THE JOURNAL OF Organic Chemistry®

VOLUME 39, NUMBER 13

JUNE 28, 1974

Direct Acylamination of Pyridine 1-Oxides[1a]

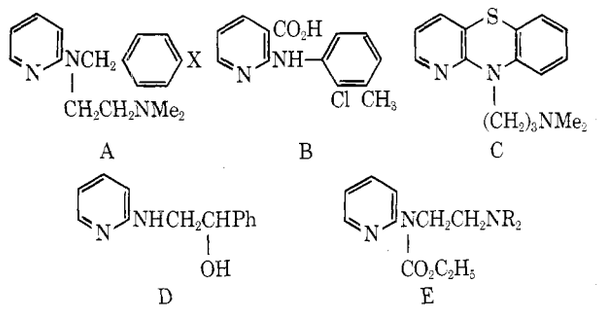
R. A. Abramovitch* and G. M. Singer

Departments of Chemistry, University of Alabama, University, Alabama 35486, and University of Saskatchewan, Saskatoon, Saskatchewan, Canada

Received October 24, 1973

Treatment of a pyridine 1-oxide with an imidoyl chloride results in the introduction of a tertiary amide function into the α position of the pyridine ring with concomitant deoxygenation of the *N*-oxide. A nitrilium salt may be used instead of the imidoyl chloride. The scope and limitations of the reaction are discussed in terms of the structural requirements in the imidoyl chloride and nitrilium salt. Some less reactive compounds which are structurally related to imidoyl chlorides did not give the desired substitution products. The main features of the mechanism of this reaction have been elucidated, and involve initial nucleophilic attack by the *N*-oxide on the imidoyl chloride or nitrilium salt, followed by intramolecular nucleophilic addition of the nitrogen atom of the imidoyl chloride or nitrilium salt to the α position of the pyridine 1-oxide and aromatization. Other possible mechanisms have been discounted. The formation of 3-chloropyridines and other products is discussed and explained.

2-Aminopyridine derivatives are of great importance in medicinal chemistry. For example, the tertiary amines tripellenamine (A, X = H) and pyrilamine (A, X = OMe) are antihistamines, B has antiinflammatory properties, prothypendil (C) is a sedative and a tranquilizer, pheniramidol (D) is an analgesic and muscle relaxant, and E is said to be a powerful analgesic.



A B C D E

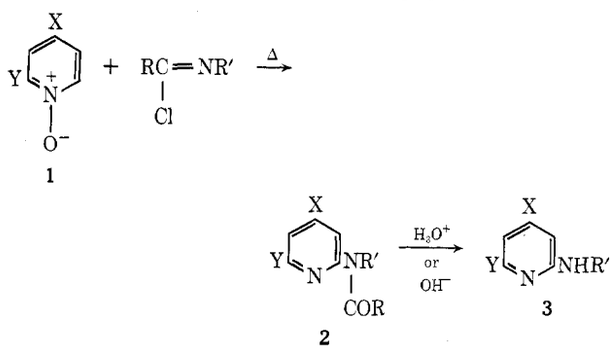
While primary 2-aminopyridines are usually readily available from the parent pyridine by the Tschitschibabin reaction, substituted amines are less readily available. Vajda and Kovacs[1b] extended the Tschitschibabin reaction to permit the use of alkylamines, but yields were generally low and the reaction failed for benzylamine and arylamines. Better yields of 2-alkylaminopyridines were reported when a pyridine was heated with a three- to fourfold excess of a primary aliphatic amine in the presence of finely divided sodium metal.[2] Secondary amines may also be prepared from aminopyridine and alkyl halides or from halopyridines and a primary amine.[3] Tertiary amines are usually available from either the secondary amine, or the halopyridine and a secondary amine.[3] The disadvantage of these methods is the relative difficulty of obtaining readily the appropriately substituted halopyridine precursor.

We have sought a method which would make available substituted secondary and tertiary aminopyridines from the parent pyridine, and would thus complement the Tschitschibabin reaction. We now report such a convenient reaction which starts with the appropriate five- or six-membered heteroaromatic *N*-oxide and an imidoyl chloride or the corresponding nitrilium salt.

Initially the desired nitrilium salt was generated *in situ* by the thermal decomposition of aryldiazonium salts in nitrile solvents.[4] Thus, when benzenediazonium tetrafluoroborate was decomposed in acetonitrile containing pyridine 1-oxide and the reaction mixture saponified, 2-anilinopyridine was obtained in low yield. If the saponification step was omitted, 2-*N*-acetylanilinopyridine could be isolated, together with 2-anilinopyridine and acetanilide.

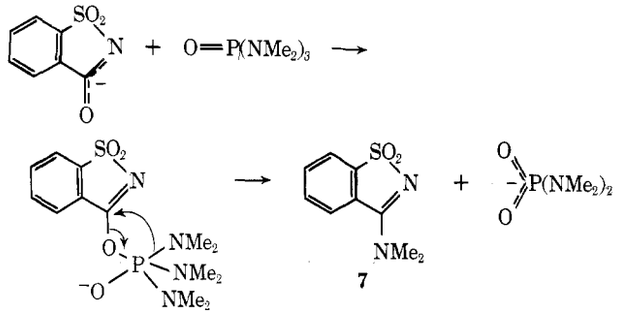
It was found to be much more convenient, and to lead to a considerable improvement in the yields of products, to use preformed nitrilium salts, or their precursors, the N-substituted imidoyl chlorides. Thus, when pyridine 1-oxide was boiled under reflux with a solution of *N*-phenylbenzimidoyl chloride in ethylene chloride, 2-*N*-benzoylanilinopyridine was obtained in respectable yield, together with some benzanilide. Hydrolysis of the reaction mixture without prior isolation of the amide gave 2-anilinopyridine directly.

The reaction appears to be quite general, the only pyridine 1-oxide having failed to react to date being 4-nitropyridine 1-oxide (1, X = NO_2). In this paper, we report the

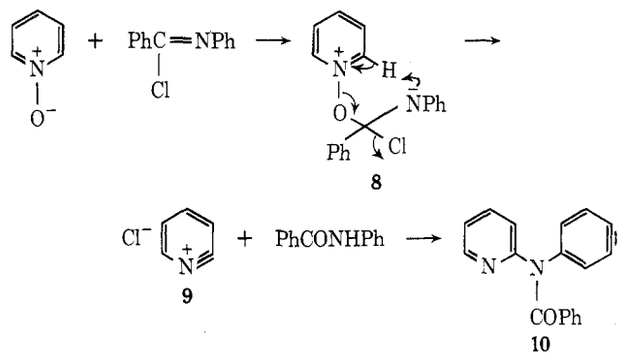


1 2 3

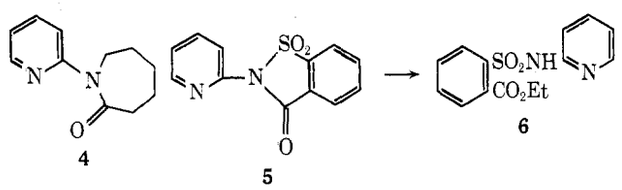
Scheme I



Scheme II



reactions with 1 (X = H or CH_3; Y = H). R and R′ can also vary widely, both alkyl and aryl groups giving the desired tertiary amide **2**. In the cases where R′ is an aryl group bearing an electron-withdrawing substituent, *e.g.*, *p*-NO_2, the reaction in boiling ethylene chloride becomes much more sluggish, and either a higher boiling solvent, for example chlorobenzene, was used or the more reactive preformed nitrilium salt was added to the *N*-oxide. R and R′ could be part of a ring, as illustrated by the synthesis of *N*-2-pyridylcaprolactam (**4**) from caprolactam pseudochloride. Also of great interest is the synthesis of *N*-2-pyridylsaccharin (**5**) by this route from saccharin pseudo-



chloride. This amide could not be obtained from sodium saccharinate and 2-bromopyridine. When this latter reaction was attempted in hexamethylphosphoramide the only product formed was 3-dimethylaminobenzoisothiazole 1,1-dioxide (**7**). A plausible pathway to **7** is as shown in Scheme I. A very low yield of authentic **5** (0.65%) was obtained from 2-fluoropyridine and sodium saccharinate. When **5** was heated in ethanol it was slowly converted to *N*-2-pyridyl-*o*-carbethoxybenzenesulfonamide.

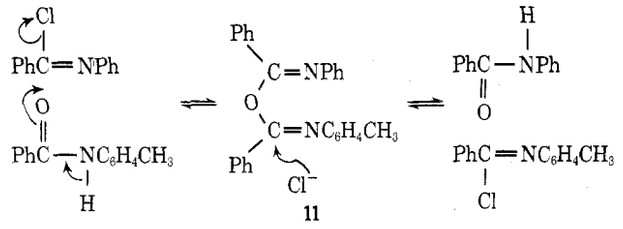
In sharp contrast, only *N*-benzoylbenzenesulfonamide was obtained from the open-chain analog of saccharin pseudochloride, *N*-benzenesulfonylbenzimidoyl chloride, and none of the desired 2-*N*-benzoylbenzenesulfonamidopyridine[5] or 2-benzenesulfonamidopyridine[6] were detected. No substitution product was formed from this imidoyl chloride and 4-ethoxypyridine 1-oxide either.

