Reaction of *N*-(4-Pyridylmethyl)benzamide *N*-Oxides with Ethyl Cyanoacetate in the Presence of Acetic Anhydride

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Reaction of *N*-(4-pyridylmethyl)benzamide *N*-oxides **2a-f** with ethyl cyanoacetate in the presence of acetic anhydride yield dimerization compounds **3a-f** and (*E*)-ethyl 2-cyano-3-(4-pyridyl)-3(benzoylamino)acrylates **4a-f**, which react with hydrazine to give 4-cyano-3-(4-pyridyl)-3-pyrazolin-5-one **9** and the corresponding benzamides **10a-f**.

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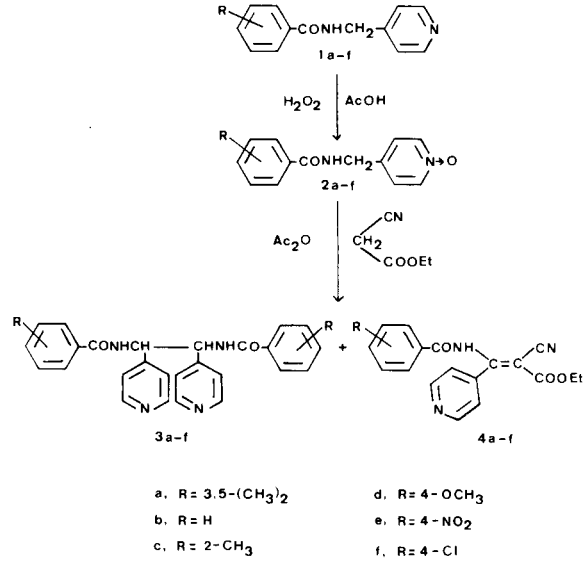
In continuation of our interest in the synthesis and pharmacological properties of new derivatives of Picobenzide **1a** [1-11] and as part of our program looking to functionalize the methylene group of **1**, we report the reaction of *N*-(4-pyridylmethyl)benzamide *N*-oxides **2** with ethyl cyanoacetate in the presence of the acetic anhydride. In previous works [7-11], we have shown that the best method to functionalize the methylene group consists in the reaction of the corresponding *N*-oxide with active methylene compounds in the presence of the acetic anhydride.

The starting materials **2** [2,6] were prepared by oxidation of the corresponding amides with hydrogen peroxide in acetic acid. Amides **1** [12] were obtained by the direct reaction of the appropriate acids with 4-aminomethylpyridine in the presence of dicyclohexylcarbodiimide.

Reaction of *N*-(4-pyridylmethyl)-3,5-dimethylbenzamide *N*-oxide **2a** with ethyl cyanoacetate in the presence of acetic anhydride afforded *N,N'*-di-(3,5-dimethylbenzoyl)-1,2-di-(4-pyridyl)ethylenediamine **3a** [5] and (*E*)-ethyl 2-cyano-3-(4-pyridyl)-3-(3,5-dimethylbenzoylamino)acrylate **4a**, both in low yield. The structure of **4a** was established on the basis of elemental analysis and spectral data (Tables I and II).

The mass spectrum of **4a** showed a molecular peak at m/e 476. The ir spectrum exhibited absorptions at 3240, 1680 (NH and CO amide), 2240 (C≡N), 1710 (CO ester) and 1600 cm^{-1} (C=C). The ^1H nmr spectrum in deuteriochloroform showed signals at δ 1.5 (t, 3H, CH_3-ester), 2.5 (s, 6H, $2CH_3$-aromatic), 4.5 (q, 2H, CH_2), 7.2-7.6 (m, 6H, phenyl, NH, H_3 and H_5-pyridine), 8.6 (d, 2H, H_2 and H_6-pyridine, J = 5 Hz). The ^{13}C nmr revealed two quartets at 13.7 and 20.9 ppm for the methyl carbons, a triplet at 62.5 ppm for the methylene group and two singlets at 86.8 and 162.5 ppm due to the olefinic carbons C_a and C_b, respectively. The singlets at 163.6 and 165.9 ppm were assigned to the carbonyl groups and the remaining seven signals were clearly part of benzene and pyridine rings (Table II).



