T. van Es, B. Staskun and P. Karuso,
S. Afr. J. Chem., 2012, **65**, 53–61,
<http://journals.sabinet.co.za/sajchem/>.

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

Theodorus van Es[a], Benjamin Staskun[b,c,*] and Peter Karuso[c]

[a]*Department of Biochemistry and Microbiology, Cook College, Rutgers University, New Brunswick, New Jersey, 08903-0232, USA.*
[b]*School of Chemistry, University of the Witwatersrand, Johannesburg, South Africa.*
[c]*Department of Chemistry and Biomolecular Sciences, Macquarie University, Sydney, NSW, 2109, Australia.*

Received 7 June 2011, revised 23 August 2011, accepted 14 February 2012.

Submitted by invitation to celebrate 2011 the International Year of Chemistry'.

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 synthesis[1].

In quinolinic anhydride **1,** and likewise in the representative imide **5 (**R=Me), ^{13}C-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 carbon[2]. 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 Tadic[3] and subsequently by others,[1,4] and is exemplified here with 1,1-diphenylmethylamine and with *p*-aminobenzenesulfonamide. The direction of the reaction has been explained by quantum-chemical methods.[1e]

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.[1,4] 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 heating[1b], a specific catalyst such as 2-oxo-3-oxazolinylphosphonate[1a], or mixed solvents having different polarities[1f]. 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 patented[1g] 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).

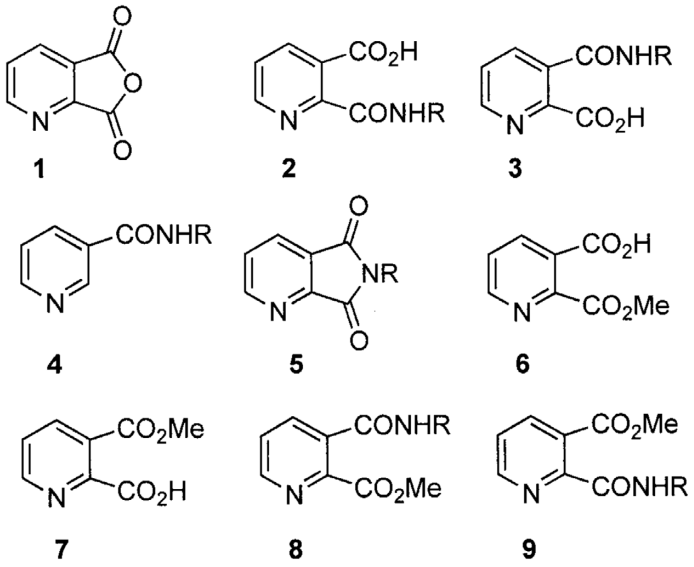
2. Results and Discussion

Comparatively little is known regarding the methanolysis of the title imides **5**.

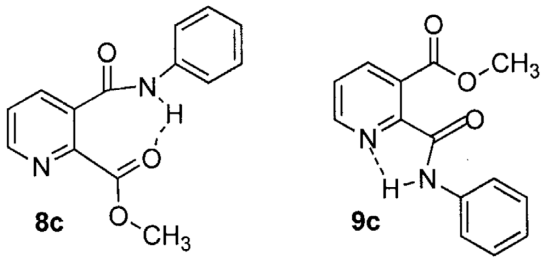
Hitchings *et al.*[4d] showed that Grignard reactions and $NaBH_4$ reductions of pyridinedicarboximides involve preferential attack at the (C-7) carbonyl group close to the pyridine nitrogen. A like preference for nucleophilic attack in related imides was reported by Blanco *et al.*[5] using strong alkoxides in the presence of the corresponding alcohols to afford quinolinamic ester intermediates and more complex products.

In the light of the foregoing[2,4d,5], the methanolysis of **5** could be expected to yield the 2-carbomethoxy-3-carbamoylpyridine derivative **8** in greater amount than the 3-carbomethoxy isomer **9**. Such has been found here (Table 1), on refluxing imide **5c** (R=C_6H_5) 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,[6] which (i) indicate that **9c** is 5.1 kcal mol^{-1} more stable than **8c,** confirming **8** as the kinetic

* To whom correspondence should be addressed. E-mail: benmina1@bigpond.com.au



a, R=*o*-FC_6H_4; **b**, R=*o*-$(NO_2)C_6H_4$; **c**, R=C_6H_5; **d**, R=$C_6H_5CH_2$; **e**, R=$(C_6H_5)_2CH$;
f, R=2,4,6-$(CH_3)_3C_6H_2$; **g**, R=*o*-$(CH_3)C_6H_4$; **h**, R=Pr; **i**, R=*tert*.-Bu; **j**, R=*p*-$C_6H_4SO_2NH_2$



Scheme 1
Surmised H-bonding in esters **8c** and **9c**.

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[6] 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[1] 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 on 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=*tert*-Bu, C_6H_5, *o*-FC_6H_4, *o*-$(CH_3O)C_6H_4$, 2,4,6-$(CH_3)_3C_6H_2$, *o*-$(CH_3)C_6H_4$, and $(C_6H_5)_2CH$, 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[6] 3-carbomethoxy-2-carbamoylpyridine C**9** 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

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 [a,b].