An attempt to use an imidate ester instead of the imidoyl chloride failed in the one case studied: when *O*-methyl-ϵ-caprolactim was heated with pyridine 1-oxide even in boiling chlorobenzene, most of it was recovered unchanged, and no **4** was detected. The nmr spectrum of **4** deserves some comment. In all of the aminopyridines prepared in this study and in 2-*N*-benzoylanilino-4-methylpyridine (**2**, X = Me; Y = H; R = R′ = Ph) and 2-*N*-benzoylcyclohexylaminopyridine (**2**, X = Y = H; R = Ph; R′ = C_6H_{11}) the chemical shift of H_3 is in the range δ 6.26–6.87, the higher field resonances corresponding to R′ = alkyl. On the other hand, H_3 in **4** resonates at δ 7.63, which is appreciably lower than in the other examples. One possible explanation of this is that in **4** the amide carbonyl may get close enough to C_3 H to deshield it, whereas in the *N*-benzoyl derivatives steric interactions between the aromatic nuclei cause twisting of the molecule so that the carbonyl group is away from C_3 H. Other examples of unhindered amide carbonyl groups at C_2 deshielding a pyridine β proton are known.[7] Thus, C_3 H in 2-acetamidopyridine resonates 1.52 ppm lower than does the corresponding proton in 2-*N*-piperidinopyridine.

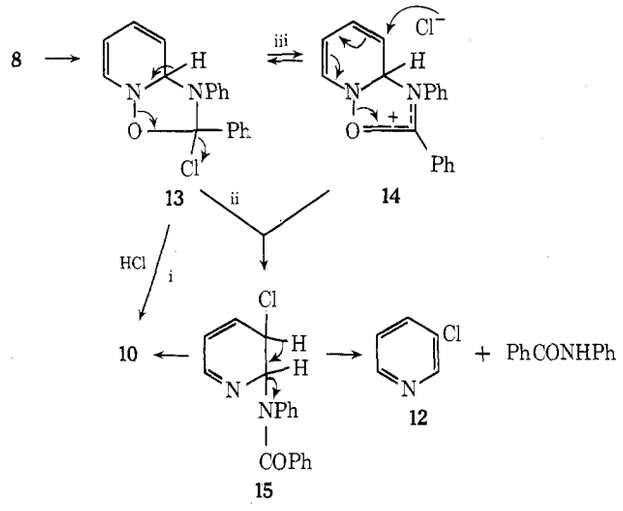
A perplexing question was the origin of the benzanilide which was obtained in all of the reactions involving *N*-phenylbenzimidoyl chloride, even when scrupulously dried reagents and solvents were used in a drybox. That this did not arise from the hydrolysis of the imidoyl chloride during the reaction was shown by the fact that the chloride was recovered when the reaction conditions were duplicated but pyridine 1-oxide was omitted. Since pyridine 1-oxides and pyridinium salts are known to undergo ready base-catalyzed proton abstraction from the α positions,[8] the initial assumption was made that intermediate **8**, resulting from the *N*-oxide attack upon the imidoyl halide, underwent intramolecular proton abstraction with the elimination of benzanilide and the formation of a 1,2-pyridynium ion (**9**). The latter might then add benzanilide to give the observed product (**10**) or the two fragments could diffuse apart, thus leading to the isolation of benzanilide (Scheme II). If this were so, it should be possible to add a different, and possibly more nucleophilic, amide to **9** and thus obtain a crossover product. Indeed, when *N*-benzoyl-*p*-toluidine was added to a mixture of pyridine 1-oxide and *N*-phenylbenzimidoyl chloride and the reaction was repeated, a mixture was obtained containing 2-*N*-benzoyl-*p*-toluidinopyridine and 2-*N*-benzoylanilinopyridine in an approximate 1:1 ratio. It thus appeared as though **9** had indeed been formed and trapped. When, however, **9** was generated from 1*H*-1,2,3,5-thiatriazole[5,4-*a*]pyridine 3-oxide[9] in the presence of benzanilide or *N*-benzoyl-*p*-toluidine, no 2-*N*-benzoylanilinopyridine derivative was obtained (reaction carried out by Dr. E. M. Smith). When *N*-benzoyl-*p*-toluidine and *N*-phenylbenzimidoyl chloride were heated together, the infrared spectrum of the product was identical with that obtained from benzanilide and *N*-*p*-tolybenzimidoyl chloride under the same conditions. The mass spectrum of the reaction mixture indicated the presence of both amides and both imidoyl chlorides in these reaction mixtures. Thus, the equilibria illustrated in Scheme III, involving the as yet unknown imidoyl anhydride **11**, appear to be set up under these reaction conditions, so that the formation of the two acylaminated pyridines from each of the individual imidoyl chlorides—or from the mixed imidoyl anhydride—would account nicely for the observations without the necessity of invoking the formation of **9**. The latter, in any case, does not give the observed product, as shown above.

This leaves the formation of benzanilide in substantial amounts still unexplained. The acylamination of pyridine 1-oxide by *N*-phenylbenzimidoyl chloride in ethylene chloride was therefore repeated and the reaction mixture was analyzed by gas chromatography without any work-up other than filtration of the pyridine 1-oxide hydrochloride formed. A 57% yield of **10** was thus obtained, together

Scheme III

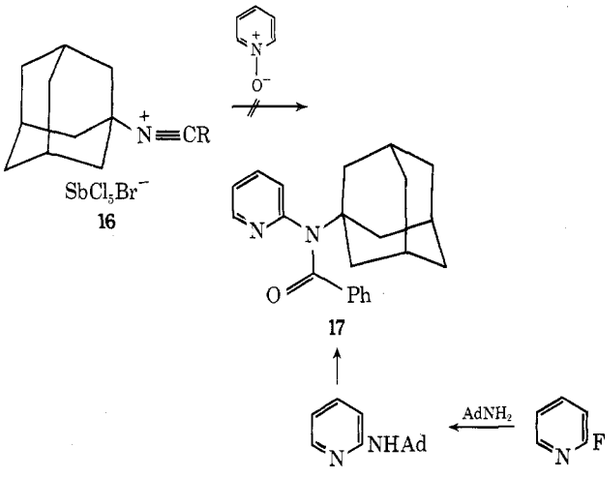


Scheme IV

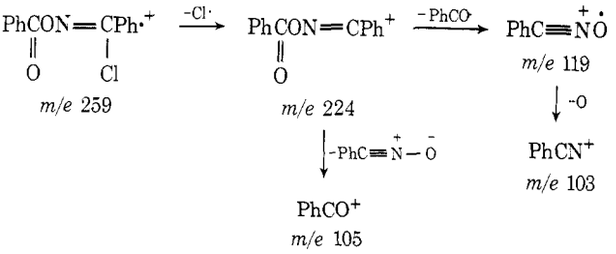


with benzanilide (36.8%) and 3-chloropyridine (**12**, 28%). Small amounts of two products, tentatively identified as 2-anilinopyridine (3.1%) and 3-benzoyloxypyridine (1.2%) on the basis of their relative retention times only, were also observed. We shall discuss the significance of these last two in a forthcoming publication. The observation that 3-chloropyridine is formed in appreciable amounts in this reaction allows us to suggest a mechanism which would account for the formation of the three major products observed (Scheme IV). The dihydro intermediate **13** (in one conformation of which the chlorine atom lies below the pyridine β position) can undergo (i) aromatization with elimination of HCl and the formation of the acylaminated product, and either (ii) intramolecular attack at C_3 or C_5 by the chlorine atom to give the 2,3-dihydropyridine derivative **15**, or (iii) ionization to give the delocalized carbonium ion **14** which undergoes intermolecular attack by Cl^- at C_3 or C_5 to give **15**. The latter can now eliminate HCl to give **10**, or eliminate benzanilide to yield 3-chloropyridine. The alternative extreme pathways ii and iii above may actually be merged so that the transition state involves appreciable stretching of the C–Cl bond, but the free carbonium ion **14** is not necessarily completely formed. The carbonium ion **14** appears, however, to be a necessary intermediate in the reaction of pyridine 1-oxides with nitrilium salts. That C–Cl bond breakage is important in the rate-determining step is shown by the fact that the addition of external chloride ion to the reaction mixture slows the reaction down considerably (likely owing to a common ion effect) and little 3-chloropyridine is formed.[10] Nucleophilic addition to a 1,2-dihydropyridine with concurrent departure of the group at nitrogen and the formation of a 2,3-dihydropyridine has already been postulated[11] to explain the formation of 2,5-diphenylpyridine from pyridine and phenylcalcium iodide,[12] and of a 3,5-disubstituted pyridine from 3-picoline and *o*-tolyllithium.[13] The formation of 3-tosyloxypyridine from pyridine 1-oxide and tosyl chloride[14] involves a similar intramolecular attack at the β position of a 1,2-dihydropyridine.[15]

The only nitrilium salts which failed to give the desired 2-acylaminopyridine were *N*-1-adamantylacetonitrilium bromopentachloroantimonate (**16a**) and *N*-1-adamantylbenzonitrilium bromopentachloroantimonate (**16b**). The latter, for example, on heating with pyridine 1-oxide gave none of the desired amide **17** (which was obtained from 2-fluoropyridine and 1-adamantanamine followed by benzoylation). The only products isolated were *N*-benzoyl-1-adamantanamine, benzonitrile, and the 1-adamantyl halides (the last two by thermal cleavage of the nitrilium salt).