The stereochemistry of **4a** was assigned by comparison of the spectral data of literature compounds [13]. Infrared and ^1H nmr spectroscopy were very useful in determining the geometrical isomerism of ethyl *N*-(pyrimidinyl)aminomethylenecyanoacetates **5** [13]. The carbonyl stretching bands of *Z*-enamines always appear at lower frequency

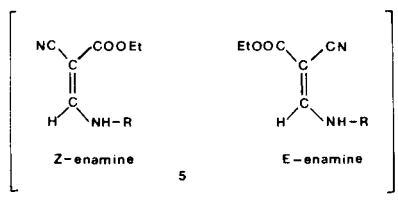


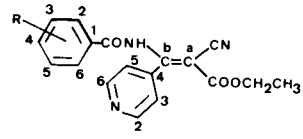
Table I

Characteristic IR Band and ^1H NMR signals of **4a-f**

Compound	R	IR, cm^{-1} (KBr) NH	CN	CO ester	CO amide	C=C	^1H NMR (deuteriochloroform, δ/ppm)
4a	3,5-$(CH_3)_2$	3240	2240	1710	1680	1600	1.5 (t, 3H, CH_3-ester), 2.5 (s, 6H, $2CH_3$), 4.5 (q, 2H, CH_2-ester), 7.2-7.6 (m, 6H, H_2, H_4 and H_6-phenyl, H_3 and H_5-pyridine, NH), 8.6 (d, 2H, H_2 and H_6-pyridine, J = 5 Hz)
4b	H	3200	2220	1700	1670	1600	1.5 (t, 3H, CH_3-ester), 4.2 (q, 2H, CH_2-ester), 72-7.6 (m, 5H, H_3, H_4 and H_5-phenyl, H_3 and H_5-pyridine), 7.8 (d, 2H, $H_2$and H_6-phenyl, J = 7 Hz), 8.7 (d, 2H, H_2 and H_6-pyridine, J = 6 Hz)
4c	2-CH_3	3200	2220	1710	1680	1600	1.4 (t, 3H, CH_3-ester), 2.4 (s, 3H, CH_3), 4.3 (q, 2H, CH_2-ester), 7.0-7.3 (m, 6H, 4H-phenyl, H_3 and H_5-pyridine), 7.4-7.6 (m, 1H, NH), 8.5 (d, 2H, H_2 and H_6-pyridine, J = 5 Hz)
4d	4-OCH_3	3200	2220	1690	1670	1600	1.5 (t, 3H, CH_3-ester), 3.9 (s, 3H, OCH_3), 4.4 (q, 2H, CH_2-ester), 6.9 (d, 2H, H_3 and H_5-phenyl, J = 9 Hz), 7.1 (d, 2H, H_3 and H_5-pyridine, J = 6 Hz), 7.8 (d, 2H, H_2 and H_6-phenyl, J = 9 Hz), 8.6 (d, 2H, H_2 and H_6-pyridine, J = 6 Hz)
4e	4-NO_2	3100	2220	1700	1680	1600	1.3 (t, 3H, CH_3-ester), 4.3 (q, 2H, CH_2-ester), 7.1 (d, 2H, H_3 and H_5-pyridine, J = 6 Hz), 7.8 (d, 2H, H_2 and H_6-phenyl, J = 9 Hz), 8.1 (d, 2H, H_3 and H_5-phenyl, J = 9 Hz), 8.6 (d, 2H, H_2 and H_6-pyridine, J = 6 Hz)
4f	4-Cl	3200	2210	1700	1680	1600	1.4 (t, 3H, CH_3-ester), 4.3 (q, 2H, CH_2-ester), 7.1-7.4 (m, 5H, NH, H_3 and H_5-phenyl, H_3 and H_5-pyridine), 7.7 (d, 2H. H_2 and H_6-phenyl, J = 8 Hz), 8.6 (d, 2H, H_2 and H_6-pyridine, J = 5 Hz)

Table II

^{13}C NMR of **4a-f** (deuteriochloroform, δ/ppm)