Reaction time	MeOH, NEt_3 (0.5 mmol) (~20 °C)			MeOH, NEt_3 (0.5 mmol) reflux			MeOH, NEt_3 (0.005 mmol) reflux			MeOH, Pyridine (0.5 mmol) reflux			MeOH, reflux		
	9c	**5c**	**8c**	**9c**	**5c**	**8c**	**9c**	**5c**	**8c**	**9c**	**5c**	**8c**	**9c**	**5c**	**8c**
2 min	48	30	22				15	53	29						
4 min	68	23	8				17	45	34						
6 min	73	21	6				19	39	38						
10 min	75	17	8				22	32	43						
15 min	81	12	8				25	25	48	2	92	6			
30 min				81	3	16	31	17	49						
45 min							33	13	50						
1 hr				80	3	16	36	12	49	4	80	15			
3.5 hr							47	10	38						
7 hr										49	12	39			
1 days										63	7	25	9	64	27
2 days													17	43	43
3 days													21	26	51
4 days													32	18	46
6 days													33	12	52
7 days													36	10	52

[a] Details in Experimental Section.
[b] Product percentage yields are quoted in the order: 3- methyl ester **9c**, imide **5c**, 2-methyl ester **8c**.

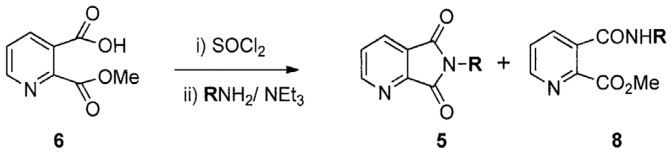
crystals of 3-carbomethoxy-2-[(*N*-(*o*-nitrophenyl)carbamoyl] pyridine **9b** separated (> 90 %).

(iii) Imide **5d** (R=$C_6H_5CH_2$) reacted relatively slowly in the MeOH/NEt_3 mixture at room temperature, but at ~50 °C had dissolved (~ 4 hr), and afforded unreacted imide **5d** (32 %) and 3-carbomethoxy-2-[(*N*-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 NEt_3 (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 NEt_3 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 NEt_3 provided ester **9c** in a shorter time than when merely refluxing **5c** in methanol.

Table 2 Formation of imide **5** in the course of treating acid **6** with $SOCl_2$ followed on by addition of amine **R**NH_2 in the presence of excess of triethylamine [a].



6 **5** **8**

R	% Imide **5**	% 2-Methyl ester **8**
tert-Butyl	28	41
C_6H_5	86	not found
$C_6H_5CH_2$	85	not found
o-FC_6H_4	44	not found
2,4,6-(triMe)C_6H_2	77	not found
$(C_6H_5)_2CH$	20	54

[a] Details in Experimental Section.

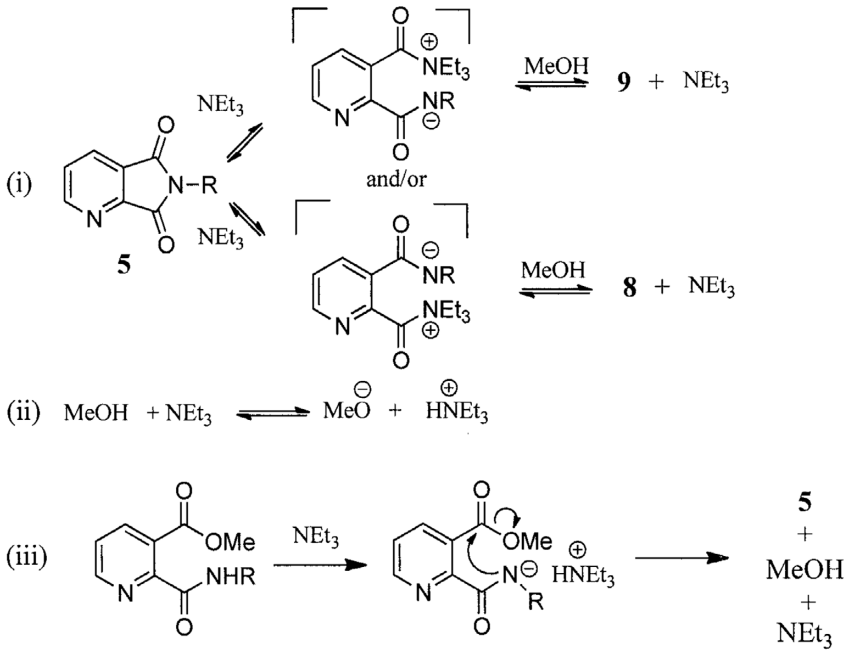
The mechanistic assumptions receive support from the following outcomes:

(i) Methyl ester **8c** was dissolved in a mixture of THF and NEt_3 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 h, 45 %); 2 h, 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 R_f) compound (**8f**) was removed from the silica gel plate and dissolved in THF containing NEt_3. HPLC monitoring revealed the rapid disappearance of **8f** and the concomitant formation of imide **5f**.

(iii) Methyl ester **8e** in THF containing NEt_3 was kept at 50 °C for 3 h. Column chromatography of the product mixture provided the *N*-(diphenymethyl)quinolinimide **5e** (20 % yield). Like treatment of methyl esters **8e** and **8i** in THF/NEt_3 mixture provided the respective imides **5e** and **5i**.

(iv) In a relevant comparative experiment, quinolinic anhydride **1** was reacted with diethylamine[4a] and the equilibrium mixture of product acids was methylated (CH_2N_2) to furnish methyl 2-(*N*-diethylcarbamoyl)-3-pyridinecarboxylate **10** (92 %) and its isomer, *viz.* **11** (8 %), (Scheme 3). Addition of NEt_3 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.



