Tetrahedron Vol. 35, pp. 2453 to 2461
Pergamon Press Ltd., 1979. Printed in Great Britain

N-HALOAMIDINES–V[1]

REACTION OF N-CHLORO-N'-AROYL-ACETAMIDINES AND -BENZAMIDINES WITH ENAMINES

LUISA CITERIO, DONATO POCAR, MARIA LUISA SACCARELLO and RICCARDO STRADI*
Istituto di Chimica Organica della Facoltà di Farmacia, Università di Milano,
Viale Abruzzi 42, 20131 Milano, Italy

(*Received in UK* 19 *April* 1979)

Abstract—The reaction between N-chloro-N'-aroyl-amidines and β,β-disubstituted enamines affords 1 - aroyl - 4 - amino - 4,5 - dihydro - imidazoles in low yields, the main reaction product being N - (2 - morpholino - 2,2 - disubstituted) - ethylidene - N' - aroyl - amidines. A similar reaction course was not observed with enamines bearing a hydrogen atom in the β-position. In this case only products derived from electrophilic chlorination on enamines were isolated.

In a previous work we reported that enamines derived from aldehydes react with N-chloro-N'-aryl-amidines according to different pathways depending upon the substituents at the enamine double bond as depicted in Scheme 1.[2]

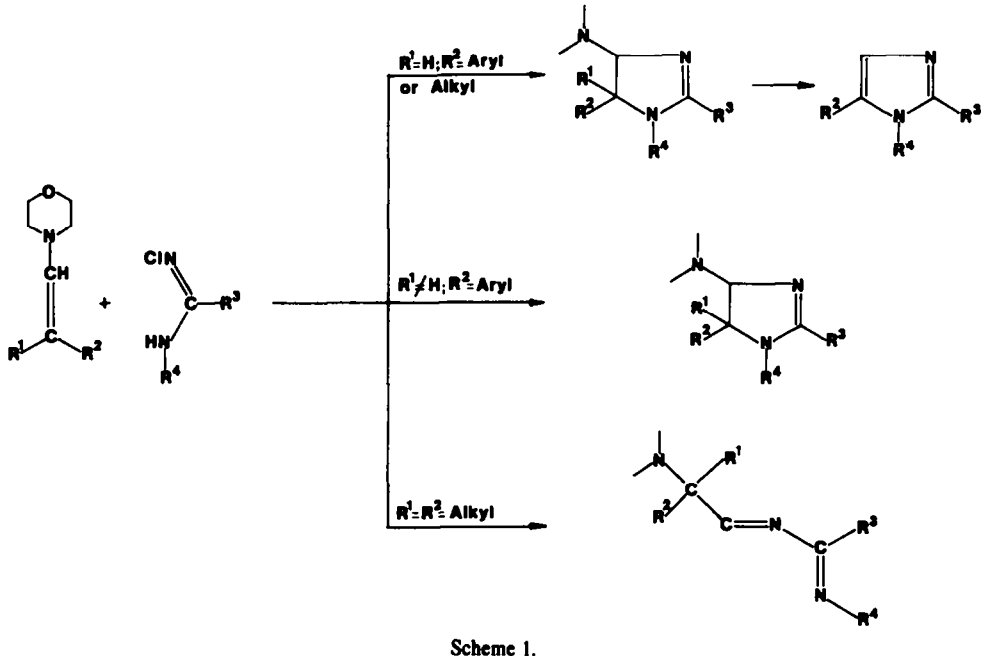
We now wish to report our findings about the reaction between the same enamines (**1**) and N-chloro-N'-aroyl-amidines (**2**). Our interest in this study was to search for an entry to imidazoles bearing a removable substituent at N_1 and to deepen the reaction mechanism.

Enamines **1a** and **1b** react in boiling chloroform with N-chloro-N'-aroyl-amidines **2a–i** affording as the main reaction products a mixture of 1 - aroyl - 4 - amino - 2,5,5 - trisubstituted - 4,5 - dihydro - imidazoles **3a–i** and N - (2 - amino - ethylidene) - N' - aroyl - benzamidines **4a–e**. The compounds **4** deriving from N-chloro-N'-aroyl-acetamidines **2f–i** could not be isolated because of their ready hydrolysability during chromatographic separation. Accordingly, only hydrolysis products **5**, **6** and **7** could be isolated and identified (Scheme 2).

