Reaction of ω-Cyanoacetophenone and Some of its Derivatives With Secondary Amines. New Synthesis of Aminopyridine Derivatives.

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ω-Cyanoacetophenone (**1a**) and its derivatives **1b-c** react with morpholine (or piperidine) to give mainly 2,4-diaryl-3-cyano-6-morpholino- (or piperidino-) pyridine derivatives (**5**); relative β-aminocinnamonitriles **6** and very small amounts of amidines **4** are also obtained. When pyrrolidine is used compounds **5** cannot be detected and enamines **6** are the main product.

A mechanism involving the intermediate formation of enamines **6** (as electrophiles) and of carbanions **11** (as nucleophiles) is proposed to explain this new synthesis of aminopyridine derivatives.

Literature reports (1,2) that ω-cyanoacetophenone (**1a**) and its ring-substituted derivatives react with secondary amines, such as morpholine (**2**) or piperidine (**3b**) in refluxing ethanol

OC_4H_8NH $(CH_2)_nNH$

2 **3a**, n = 4; **3b**, n = 5

to give amidines **4**; salicylaldehyde is used as catalyst:

1. $Ar\text{-}CO\text{-}CH_2\text{-}CN + R_2NH \xrightarrow[(o.HOC_6H_4\text{-}CHO)]{C_2H_5OH,\ reflux} Ar\text{-}CO\text{-}CH_2\text{-}C(=NH)\text{-}NR_2$

1 **4**

We found that compounds **1**, when refluxed for 2-3 hours with **2** or **3b** without solvent and catalyst, gave chiefly 2,4-diaryl-3-cyano-6-morpholino- (or piperidino-) pyridines (**5a-f**). The relative β-aminocinnamonitriles **6** and, occasionally, very small amounts of amidines **4** were also obtained in these conditions:

2. $Ar\text{-}CO\text{-}CH_2\text{-}CN \xrightarrow{R_2NH}$ **5** + $Ar\text{-}C(NR_2)\text{=}CH\text{-}CN$ + **4**

1 **5** **6**

4, **6**

a, Ar = C_6H_5-
b, Ar = *p*-$CH_3C_6H_4$-
c, Ar = *p*-ClC_6H_4-

a, Ar = Ar' = C_6H_5-
$R_2N = OC_4H_8N$-
b, Ar = Ar' = C_6H_5-
$R_2N = C_5H_{10}N$-
c, Ar = Ar' = *p*-$CH_3C_6H_4$-
$R_2N = OC_4H_8N$-

a, Ar = C_6H_5-; $R_2N = OC_4H_8N$-
b, Ar = C_6H_5-; $R_2N = C_5H_{10}N$-
c, Ar = C_6H_5-; $R_2N = C_4H_8N$-
d, Ar = *p*-$CH_3C_6H_4$-
$R_2N = OC_4H_8N$-
e, Ar = *p*-$CH_3C_6H_4$-
$R_2N = C_5H_{10}N$-
f, Ar = *p*-$CH_3C_6H_4$-
$R_2N = C_4H_8N$-
g, Ar = *p*-ClC_6H_4-
$R_2N = OC_4H_8N$-
h, Ar = *p*-ClC_6H_4-
$R_2N = C_5H_{10}N$-
i, Ar = *p*-ClC_6H_4-
$R_2N = C_4H_8N$-

In order to confirm the assigned structure, compound **5a** was obtained also starting from 2,4-diphenyl-3-cyano-6-chloropyridine (**7**):

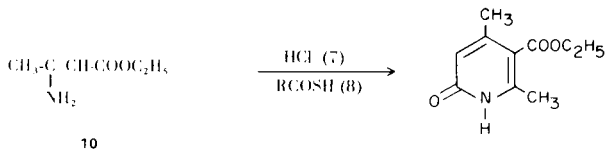
3. **7** $\xrightarrow{OC_4H_8NH}$ **5a**

To our knowledge this is the first report on a reaction of compounds **1** which gives pyridine derivatives.