Scheme 2
Outline of proposed reaction events/sequences occurring in the methanolysis of imide **5** in the presence of triethylamine.

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 **5** 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*-aminobenzenesulfonamide in dioxane for 4 hour at ~20 °C. Methylation (CH_2N_2) of acid **2j** provided the

Table 3 The use of polyphosphoric acid for preparing N-substituted quinolinirnides **5a**

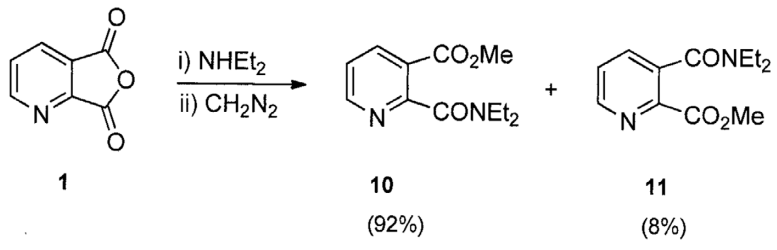
Amine RNH_2 **R**	*Reagent* quinolinic anhydride **1**	*Reagent* pyridine-2,3-dicarboxylic acid
$C_6H_5CH_2$	75 % [b]	c
C_6H_5	74 %	90 % [b]
o-$CH_3C_6H_4$	70 %	86 %
o-FC_6H_4	c	93 %
o-ClC_6H_4	c	60 %

[a] Details in Experimental Section.
[b]Percentage yield of (crude) imide **5**.
[c]Not performed.

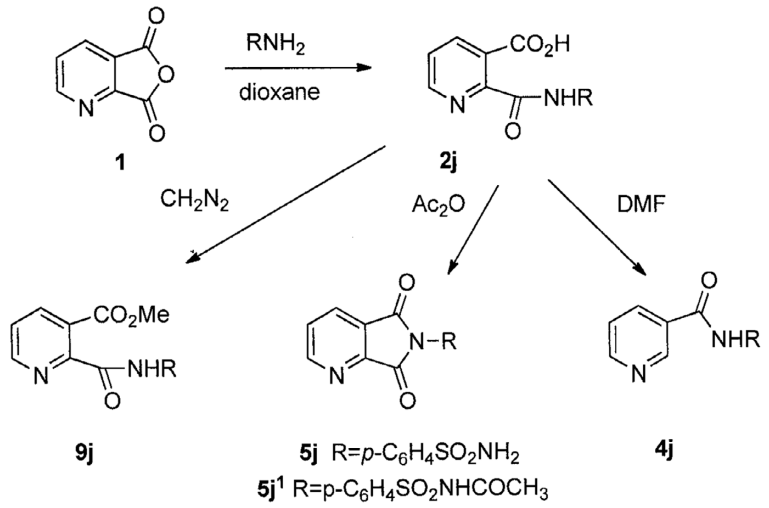
corresponding 3-carbomethoxy ester **9j**. Refluxing acid **2j** with acetic anhydride led to a mixture (~1.75:1) of imide **5j** and its acetylated derivative **5j**[1], as was established from comprehensive ^{1}H- and ^{13}C-NMR spectral analyses. Also, heating acid **2j** in DMF gave the corresponding 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-dihydro-thieno[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 propylaminolysis of 7,7-dichloro-5,7-dihydro-thieno[3,4-b]



Scheme 3



Scheme 4
Preparation of 2-[(4-sulfamoylphenylamino)carbonyl]-3pyridinecarboxylic acid **2j** and related reactions.

pyridine-5-one **12**. The outcomes were indicative of the amine preferably substituting the C-5 carbonyl in **12**. The relevant ^{1}H- and ^{13}C- NMR spectral assignments of **12** have been redetermined here and make evident that the earlier δ_H values reported[10] for the 2-H and 4-H protons in **12** and in several related pyrrolopyridines[10] 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 related[4d,5] nucleophilic substitutions of imide **5**. The current methodology offers an alternative and convenient access to the aforementioned esters which are generally[1] obtained by the aminolysis of quinolinic anhydride **1** followed on by methylation of the respective product acids **2** and **3** with (non-basic) CH_2N_2.

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 generally used to elute material was hexane/isopropyl alcohol (9:1). NMR spectra were recorded on a Bruker AC-200 (200.13 MHz for ^{1}H), a Bruker DPX (399.9 MHz for ^{1}H) or a Bruker DRX (600.18 MHz for ^{1}H) spectrometer. $CDCl_3$ was used as solvent unless otherwise noted, with residual solvent as internal standard. COSY, HSQC and HMBC-correlated spectra were routinely used for assignments of signals, supplemented on occasion, when warranted, by ROESY and NOE difference experiments. HRMS spectra were recorded at 70 ev on a VG 70 SEQ mass spectrometer. Several of the compounds formed in the methanolysis and in the aminolysis reactions were very similar by TLC while analytical HPLC showed a number of compounds to have similar retention times. Therefore the compounds were very difficult to separate cleanly by column (silica gel) chromatography. Even semi-preparative HPLC (on a 1-cm diameter column) was unsuccessful because of overlap of peaks. It should be emphasized that silica gel chromatography can also catalyze the methanolysis of imide **5** and of ester **8/9** isomerization. This is important if one attempts to isolate the **8** and **9** esters from large scale preparations by silica gel chromatography; however, shortening the residence time on the column will reduce the **8** to **9** conversion. Accordingly, in order to isolate a specific product, reaction conditions such as time, temperature, concentration, or a solvent had to be manipulated to afford the desired compound in satisfactory yield. A useful guide in aiding product identification and yield estimation utilized the observations (i) that a 2-carbomethoxy-3-carbamoylpyridine **8** exhibited a lower H-NMR amide δ_H value, and (ii) a R_f value (was less mobile) on a silica gel plate, than did its isomer **9**.