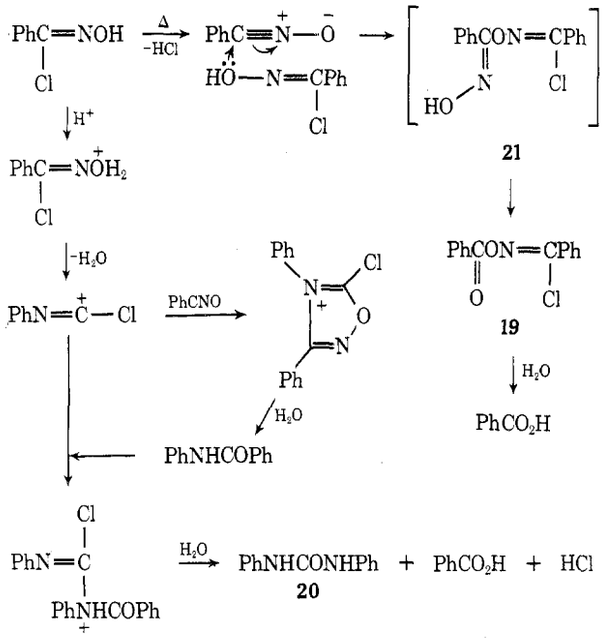


It was hoped that the acylamination reaction could be extended to the α-chloroaldoximes, which would have been expected to yield 2-pyridylhydroxylamine derivatives. Reaction of pyridine 1-oxide with α-chlorobenzaldoxime gave none of the desired *N*-2-pyridylhydroxamic acid (**18**). Instead, the *N*-oxide appeared to function as a weak base in this reaction and most of the products appear to be derived from benzonitrile oxide (α-chlorobenzaldoxime eliminates HCl in boiling chlorobenzene[16]). The major product (30%) was identified (literature melting point, nmr, ir, mass spectrum) as *N*-benzoyloxybenzimidoyl chloride (**19**).[17a] Benzanilide (11.4%) carbanilide (*N,N'*-diphenylurea, **20**, 7.6%), and benzoic acid (7%) were also isolated. The nmr spectrum of **19** consisted of two complex multiplets at δ 8.25–8.00 and 8.67–8.35 in the area ratio of 4:6 (ortho protons:meta and para protons). The mass spectrum exhibited a weak molecular ion [M^+ (^{35}Cl) at *m/e* 259] which lost Cl· to give a peak at *m/e* 224. The base peak was at *m/e* 105 ($PhCO^+$). A peak at *m/e* 103 may be attributed to $PhCN\cdot^+$. Carbanilide gave



the expected nmr and mass spectra and was identical with an authentic sample. Possible routes to these products are illustrated in Scheme V. Conversion of **21** to **19** probably occurs on chromatographic work-up, as does the hydrolysis of **19** to benzoic acid. The formation of benzanilide requires a Beckmann rearrangement, perhaps of the protonated oxime, and a speculative route to it and to

Scheme V

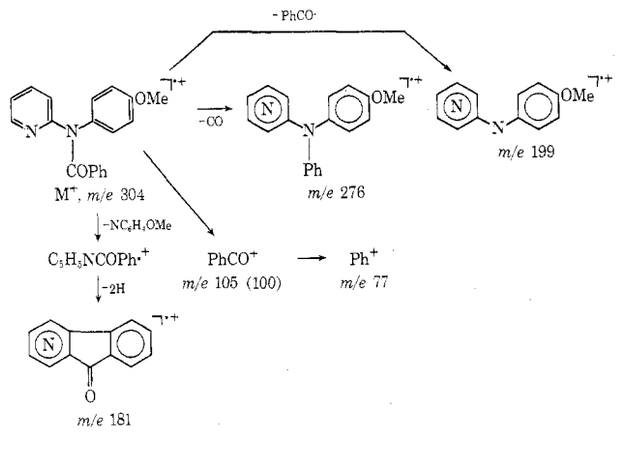


carbanilide is sketched. It is not clear at present why, if a nitrilium ion is formed as an intermediate, it would not react with pyridine 1-oxide. Blocking the hydroxyl function in the original oxime should prevent this degradation and perhaps cause the desired acylamination to occur. This is under investigation.

Mass Spectra of the 2-Acylaminated Pyridines. These were similar to that of *N*-benzoyldiphenylamine and the behavior of 2-(*N*-benzoyl-*p*-methoxyanilino)pyridine (Scheme VI) is typical. In all cases, the base peak is $PhCO^+$ while the second most prominent one is due to $C_6H_5^+$. All the other processes are minor. While loss of benzoyl from *N*-benzoyldiphenylamine is not detectable, formation of fluorenone (or its equivalent) by loss of the equivalent of aniline is (*m/e* 180). The latter process could involve a Fries-type rearrangement to give an anilinobenzophenone ion (precedent for such a rearrangement in solution exists[17b]) followed by loss of an arylnitrene fragment and cyclization.

When R′ in **2** is alkyl, the base peak is no longer at *m/e* 105. For example, when R = $PhCH_2$, the base peak is at *m/e* 43. When R′ = 1-adamantyl, the base peak is the adamantyl cation (*m/e* 135), and $PhCO^+$ and Ph^+ give rise to very intense fragments. In *N*-2-pyridylcaprolactam the base peak is the pyridinium radical cation (*m/e* 79). The mass spectrum of *N*-2-pyridylsaccharin is characterized by consecutive losses of SO_2 and CO. The base peak is at *m/e* 43. A similar fragmentation occurs in 2-substituted benzimidazoles.[18] More detailed discussion of these mass spectra does not seem warranted in the absence of high-resolution, isotopic-labeling, and metastable-peak data.

Scheme VI



Experimental Section

Reagents and Solvents. These were, in general, of reagent grade and were used without further purification. Solvents for reactions requiring anhydrous conditions were dried and distilled prior to use. Halocarbons were dried with phosphorus pentoxide, ethers and hydrocarbons with sodium wire, and pyridines with potassium hydroxide pellets. Amine oxides were completely dehydrated by azeotroping with benzene followed by distillation, and were kept under anhydrous conditions. They were distilled in the drybox again just before use.

Drybox experiments were carried out under a nitrogen atmosphere maintained at positive pressure and with phosphorus pentoxide as desiccant.

Thin layer chromatography was carried out on silica gel (Camag Kieselgel DS-5) and column chromatography on Baker silica gel powder (60–200 mesh).

Nmr spectra were recorded on a Varian HA-100 spectrometer and infrared spectra on a Perkin-Elmer 337 or 257 spectrometer. Melting points are uncorrected.

Benzenediazonium tetrafluoroborate, *p*-chlorobenzenediazonium tetrafluoroborate, and *p*-nitrobenzenediazonium tetrafluoroborate were prepared according to the procedure of Roe.[19]

N-Phenylbenzimidoyl chloride was prepared from benzanilide by boiling under reflux for 90 min with phosphorus pentachloride (1 molar equiv) or, preferably, with thionyl chloride (1.1 molar equiv). The mixture was distilled to give *N*-phenylbenzimidoyl chloride (*ca.* 90% yield), bp 100° (0.05 mm) [lit.[4] bp 174–176° (12 mm)], mp 34–35° (lit.[4] mp 40°).

N-*p*-Tolylbenzimidoyl chloride, bp 104° (0.005 mm) [lit.[20] bp 106–109° (0.02 mm)], *N*-*p*-anisylbenzimidoyl chloride, bp 154–160° (0.53 mm) [lit.[20] bp 198–200° (20 mm)], *N*-*p*-chlorophenylbenzimidoyl chloride, bp 123° (0.01 mm) (lit.[21] mp 63–65°), and *N*-*p*-nitrophenylbenzimidoyl chloride, mp 110–111° (lit.[20] mp 114–116°), were prepared similarly.

N-Benzylbenzimidoyl chloride was prepared from *N*-benzoylbenzylamine (4.22 g, 0.92 mol) and phosphorus pentachloride (4.16 g, 0.02 mol). These were boiled under reflux until hydrogen chloride evolution ceased. The mixture was immediately distilled *in vacuo* to remove phosphorus oxychloride and any benzonitrile and benzyl chloride which had formed from the decomposition of the imidoyl chloride. The clear, yellow residue (3.33 g, 70%) of *N*-benzylbenzimidoyl chloride was used immediately without further purification.

