and fluorine is smaller than methyl so that its steric effect should not be of consequence. A small repulsive influence by the electronegative fluorine upon the nucleophile approaching C_2 could explain the isomer ratio, though other factors may well come into play.

Experimental Section

Reactants and solvents were purified prior to use either by recrystallization or distillation. Solvents were dried and distilled prior to use. Thus, all halocarbon solvents were boiled under reflux for 12 hr over phosphorus pentoxide and then distilled. Anhydrous diethyl ether was used directly from freshly opened cans. Tetrahydrofuran was purified by distillation from calcium hydride and then from lithium aluminum hydride. Light petroleum refers to that fraction with a boiling range of 60–110°, unless specified otherwise.

All nuclear magnetic resonance spectra were determined using a Varian Associates Model HA-100 spectrometer. Mass spectra were recorded on a C. E. C. Model 21-104 spectrometer, usually at an ionizing voltage of 70 eV. Infrared spectra were recorded on a Perkin-Elmer Model 337 spectrometer. Solid compounds were run as KBr disks while liquids were run as liquid films. Each spectrum was calibrated using polystyrene as a reference at 1944 and 906 cm^{-1}. Melting points are uncorrected. Gas chromatographic analyses were carried out using either a Varian Associates Model 200 or Model 1700 gas chromatograph with helium as the carrier gas. They were performed using one or, in some cases, both sets of conditions described below, using the internal standard technique.

(A) The analysis was performed using a Varian Aerograph Model 200 gas chromatograph equipped with dual columns (7 ft × 3/16 in.) packed with 20% SE-30 on Gas-Chrom Q (60–100 mesh).

(B) The analysis was performed using a Varian Aerograph Model 1700 gas chromatograph equipped with dual columns (6 ft × 3/16 in.) packed with 20% OV-17 on Gas-Chrom Q (60–100 mesh).

In all cases each peak was identified by collecting the compound as it eluted from the chromatograph and comparing its infrared spectrum with that of an authentic sample. The per cent yields are based on starting imidoyl chloride.

The aromatic amine oxides were prepared using either peracetic or permaleic acid. The latter procedure is illustrated below for the preparation of 3-fluoropyridine 1-oxide. The *N*-oxides were azeotroped if necessary, distilled, and redistilled just before use to ensure that they were completely anhydrous.

3-Fluoropyridine 1-Oxide. 3-Fluoropyridine (7.0 g, 0.072 mol) was added to a stirred solution of permaleic acid (9.9 g, 0.075 mol, from maleic anhydride and 90% H_2O_2) in $CHCl_3$ (100 ml) at 0°. The mixture was stirred at 0° for 1 hr, then at 25° for 45 min. A white solid precipitated. A paste of K_2CO_3 and water was added and the mixture was stirred for 1 hr. The organic layer was filtered, dried (K_2CO_3), and evaporated. The residual oil was distilled, bp 78–80° (0.3 mm), to give the *N*-oxide (3.1 g, 38%), mp 63–64° (lit.[17] mp 64°).

3-*N*-Methanesulfonamidopyridine 1-Oxide. Prepared from 3-*N*-methanesulfonamidopyridine[18] and permaleic acid, it was obtained in 45% yield: mp 187–188°; mass spectrum *m/e* (rel intensity) 189 (6.4), 188 (52, M^+), 187 (100, $M - 1^+$).

Anal. Calcd for $C_6H_8N_2O_3S$: C, 38.30; H, 4.26. Found: C, 38.48; H, 4.46.

N-Phenylbenzimidoyl chloride was prepared from benzanilide (0.058 mol) and thionyl chloride (0.10 mol) and was distilled before use. It had bp 104–107° (0.25 mm) [lit.[19] bp 174–176° (12 mm)].

Authentic samples of 2-anilinopyridines (Table I lists the new ones) were prepared either from the 2-chloro- or 2-bromopyridine derivative and aniline. The following are typical examples.

