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A New Method for the Synthesis of N, N'-Disubstituted Picolinic Amides

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Reaction of N-substituted pyrrolopyridine dione with appropriate amines had led to the formation of a series of new N, N'-disubstituted picolinic amides in good yields. These products have been investigated by spectroscopic analyses.

INTRODUCTION

We have recently described a new procedure[1] for the synthesis of N,N'-dialkyl and N,N'-diarylquinolinic amides from N-substituted quinolinic imides. In the present paper and continouing our interest in this field[2], it is worthwhile to obtain N, N'-disubstituted picolinic amides by the reaction of amines with N-substituted picolinic imides so as to generalize the strategy for the synthesis of analouge systems.

RESULTS AND DISCUSSION

When excess amines (2) allowed to react with imides (1), at ambient temperature, crystalline solid products of structure (3) were obtained in good yields (Table 1). Structural assignments for all compounds are strongly supported by infrared, proton- and ^{13}C-NMR spectroscopy (Table 2).

TABLE 1

THE REACTION OF 5-SUBSTITUTED IMIDES (1) WITH DIFFERENT AMINES

Products	R	Yield %	M. pt °C	Solvent
3a	Isopropyl	70	210	Chloroform
b	n-Butyl	65	76	Cyclohexane
c	Benzyl	62	159–160	Ethylacetate
d	Phenyl	75	245	Ethanol
e	p-Ethylphenyl	53	171–172	Ether
f	2, 5-Dimethoxyphenyl	48	180–181	Ethanol

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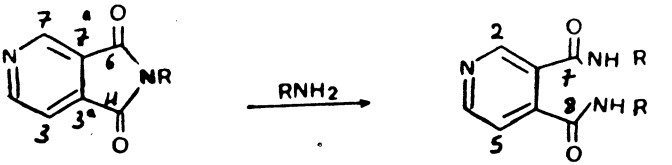
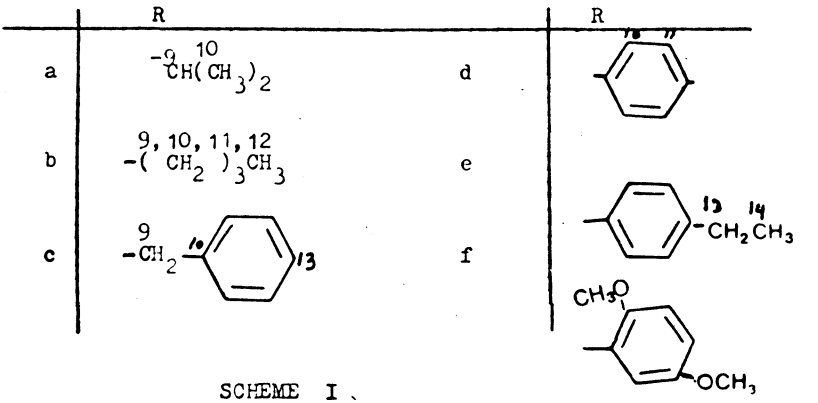


(1) (2) (3)



SCHEME I

TABLE 2

SPECTROSCOPIC DATA OF BIS AMIDES (3a–f)

Products	I.r. (cm^{-1}) (C=O)	(N–H)	^{1}H—n.m.r. (δ)* (J in Hz)
3a	1650	3300	1.2, d, J=7.5, 12H(4CH$_3$); 4.2, m, 2H(2CH); 7.35, d, J=8, 1H(5-H); 7.5, b(D$_2$O-exchangeable), 2H(2NH); 8.6, d, J=8, 1H(6-H); 8.7, s, 1H(2-H).
3b	1655	3310	0.9, t, J=8, 6H(2CH$_3$); 1.5, m, 4H(2CH$_2$); 2.1, m, 4H(2CH$_2$); 3.4, q, J=8, 4H(2NCH$_2$); 7.4, d, J=8, 1H(5-H); 8.1, b(D$_2$O-exchangeable), 2H(2NH); 8.6, d, J=8, 1H(6-H); 8.7, s, 1H(2-H).
3c	1650	3300	3.9, s, 4H(2CH$_2$); 7.4, m, 10H (aromatic); 7.7, d, J=8, 1H(5-H); 7.8, b(D$_2$O-exchangeable) 2H(2NH); 8.7, d. J=8, 1H(6-H); 9.1, s, 1H(2-H).
3d	1660	3315	7.4, m, 10H (aromatic); 7.7, m, 1H(5-H), 7.8, b(D$_2$O-exchangeable), 2H(2NH), 8.9, m, 1H(6-H), 10.7, s, 1H(2-H).
3e	1650	3310	1.2, t, J=7, 6H(2CH$_3$); 2.6, t, J=7, 4H(2CH$_2$); 6.9, m, 4H (aromatic); 7.4, m, 4H (aromatic); 8.2, m, 1H(5-H); 8.4, b(D$_2$O-exchangeable), 2H(2NH); 9.0, m, 1H(6-H); 10.45, m, 1H(2-H).
3f	1655	3315	3.70, s, 6H (2 OCH$_3$), 3.75, s, 6H$_s$ (2 OCH$_3$); 7.1, m, 6H (aromatic); 7,3 m, 1H(5-H); 8.0, m, 1H(6-H); 8.4, b(D$_2$O-exchangeable), 2H(2NH); 9.2, m, 1H(2-H).