Many examples, on the contrary, are reported about pyridine syntheses starting from β-aminocinnamonitrile (**8**) (3-5) and from other compounds such as **9** (6) or **10** (7,8). In fact compounds **8-10** give self-condensation in various conditions (but generally in acidic medium) to pyridine derivatives (equation *4*) (9).

4. $R\text{-}C(NH_2)\text{=}CH\text{-}CN \xrightarrow{HX}$

8, R = C_6H_5-; **9**, R = CH_3-.



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This possible pathway, however, must be discarded for the production of compounds **5** because when enamines **6** or **8** were refluxed for 2-3 hours with amines **2-3a,b** only trace amounts of pyridine derivatives were obtained.

Moreover, compound **8** by prolonged reflux (40 hours) with **2-3a,b** gave, in part, the relative enamines **6a,c**. On the other hand, compound **8** itself reacted rather quickly in refluxing morpholine with the ω-cyanoacetophenones **1a-c** to give compound **5a** or the mixed compounds **5g,h**, respectively (equation *6*). Tlc showed that in the last two cases only trace amounts of compounds **5c,e**, deriving from the reaction of the only **1b,c**, were formed.

6. **6** $\underset{40\text{ hours}}{\overset{R_2NH}{\longleftarrow}}$ **8** $\xrightarrow[2\text{ hours}]{\textbf{1a-c};\ R_2NH}$ **5a,g,h**

The somewhat rapid decrease of compound **8** when it was refluxed in morpholine together with compounds **1** and the following production of mixed compounds **5g,h** point out that both **1** and **8** take part in the cyclisation process.

The results suggest that the reaction of compounds **1** with morpholine or piperidine to give **5** begins by a nucleophilic attack of carbanions **11** to enamines **6** (11)

TABLE I

Nmr Values for Substituted Pyridines (a)

Compound						
5a	7.93 (2H,m) (b)	7.55 (8H,m) (c)	6.57 (H,s) (d)	3.80 (8H,bp) (e)		
5b	7.90 (2H,m) (b)	7.51 (8H,m) (c)	6.52 (H,s) (d)	3.76 (4H,bp) (f)	1.70 (6H,bp) (g)	
5c	7.80 (2H,m) (b)	7.31 (6H,m) (c)	6.50 (H,s) (d)	3.75 (8H,bp) (e)	2.39 (6H,s) (h)	
5d	7.78 (2H,m) (b)	7.36 (6H,m) (c)	6.41 (H,s) (d)	3.72 (4H,bp) (f)	2.43 (6H,s) (h)	1.67 (6H,bp) (g)
5e	7.89 (2H,m) (b)	7.25 (6H,m) (c)	6.39 (H,s) (d)	3.71 (8H,bp) (e)		
5f	7.73 (2H,m) (b)	7.28 (6H,m) (c)	6.41 (H,s) (d)	3.65 (4H,bp) (f)	1.68 (6H,bp) (g)	
5g	7.88 (2H,m) (b)	7.45 (7H,m) (c)	6.56 (H,s) (d)	3.76 (8H,bp) (e)	2.40 (3H,s) (h)	
5h	7.69 (2H,m) (b)	7.29 (7H,m) (c)	6.42 (H,s) (d)	3.72 (8H,bp) (e)		
5i	7.91 (2H,m) (b)	7.40 (3H,m) (c)	6.46 (H,s) (d)	3.75 (8H,bp) (e)	2.50 (3H,s) (h)	
13	8.13 (4H,m) (b)	7.82 (H,s) (d)	7.44 (11H,m) (c)			
14	8.11 (2H,m) (b)	7.69 (H,s) (d)	7.35 (8H,m) (c)	2.91 (3H,s) (h)		

(a) S = singlet, m = multiplet, b.p. = broad peak. (b) *o*-Hydrogens on the C_{α}-phenyls. (c) Other aromatic protons. (d) H_5. (e) Morpholine ring protons. (f) $-CH_2-\underset{|}{N}-CH_2-$piperidine ring protons. (g) $-CH_2-CH_2-CH_2-$piperidine ring protons. (h) $-CH_3$ protons on an aromatic ring.