N-Cyclohexylbenzimidoyl chloride was prepared from *N*-benzoylcyclohexylamine and thionyl chloride and had bp 84–86° (0.07 mm) [lit.[20] bp 110–112° (1 mm)]. Saccharin pseudochloride had mp 138–140° (lit.[22a] mp 143°). *N*-Phenylbenzonitrilium hexachloroantimonate was obtained from freshly prepared and distilled *N*-phenylbenzimidoyl chloride and antimony pentachloride in anhydrous ethylene chloride (drybox).[22b]

Amidation of Pyridine 1-Oxide. 2-Anilinopyridine and 2-*N*-Benzoylanilinopyridine. A. From Benzenediazonium Tetrafluoroborate. 1. A solution of benzenediazonium tetrafluoroborate (3.84 g, 0.02 mol) and pyridine 1-oxide (1.90 g, 0.02 mol) in dry (P_2O_5) acetonitrile (15 ml) was stirred at 50–60° for 1 hr. The acetonitrile was distilled *in vacuo* and the residue was boiled under reflux with 5% aqueous sodium hydroxide (50 ml) for 0.5 hr. The basic solution was steam distilled to give 2-anilinopyridine (0.63 g, 18.6%), mp 104–106° (lit.[23] mp 108°), identical with an authentic sample.

2 (Experiment Carried Out by Mr. F. F. Gadallah). A solution of benzenediazonium tetrafluoroborate (2.4 g) in acetonitrile (12 ml) containing pyridine 1-oxide (0.95 g) was heated for 8 hr at 65°. The excess acetonitrile was evaporated and the residue was chromatographed on a column of alumina (14 × 0.25 in.). Elution with benzene–ethanol (85:15 v/v) gave a fraction which, on glc on a column (4 ft × 0.25 in.) of 20% ethylene glycol adipate on Chromosorb W at 170°, gave six small peaks, the fourth one corresponding to 2-phenylpyridine. A subsequent fraction gave rise to three peaks on glc. These were collected and characterized. The first corresponded to acetanilide, mp 113–114°, the second to 2-anilinopyridine, mp 109–110°. The third component had bp 136° (0.6 mm), ir (KBr) 1670 cm^{-1} (s), and was identical with an au-

thentic sample of **2-*N*-acetylanilinopyridine** (prepared in 85% yield from 2-anilinopyridine, acetic anhydride, and 2 drops of perchloric acid).

Anal. Calcd for $C_{13}H_{12}N_2O$: C, 73.58; H, 5.66; N, 13.21. Found: C, 73.47; H, 5.78; N, 13.47.

Quantitative analysis (on duplicate runs) was effected by glc using a 3.5 ft × 0.25 in. column packed with 20% ethylene glycol adipate on Gas-Chrom P at 170° with a helium flow rate of 90 ml/min and using 2-*o*-bromophenylpyridine as the internal standard. The yields thus obtained follow: acetanilide, 20.7 ± 0.1%; 2-anilinopyridine, 7.7 ± 0.2%; and 2-*N*-acetylanilinopyridine, 5.7 ± 0.1%.

B. From *N*-Phenylbenzimidoyl Chloride. In a drybox, a solution of *N*-phenylbenzimidoyl chloride (2.45 g, 0.0114 mol) and pyridine 1-oxide (2.17 g, 0.0228 mol) in ethylene chloride (25 ml) was boiled under reflux for 10 hr. After cooling to room temperature, the reaction mixture was filtered to remove pyridine 1-oxide hydrochloride (1.10 g, 42%), mp 179.5–182° (lit.[24] mp 180°). One-half of the filtrate was evaporated and boiled under reflux for 0.5 hr with 5% aqueous sodium hydroxide. Steam distillation of the basic solution provided 2-anilinopyridine (0.44 g, 47%), mp 105–107° (lit.[23] mp 108°), identical with an authentic sample. Benzanilide (0.51 g, 45%), mp 162–163° (lit.[25] mp 163°), crystallized from the distillation residue.

The other half of the original filtrate was also evaporated. The residue was fractionally crystallized from ethanol to afford **2-*N*-benzoylanilinopyridine** (0.73 g, 47%): mp 163–167°; ir (KBr) identical with that of an authentic sample prepared from 2-anilinopyridine and benzoyl chloride in benzene; ir (KBr) 1660 cm^{-1}; nmr ($CDCl_3$) δ 8.30 (d of d, 1 H, $J_{5,6}$ = 5, $J_{4,6}$ = 1 Hz, H_6), 7.55–6.80 (m, 13 H, aromatic H); mass spectrum (70 eV) *m/e* (rel intensity) 274 (8, M^+), 246 (15), 245 (10), 106 (13), 105 (100), 78 (11), 77 (96).

Recrystallization from ethanol gave the analytical sample, mp 167–169°.

Anal. Calcd for $C_{18}H_{14}N_2O$: C, 78.81; H, 5.14; N, 10.21. Found: C, 78.92; H, 5.26; N, 10.43.

Benzanilide (0.43 g, 40%) was also obtained from the fractional crystallization and was identified by its infrared spectrum.

C. From *N*-Phenylbenzonitrilium Hexachloroantimonate. *N*-Phenylbenzonitrilium hexachloroantimonate (3.90 g, 0.0076 mol) was suspended in ethylene chloride (40 ml) (drybox). A solution of pyridine 1-oxide (1.44 g, 0.0152 mol) in ethylene chloride (20 ml) was added dropwise over a period of 5 min. All of the suspended nitrilium salt dissolved as the *N*-oxide was added. The reaction mixture was stirred at room temperature for 10 hr. The reaction mixture was concentrated and chromatographed on a column of silica gel (100 g). Elution with chloroform gave first benzanilide and then 2-*N*-benzoylanilinopyridine (0.39 g, 34%), identical with an authentic sample (melting point, ir).

Detailed Study of the Reaction of Pyridine 1-Oxide with *N*-Phenylbenzimidoyl Chloride. The reaction of pyridine 1-oxide with *N*-phenylbenzimidoyl chloride was carried out as described in B above. After removal of the pyridine 1-oxide hydrochloride, the reaction mixture was analyzed by glc [20% SE-30 on Chromosorb W (60–80 mesh), 6 ft × 3/16 in., He carrier gas, flow rate 60 ml/min, column temperature 100°]. 3-Chloropyridine was identified by its retention time (4.73 min) and, after collection, by its infrared and nmr spectra. The column temperature was raised to 250°. Four more compounds were detected. Benzanilide (6.80 min) and 2-*N*-benzoylanilinopyridine (17.77 min) were identified on the basis of respective retention times, melting points, and infrared and nmr spectra. The other two components, present in very low concentrations, had retention times identical with those of 2-anilinopyridine (3.15 min) and 3-benzoyloxypyridine (3.55 min).

In a separate experiment, weighed amounts of 2-bromopyridine and *N*-benzoyl-*p*-toluidine were added to serve a internal standards. Relative molar response factors of two minor components were assumed to be equal to 1.0 (The error introduced by this assumption is less than the experimental error.) Glc conditions were the same as given above. The yields were as follows: 3-chloropyridine, 28.1%; 2-*N*-benzoylanilinopyridine, 57.2%; benzanilide, 36.8%; 2-anilinopyridine, 3.1%; and 3-benzoyloxypyridine, 1.2%. The last two were only tentatively identified.

2-*N*-Benzoyl-*p*-toluidinopyridine. A. From *N*-*p*-Tolylbenzimidoyl Chloride. *N*-*p*-Tolylbenzimidoyl chloride (1.70 g, 0.00742 mol) and pyridine 1-oxide (1.41 g, 0.0144 mol) were dissolved in ethylene chloride (25 ml). The solution was boiled under reflux for 10 hr. After cooling to room temperature, the solution was filtered to remove pyridine 1-oxide hydrochloride (0.65 g, 68%). The filtrate was concentrated and chromatographed on silica gel (100 g). Elution with chloroform produced *N*-benzoyl-*p*- toluidide (0.66 g, 42%), mp 157–159° (lit.[25] *mp 158*°), identical with an authentic sample. Further elution gave **2-*N*-benzoyl-*p*-toluidinopyridine** (1.23 g, 57%), mp 149–151°, identical with an authentic sample (melting point, ir).

Anal. Calcd. for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59. Found: C, 79.45; H, 5.95.

B. Authentic 2-*N*-Benzoyl-*p*-toluidinopyridine. 2-*p*-Toluidinopyridine (0.46 g, 0.0025 mol) was treated with benzoyl chloride (0.7 g, 0.005 mol) in boiling benzene to give 2-*N*-benzoyl-*p*-toluidinopyridine (0.33 g, 46%): mp 148–151.5°; ir (KBr) 2990 (aromatic CH_3) and 1660 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 8.30 (d of d of d, 1 H, $J_{5,6}$ = 4.8, $J_{4,6}$ = 1.8, $J_{3,6}$ = 0.8 Hz, H_6), 7.7–6.9 (m, 12 H, aromatic H), 2.27 (s, 3 H, CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 288 (9, M^+), 260 (9), 105 (100), 77 (48), 43 (35).

2-*p*-Toluidinopyridine. A solution of *N*-*p*-tolylbenzimidoyl chloride (2.99 g, 0.01 mol) and pyridine 1-oxide (1.90 g, 0.1 mol) in ethylene chloride (30 ml) was boiled under reflux for 11 hr. After cooling to room temperature, the solution was filtered to remove pyridine 1-oxide hydrochloride (0.72 g, 56%). The filtrate was evaporated and the residue was boiled under reflux for 4 hr with 5% aqueous sodium hydroxide (30 ml). After cooling to room temperature, the basic solution was filtered to remove a solid (1.90 g), mp 90–95°. Fractional crystallization from methanol afforded *N*-benzoyl-*p*-toluidide (0.23 g, 11%) and **2-*p*-toluidinopyridine** (1.48 g, 80%), mp 108–109°, identical with an authentic sample (melting point, ir).