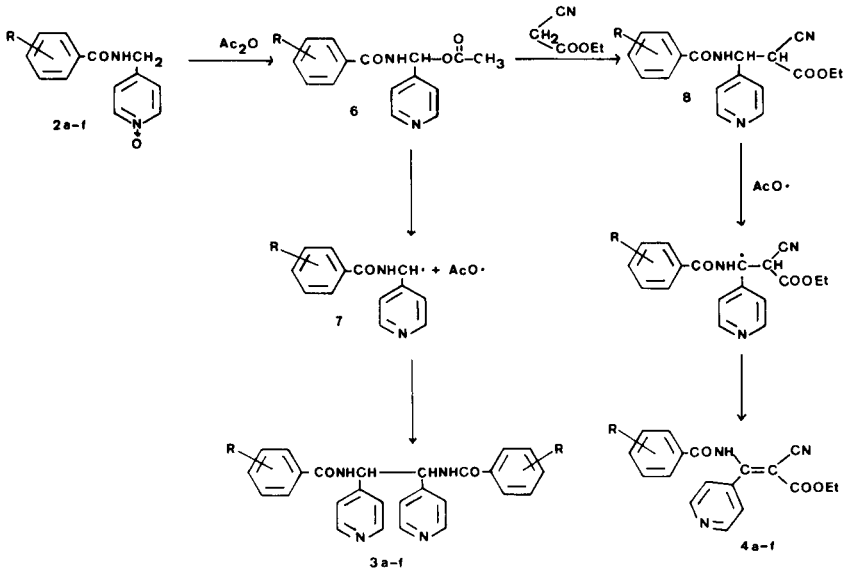


Compound	R	R	CH_3	CH_2	C_a	CN	benzene ring C_1	C_2	C_3	C_4	C_5	C_6	pyridine ring C_3,C_5	C_4	C_2,C_6	C_b	C=O ester	C=O amide
4a	3,5-$(CH_3)_2$	20.9	13.7	62.5	86.8	114.4	131.1	125.6	138.7	135.3	138.7	125.6	121.2	140.6	149.7	162.5	163.6	165.9
4b	H	---	13.8	62.6	87.0	114.3	131.3	128.9	127.7	133.7	127.7	128.9	121.2	140.5	149.8	162.2	163.3	166.0
4c	2-CH_3	20.1	13.5	62.2	86.7	114.3	131.9	138.7	127.2	131.7	125.9	127.2	121.1	140.3	149.3	162.1	165.0	165.5
4d	4-OCH_3	55.3	13.7	62.4	86.1	114.5	123.4	129.9	114.2	162.7	114.2	129.9	121.1	140.6	149.6	162.4	163.8	166.1
4e	4-NO_2	---	13.9	63.2	88.7	114.0	140.0	124.2	129.1	150.6	129.1	124.2	121.3	140.0	150.1	161.6	162.1	166.2
4f	4-Cl	---	13.7	62.8	87.4	114.2	129.8	129.3	129.2	140.2	129.2	129.3	121.2	140.2	149.8	162.2	162.4	166.1

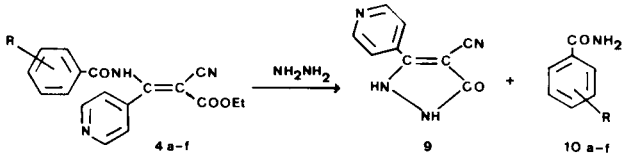
(~1680 cm^{-1}) than those of the *E*-enamines (~1710-1730 cm^{-1}). The shifts into a lower frequency of the *Z*-enamines are attributed to an intramolecular hydrogen-bonding effect, which is consistent with the results of the ^1H nmr in the *Z*-enamine the NH proton is at down-field (~10.6-11.3 ppm) than in the *E*-isomer. So, comparison of these data with those of **4a** allowed us to assign the structure of the *E*-isomer for **4a**.

In order to confirm the extension of this reaction, other *N*-(4-pyridylmethyl)benzamide *N*-oxides **2b-f** were treated with ethyl cyanoacetate in the presence of acetic anhydride to give the *N,N'*-dibenzoyl-1,2-di-(4-pyridyl)ethylenediamines **3b-f** [6] and the corresponding (*E*)-ethyl 2-cyano-3-(4-pyridyl)-3-(benzoylamino)acrylates **4b-f** (Tables I and II).

The fact that **3** and **4** were isolated seems to suggest that the reaction takes place *via* the intermediate **6** [5]. Homolytic cleavage in **6** can give radicals **7**, dimerization of which explains the formation of **3**. Reaction of **6** with ethyl cyanoacetate affords **8**, which, in a transfer reaction followed by a radical disproportionation process would give rise to **4** (Scheme I).