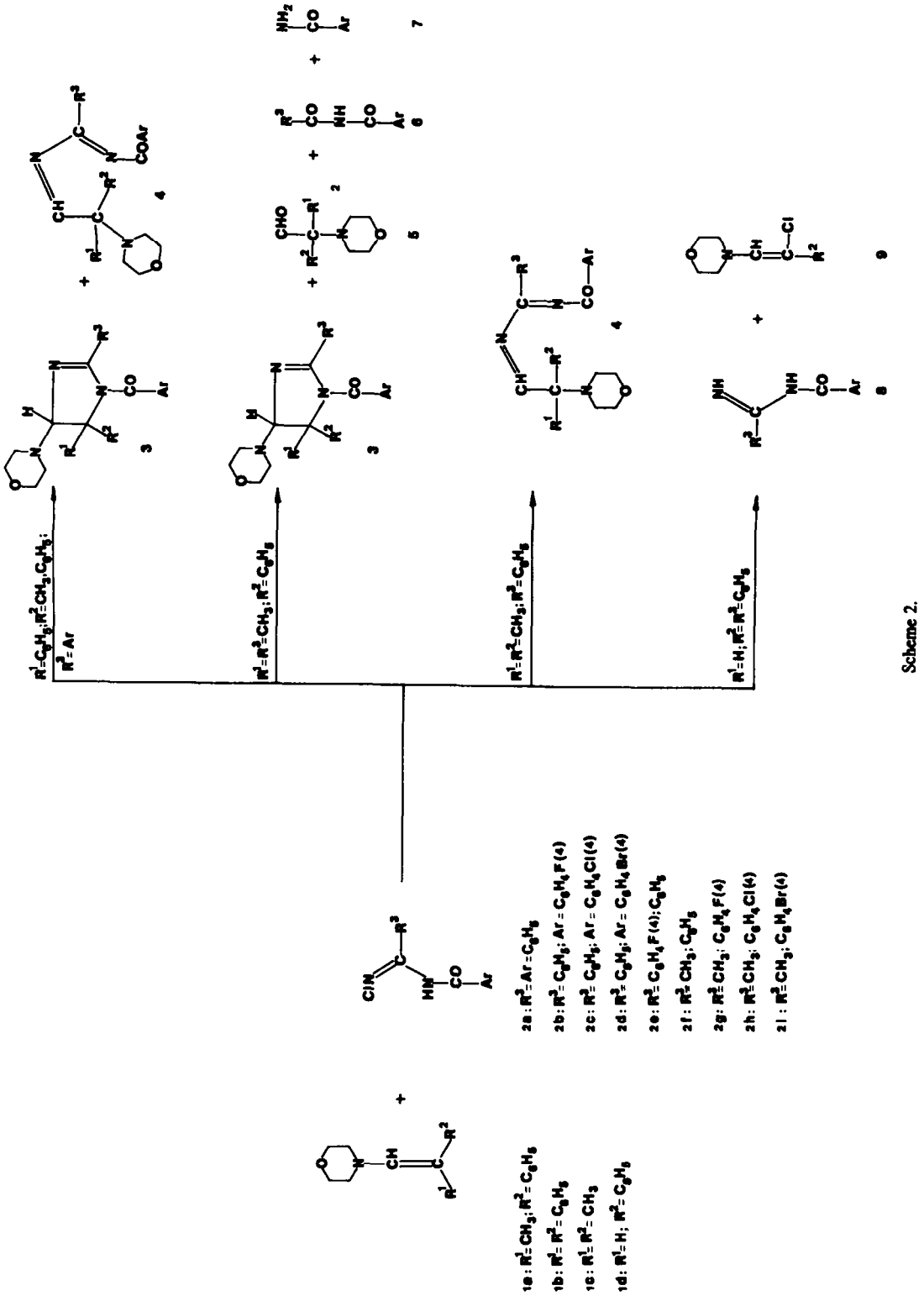
It is interesting to observe that the formation of imidazole derivative **3** was not observed in the reaction of 1-morpholino-2-methyl-propene **1c** with chloro-amidine **2a**: only the 2-amino-butylidene-amidine **4f** was isolated as the main product in this case.

The yields of isolated **3** and **4** are reported in Table 1.