7.2. Starting Materials

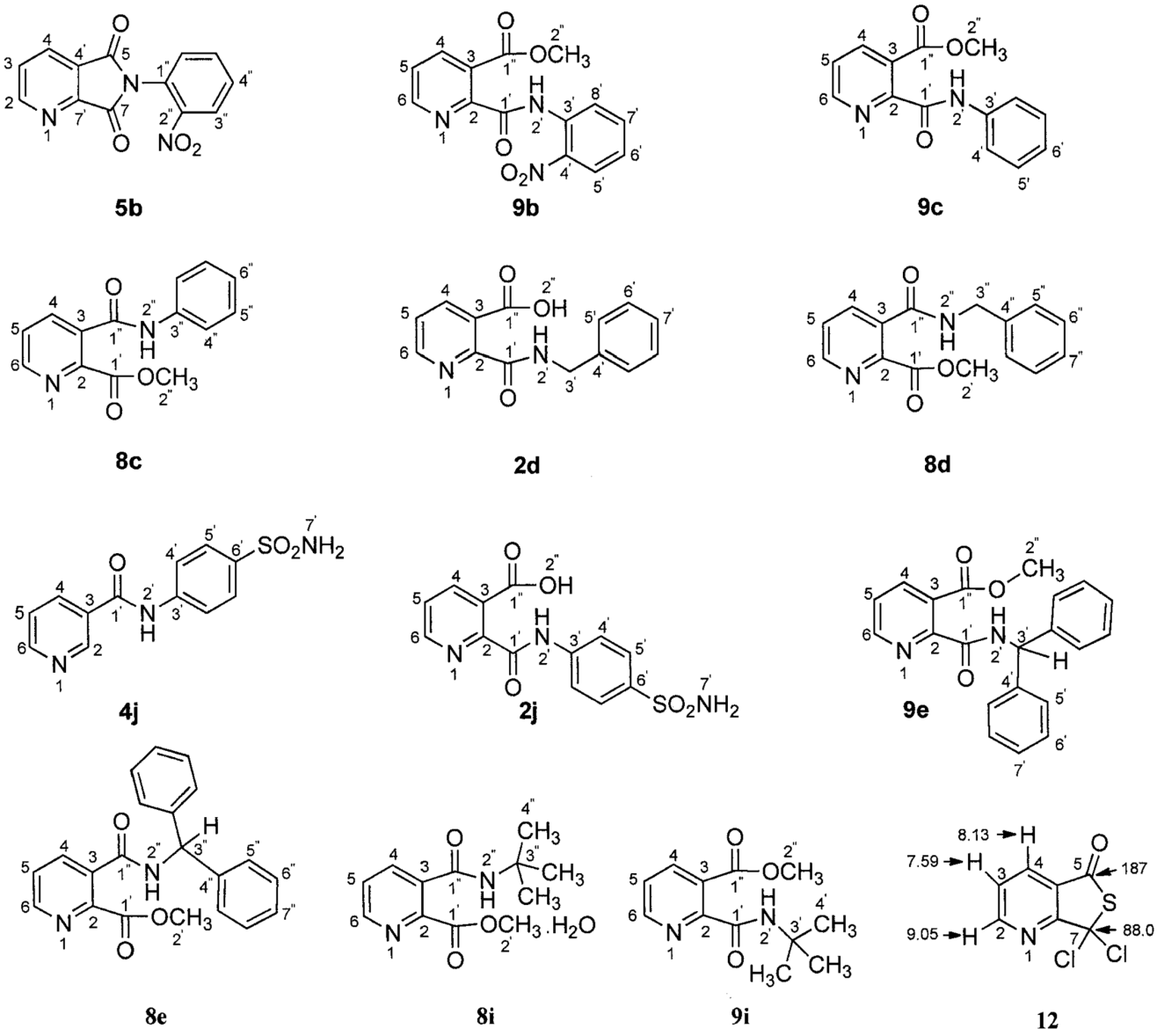
The requisite quinolinimides **5**, 3-pyridinecarboxamides **4,** 3-pyridinecarboxylic acids **2,** and methyl esters **8** and **9**, were prepared by appropriate literature methods[1], and/or by the current procedures herein. Isomeric products were separated successfully by preparative chromatography. The thrust of the current research made requisite that the unequivocal structure of each utilized new/literature substrate and/or reaction product be established and/or corroborated. Hence, extensive HSQC and HMBC spectra were obtained for each compound to assign every ^{13}C and ^{1}H resonance.

Generally, the methanolyses of imides **5** (*vide infra*) were monitored by TLC (silica gel) and/or by HPLC. The latter (using hexanes/*iso*-PrOH/$CHCl_3$: 64/16/20), gave good separation of products **5, 8**, and **9**, (except for **5h**/**5i** and **9h**/**9i**).

