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# Studies of Substituted *N*-Benzoyl-2-pyridinecarboxamides. Reactions with Acyl Chlorides and Other Electrophiles

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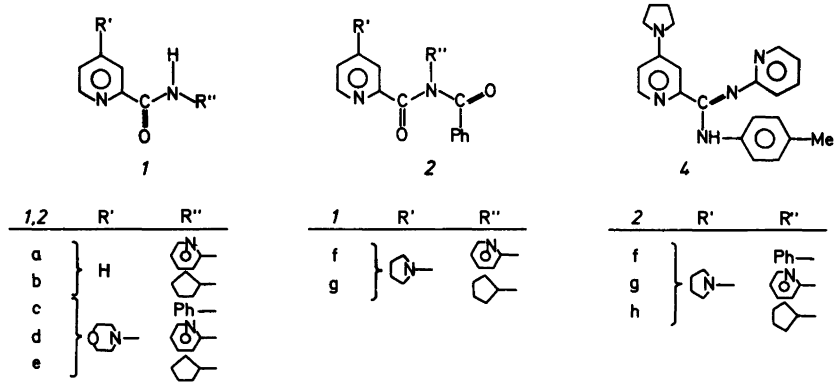
*N*-Benzoyl-4-(4-morpholinyl)-2-pyridinecarboxamides react as nucleophiles towards benzoyl chloride to give adducts which are stabilized by further addition of one mol of water. The structure of these compounds is elucidated by chemical and spectroscopic methods. The same compounds can be obtained from reactions of 4-(4-morpholinyl)-2-pyridinecarboxamides with two molar equivalents of benzoyl chloride and triethylamine. *N*-Benzoyl-4-(1-pyrrolidinyl)-2-pyridinecarboxamides react with benzoyl chloride to give less stable adducts, whereas *N*-benzoyl-2-pyridinecarboxamides are unreactive towards benzoyl chloride. Methyl iodide, *N*,*N*-diphenylcarbamoyl chloride and acetic anhydride are unreactive towards the 4-*N*,*N*-dialkylamino-2-pyridinecarboxamides and their *N*-benzoyl derivatives. These *N*-benzoylamides give unstable adducts with methyl chloromethanoate, acetyl chloride or *p*-toluenesulfonyl chloride. The adducts decompose to the hydrochlorides of the rearranged *N*-benzoylamides and the acyl imidate hydrochlorides are isolated from these reactions. 2-(Benzoylamino)pyridine reacts with a mixture of thionyl chloride and phosphorus(V) chloride to give the corresponding imidoyl chloride hydrochloride.

Compounds *2*, see Scheme 1, have two important features which are of interest to us. Firstly, the *N*-acylamide function has a spatial arrangement so that an acyl-group transfer from the amide nitrogen to the pyridine nitrogen would go through a five-membered ring transition state. Secondly, the pyridine-4-*N*,*N*-dialkylamino substituent of *2c–h* will enhance the nucleophilicity of the pyridine nitrogen and, therefore, is expected to promote such intramolecular acyl-group transfers.

Recent studies have shown[1] that *N*-acyl-2-pyridinecarboxanilides, which are closely related to *2*, can be prepared by various methods. Presently *2a* is prepared in almost quantitative yield by direct benzoylation of *1a*, *cf.* Scheme 1, whereas 2-




*Scheme 1.*

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pyridinecarboxanilides were quite resistant to acylation.[1] Therefore, the amide *N*-substituent is of importance for the reactivity of these amides towards acyl halides. The present studies also show the importance of the pyridine-4-*N*,*N*-dialkylamino substituent of both *1* and *2*. For instance, if *2a* or *2d* is treated with benzoyl chloride compound *2a* is recovered unchanged whereas *2d* forms an addition compound with the acid chloride. Moreover, the same addition compound also is obtained from *1d* and two mol equivalents of benzoyl chloride and triethylamine.

## RESULTS

Various reaction sequences are expected [1] to give the *N*-benzoylamides *2a–h*. Compounds *2a*, *2d* and *2g* are prepared from the triethylammonium 2-pyridinecarboxylates and *N*-(2-pyridyl)benzimidoyl chloride hydrochloride. A good yield of this imidoyl chloride hydrochloride is obtained from the chlorination of 2-(benzoylamino)pyridine with a mixture of phosphorus(V) chloride and thionyl chloride.[2] Other workers [3a] have reported unsuccessful attempts to prepare this imidoyl chloride by chlorinating 2-(benzoylamino)pyridine with either phosphorus(V) chloride or thionyl chloride. An alternative method of preparing *2a*, *2d* and *2g* would be reaction of benzoic acid and a base with the imidoyl chlorides derived from the amides *1a*, *1d* and *1f*. This method, however, would be of little practical use since the chlorination products of *1a*, *1d* and *1f* are extremely hygroscopic. The chlorination product from *1f* gives a moderate yield of the amidine *4*, *cf.* Scheme 1, from a reaction with 4-methylaniline thus identifying the chlorination product as either the mono- or the dihydrochloride of the imidoyl chloride derived from *1f*.

Compound *2a* also is obtained in excellent yield by direct benzoylation of *1a* with benzoyl chloride in the presence of triethylamine. This reaction may be compared to the rapid dibenzoylation of 2-aminopyridine with benzoyl chloride alone [3b] or in the presence of triethylamine.[3c] Thus, analogous to the postulated mechanism for these reactions [3b] the aminopyridine ring-nitrogen of *1a* might initially be benzoylated and a rapid intramolecular transfer of the benzoyl group to the amide nitrogen would give *2a*. Such a mechanism also would explain the enhanced reactivity of *1a* compared to the reactivity of 2-pyridinecarboxanilides [1] towards benzoyl chloride. Similarly, *1b* is less reactive than *1a* towards benzoyl chloride and a fair yield (40 %) of *2b* is obtained from a reaction of *1b* with benzoyl chloride and triethylamine.

