The Transposing of Isomer Yields in the Methanolyis of N-Substituted Quinolinimides by Triethylamine

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ABSTRACT
The effect of triethylamine in transposing the respective yields of the two isomeric esters ensuing from the methanolysis of N-substituted quinolinimides is described and is rationalized with a mechanism.

KEYWORDS
N-Substituted quinolinimides, methyl 2-carbamoyl-3-pyridinecarboxylates, methyl 3-carbamoyl-2-pyridinecarboxylates, benzenesulfonamide derivatives, triethylamine-induced rearrangements, reaction mechanisms.

1. Introduction
The aminolysis of quinolinic anhydride 1 has been widely utilized to access a variety of substituted pyridine derivatives such as 2-carbamoyl-3-pyridinecarboxylic acids 2, 3-carbamoyl-2-pyridinecarboxylic acids 3, 3-pyridinecarboxamides 4, and N-substituted quinolinimides 5 (Scheme 1). There is continued interest in this methodology in view of the medicinal, pharmaceutical and industrial utility of the products, their efficacy as effective plant growth regulators and weed killers, and as intermediates in organic synthesis1.

In quinolinic anhydride 1, and likewise in the representative imide 5 (R=Me), 13C-NMR chemical shifts have been used as evidence to imply that the C-7 carbonyl carbon is more electropositive than is the C-5 carbonyl carbon2. On this basis the initial mono-substituted products when 1 is treated with a nucleophilic reagent, e.g. an amine, were predicted to be the two intermediate isomeric quinolinic acids 2 and 3, with the former in higher yield. Such an expectation was initially experimentally confirmed by Dimitrijevic and Tadic1 and subsequently by others,3,4 and is exemplified here with 1,1-diphenylethylamine and with p-aminobenzenesulfonamide. The direction of the reaction has been explained by quantum-chemical methods.4,5

It is now generally accepted that this methodology invariably gives mainly the 2-carbamoyl-3-pyridinecarboxylic acid 2 independent of the nature of the amine used.

Several mechanistic schemes have been presented to account for the events and experimental findings and outcomes.2,4 These propose that following on from the initial production of 2 and 3, subsequent heating of the reaction mixture, gives, usually in acetic acid, the corresponding relatively stable N-substituted imide 5, by dehydration of either intermediate. Further, in the course of the heating, thermal decarboxylation of 3 produces the 3-pyridinecarboxamide 4.

Low yields of products 2, 3 and 5 are often observed owing to causes such as (i) the formation of stable 4 resulting from thermal decarboxylation of acid 3, (ii) the use of deactivated amines, (iii) difficulties in product separation and/or isolation, and (iv) product isomerization. Nevertheless, remarkable rate enhancements, yields and/or dramatic savings in reaction times have been observed in preparing, for example, N-substituted quinolinimides 5, by using microwave heating6, a specific catalyst such as 2-oxo-3-oxazolinylphosphonate 1a, or mixed solvents having different polarities7. Quinolinimides 5 have also been obtained here in good yield by heating 2,3-pyridinedicarboxylic acid or its anhydride 1 with the amine in polyphosphoric acid. A patented8 method for improving the yield of 2-carbamoyl-3-pyridinecarboxylic acids 2, while minimizing the production of the accompanying isomeric 3-carbamoyl-2-pyridinecarboxylic acids 3, conducts the aminolysis of quinolinic anhydride 1 in the presence of both a tertiary base (e.g. triethylamine) and an acid (e.g. acetic acid).

2. Results and Discussion
Comparatively little is known regarding the methanolyis of the title imides 5.

Hitchings et al.9 showed that Grignard reactions and NaBH4 reductions of pyridinedicarboximides involve preferential attack at the (C-7) carbonyl group close to the pyridine nitrogen. A like preference for nucleophilic attack in related imides was reported by Blanco et al.5 using strong alkoxides in the presence of the corresponding alcohols to afford quinolinimide ester intermediates and more complex products.