TABLE II

Infrared and Ultraviolet Spectra Data of Compounds **5** and **6**.

Compound No.	Infrared Spectra, ν max, cm^{-1}					U.V. (ethanol) λ max log ε), mμ	
	C-H	C≡N	C=C and C=N	C-N-C (C)	C-O-C		
5a	2865-2809	2183	1626, 1584, 1562	1123	1116	229 (4.30)	253 (4.43)
5b	2932-2840	2197	1600, 1584, 1564	1123		302 (4.33)	242 (4.45)
5c	2949-2849	2207	1613, 1587, 1562	1123	1113	296 (4.17)	259 (4.37)
5d	2967-2849	2178	1597, 1587, 1562	1125		303 (4.18)	252 (4.44)
5e	2976-2865	2202	1597, 1569	1121	1112	303 (4.28)	255 (4.49)
5f	2932-2865	2188	1597, 1560	1118		306 (4.23)	254 (4.48)
5g	2941-2840	2192	1602, 1582, 1560	1118	1112	298 (4.25)	256 (4.40)
5h	2915-2849	2202	1602, 1594, 1569	1122	1113	298 (4.22)	252 (4.41)
5i	2941-2777	2212	1602, 1582, 1545	1119	1111	290 (4.35)	241 (4.25)
			C=C and aromat. C=C				
6b	2932 2840	2183	1626, 1597 -1569	1116		273 (4.16)	223 (4.14)
6c	2932 2873	2174	1633, 1584-1550	1116		280 (4.06)	225 (3.98)
6f	2949 2832	2178	1610, 1579-1545	1116		277 (4.12)	230 (4.06)
6h	2923 2824	2174	1607, 1584-1550	1112		284 (3.99)	236 (4.22)
6i	2959 2832	2174	1618, 1594-1540	1113		284 (3.87)	220 (4.02)

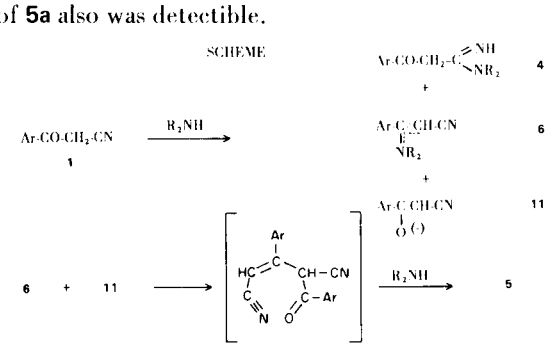
which are formed competitively to them.

The conjugation in compounds **6** of the vinyl group with the electron withdrawing nitrile group and the decreased assistance of the lone pair of the morpholino or piperidino nitrogen owing to same steric hindrance, as shown by models, make possible this attack.

The reaction proceeds by a subsequent nucleophilic attack of the nitrogen of the nitrile group (13) (Scheme).

In agreement with all that, compounds **1a** and **9** reacted in refluxing morpholine to give the 2-phenyl-4-methyl-pyridine derivative **5i**; in this case only trace amounts (tlc) of **5a** also was detectible.

SCHEME



Structure **5i** rather **5l** was assigned to the compound on the basis of a comparison of its nmr spectrum with the ones of **5a-h, 13** and **14** (Table I) (16).

A useful feature of the nmr spectra of these compounds, in fact, is the multiplet centered at about δ 8 ppm which is due to o.hydrogens on the C_α-phenyls. In fact this multiplet integrates for four protons in the case of **13** and for two protons in the case of compounds **5a-h, 14** and also in the case of phenyl methyl derivative, whose structure then is **5i** and not **5l** (17).