Direct benzoylation of compound *1d* in benzene with two molar equivalents of benzoyl chloride and triethylamine yields a benzene insoluble precipitate which is dissolved in dichloromethane. Triethylammonium chloride is removed by extraction with aqueous sodium hydrogen carbonate and the derivative of *1d* is crystallized from acetone. The same product also is obtained from a reaction of a benzene solution of *2d* with benzoyl chloride. However, the *N*-benzoylamide *2a* is recovered unchanged after treatment with benzoyl chloride. This indicates that the increased nucleophilicity of the 4-(4-morpholinyl)pyridine moiety of *1d* or *2d* is of importance for these reactions. Furthermore, both *2c* and *2e* give similar addition products with benzoyl chloride whereas *2b* is unreactive towards benzoyl chloride. The proposed structures *3a–c*, *cf.* Scheme 2, are indicated by the following observations. Analyses, C, H, Cl and N, for *3a* and *3b* are correct for the addition of 1 mol each of benzoyl chloride and water to *2c* or *2d*. Compound *3a* does not react with triethylamine, and it also is formed in a reaction of *2c* with benzoyl chloride and triethylamine. Therefore, no acidic protons such as pyridinium protons are present in *3a–c*. However, sodium hydride, which is able to react as a base towards hydroxyl hydrogens, does in fact react with *3a* and a 65 % yield of *2c* is obtained. The purple color of this reaction mixture indicates that the fair yield of *2c* may be due to cleavage of the pyridine ring.

A reaction of *3b* with cyclopentylamine in acetonitrile indicates reactions of the amine both as a base and as a nucleophile. Thus, GLC analysis of the reaction mixture shows the presence of equimolar amounts of the three amides *1e*, 2-(benzoylamino)pyridine and *N*-cyclopentylbenzamide. This product mixture may be explained as follows. A nucleophilic attack by cyclopentylamine on the protonated benzoyl group at the pyridine nitrogen of *3b* would give an adduct which by assistance of another molecule of the base would deprotonate. A subsequent dehydration and fragmentation would give equimolar amounts of *N*-cyclopentylbenzamide and *2d*. The latter compound reacts with a third molecule of cyclopentylamine to give *1e* and 2-(benzoylamino)pyridine.

From a similar reaction of cyclopentylamine with

a suspension of *3b* in benzene a 73% yield of cyclopentylammonium chloride was isolated as benzene insoluble material after 21 h. Equimolar amounts of *1e*, 2-(benzoylamino)pyridine and *N*-cyclopentylbenzamide were present in the filtrate which was analyzed by GLC.

IR absorptions also support structures *3a–c*; these compounds show two absorptions of medium strength in the hydroxyl region 3440–3350 $cm^{-1}$, *3a* and *3b* show two strong absorptions whereas *3c* has one strong absorption in the carbonyl region 1760–1730 $cm^{-1}$. Finally, the strong absorption at 1655–1660 $cm^{-1}$ shown by these compounds is in the area of an immonium ($C=N^+$) bond.

$^1H$ NMR resonances of nitromethane-$d_3$ solutions of compounds *3* indicate the presence of two hydroxyl hydrogens, $\delta$ 2.3 for *3a*, $\delta$ 2.7 for *3b* and $\delta$ 7.4 for *3c*. The pyridine protons of *3* resonate at $\delta$ 7.1–8.3 and, therefore, structures similar to *3* but with the hydroxyl group bound to the pyridine-6 carbon are ruled out. The latter type of compounds is expected to show a doublet at $\delta$ 4–6 due to the proton at the saturated pyridine-6 carbon.[4] Both *N*-acyl-[5a] and *N*-alkoxycarbonyl-[5b,c] 4-*N*,*N*-dimethylpyridines show $^1H$ NMR resonances at $\delta$ 8.6–8.8 for the pyridine $H_\alpha$ and at $\delta$ 7–7.2 for the pyridine $H_\beta$ atoms. These observations therefore are in accordance with the slightly lower $\delta$-value, 8.2–8.3, assigned to the $H_\alpha$ atom at the pyridine-6 carbons of *3a–c*, and the $\delta$-values, 7.1–7.2 assigned to the $H_\beta$-atom at the pyridine-5 carbons of *3*.

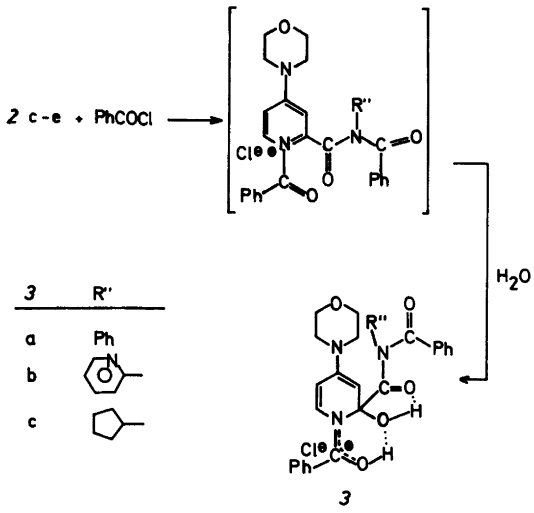
Additional evidence for structure *3* also may be deduced from the $^{13}C$ NMR resonances which are shown in Table 1. *N*-Protonated pyridines are known to have shielded $C_\alpha$ atoms and a deshielded $C_\gamma$ compared to pyridine itself.[6] Such changes are observed for the pyridine-carbons 2, 4 and 6 of *2c·HCl* compared to *2c*. However, the $\delta$-values of these atoms in *2c·HCl* and *3a* are about equal and this observation may be explained by two counteracting effects. Since pyridine *N*-acylation[7] has a somewhat less shielding effect than pyridine *N*-protonation,[6] pyridine *N*-benzoylation as in *3a* might deshield the pyridine carbons 2 and 6 as compared to *2c·HCl*. However, loss of aromaticity in the pyridine ring by introduction of the 2-hydroxyl group is expected to have a shielding effect on carbons 2 and 6 and the result might be as observed.

