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N-HALOAMIDINES—III[1]

S-TRIAZINE DERIVATIVES FROM N-HALOBENZAMIDINES AND ENAMINES

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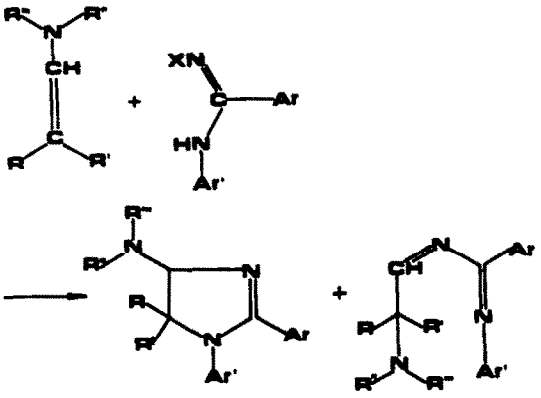
Abstract—The reaction of N-haloamidines with enamines affords 1,4-dihydro-s-triazine derivatives as the main reaction product. The dihydro derivatives are aromatisable through oxidation with chloranil. The mass spectra of the isolated products are discussed in detail.

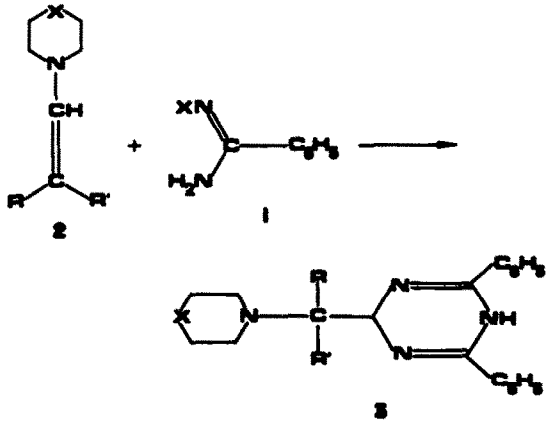
Recently, we reported that N-halo-N′-arylamidines react with enamines derived from aldehydes affording 4,5-dihydro-imidazoles and N-(aminoethylidene)-aryl-amidines derivatives according to Scheme 1.[1]



Scheme 1.

In this paper we wish to report our findings about the reaction of the above enamines with N-halo-N′-unsubstituted-benzamidines.

By reacting N-haloamidines (1) with enamines (2), 1,4-dihydro-s-triazine-derivatives (3) were obtained as the main reaction products (Scheme 2).



Scheme 2.†

†X = O or CH_2 as in Table 1.

The structure of compounds 3 was inferred from analytical, IR and ^{1}H NMR data. Conclusive evidence was given by mass spectrometry. The fragmentation pattern of compounds 3a–h is depicted in Scheme 3.

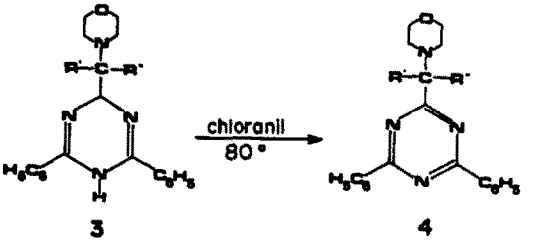
The mass spectral abundance data for selected peaks for 1,4-dihydro-s-triazines isolated are given in Table 1.

The molecular ion is generally absent but the molecular weight is confirmed by the presence of the M + 1 and in some cases also by the M − 1 ions. The main fragmentation leads to the formation of the ion **b** which is always the base peak of the spectrum except when R′ = R″ = Ph (4e). When R′ = C_6H_5 and R″ = C_6H_5 or alkyl the ion **b** gives rise to ion b_1 through amine elimination accompanied by hydrogen rearrangement. The ion **b** arising from compound 4e loses C_6H_4 (76) giving rise to the ion *m/e* 176 as confirmed by the corresponding metastable peak.

The same fragmentation path leading to ion **b** can also give fragments **c** and **d**.

Finally fragment **a** arising from the molecular ion through amine elimination and fragments **e** and **f** arising from the dihydro-triazine ring cleavage are always present in the spectra.