2-Anilino-3-methylpyridine. A mixture of 2-bromo-3-methylpyridine[20] (6.63 g, 0.039 mol) and freshly distilled aniline (3.58 g, 0.039 mol) was heated at 180° for 30 min. The gum was dissolved in 2 *N* HCl (50 ml), cooled in ice, and basified with 6 *N* NaOH to give dark crystals. Chromatography on silica gel (200 g, 4 ft × 1.5 in.) and elution with chloroform gave pale yellow crystals of the amine (3.81 g, 52%): mp 123–125° (from benzene); ir (KBr) 3305 cm^{-1} (NH); nmr ($CDCl_3$) δ 7.97 (br d, 1 H, $J_{5,6}$ = 5 Hz, $J_{4,6}$ not resolved, H_6), 7.30 (m, 5 H, ArH), 6.81 (t, 1 H, $J_{4,5}$ = 7 Hz, $J_{4,6}$ not resolved, H_4), 6.53 (d or d, 1 H, $J_{4,5}$ = 7, $J_{5,6}$ = 5 Hz, H_5), 6.0 (br s, 1 H, NH), 2.11 (s, 3 H, CH_3).

2-Anilino-5-methylpyridine was similarly prepared from 2-bromo-5-methylpyridine: nmr ($CDCl_3$) δ 7.98 (br s, 1 H, H_6), 7.49 (br s, 1 H, NH exchangeable), 7.32–6.84 (m, 7 H), 6.76 (d, 1 H, $J_{3,4}$ = 8 Hz, H_3), 2.14 (s, 3 H, CH_3).

2-Anilino-3-fluoropyridine. A mixture of 2-chloro-3-fluoropyridine[21] was heated with aniline as above and the products were chromatographed. Elution with $CHCl_3$ gave the product (9%): mp 69–70° (from light petroleum); ir (KBr) 3440 cm^{-1} (NH); nmr ($CDCl_3$) δ 7.94 (d of d, 1 H, $J_{5,6}$ = 5, $J_{4,6}$ = 0.8 Hz, H_6), 7.67–7.45 (m, 2 H), 7.35–7.10 (m, 3 H), 7.09–6.80 (m, 2 H), 6.71–6.45 (m, 1 H, H_5).

The authentic *N*-benzoyl derivatives were made by Schotten–Baumann benzoylation of the secondary amines. An example is given below.

2-(*N*-Benzoylanilino)-3-methoxypyridine. Benzoyl chloride (0.14 g) was added to a solution of 2-anilino-3-methoxypyridine (0.20 g) in pyridine (2 ml). The solution was heated at 90° for 1 hr, water (10 ml) was added, and the mixture was cooled in the refrigerator overnight to give the *N*-benzoyl derivative (0.12 g, 40%), mp 177–178°, identical with the material obtained from 3-methoxypyridine 1-oxide as described below.

2-Bromo-5-fluoropyridine. Ethyl nitrite (0.12 mol) was slowly bubbled into a solution of 5-amino-2-bromopyridine (7.3 g, 0.042 mol) in ethanol (40 ml) and tetrafluoroboric acid (37%, 24 ml) at 0° over a 10-min period. The diazonium salt precipitated. Ether (60 ml) was added, and the salt was filtered and washed with cold ether and then with light petroleum. The damp diazonium salt was suspended in *n*-heptane (50 ml) and the mixture was boiled under reflux for 4 hr; concentrated HCl (10 ml) was added and the solvent was evaporated *in vacuo*. The dark oily residue was basified with 30% aqueous NaOH and then steam distilled to give 2-bromo-5-fluoropyridine (1.1 g, 15%): bp 80–83° (44 mm): mp 27.5–29°; nmr ($CDCl_3$) δ 8.21 (d, 1 H, $J_{4,6}$ = 3 Hz), 7.53–7.11 (m, 2 H); mass spectrum *m/e* (rel intensity) 177 (46), 175 (48, M^+), 96 (100).

Anal. Calcd for C_5H_3BrFN: C, 34.11; H, 1.71. Found: C, 34.12; H, 1.69.