The formation of compounds *3a–c* might deserve some brief comments. Initially an addition of the benzoyl group to the pyridine-nitrogen of *2c–e* certainly occurs. However, Catalin models of 4-(4-morpholinyl)pyridine show a considerable steric hindrance to coplanarity between the pyridine and the morpholine rings. Therefore, even if morpholine will enhance the nucleophilicity of the pyridine nitrogen of *2c–e*, much of the positive charge is expected to remain on the pyridine nitrogen of the initial adducts with benzoyl chloride. These adducts, like most *N*-acylpyridinium salts are expected to be sensitive to moisture.[8] No precautions except using dry solvents were taken to protect these reaction products from moisture, therefore, water easily might add across the pyridine-*N* carbonyl and the pyridine-2 carbon as shown in Scheme 2. This addition may be compared to the formation of Reissert compounds from *N*-acylpyridinium salts. Most acylpyridinium salts are known to react with nucleophiles at the pyridine-4 position giving 1,4-

*Table 1.* $^{13}C$ NMR resonances.[a]

| Compound | Solvent | Pyridine carbon | | | | | Carbonyl | Morpholine |
|---|---|---|---|---|---|---|---|---|
| | | 2 | 3 | 4 | 5 | 6 | | |
| *1c* | $CDCl_3$ | 156.2 | 106.5 | 150.6 | 109.7 | 148.5 | 162.6 | 66.2; 46.1 |
| *2c* | $CDCl_3$ | 155.6 | 108.9 | 152.9 | 109.9 | 148.9 | 173.1; 172.5 | 66.2; 46.0 |
| *2c·HCl* | $CD_3OD$ | 140.6 | 104.2 | 158.4 | 111.8 | 136.9 | 159.8[b] | 67.1 [c] |
| | DMSO-$d_6$ | 139.0 | 102.4 | 157.0 | 110.3 | 135.8 | 157.6[b] | |
| *3a* | $CDCl_3$ | 139.9 | 102.1 | 158.3 | 114.8 | 136.0 | 163.9; 158.3[d] | 66,6, 65.9; 49.2, 48.0 |
| | DMSO-$d_6$ | 139.2 | 103.4 | 157.7 | 110.7 | 135.8 | 163.7; 158.2 | 65.5; 47.8, 47.0 |
| | DMF-$d_7$ | 140.6 | 104.0 | 158.9 | 111.7 | 136.7 | 163.7; 161.4 | 66.5; 48.8 |

[a] A complete $^{13}C$ NMR analysis of these and related compounds is in preparation. [b] This resonance probably is due to both C=O and C=N of the acyl imidate structure of this compound, *cf.* Ref. 1. [c] Overlap with $CD_3OD$ resonances. [d] Resolution into two resonances, $\delta$ 158.35 and 158.23 at 400 MHz on a Bruker VM-400 instrument.




*Scheme 2.*

dihydropyridines,[9] but one fairly stable 1,2-dihydropyridine, the first known Reissert compound in the pyridine series, has been isolated.[10] However, initial attack at the pyridine-2 position also has been postulated in some other cases,[11] but unfavorable equilibria might be responsible for the difficulty in isolating such 1,2-dihydropyridines.[10] Thus, we may conclude that nucleophilic attack by water at the pyridine-2 position of the benzoylpyridinium adducts of *2c–e* yields the 1,2-dihydropyridine derivatives *3a–c*. These are stabilized by both charge delocalization and intramolecular hydrogen bonding and, therefore, are isolated without difficulty.

Compounds *3* might be mixtures of two rotational isomers since for instance 1-ethoxycarbonyl-2,4-di-*tert*-butyl-1,2-dihydropyridine was found[4a] to be a mixture of two such isomers. Another explanation for the relatively wide melting range of compounds *3a* and *3c* might be the existence of dimorphic forms which are reported[9b] for some Reissert compounds.

The *N*-acylamides *2f* and *2g* which have pyrrolidine as the pyridine-4 substituent also give addition compounds with benzoyl chloride. However, these compounds seem to be less stable than *3a–c*. Other electrophiles also react with compounds *2*, but pure products are not obtained from reactions of *2c* with either methyl chloromethanoate or with acetyl chloride. The latter product decomposes slowly when dissolved in nitromethane and yields *2c·HCl* after several weeks. Only *2c·HCl* is obtained from a reaction of *2c* with *p*-toluenesulfonyl chloride. No addition compounds are obtained from *1d*, *2d* or *2f* and *N,N*-diphenylcarbamoyl chloride, from *2f* and acetic anhydride or from *2f* and methyl iodide. Even if steric effects might be responsible for the low reactivity *N,N*-diphenylcarbamoyl chloride, electronic effects certainly are important in the other reactions.

Compounds *2c* and *2f* react with hydrogen chloride to give the expected acyl imidate hydrochlorides[1,12] whereas *2d* decomposes when reacted similarly.