In the light of the foregoing8,9, the methanolyis of 5 could be expected to yield the 2-carbethoxy-3-carbamoylpyridine derivative 8 in greater amount than the 3-carbethoxy isomer 9. Such has been found here (Table 1), on refluxing imide 5c (R=C6H5) in methanol and removing aliquots at intervals for HPLC analysis; the monitoring revealed the gradual production of the isomeric esters 8c and 9c, with the former (the kinetic product) predominating in the earlier stages of the reaction, but after 7 days the relative proportion of 9c was seen to rise, suggesting it to be the thermodynamic product and so would accumulate over time. The suggestion is substantiated by DFT/B-86/TZVPP calculations,7 which (i) indicate that 9c is 5.1 kcal mol–1 more stable than 8c, confirming 8 as the kinetic...
product and 9 as the thermodynamic product, and (ii) that the positive charges on the two carbonyl carbons in imide 5 are not all that different. This latter verdict is supported from the $^{13}$C-NMR of $5b$ and $5j$ (Experimental) and the $^{13}$C-NMR spectra predicted for numerous other imides [including $5 (R=Me)$], and for quinolinic anhydride 1).

2.1. The Methanolysis of Imide 5 in the Presence of Triethylamine

Adding a tertiary base such as triethylamine (pKa = 11.01) (Table 1) catalysed the reaction of $N$-phenylquinolinimide $5c$ such that even after 15 min at room temperature (~20 °C) with 1 equivalent of triethylamine an equilibrium distribution of $8c$ and $9c$ was reached. With 0.01 equivalent, the equilibrium is much slower and at reflux the equilibrium is faster but somewhat shifted, as expected, towards $9c$.

This synthetically useful and novel methodology consequently increases access to, and the yield of, the usually minor ester 9. A repercussion of this finding is that the attempted production of an ester of type 8 by treating a 2-carbomethoxy-3-pyridinecarboxylic acid 6 with thionyl chloride followed by an amine, in the presence of triethylamine (in large excess, to remove HCl), may result in the formation of the corresponding imide 5 as well as the anticipated ester 8 (Table 2).

Various reaction conditions were explored with the methanolysis of $N$-phenylimide $5c$ as a model substrate utilizing NEt$_3$ as catalyst. The yields of $8c$ and $9c$ were found to vary considerably, being dependent on the reaction temperature, the reaction time, the solvent utilized, and the molar proportion of the catalyst utilized (Table 1). Using $5c$ and NEt$_3$, in equimolar molar ratio, in methanol, the rate of reaction, even at room temperature (~20 °C), was just too fast for conveniently isolating a useful amount of the 2-methyl ester 8c. However, with use of a much reduced proportion of NEt$_3$ (viz. 1:0.01), refluxing led to $8c$ in more acceptable yields and this was the general condition used to obtain 2-methyl esters 8 from imide 5.

The $N$-substituted quinolinimides $5, R=\text{tert}-\text{Bu}, \text{C}_6\text{H}_5, o-\text{FC}_6\text{H}_4, o-(\text{CH}_3\text{O})\text{C}_6\text{H}_4, 2,4,6-(\text{CH}_3)_3\text{C}_6\text{H}_2, o-(\text{CH}_3)\text{C}_6\text{H}_4$, and $(\text{C}_6\text{H}_5)_2\text{CH}$, were all found to react readily at reflux in methanol containing triethylamine (in the proportion 1:0.01) to eventuate in the appropriate thermodynamically more stable 3-carbomethoxy-2-carbamoylpyridine C9 in higher amount than the initial kinetic product, viz. the 2-carbomethoxy-3-carbamoylpyridine 8; only in the early stages of each reaction was the yield of ester 8 (kinetic product) significant (Table 1).

The following outcomes are illustrative:

(i) $N$-Phenylquinolinimide $5c$ (0.5 mmol) reacted rapidly in MeOH (5 mL) containing NEt$_3$ (0.5 mmol) at room temperature to afford, after ~15 min, 3-carbomethoxy-2-($N$-phenylcarbamoyl)pyridine 9c (81 %), and 2-carbomethoxymethyl 3-($N$-phenylcarbamoyl)pyridine 8c (8 %). (Table 1).

