2-Imidazolines. Part 2.[1] Pyrolysis of 1-Acyl-4,5-diamino-4,5-dihydroimidazoles: a Novel Pyrimidine Synthesis

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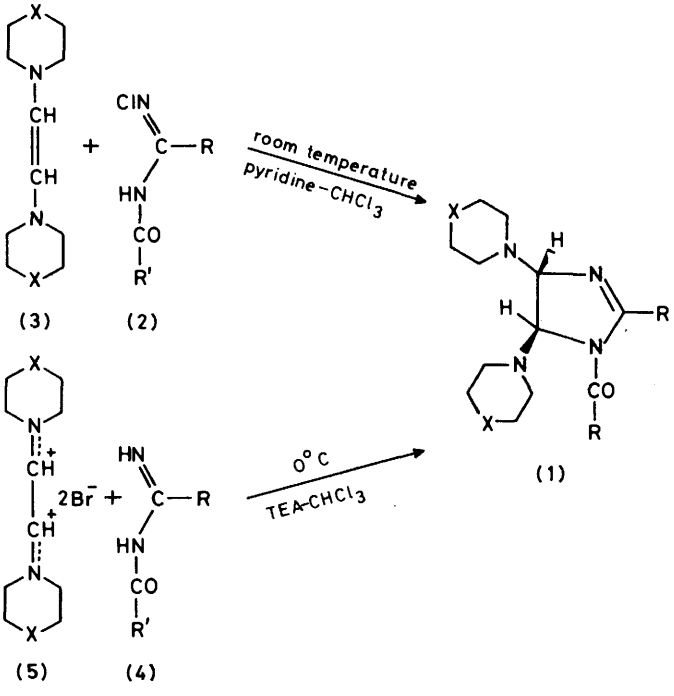
1-Acyl-2-phenyl- (or methyl-)4,5-diamino-4,5-dihydroimidazoles (1), when heated in refluxing xylene, afford 2,4-disubstituted-5,6-diaminopyrimidines in good yield. The relative position of the substituent at C-2 or C-4 of the pyrimidine ring depends on the basicity of the amino-group and the nature of the substituent at C-2 of the imidazole ring. The mechanism of the ring expansion is discussed.

RECENTLY, we reported the synthesis of 1-acyl-4,5-diamino-4,5-dihydroimidazoles (1) from *N*-chloro-*N'*-acylamidines (2) and 1,2-diaminoethylenes (3) [2] or, more practicably, from *N*-acylamidines (4) and the di-immonium dibromide (5) [1] (Scheme 1).



SCHEME 1

In this paper we report the results of our study on the behaviour of the imidazolines (1) under mild pyrolytic conditions.

RESULTS

1-Acyl-4,5-diamino-4,5-dihydroimidazoles (1a—o) undergo a ring expansion reaction to pyrimidine derivatives (6a—g) when refluxed for several hours in dry xylene.[3]

As shown in Scheme 2, the substituents R and R' on the imidazoline ring play an important role in determining the course of the reaction. When R = R' = Ar and the amino-residue is a morpholino-group (X = O) the corresponding pyrimidines (6a—e) were obtained with elimination of H_2O, whereas for imidazolines in which R' = OMe, OCH_2-Ph, or OPh (1f—h) the ring expansion does not proceed with elimination of water but by loss of a molecule of R'OH. 2-Aryl-4-hydroxy-5,6-diaminopyrimidine (6f) is thus formed. The above pyrolytic conversion was accelerated by adding a catalytic amount of triethylammonium chloride.

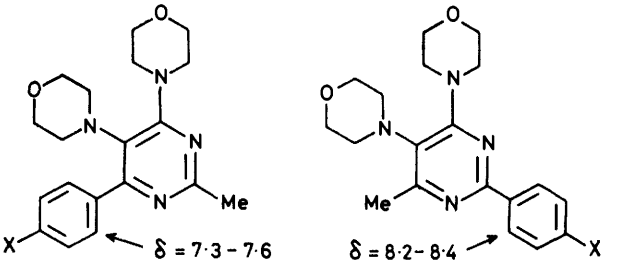
Somewhat surprisingly, under the same conditions, the imidazolines (1i—l) gave an almost equimolecular mixture of the isomeric pairs (6g, h), (6i, j), (6k, l), and (6m, n), respectively.