The relative positions of the substituents at C_4 and C_5 as well as the E configuration of compounds **3a-i** were hypothesized on the basis of mechanistic considerations and confirmed by the crystallographic analysis of **3l**[3] (Fig. 1). An interesting feature in the ^{1}H NMR spectrum of the imidazolines **3f-i** is the remarkably high value of the long-range coupling constant between H_4 and the Me group at C_2. This constant appears to be a general



Scheme 1.



Scheme 2.

Table 1.

R^1	R^2	R^3	R^4	Imidazolines	Yield %	Ethylidene-amidines	Yield %
CH_3	C_6H_5	C_6H_5	C_6H_4F	3a	20	4a	55
CH_3	C_6H_5	C_6H_5	C_6H_4Cl	3b	30	4b	50
CH_3	C_6H_5	C_6H_5	C_6H_4Br	3c	25	4c	50
CH_3	C_6H_5	C_6H_4F	C_6H_5	3d	15	4d	60
C_6H_5	C_6H_5	C_6H_5	C_6H_4Cl	3e	20	4e	50
CH_3	CH_3	C_6H_5	C_6H_5			4f	80
CH_3	C_6H_5	CH_3	C_6H_5	3f	15	a)	
CH_3	C_6H_5	CH_3	C_6H_4F	3g	25	a)	
CH_3	C_6H_5	CH_3	C_6H_4Cl	3h	40	a)	
CH_3	C_6H_5	CH_3	C_6H_4Br	3i	25	a)	

a) After the chromatographic separation only hydrolysis products 5,6,7 could be isolated

property of the 4-amino-4,5-dihydro-imidazole ring system and was already observed for other differently substituted 4-amino-imidazolines.[1,4]

The structure of compounds **4a–f** was inferred from analytical, IR, and ^1H NMR data. Conclusive evidence was given by mass spectrometry.

The mass spectra of compounds **4a–f** show a weak molecular ion and the ions associated to the fragmentation pattern depicted in Scheme 3.[5] The base peak is always due to the ion deriving from fragmentation b; the loss of morpholine (process a) is probably due to a McLafferty type mechanism.

Enamine **1d** which has one hydrogen atom at the β position reacts with the N-chloro-N'-benzoyl-amidine **2a** in a different way affording, after chromatographic separation, a mixture of N-benzoyl-benzamidine **8** and 2-chloro-2-phenyl-acetaldehyde **9** (hydrolysis product).

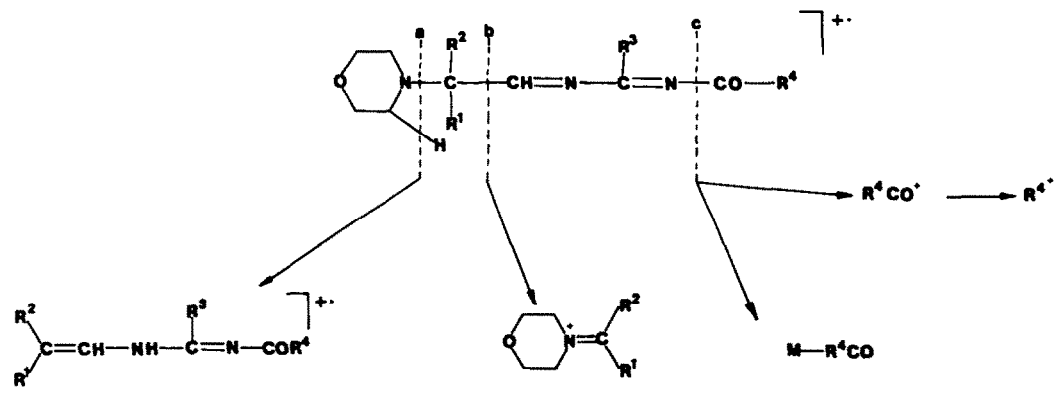
DISCUSSION

The proposed mechanism of this reaction is depicted in Scheme 5 and parallels the mechanism already discussed for the reaction of enamines with N-chloro-N'-aryl-amidines.[2]

The chloroimmonium ion **10** which arises through an electrophilic attack of the N-haloamidine upon the enamine system evolves through nucleophilic attack of the anion **11** leading to the labile intermediate **12** from which imidazolines **3** are formed through cyclization with HCl elimination or compound **4** through a rearrangement of the amino group.

However, in this case, the cyclization of intermediate **12** to imidazoline ring appears to be less favoured with respect to that observed for the N-aryl derivatives.