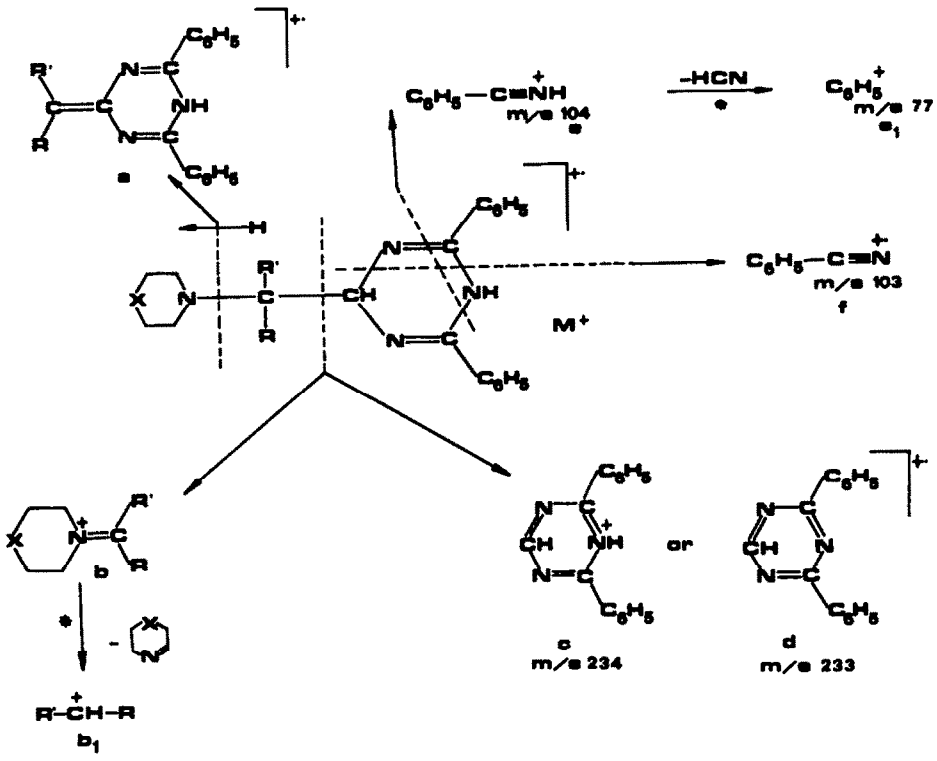
In good agreement with their structure, compounds 3 were easily converted into the corresponding s-triazine derivatives by reaction with chloranil in boiling benzene.



In this case, too, the fragmentation pattern (Scheme 4) confirms the assigned structure. The detailed fragmentation data are given in Table 2.

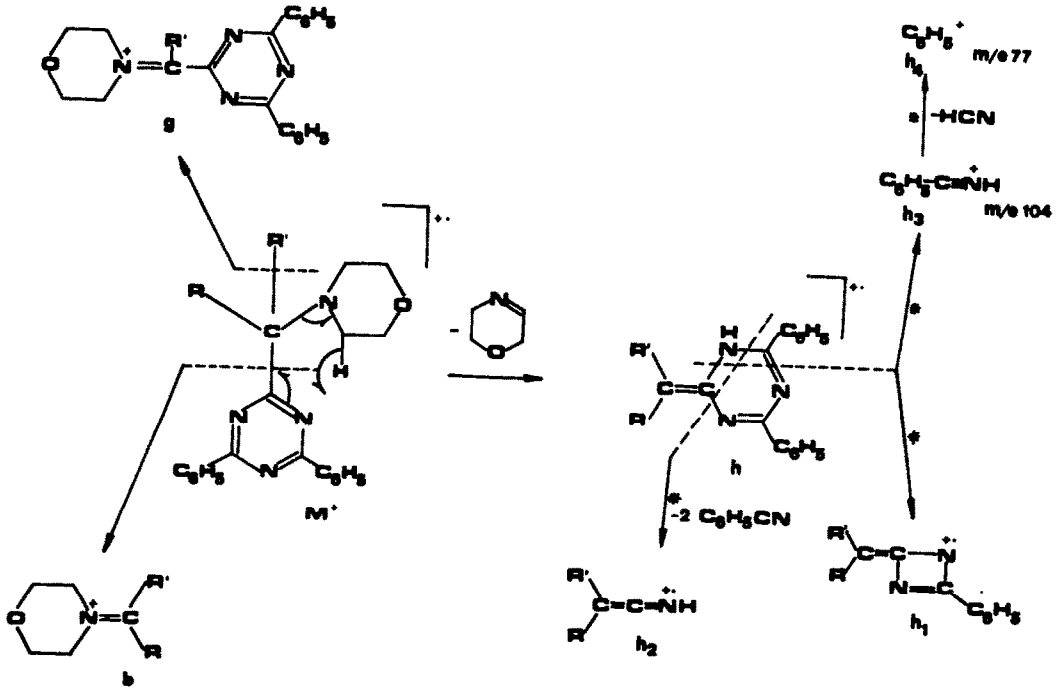
The molecular ion is absent or of small intensity, but the molecular weight is confirmed by the presence of M + 1 ion.