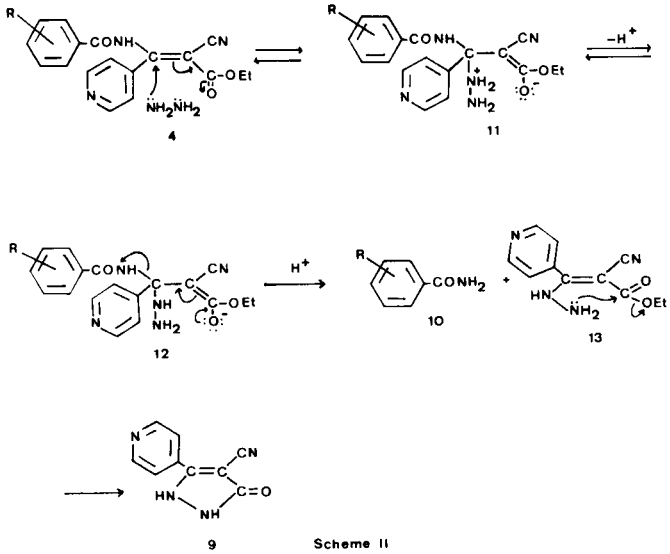


Scheme I



In an attempt to react a nucleophile with **4a**, the hydrazine was used and the major product was 4-cyano-3-(4-pyridyl)-3-pyrazolin-5-one **9** (65%). 3,5-Dimethylbenzamide **10a** [14] was also isolated in a 30% yield. The structure of **9** was established on the basis of elemental analysis and spectral data (see Experimental).

Similar results have been obtained in the reaction of **4b-f** with hydrazine.



Scheme II

The formation of **9** and **10** can be explained by the addition-elimination mechanism (Scheme II). Thus, nucleophilic attack by the hydrazine at the β-carbon of **4** (electron-deficient position) generates **11**, which looses a proton to yield **12**. The intermediate thus formed undergoes fragmentation to give the corresponding amide **10** and ethyl 2-cyano-3-hydrazino-3-(4-pyridyl)acrylate **13**. The latter undergoes an internal cyclization by nucleophilic attack for NH_2 to the C=O group to give the pyrazolone **9**.

EXPERIMENTAL

Melting points are uncorrected. The ir spectra were determined on a Perkin Elmer 781 spectrophotometer. The ^1H nmr spectra were recorded on a Varian T-60 A using TMS as internal standard. The ^{13}C nmr spectra were obtained on a Varian FT-80 A spectrometer. Mass spectrometry was performed with a Varian MAT-711 apparatus.

N-(4-Pyridylmethyl)benzamides **1a-f** [12] and the corresponding *N*-oxides **2a-f** [6] were prepared according to the previously reported procedures.

Reaction of *N*-(4-Pyridylmethyl)benzamide *N*-oxides **2a-f** with Ethyl Cyanoacetate. General Procedure.

A suspension of the corresponding *N*-oxide **2a-f** (0.01 mole) and ethyl cyanoacetate (1.13 g, 0.01 mole) in 4 ml of acetic anhydride was heated at 100° for 2 hours. The reaction mixture was left overnight at room temperature and the precipitate formed was filtered giving the corresponding *N,N'*-dibenzoyl-1,2-(4-pyridyl)ethylenediamines **3a-f** [5,6] in low yield (< 15% in all cases).

After filtration and evaporation of the solvent, the residual oil was purified by column chromatography on silica gel to yield the (*E*)-ethyl 2-cyano-3-(4-pyridyl)-3-(benzoylamino)acrylates **4a-f**.

(*E*)-Ethyl 2-Cyano-3-(4-pyridyl)-3-(3,5-dimethylbenzoylamino)acrylate (**4a**).

This compound was chromatographed on a silica gel column with

benzene-ethyl acetate (5:5), Rf = 0.52 (benzene-ethanol 8:2), yield 20%, mp 202-203° (ethanol).

Anal. Calcd. for $C_{20}H_{19}N_3O_3$: C, 68.75; H, 5.48; N, 12.02. Found: C, 68.84; H, 5.65; N, 11.81.