The present exploratory studies have clearly demonstrated the effect by the pyridine-4-*N,N*-dialkylamino substituent of compounds *2c–h*. These compounds react as nucleophiles towards acyl chlorides and related electrophiles whereas the unsubstituted compounds *2a–b* are unreactive towards the same electrophiles. However, there are several unanswered questions pertaining to the exact mechanisms of the observed acylations of compounds *1*. There also are unanswered questions about the relative importance of steric and electronic effects for the reactivity of *1* and *2* as nucleophiles or as bases. Further studies of these and similar compounds are in progress.

## EXPERIMENTAL

*General.* IR spectra were recorded on a Perkin Elmer 254 grating spectrometer. Mass spectra were obtained on an AEI MS902 spectrometer with 70 eV bombarding electron energy. $^1$H NMR and $^{13}$C NMR spectra were obtained at 100 MHz on a Jeol JNM-FX100 Fourier Transform NMR spectrometer. GLC analyses were carried out on a Pye Unicam 104 instrument with flame ionization detector and a glass column: 5% OV–17 (150 cm, 2.2 mm i.d.) on Chromosorb W AW–DMCS 80 –100 mesh. All melting points are uncorrected and were obtained on a Büchi "Tottoli" melting point apparatus. Elemental analyses were carried out at Analytische Laboratorium, Elbach, Germany. Silica gel, 63–200 μm, for column chromatography was obtained from Merck, Merck kieselgel 60 F 254 was used for TLC.

Cyclopentylamine, 4-methylaniline, *N,N*-diphenylcarbamoyl chloride, all *purum*, and sodium hydride, 55–60% in oil, practical grade were obtained from Fluka. Methyl chloromethanoate, reagent grade was obtained from BDH, *p*-toluenesulfonyl chloride, reagent grade, from Baker

and methyl iodide, reagent grade, from Merck.

*2-Pyridinecarboxamides*, 1a – g. The preparation of compound *1c* has been described.[2] The same method of preparation was used for *1a*, *1b*, *1d* – *1g* except that triethylamine was used instead of pyridine as a base.

*1a* (78%) m.p. 116 – 117 °C (ligroin), lit.[13] no physical constants reported. IR (nujol): 3350 (s), 1695 (s) $cm^{-1}$.

*1b* (82%) m.p. 80 – 81 °C (hexane). MS [*m/e* (% rel. int.)]: 190 (28.0, M). Mol. wt., obs. 190.1101, calc. for $C_{11}H_{14}N_2O$ 190.1106. IR (nujol): 3320 (m), 1655 (s) $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 1.46 – 2.17 (8H, m), 4.40 (1H, m), 7.31 – 8.56 (5H, m).

*1d* (72%) m.p. 140 – 141 °C (benzene). MS [*m/e* (% rel. int.)]: 284 (50.3, M). Mol. wt., obs. 284.1280, calc. for $C_{15}H_{16}N_4O_2$ 284.1273. IR (nujol): 3360 (s), 1700 (s) $cm^{-1}$. $^1H$ NMR ($CD_3NO_2$): $\delta$ 3.43 (4H, m), 3.83 (4H, m), 6.9 – 8.4 (7H, m), 10.49 (1H, broad s).

*1e* (50 %) m.p. 85 – 87 °C. MS [*m/e* (% rel. int.)]: 275 (23.5, M). Mol. wt., obs. 275.1636, calc. for $C_{15}H_{21}N_3O_2$ 275.1634. IR (nujol): 3250 (s), 1650 (s) $cm^{-1}$. $^1H$ NMR ($CD_3NO_2$): $\delta$ 1.1 – 2.3 (8H, m), 3.37 (4H, m), 3.77 (4H, m), 4.3 (1H, m). 6.81 (1H, dd, *J* 2.9 Hz), 7.64 (1H, d, *J* 2.9 Hz), 8.0 (1H, s), 8.11 (1H, d, *J* 5.7 Hz).

*1f* (62%) m.p. 175 – 176 °C (benzene). MS [*m/e* (% rel. int.)]: 268 (44.7, M). Mol. wt., obs. 268.1327, calc. for $C_{15}H_{16}N_4O$ 268.1324. IR (nujol): 3300 (s), 1685 (s) $cm^{-1}$. $^1H$ NMR ($CD_3NO_2$): $\delta$ 2.1 (4H, m), 3.46 (4H, m), 6.6 – 8.4 (7H, m), 10.5 (1H, broad s).

*1g* (50 %) m.p. 92 – 94 °C (hexane – diethyl ether). MS [*m/e* (% rel. int.)]: 259 (22.4, M), Mol. wt., obs. 259.1687, calc. for $C_{15}H_{21}N_3O$ 259.1685. IR (nujol): 3290 (m), 1645 (s) $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 1.44 – 2.14 (12H, m), 3.34 (4H, m), 4.34 (1H, m), 6.37 (1H, dd, *J* 2.9 Hz), 7.31 (1H, d, *J* 2.9 Hz), 7.97 (1H, s), 8.06 (1H, d, *J* 5.7 Hz).

*N-(2-Pyridyl)benzimidoyl chloride hydrochloride*. A solution of 2-(benzoylamino)pyridine[14] (790 mg, 4 mmol) and phosphorus(V) chloride (860 mg, 4.1 mmol) in 6 ml of thionyl chloride was heated at 60 °C for 20 min. Dry benzene (10 ml) was added and the solvents were removed under reduced pressure. Acetone (3 ml) was added to the residue which was filtered and gave 700 mg (69%) of *N*-(2-pyridyl)benzimidoyl chloride hydrochloride m.p. 151 – 155 °C dec. Lit.[3a] m.p. 152 – 157 °C dec. IR (nujol): 1670 (s) $cm^{-1}$.