The main fragmentation pathway is a McLafferty rearrangement involving the hydrogen atom in α position with respect to the amine nitrogen. The ion **h** so formed, which is in most cases the base peak, loses C_6H_5—CNH or two molecules of Ph–CN giving rise to ions h_1 and h_2 respectively. The last two fragmentation processes are



Scheme 3.†

†X = O or CH_2 as in Table 1.



Scheme 4.

Table 1.

Compound 3	R	R'	X	M + 1	M^+	M - 1	a	b	b_1	c	d	e	e_1	f	b-76
a	CH_3	CH_3	O	363(0.15)	362(-)	361(0.04)	275(1)	128(100)	-	234(1)	233(2)	104(11)	77(5)	103(7)	-
b	C_2H_5	C_2H_5	O	391(0.1)	390(-)	389(-)	303(0.4)	156(100)	-	234(2)	233(3)	104(16)	77(7)	103(10)	-
c	H	C_6H_5	O	411(0.15)	410(0.05)	409(-)	323(2)	176(100)	91(9)	234(7)	233(3)	104(19)	77(7)	103(7)	-
d	CH_3	C_6H_5	O	425(0.1)	424(-)	423(0.02)	337(4)	190(100)	105(14)	234(6)	233(2)	104(14)	77(12)	103(10)	-
e	C_6H_5	C_6H_5	O	487(0.4)	486(-)	485(-)	399(1)	252(26)	167(88)	234(11)	233(61)	104(23)	77(18)	103(100)	176(32)
f	$-(CH_2)_5-$		O	403(0.1)	402(-)	401(0.03)	315(1)	168(100)	-	234(6)	233(3)	104(11)	77(4)	103(7)	-
g	CH_3	CH_3	CH_2	361(0.15)	360(-)	359(0.05)	275(0.4)	126(100)	-	234(1)	233(2)	104(10)	77(5)	103(7)	-

Table 2.

Compound 4	R	R'	M + 1	M^+	M - 1	b	g	h	h_1	h_2	h_3	h_4	h-CH_3
a	CH_3	CH_3	361(0.25)	360(-)	359(0.2)	128(43)	345(1)	275(100)	171(-)	69(9)	104(56)	77(16)	260(14)
b	C_2H_5	C_2H_5	389(2)	388(-)	387(0.6)	156(41)	359(28)	303(73)	199(-)	97(-)	104(100)	77(32)	288(82)
c	H	C_6H_5	409(2)	408(0.1)	407(0.3)	176(17)	-	323(100)	219(9)	117(37)	104(60)	77(19)	-
d	CH_3	C_6H_5	423(0.25)	422(-)	421(0.1)	190(21)	-	337(100)	233(4)	131(22)	104(61)	77(22)	322(1)
e	C_6H_5	C_6H_5	485(0.1)	484(-)	483(-)	252(21)	407(0.3)	399(100)	295(9)	193(27)	104(45)	77(20)	-
f	$-(CH_2)_5-$		401(0.3)	400(0.1)	399(0.2)	168(27)	-	315(100)	211(0.5)	109(1)	104(27)	77(7)	-

not so important when R′ = R″ = alkyl. The fragment ion **h** also gives rise to the ion h_3 (*m/e* 104).

Another noteworthy fragmentation process leads to the ion **b** which was already observed in the fragmentation of compounds **4**.

Finally, the loss of R′ or R″ from the molecular ion gives rise to ion **g** which is abundant only when R′ = alkyl.

DISCUSSION

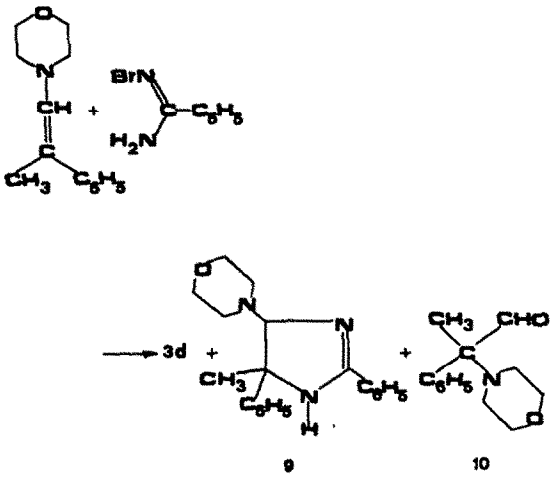
The formation of the dihydro-triazine derivatives probably occurs according the mechanism depicted in Scheme 5.