(ii) $N$-($o$-Nitrophenyl)quinolinimide $5b$ was dissolved in a mixture of methanol and NEt$_3$, at room temperature; soon after
crystals of 3-carbomethoxy-2-carbamoylpyridine 9b separated (> 90 %).

(iii) Imide 5d \((R=C_6H_5CH_2)\) reacted relatively slowly in the MeOH/NEt₃ mixture at room temperature, but at ~50 °C had dissolved (~ 4 hr), and afforded unreacted imide 5d (32 %) and 3-carbomethoxy-2-\([N\text{-benzyl})carbamoyl\]pyridine 9d (68 %); the isomeric 2-carbomethoxy ester 8d was present during the earlier stages of the reaction, and must, therefore be the kinetic product.

3. Mechanistic Aspects

The data (Table 1) suggest that NEt₃ (and to a lesser extent, pyridine), increases the reaction rate by lowering the energy of the transition state. This may be associated with the production of a complex intermediate, and/or by ion pairing with methoxide ion (Scheme 2). Overall, the function of NEt₃ is to speed up the rate of formation of both 8 and 9 and to arrive at an equilibrium mixture of the more stable 3-methyl ester 9 in excess of isomer 8.

Even the use of 1 mol % of NEt₃ provided ester 9c in a shorter time than when merely refluxing 5c in methanol.

The mechanistic assumptions receive support from the following outcomes:

(i) Methyl ester 8c was dissolved in a mixture of THF and NEt₃ and the reaction at room temperature was monitored by HPLC. The estimated yields of \(N\text{-phenylquinolinimid}e\) 5c at different times were: 15 min, 21 %; 1 hr, 45 %; 2 hr, 66 %; and after 20 h, 100 %.

(ii) The methanolysis of \(N\)-(2,4,6-trimethylphenyl)quinolinimide 5f in the presence of triethylamine was monitored by TLC and furnished the isomeric esters 8f and 9f, with the latter as principle product. The less mobile (lower Rf) compound (8f) was removed from the silica gel plate and dissolved in THF containing NEt₃. HPLC monitoring revealed the rapid disappearance of 8f and the concomitant formation of imide 5f.

(iii) Methyl ester 8e in THF containing NEt₃ was kept at 50 °C for 3 h. Column chromatography of the product mixture provided the \(N\)-(diphenylmethyl)quinolinimide 5f in the presence of triethylamine was monitored by TLC and furnished the isomeric esters 8f and 9f, with the latter as principle product. The less mobile (lower Rf) compound (8f) was removed from the silica gel plate and dissolved in THF containing NEt₃. HPLC monitoring revealed the rapid disappearance of 8f and the concomitant formation of imide 5f.

(iv) In a relevant comparative experiment, quinolinic anhydride 1 was reacted with diethylamine 4a and the equilibrium mixture of product acids was methylated (CH₂N₂) to furnish methyl 2-\([N\text{-diethylcarbamoyl})-3\text{-pyridinecarboxylate}\) 10 (92 %) and its isomer, viz. 11 (8 %), (Scheme 3). Addition of NEt₃ to this mixture of esters in THF led to no significant change in the respective yields over time as was to be expected in view of imide 5 intervention not being possible.

Table 1: Percentage formation of 3-carbomethoxy-2-carbamoylpyridine 9c and 2-carbomethoxy-3-carbamoylpyridine 8c during methanolysis of \(N\)-phenylquinolinimide 5c (0.5 mmol) under various conditions.

