Some Cyano-amides and Dicyano-glutaconimides derived from Pyridine Aldehydes

By **J. S. A. Brunskill**, Department of Chemistry, University of Wales Institute of Science and Technology, Cardiff CF1 3NU

2-Cyano-3-pyridylacrylamides, 2-cyano-3-pyridylpropionamides, and salts of 3,5-dicyano-6-hydroxy-4-pyridyl-2-pyridones have been prepared from four pyridine aldehydes and tested for pharmacological and antimicrobial activity. Spectra–structure correlations include evidence that in the acrylamides the carbamoyl and pyridyl groups are *trans*.

MANY α-substituted β-pyridylacrylonitriles have been described,[1-15] some as potentially useful biological agents. Our attention was drawn to the cyano-acrylamides (Ia; R = pyridyl) (Table 1), which have been prepared by Knoevenagel condensations with cyanoacetamide,[16] by reports of the fungistatic and antibacterial properties of

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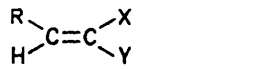
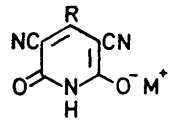
analogous acrylamides [*e.g.* (Ia; R = 4-$Me_2N{\cdot}C_6H_4$) [17,18]]. The corresponding propionamides (II; R = pyridyl)



(I) a; X = CN, Y = $CO{\cdot}NH_2$
b; X = $CO{\cdot}NH_2$, Y = CN
c; X = Y = $CO{\cdot}NH_2$
d; X = Y = CN

$RCH_2{\cdot}CH(CN){\cdot}CONH_2$ (II)



(III)

(Table 1), members of another class of pyridinecarboxylic acid derivatives not previously investigated, have been obtained as major products of the Guareschi condensation in alcoholic ammonia,[19,20] and by selective reduction of the more stable acrylamides,[21] although attempted Knoevenagel condensations under reducing conditions [22] gave intractable mixtures. Only half the aldehyde in the Guareschi reaction can be converted into the corresponding propionamide, but this approach also provided examples of a new type of bipyridyl derivative (III; R = pyridyl, M = NH_4) (Table 2) [20] for biological testing. Several new compounds with similar structures, amides and hydroxypyridones derived from other aldehydes (Table 3), have also been examined.

Whereas 2-cyano-3-(3-pyridyl)acrylamide was readily prepared by several standard methods, pyridine-4-carbaldehyde, 6-methylpyridine-2-carbaldehyde, and pyridine-2-carbaldehyde showed an increasing tendency to undergo competing reactions in condensations with cyanoacetamide. Similar difficulties, particularly in obtaining pure 3-(2-pyridyl)acrylonitriles have been described before,[2,12,23,24] and when the amide (Ia; R = 2-C_5H_4N) was isolated eventually from a condensation at a liquid–liquid interface, it was found to be unstable, decomposing rapidly in hot solvents.

Usually only one geometrical isomer results from similar Knoevenagel condensations. In studies of their stereochemistry, Zabicky [25] obtained substituted cinnamic acid derivatives from aromatic aldehydes and ethyl cyanoacetate or cyanoacetamide, in which the larger aryl and ethoxycarbonyl or carbamoyl groups assume a *trans*-configuration to attain planar conjugated systems without steric strain, but Patai and Rappoport [26,27] noted several reports of the formation of both *cis*- and *trans*-isomers and described the rapid isomerisation of a '*cis*'-3-aryl-2-cyanoacrylate even in the absence of base. In order to confirm their assignment the spectra of the 2-cyano-3-pyridylacrylamides have been examined.

The u.v. absorptions, which have been recorded * with those of the other pyridine derivatives [(II) and (III)] provide little information, and interpretative methods which had been adopted for their aryl analogues [26,28] were inapplicable because of lack of data for a sufficient number of reference compounds. Marvel and Stille [29] noted that the absorption curves for the α- and β-picolylideneacetones in the 220—280 nm region could be resolved into two maxima showing bathochromic and hypsochromic shifts from the single peak of the γ-pyridyl isomer, their wavelengths depending on the length of the absorption system from pyridine nitrogen to carbonyl oxygen atom and associated with two paths of different length around the pyridine ring. In these amides (Ia) the γ-pyridyl derivative also shows a single peak at 267 nm in the 260—310 nm region in place of two near 265 and 305 nm in the spectra of the condensation products from the α- and β-pyridinecarbaldehydes, but this does not preclude the non-planar configuration (Ib), provided that the pyridine rings are not twisted to a significant degree.