The two isomers are easily distinguishable by ^1H n.m.r. spectroscopy because of the large difference between the chemical shifts of the *ortho*-hydrogens of the aryl group at C-2 of the pyrimidine ring compared with the same hydrogens of the aryl group at C-4.

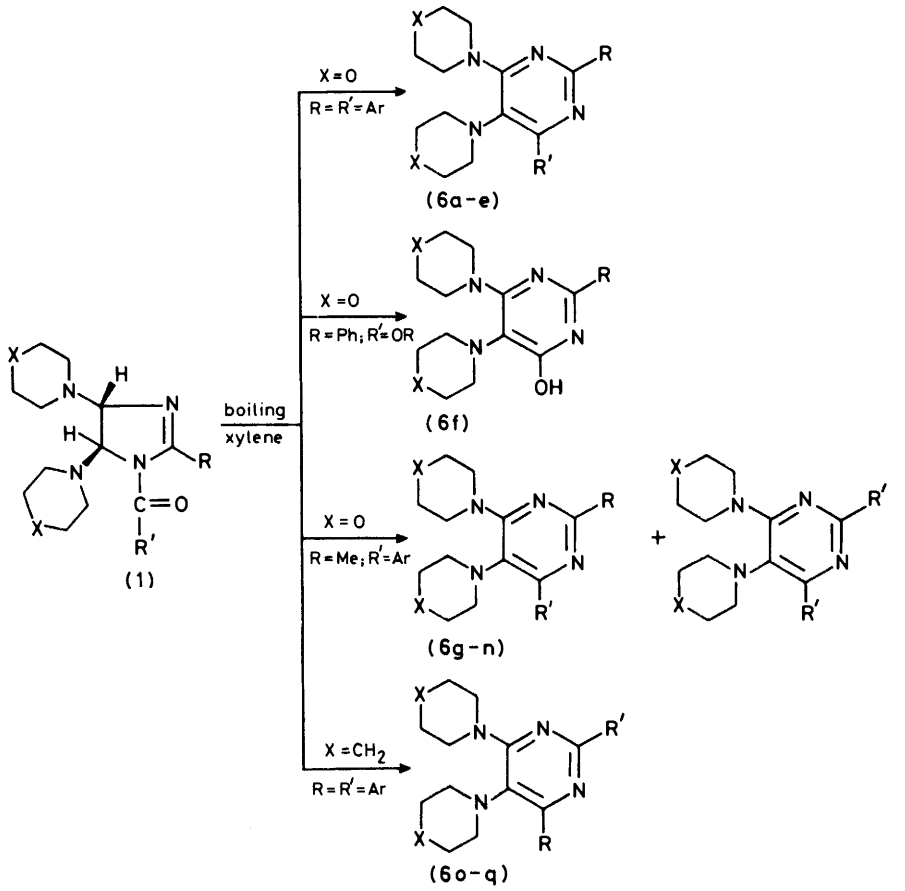
Other physico-chemical properties are very similar and no efforts were made to obtain pure samples of each isomer, except for the isomeric pair (6i, j) which was resolved with several chromatographic separations.

It is interesting to observe that 1-acetyl-2-phenyl-4,5-dimorpholino-4,5-dihydroimidazole (1p), after refluxing in pure xylene for several hours, was recovered unchanged. But in the presence of acidic (Scheme 3) catalysts, pyrimidines (6g and h) were obtained in the same ratio as found for the ring expansion involving imidazoline (1i).

The basicity of the amino-groups also seems to play an important role in the ratio between the components of the isomeric pair. Thus 1-(4-chlorobenzoyl)- and 1-(4-bromobenzoyl)-2-phenyl-4,5-dipiperidinoimidazolines (1o) and (1n)