<table>
<thead>
<tr>
<th>Reaction time</th>
<th>MeOH, NEt₃ ((0.5 \text{ mmol}, \sim 20 °C))</th>
<th>MeOH, Pyridine, NEt₃ ((0.5 \text{ mmol}, \text{reflux}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 min</td>
<td>48  30  22</td>
<td>9c  5c  8c</td>
</tr>
<tr>
<td>4 min</td>
<td>68  23  8</td>
<td>15  53  29</td>
</tr>
<tr>
<td>6 min</td>
<td>73  21  6</td>
<td>17  45  34</td>
</tr>
<tr>
<td>10 min</td>
<td>75  17  8</td>
<td>19  39  38</td>
</tr>
<tr>
<td>15 min</td>
<td>81  12  8</td>
<td>22  32  43</td>
</tr>
<tr>
<td>30 min</td>
<td>81  3  16</td>
<td>25  25  48</td>
</tr>
<tr>
<td>45 min</td>
<td>80  3  16</td>
<td>31  17  49</td>
</tr>
<tr>
<td>1 hr</td>
<td>80  3  16</td>
<td>33  13  50</td>
</tr>
<tr>
<td>3.5 hr</td>
<td>80  3  16</td>
<td>36  12  49</td>
</tr>
<tr>
<td>7 hr</td>
<td>80  3  16</td>
<td>47  10  38</td>
</tr>
</tbody>
</table>

**Table 2**: Formation of imide 5 in the course of treating acid 6 with SOCl₂ followed on by addition of amine RNH₂ in the presence of excess of triethylamine.

<table>
<thead>
<tr>
<th>R</th>
<th>% Imide 5</th>
<th>% 2-Methyl ester 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>tert-Butyl</td>
<td>28</td>
<td>41</td>
</tr>
<tr>
<td>C₆H₅</td>
<td>86</td>
<td>not found</td>
</tr>
<tr>
<td>C₆H₅CH₂</td>
<td>85</td>
<td>not found</td>
</tr>
<tr>
<td>o-FC₆H₄</td>
<td>44</td>
<td>not found</td>
</tr>
<tr>
<td>2,4,6-(triMe)C₆H₂</td>
<td>77</td>
<td>not found</td>
</tr>
<tr>
<td>(C₆H₅)₂CH</td>
<td>20</td>
<td>54</td>
</tr>
</tbody>
</table>

* Details in Experimental Section.

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(i) Methyl ester 8c was dissolved in a mixture of THF and NEt₃, and the reaction at room temperature was monitored by HPLC. The estimated yields of \(N\)-phenylquinolinimide 5c at different times were: 15 min, 21 %; 1 hr, 45 %; 2 h, 66 %; and after 20 h, 100 %.

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Tertiary bases of relatively simple structure and low pKa value may not function as does triethylamine (pKa = 11.01). In a trial methanolysis (Table 1) of imide $5c$ (0.5 mmol) with pyridine (pKa = 5.25; 0.5 mmol) as catalyst, refluxing for 1 h provided 3-methyl ester $9c$ (4%) and 2-methyl ester $8c$ (15%), and after 24 h, $9c$ (63%) and $8c$ (25%).

4. Access to N-Substituted Quinolinimides $5a$ using Polyphosphoric Acid

The quinolinimide substrates $5$ requisite in the current work were generally prepared by literature$^1$ methods. Mederski et al.$^7$ have described an efficient one-pot synthesis of glutarimides, succinimides and maleimides utilizing PPA. This reagent in our hands also served to conveniently access $N$-substituted quinolinimides $5$. Thus heating aniline with pyridine-2,3-dicarboxylic acid or with quinolinic anhydride $1$ in PPA provided $N$-phenylquinolinimide $5c$ in good yield (Table 3).

5. The Aminolysis of Quinolinic Anhydride $1$ with $p$-Aminobenzenesulfonamide

The sulfonamides represent an important class of biologically active compounds. In the course of the current investigation several derivatives of relevant interest$^{8,9}$ were prepared (Scheme 4), their structures established, and some chemical properties noted.