7.3. The Preparation of *N*-Substituted Quinolinimides 5 using Polyphosphoric Acid

General Procedure

To 1 mmol of anhydride **1** was added 1.5 mmol of the requisite arylamine followed on by PPA (~5 g). The mixture was heated with stirring at ~110 °C for ~15 mins then poured onto ice, and the crude product imide **5 (**Table 3) filtered and purified by crystallization. In the case of 2,3-pyridinedicarboxylic acid (1.1 mmol) this was converted initially to anhydride **1** by heating with PPA (5 g) at ~110 °C for ~15 min, then adding the amine, and continuing as above. Heating representative 2-carbamoylpyridine-3 carboxylic acid **2d** with PPA as above gave



Scheme 5

~100 %) crude imide **5d**. For R = *o*-$NO_2C_6H_4$, the outcome in the general procedure was appreciable *o*-nitroaniline (~20 %) + imide **5b** (~40 %). For R= *p*-$NH_2SO_2C_6H_4$, the reaction product was difficult to purify.

7.4. The Methanolyses of *N*-Substituted Quinolinimides

Preliminary Studies:
With N-Phenylquinolinimide **5c** (R=C_6H_5), (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 $CHCl_3$ and analysed by HPLC (on a silica gel column) using hexane/*iso*-PrOH/$CHCl_3$ (64:16:20), and the eluted product was then identified by spectral comparison with authentic product.

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=C_6H_5, R=2,4,6-$(CH_3)_3C_6H_2$, R=o-FC_6H_4, 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[1] compound. The substrates/products were crystallized from ethyl acetate/hexane unless otherwise indicated.

(ii) *At reflux*

The following imides[1] **5a,d,e,f,g,h,i** (Scheme 1) (0.5 mmol), in MeOH (5.0 mL) and NEt_3 (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 NEt_3 (450 mg, 4.46 mmol) was stirred at room temperature (~20 °C) until homogeneous (~30 min).The MeOH/NEt_3 was removed at room temperature under vacuum after which the

residual solid was dissolved in the minimum amount of $CHCl_3$/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**

3-(2-Nitrophenylcarbamoyl)picolinic acid **3b** (250 mg, 0.87 mmol) in acetic anhydride (10 mL) was heated under reflux for 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.138 °C. δ_H 7.53 (1H, d, H-6″), 7.65 (1H, m, H-4″), 7.71 (1H, m, H-3), 7.79 (1H, m, H-5″), 8.21 (1H, d, H-3″), 8.27 (1H, d, H-4), 9.06 (1H, d, H-2). δ_C 124.9 (C-1′), 126.0 (C-3″), 127.3 (C-4′), 128.0 (C-3), 130.2 (C-4″), 132.1 (C-4), 134.4 (C-5″), 145.4 (C-2″), 151.3 (C-7′), 155.1 (C-2), 164.3 (C-5), 164.5 (C-7).

2-[[(2-Nitrophenyl)amino]carbonyl]-3-pyridinecarboxylic acid, methyl ester **9b**

A mixture of imide **5b** (157 mg, 0.58 mmol), MeOH (5 mL) and NEt_3 (0.7 mmol) was stirred at ~20 °C after which the solution turned cloudy and crystals of title product separated. After ~0.5 h, these were filtered (170 mg, 0.56 mmol, 97 %), and recrystallized from ethyl acetate/hexane; m.p., 175–176 °C. δ_H 3.99 (3H, s, OCH_3, H-2″), 7.21 (1H, m, H-6′), 7.56 (1H, m, H-5), 7.67 (1H, m, H-7′), 7.86 (1H, d, H-4), 8.24 (1H, d, H-5′), 8.77 (1H, d, H-6), 8.94 (1H, d, H-8′), 12.57 (1H, br, NH, H-2′). δ_C. 53.14 (C-2′), 122.2 (C-8′), 123.7 (C-6′), 125.9 (C-5′), 126.3 (C-5), 130.7 (C-3), 134.1 (C-3′), 135.7 (C-7″), 136.4 (C-4), 137.1 (C-4′), 149.4 (C-6), 162.3 (C-1′), 168.4 (C-1′′).

6-Phenyl-5H-pyrrolo[3,4-b]pyridine-5,7-(6H)-dione **5c**[1b]

2-[(Phenylamino)carbonyl]-3-pyridinecarboxylic acid, methyl ester **9c**

(From ethanol/hexane; m.p. 92–93 °C. δ_H 3.99 (3H, OCH_3, s, H-2″), 7.13 (1H, m, H-6′), 7.36 (2H, m, H-5′), 7.52 (1H, m, 5-H), 7.71 (2H, dd, H-4′), 7.84 (1H, dd, H-4), 8.66 (1H, m, H-6), 9.81 (1H, br, NH, H-2′). δ_C 53.2 (C-2″), 119.1 (C-4′), 124.6 (C-6′), 125.9 (C-5), 129.1 (C-5′), 136.4 (C-4), 146.7 (C-2), 148.4 (C-6), 160.8 (C-1′), 168.8 (C-1″).

3-[(Phenylamino)carbonyl]-2-pyridinecarboxylic acid, methyl ester **8c**

(From ethanol/hexane; m.p. 160 °C (lit.[4a], m.p. 159 °C).

δ_H 3.96 (3H, OCH_3, s, H-2′), 7.16 (1H, t, H-6″), 7.36 (2H, t, H-5″), 7.54 (1H, m, H-5), 7.61 (2H, d, H-4″), 8.04 (1H, d, H-4), 8.19 (1H, br, NH, H-2″), 8.75 (1H, d, H-6). δ_C 53.5 (C-2′), 120.3 (C-4″), 125.1 (C-6″), 126.1 (C-5), 129.2 (C-5″), 133.8 (C-3), 137.0 (C-4), 146.2 (C-2), 150.6 (C-6), 164.7 (C-1″), 166.3 (C-1′).