(*E*)-Ethyl 2-Cyano-3-(4-pyridyl)-3-(benzoylamino)acrylate (**4b**).

This compound was chromatographed on a silica gel column with benzene-ethyl acetate (8:2), Rf = 0.51 (benzene-ethanol 8:2), yield 16%, mp 180-181° (ethanol-water).

Anal. Calcd. for $C_{18}H_{15}N_3O_3$: C, 67.28; H, 4.71; N, 13.07. Found: C, 67.55; H, 4.81; N, 12.83.

(*E*)-Ethyl 2-Cyano-3-(4-pyridyl)-3-(2-methylbenzoylamino)acrylate (**4c**).

This compound was chromatographed on a silica gel column with ethyl ether, Rf = 0.58 (benzene-ethanol 8:2), yield 21%, mp 117-118° (ethanol-water).

Anal. Calcd. for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53. Found: C, 67.88; H, 5.11; N, 12.53.

(*E*)-Ethyl 2-Cyano-3-(4-pyridyl)-3-(4-methoxybenzoylamino)acrylate (**4d**).

This compound was chromatographed on a silica gel column with ethyl ether, Rf = 0.50 (benzene-ethanol 8:2), yield 27%, mp 162-163° (ethanol).

Anal. Calcd. for $C_{19}H_{17}N_3O_4$: C, 64.95; H, 4.87; N, 11.96. Found: C, 65.06; H, 4.99; N, 11.96.

(*E*)-Ethyl 2-Cyano-3-(4-pyridyl)-3-(4-nitrobenzoylamino)acrylate (**4e**).

This compound was chromatographed on a silica gel column with ethyl ether, Rf = 0.52 (benzene-ethanol 8:2), yield 17%, mp 198-199° (ethanol).

Anal. Calcd. for $C_{18}H_{14}N_4O_5$: C, 59.01; H, 3.58; N, 15.29. Found: C, 58.72; H, 3.72; N, 15.22.

(*E*)-Ethyl 2-Cyano-3-(4-pyridyl-3-(4-pyridyl)-3-(4-chlorobenzoylamino)-acrylate (**4f**).

This compound was chromatographed on a silica gel column with ethyl ether, Rf = 0.57 (benzene-ethanol 8-2), yield 19%, mp 183-184° (ethanol).

Anal. Calcd. for $C_{18}H_{14}ClN_3O_3$: C, 60.76; H, 3.96; N, 11.81; Cl, 9.96. Found: C, 60.48; H, 3.95; N, 11.69; Cl, 9.70.

Reaction of (*E*)-Ethyl 2-Cyano-3-(4-pyridyl)-3-(3,5-dimethylbenzoylamino)-acrylate (**4a**) with Hydrazine.

A suspension of **4a** (2.5 g, 0.007 mole) and 80% hydrazine (0.3 g, 0.01 mole) in 30 ml of ethanol was refluxed until the completion of the reaction (determined by tlc). The precipitate formed was filtered off to give 4-cyano-3-(4-pyridyl)-3-pyrazolin-5-one **9** (0.9 g, 65%), mp >250° (*N,N*-dimethylformamide-water); ir: 3200-2300 (br, NH), 2220 (C≡N), 1650 (C=O); ^{1}H nmr (DMSO-d_6): δ 7.7 (d, 2H, H_3 and H_5-pyridine, J = 6 Hz), 8.2-8.8 (m, 4H, H_2 and H_6-pyridine, 2NH); (trifluoroacetic acid): δ 8.4 (d, 2H, H_3 and H_5-pyridine, J = 6 Hz), 8.8 (d, 2H, H_2 and H_6-pyridine, J = 6 Hz); ms: m/e (relative intensity) 186 (M^+, 100), 129 ($C_8H_5N_2^+$, 53), 102 ($C_7H_4N^+$, 24), 78 ($C_5H_4N^+$, 9).

Anal. Calcd. for $C_9H_6N_4O$: C, 58.04; H, 3.25; N, 30.09. Found: C, 58.15; H, 3.26; N, 30.08.

Removal of the solvent *in vacuo* afforded an oil, which solidified with hexane giving 0.4 g (30%) of 3,5-dimethylbenzamide **10a**, mp 197-198° (lit [14] mp 200°).

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