I.r. spectral data for the functional groups of the 2-cyano-3-pyridylacrylamides* have been compared with equivalent data for some condensation products of similar structure and with the spectra of the 3-aryl-2-cyanoacrylamides reported by Zabicky.[25] In the identification of the amide I and olefinic stretching frequencies other bands which have been observed include several characteristic of the pyridine ring,* in good agreement with the ranges specified for α-, β-, and γ-monosubstituted pyridines.[30] The C=C stretching bands appear in the same region (1585—1630 cm^{-1}) as in the planar cinnamamides (Ia; R = Ar) and malononitriles (Id; R = Ar), but they would be expected at lower wavelength (*ca.* 1665—1685 cm^{-1}), as in the malonamides (Ic; R = Ar), if the less conjugated, non-planar '*cis*'-isomers (Ib) had been obtained. In the cinnamamides carbonyl absorption is observed in a region (1685—1710 cm^{-1}) close to that for the malonamides (1665—1685 cm^{-1}), both being strongly hydrogen bonded. Zabicky predicted that the weakly bonded '*cis*'-isomers would absorb at higher frequencies, so

* See Supplementary Publication No. SUP 20522 (6 pp., 1 microfiche); for details of Supplementary Publications see *J. Chem. Soc.* (*A*), 1970, Issue No. 20 (Notice to Authors No. 7).

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observations of amide I bands in the pyridine derivatives over a similar range (1670—1705 cm^{-1}), as in their aryl analogues (Ia), also indicate the '*trans*'-configuration. However, such evidence is controvertible because of overlap with other bands, varying hydrogen bonding and field effects according to the orientation of the ring nitrogen atom, and double carbonyl bands in the solid state spectra, although over a narrow region measurements on dilute solutions suggest that the band multiplicity results from hydrogen bonding in the disc, rather than from the presence of both isomers or *s-cis*- and *s-cis*-conformations of the carbonylethene system.[31]

In a comparison of the n.m.r. spectra of the 2-cyano-3-pyridylacrylamides with those of the aryl analogues and of the corresponding benzylidenemalononitriles and benzylidenemalonamides * the displacements of the olefinic protons provide less ambiguous evidence for the '*trans*'-configuration (Ia). In estimating the chemical shifts of olefinic protons downfield from internal tetramethylsilane by use of additive increments the following equation has been proposed:[32] $\delta = 5{\cdot}25 + \Sigma_i z_i$. The z_i values are 0·98 for *cis*-CO·NH_2, 0·46 for *trans*-CO·NH_2, 0·75 for *cis*-CN, 0·55 for *trans*-CN, and 1·38 for *gem*-Ar. These give calculated τ values of 2·07 for the benzylidenemalononitriles (Id; R = Ar), 1·93 for the malonamides (Ic; R = Ar), 1·84 for the '*trans*'-acrylamides (Ia; R = Ar), and 2·16 for the '*cis*'-acrylamides (Ib; R = Ar). Small deviations should result from the application of the method to pyridine derivatives with dimethyl sulphoxide as solvent, but although relatively few compounds have been prepared for comparison, the data for similar acrylamides (Ia; R = Ar), malononitriles (Id; R = Ar), and '*trans*'-α-cyanocinnamates [33,34] are in close agreement with the peaks observed. These differ most from the calculated values in the non-planar malonamides [(Ic; R = 4-Me_2N·C_6H_4) τ 2·74; (Ic; R = 4-AcNH·C_6H_4) τ 2·70], the shielding effect being the result of steric restraint on conjugation, whilst in the planar malononitriles [(Id; R = 4-Me_2N·C_6H_4) τ 1·95; (Id; R = 4-AcNH·C_6H_4) τ 1·61] the olefinic protons absorb at lower field than expected. They are also less shielded in two of the α-cyano-β-pyridylacrylamides than predicted for the '*trans*'-configuration {(Ia; R = 2-C_5H_4N) τ 1·84; [Ia; R = 2-(6-MeC_5H_3N)] τ 1·85; (Ia; R = 3-C_5H_4N) τ 1·68; (Ia; R = 4-C_5H_4N) τ 1·74}, but in their aryl analogues electron-donating substituents produce a small shielding increment [(Ia; R = 4-Me_2N·CH_4) τ 1·99; (Ia; R = 4-AcNH·C_6H_4) τ 1·88], a factor also exemplified in the relatively high τ values for the ring protons H-3 and -5 in the presence of the 4-dimethylamino-group [(Ia) 3·15; (Ic) 3·38; (Id) 3·12], and by the higher olefinic values shown by dimethylaminophenyl than by acetamidophenyl derivatives. If the cyanoacrylamides had bulky amide and pyridyl groups in the '*cis*'-configuration (Ib) steric inhibition of conjugation would have the same effect as in the malonamides, and the olefinic proton resonances would