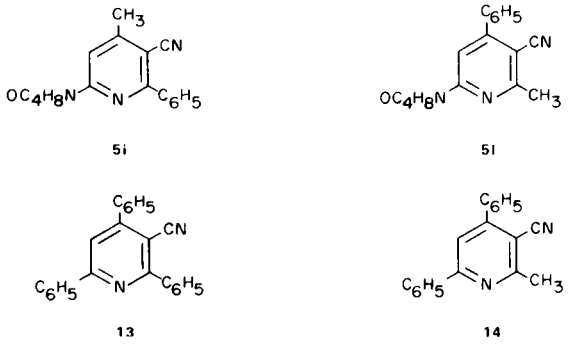


TABLE III

Pyridine Derivatives

Compound No.	Starting Compounds	Amine	Yield %	M.p. °C (Recryst. solvent) (a)	Formula	Calcd. % C	H	N	Found, % C	H	N
5a	**1a**	**2**	32	215-216 (E)	$C_{22}H_{19}N_3O$	77.39	5.61	12.31	77.51	5.84	12.62
5b	**1a**	**3b**	28	201-202 (E-W)	$C_{23}H_{21}N_3$	81.39	6.23	12.38	81.24	6.45	12.48
5c	**1b**	**2**	25	175-176 (E-W)	$C_{24}H_{23}N_3O$	78.02	6.27	11.38	78.23	6.37	11.52
5d	**1b**	**3b**	12	175-177 (E-W)	$C_{25}H_{25}N_3$	81.70	6.86	11.44	81.47	6.75	11.26
5e	**1c**	**2**	40	264-265 (B)	$C_{22}H_{17}Cl_2N_3O$	64.40	4.18	10.24	64.32	4.40	10.49 (b)
5f	**1c**	**3b**	36	202-204 (E-W)	$C_{23}H_{19}Cl_2N_3$	67.65	4.69	10.29	67.84	4.80	10.35 (c)
5g	**1b + 8**	**2**	38	196-197 (E-W)	$C_{23}H_{21}N_3O$	77.72	5.96	11.82	77.97	6.18	11.96
5h	**1c + 8**	**2**	44	236-237 (B)	$C_{22}H_{18}ClN_3O$	70.30	4.83	11.18	70.04	4.64	11.04 (d)
5i	**1a + 9**	**2**	26	189-190 (E)	$C_{17}H_{17}N_3O$	73.09	6.14	15.04	73.41	6.42	15.32

(a) E = ethanol, E-W = ethanol-water, B = benzene. (b) Calcd. 17.28. Found, 17.46. (c) Cl Calcd. 17.37. Found, 17.24. (d) Cl Calcd. 9.43. Found, 9.67.

TABLE IV

β-(*N,N*-Disubstituted) aminocrotononitriles (a)

Compound No.	Starting Compound	Amine	Yield %	M.p. °C	Formula	Calcd. % C	H	N	Found, % C	H	N
6b	**1a**	**3b**	15	86-87	$C_{14}H_{16}N_2$	79.20	7.60	13.20	79.54	7.81	13.42 (b)
6c	**1a**	**3a**	24	103-105	$C_{13}H_{14}N_2$	78.75	7.12	14.13	78.91	7.30	14.02 (c)
6f	**1b**	**3a**	18	92-94	$C_{14}H_{16}N_2$	79.20	7.60	13.20	79.04	7.88	13.42
6h	**1c**	**3b**	12	125-127	$C_{14}H_{15}ClN_2$	68.15	6.13	11.35	68.32	6.38	11.47 (d)
6i	**1c**	**3a**	22	78-79	$C_{13}H_{13}ClN_2$	67.09	5.63	12.04	67.42	5.81	12.20 (e)