The 2-benzenesulfonamido-3-pyridinecarboxylic acid $2j$ was obtained (admixed with nicotinamide $4j$) on reacting quinolinic anhydride $1$ with $p$-aminobenzenesulfonyl chloride in dioxane for 4 hour at ~20 °C. Methylation (CH$_2$N$_2$) of acid $2j$ provided the corresponding 3-carbomethoxy ester $9j$. Refluxing acid $2j$ with acetic anhydride led to a mixture (~1.75:1) of imide $5j$ and its acetylated derivative $5j'$, as was established from comprehensive $^1$H- and $^{13}$C-NMR spectral analyses. Also, heating acid $2j$ in DMF gave the corresponding 3-pyridinecarboxamide $4j$ (identical to the product obtained by treating nicotinic acid with SOCl$_2$ followed by $p$-aminobenzenesulfonamide in benzene/triethylamine).

6. The Aminolysis of 7,7-Dichloro-5,7-dihydrothieno[3,4-b]pyridine-5-one $12$

Recently$^{10}$ it was shown that novel and/or hitherto undocumented sulphur-containing products can be derived by the propylinolysis of 7,7-dichloro-5,7-dihydro-thieno[3,4-b]...
pyridine-5-one 12. The outcomes were indicative of the amine preferably substituting the C-5 carbonyl in 12. The relevant 1H- and 13C- NMR spectral assignments of 12 had been redetermined here and make evident that the earlier δH values reported26 for the 2-H and 4-H protons in 12 and in several related pyrrolopyridines3 which were assigned on the basis of an anisotropic effect, are to be transposed.

In summary, it is shown, with a mechanism, that conducting the methanolysis of a N-substituted quinolinimide 5 in the presence of varying amounts of triethylamine, at room temperature or under reflux, eventuates in the production of the more thermodynamically stable 3-carbomethoxy-2-carbamoylpyridine 9 in higher yield than the isomeric 2-carbomethoxy-3-carbamoylpyridine 8 (kinetic product). This outcome differs from expectations based on related4d,5 nucleophilic substitutions of imide 5. The current methodology offers an alternative and convenient access to the aforementioned esters which are generally obtained by the aminolysis of quinolinic anhydride 1 followed on by methylation of the respective product acids 2 and 3 with (non-basic) CH2N2.

7. Experimental

7.1. General Methods

Melting points were recorded on a hot-stage microscope and are uncorrected. TLC was performed on aluminium-backed plates, precoated with 0.25 mm silica gel 60 F254. Column chromatography was carried out on silica gel. The HPLC solvent was CDCl3 used as solvent of imide 5, 8/9 (vide infra) and of ester 1H, values reported for the 2-H and 4-H protons in 12 and in several related pyrrolopyridines which were assigned on the basis of an anisotropic effect, are to be transposed.

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~100 %) crude imide 5d. For R = o-NO₂C₆H₄, the outcome in the general procedure was appreciable o-nitroaniline (~20 %) + imide 5b (~40 %). For R = p-NH₂SO₂C₆H₄, the reaction product was difficult to purify.

7.4. The Methanyses of N-Substituted Quinolinimides

Preliminary Studies:
With N-Phenylquinolinimide 5c (R=C₆H₅), (Table 1).

Imide 5c (0.5 mmol), MeOH (5 mL), and the indicated quantity of triethylamine or of pyridine was stirred at room temperature (~20 °C), or was refluxed. At the appropriate time several drops of the reaction mixture was diluted with CHCl₃ and analysed by HPLC (on a silica gel column) using hexane/iso-PrOH/CHCl₃ (64:16:20), and the eluted product was then identified by spectral comparison with authentic compound.

With other N-Substituted Quinolinimides 5.
(i) At room temperature (~20 °C)
The imide 5 (~25 mg) was dissolved/suspended in methanol (~0.5 mL) at room temperature., several of substrates, viz. R = C₆H₅, R = 2,4,6-(CH₃)₃C₆H₄, R = o-FC₆H₄, were poorly soluble.

Triethylamine (~10 mg) was added with stirring. There was generally a rapid dissolution of imide and formation of the respective 2-methyl and 3-methyl esters 8 and 9. A few drops of reaction solution were removed at appropriate times for HPLC analysis and the eluted product was then identified by spectral comparison with authentic compound. The substrates/products were crystallized from ethyl acetate/hexane unless otherwise indicated.