Reaction of 3-Methylpyridine 1-Oxide with *N*-Phenylbenzimidoyl Chloride. Preparative Run. A solution of 3-methylpyridine 1-oxide (3.30 g, 0.03 mol) in dry 1,2-dichloroethane (50 ml) was added to a freshly prepared solution of *N*-phenylbenzimidoyl chloride (3.23 g, 0.015 mol) in dry 1,2-dichloroethane (30 ml). The mixture was boiled under reflux for 6 hr and cooled in an ice bath, and the precipitated 3-methylpyridine 1-oxide hydrochloride (1.9 g, 85%) was filtered. Its infrared spectrum was identical with that of an authentic sample. The filtrate was evaporated and the residue was chromatographed on a column of silica gel (200 g, 4 ft × 1.5 in.) using light petroleum–acetone (9:1 v/v) as the eluent. Benzanilide (0.10 g, 30%), mp 160–163° (lit.[22] mp 162–163°), eluted first. Its infrared spectrum was identical with that of an authentic sample. The second product, which overlapped somewhat with the third, was recrystallized from ethanol and gave **2-(*N*-benzoylanilino)-5-methylpyridine** (**4a**, 1.95 g, 47%): mp 104–105°; ir (KBr) 1660 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 7.93 (br d, 1 H, $J_{4,6}$ = 2 Hz, H_6), 7.44–6.88 (m, 12 H), 2.15 (s, 3 H, CH_3); mass spectrum *m/e* (rel intensity) 288 (4, M^+), 105 (100, $PhCO^+$); identical (ir, melting point) with an authentic sample (Table I).

The last product to elute was **2-(*N*-benzoylanilino)-3-methylpyridine** (**3a**, 0.043 g, 1%): mp 122–123°; ir (KBr) 1650 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 8.25 (d of d, 1 H, $J_{5,6}$ = 4.2, $J_{4,6}$ = 1.5 Hz, H_6), 7.57–7.35 (m, 3 H), 7.27–6.97 (m, 9 H), 2.24 (s, 3 H, CH_3); mass spectrum *m/e* (rel intensity) 288 (9, M^+), 260 (5.5), 105 (100); identical with an authentic sample.

The quantitative analyses (results summarized in Table II) were carried out after heating 2 equiv of the *N*-oxide with 1 equiv of *N*-phenylbenzimidoyl chloride for 14–16 hr. A typical example is given below.

Reaction of 3-Methylpyridine 1-Oxide with *N*-Phenylbenzimidoyl Chloride. Quantitative Analysis. A solution of 3-methylpyridine 1-oxide (2.30 g, 0.024 mol) and *N*-phenylbenzimidoyl chloride (2.303 g, 0.0107 mol) in 1,2-dichloroethane (15 ml) was boiled under reflux for 14 hr. The mixture was cooled, transferred quantitatively to a volumetric flask (25 ml), and made up to volume with 1,2-dichloroethane. Exactly 2.5 ml of this solution was added to *n*-octadecane (0.0754 g, 2.97×10^{-4} mol), and the solution was extracted with aqueous potassium bicarbonate, dried, and analyzed by gas chromatography under both conditions A and B.

Reaction of Methyl Nicotinate 1-Oxide with *N*-Phenylbenzimidoyl Chloride. Preparative Run. A solution of 3-carbomethoxypyridine 1-oxide[23] (6.0 g) in dry 1,2-dichloroethane (70 ml) was added in one portion to a solution of *N*-phenylbenzimidoyl chloride (4.25 g) in 1,2-dichloroethane (30 ml). The mixture was boiled under reflux for 6 hr, the solvent was evaporated *in vacuo*, and the residue was chromatographed on silica gel (350 g, 6 ft × 1.5 in.) using light petroleum–acetone (9:1 v/v) as eluent. The first product to elute was 5-carbomethoxy-3-chloropyridine (0.31 g, 18%): mp 86–87° (from light petroleum) (lit.[24] mp 88–89°); ir (KBr) 1735 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 9.03 (d, 1 H, $J_{4,6}$ = 2 Hz, H_6), 8.69 (d, 1 H, $J_{2,4}$ = 2.2 Hz, H_2), 8.21 (t, 1 H, H_4), 3.92 (s, 3 H, CH_3); mass spectrum *m/e* (rel intensity) 173 (20), 171 (55, M^+), 140 (100); identical (ir, melting point) with an authentic sample. Benzanilide (1.96 g, 51%), mp 162–163°, eluted next. Overlapping slightly with benzanilide, **2-(*N*-benzoylanilino)-5-carbomethoxypyridine (4b,** 1.79 g, 28%), followed: mp 116–117° (ethanol); ir (KBr) 1735 (ester C=O), 1685 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 8.85 (d, 1 H, $J_{4,6}$ = 2 Hz, H_6), 8.14 (d of d, 1 H, $J_{3,4}$ = 8.5, $J_{4,6}$ = 2 Hz, H_4), 7.54–7.02 (m, 11 H, aromatic protons), 3.81 (s, 3 H, ester CH_3); mass spectrum *m/e* (rel intensity), 332 (5.6, M^+), 227 (5.6), 105 (100); identical with an authentic sample (Table I).