The first stage is the direct electrophylic attack of the N-halo-amidine upon the unsaturated enamine system. An intermediate chloro-immonium ion (**5**) is thus formed which evolves through the nucleophylic attack of amidine anion (**6**) leading to intermediate (**7**) which rearranges to **8**. The formation of the triazine ring is likely to occur through a subsequent attack by the anion (**6**) upon cationic intermediate (**8**) followed by ammonia elimination.

The formation of intermediate **7** parallels the previously discussed mechanism of the reaction between enamines and N-chloro-N′-arylbenzamidines.[1] However, the aryl substituted analogue of **7** evolves preferably either to a 4,5-dihydro-imidazole derivative by cyclization or rearranges to the aryl substituted analogue of **8** which, by simple deprotonation, gives N-(amino-ethylidene)-benzamidine (Scheme 1) probably because of the higher steric hindrance preventing the formation of the triazine ring.

The cyclization to imidazole ring is possible also from intermediate **7** even if as a secondary process. Actually, in the case of the reaction between N-bromo-benzamidine and 2-phenyl-1-morpholino-propene, besides the dihydro-triazine (**3d**), 2,5(4) - diphenyl - 4(5) - morpholino - 5(4) - methyl - 4,5 - dihydro - imidazole (**9**) was isolated in low yield.[a]

From the above reaction the 2-morpholino-2-phenyl-propionaldehyde (**10**) was also isolated in low yield. This product probably arises from the hydrolysis of the haloimonium ion (**5**)[2] owing to traces of water present in the reaction system.

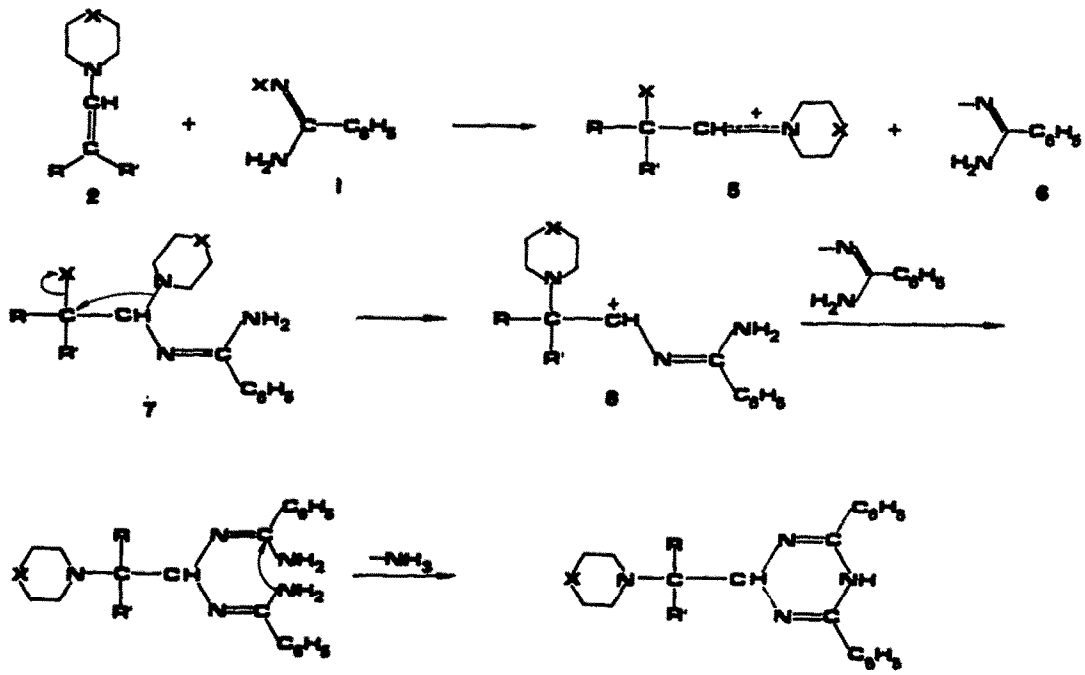


[a]Traces of dihydro-imidazoles are detectable in all crude reaction mixtures. However, no effort was made to isolate these compounds in a pure form.