TABLE 1

2-Cyano-3-pyridylacrylamides and 2-cyano-3-pyridylpropionamides

Compound Formula	M.p. (°C) [a] (solvent)	% Found (Reqd.) C	H	N	Method [b]	Yield (%)
(Ia; R = 2-C_5H_4N) $C_9H_7N_3O$	156°d (EtOH)	62·4 (62·4)	4·1 (4·1)	24·5 (24·3)	A	26 [c]
[Ia; R = 2-(6-MeC_5H_3N)] $C_{10}H_9N_3O$	141d (C_6H_6)	64·2 (64·2)	4·8 (4·8)	22·6 (22·4)	B	20 [d]
(Ia; R = 3-C_5H_4N) $C_9H_7N_3O$	220d (EtOH)	62·1 (62·4)	4·2 (4·1)	24·3 (24·3)	C	79 [c,e]
(Ia; R = 4-C_5H_4N) $C_9H_7N_3O$	208d (MeOH)	62·0 (62·4)	4·1 (4·1)	24·3 (24·3)	B	73 [c,f]
(II; R = 2-C_5H_4N) $C_9H_9N_3O$	160 (C_6H_6)	61·4 (61·7)	5·2 (5·2)	24·2 (24·0)	D	7 [g,h]
[II; R = 2-(6-Me)C_5H_3N] $C_{10}H_{11}N_3O$	146 (Me_2CO)	63·7 (63·5)	5·9 (5·9)	22·2 (22·2)	D E	13 [c,h] 5
(II; R = 3-C_5H_4N) $C_9H_9N_3O$	176 (Pr^iOH)	61·3 (61·7)	5·2 (5·2)	24·0 (24·0)	D E	36 [c,h] 14
(II; R = 4-C_5H_4N) $C_9H_9N_3O$	153 (Pr^iOH)	61·9 (61·7)	5·1 (5·2)	24·0 (24·0)	D E	26 [c,h] 6

[a] d = decomp. [b] A, modified Knoevenagel condensation as recorded; B, Knoevenagel condensation [16] with 0·2% Et_2NH–EtOH, 0 → 80° in 1 h; C, like B at 20° for 16 h; D, Guareschi condensation [19] with excess of NH_3–EtOH, −33 → 20° in 5—7 days; E, selective reduction of (Ia) with $NaBH_4$–Pr^iOH, 0 → 20° in 3 h;[21] F, Cope modification [35] with $C_5H_{11}N$–HOAc–C_6H_6 in 20 h; G, like F but in C_5H_4N–C_6H_6; H, like B with Amberlite 1R4B for 16 h;[36] I, like B with Et_3N–Me_2SO, 0 → 50° in 4 h.[37] [c] White needles. [d] Pink needles, after several crystallisations, *cf.* Table 3, note *d*. [e] *Cf. ca.* 75% yields by methods B and F, below 30% by methods G, H, and I. [f] *Cf. ca.* 10% yields by methods C, F, and H. [g] White plates after several recrystallisations. [h] Based on total aldehyde.

* See footnote p. 2947.