*Dimethyl sulphoxide-d$_6$ is used for the measurements.

The IR spectra showed a strong band at around 3300 cm^{-1} characteristic for the amide —NH group. A significant change in the stretching frequency of the carbonyl group from 1735 in (1) to 1650 cm^{-1} in the product strongly support structure (3). The ^1H —NMR spectrum of compound (3a) in DMSO (Table 2 for the others) showed three aromatic protons at δ 8.7, 7.3 and 8.6 ppm due to the pyridine protons 2, 5 and 6, respectively. A D_2O-exchangeble signal at δ 7.5 ppm accounting for two N–H protons, two signals at δ 4.2 associated with methine protons and twelve-protons resonated at δ 1.24 ppm assigned for four methyl groups.

^{13}C-NMR was also used for further structure elucidation of the bis-amide (3), which shows the exact number of ^{13}C-signals. We decided to examine the ^{13}C-NMR spectra of (3) in more detail in order to check the assignments of structure (Table 3). We first examined (3a) as a model for compounds (3a–f). By broad band experiments, the signal at δ 164.5 and 164.9 ppm were assigned to the two carbonyl carbons. The signals at δ 130.1 and 142.6 ppm were attributed to two quaternary carbon atom (C–3 and C–4) and were easily distinguished from that protonated carbon-signals (C–2, C–5 and C–6). The remaining ^{13}C-signals were assigned on the basis of its chemical shifts.[3,4]

In the preceding paper[1] we described the effect of changing R groups in system analogue to the bis-amide (3). It is difficult to distinguish between C–7 and C–8 and the different in chemical shift is not a result of different in inductive or resonance of the pyridine nitrogen. Indeed the two carbonyl carbon signals in compound (1) showed the same chemical shift, therefore the difference in compound (3) is through space effect.

TABLE 4

INDUCED CARBON-13 CHEMICAL SHIFT* BY CONVERSION OF IMIDE (1) TO THE CORRESPONDING BIS-AMIDE (3)

Compound	Δδ C–2	Δδ C–3	Δδ C–4	Δδ C–5	Δδ C–6	Δδ C–7, 8
a	−4.5	+4.7	+3.8	−5.0	−4.5	−1.7 −2.1
d	−3.9	+4.7	+4.0	−4.3	−3.9	−2.0 −2.5
e	−4.8	+5.0	+4.4	−4.8	−4.8	−1.4 −1.7
f	−4.0	+13.0	+2.4	−3.9	−3.8	−1.1 −1.4

*Δδ C = δ C of compound 3 − δ C of compound 1.

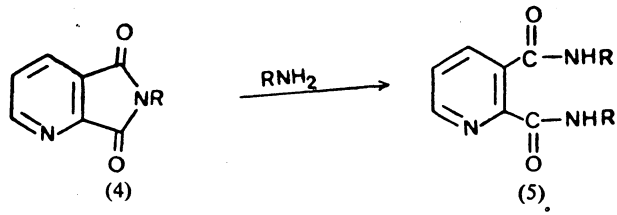
TABLE 3

CARBON-13 CHEMICAL SHIFTS ASSIGNMENTS OF COMPOUND (3) RELATIVE TO TMS

Compound	C-2	C-3	C-4	C-5	C-6	C-7, 8	C-9	C-10	C-11	C-12	C-13	C-14	C-15	C-16
3a	147.8	130.1	142.6	121.3	150.1	164.9 164.5	40.9	21.7						
3d	148.2	130.3	143.2	121.4	152.1	164.4 163.9	138.4	119.4	128.4	123.4				
3e	147.9	130.4	143.2	121.4	150.7	164.2 163.9	138.9	119.5	127.3	127.3	27.5	15.6		
3f	148.5	138.6	143.9	119.9	152.5	165.4 165.1	125.0	155.5	119.9	115.6	152.0	113.0	56.1	55.4