(ii) At reflux
The following imides' 5a,d,e,f,g,h,i (Scheme 1) (0.5 mmol), in MeOH (5.0 mL) and NEt₃ (0.005 mmol) were refluxed. The highest yield of 8 (in the sequence 9, 5, 8) was found at (time): 5a; 28, 18, 52 (just prior to start of reflux). 5d; 51, 39, 7 (2 min). 5e; 39, 13, 46 (4 min). Using ester 9e or 8e instead of 5e gave similar outcomes. 5f; 37, 43, 18 (30 min). 5g; 31, 37, 31 (just prior to start of reflux). 5h; 45, 53, 2. (10 min). 5i; 2, 52, 40 (1 h).

Preparative Study with N-Phenylquinolinimide 5c
A mixture of imide 5c (1.00 g, 4.46 mmol), MeOH (5.0 mL), and NEt₃ (450 mg, 4.46 mmol) was stirred at room temperature (~20 °C) until homogeneous (~30 min). The MeOH/NEt₃ was removed at room temperature under vacuum after which the
residual solid was dissolved in the minimum amount of CHCl3/acetone (1:1), applied to a column of silica gel, and developed with 30 % acetone in benzene to give 3-methyl ester 9c, m.p. 92–93 °C (0.82 g, 3.20 mmol, 72 %), and 2-methyl ester 8c, m.p. 160 °C (80 mg, 8 % yield).

7.5. Specific Preparations and Properties

6-(2-Nitrophenyl)-5H-pyrrolo[3,4-b]pyridine-5,7(6H)-dione 5b

A mixture of imide 5b (157 mg, 0.58 mmol), MeOH (5 mL) and NEt3 (0.7 mmol) was stirred at ~20 °C after which the solution turned cloudy and crystals of title product separated. After ~30 min, the reaction mixture was evaporated and the residue was crystallized from ethyl acetate/hexane to yield the title compound, 220 mg, 0.82 mmol, 93 %; m.p. 160 °C (80 mg, 8 %) yield).

To the residue was added dry benzene (10 mL), cooled, followed by a solution of 1,1-diphenylylmethylamine (600 mg, 3.28 mmol), in benzene (5 mL) containing NEt3 (1.0 mL) with stirring which was continued overnight at room temperature. Extraction of the mixture with CHCl3/H2O, followed by evaporation of the CHCl3 layer gave a residue (1.01 g). This was crystallized from ethyl acetate to give title ester 8e (0.61 g, 1.76 mmol, 54 %), m.p. 187–8 °C. δ: 3.77 (3H, s, OCH3, H-2'), 6.39 (1H, d, H-3'), 7.04 (1H, NH, H-2'), 7.26–7.33 (10H, aromatic), 7.39 (1H, m, H-5), 7.87 (1H, d, H-4), 8.63 (1H, d, H-6). δ: 53.1 (C-2'), 57.6 (C-3'), 125.6 (C-5), 127.5–128.7 (aromatic), 133.0 (C-3), 136.3 (C-4), 141.4 (C-1'), 147.0 (C-2), 150.4 (C-6), 165.1 (C-1'), 166.0 (C-1'). Found: C, 72.55; H, 5.45; N, 8.06. Calc. for C21H15N3O2: C, 72.32; H, 5.24; N, 8.09.

A mixture of anhydride 1 (0.25 g, 1.67 mmol) in dry methylene chloride (5 mL) cooled in ice was added a solution of 1,1-diphenylmethylamine (1.69 mmol) in methylene chloride (5 mL). The reaction mixture was kept at room temperature overnight and evaporated to dryness. The residue was taken up in THF (10 mL) and treated with diazomethane in ether till excess diazomethane was present. The solution was evaporated at room temperature and the residue was applied to a column of silica gel and developed with 30 % acetone in benzene to give title compound 9e (212 mg, 0.68 mmol, 20 %), m.p. 162 °C (from ethyl acetate); Found: C, 76.00; H, 4.73; N, 8.81. Calc. for C21H15N3O2: C, 76.42; H, 4.49; N, 8.81.