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TABLE 2

Salts of 3,5-dicyano-6-hydroxy-4-pyridyl-2-pyridones

Compound (III)	M.p. (°C) [a] (solvent)	Formula	% Found (Reqd.) C	H	N	Yield (%) [b]
R = 2-C_5H_4N	274d	$C_{12}H_9N_5O_2$	56·2	3·7	27·0	*c*
M = NH_4	(EtOH)		(56·5)	(3·6)	(27·4)	
R = 2-C_5H_4N	287	$C_{17}H_{17}N_5O_2$	62·8	5·4	21·7	6 [d]
M = $C_5H_{12}N$	(H_2O)		(63·1)	(5·3)	(21·7)	
R = 2-(6-Me·C_5H_3N)	289d	$C_{13}H_{13}N_5O_3$ [e]	54·4	4·3	24·6	14 [f]
M = NH_4	(H_2O)		(54·3)	(4·6)	(24·4)	
R = 2-(6-Me·C_5H_3N)	312 [g]	$C_{18}H_{19}N_5O_2$	64·4	5·6	21·0	6 [f]
M = $C_5H_{12}N$	(H_2O)		(64·1)	(5·7)	(20·8)	41 [h]
R = 3-C_5H_4N	335d	$C_{12}H_9N_5O_2$	56·4	3·7	27·3	14 [f]
M = NH_4	(MeOH)		(56·5)	(3·6)	(27·4)	
R = 3-C_5H_4N	288	$C_{17}H_{17}N_5O_2$	63·1	5·2	21·7	8 [f]
M = $C_5H_{12}N$	(MeOH)		(63·1)	(5·3)	(21·7)	58 [h]
R = 4-C_5H_4N	*ca.* 365d	$C_{12}H_9N_5O_2$	56·9	3·5	27·7	10 [i]
M = NH_4	(MeOH)		(56·5)	(3·6)	(27·4)	
R = 4-C_5H_4N	351 [g]	$C_{17}H_{17}N_5O_2$	63·4	5·4	21·7	3 [j]
M = $C_5H_{12}N$	(H_2O)		(63·1)	(5·3)	(21·7)	34 [h]

[a] d = decomp. without melting. [b] Based on total aldehyde unless otherwise stated. [c] Unstable, pink needles; little isolated before conversion into piperidinium salt. [d] White plates. [e] Monohydrate. [f] White needles. [g] With decomp. above 200°. [h] Based on NH_4 salt. [i] Yellow needles. [j] Yellow plates.

TABLE 3

Similar products derived from other aldehydes [a]

Compound	M.p. (°C) (solvent)	% Found (Reqd.) C	H	N	Method [b]	Yield (%)
(Ia; R = 4-AcNH·C_6H_4) $C_{12}H_{11}N_3O_2$	296 (C_6H_6)	63·3 (62·9)	4·6 (4·8)	18·5 (18·3)	C	50 [c,d]
(Ia; R = $Me[CH_2]_8$) $C_{13}H_{22}N_2O$	184 (EtOH)	70·1 (70·2)	10·0 (10·0)	12·6 (12·6)	J	7 [e]
(II; R = 4-Me_2N·C_6H_4) $C_{12}H_{15}N_3O$	121 (C_6H_6)	66·2 (66·3)	7·0 (7·0)	19·4 (19·3)	K	*e, g*
(II; R = 4-AcNH·C_6H_4) $C_{12}H_{13}N_3O_2$	190 (MeOH)	62·2 (62·3)	5·7 (5·7)	18·1 (18·2)	K	*g, h*
(II; R = $Me[CH_2]_8$) $C_{13}H_{24}N_2O$	127 (C_6H_6)	69·6 (69·6)	10·6 (10·8)	12·5 (12·5)	D	22 [h,i]
(III; R = 4-Me_2N·C_6H_4, M = NH_4) $C_{15}H_{15}N_5O_2$	360 [j] (H_2O)	60·6 (60·6)	5·3 (5·1)	23·2 (23·6)	K	*c, g*
(III; R = 4-AcNH·C_6H_4, M = NH_4) $C_{15}H_{13}N_5O_3$ [k]	316 [j] (aq. MeOH)	57·8 (57·9)	4·2 (4·2)	22·5 (22·5)	K	*e, g*
(III; R = $Me[CH_2]_8$, M = NH_4) $C_{16}H_{24}N_4O_2$	312 [j] (aq. EtOH)	63·5 (63·1)	7·9 (8·0)	18·8 (18·4)	D	38 [e,i]
(Ic; R = 4-Me_2N·C_6H_4) $C_{12}H_{15}N_3O_2$	251 (MeOH–Et_2O)	61·8 (61·8)	6·5 (6·5)	17·9 (18·0)	G	12 [e,m]
(Ic; R = 4-AcNH·C_6H_4) $C_{12}H_{13}N_3O_3$ [l]	284 (aq. EtOH)	58·6 (58·3)	5·3 (5·3)	16·6 (17·0)	F	12 [e,m]