Anal. Calcd for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57. Found: C, 77.88; H, 6.65.

An authentic sample was prepared as follows. 2-Bromopyridine (3.32 g, 0.02 mol) and *p*-toluidine (2.0 g, 0.02 mol) were boiled together under reflux for 45 min. The mixture was dissolved in 2 *N* hydrochloric acid (15 ml). Basification with 20% aqueous sodium carbonate gave 2-*p*-toluidinopyridine (3.56 g, 97% crude). Recrystallization from aqueous ethanol gave pure material (2.44 g, 67%): mp 105–106°; ir (KBr) 3230 (free NH), 3180 (hydrogen-bonded NH), 1610, 1540, 1470, 1460, 1340, 995, and 775 cm^{-1}; nmr ($CDCl_3$) δ 8.48 (br s, 1 H, exchangeable with D_2O, NH), 8.00 (br d, 1 H, $J_{5,6}$ = 5 Hz, H_6), 7.36–6.90 (m, 5 H, pyridyl H_4 and phenyl H), 6.70 (d, 1 H, $J_{3,4}$ = 8 Hz, H_3), 6.46 (d of d, 1 H, $J_{4,5}$ = 8, $J_{5,6}$ = 5 Hz, H_5), 2.25 (s, 3 H, CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 185 (8, M^+), 184 (52), 183 (100), 182 (6), 181 (6), 169 (6), 168 (12), 97 (14), 95 (12), 93 (6), 91 (13), 85 (7), 83 (13), 81 (13), 79 (14), 78 (17), 77 (12), 71 (12), 69 (19), 67 (23), 65 (13), 57 (21), 56 (8), 55 (26), 53 (7), 52 (9), 51 (17), 44 (10), 43 (23), 41 (28), 40 (22), 39 (18). The following were prepared similarly.

2-*N*-Benzoyl-*p*-chloroanilinopyridine (53%): mp 123.5–125° (EtOH); ir (KBr) 2890 (OCH_3), 1650 cm^{-1} (CO); nmr ($CDCl_3$) δ 8.22 (d of d of d, 1 H, $J_{5,6}$ = 5, $J_{4,6}$ = 2, $J_{3,6}$ = 1 Hz, H_6), 7.7–6.7 (m, 12 H, aromatic H), 3.69 (s, 3 H, OCH_3); mass spectrum *m/e* (rel intensity) 304 (9, M^+), 276 (6), 181 (11), 106 (6), 105 (100), 78 (7), 77 (35), 69 (6), 57 (6), 55 (6), 52 (12), 43 (7), 41 (8).

Anal. Calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30. Found: C, 74.66; H, 5.62.

This, on acid-catalyzed hydrolysis, gave 2-*p*-anisidinopyridine, mp 87.5–88.5° (lit.[26] mp 85–86°), identical with an authentic sample (melting point, ir).

2-*N*-Benzoyl-*p*-chloroanilinopyridine (53%): mp 123.5–125° (EtOH); ir (KBr) 1650 cm^{-1} (CO); nmr ($CDCl_3$) δ 8.34 (d, 1 H, H, $J_{5,6}$ = 5, $J_{4,6}$ = 1.5 Hz, H_6), 7.7–7.0 (m, 12 H, aromatic H); mass spectrum *m/e* (rel intensity) 307 (5), 280 (6), 106 (9), 105 (100), 77 (42), 75 (7), 51 (10), 43 (13).

Anal. Calcd for $C_{18}H_{13}ClN_2O$: C, 70.02; H, 4.24. Found: C, 70.14; H, 4.17.

Acid-catalyzed hydrolysis of the amide gave 2-*p*-chloroanilinopyridine, mp 112–115° (lit.[27] mp 116°), identical with an authentic sample.

2-*N*-Benzoylbenzylaminopyridine (54%): mp 111–113° (EtOH); ir (KBr) 1650 cm^{-1} (CO); nmr ($CDCl_3$) 8.34 (d, 1 H $J_{5,6}$ = 5 Hz, H_6), 7.4–6.4 (m, 13 H, aromatic H), 5.30 (s, 2 H, $PhCH_2$); mass spectrum *m/e* (rel intensity) 288 (0.15, M^+), 287 (0.1), 259 (0.7), 212 (8), 211 (48), 210 (17), 105 (14), 77 (9), 58 (32), 43 (100).

Anal. Calcd for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59. Found: C, 79.45; H, 5.95.

Hydrolysis of the amide with 2 *N* HCl gave 2-benzylaminopyridine, mp 95–96° (lit.[2] mp 94–95°), identical with authentic sample.

2-*N*-Benzoylcyclohexylaminopyridine (64%): mp 132.5–134°

(lit.[28] mp 129–130°); ir (KBr) 1640 cm^{-1} (CO); nmr ($CDCl_3$) δ 8.40 (d of d, 1 H, $J_{5,6}$ = 5, $J_{4,6}$ = 2 Hz, H_6), 7.5–6.9 (m, 7 H, aromatic H), 6.75 (d of d, 1 H, $J_{3,4}$ = 8, $J_{3,5}$ = 2 Hz, H_3), 2.5–1.0 (m, 11 H, C_6H_{11}); mass spectrum m/e (rel intensity) 280 (6, M^+), 198 (13), 197 (21), 176 (15), 175 (100), 121 (22), 106 (7), 105 (89), 78 (18), 77 (55), 55 (5), 51 (5), 51 (11), 41 (8).

Hydrolysis with 2 *N* HCl gave 2-cyclohexylaminopyridine, mp 125–127° (lit.[28] mp 123–125°), m/e (rel intensity) 189 (19, M^+).

***p*-Nitroanilinopyridine. A.** *N*-*p*-Nitrophenylbenzimidoyl chloride (2.30 g) and pyridine 1-oxide (1.68 g) in chlorobenzene (30 ml) were boiled under reflux for 32 hr. The cooled solution was filtered to remove pyridine 1-oxide hydrochloride (0.70 g, 61%), and the filtrate was concentrated and chromatographed on a silica gel column (200 g). Elution with benzene–chloroform (1:4 v/v) gave *N*-benzoyl-*p*-nitroaniline (0.42 g, 19%), mp 198–200° (lit.[25] mp 199°), identical with an authentic sample. Further elution with the same solvent gave **2-*N*-benzoyl-*p*-nitroanilinopyridine** (0.94 g, 33%) as a yellow oil, ir (film) 1670 (CO), 1510, 1340 cm^{-1} (NO_2). Attempted crystallization of the oil resulted in its hydrolysis to 2-*p*-nitroanilinopyridine and the amide was never obtained analytically pure.

The amide could either be hydrolyzed, or the concentrated reaction solution itself could be saponified with 5% aqueous NaOH for 3 hr to give 2-*p*-nitroanilinopyridine (71%, based on imidoyl chloride), mp 174–175° (lit.[29] mp 174–175°), identical with an authentic sample: nmr (acetone-d_6) δ 8.23 (d of d of d, 1 H, $J_{5,6}$ = 5.0, $J_{4,6}$ = 1.8, $J_{3,6}$ = 1.0 Hz, H_6), 8.10 (d, 2 H, J_o = 9.5 Hz, phenyl H_3, H_5), 7.92 (d, 2 H, J_o = 9.5 Hz, phenyl H_2, H_4), 7.51 (d of d of d, 1 H, $J_{3,4}$ = 8.7, $J_{4,5}$ = 7.5, $J_{4,6}$ = 1.8 Hz, H_4) 6.93 (d of d of d, 1 H, $J_{4,5}$ = 7.5, $J_{5,6}$ = 5.0, $J_{3,5}$ = 1.0 Hz, H_5), 6.87 (d of d of d, 1 H, $J_{3,4}$ = 8.7, $J_{3,5}$ = 1.0, $J_{3,6}$ = 1.0 Hz, H_3).

B. *N*-*p*-Nitrophenylbenzimidoyl chloride (1.76 g) in ethylene chloride (30 ml) was treated with antimony pentachloride (2.02 g) at room temperature in a drybox. The deep orange solution was treated dropwise with a solution of pyridine 1-oxide (1.29 g) in ethylene chloride (10 ml). A pale precipitate formed which gradually dissolved as the addition continued. The solution was then boiled under reflux for 17 hr, the solvent was distilled off *in vacuo*, and the residue was hydrolyzed with 2 *N* HCl to give 2-*p*-*nitroanilinopyridine* (1.30 g, 89%), identical with an authentic sample.