2-[[(Phenylmethyl)amino]carbonyl]-3-pyridinecarboxylic acid **2d**

(Crystals from ethanol), m.p. 133–134 °C); lit.[4a], m.p. 137 °C). δ_H 4.70 (2H, d, H-3′), 7.3–7.4 (5H, m, aromatic), 7.64 (1H, m, H-5), 8.67 (1H, d, H-6), 8.90 (1H, d, H-4), 9.29 (1H, br, NH, H-2′), 17.10 (1H, v.br, CO_2H, H-2″). δc 44.3 (C-3′), 127.3 (C-5), 128.2–136.3 (aromatic), 144.4 (C-4), 145.4 (C-2), 150.3 (C-6), 164.5 (C-1″), 166.6 (C-1′).

3-[[(1,1-Diphenylmethyl)amino]carbonyl]-2-pyridinecarboxylic acid, methyl ester **8e**

2-(Methoxycarbonyl)pyridine-3-carboxylic acid **6**[1h] (601 mg, 3.32 mmol) in thionyl chloride (10 mL) was stirred at room temperature for 3 h after which the suspension was heated briefly (5 min) to give a clear solution. Excess $SOCl_2$ was evaporated, the last traces in a vacuum dessicator (over KOH pellets). To the residue was added dry benzene (10 mL), cooled, followed by a solution of 1,1-diphenylmethylamine (600 mg, 3.28 mmol), in benzene (5 mL) containing NEt_3 (1.0 mL) with stirring which was continued overnight at room temperature. Extraction of the mixture with $CHCl_3/H_2O$, followed by evaporation of the $CHCl_3$ 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_H 3.77 (3H, s, OCH_3, 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_C 53.1 (C-2′), 57.6 (C-3″), 125.6 (C-5), 127.5–128.7 (aromatic), 133.0 (C-3), 136.6 (C-4), 141 (C-4″), 147.0 (C-2), 150.4 (C-6), 165.6 (C-1′), 166.0 (C-1″). Found: C, 72.55; H, 5.45; N, 8.06. Calc. for $C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.24; N, 8.09.

6-(1,1-Diphenylmethyl)-5H-pyrrolo[3,4-b]pyridine-5,7-dione **5e**[1j]

The mother liquor from the aforementioned crystallization of **8e** was evaporated and the residue was applied to a column of silica gel and developed with 30 %) acetone in benzene to give title compound **5e** (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 $C_{20}H_{14}N_2O_2$: C, 76.42; H, 4.49; N, 8.91.

2-[[(1,1-Diphenylmethyl)amino]carbonyl]-3-pyridinecarboxylic acid, methyl ester **9e**

To 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 (0.31 g, 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 **9e** (420 mg, 1.21 mmol, 72 %); crystals from ethyl acetate/hexane, m.p. 110 °C). δ_H 3.92 (3H, OCH_3, s, H-2″), 6.40 (1H, d, H-3′), 7.46 (1H, m, H-5), 7.25–7.31 (10H, aromatic), 7.79 (1H, d, H-4), 8.49 (1H, br, NH, H-2′), 8.58 (1H, d, H-6). δ_C 53.1 (C-2″), 56.8 (C-3′), 125.6 (C-5), 127–128 (aromatic) , 130.3 (C-3), 136.1 (C-4), 141.3 (C-4′), 146.9 (C-2), 149.0 (C-6), 162.4 (C-1″), 168.7 (C-1′). Found: C, 72.15; H, 5.38; N, 7.94. Calc. for $C_{21}H_{18}N_2O_3$: C, 72.82: H, 5.24; N, 8.09.

3-[[(1,1-Dimethylethyl)amino]carbonyl]-2-pyridinecarboxylic acid, methyl ester, monohydrate **8i**

2-(Methoxycarbonyl)pyridine-3-carboxylic acid **6**[1h] (788 mg, 4.78 mmol) was reacted with *tert*-butylamine (318 mg, 4.36 mmol) as described for **8e**. Column chromatography (silica gel; 30 %) acetone in benzene) yielded imide **5i**[1b] (m.p. 65–66 °C); 239 mg, 1.17 mmol, 27 %)) and 2-methyl ester **8i** (420 mg, 1.91 mmol, 44 %); (crystals from hexane/ethyl acetate), m.p. 61–63 °C. δ_H 1.44 (9H, [3 × (CH_3], s, H-4″), 1.65 (*ca.* 2H, H_2O), 3.94 (3H, OCH_3, s, H-2′), 5.86 (1H, br, NH, H-2″), 7.42 (1H, m, H-5), 7.82 (1H, d, H-4), 8.66 (1H, d, H-6). δ_C 28.6 (C-4″), 52.3 (C-3″), 53.0 (C-2′), 125.7 (C-5), 134.6 (C-3), 136.3 (C-4), 146.5 (C-2), 149.9 (C-6), 165.9 (C-1′), 166.2 (C-1″). Found: C, 56.77; H, 7.02; N, 10.90. Calc. for $C_{12}H_{16}N_2O_3.H_2O$: C, 56.68; H, 7.14; N; 11.01.