When a portion of the original reaction mixture was subjected to gas chromatographic analysis, a small additional peak was found. The compound was collected (an oil) and found to be **2-anilino-3-carbomethoxypyridine** (*ca.* 1%): ir (KBr) 3340, 3295 (NH), 1695 cm^{-1} (C=O); nmr (CCl_4) δ 10.15 (br s, 1 H, NH), 8.28 (d of d, 1 H, $J_{5,6}$ = 5, $J_{4,6}$ = 2 Hz, H_6), 7.96 (d of d, 1 H, $J_{4,5}$ = 8, $J_{4,6}$ = 2 Hz, H_4), 7.64 (br d, 2 H, J = 7 Hz, ortho protons on phenyl ring), 7.16 (br t, 2 H, J = 7 Hz, meta protons on phenyl ring), 6.85 (br t, 1 H, J = 7 Hz, para proton on phenyl ring), 6.44 (d of d, 1 H, $H_{4,5}$ = 8, $J_{5,6}$ = 5 Hz, H_5), 8.70 (s, 3 H, ester CH_3); mass spectrum *m/e* (rel intensity) 229 (11), 228 (67, M^+), 227 (75), 168 (100). It was identical with an authentic sample prepared from 2-anilinonicotinic acid[25] and diazomethane. The oil formed a picrate, mp 192–194° (ethanol).

Anal. Calcd for $C_{13}H_{12}N_2O_2 \cdot C_6H_3N_3O_7$: C, 49.89; H, 3.28. Found: C, 49.86; H, 3.48.

The crude reaction mixture for another run was hydrolyzed with boiling 6 *N* NaOH solution (100 ml) for 3 hr, the solution was acidified with 6 *N* HCl and cooled to −10°, and the precipitate was filtered. The solid was added to an excess of a solution of diazomethane in ether and, when N_2 evolution had ceased, the solution was filtered from NaCl and subjected to gas chromatography on a 10 ft × 0.25 in. column packed with 15% Apiezon N on Anakrom at 230°. The products were collected and identified (relative retention times and ir). In order of elution these were methyl benzoate, 3-carbomethoxy-5-chloropyridine, methyl nicotinate 1-oxide, benzanilide, 2-anilino-3-carbomethoxypyridine (<1%), and 2-anilino-5-carbomethoxypyridine.

Hydrolysis of 2-(*N*-Benzoylanilino)-5-carbomethoxypyridine. A solution of 2-(*N*-benzoylanilino)-5-carbomethoxypyridine (0.234 g) in concentrated HCl (1.30 g) and methanol (6.4 g) was boiled under reflux for 12 hr, water (30 ml) was added, and the mixture was concentrated to about 15 ml. The concentrate was basified with 10% aqueous sodium bicarbonate and the resulting 2-anilino-5-carbomethoxypyridine was filtered, dried, and recrystallized from benzene (0.106 g, 66%): mp 119–120°; ir (KBr) 3250, 3195 (NH), 1710 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 8.84 (d, 1 H, $J_{4,6}$ = 2.5 Hz, H_6), 8.06 (d of d, 1 H, $J_{4,6}$ = 2.5, $J_{3,4}$ = 9 Hz, H_4), 7.88 (br s, 1 H, NH), 7.63–7.03 (m, 5 H, aromatic protons), 6.8 (d, 1 H, $J_{3,4}$ = 9 Hz, H_3), 3.85 (s, 3 H, CH_3); mass spectrum *m/e* (rel intensity) 229 (8.2), 228 (54, M^+), 277 (100); identical with an authentic sample (Table I).