***N*-2-Pyridylcaprolactam.** Phosgene (3.2 g, 0.036 mol) was dissolved in chloroform (10 ml). A solution of caprolactam (3.68 g, 0.036 mol) in chloroform was added dropwise over a period of 1 hr. The oil heating bath was maintained at 38°. (There was an exothermic reaction as the addition proceeded and a gas was evolved which turned litmus paper red, although the literature[30] indicates that caprolactam pseudochloride hydrochloride is the substance produced. All attempts to isolate this hydrochloride failed.) The reaction mixture was kept at 55° for 4.25 hr and was then used as such. It was boiled under reflux while a solution of pyridine 1-oxide (9.3 g, 0.0978 mol) in chloroform (20 ml) was added over a period of 10 min. The addition caused an exothermic reaction, the solution became orange, and a white solid precipitated. After 15 hr the reaction mixture was cooled and pyridine 1-oxide hydrochloride was collected (2.60 g, 61%). The filtrate was evaporated and the residue was chromatographed on a column of silica gel (100 g). Elution with chloroform–benzene (1:1 v/v) gave ***N*-2-pyridylcaprolactam** as an oil (0.76 g, 11%): bp 106° (0.05 mm); ir (film) 2930 and 2850 (aliphatic CH) and 1665 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 8.37 (d of d of d, 1 H, $J_{5,6}$ = 5, $J_{4,6}$ = 1.5, $J_{3,6}$ = 1.3 Hz, H_6), 7.63 (m, 2 H, H_3, H_4), 7.00 (d of d of d, 1 H, $J_{4,5}$ = 6, $J_{5,6}$ = 5, $J_{3,5}$ = 2.3 Hz, H_5), 4.04 (br m, 2 H, $COCH_2$), 2.72 (br m, 2 H, NCH_2), 1.90 (br s, 6 H, aliphatic CH); m/e (rel intensity) 190 (34, M^+).

Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.44; H, 7.42. Found: C, 69.21; H, 7.58.

The picrate had mp 133–135° (from ethanol).

Anal. Calcd for $C_{17}H_{17}N_5O_8$: C, 48.69; H, 4.09. Found: C, 48.32; H, 3.67.

***N*-2-Pyridylsaccharin. A. Reaction of Pyridine 1-Oxide with Saccharin Pseudochloride.** 1. A solution of saccharin pseudochloride (0.35 g, 0.0017 mol) and pyridine 1-oxide (0.16 g, 0.0017 mol) in chlorobenzene (10 ml) was boiled under reflux for 18 hr. Tlc (2.5 and 5% MeOH–$CHCl_3$) showed the absence of saccharin pseudochloride and saccharin. There were two major components (R_f *ca.* 0.89 and 0.76) and several slower moving components (R_f 0.22 and 0.11) present. The solution was concentrated to 5 ml and chromatographed on a column of silica gel (50 g). The first fraction, eluted with 1% methanol–chloroform and crystallized from ethanol, was ***N*-2-pyridyl-*o*-carbethoxybenzenesulfonamide** (0.54 g, 10.4%): mp 170–172°; ir (KBr) 3250 (NH), 1750 (ester C=O), 1660, 1630, 1330 (SO_2), 1160 (SO_2), 1140, and 605 cm^{-1}; nmr ($CDCl_3$) δ 8.81 (br d, 1 H, $J_{5,6}$ = 5.5 Hz, pyridyl H_6), 8.57 (d of d, 1 H, $J_{5,6}$ = 8, $J_{4,6}$ = 4 Hz, phenyl H_6), 8.3–7.6 (m, 6 H, aromatic H and NH), 7.33 (d of d, 1 H, $J_{4,5}$ = 8, $J_{5,6}$ = 5.5 Hz, pyridyl H_5), 4.34 (q, 2 H, J_{vic} = 7 Hz, CH_3CH_2–), 1.30 (t, 3 H, J_{vic} = 7 Hz, CH_3CH_2–); mass spectrum (70 eV) m/e (rel intensity) 306 (2, M^+), 261 (17), 260 (30), 241 (13), 213 (26), 196 (64), 185 (93), 169 (100), 168 (54), 121 (38), 104 (25), 93 (28), 78 (50), 77 (28), 76 (61), 69 (10), 65 (38), 51 (32), 50 (45), 45 (27), 43 (37).

Anal. Calcd for $C_{14}H_{14}N_2O_4S$: C, 54.89; H, 4.61. Found: C, 54.88; H, 4.67.

The second fraction, eluted with 5% methanol–chloroform, was pyridine 1-oxide (0.062 g, 39%).

2. A solution of saccharin pseudochloride (0.60 g, 0.0030 mol) and pyridine 1-oxide (0.57 g, 0.0060 mol) in chlorobenzene (20 ml) was boiled under reflux for 50 hr. After cooling to room temperature, the solvent was decanted from a residual water-soluble, brown oil. This gave a positive halogen test with aqueous silver nitrate solution and was presumably pyridine 1-oxide hydrochloride. The solvent was evaporated from one-half of the reaction mixture and the semicrystalline residue was fractionally crystallized from aqueous ethanol to give ***N*-2-pyridylsaccharin** (0.30 g, 38.4%): mp 210–211°; ir (KBr) 1740 (five-membered lactam C=O), 1360 (SO_2), 1330, 1310, 1190 (SO_2), 1145, 774, and 580 cm^{-1}; nmr ($CDCl_3$) δ 8.58 (d of d, 1 H, $J_{5,6}$ = 5.5, $J_{4,6}$ = 1 Hz, pyridyl H_6), 8.1–7.6 (m, 6 H, aromatic H), 7.26 (d of d of d, 1 H, $J_{4,5}$ = 6, $J_{5,6}$ = 5.5, $J_{3,5}$ = 1 Hz, pyridyl H_5); mass spectrum m/e (rel intensity) 260 (25, M^-), 197 (7), 196 (42), 195 (6), 196 (7), 168 (29), 97 (9), 95 (9), 93 (9), 92 (9), 81 (9), 79 (8), 78 (24), 77 (31), 76 (30), 69 (12), 58 (32), 57 (13), 55 (16), 51 (20), 50 (22), 44 (10), 43 (100), 42 (8), 41 (16).

Anal. Calcd for $C_{12}H_8N_2O_3S$: C, 55.38; H, 3.10. Found: C, 55.52; H, 2.93.

The second half of the reaction mixture was concentrated and chromatographed on a column of silica gel (50 g). Elution with 1% methanol–chloroform and crystallization from ethanol gave *N*-2-pyridyl-*o*-carbethoxybenzenesulfonamide (0.096 g, 21%), ir identical with that of the product described above.

B. Preparation of Authentic *N*-2-Pyridylsaccharin. 1. A warm solution of sodiosaccharinate (1.03 g, 0.005 mol) in hexamethylphosphoramide (HMPA, 5 ml) was stirred while a solution of 2-bromopyridine (0.79 g, 0.005 mol) in HMPA (5 ml) was added dropwise. The solution was boiled under reflux for 10 min. After partial cooling, water (10 ml) was added. The mixture was cooled to room temperature and filtered to give 3-*N*,*N*-dimethylaminopseudosaccharin (0.85 g, 85%), mp 298–299°. One recrystallization from acetonitrile gave the analytical sample: mp 301–306° (lit.[31] mp 273–274°); ir (KBr) 2980 (NCH_3) and 1630 cm^{-1} (C=N); nmr, insufficiently soluble; mass spectrum m/e (rel intensity) 210 (22, M^-), 146 (10), 145 (61), 104 (10), 103 (46), 102 (14), 76 (14), 44 (100), 43 (12), 42 (12).

Anal. Calcd for $C_9H_{10}N_2O_2S$: C, 51.41; H, 4.79. Found: C, 51.72; H, 4.92.

2. Sodiosaccharinate (2.05 g, 0.01 mol) and 2-fluoropyridine (1.94 g, 0.02 mol) were boiled under reflux for 15 hr. The mixture was cooled and poured into water (10 ml) to dissolve any remaining sodiosaccharinate. The solution was extracted with chloroform (2 × 25 ml), and the extract was dried (Na_2CO_3) and evaporated. The residue was crystallized from aqueous ethanol to give *N*-2-pyridylsaccharin (0.017 g, 0.65%), identical with the material obtained above.

***N*-2-Pyridyl-*o*-carbethoxybenzenesulfonamide from *N*-2-Pyridylsaccharin.** *N*-2-Pyridylsaccharin (0.1 g) was boiled in ethanol under reflux for 10 hr. Undissolved *N*-2-pyridylsaccharin (0.067 g, 67%) was recovered from the cooled mixture. Evaporation of the solvent gave *N*-2-pyridyl-*o*-carbethoxybenzenesulfonamide (0.013 g, 11%), mp 170–172°, identical with the compound obtained above.

Reaction of Pyridine 1-Oxide, *N*-Phenylbenzimidoyl Chloride, and *N*-Benzoyl-*p*-toluidine. A solution of the *N*-oxide (1.68 g) in ethylene chloride (20 ml) and a suspension of *p*-benzotoluidide (3.8 g, 0.018 mol) in ethylene chloride (35 ml) were added to freshly prepared and distilled *N*-phenylbenzimidoyl chloride (1.9 g, 0.0085 mol) and the mixture was boiled under reflux for 8 hr. Pyridine 1-oxide hydrochloride (0.45 g, 39%) separated from the cooled solution. The filtrate was concentrated and analyzed by glc (5 ft × 0.25 in. column packed with 20% SE-30 on Gas-Chrom

Q at 250°, *N*-benzoyl-*p*-anisidine internal standard) and the products were collected and characterized. In addition to small amounts of the secondary amines, the following were formed: 2-*N*-benzoylanilinopyridine (23.6%); 2-*N*-benzoyl-*p*-toluidinopyridine (24.7%).