[a] New compounds for comparison. [b] A—I see Table 1; *J*. like I but in HCO·NMe_2; K, like D, but with increased aldehyde–ester ratio.[34] [c] Yellow needles. [d] Methods B and C gave 85—88% yields of (Ia; R = 4-Me_2N·C_6H_4), m.p. 198—199°.[25] [e] White needles. [f] Like I but 83—84% yields of (Id; R = 4-Me_2N·C_6H_4), m.p. 184° (lit.,[38] m.p. 179—180°) and (Id; R = AcNH·C_6H_4), m.p. 239° (lit.,[39] 236°). [g] Only isolated from more complex mixture. [h] White plates. [i] Based on total aldehyde. [j] Decomp. without melting. [k] Also monohydrate, white plates from water (Found: C, 54·6; H, 4·4; N, 21·3. $C_{15}H_{15}N_5O_4$ requires C, 54·7; H, 4·6; N, 21·3%). [l] Also monohydrate, yellow plates from water (Found: C, 54·6; H, 5·7; N, 16·0. $C_{12}H_{15}N_3O_4$ requires C, 54·3; H, 5·7; N, 15·8%). [m] From similar attempts to prepare (Ic; R = pyridyl) only $CH_2(CO·NH_2)_2$ recovered

be expected at even higher field than the calculated τ 2·16, but the highest measured signal was at τ 1·85.

The 2-cyano-3-(2-pyridyl)acrylamide was too unstable to be examined, and the primary neuropharmacological and parasitological test reports on the other β-substituted α-cyanoacrylamides and the hydroxypyridones have revealed no marked activity. Of the more active saturated amides, 2-cyano-3-(3-pyridyl)propionamide has the most pronounced anti-inflammatory and analgesic properties, but none appears to be a potential antimicrobial agent.

EXPERIMENTAL (with S. J. NIELSEN, C. J. TREHARNE, and R. C. WILLIAMS *)

The u.v. and i.r., and n.m.r. spectra were recorded with Unicam SP 700, Perkin-Elmer 521, and Perkin-Elmer R14 spectrometers respectively.

* Projects for B.Sc.(Tech.) in Industrial Chemistry, U.W.I.S.T., 1967 (S.J.N.), 1968 (C.J.T.), 1970 (R.C.W.).

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2-*Cyano*-3-*pyridylacrylamides*.—Other acrylamides (Ia) were prepared by standard methods [16] but for the least stable product (Ia; R = 2-C_5H_4N) several other approaches including ammonolysis of the corresponding ester,[3] the Cope modification,[35] the use of ion-exchange resins,[36] and reactions in polar aprotic solvents [37] were also found inapplicable (Tables 1 and 3). Although pyridine-2-carbaldehyde condensed with cyanoacetamide under mild conditions, only the apparently less contaminated product from a two-phase reaction could be induced to recrystallise without further degradation: thus the aldehyde (21·4 g), cyanoacetamide (16·8 g), ether (150 ml), and water (150 ml) were stirred together at ambient temperature for 90 min with addition of diethylamine (4 ml in portions); then, after the mixture had been cooled to 0°, the precipitate was collected, washed with cold ethanol, and recrystallised (charcoal) as quickly as possible to obtain the *amide* (Ia; R = 2-C_5H_4N) (8·9 g).

2-*Cyano*-3-*pyridylpropionamides*.—The mixed products from condensations of two moles of ethyl cyanoacetate, one mole of the aldehyde, and ammonia were extracted with benzene.[19] Owing to the formation of cyanoacetamide, the isolation of some propionamides (II) required repeated crystallisation, but lower yields resulted from condensations with increased proportions of aldehyde because of greater difficulties in separating the acrylamides (Ia), which may become the major products as the reactant ratio approaches equimolar [34] (Tables 1 and 3). In the reduction of the acrylamides,[21] the low yields appeared due to the formation of resinous material (Table 1).

3,5-*Dicyano*-6-*hydroxy*-4-*pyridyl*-2-*pyridones*.—The cyclisations gave only one bipyridyl derivative (III; R = 3-C_5H_4N) forming an ammonium salt which seemed sufficiently stable to be easily isolated, so the other residual products after extraction were converted into piperidinium salts for examination (Table 2).[19]

I thank Messrs. Allen and Hanburys Ltd. for the biological testing of these compounds and Dr. D. A. Wilson, University College, Cardiff, for a discussion.

[2/813 *Received*, 24*th July*, 1972]