3-(2-Nitrophenylcarbamoyl)picolinic acid

3-(2-Nitrophenylcarbamoyl)picolinic acid, methyl ester 9f

(Crystals from ethanol), m.p. 133–134 °C); lit.4a, m.p. 137 °C).

A mixture of imide 5f (157 mg, 0.58 mmol), MeOH (5 mL) and NEt3 (1.0 mL) with stirring which was continued overnight at room temperature. Extraction of the mixture with CHCl3/H2O, followed by evaporation of the CHCl3 layer gave a residue (1.01 g). This was crystallized from ethyl acetate to give title ester 8f (0.61 g, 1.76 mmol, 54 %), m.p. 187–8 °C. δ: 3.77 (3H, s, OCH3, H-2'), 6.39 (1H, d, H-3'), 7.04 (1H, NH, H-2'), 7.26–7.33 (10H, aromatic), 7.39 (1H, m, H-5), 7.87 (1H, d, H-4), 8.63 (1H, d, H-6). δ: 53.1 (C-2'), 57.6 (C-3'), 125.6 (C-5), 127.5–128.7 (aromatic), 133.0 (C-3), 136.3 (C-4), 141.4 (C-1'), 147.0 (C-2), 150.4 (C-6), 165.1 (C-1'), 166.0 (C-1'). Found: C, 72.55; H, 5.45; N, 8.06. Calc. for C21H15N3O2: C, 76.42; H, 4.49; N, 8.81.

3-(2-Nitrophenylcarbamoyl)picolinic acid, methyl ester 9g

(Crystals from ethanol), m.p. 133–134 °C); lit.4a, m.p. 137 °C).

A mixture of imide 5g (157 mg, 0.58 mmol), MeOH (5 mL) and NEt3 (1.0 mL) with stirring which was continued overnight at room temperature. Extraction of the mixture with CHCl3/H2O, followed by evaporation of the CHCl3 layer gave a residue (1.01 g). This was crystallized from ethyl acetate to give title ester 8g (0.61 g, 1.76 mmol, 54 %), m.p. 187–8 °C. δ: 3.77 (3H, s, OCH3, H-2'), 6.39 (1H, d, H-3'), 7.04 (1H, NH, H-2'), 7.26–7.33 (10H, aromatic), 7.39 (1H, m, H-5), 7.87 (1H, d, H-4), 8.63 (1H, d, H-6). δ: 53.1 (C-2'), 57.6 (C-3'), 125.6 (C-5), 127.5–128.7 (aromatic), 133.0 (C-3), 136.3 (C-4), 141.4 (C-1'), 147.0 (C-2), 150.4 (C-6), 165.1 (C-1'), 166.0 (C-1'). Found: C, 72.55; H, 5.45; N, 8.06. Calc. for C21H15N3O2: C, 76.42; H, 4.49; N, 8.81.

3-(2-Nitrophenylcarbamoyl)picolinic acid, methyl ester 9h

(Crystals from ethanol), m.p. 133–134 °C); lit.4a, m.p. 137 °C).