(a) The compound **6a** has been already known (ref. 13). The compounds **6d**, e.g., were not isolated. (b) nmr (deuteriochloroform) 7.41 (5H, m, aromatic protons), 4.19 (H, s vinyl proton), 3.03 (4H, broad peak. $-CH_2-N-CH_2-$piperidine ring protons) 1.57 (6H, broad peak, $-(CH_2)_3-$piperidine ring protons). (c) nmr (deuteriochloroform) 7.39 (5H, m, aromatic protons), 3.87 (H, s, vinyl proton), 3.13 (4H, broad peak, $-CH_2-N-CH_2-$pyrrolidine ring protons), 1.92 (4H, broad peak, $-(CH_2)_2-$pyrrolidine ring protons). (d) Cl Calcd. 14.37. Found, 14.54. (e) Cl Calcd. 15.24. Found, 15.42.

TABLE V

Aroylaceto (*N*,*N*-disubstituted) amidines (a)

Compound No.	Starting Compound	Amine	M.p. °C	Formula	Calcd. % C	Calcd. % H	Calcd. % N	Found, % C	Found, % H	Found, % N
4c	**1a**	**3a**	188-189	$C_{13}H_{16}N_2O$	72.19	7.46	12.95	72.44	7.60	13.14 (b)
4e	**1b**	**3b**	148-149	$C_{15}H_{20}N_2O$	73.73	8.25	11.47	73.41	8.12	11.30 (c)
4f	**1b**	**3a**	212-214	$C_{14}H_{18}N_2O$	73.01	7.88	12.16	73.24	7.75	12.34 (d)

(a) The compounds **4a**, g has been already know (ref. 2 and 21, respectively). The compounds **4b**, **d**, **h**, **i** were not isolated. (b) λ max (ethanol) (log ξ), mμ 323 (4.20), 236 (4.16). (c) λ max (ethanol) (log ξ), mμ 323 (4.16), 242 (4.11). (d) λ max (ethanol) (log ξ), mμ 323 (4.27), 240 (4.17).

Structures **5g,h** were assigned by analogy.

When pyrrolidine (**3a**) was allowed to react with **1a-c** enamines **6c,f,i** were obtained but no trace amounts of relative pyridine derivatives.

The different behaviour of pyrrolidine is not surprising because literature reports other examples of this, relative either to the formation of enamines or to their reactions (18).

In this case a possible reason for this difference could be the lesser electrophilicity of the pyrrolidine enamines as the result of a greater conjugation of the lone pair of the nitrogen with the π electrons of the cinnamonitrile system. This is made possible by a lesser steric hindrance of the five-membered pyrrolidine ring (19).

In agreement with all that and with the suggested mechanism relative to the cyclisation process (Scheme), enamines **6a,b** reacted with **1b,c**; on the contrary **6c** had no reaction with **1b,c**.

EXPERIMENTAL

Nmr spectra were determined for deuteriochloroform solutions at 60 MHz and the chemical shifts are expressed in δ values (ppm) with TMS as the internal standard. Ir spectra were determined using potassium bromide discs and uv spectra were recorded in ethanol. Melting points are uncorrected. Tlc were carried out with silica gel F-254 plates and developing solvents were petroleum ether-benzene (20:80), benzene-ethyl acetate (90:10 and 70:30) and ethyl acetate. Merck silica gel (0.05-0.2 mm) was used for chromatographic separations.

General Procedure for the Reaction of Compounds **1** with Amines **2-3**.

A solution of compounds **1** (0.01 mole) in 0.01 mole of amine (20) was refluxed for 2 hours. In the case of **1b**, pyridine (3 ml.) was added to reduce the production of gums; the solvent was then removed *in vacuo*. The reaction mixtures were dissolved in chloroform; the solutions were washed with water, dried and evaporated. The residues crystallized from the specified solvent (Table III) to provide compounds **5** (analytical data are recorded in Tables I-III). The solutions were concentrated and chilled to remove **5** as much as possible and then evaporated *in vacuo*; the residues were repeatedly extracted with hot ligroin; the solutions were decanted several times from some oily residues and at last compounds **6** crystallized. Data relative to compounds **6** are given in Tables II and IV.