Reaction between *N*-Phenylbenzimidoyl Chloride and *N*-Benzoyl-*p*-toluidine (Work with Dr. E. M. Smith). In a drybox, a solution of *N*-benzoyl-*p*-toluidine (1.9 g, 0.009 mol) in ethylene chloride (25 ml) was added to freshly prepared and distilled *N*-phenylbenzimidoyl chloride (1.9 g, 0.009 mol) and the solution was boiled under reflux for 3.5 hr. The solvent was distilled *in vacuo* and the solid residue was examined by mass spectrometry with minimum exposure to the atmosphere (70 eV, direct inlet, 50°). Molecular ions were observed at *m/e* 229, 215, 211, and 197, corresponding to *N*-*p*-tolylbenzimidoyl chloride, *N*-phenylbenzimidoyl chloride, *N*-benzoyl-*p*-toluidine, and benzanilide, respectively. The first two M^+ peaks showed the cluster characteristic of an ion containing one Cl atom. The relative intensities of the *m/e* 229 and 215 ions were 229:215 = 1.66:1.

The above solid had an infrared spectrum identical with that obtained when a mixture of benzanilide and *N*-*p*-tolylbenzimidoyl chloride was heated under the same conditions.

2-*N*-Benzoylanilino-4-picoline. A solution of *N*-phenylbenzimidoyl chloride (3.9 g, 0.018 mol) and 4-picoline 1-oxide (3.83 g, 0.036 mol) in ethylene chloride (35 ml) was boiled under reflux for 3 hr. The reaction mixture was concentrated and chromatographed on a column of silica gel (200 g). Elution with chloroform–benzene (1:4 v/v) gave benzanilide (1.28 g, 36%), mp 164–165°. Elution with chloroform–benzene (1:1 to 3:1 v/v) yielded 2-*N*-benzoylanilino-4-picoline (1.32 g, 45%): mp 158.5–159.5° (from EtOH); ir (KBr) 2900 (aromatic CH_3), 1650 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 8.21 (d, 1 H, $J_{5,6}$ = 5 Hz, H_6), 7.5–7.0 (m, 11 H, aromatic H), 6.87 (d of d, 1 H, $J_{5,6}$ = 5 Hz, H_5), 2.27 (s, 3 H, CH_3); mass spectrum *m/e* (rel intensity) 288 (5, M^+), 260 (12), 259 (11), 106 (7), 105 (100), 77 (60), 51 (10).

Anal. Calcd for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59. Found: C, 79.20; H, 5.69.

2-Anilino-4-picoline. 2-*N*-Benzoylanilino-4-picoline (0.200 g, 0.00069 mol) was boiled under reflux with 2 *N* hydrochloric acid for 12 hr. After cooling to room temperature, the solution was filtered to remove benzoic acid (0.31 g, 37%). Basification with 5% aqueous sodium hydroxide produced 2-anilino-4-picoline (0.095 g, 74%): mp 118.5–119.5° (lit.[32] mp 119°); ir (KBr) 3220 (NH), 1615, and 1595 cm^{-1}; nmr ($CDCl_3$) δ 8.09 (d, 1 H, $J_{5,6}$ = 5 Hz, H_6), 7.4–7.0 (m, 6 H, phenyl H and NH), 6.72 (d, 1 H, $J_{3,5}$ = 1 Hz, H_3), 6.56 (d of d, 1 H, $J_{5,6}$ = 5, $J_{3,5}$ = 1 Hz, H_5), 2.27 (s, 3 H, CH_3); mass spectrum *m/e* (rel intensity) 185 (6, M^+), 184 (45), 183 (100), 182 (9), 97 (9), 95 (11), 93 (8), 92 (11), 91 (12), 83 (9), 81 (12), 80 (13), 79 (8), 77 (16), 71 (8), 69 (14), 67 (11), 65 (13), 57 (15), 55 (22), 51 (14), 43 (16), 41 (25), 40 (16), 39 (20).

Attempted Reaction of Pyridine 1-Oxide with Benzenesulfonylbenzimidoyl Chloride. A solution of *N*-benzenesulfonylbenzimidoyl chloride (0.35 g) and dry pyridine 1-oxide (0.24 g, freshly azeotroped with dry benzene) in chlorobenzene (5 ml) was boiled under reflux for 15 hr. Pyridine 1-oxide hydrochloride (0.1 g, 59%) sublimed in the condenser. The filtered solution was concentrated and chromatographed on a column of silica gel (50 g). Elution with chloroform gave *N*-benzoylbenzenesulfonamide (0.1 g, 31%), mp 145–146° (lit.[33] mp 147°). Two minor fractions eluted with 5% MeOH in $CHCl_3$ were not identified but were different from authentic 2-*N*-benzoylbenzenesulfonamidopyridine or from 2-benzenesulfonamidopyridine.

Reaction of Pyridine 1-Oxide with α-Chlorobenzaldoxime. A solution of pyridine 1-oxide (1.90 g) and α-chlorobenzaldoxime (1.55 g) in chlorobenzene (25 ml) was boiled under reflux for 12 hr. A white sublimate (0.4 g) formed in the condenser. The dark red solution was concentrated and chromatographed on a column of silica gel (100 g). Elution gave *N*-benzoyloxybenzimidoyl chloride (0.40 g, 30%): mp 109–110° (lit.[17a] mp 109°); ir (KBr) 1750 (C=O), 1250 cm^{-1}; nmr ($CDCl_3$) δ 8.25–8.00 (m, 4 H, ortho H), 7.65–7.35 (m, 6 H, meta and para H); *m/e* (rel intensity) 259 (0.09, M^+), 105 (100). Further elution gave benzanilide (0.10 g, 11.4%), mp 163.5–164.5°, identical with an authentic sample. The third product to elute was carbanilide (0.081 g, 7.6%), mp 247–248° (from EtOH) (lit.[25] mp 238°), identical with an authentic sample: nmr (DMSO-d_6) δ 9.02 (br s, 2 H, exchangeable with D_2O, NH), 7.9–7.5 (m, 8 H, ortho and meta H), 7.32 (t, 2 H, $J_{m,p}$ = 6.5 Hz, para H); *m/e* (rel intensity) 213 (2, M^+), 93 (100). Further elution gave benzoic acid (0.087 g, 7.1%), mp 120–121°. No derivatives of pyridine were isolated.

In a control experiment omitting the pyridine 1-oxide, tlc (10% benzene–chloroform) indicated the presence of *N*-benzoyloxybenzimidoyl chloride and a second minor unidentified compound. No α-chlorobenzaldoxime and carbanilide were present in the reaction mixture after it had been boiled under reflux for a period of 22 hr.

Reaction of *N*-Benzoyl-1-adamantanamine with Thionyl Chloride. A. Neat. *N*-Benzoyl-1-adamantanamine (2.04 g) was heated gently with thionyl chloride (1.3 ml) until HCl evolution ceased. The mixture was distilled under vacuum to remove HCl, SO_2, and $SOCl_2$, the residue was dissolved in ethylene chloride (15 ml), and a solution of pyridine 1-oxide (1.9 g) in ethylene chloride (20 ml) was added. The solution was boiled under reflux for 10 hr. On cooling the solution pyridine 1-oxide hydrochloride (0.30 g, 23%) separated. Tlc ($CHCl_3$) analysis indicated the presence of benzonitrile, 1-chloroadamantane, and pyridine 1-oxide, but no 2-*N*-benzoyl-1-adamantanaminopyridine.

B. In Ether. The chlorination of *N*-benzoyl-1-adamantanamine with thionyl chloride was carried out as above except in ether (30 ml) solution. The results were the same as in the reaction carried out in the absence of solvent.

Phosgene did not effect the chlorination of *N*-benzoyl-1-adamantanamine either at room temperature or at 50°.

Reaction of Pyridine 1-Oxide with an *N*-Adamantylacetonitrilium Salt. A solution of pyridine 1-oxide (0.95 g) was added to a suspension of 1-adamantanamine (1.51 g) in acetonitrile (35 ml). The suspension was stirred at room temperature while isoamyl nitrite (1.28 g) was added dropwise over a period of 5 min. There was no gas evolution at room temperature. Gentle heating on the steam bath produced quantitative gas evolution within 20 hr. The solution was concentrated (*ca.* 10 ml) and poured into water (50 ml). The organic layer was extracted with chloroform, and the chloroform layer was dried (Na_2CO_3) and evaporated to give 1-acetamidoadamantane (1.35 g, 70%): mp 147–148° (lit.[34] mp 149°); ir (KBr) 3260 (NH), 1640 cm^{-1} (CO); *m/e* (rel intensity) 193 (14, M^+).