*N-Cyclopentylbenzimidoyl chloride*. A mixture of *N*-cyclopentylbenzamide[15] (1.9 g, 10 mmol) and phosphorus(V) chloride (2.1 g, 10 mmol) in 30 ml of benzene was heated under reflux for 1 h. The solvent was removed under reduced pressure. The residue was boiled with 20 ml of hexane, the hot solution was filtered and 2.0 g (95%) liq. of the title compound was obtained from the filtrate. IR (film): 1665 (s) $cm^{-1}$.

*N-Benzoyl-2-pyridinecarboxamides*, 2a – h. Compounds *2c* and *2f* have been described.[16] Compounds *2a*, *2b*, *2d*, *2e*, *2g* and *2h* were prepared by the following procedure. To a mixture of the 2-pyridinecarboxylic acid (2 mmol) and triethylamine (4 mmol) in 30 ml of acetonitrile was added either *N*-(2-pyridyl)benzimidoyl chloride hydrochloride (2 mmol) or *N*-cyclopentylbenzimidoyl chloride (2 mmol). The reaction mixture was heated at 50 – 60 °C for 2 h. The solvent was removed under reduced pressure, and 15 ml of benzene was added to the residue. Triethylammonium chloride was removed by filtration and the filtrate was chromatographed on silica gel. Compounds *2a* and *2b* were eluted with chloroform whereas compounds *2d*, *2e*, *2g* and *2h* were eluted with acetone.

*2a* (92%) m.p. 130 – 131 °C (diethyl ether and hexane). MS [*m/e* (% rel. int.)]: 303 (39.2, M). Mol. wt., obs. 303.1014, calc. for $C_{18}H_{13}N_3O_2$ 303.1008. IR (nujol): 1710 (s), 1695 (s) $cm^{-1}$. $^1H$ NMR ($CD_3NO_2$): $\delta$ 7.2 – 7.6 (6H, m), 7.8 – 8.0 (5H, m), 8.3 – 8.5 (2H, m).

*2b* (79%) m.p. 71 – 73 °C. MS [*m/e* (% rel. int.)]: 294 (3.0, M). Mol. wt., obs. 294.1368, calc. for $C_{18}H_{18}N_2O_2$ 294.1368. IR (nujol): 1705 (s), 1650 (s) $cm^{-1}$. $^1H$ NMR ($CD_3NO_2$): $\delta$ 1.6 – 2.0 (8H, m), 5.0 (1H, m), 7.15 – 7.70 (8H, m), 8.34 (1H, d, *J* 4.9).

*2d* (45%) m.p. 178 – 181 °C dec. (diethyl ether). MS [*m/e* (% rel. int.)]: 388 (41.7, M). Mol. wt., obs. 388.1540, calc. for $C_{22}H_{20}N_4O_3$ 388.1535. IR (nujol): 1705 (s), 1695 (s) $cm^{-1}$. $^1H$ NMR ($CD_3NO_2$): $\delta$ 3.4 (4H, m), 3.8 (4H, m), 6.7 – 8.4 (12H, m).

*2e* (44%) m.p. 146 – 147 °C (diethyl ether). MS [*m/e* (% rel. int.)]: 379 (22.7, M). Mol. wt., obs. 379.1900, calc. for $C_{22}H_{25}N_3O_3$ 379.1896. IR (nujol): 1705 (s), 1670 (s) $cm^{-1}$. $^1H$ NMR ($CD_3NO_2$): $\delta$ 1.5 – 2.2 (8H, m), 3.2 (4H, m), 3.7 (4H, m), 4.9 (1H, m), 6.6 (1H, dd, *J* 2.9 Hz), 7.0 – 7.6 (6H, m), 7.95 (1H, d, *J* 5.7 Hz).

*2g* (48%) m.p. 170 – 172 °C dec. (diethyl ether). MS [*m/e* (% rel. int.)]: 372 (29.6, M). Mol. wt., obs. 372.1584, calc. for $C_{22}H_{20}N_4O_2$ 372.1586. IR (nujol): 1710 (s), 1690 (s) $cm^{-1}$. $^1H$ NMR ($CD_3NO_2$): $\delta$ 2.2 (4H, m), 3.6 (4H, m), 6.7 – 8.5 (12H, m).

*2h* (49%) m.p. 98 – 100 °C (diethyl ether and hexane). MS [*m/e* (% rel. int.)]: 363 (24.3, M). Mol. wt., obs. 363.1945, calc. for $C_{22}H_{25}N_3O_2$ 363.1947. IR (nujol): 1705 (s), 1660 (s) $cm^{-1}$. $^1H$ NMR ($CD_3NO_2$): $\delta$ 1.5 – 2.15 (12H, m) 3.4 (4H, m), 4.8 (1H, s), 6.6 (1H, dd, *J* 2.9 Hz), 7.25 (1H, d, *J* 2.9 Hz), 7.4 – 7.6 (4H, m), 8.0 – 8.15 (2H, m).

## Reactions of *1* with Acyl Chlorides

*Benzoylation of* 1a. A solution of *1a* (200 mg, 1 mmol), benzoyl chloride (140 mg, 1 mmol) and triethylamine (152 mg, 1.5 mmol), in 8 ml of benzene

was heated at 80 °C for 17 h. Triethylammonium chloride (140 mg, 1 mmol) was removed by filtration. The benzene filtrate was concentrated, chromatographed on silica gel with chloroform as the eluent and 270 mg (90%) of *2a* m.p. 129–130 °C was obtained. The IR absorptions, the TLC Rf (chloroform) and the molecular weight of this compound were identical to those of *2a* which has been obtained from triethylammonium 2-pyridinecarboxylate and *N*-(2-pyridyl)benzimidoyl chloride hydrochloride.