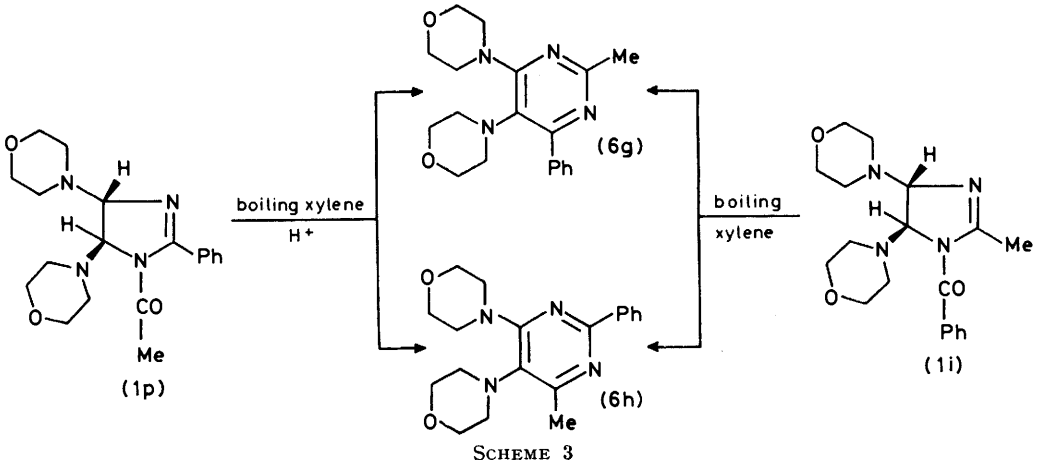


under the usual pyrolytic conditions afforded 2-(4-chlorophenyl)- and 2-(4-bromophenyl)-4-phenyl-5,6-dipiperidinopyrimidines (6q) and (6p) as the sole products of the expansion process.



a; X = O, R = Ph, R′ = Ph
b; X = O, R = Ph, R′ = C_6H_4Me-*p*
c: X = O, R = Ph, R′ = C_6H_4F-*p*
d: X = O, R = Ph, R′ = C_6H_4Br-*p*
e: X = O, R = Ph, R′ = C_6H_4Cl-*p*
f: X = O, R = Ph, R′ = OMe
g: X = O, R = Ph, R′ = OCH_2Ph
h: X = O, R = Ph, R′ = OPh
i; X = O, R = Me, R′ = Ph
j: X = O, R = Me, R′ = C_6H_4F-*p*
k: X = O, R = Me, R′ = C_6H_4Br-*p*
l: X = O, R = Me, R′ = C_6H_4Cl-*p*
m: X = CH_2, R = Ph, R′ = Ph
n: X = CH_2, R = Ph, R′ = C_6H_4Br-*p*
o: X = CH_2, R = Ph, R′ = C_6H_4Cl-*p*

SCHEME 2



SCHEME 3

Pyrimidine derivatives (6a—q)