Reaction of 3-Cyanopyridine 1-Oxide with *N*-Phenylbenzimidoyl Chloride. Preparative Run. A suspension of 3-cyanopyridine 1-oxide (7.55 g, 0.064 mol) in 1,2-dichloroethane (60 ml) was added to *N*-phenylbenzimidoyl chloride (7 g, 0.032 mol) and the mixture was heated under reflux for 12 hr. After cooling to room temperature, 3-cyanopyridine 1-oxide (1.6 g) precipitated. The solvent was evaporated and the residue was chromatographed on silica gel (100 g/g of solvent-free product mixture). Elution with light petroleum–acetone (9:1 v/v) gave four products. The first was 3-chloro-5-cyanopyridine (**5c,** 25%): mp 98–99° (lit.[25] mp 60°); ir (KBr) 2240 cm^{-1} (C≡N); nmr ($CDCl_3$) δ 8.77 (t, 2 H, $J \cong 1$ Hz, H_2, H_6), 7.96 (t, 1 H, $J \cong 1$ Hz, H_4); mass spectrum *m/e* (rel intensity) 140 (34), 138 (100, M^+); identical (melting point, ir) with an authentic sample. (On hydrolysis followed by esterification with diazomethane it gave methyl 3-chloro-5-pyridinecarboxylate.)

Anal. Calcd for $C_6H_3ClN_2$: C, 51.99; H, 2.09. Found: C, 52.11; H, 2.08.

Benzanilide (33%) eluted next (ir).

The third product obtained was **2-(*N*-benzoylanilino)-5-cyanopyridine (4c,** 15%): mp 155–157° (EtOH); ir (KBr) 2240 (C≡N), 1685 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 8.51 (d, 1 H, $J_{4,6}$ = 2.1 Hz, H_6), 7.86 (d of d, 1 H, $J_{4,6}$ = 2.1, $J_{3,4}$ = 9 Hz, H_4). 7.60–7.06 (m, 11 H, H_3 and phenyl protons); mass spectrum *m/e* (rel intensity) 299 (10, M^+), 194 (9.6), 105 (100).

Anal. Calcd for $C_{19}H_{13}N_3O$: C, 76.26; H, 4.27. Found: C, 76.48; H, 4.58.

The fourth product, which overlapped slightly with the third, was **2-(*N*-benzoylanilino)-3-cyanopyridine (3c,** 30%): mp 139–141° (EtOH); ir (KBr) 2240 (C≡N): 1655 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 8.45 (d of d, 1 H, $J_{5,6}$ = 5, $J_{4,6}$ = 2 Hz, H_6), 7.85 (d of d, 1 H, $J_{4,5}$ = 8, $J_{4,6}$ = 2 Hz, H_4), 7.76–7.58 (m, 2 H, H_5 and phenyl proton in the deshielding region of C≡N), 7.27–6.98 (m, 9 H, phenyl protons); mass spectrum *m/e* (rel intensity) 299 (7.5, M^+), 105 (100).

Anal. Calcd for $C_{19}H_{13}N_3O$: C, 76.26; H, 4.37. Found: C, 76.44; H, 4.59.

Hydrolysis products of the amides were obtained if the reaction mixture was resolved by chromatography on alumina (100 g/g of solvent-free product mixture). Thus, from an alumina column using benzene as eluent were obtained the following compounds (in order of their elution): 3-chloro-5-cyanopyridine, mp 97–98°; **2-anilino-3-cyanopyridine** [mp 131–132° (EtOH); ir (KBr) 3340, 3250 (NH), 2225 cm^{-1} (C≡N); nmr ($CDCl_3$) δ 8.27 (d of d, 1 H, $J_{5,6}$ = 5, $J_{4,6}$ = 2 Hz, H_6) 7.65 (d of d, 1 H, $J_{4,6}$ = 2, $J_{4,5}$ = 7.8 Hz, H_4), 7.59–6.92 (m, 6 H, phenyl and NH), 6.65 (d of d, 1 H, $J_{5,6}$ = 5, $J_{4,5}$ = 7.8 Hz, H_5); mass spectrum *m/e* (rel intensity) 195 (45, M^+), 194 (85), 105 (100)].