*Benzoylation of* 1b. Benzoyl chloride (112 mg, 0.8 mmol) was added to a solution of *1b* (150 mg, 0.79 mmol) and triethylamine (80 mg, 0.8 mmol) in 10 ml of benzene. The reaction mixture was heated under reflux for 44 h, triethylammonium chloride (75 mg, 0.55 mmol) was removed by filtration and the filtrate was chromatographed on silica gel. The chloroform eluate yielded 80 mg of a liquid which was shown by TLC to be a mixture of *1b* and *2b*, and 90 mg (39%) of *2b* m.p. 70–72 °C.

*Benzoylation of* 1d. To a 10 ml benzene solution of benzoyl chloride (155 mg, 1.1 mmol) and triethylamine (120 mg, 1.2 mmol) was added *1d* (150 mg, 0.5 mmol). The yellow solution was heated at 60–80 °C for 1.5 h. The solvent was removed under reduced pressure and the solid residue was extracted with dichloromethane and aqueous sodium hydrogencarbonate. The dichloromethane extract gave, after drying and removal of the solvent, a solid residue. Addition of acetone to this residue yielded 160 mg (55%) of *3b* m.p. 159–160 °C dec.

Anal. $C_{29}H_{27}ClN_4O_5$: C, H, Cl, N. IR (nujol): 3430 (m), 3360 (m), 1760 (s), 1730 (s) and 1660 (s) $cm^{-1}$. $^1H$ NMR ($CD_3NO_2$): $\delta$ 2.74 (2H, broad s), 3.89 (4H, s), 4.0 (4H, s) 7.14–8.3 (17H, m).

*Benzoylation of* 1f. Benzoyl chloride (141 mg, 1 mmol) was added to a solution of *1f* (134 mg, 0.5 mmol) and triethylamine (101 mg, 1 mmol) in 10 ml of benzene. The reaction mixture was heated at 50 °C for 2 h, and then left at ambient temperature for 60 h. The white precipitate was removed by filtration and yielded 320 mg m.p. 155–250 °C dec. IR (nujol): 3450 (m), 3350 (m), 2600 (s), 2490 (s), 1770 (s), 1730 (s), 1665 (s), 1575 (s). This product mixture was extracted with 40 ml of chloroform and 15 ml of water. The chloroform extract was dried over magnesium sulfate and yielded an oily residue upon removal of the solvent. Diethyl ether (10 ml) was added to the residue which crystallized and was filtered after 2h, dried at 0.1 mm Hg and gave 180 mg m.p. 127–137 °C dec. IR (nujol): 3400–3300 (m), 1750–1730 (s), 1665 (s), 1575 (s) $cm^{-1}$. $^1H$ NMR ($CD_3NO_2$): $\delta$ 2.0–2.6 (6H, broad s), 3.65–4.0 (4H, m), 7.1 (1H, dd, *J* 2.9 Hz), 7.2–8.3 (16H, m).

*Benzoylation of* 1g. Benzoyl chloride (141 mg, 1 mmol) was added to a solution of *1g* (130 mg, 0.5 mmol) and triethylamine (101 mg, 1 mmol) in 10 ml of benzene. White needles were removed by filtration after 1 h at 55 °C and yielded 120 mg (0.87 mmol) of triethylammonium chloride, m.p. 257–260 °C subl. The filtrate was left at ambient temperature for 2h, some white crystalline material was removed by filtration and gave 150 mg m.p. 95–117 °C gas ev. IR (nujol): 3440–3340 (s), 2600 (w), 2500 (w), 1740 (s), 1660 (s), 1575 (s) $cm^{-1}$. This product was extracted with 15 ml of chloroform and 3 ml of water. The dried chloroform extract yielded, upon removal of the solvent, and oily residue. The residue was triturated with diethyl ether, the solid was filtered, dried at 0.1 mm Hg and gave 95 mg m.p. 92–110 °C gas ev.; 165–175 °C dec. IR (nujol): 3440–3340 (s), 1740 (s), 1665 (s), 1575 (s) $cm^{-1}$. $^1H$ NMR ($CD_3NO_2$): $\delta$ 1.5–2.0 (4H, m), 2.2 (4H, m), 2.52 (6H, s), 3.6–3.8 (3H, m), 6.8–8.2 (8H, m).

*Reaction of* 1d *with* N,N-*diphenylcarbamoyl chloride.* A solution of *N,N*-diphenylcarbamoyl chloride (163 mg, 0.7 mmol) in 5 ml of benzene was added to a solution of *1d* (200 mg, 0.7 mmol) and triethylamine (100 mg, 1 mmol) in 10 ml of benzene. The clear solution was heated at 60 °C for 1 h and then left at ambient temperature for 60 h. The solvent was removed under reduced pressure, 4 ml of diethyl ether was added to the residue and 170 mg (85%) of *1d*, m.p. 137–139 °C was removed by filtration. The filtrate was concentrated and yielded 130 mg (80%) m.p. 79–83 °C of *N,N*-diphenylcarbamoyl chloride.

## Reactions of *2* with Acyl Chlorides

*Reactions with benzoyl chloride.* Benzoyl chloride was added to a benzene solution of an equimolar amount of *2*. After a given reaction time at a specified temperature the product was removed by filtration, washed with benzene and was dried at ambient temperature at 0.1 mmHg.