†X = O or CH_2 as in Table 1.

EXPERIMENTAL

M.ps were taken with a Büchi apparatus and are not corrected. ^{1}H NMR spectra were recorded with both Varian HA-100 and Varian A-60 instruments (Me_4Si as internal standard). IR Spectra were recorded with a Beckmann Acculab 4 spectrometer and



Scheme 5.†

Table 3.

Compound 3	N-halo-amidine reacted*	Reaction time (h)	Reac. temp. °C	m.p.	Crist. solvent	Yield** %	Found C	Found H	Found N	Formula	Required C	Required H	Required N	IR Nujol (cm⁻¹)	¹H NMR ($CDCl_3$, δ from TMS)
a	N-bromo	0.5	20	186°	ethanol	35	72.7	7.4	13.3	$C_{22}H_{26}N_4O$	72.9	7.2	13.45	3350	1.15 s (CH_3), 2.6 t $(CH_2)_2N$, 3.8 t $(CH_2)_2O$, 5.2 s (CH), 7.2-7.6 m and 7.9-8.3 m (C_6H_5)
b	N-bromo	0.5	20	150°	isopropylether + pentane	45	73.6	7.9	14.15	$C_{24}H_{30}N_4O$	73.8	7.7	14.3	3310	1.0 t (CH_3), 1.85 q (CH_2), 2.8 t $(CH_2)_2N$, 3.72 t $(CH_2)_2O$, 5.15 s (CH), 7.20-7.50 m and 7.90-8.20 m (C_6H_5)
c	N-iodo	0.5	25	206°	isopropylether	50	75.9	6.5	13.4	$C_{26}H_{26}N_4O$	76.1	6.4	13.6	3380-3420	2.6 t $(CH_2)_2N$, 3.78 m $(CH_2)_2O$ and (CH-Ph), 5.80 d [6.5 Hz (N-CH-N)], 7.2-8.1 m (C_6H_5)
d	N-chloro	4	40	191°	isopropylether	20	76.2	6.7	13.1	$C_{27}H_{25}N_4O$	76.4	6.6	13.2	3410	2.65 s (CH_3), 2.80 m $(CH_2)_2N$, 3.80 t $(CH_2)_2O$, 5.70 s (CH), 7.10-8.10 m (C_6H_5)
e	N-chloro	24	40	191°	isopropylether + benzene	35	78.8	6.1	11.3	$C_{32}H_{30}N_4O$	79.0	6.2	11.5	3400	2.5 m $(CH_2)_2N$, 3.8 m $(CH_2)_2O$, 6.77 s (CH), 7.0-8.1 m (C_6H_5)
f	N-chloro	24	40	81°	cicloexane	30	74.4	7.4	13.6	$C_{25}H_{30}N_4O$	74.6	7.5	13.9	3365	1.35-1.95 m $(CH_2)_5$, 2.92 t $(CH_2)_2N$, 3.28 t $(CH_2)_2O$, 5.12 s (CH), 7.3-7.6 m and 7.85-8.15 m (C_6H_5)
g	N-bromo	0.5	20	176°	isopropylether + ethanol	24	76.4	7.9	15.4	$C_{23}H_{28}N_4$	76.6	7.8	15.5	3350	1.13 s (CH_3), 1.58 m $(CH_2)_3$, 2.68 m $(CH_2)_2N$, 5.21 s (CH), 7.20-8.60 m (C_6H_5)

* The reaction course is almost the same with the three N-halo-benzamidines. Here is reported the N-halo-amidine which gave the higher yield of 3.

** Yields of crude product after chromatographic separation.

Table 4.