***N*-1-Adamantylacetonitrilium Bromopentachloroantimonate.** In a drybox, antimony pentachloride (3.0 g) was added to a solution of acetonitrile (0.41 g) in chlorobenzene (15 ml) to form a bright yellow precipitate. A solution of 1-bromoadamantane (2.25 g) in chlorobenzene (10 ml) was added dropwise and a voluminous precipitate formed in an exothermic reaction. The precipitate was collected and washed thoroughly with chlorobenzene and petroleum ether to afford bright yellow ***N*-1-adamantylacetonitrilium bromopentachloroantimonate** (4.0 g, 72%); ir (Nujol) 2360 cm^{-1} (C≡N$^+$).

Anal. Calcd for $C_{12}H_{18}BrCl_5NSb$: C, 25.96; H, 3.27. Found: C, 25.88; H, 3.31.

***N*-1-Adamantylbenzonitrilium Bromopentachloroantimonate.** From $SbCl_5$, PhCN, and 1-bromoadamantane in *o*-dichlorobenzene, the benzonitrilium salt (53–75%) was obtained, ir (Nujol) 2330 cm^{-1}.

Anal. Calcd for $C_{17}H_{20}BrCl_5NSb$: C, 33.08; H, 3.27. Found: C, 33.07; H, 3.45.

Attempted Reaction of Pyridine 1-Oxide with *N*-1-Adamantylbenzonitrilium Bromopentachloroantimonate. The above salt (6.2 g) was suspended in ethylene chloride (75 ml), and the suspension was stirred at room temperature (drybox) while a solution of pyridine 1-oxide (1.90 g) in ethylene chloride (20 ml) was added. All of the salt dissolved during the addition of the *N*-oxide. The solution was boiled under reflux for 8 hr, cooled, and stirred with water. The mixture was filtered and the organic layer was separated and concentrated when pyridine 1-oxide–$SbCl_5$ adduct (1.0 g, 26%), mp 195–202° (lit.[35] mp 195–196°), crystallized. The filtrate was further concentrated and chromatographed on a column of silica gel. The only products isolated (identified by tlc and ir) were the 1-adamantyl halide (mixture of chloro and bromo), benzonitrile, and *N*-benzoyl-1-adamantanamine.

2-(1-Adamantanamino)pyridine. 2-Fluoropyridine (3.88 g) and 1-adamantanamine (3.01 g) were boiled together under reflux for 16 hr. The mixture was dissolved in 2 *N* HCl (10 ml) and the solution was basified with 5% aqueous NaOH to give a solid consisting of a mixture of the starting amine and of the desired product . Chromatography on a silica gel column (50 g) gave 2-(1-adamantanamino)pyridine (0.41 g, 8.9%): mp 165–166.5° (chloroform–light petroleum); ir (KBr) 3345 cm^{-1} (NH); nmr ($CDCl_3$) δ 8.00 (d of d of d, 1 H, $J_{5,6}$ = 4.5, $J_{4,6}$ = 2, $J_{3,6}$ = 1 Hz, H_6), 7.28 (d of d of d, 1 H, J = 7.8, 7.5, $J_{4,6}$ = 2 Hz, H_4), 6.44 (m, 2 H, H_3 and H_5), 4.38 (br s, 1 H, exchangeable with D_2O, NH), 2.04 and 1.70 (15 H, aliphatic H); *m/e* (rel intensity) 229 (14, M^+), 171 (100).

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.

References and Notes

(1) (a) Preliminary communication: R. A. Abramovitch and G. M. Singer, *J. Amer. Chem. Soc.*, **91**, 5672 (1969). (b) T. Vajda and K. Kovacs, *Recl. Trav. Chim. Pays-Bas*, **80**, 47 (1961).
(2) K. Kovacs and T. Vajda, *Acta Pharm. Hung., Suppl.*, **31**, 72 (1961); *Chem. Abstr.*, **57**, 5892 (1962); *Acta Chim. Acad. Sci. Hung.*, **29**, 245 (1961); *Chem. Abstr.*, **57**, 5892 (1962).
(3) C. S. Giam in "Pyridine and Its Derivatives: a Supplement," Vol. 3, R. A. Abramovitch, Ed., Wiley-Interscience, New York, N. Y., 1974, 46.
(4) H. Meerwein, P. Lasch, R. Mersch, and J. Spille, *Chem. Ber.*, **89**, 209 (1956).
(5) P. Oxley and W. F. Short, *J. Chem. Soc.*, 382 (1947).
(6) R. O. Roblin, Jr. and P. S. Winnek, *J. Amer. Chem. Soc.*, **62**, 1999 (1940); J. P. English, D. C. Campbell, P. H. Bell, and R. O. Roblin, Jr., *ibid.*, **64**, 2525 (1942).
(7) W. Brügel, *Z. Elektrochem.*, **66**, 159 (1962).
(8) R. A. Abramovitch, G. M. Singer, and A. R. Vinutha, *Chem. Commun.*, 55 (1967); R. A. Abramovitch, M. Saha, E. M. Smith, and R. T. Coutts, *J. Amer. Chem. Soc.*, **89**, 1537 (1967); R. A. Abramovitch and A. R. Vinutha, *J. Chem. Soc. B*, 131 (1971); R. A. Abramovitch, E. M. Smith, and R. T. Coutts, *J. Org. Chem.*, **37**, 3584 (1972); R. A. Abramovitch, J. Campbell, E. E. Knaus, and S. Silhankova, *J. Heterocycl. Chem.*, **9**, 1367 (1972).
(9) T. Kauffmann and H. Marhan, *Chem. Ber.*, **96**, 2519 (1963).
(10) R. A. Abramovitch and P. Tomasik, unpublished results.
(11) R. A. Abramovitch and J. G. Saha, *Advan. Heterocycl. Chem.*, **6**, 275 (1966).
(12) D. Bryce-Smith and A. C. Skinner, *J. Chem. Soc.*, 577 (1963).
(13) R. A. Abramovitch, C. S. Giam, and G. A. Poulton, *J. Chem. Soc. C*, 128 (1970).
(14) M. Murakami and E. Matsumura, *Nippon Kagaku Zasshi*, **70**, 393 (1949).
(15) S. Oae, T. Kitao, and Y. Kitaoka, *Tetrahedron*, **19**, 827 (1963).
(16) H. Ulrich, "The Chemistry of Imidoyl Halides," Plenum Press, New York, N. Y., 1968, p 168.
(17) (a) H. Wieland and K. Kitasato, *Ber.*, **62**, 1250 (1929); (b) J. M. Birchall and M. T. Clark, *J. Chem. Soc., Perkin Trans. 1*, 1259 (1973).
(18) S.-O. Lawesson, G. Schroll, J. H. Bowie, and R. G. Cooks, *Tetrahedron*, **24**, 1875 (1968).
(19) A. Roe, *Org. React.*, **5**, 192 (1949).
(20) I. Ugi, F. Beck, and U. Fetzer, *Chem. Ber.*, **95**, 126 (1962).
(21) S. A. Sulkorni and R. C. Shah, *J. Indian Chem. Soc.*, **27**, 111 (1950).
(22) (a) H. Bohme and H. Opfer, *Z. Anal. Chem.*, **139**, 255 (1953); (b) H. Meerwein, P. Lasch, R. Mersch, and J. Spille, *Chem. Ber.*, **89**, 209 (1956).
(23) A. S. Tomcufcik and L. N. Starker, "Pyridine and Its Derivatives," Vol. 3, E. Klingsberg, Ed., Wiley-Interscience, New York, N. Y., 1962, p 90.
(24) E. N. Shaw, "Pyridine and Its Derivatives," Vol. 2, E. Klingsberg, Ed., Wiley-Interscience, New York, N. Y., 1959, p 99.
(25) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed, Wiley, New York, N. Y., 1956, pp 288–289.
(26) A. Mangini and M. Colonna, *Gazz. Chim. Ital.*, **73**, 313 (1943).
(27) R. R. Burtner, U. S. Patent 2,802,008 (1957); *Chem. Abstr.*, **52**, 1280*g* (1958).
(28) M. Viscontini, C. Ebnöther, and P. Karrer, *Helv. Chim. Acta*, **34**, 2438 (1951).
(29) C. Runti, *Ann. Chim. (Rome)*, **46**, 406 (1956); *Chem. Abstr.*, **51**, 3480*g* (1957).
(30) Stannicarbon N. V., Belgian Patent 609,822 (1962); *Chem. Abstr.*, **57**, 16505*e* (1962).
(31) S. J. Mehta and G. H. Hamor, *J. Pharm. Sci.*, **50**, 672 (1961); *Chem. Abstr.*, **55**, 25918*h* (1961).
(32) R. R. Burtner, U. S. Patent 2,784,195 (1957); *Chem. Abstr.*, **51**, P12985*d* (1957).
(33) Q. E. Thompson, *J. Amer. Chem. Soc.*, **73**, 5841 (1951).
(34) H. Stetter, J. Mayer, M. Schwarz, and K. Wulff, *Chem. Ber.*, **93**, 226 (1960).
(35) G. Hilgetag and H. Teichmann, *Chem. Ber.*, **96**, 1446 (1963).

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

R. A. Abramovitch* and Richard B. Rogers

Department of Chemistry, University of Alabama, University, Alabama 35486

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