Compound	R	R′	X	Reaction time/h	Cryst. solvent	M.p. (°C)	Yield (%)	M^+	Found C	Found H	Found N	Formula	Required C	Required H	Required N	δ(CDCl$_3$)
(6a)	Ph	Ph	O	20	EtOH	198	65	402	71.8	6.7	14.0	$C_{24}H_{26}N_4O_2$	71.6	6.5	13.9	2.75 [m, 4 H, (CH_2–N–CH_2) morph. at 5]; 3.5 [m, 4 H, (CH_2–O–CH_2) morph. at 5]; 3.75 (m, 8 H, morph. at 6); 7.0—7.5 (m, 8 H, arom); 8.2—8.5 (m, 2 H, arom)
(6b)	Ph	C_6H_4Me-*p*	O	24	EtOH	176	65	416	71.8	7.0	13.9	$C_{25}H_{28}N_4O_2$	72.1	6.8	13.45	2.39 (s, 3 H, CH_3); 2.76 [m, 4 H, (CH_2–N–CH_2) morph. at 5]; 3.55 [m, 4 H, (CH_2–O–CH_2) morph. at 5]; 3.77 (m, 8 H, morph. at 6); 7.15—7.4 (m, 7 H, arom); 8.15—8.45 (m, 2 H, arom)
(6c)	Ph	C_6H_4F-*p*	O	14	EtOH	221	75	420	68.15	5.8	13.2	$C_{24}H_{25}FN_4O_2$	68.55	6.0	13.3	2.76 [m, 4 H, (CH_2–N–CH_2) morph. at 5]; 3.56 [m, 4 H, (CH_2–O–CH_2) morph. at 5]; 3.76 (m, 8 H, morph. at 6); 6.85—7.45 (m, 7 H, arom); 8.15—8.45 (m, 2 H, arom)
(6d)	Ph	C_6H_4Br-*p*	O	12	EtOH	226	80	481	59.6	5.1	11.35	$C_{24}H_{25}BrN_4O_2$	59.9	5.2	11.6	2.77 [m, 4 H, (CH_2–N–CH_2) morph. at 5]; 3.58 [m, 4 H, (CH_2–O–CH_2) morph. at 5]; 3.77 (m, 8 H, morph. at 6); 7.15—7.65 (m, 7 H, arom); 8.15—8.45 (m, 2 H, arom)
(6e)	Ph	C_6H_4Cl-*p*	O	20	EtOH	222	75	436	66.0	5.7	12.6	$C_{24}H_{25}ClN_4O_2$	66.0	5.8	12.8	2.77 [m, 4 H, (CH_2–N–CH_2) morph. at 5]; 3.56 [m, 4 H, (CH_2–O–CH_2) morph at 5]; 3.77 (m, 8 H, morph. at 6); 7.15—7.45 (m, 7 H, arom); 8.1—8.5 (m, 2 H, arom)
(6f)	Ph	OH	O	24	EtOH	288d	30	342	63.0	6.4	16.3	$C_{18}H_{22}N_4O_3$	63.1	6.5	16.4	3.0—3.4 [m, 4 H, (CH_2N–CH_2) morph. at 5]; 3.55—4.35 [m, 12 H, CH_2–O–CH_2) morph. at 5, morph. at 6]; 7.25—7.65 (m, 3 H, arom); 8.15—8.45 (m, 2 H, arom)
(6g)	Me	Ph	O	5	Pr^i_2O	158	30	340	67.1	7.15	16.3	$C_{18}H_{24}N_4O_2$	67.0	7.1	16.45	2.55 (s, 3 H, CH_3); 2.7 [m, 4 H, (CH_2–N–CH_2) morph. at 5]; 3.56 [m, 4 H, (CH_2–O–CH_2) morph. at 5]; 3.76 (m, 8 H, morph. at 6); 7.25—7.55 (m, 5 H, arom)
(6h)	Ph	Me	O	5	Pentane		40	340	66.9	7.0	16.7	$C_{19}H_{24}N_4O_2$	67.0	7.1	16.45	2.54 (s, 3 H, CH_3); 3.1 [m, 4 H, (CH_2–N–CH_2) morph. at 5]; 3.4—4.0 [m, 12 H, (CH_2–O–CH_2) morph. at 5, morph. at 6]; 7.1—7.7 (m, 3 H, arom); 8.15—8.55 (m, 2 H, arom)
(6i)	Me	C_6H_4F-*p*	O	3	Pr^i_2O	145	20	358	63.9	7.45	15.25	$C_{19}H_{23}FN_4O_2$	63.7	6.5	15.6	2.55 (s, 3 H, CH_3); 2.73 [m, 4 H, (CH_2–N–CH_2) morph. at 5]: 3.6[m,4 H, (CH_2–O–CH_2) morph. at 5]; 3.8 (m, 8 H, morph. at 6); 7.0—7.55 (m, 4 H, arom)
(6j)	C_6H_4F-*p*	Me	O	3	Pr^i_2O	161	20	358	63.7	6.4	15.6	$C_{19}H_{23}FN_4O_2$	63.7	6.5	15.6	2.54 (s, 3 H, CH_3); 3.11 [m, 4 H, (CH_2–N–CH_2) morph. at 5]; 3.6—4.1 [m, 12 H, (CH_2–O–CH_2) morph. at 5, morph. at 6]; 6.9—7.35 (m, 2 H, arom); 8.25—8.55 (m, 2 H, arom)
(6k)	Me	C_6H_4Br-*p*	O	3	Pr^i_2O		80	419	54.5	5.5	13.4	$C_{19}H_{23}BrN_4O_2$	54.4	5.5	13.4	2.54 (s, 3 H, CH_3); 2.72 [m, 4 H, (CH_2–N–CH_2) morph. at 5]; 3.58 [m, 4 H, (CH_2–O–CH_2) morph. at 5]; 3.78 (m, 8 H, morph. at 6); 7.42—7.58 (m, 4 H, arom)
(6l)	C_6H_4Br-*p*	Me	O	3	Pr^i_2O											2.54 (s, 3 H, CH_3); 3.1 [m, 4 H, (CH_2–N–CH_2) morph. at 5]; 3.6—4.0 [m, 12 H, (CH_2–O–CH_2) morph. at 5, morph. at 6]; 7.12—7.35 (m, 2 H, arom); 8.1—8.3 (m, 2 H, arom)
(6m)	Me	C_6H_4Cl-*p*	O	5	Pr^i_2O		80	374	61.0	6.2	15.0	$C_{19}H_{23}ClN_4O_2$	60.9	6.2	14.9	2.55 (s, 3 H, CH_3); 2.74 [m, 4 H, (CH_2–N–CH_2) morph. at 5]; 3.6 [m, 4 H, (CH_2–O–CH_2) morph. at 5]; 3.8 (m, 8 H, morph. at 6); 7.3—7.5 (m, 4 H, arom)
(6n)	C_6H_4Cl-*p*	Me	O	5	Pr^i_2O											2.55 (s, 3 H, CH_3); 3.1 [m, 4 H, (CH_2–N–CH_2) morph. at 5]; 3.6—4.1 [m, 12 H, (CH_2–O–CH_2) morph. at 5, morph. at 6]; 7.25—7.6 (m, 2 H, arom); 8.2—8.55 (m, 2 H, arom)
(6o)	Ph	Ph	CH_2	8	EtOH	135	80	398	78.05	7.25	13.9	$C_{26}H_{30}N_4$	78.35	7.6	14.05	1.4 [m, 6 H, $(CH_2)_3$ pip. at 5; 1.7 [m, 6 H, $(CH_2)_3$ pip. at 6]; 2.5—2.9 [m, 4 H, (CH_2–N–CH_2) pip. at 5]; 3.45—3.8 [m, 4 H, CH_2–N–CH_2) pip. at 6]; 7.15—7.5 (m, 8 H, arom); 8.15—8.45 (m, 2 H, arom)
(6p)	C_6H_4Br-*p*	Ph	CH_2	10	EtOH	150	85	477	65.3	6.2	11.8	$C_{26}H_{29}BrN_4$	65.4	6.1	11.7	1.41 [m, 6 H, $(CH_2)_3$ pip. at 5]; 1.7 [m, 6 H, $(CH_2)_3$ pip. at 6]; 2.5—2.9 [m, 4 H, (CH_2–N–CH_2) pip. at 5]; 3.45—3.8 [m, 4 H, (CH_2–N–CH_2) pip. at 6]; 7.2—7.75 (m, 7 H, arom); 8.15—8.5 (m, 2 H, arom)
(6q)	C_6H_4Cl-*p*	Ph	CH_2	8	EtOH	162	80	432	71.9	6.6	12.7	$C_{26}H_{29}ClN_4$	72.1	6.75	12.9	1.6 [m, 6 H, $(CH_2)_3$ pip. at 5]; 1.7 [m, 6 H, $(CH_2)_3$ pip. at 6]; 2.5—2.9 [m, 4 H, (CH_2–N–CH_2) pip. at 5]; 3.5—3.9 [m, 4 H, (CH_2–N–CH_2) pip. at 6]; 7.0—7.9 (m, 7 H, arom); 8.15—8.55 (m, 2 H, arom)