Anal. Calcd for $C_{12}H_9N_3$: C, 73.33; H, 5.13. Found: C, 73.54; H, 4.89.

Benzanilide eluted third.

Eluting fourth was **2-anilino-5-cyanopyridine:** mp 180–181° (from ethanol); ir (KBr) 3245, 3190 (NH), 2220 cm^{-1} (C≡N); nmr ($CDCl_3$) δ 8.44 (d, 1 H, $J_{4,6}$ = 2 Hz, H_6), 7.62 [d of d (partially obscured by phenyl protons), 1 H, $J_{4,6}$ = 2, $J_{3,4}$ = 9 Hz, H_4], 7.60–7.04 (m, 6 H, phenyl and NH), 6.77 (d, 1 H, $J_{3,4}$ = 9 Hz, H_3); mass spectrum *m/e* (rel intensity) 195 (47, M^+), 194 (100).

Anal. Calcd for $C_{12}H_9N_3$: C, 73.33; H, 5.13. Found: C, 73.55; H, 4.92.

Hydrolysis of 2-(*N*-Benzoylanilino)-5-cyanopyridine. A solution of 2-(*N*-benzoylanilino)-5-cyanopyridine (0.10 g) in ethanol (10 ml) and water (10 ml) containing sodium hydroxide (0.40 g) was boiled under reflux for 4 hr, and the solution concentrated to *ca.* one-half of its original volume and carefully acidified with 6 *N* HCl. At pH 5–6 the solution became cloudy and when it was cooled in a methanol–ice solution (−15°) a solid precipitated. This was filtered and added to a solution of diazomethane in ether. The excess diazomethane was distilled, the remaining ether solution was dried ($MgSO_4$) and filtered, and the ether was removed *in vacuo*. The residue was recrystallized from benzene to give 2-anilino-3-carbomethoxypyridine, identical (ir, melting point) with an authentic sample (Table I).

Hydrolysis of 2-(*N*-Benzoylanilino)-3-cyanopyridine. Using a procedure identical with that described for the hydrolysis of the corresponding 2,5 isomer, **4c** was hydrolyzed and esterified. A yellow, viscous oil was obtained which could not be made to crystallize. Gas chromatography (5 ft × 0.25 in. column packed with 15% Apiezon M on Anakrom, operated at 230°) gave only one peak. The infrared spectrum of this compound was identical with

that of authentic 2-anilino-3-carbomethoxypyridine (Table I).

Similar results were obtained when 2-anilino-3- and -5-cyanopyridine were hydrolyzed and esterified with diazomethane.

Reaction of 3-Fluoropyridine 1-Oxide with *N*-Phenylbenzimidoyl Chloride. Preparative Run. A solution of 3-fluoropyridine 1-oxide (3.0 g) and *N*-phenylbenzimidoyl chloride (2.87 g) in dry 1,2-dichloroethane (50 ml) was boiled under reflux for 48 hr. The solvent was removed *in vacuo* and the residue was chromatographed on silica gel (300 g, 6 ft × 1.5 in.) using a mixture of light petroleum–acetone (9:1 v/v) as eluent. Three compounds were obtained. Benzanilide (0.30 g, 12%) eluted first. The second compound was **2-(*N*-benzoylanilino)-5-fluoropyridine (4d,** 1.72 g, 44%): mp 142–144° (from aqueous EtOH); ir (KBr) 1675 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 8.14 [br d (m on expansion), 1 H, J = 2 Hz, H_6], 7.55–6.95 (m, 12 H); mass spectrum m/e (rel intensity) 292 (3.6, M^+), 105 (100); identical with an authentic sample (Table I). The final product obtained was **2-(*N*-benzoylanilino)-3-fluoropyridine (3d,** 0.83 g, 20%): mp 123.5–124.5° (EtOH); ir (KBr) 1670 cm^{-1} (amide C=O); nmr ($CDCl_3$), δ 8.28 (q, 1 H, $J_{5,6}$ = 4.5, $J_{4,6}$ = 2 Hz, H_6), 7.56–6.0 (m, 12 H); mass spectrum (70 eV) m/e (rel intensity) 292 (9.6, M^+), 105 (100); identical with an authentic sample (Table I).