2-[[(1,1-Dimethylethyl)amino]carbonyl]-3-pyridinecarboxylic acid, methyl ester **9i**[1c]

The preparation of ester **9i** was similar to that of **9e** except that anhydride **1** (500 mg, 3.36 mmol) and *tert*-butylamine (245 mg, 3.36 mmol) were used. Column chromatography gave **9i** as a syrup (496 mg, 2.25 mmol, 67 %) and also methyl ester **8i** (70 mg, 0.32 mmol, m.p. 61–63 °C). δ_H 1.38 (9H, 3(CH_3), s, H-4′), 3.86 (3H, s, OCH_3, H-2″), 7.36 (1H, m, H-5), 7.58 (1H, br, NH, H-2′), 7.72 (1H, t, H-4), 8.48 (1H, t, H-6). δ_C 28.48 (C-4′), 51.02 (C-3′), 52.83 (C-2″), 124.9 (C-5), 129.3 (C-3), 136.1 (C-4), 148.5 (C-6), 148.6 (C-2), 162.4 (C-1′), 168.6 (C-1″).

2-[[(4-Aminosulfonylphenyl)amino]carbonyl]-3-pyridinecarboxylic acid **2j**

Anhydride **1** (1.00 g, 6.72 mmol), was added to a solution of *p*-aminobenzenesulfonamide (1.2 g, ~7.0 mmol) 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 carboxamide **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, 71t%) from ($CH_3OCH_2CH_2OH$). m.p. > 240 °C. δ_H 7.28 (2H, SO_2NH_2, H-7′), 7.67 (1H, m, H-5), 7.80 (2H, d, H-5′), 7.91 (2H,d, H-4′), 8.21 (1H, d, H-4), 8.77 (1H, d, H-6), 10.88 (1H, s, NH, H-2′). δ_C 119.4 (C-4′), 125.4 (C-5), 126.7(C-5′), 127.7 (C-3), 137.7 (C-4), 138.9 (C-6′), 141.8 (C-3′, 150.7 (C-6), 152.1 (C-2), 164.9 (C-1′), 167.1 (C-3″).

The ^{1}H 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 = 8.57 Hz) at 7.91 ppm and the latter to the other 2H doublet (J = 8.57, d, J = 7.80 Hz) at 7.80 ppm thus defining the *p*-disubstituted benzene ring. The amide (δ_H 10.88) was coupled to the carbonyl at 164.9 ppm and the quaternary carbon in the pyridine ring (δ_C 152.1) in the HMBC spectrum. This quaternary carbon also showed strong $^3J_{CH}$ couplings to proton doublets at 8.77 ppm (1H; J = 4.70 Hz) and at 8.21 (1H; J = 7.80 Hz). Both these protons were coupled to a doublet of doublets at 7.67 ppm thus defining all the resonances of the pyridine ring and confirming the position of the amide at C-2. The carboxylate at C-3″ (δ_C 167.1) was coupled only to H-4 (δ_H 8.21) as expected.

N-[4-(Aminosulfonylphenyl)]-3-pyridinecarboxamide **4j**

A mixture of 3-pyridinecarboxylic acid (1.23 g, 10 mmol) in thionyl chloride (15 mL) was refluxed for 0.5 h. The excess $SOCl_2$ was removed by evaporation under vacuum and the last traces in a vacuum desiccator (over KOH). The residue was treated with dry tetrahydrofuran (5 mL) followed on by slow addition, with cooling, of a solution of *p*-aminobenzenesulfonamide (1.72 g, 10 mmol) and triethylamine (1.5 g) in dry THF (25 mL). The mixture was stirred at room temperature for 24 h, poured into water, filtered, the residue washed with water, then aqueous $NaHCO_3$, and water to yield crude title compound **4j** (1.3 g, 4.7 mmol, 47 %); crystals from $CH_3OCH_2CH_2OH$; m.p. >250 °C., lit.[9]m.p. 257 °C. δ_H 7.48 (1H, br, NH, H-2′), 7.55 (1H, m, H-5), 7.78 (2H, d, H-5′), 7.90 (2H, d, H-4′), 8.27 (1H, d, H-4), 8.74 (1H, d, H-6), 9.08 (1H, s, H-2). δ_C 119.9 (C-4′), 124.0 (C-5), 126.6 (C-5′), 130.3 (C-3), 136.0 (C-4), 139.1 (C-6′), 148.8 (C-2), 152.4 (C-6), 164.5 (C-1′).

The ^{1}H NMR spectrum showed eight aromatic protons, including the AB system (four protons) of the sulfonamide (δ_H 7.90, 7.78; J = 8.57 Hz) and the three-proton spin system of the pyridine ring (δ_H 8.74, d, J = 4.75 Hz; 7.55, dd, J = 4.75, 7.80 Hz; 8.27, d, J = 7.80 Hz) plus a singlet at 9.08 Hz. The singlet was attached to a carbon at 148.8 ppm (HSQC). This proton was coupled to C-6 (152 ppm), C-3 (136.0 ppm) and the single carbonyl at 164.5 ppm (HMBC). The only other coupling to this proton was from H-4 (δ_H 8.27) confirming that it was attached to the pyridine ring at C-2. As none of the exchangeable protons could be observed in the ^{1}H NMR spectrum save for a very broad absorbance centred at 7.48 ppm, it was not possible to directly correlate the two aromatic rings.

However, given the above evidence, there is no alternative structure possible for this compound.