Compound 4	m.p.	Crist. solvent	Yield %	Found C	Found H	Found N	Formula	Required C	Required H	Required N	^{1}H NMR ($CDCl_3$, δ from TMS)
a	117°	isopropylether	85	73.2	7.0	15.6	$C_{22}H_{24}N_4O$	73.3	6.7	15.5	1.7 s(CH_3), 2.7 t $(CH_2)_2N$, 3.71 t $(CH_2)_2O$, 7.4-7.9 m and 8.2-8.5 m (C_6H_5)
b	143°	isopropylether	80	73.9	7.2	14.2	$C_{24}H_{28}N_4O$	74.2	7.3	14.4	0.87 t(CH_3), 2.12 m (CH_2), 2.58 t $(CH_2)_2N$, 3.60 t $(CH_2)_2O$, 7.3-7.55 m and 8.18-8.4 m (C_6H_5)
c	167°	isopropylether + ethanol	80	76.4	6.1	13.8	$C_{26}H_{24}N_4O$	76.4	5.9	13.7	2.65 m $(CH_2)_2N$, 3.80 t $(CH_2)_2O$, 4.78 s (CH), 7.25-7.90 m and 8.25-8.45 m (C_6H_5)
d	163°	isopropylether	85	77.0	5.9	13.3	$C_{27}H_{26}N_4O$	76.7	6.2	13.3	2.0 s(CH_3), 2.68 $(CH_2)_2N$, 3.79 t $(CH_2)_2O$, 7.2-7.8 m and 8.55-8.75 m (C_6H_5)
e	232°	isopropylether + ethanol	80	79.1	5.9	11.5	$C_{32}H_{28}N_4O$	79.3	5.8	11.6	2.55 t $(CH_2)_2N$, 3.90 t $(CH_2)_2O$, 7.10-7.75 m and 8.50-8.70 m (C_6H_5)
f	166°	iscpropylether	75	74.9	7.2	13.8	$C_{25}H_{28}N_4O$	75.0	7.0	14.0	1.2-2.8 m $(CH_2)_5$, 2.65 t $(CH_2)_2N$, 3.7 t $(CH_2)_2O$, 7.35-7.75 m and 8.65-8.85 m (C_6H_5)

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°.

The enamines,[3] the N-chloro-,[4] the N-bromo-[5] and the N-iodo-benzamidines[6] employed in this work are known compounds and were prepared according to the literature methods.

Reactions of enamines with N-halo-amidines. A soln of 20 mmol of enamine dissolved in anhyd $CHCl_3$ (50 ml) containing an equimolar amount of pyridine was reacted at the temp. reported in Table 3 with an equimolar amount of N-halo-amidine in anhyd $CHCl_3$ (25 ml). The mixture was analyzed by tlc until no more halo-amidine was detectable, then the crude mixture was cooled and washed with a saturated $NaHCO_3$ aq. The organic layer, dried over $MgSO_4$ was freed from the solvent under *vacuo* and chromatographed on a silica column (Kieselgel 60, Merck). The column was eluted with benzene–THF (80–20) at a flow rate of 3 ml/min yielding as the main product the dihydro-s-triazines **3a–g**. The isolated products data together with reaction and isolation parameters are given in Table 3.

Oxidation of dihydro-s-triazines **3** *to s-triazines* **4.** To a soln of 5 mmol of **3** dissolved in anhyd benzene (30 ml), an equimolar amount of chloranil was added. The mixture was then refluxed until no more dihydro-compound was detectable by tlc (*ca* 2 hr). The cooled soln was stirred for 30 min with a 5% $NaHSO_3$ aq, the organic layer was separated, dried over $MgSO_4$ and freed from the solvent at reduced pressure. The crude residue was purified by chromatography on a silica gel column. The data of the isolated products are given in Table 4.

Isolation of dihydro-imidazole **9** *and* 2 - *morpholino* - 2 - *phenyl* - *propionaldehyde* **10.** 4.0 g of the crude mixture obtained from 1-morpholino-2-phenyl-propene and N-bromo-benzamidine were chromatographed on a silica column containing 200 g of kieselgel 60 (Merck). The column was eluted with benzene–ethyl acetate (80–20) at a flow rate of 2 ml/min.

The following products were progressively eluted: 2 - morpholino - 2 - phenyl - propionaldehyde **10** (0.4 g), m.p. 92°C,[7] ^{1}H NMR ($CDCl_3$): 1.5 (3 H, s, Me); 2.48 (4 H, m, $(CH_2)_2N$); 3.78 (4 H, t, $(CH_2)_2O$); 7.20–7.75 (5 H, m, aromatics); 9.3 (1 H, s, CHO). (Found: C, 71.4; H, 7.85; N, 6.25. Calc. for $C_{13}H_{17}NO_2$: C, 71.25; H, 7.75; N, 6.4%). Dihydro-imidazole **9** (0.8 g), oil. ^{1}H NMR ($CDCl_3$); 1.81 (3 H, s, Me); 2.75 (4 H, m, $(CH_2)_2N$); 3.71 (4 H, t, $(CH_2)_2O$); 4.77 (1 H, s, CH); 7.0–8.2 (11 H, aromatics and NH). MS: 322 (7), M + 1; 202 (100); 105 (39); 99 (79); 86 (34); 77 (41); 71 (39) and the dihydro-s-triazine **3d** (1.9 g).

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