A mixture of imide 5h (157 mg, 0.58 mmol), MeOH (5 mL) and NEt3 (1.0 mL) with stirring which was continued overnight at room temperature. Extraction of the mixture with CHCl3/H2O, followed by evaporation of the CHCl3 layer gave a residue (1.01 g). This was crystallized from ethyl acetate to give title ester 8h (0.61 g, 1.76 mmol, 54 %), m.p. 187–8 °C. δ: 3.77 (3H, s, OCH3, H-2'), 6.39 (1H, d, H-3'), 7.04 (1H, NH, H-2'), 7.26–7.33 (10H, aromatic), 7.39 (1H, m, H-5), 7.87 (1H, d, H-4), 8.63 (1H, d, H-6). δ: 53.1 (C-2'), 57.6 (C-3'), 125.6 (C-5), 127.5–128.7 (aromatic), 133.0 (C-3), 136.3 (C-4), 141.4 (C-1'), 147.0 (C-2), 150.4 (C-6), 165.1 (C-1'), 166.0 (C-1'). Found: C, 72.55; H, 5.45; N, 8.06. Calc. for C21H15N3O2: C, 76.42; H, 4.49; N, 8.81.
Anhydride 1 (1.00 g, 6.72 mmol) was added to a solution of p-aminobenzenesulfonylamide (1.2 g, 7.0 mol) in dry dioxane (25 mL) and the mixture was stirred for 3 days at room temperature and evaporated to dryness. The residue was treated with saturated sodium bicarbonate solution (25 mL) and some insoluble carbamidoxime 4j (~50 mg) removed by filtration. If the reaction mixture was refluxed for 1 h as much as ~150 mg 4j was obtained. Acidification of the filtrate to pH 2 gave the title compound 2j; crystals (1.54 g, 4.80 mmol, 71%) from CH3OH/CH2OH; m.p. > 240°C. δC 137.4 (C-4), 141.7 (C-1'), 154.7 (C-6), 160.5 (C-3), 161.5 (C-2), 164.9 (C-2'), 165.2 (C-7'), 171.3 (C-2'), 175.0 (C-1').

1H NMR spectrum showed nine aromatic protons, as expected, with two exchangeable signals at 10.88 and 7.28. The former showed a NOE to a 2H doublet (J = 4.70 Hz) and at 8.21 (J = 7.80 Hz) confirming that it was attached to H-4 (δ = 8.74, d, H-4), 9.05 (1H, dd, H-2). These both protons were coupled to a doublet of doublets at 7.67 ppm thus defining the two resonances of the pyridine ring and confirming the position of the amide at C-2. The carbonylate at C-3 (δ = 176.1) was coupled only to H-4 (δ = 8.21) as expected.

Acid 2j (1.00 g, 3.12 mmol) in acetic anhydride (90 mL) was refluxed for 1 h. On cooling crystals separated, 0.58 g. These were filtered and the mother liquor was evaporated to obtain a further 0.25 g crystals. The combined product was recrystallized from acetic anhydride to obtain [as revealed from a comprehensive NMR examination a mixture (vide infra) of imide 5j and its N-acetyl derivative 5j1 in the proportion (ca.) 1.7:1. δC 166.6 (C-2), 170.2 (C-3), 170.4 (C-3'), 178.6 (C-1'), 203.4 (C-6), 212.7 (C-6').

2j-[4-Aminosulfonylphenyl]amino[carbonyl]-3-pyridinecarboxylic acid methyl ester 9j

The relevant 1H- and 13C-NMR spectral assignments of 12 have been determined and make evident that the values earlier reported for the 2-H and 4-H protons in several pyrrolopyridines which were assigned on the basis of an anisotropic effect, are to be transposed: δC 7.59 (1H, m, H-5), 8.13 (1H, dd, H-4), 9.05 (1H, dd, H-2). δH 88.0 (C-7), 124.8 (C-4'), 125.3 (C-3), 126.4 (C-5), 156.2 (C-6').

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References and Notes


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According to our DFT/B-P86/TZVPP calculations the Mulliken charges and Paboon bond orders in quinolinic anhydride 1 and in N-substituted quinolinimides 5 indicate that: (i) the calculated charges (\textit{ab initio}) of the two carbonyls are not that different), and (ii) the 3-methyl ester 9c is more thermodynamically stable than is the isomeric 2-methyl ester 8c. SciFinder presents the predicted $^{13}$C-NMR data for numerous N-substituted quinolinimides 5, and also for quinolinic anhydride 1, calculated using Advanced Chemistry Development, Inc. (ACD/Labs) Software V9.07, which likewise confirm the relevant two carbonyl charges to be similar.