Before the crystallization of enamines **6e,f** from the ligroin extracts the relative amidines **4e,f** separated as greyish dusts. Amidine **4a** instead separated by evaporation to nearly the dryness of the ethanolic mother liquor of compound **5a** and dilution with water. Amidines **4c,g** separated from the solutions in dilute ethanol of the brownish oily residues which were left when the reaction mixtures of **1a** with **3a** or of **1c** with **2** were extracted with ligroin. Data relative to some compounds **4** are reported in Table V.

Separation of reaction compounds could be made better by column chromatography which allowed, in the case of the reaction between **1a** and morpholine, the obtaining of a white compound, m.p. 310°, in a very small amount.

The yields of **5** and **6** were not great (Tables III and IV) because of the fragmentation processes which led to the production of acetonitrile, aroylamides and arylcarboxylic acids as shown by tlc and gc; gums were also formed.

Moreover tlc showed the presence of an unidentified yellow compound.

Reaction of Compounds **1a-c** with **8** and Morpholine (2).

Compounds **1a-c** (0.005 mole), **8** (0.005 mole) and morpholine (0.01 mole) were allowed to react as described above; the yield of **5a** was 41.5%, m.p. and mixed m.p. 215-216° (with a sample obtained starting only from **1a**). Data relative to compounds **5g,h** derived, respectively, from **1b**, **2** and **8** and from **1c**, **2** and **8** are recorded in Tables I-II.

Reaction of **1a** with **9** and Morpholine.

Compound **1a** (0.005 mole), **9** (0.005 mole) and morpholine (0.01 mole) were refluxed for 3 hours and the reaction mixture was worked-up as above. Data relative to compound **5i** are given in Tables I-III. Tlc showed the presence of a little **5a**, **6a** and **9**.

Reaction of **1b,c** with **6a-c** and Amines.

Compound **1b** was refluxed with **6a** and **2**, with **6b** and **3b** and with **6c** and **2**. Compound **1c** was refluxed with **6a** and **2**. In all cases the molar ratio 1:1:1 was used and the reactions were stopped after 5 hours.

All mixtures gave its own relative mixed pyridine derivative (tlc) except that of **1b** with **6c** and **2**.

Reaction of β-Aminocinnamonitrile (**8**) with Amines.

Compound **8** (0.01 mole) and morpholine (0.02 mole) were refluxed and the reaction course was followed by tlc; after 40 hours the area of the two spots relative to **6a** and **8** was nearly

equal.

The addition of a crystal of *p*-toluenesulfonic acid little affected the rate of the reaction which was completed only after 80 hours. Tlc showed only trace amount of compounds **5a** and **8**. The reaction was repeated by using an excess of amine (ratio **1** to amine, 1:3) which did not increase the reaction rate. The reaction mixture was dissolved in chloroform; the solution was washed with water, dried and the solvent was removed. The residue crystallized from ligroin provided **6a** (yield 42%) which was identical with an authentic sample (15).

The reactions with piperidine and with pyrrolidine were carried out likewise by refluxing the solutions for 28 and 20 hours respectively. The compounds **6b** (yield 28.5% and **6c** (yield 51%) so obtained, were identical with the ones isolated from the reaction mixtures of **1a** with piperidine and pyrrolidine respectively (Table IV).

2,4-Diphenyl-3-cyano-6-chloropyridine (**7**).

Compound **7** was prepared as reported (22) starting, however, from β-aminocinnamonitrile (**8**) rather than from β-aminocinnamamide, m.p. 179-182° (lit. (22) m.p. 178-180°) after crystallization from ethanol containing a few drops of hydrochloric acid.

Reaction of **7** with Morpholine.

A solution of 1 g. of **7** and 3 ml. of **2** was refluxed for 2 hours. Following the aforesaid procedure compound **5a** (0.7 g., yield 52.2%) was obtained, m.p. 215-216°. Spectral data and Rf were identical with those of the compound obtained by reaction of **1a** with morpholine.