Reaction between 3-Methoxypyridine 1-Oxide and *N*-Phenylbenzimidoyl Chloride. Preparative Run. A solution of 3-methoxypyridine 1-oxide (1.5 g) in 1,2-dichloroethane (20 ml) was added to freshly distilled *N*-phenylbenzimidoyl chloride (1.13 g) in 1,2-dichloroethane (20 ml). The mixture was heated under reflux for 8 hr and the solvent was evaporated. The residue was chromatographed on a silica gel column (200 g, 4 ft × 1.5 in.) using light petroleum–acetone (9:1 v/v) as eluent. Three compounds were obtained. Benzanilide (0.26 g, 26%) eluted first. The second compound off the column was **2-(*N*-benzoylanilino)-5-methoxypyridine (4f,** 0.114 g, 7.3%): mp 102–103° (light petroleum–$CHCl_3$); ir (KBr) 1650 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 8.38 (d, 1 H, $J_{4,6}$ = 1.5 Hz, H_6), 7.85–7.30 (m, 12 H), 3.86 (s, 3 H, CH_3); mass spectrum m/e (rel intensity) 304 (4.5, M^+), 105 (100).

Anal. Calcd for $C_{19}H_{16}N_2O_2$: C, 75.00; H, 5.26. Found: C, 74.97; H, 5.40.

The final product obtained was **2-(*N*-benzoylanilino)-3-methoxypyridine (3f,** 0.784 g, 50%): mp 177–178° (from light petroleum–chloroform); ir (KBr) 1650 cm^{-1} (C=O); nmr ($CDCl_3$) δ 8.34 (overlapping d of d, 1 H, $J_{5,6}$ = 2.8 Hz, H_6), 7.85–7.29 (m, 12 H), 3.71 (s, 3 H, CH_3); mass spectrum m/e (rel intensity) 304 (4.5, M^+), 105 (100); identical with an authentic sample (Table I).

Reaction of 3-(*N*-Methanesulfonamido)pyridine 1-Oxide with *N*-Phenylbenzimidoyl Chloride. To a solution of freshly distilled *N*-phenylbenzimidoyl chloride (1.2 g) in 1,2-dichloroethane (50 ml) was added 3-(*N*-methanesulfonamido)pyridine 1-oxide (1.1 g) and the mixture was heated under reflux for 13 hr. The solution was allowed to cool to room temperature, and it was then chromatographed on a column of silica gel (300 g, 6 ft × 1.5 in.) using chloroform as eluent. The first product was benzanilide (0.30 g, 26.6%). The second compound obtained was **2,3-diphenyl-3*H*-imidazo[4,5-*b*]pyridine** (0.612 g, 40%): mp 159.5–160° (light petroleum); ir (KBr) no C=O, NH, or S=O bands; nmr ($CDCl_3$) δ 8.33 (d of d, 1 H, $J_{5,6}$ = 5, $J_{4,6}$ = 1.7 Hz, H_6), 8.10 (d of d, 1 H, $J_{4,5}$ = 8, $J_{4,6}$ = 1.7 Hz, H_4), 7.64–7.10 (m, 11 H); mass spectrum (70 eV) m/e (rel intensity) 272 (6.4), 271 (45), 270 (72), 77 (100); mass spectrum (10 eV) m/e (rel intensity) 272 (20), 271 (100), 270 (12); identical with an authentic sample.

Anal. Calcd for $C_{18}H_{13}N_3$: C, 79.70; H, 4.80. Found: C, 79.50; H, 4.91.

The third compound to elute was **2-chloro-5-(*N*-methanesulfonylamino)pyridine (5e,** 0.12 g, 10%): mp 131–132° (from water); ir (KBr) 3125 (NH), 1155 cm^{-1} (S=O); nmr (acetone-d_6) δ 8.86 (br s, 1 H, NH, exchangeable with D_2O), 8.31 (d, 1 H, $J_{4,6}$ = 3 Hz, H_6), 7.77 (d of d, 1 H, $J_{4,6}$ = 3, $J_{3,4}$ = 8.5 Hz, H_4), 7.37 (d, 1 H, $J_{3,4}$ = 8.5 Hz, H_3), 3.05 (s, 3 H, CH_3); mass spectrum m/e (rel intensity) 208 (9.7), 207 (3.2), 206 (24), 129 (29), 127 (100); identical with an authentic sample prepared from 5-amino-2-chloropyridine[26] and methanesulfonyl chloride in pyridine (69% yield).