*Benzoyl chloride and* 2a gave no benzene-insoluble material after 21 h at ambient temperature; *2a* (85%) m.p. 128–130 °C was recovered from the benzene solution.

*Benzoyl chloride and* 2b gave no benzene insoluble material after 3 h at 50 °C. The benzene solution was chromatographed on silica gel and *2b* (85%) m.p. 71–72 °C was obtained from the chloroform eluate.

*Benzoylation of* 2c yielded after 1 h at 30–40 °C a product m.p. 148–158 °C dec. This product was stirred with 3 ml of acetone for 1 h and yielded after filtration and drying *3a* (64%) m.p. 158–168 °C dec. Anal. $C_{30}H_{28}ClN_3O_5$: C, H, Cl, N. IR (nujol): 3420 (m), 3350 (m), 1755 (s), 1735 (s), 1655 (s) $cm^{-1}$. $^1H$ NMR ($CD_3NO_2$): $\delta$ 2.3 (2H, s), 4.0 (8H, m), 7.1–8.2 (18H, m). Compound *3a* (71%) m.p. 156–164 °C dec. also was obtained from the same reactants except that acetone instead of benzene was used as the solvent.

In another experiment equimolar amounts of benzoyl chloride and triethylamine were dissolved in benzene. A benzene solution of one molar equivalent of *2c* was added. The white precipitate was filtered after 30 min at 35 °C, then triturated with water and yielded after drying *3a* (85%) m.p. 160–170 °C dec. This product showed identical IR absorptions and $^1$H NMR resonances to *3a* which had been obtained from *2c* and benzoyl chloride.

*Benzoylation of* 2d yielded after 2 h at 40 °C *3b* (67%) m.p. 161–163 °C dec. IR absorptions and $^1$H NMR resonances of this product were identical to those of the product which was obtained by benzoylation of *1d*.

*Benzoylation of* 2e yielded after 1 h at ambient temperature *3c* (93%) m.p. 137–145 °C gas ev. IR (nujol): 3440 (m), 3360 (m), 1745 (s), 1660 (s), cm$^{-1}$. $^1$H NMR ($CD_3NO_2$): $\delta$ 1.4–2.3 (8H, m), 4.33 (8H, m), 7.15–8.25 (16H, m). Compound *3c* was recovered unchanged from a nitromethane solution. MS [*m/e* (% rel. int.)]: 379 (8.1, M–PhCOCl $-H_2O$).

*Benzoylation of* 2f. To a solution of *2f* (75 mg, 0.2 mmol) in 8 ml of benzene was added benzoyl chloride (30 mg, 0.2 mmol). The reaction mixture was stirred at 45 °C for 30 min. The white precipitate was filtered, washed with benzene and yielded after drying 85 mg m.p. 124–126 °C dec. Anal. Found: C, 67.77; H, 5.25; Cl, 6.14; N, 7.34. Calc. for $C_{30}H_{28}ClN_3O_4$ (*2f*+PhCOCl+$H_2O$): C, 67.98; H, 5.32; Cl, 6.69; N, 7.92. IR (nujol): 3350 (m, broad), 1740 (s), 1665 (s), 1580 (s) cm$^{-1}$. $^1$H NMR ($CD_3NO_2$): $\delta$ 2.2 (4H, m), 3.7–4.0 (5H, m), 7.0–8.2 (18H, m).

*Benzoylation of* 2g. To a solution of *2g* (56 mg, 0.15 mmol) in 5 ml of benzene was added benzoyl chloride (20 mg, 0.15 mmol). The reaction mixture was stirred at 35 °C for 15 min, the white precipitate was filtered, washed with benzene and yielded 75 mg m.p. 115–120 °C gas ev. IR (nujol): 3400–3300 (m), 1750–1730 (s), 1665 (s), 1575 (s) cm$^{-1}$.

This product had decomposed after 3–4 weeks at ambient temperature.

## Reactions of *2* with other electrophiles

The electrophile was added to a benzene solution of an equimolar amount of *2*. After a given reaction time at a specified temperature the product was removed by filtration, washed with benzene and was dried at 0.1 mmHg.

2c *and methyl chloromethanoate* were reacted for 30 min. at 30 °C and gave white crystals m.p. 110–120 °C gas ev. Anal. Found: C, 64.39; H, 5.14; N, 9.36. Calc. for $C_{25}H_{24}ClN_3O_5$ (*2c*+$ClCOOCH_3$): C, 62.30; H, 5.01; N, 8.71. Calc. for $C_{23}H_{22}ClN_3O_2$ (*2c*+HCl): C, 67.72; H, 5.44; N, 10.30. IR (nujol): 3400–3320 (w) 1770 (s, broad), 1665 (s) cm$^{-1}$. $^1$H NMR ($CD_3NO_2$): $\delta$ 3.4–3.57 (4H, m), 3.76–4.1 (7H, m), 6.8–8.11 (15H, m).

2c *and acetyl chloride* were reacted for 30 min at 30–35 °C and gave white crystals m.p. 130–145 °C gas ev. IR (nujol): 3420–3320 (w), 1770 (sh), 1750 (s), 1660 (s) cm$^{-1}$. $^1$H NMR ($CD_3NO_2$): $\delta$ 2.36 (3H, s), 3.5–4.0 (10H, m), 7.1–8.2 (13H, m). This product had decomposed to *2c·HCl* after four weeks in a nitromethane solution.