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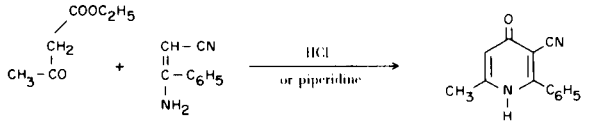
(9) Compounds such as **8** or **9**, by acting as nucleophiles react with, for example, β-dicarbonyl compounds to give again pyridine derivatives (3,10), *e.g.*:



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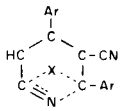
(10) E. Meyer, *J. Prakt. Chem.*, [2], **78**, 524 (1908).

(11) *N*-Hemiaminals (Ar-C(OH)-CH_2-CN) or aminals (Ar-C(NR_2)-CH_2-CN)

relative to compounds **6** could take part in the pyridine ring formation rather than enamines. Nevertheless if *N*-hemiaminals were the reactive electrophilic species then in the reaction mixtures of **1b,c** and **6a** or **8** in morpholine the symmetrically substituted compounds **5c,e**, deriving from the reaction of the **1b,c** only, should be present in a great quantity since compounds **6** and **8** cannot give the relative *N*-hemiaminals in the reaction conditions. Also the sharing of aminals in the cyclisation process seems to be discarded; unlike aldehydes, ketones do not give aminals as intermediates in the production of the enamines (12), thus indicating a greater stability of the enamines themselves. This fact suggest that the slow transamination process rate is due to the slow rate of production of the intermediate aminals rather than to their slow rate of decomposition. If the cyclisation process proceeded *via* aminals its rate also might be rather slow and this is not the case.

(12a) L. W. Haynes in "Enamines: Synthesis, Structure and Reactions," A. C. Cook, Ed., M. Dekker, Inc., New York, N. Y., 1969, p. 61; (b) M. E. Kuehne, *ibid.*, p. 317.

(13) The presence of the morpholino group rather than the -OH or the -NH_2 groups in the compounds obtained by reaction between **1** and **8** in the presence of morpholine allows the exclusion that a four-centre intermediate (14), *e.g.*, **12**, could be



12

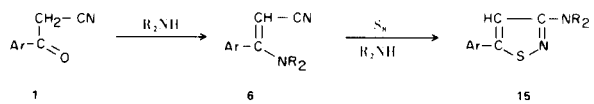
the intermediate to the production of **5**. On the other hand owing to the poor reactivity of amidines **4** in basic medium (15) their process-sharing could be rejected. In fact compounds **4** were recovered unchanged when they were allowed to react with compounds **1** or **6**.

(14) S. J. Davis, J. A. Elvidge and A. B. Foster, *J. Chem. Soc.*, 3638 (1962).

(15) A. Bruno and G. Purrello, *Gazz. Chim. Ital.*, **96**, 986 (1966).

(16) Compounds **13** and **14** were prepared according to ref. 10.

(17) It is worthy of note that when sulphur was added to the reaction mixture of **1a** and morpholine, no trace-amount of **5a** was obtained but thiazole derivative **15** was formed together with other compounds (13). This fact agrees with the assumption that enamines **6** are interested in both processes which lead to **15** (15) and to **5**:



1 6 15

(18a) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963); (b) D. Pocar, G. Bianchetti and P. Dalla Croce, *Gazz. Chim. Ital.*, **95**, 1220 (1965).

(19) W. Maas, M. J. Janssen, E. J. Stamhuis and H. Winberg, *J. Org. Chem.*, **32**, 1111 (1967).

(20) Ratio **1** to amines, 1:0.5 did not allow the reactions to be completed and a larger excess of amines was ineffective.

(21) A. Bruno and G. Purrello, *Gazz. Chim. Ital.*, **96**, 1009 (1966).

(22) S. Checchi and P. Papini, *ibid.*, **90**, 46 (1960).