Going from compound (1) to the bis-amide (3) showed rather a large effect on the pyridine moiety carbon-13 chemical shifts (Table 3). C-2, C-6 and C-5 showed up field shift as a result of amide formation. This indicate the involvement of the amide lone pair in the resonance and shielded the ortho and para carbon to amide group. However, C-3 and C-4 showed rather deshielding effect and this could be due to the steric approximity.

Similar trend of effect were observed on going from the imide (4) to the bis-amide (5). (Table 5.)



(4) (5)

TABLE 5

INDUCED CARBON-13 CHEMICAL SHIFT* BY CONVERSION OF IMIDE 4 TO THE CORRESPONDING BIS-AMIDE 5

Compound	Δδ C-2	Δδ C-3	Δδ C-4	Δδ C-5	Δδ C-6	Δδ C-7, 8
a	−4.1	+7.7	+5.0	−4.3	−7.8	−2.6
c	−4.9	+5.8	+7.5	−4.1	−6.3	−0.3 −1.8
f	−5.3	+5.6	+7.8	−1.6	−6.7	+0.1 −1.2
g	−1.8	+6.7	+4.7	−5.8	−5.1	+0.5

*Δδ C – Δδ C of compound 5–Δδ C of compound 4.

The formation of (3) were formally similar to the formation of N,N'-disubtiuted quinolinic amides[1] and the mechanism is presumably similar.

EXPERIMENTAL

Melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were recorded in potassium bromide disc using Pye-Unicam SP 3-300 infrared spectrophotometer. ^{1}H and ^{13}C NMR spectra were determined with a Bruker WH90 DS spectrometer operating at 90 and 22.63 MHz for proton and carbon-13 respectively, with deuterium internal lock and TMS as internal reference.

Pyridine-3,4-dicarboxylic anhydride

Pyridine-3,4-dicarboxylic acid (25.0 g, 0.15 mole) in acetic anhydride (100 ml) was heated under reflux for 30 minutes. The solution was filtered while hot and the solvent was removed by evaporation giving pyridine-3,4-dicarboxylic anhydride (21.0g, 94%), m.pt. 74–76° (lit.[5], 77°); ^{1}H-NMR ($CDCl_3$ + DMSO). 8.05(1H, d, J = 6Hz, 5-H), 9.25 (1H, d, J = 6Hz, 6-H), 9.32 (1H, s, 2-H).

Preparation of 5-substituted-6H-pyrrolo [3, 4-C] pyridine-4,6-dione (1 a-f) (General procedure)

Pyridine-3,4-dicarboxylic anhydride (2.8g, 0.08 mole and amine (0.38 mole) in the presence of anhydrous sodium sulfate were refluxed in acetic acid (20 ml) for 3 hrs. Water was added and the reaction mixture was extracted with ethylacetate. The extract was dried over sodium sulfate and evaporated under vacuum to give the required product.

Synthesis of N,N'-disubstituted picolinic amides (3a-f) (General procedure)

To a solution of pyridinedicarboximides (1a-f) (0.01 mole) in suitable solvent (Table 1), excess amines (2a-f) (0.02 mole) were added with stirring for 2 hrs. at room temperature. The desired products were separated by filtration or by evaporation of the solvent to dryness under vacuum and crystallised from suitable solvent.

REFERENCES

1. S. H. Hussein, B. A. Ahmed, K. F. Al-Shahiry and J. M. A. Al-Rawi, *J. Educ. Scien.*, (1989) (in press).
2. S. H. Hussein, B. A. Ahmed, K. F. Al-Shahiry, *J. Educ. Scien.*, (1989) (in press).
3. G. C. Levy, R. L. Lichter and G. L. Nelson, *Carbon-13 Nuclear Magnetic Resonance Spectroscopy*, John Wiley and Sons, Inc. (1980).
4. M. A. Khadim and L. D. Colebrook, *Man. Reson. Chem.*, **23**, 259 (1985).
5. G. B. Bachman and P. S. Barker, *J. Org. Chem.*, **14**, 97 (1949).

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National symposium on Biophysics will be held during 7–9 February 1991 at the Department of crystallography and Biophysics, University of Madras. For further information contact.

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