Indeed, in the present case the open chain compounds **4** are always formed as the main products (Table 1)



Scheme 3. Mass fragmentation pattern of compounds **4a–g**.

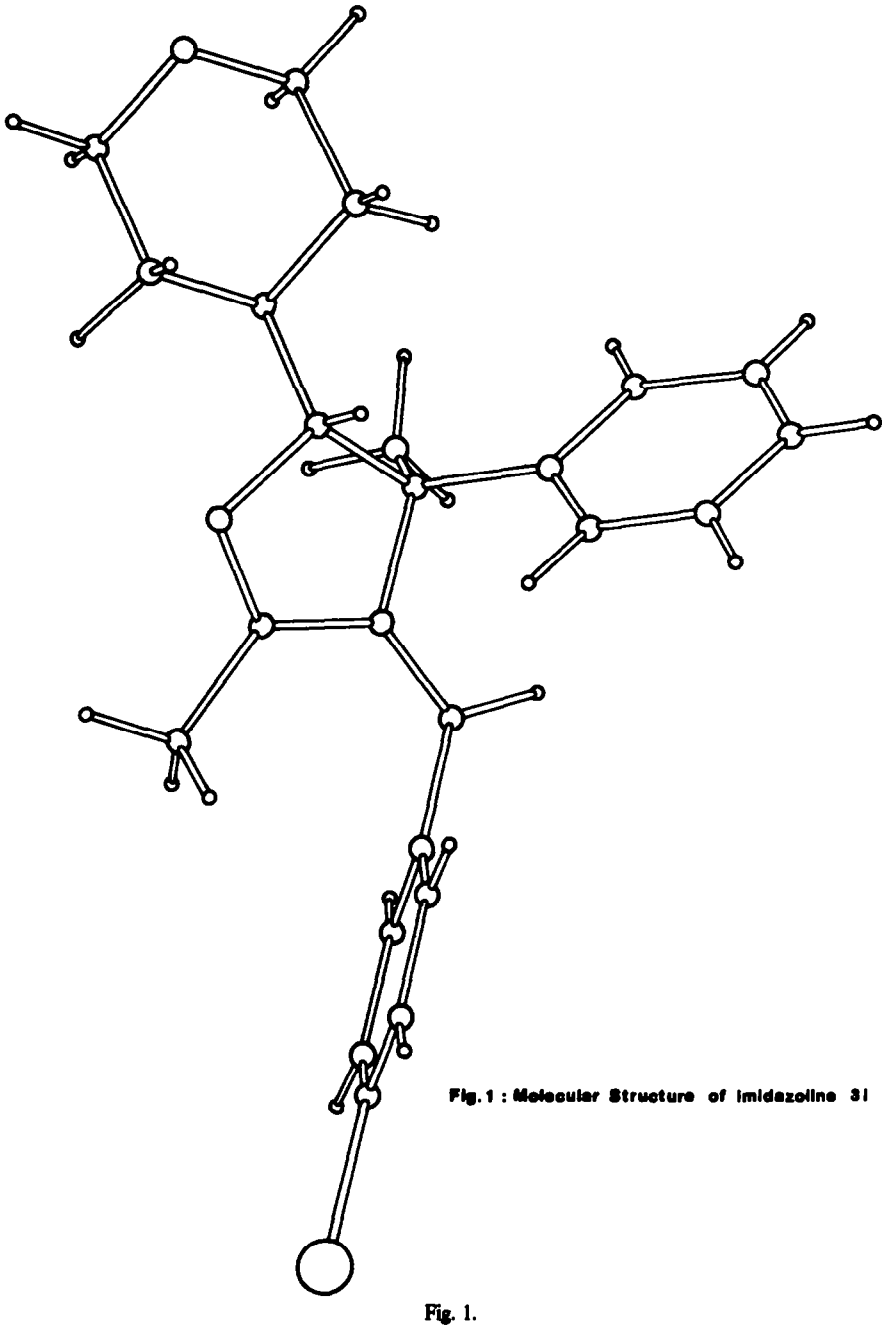


Fig. 1 : Molecular Structure of Imidazoline 3l

Fig. 1.