2c *and* p-*toluenesulfonyl chloride* gave no immediate precipitate at ambient temperature. White crystals formed slowly and were filtered after 120 h to yield 91% of *2c·HCl* m.p.149–152 °C dec. The product was identified by IR and $^{13}$C NMR.

2c *and hydrogen chloride*. Hydrogen chloride was led over a benzene solution of *2c* for about 1 min. The oily precipitate crystallized slowly, the crystals were filtered off after 1 h and gave *2c·HCl* (99%) as a white powder, m.p. 149–152 °C dec. IR (nujol): 1740 (s), 1660 (s) cm$^{-1}$. $^1$H NMR ($(CD_3)_2SO$): $\delta$ 3.79 (8H, s), 7.3–7.8 (12H, m), 8.35 (1H, d, *J* 8 Hz), 10.67 (1H, s). $^1$H NMR ($CD(O)N(CD_3)_2$): $\delta$ 3.9 (4H, s, broad), 4.3 (4H, s, broad), 7.3–7.7 (11H, m), 7.8 (1H, d, *J* 2.9 Hz), 8.45 (1H, d, *J* 7.4 Hz), 11.7 (1H, s, broad).

2d *and* N,N-*diphenylcarbamoyl chloride*. Compound *2d* (80%) was recovered from the clear solution after 18 h at 50 °C.

2d *and hydrogen chloride*. The oily precipitate which formed was triturated with diethyl ether for 15 min and gave crystals m.p. 90 °C gas ev.; 150 °C dec. The product was somewhat hygroscopic and a good nujol mull could not be prepared. IR (nujol): 1780 (sh), 1710–1700 (s) cm$^{-1}$.

2f *and* N,N-*diphenylcarbamoyl chloride*. Compound *2f* (82%) was recovered after 29 h at 30–40 °C.

2f *and acetic anhydride*. Compound *2f* (80%) was recovered after 2 h at 70 °C.

2f *and methyl iodide*. Compound *2f* (95%) was recovered after 1 h at 30–40 °C.

2f *and hydrogen chloride*. The oily precipitate which formed crystallized in about 5 min and yielded *2f·HCl* (97%) m.p. 137–139 °C dec. MS [*m/e* (% rel. int.)]: 371 (9.3, M–HCl). IR (nujol): 1740 (s), 1670 (s) cm$^{-1}$. $^1$H NMR ($CD_3NO_2$): $\delta$ 2.2 (4H, m), 3.7 (5H, m), 6.9 (1H, dd, *J* 2.9 Hz), 7.3–7.6 (11H, m), 7.95 (1H, d, *J* 7.1 Hz).

## Reactions of *3*

3a *and triethylamine*. To a suspension of *3a* (55 mg, 0.1 mmol) in 6 ml of benzene was added triethylamine (50 mg, 0.5 mmol). The reaction mixture was stirred at 40–50 °C for 2 h and was filtered. The white solid was washed with benzene and yielded 50 mg (91%) of *3a* m.p. 156–163 °C dec.

3a *and sodium hydride.* To a solution of *3a* (65 mg, 0.12 mmol) in 8 ml of dichloromethane was added sodium hydride (12 mg, 0.24 mmol). The reaction mixture was filtered after 15 min at ambient temperature, and the filtrate yielded 30 mg (65 %) of *2c* m.p. 160 – 165 °C. The identity of *2c* was verified by TLC and IR. The liquid components of the filtrate were not identified, but the purple color indicates some decomposition.

3b *and cyclopentylamine.* A solution of *3b* (18 mg, 0.03 mmol) and cyclopentylamine (40 mg, 0.5 mmol) in 5 ml of acetonitrile was analyzed by GLC at 290 °C after 1 h at ambient temperature. Equimolar amounts of *1e*, 2-(benzoylamino)pyridine and *N*-cyclopentylbenzamide were the only products present in this reaction mixture. In another experiment, *3b* (140 mg, 0.26 mmol) was suspended in 7 ml of benzene, cyclopentylamine (140 mg, 1.6 mmol) was added and the reaction mixture was stirred at ambient temperature for 21 h. Undissolved material was removed by filtration and yielded 23 mg (73 %) of cyclopentylammonium chloride m.p. 199 – 201 °C subl. GLC analysis at 300 °C of the filtrate showed the presence of equimolar amounts of *1e*, 2-(benzoylamino)pyridine and *N*-cyclopentylbenzamide.

*Preparation of 4.* A solution of *1f* (430 mg, 1.6 mmol) and phosphorus(V) chloride (350 mg, 1.7 mmol) in 10 ml of dichloromethane was stirred at 20 °C for 15 min. The solvent was removed under reduced pressure and a solution of 4-methylaniline (170 mg, 1.6 mmol) in 5 ml of dichloromethane was added to the yellow hygroscopic residue. Triethylamine (200 mg, 2 mmol) was added and the reaction mixture was stirred at 20 °C for 2 h. The solvent was removed, the residue was dissolved in 15 ml of aqueous sodium carbonate and was extracted with 2 × 15 ml of benzene. The benzene extracts gave a liquid residue upon removal of the solvent and the residue was extracted with a mixture of tetrachloromethane (10 ml) and hexane (5 ml). Some undissolved material, 230 mg, m.p. 115 – 150 °C was removed by filtration and was found to be *1f* in admixture with a small amount of *4*. The tetrachloromethane – hexane extract yielded 130 mg (23 %) of *4*, m.p. 98 – 101 °C. MS [*m/e* (% rel. int.)]: 357 (100, M). Mol. wt., obs. 357.1950, calc. for $C_{22}H_{23}N_5$ 357.1953. IR (nujol): 3300 (m), 1640 (m), 1610 (s) $cm^{-1}$.

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