6-(4-Aminosulfonylphenyl)-5H-pyrrolo[3.4-b]pyridine-5,7(6H)-dione **5j**[8]

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 **5j**[1] in the proportion (*ca.*) 1.7:1. δ_H 7.72 (2H, H-2″), 7.80 (1H, H-3), 8.07 (2H, H-3″), 8.41 (1H, H-4), 9.04 (1H, H-2). δ_C 127.2 (C-4′), 127.5 (C-2″), 128.3 (C-3), 128.4 (C-3″), 131.9 (C-4), 136.0 (C-1″), 138.5 (C-4″), 151.2 (C-7′), 155.4 (C-2), 165.0 (C-5), 165.0 (C-7).

N-*Acetyl derivative* **5j**[1]

δ_H 1.96 (3H, CH_3, H-7″), 7.41 (1H, NH, H-5″), 7.66 (2H, H-2″), 7.86 (1H, H-3), 7.97 (2H, H-3″), 8.41 (1H, H-4), 9.05 (1H, H-2). δ_C 23.3 (C-7″), 126.4 (C-2″) 127.3 (C-4′),127.7 (C-3″), 128.3 (C-3), 131.8 (C-4), 134.5 (C-1″), 143.5 (C-4″), 151.2 (C-7′), 155.3 (C-2), 165.1 (C-5), 165.1 (C-7).

2-[[(4-Aminosulfonylphenyl)amino]carbonyl]-3-pyridinecarboxylic acid, methyl ester **9j**

The aforementioned (**5j**/**5j**[1]) 1.7:1 mixture (170 mg., ~0.5 mmol) in MeOH (20 mL) containing NEt_3 (~50 mg, ~0.5 mmol) was stirred at room temperature, and went into solution in ~2 hours. Stirring was continued for ~24 hours. Evaporation under reduced pressure afforded a residue which was crystallized from MeOH/H_2O to provide methyl ester **9j**. Found: C, 49.73; H, 3.85; N, 12.28. Calc. for $C_{14}H_{13}N_3O_5S$: C, 50.14; H, 3.91; N, 12.53. *m/z* 335 (M^+; 10 %)), 164 (100 %), 136 (42 %).

7,7-Dichloro-5,7-dihydro-thieno[3,4-b]pyridin-5-one **12**[10]

The relevant ^{1}H- and ^{13}C-NMR spectral assignments of **12** have been redetermined and make evident that the δ_H values earlier reported[10] 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: δ_H 7.59 (1H, m, H-3), 8.13 (1H, dd, H-4), 9.05 (1H, dd, H-2). δ_C 88.0 (C-7), 124.8 (C-4′), 125.3 (C-3), 132.4 (C-4), 156.1 (C-2), 165.8 (C-7′),187 (C-5).

Acknowledgements

B.S. thanks Professor H.Nevalainen and Professor P .Karuso of the Department of Chemistry and Biomolecular Sciences at Macquarie University for facilitating his stay in the Department, and Dr S.R. Shengule for several preliminary ^{1}H NMR determinations.

References and Notes

1 Among others: (a) A.A.- M. Abdel-Aziz, *Eur. J. Med. Chem.*, 2007, **42**(5), 614–626. (b) M.M. Blanco, G.J. Levin, C.B. Schapira and I.A. Perillo, *Heterocycles,* 2002, **57**(10), 1881–1890. (c) S.R. Rahalkar and K.S. Nargund, *Indian Drugs,* 1986, **23**(10), 545–548. (d) P.M. Harrington, *Heterocycles,* 1993, **35**(2), 683–687. (e) A. Toth and G.Meyer, *US 3966726* (1976). (f) M. Los, *US 4921961* (1990) (g) J.J. Pascavage, *US 1984–677647*. (h) J. Kenyon and K. Thaker, *J. Chem. Soc.,* 1957, 2531. (i) R.L. Jacobs, *US 3960877* (1976). (j) R.A. Barnes and J.C. Godfrey, *J. Org. Chem.*, 1957, **22**, 1043–1045; (k) M.M. Blanco, I.A. Perillo and C.B. Schapira, *J. Heterocycl. Chem.*, 1999, **36**(4), 979–984.

2 A. Bigotto, V. Galasso, F.P. Colonna and G. Distefano, *J. Chem. Soc., Perkin Trans.* **2**, 1978, 1194–1198.

3 D.M. Dimitrijevic and Z.D.Tadic, *J. Serb. Chem. Soc.,*1957, **22**, 207–216.

4 Among others: (a) D.M. Dimitrijevic, Z.D. Tadic and R.P. Saper, *J. Serb. Chem. Soc.,*1957, **22**, 201–206. (b) P.M. Harrington[1d]. (c) T. Goto, M. Konno, M. Saito and R. Sato, *Bull. Chem. Soc. Jpn.*, 1989, **62**(4), 1205–10. (d) G.J. Hitchings and J.M. Vernon, *J. Chem. Soc. Perkin Trans.* **1**, 1990, 1757–63.

5 M.M. Blanco, M.S. Shmidt and I.A. Perillo, *Arkivoc,* 2005, **12**, 195–204.

6 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 (*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.

7 W.W.K.R. Mederski, M. Baumgarth, M. Germann, D. Kux and T. Weitzel, *Tetrahedron Lett.,* 2003, **44**(10), 2133–2136.

8 A. Scozzafava, L. Menabuoni, F. Mincione, F. Briganti, G. Mincione and C.T. Supuran, *J. Med. Chem.*, 1999, **42**(14), 2641–2650.

9 B.C. Jain, B.H. Iyer and P.C. Guha, *J. Indian Chem. Soc.*, 1947, **24**, 177–180.

10 T. van Es, B. Staskun and M.A. Fernandes, *J. Chem. Res. Synop.,* 2007, 373–376.