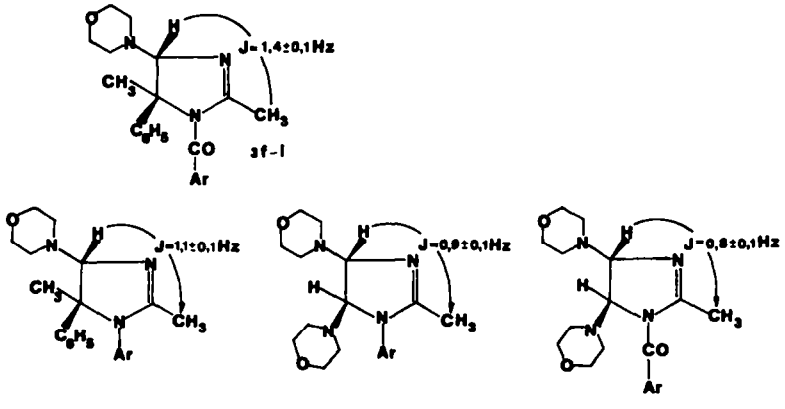
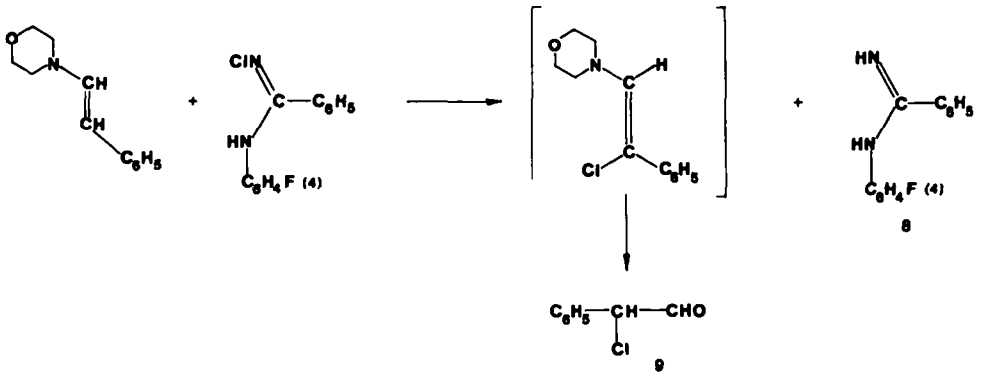
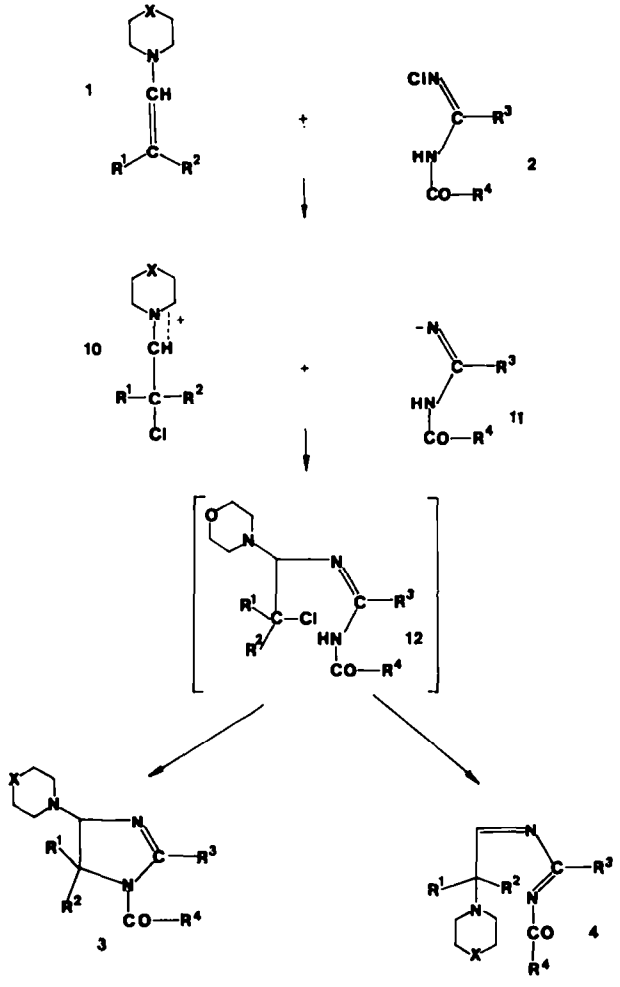


Fig. 2.



Scheme 4.