Anal. Calcd for $C_6H_7ClN_2O_2S$: C, 34.87; H, 3.39. Found: C, 34.96; H, 3.59.

The last compound to elute was **2-(*N*-benzoylanilino)-5-(*N*-methanesulfonylamino)pyridine (4e,** 0.779 g, 37.5%): mp 175.5–177° (EtOH); ir (KBr) 3150 (NH), 1650 (C=O), 1155 cm^{-1} (S=O); nmr ($CDCl_3$) δ 8.13 (d, 1 H, $J_{4,6}$ = 2.8 Hz, H_6), 7.93 (br s, 1 H, NH, exchangeable with D_2O), 7.54 (d of d, 1 H, $J_{4,6}$ = 2.8, $J_{4,5}$ = 8.5 Hz, H_4), 7.50–6.94 (m, 11 H), 2.90 (s, 3 H, CH_3); mass spectrum m/e (rel intensity) 367 (1.7), 366 (7.3), 105 (100).

Anal. Calcd for $C_{19}H_{17}N_3O_3S$: C, 62.13; H, 4.36. Found: C, 61.98; H, 4.61.

2,3-Diphenyl-3*H*-imidazo[4,5-*b*]pyridine. A solution of 3-amino-2-anilinopyridine[27] (0.50 g) and benzoyl chloride (0.39 g) in pyridine (10 ml) was boiled under reflux for 4 hr and cooled, and water (50 ml) was added. The precipitate was filtered and recrystallized from light petroleum to give 2,3-diphenyl-3*H*-imidazo[4,5-*b*]pyridine (0.48 g, 63%), identical (melting point, ir) with the sample obtained above.

Acknowledgments. This work was carried out with the financial support of an NIH grant (GM 16626) for which we are grateful. We also wish to thank Reilly Tar and Chemical Corp. for the gift of pyridine derivatives.

Registry No.—1a, 1003-73-2; **1b,** 15906-18-7; **1c,** 14906-64-0; **1d,** 695-37-4; **1e,** 51269-71-7; **1f,** 14906-61-7; **2,** 4903-36-0; **3a,** 51269-72-8; **3c,** 51269-73-9; **3d,** 51269-74-0; **3f,** 51269-75-1; **4a,** 51269-76-2; **4b,** 51269-77-3; **4c,** 34941-75-8; **4d,** 51269-78-4; **4e,** 51269-79-5; **4f,** 51269-80-8; **5b,** 51269-81-9; **5c,** 51269-82-0; **5e,** 51269-83-1; **7** (R = 3-Me), 43191-22-6; **7** (R = 5-Me), 43191-23-7; **7** (R = 3-CO_2Me), 51269-84-2; **7** (R = 3-CO_2Me) picrate, 51269-85-3; **7** (R = 5-CO_2Me), 51269-86-4; **7** (R = 3-F), 51269-87-5; **7** (R = 5-F), 51269-88-6; **7** (R = 3-OMe), 51269-89-7; **7** (R = 3-OMe) picrate, 51269-90-0; **7** (R = 3-CN), 16344-18-6; **7** (R = 5-CN), 15871-89-3; **9,** 51269-91-1; 3-fluoropyridine, 372-47-4; 3-*N*-methanesulfonamidopyridine, 51269-92-2; benzanilide, 93-98-1; thionyl chloride, 7719-09-7; 2-bromo-3-methylpyridine, 3430-17-9; aniline, 62-53-3; 2-bromo-5-methylpyridine, 3510-66-5; 2-chloro-3-fluoropyridine, 17282-04-1; benzoyl chloride, 98-88-4; 2-bromo-5-fluoropyridine, 41404-58-4; 5-amino-2-bromopyridine, 13534-97-9.

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