Scheme 5.

whereas from the reaction of the same enamines 2 and N-aryl-N'-chloroamidines (Scheme 1) the *imidazolines* were always obtained as the principal reaction products.

These results are rationalized by taking into account the lower nucleophilicity of the amide N atom which opposes the cyclisation process making easier the rearrangement to amidines 4. In good agreement with the above, from the intermediate derived from enamine 1c in which two Me groups lower the reactivity of the quaternary carbon atom, only 4f was obtained with excellent yields.

In the case of reaction involving enamine 1d, failure to obtain products derived from intermediate 12 can be explained by the reduced nucleophilicity of anion 11. The deprotonation of the immonium ion 10 becomes in this case the main process.

Table 2.

Compound	m.p.	Cryst. solvent	Found			Formula	Required			IR	^{1}H NMR ($CDCl_3$, δ from TMS)
			C	H	N		C	H	N	Nujol (C=O)	
3a	192°	isopropylether	73.0	5.7	9.3	$C_{27}H_{26}FN_3O_2$	73.1	5.9	9.5	1660	1.98(s, 3H, $-CH_3$); 2.84(m, 4H, $-CH_2-N-CH_2-$); 3.75(m, 4H, $-CH_2-O-CH_2-$); 4.74(s, 1H, H_4); 6.55-7.68(m, $14H_{arom}$)
3b	191°	isopropylether	70.35	5.9	9.15	$C_{27}H_{26}ClN_3O_2$	70.5	5.7	9.1	1650	1.92(s, 3H, $-CH_3$); 2.8(m, 4H, $-CH_2-N-CH_2-$); 3.74(m, 4H, $-CH_2-O-CH_2-$); 4.71(s, 1H, H_4); 6.9-7.65(m, $14H_{arom}$)
3c	200°	isopropylether + benzene	64.0	5.1	8.15	$C_{27}H_{26}BrN_3O_2$	64.3	5.2	8.3	1650	1.92(s, 3H, $-CH_3$); 2.8(m, 4H, $-CH_2-N-CH_2-$); 3.68(m, 4H, $-CH_2-O-CH_2-$); 4.7(s, 1H, H_4); 7.0-7.6(m, $14H_{arom}$)
3d	184°	isopropylether	72.8	6.2	9.3	$C_{27}H_{26}FN_3O_2$	73.1	5.9	9.5	1650	1.92(s, 3H, $-CH_3$); 2.8(m, 4H, $-CH_2-N-CH_2-$); 3.7(m, 4H, $-CH_2-O-CH_2-$); 4.66(s, 1H, H_4); 6.55-7.6(m, $14H_{arom}$)
3e	125°	isopropylether	73.5	5.6	8.15	$C_{32}H_{28}ClN_3O_2$	73.6	5.4	8.05	1660	2.48(m, 4H, $-CH_2-N-CH_2-$); 3.3(m, 4H, $-CH_2-O-CH_2-$); 5.48(s, 1H, H_4); 6.7-7.8(m, $20H_{arom}$)
4a	135°	ethanol	73.0	5.9	9.3	$C_{27}H_{26}FN_3O_2$	73.1	5.9	9.5	1625	1.55(s, 3H, $-CH_3$); 2.6(m, 4H, $-CH_2-N-CH_2-$); 3.68(m, 4H, $-CH_2-O-CH_2-$); 6.75-8.0(m, -OH-, $14H_{arom}$)
4b	143°	ethanol	70.8	5.6	8.9	$C_{27}H_{26}ClN_3O_2$	70.5	5.7	9.1	1625	1.56(s, 3H, $-CH_3$); 2.64(m, 4H, $-CH_2-N-CH_2-$); 3.7(m, 4H, $-CH_2-O-CH_2-$); 7.0-8.1(m, -OH-, $14H_{arom}$)
4c	145°	ethanol	63.95	5.3	7.95	$C_{27}H_{26}BrN_3O_2$	64.3	5.2	8.3	1620	1.56(s, 3H, $-CH_3$); 2.65(m, 4H, $-CH_2-N-CH_2-$); 3.72(m, 4H, $-CH_2-O-CH_2-$); 7.05-8.1(m, -OH-, $14H_{arom}$)
4d	141°	acetonitril	73.0	6.2	9.25	$C_{27}H_{26}FN_3O_2$	73.1	5.9	9.5	1625	1.58(s, 3H, $-CH_3$); 2.64(m, 4H, $-CH_2-N-CH_2-$); 3.71(m, 4H, $-CH_2-O-CH_2-$); 6.7-8.2(m, -OH-, $14H_{arom}$)
4e	166°	isopropylether	74.0	5.6	8.2	$C_{32}H_{28}ClN_3O_2$	73.6	5.4	8.05	1625	2.34(m, 4H, $-CH_2-N-CH_2-$); 3.7(m, 4H, $-CH_2-O-CH_2-$); 7.0-8.1 (m, -OH-, $19H_{arom}$)
4f	101°	isopropylether	72.5	6.7	11.8	$C_{22}H_{25}N_3O_2$	72.7	6.9	11.6	1630	1.25(s, 6H, $-CH_3$); 2.88(m, 4H, $-CH_2-N-CH_2-$); 3.72(m, 4H, $-CH_2-O-CH_2-$); 7.3-8.4(m, -OH-, $10H_{arom}$)

Table 3.

Compound	R^4	m.p.	Crist. solvent	Found			Formula	Required			IR	^{1}H NMR ($CDCl_3$, δ from TMS)
				C	H	N		C	H	N	Nujol(C=O)	
3f	C_6H_5	124°	isopropylether	72.6	6.7	11.45	$C_{22}H_{25}N_3O_2$	72.7	6.9	11.6	1630-1660	1.85[s, 3H, CH_3(5)]; 1.85[d, 3H, CH_3(2), $J_{CH_3(2)-H_4}$=1.4Hz]; 2.64(m, 4H, $-CH_2-N-CH_2-$); 3.78 (m, 4H, $-CH_2-O-CH_2-$); 4.39[q, 1H, H_4, $J_{H_4-CH_3(2)}$= 1.4Hz]; 7.22(s, 5H$_{arom}$); 7.35(s, 5H$_{arom}$)
3g	$C_6H_4F(4)$	151°	isopropylether	68.95	6.3	10.8	$C_{22}H_{24}FN_3O_2$	69.3	6.3	11.0	1630-1660	1.85[s, 3H, CH_3(5)]; 1.95[d, 3H, CH_3(2), $J_{CH_3(2)-H_4}$=1.4Hz]; 2.65(m, 4H, $-CH_2-N-CH_2-$); 3.71 (m, 4H, $-CH_2-O-CH_2-$); 4.61[q, 1H, H_4, $J_{H_4-CH_3(2)}$= 1.4Hz]; 6.85-7.7(m, 9H$_{arom}$)
3h	$C_6H_4Cl(4)$	141°	isopropylether	66.2	6.1	10.5	$C_{22}H_{24}ClN_3O_2$	66.4	6.1	10.6	1615-1660	1.85[s, 3H, CH_3(5)]; 1.98[d, 3H, CH_3(2), $J_{CH_3(2)-H_4}$=1.4Hz]; 2.68(m, 4H, $-CH_2-N-CH_2-$); 3.75 (m, 4H, $-CH_2-O-CH_2-$); 4.48[q, 1H, H_4, $J_{H_4-CH_3(2)}$= 1.4Hz]; 7.34(s, 4H$_{arom}$); 7.4(s, 5H$_{arom}$)
3i	$C_6H_4Br(4)$	149°	isopropylether	59.65	5.50	9.35	$C_{22}H_{24}BrN_3O_2$	59.7	5.45	9.5	1630-1660	1.82[s, 3H, CH_3(5)]; 1.95[d, 3H, CH_3(2), $J_{CH_3(2)-H_4}$=1.4Hz]; 2.62 (m, 4H, $-CH_2-N-CH_2-$); 3.66 (m, 4H, $-CH_2-O-CH_2-$); 4.4[q, 1H, H_4, $J_{H_4-CH_3(2)}$= 1.4Hz]; 7.1-7.65(m, 9H$_{arom}$)

Table 4.

Chloroamidines reacted	2-Amino-propionaldehyde	Yield %	m.p.	N-acetyl benzamides	Yield %	m.p.	Benzamides	Yield %	m.p.
2f	5	35	92°(Lit.[7] 92°)	6a	15	118°(Lit.[10] 117°)	7a	8	129°(Lit.[8] 129°)
2g	5	38		6b	22	110°(109°)[a]	7b	10	156°(Lit.[9] 157,5°)
2h	5	36		6c	20	143°(143°)[a]	7c	10	178°(Lit.[8] 179°)
2i	5	40		6d	24	150°(150°)[a]	7d	12	189°(Lit.[8] 189°)

[a] Prepared as described in ref 10 for N-acetyl-benzamide

EXPERIMENTAL

M.ps were taken with a Büchi apparatus and are not corrected. ^{1}H NMR spectra were recorded with Varian HA-100 and Varian A-60 instruments (Me_4Si as internal standard). IR Spectra were recorded with a Beckmann Acculab 4 spectrometer and Mass spectra with a Perkin Elmer 270 mass spectrometer at an electron energy of 80 eV. The direct insertion technique was used with a probe temp. of 130–170° and an ion source temperature of 150–200°.

Enamines and halo-amidines. The enamines[6] and the N-chloro-N'-aroyl-amidines[4] employed in this work are known compounds and were prepared according to described methods.

Reaction of enamines with N-*chloro-benzamidines* **2a–i.** A soln of 20 mmol of enamine dissolved in anhyd $CHCl_3$ (50 ml) containing an equimolar amount of pyridine was refluxed for 2–3 hr with an equimolar amount of N-halo-amidine in anhyd $CHCl_3$ (25 ml). The mixture was analyzed by tlc until no more haloamidine was detectable, then the crude mixture was cooled and washed with a sat. $NaHCO_3$aq. The organic layer, dried over molecular sieves, was freed from the solvent *in vacuo* and chromatographed on a silica gel column (Kieselgel 60, Merck). The column was eluted with benzene: EtOAc (90:10) or ethyl ether at a flow rate of 3 ml/min yielding progressively the amidines **4** and the imidazolines **3**.

The isolated product data together with reaction and isolation parameters are given in Table 2.

Reaction of enamine **1a** *with* N-*chloro-acetamidines* **2f–i.** The reaction was carried out and worked up in the same manner as for **2a–e**. The mixtures were chromatographed on a silica gel column containing 50 g of silica gel per g of crude mixture at a flow rate of 2 ml/min. The eluent employed for the complete separation of the mixtures was benzene with an increasing amount of EtOAc followed by EtOAc with an increasing amount of EtOH.

The following compounds were progressively eluted: **5**, **6a–d**, **7a–d** and **3f–i**.

The physicochemical properties of **3f–i** are collected in Table 3. The other isolated products are set forth in Table 4.

Reaction of β-morpholino styrene **1d** *with* N-*chloro*-N'-*benzoyl-amidine* **2a.** A soln of **1d** (1.89 g) in dry CH_2Cl_2 (100 ml) was added of pyridine (0.8 g) and **2a** (2.58 g). The mixture was refluxed until no more N-chloro-amidine was detectable by tlc (*ca.* 90 min), then the solvent was evaporated under reduced pressure and 2 g of the crude residue were chromatographed on a silica gel column containing 90 g of solid phase. Employing benzene–EtOAc 95:5 as eluent two main fractions were isolated. The first (0.4 g) proved to be (IR, NMR compared with an authentical sample)[11] **9**, the second (0.7 g) was identical to **8** (m.m.p. and IR).

REFERENCES

[1] L. Citerio, M. L. Saccarello, R. Stradi and B. Gioia, *J. Chem. Soc.* Perkin I (1979). In press.

[2] L. Citerio, D. Pocar and R. Stradi, *Ibid.* Perkin I, 309 (1978).

[3] R. Destro, *Acta Crystall.* (1979). In press.

[4] L. Citerio, M. L. Saccarello and R. Stradi, *Synthesis* (1979). In press.

[5] We would like to thank Dr. B. Gioia for helpful discussion on the analysis of the mass spectra.

[6] R. Stradi, P. Trimarco and A. Vigevani, *J. Chem. Soc.* Perkin I, 1 (1978).

[7] L. Citerio, D. Pocar, R. Stradi and B. Gioia, *Tetrahedron* **35**, 69 (1979).

[8] A. Vogel, *Textbook of Practical Organic Chemistry.* Longman, New York (1978).

[9] G. Lock, *Chem. Ber. Dtsch. Chem. Ges.* **69**, 2253 (1936).

[10] A. W. Titherley and T. H. Holden, *J. Chem. Soc.* **101**, 1880 (1912).

[11] A. Kirrmann, L. Duhamel and P. Duhamel, *Bull. Soc. Chim. Fr.* 1732 (1966).