The relevant properties of the pyrimidine derivatives (6a—q) are shown in the Table.

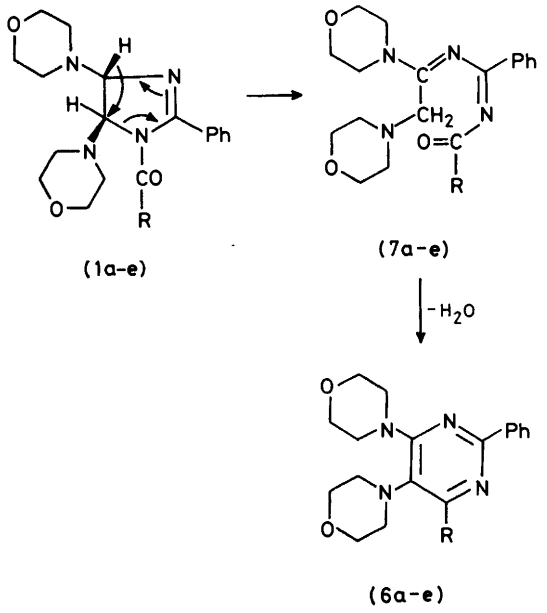
DISCUSSION

From a mechanistic point of view the ring expansion of the 2-imidazolines (1a—e) to the pyrimidines (6a—e) can be seen as a cleavage of the N-1–C-5 bond leading to the formation of an open-chain intermediate (7), which then undergoes cyclization *via* water or alcohol elimination (Scheme 4).

In the pyrolytic process involving 2-imidazoline (1a) the hypothesized intermediate could be isolated by carrying out the reaction in boiling benzene and stopping it before completion.

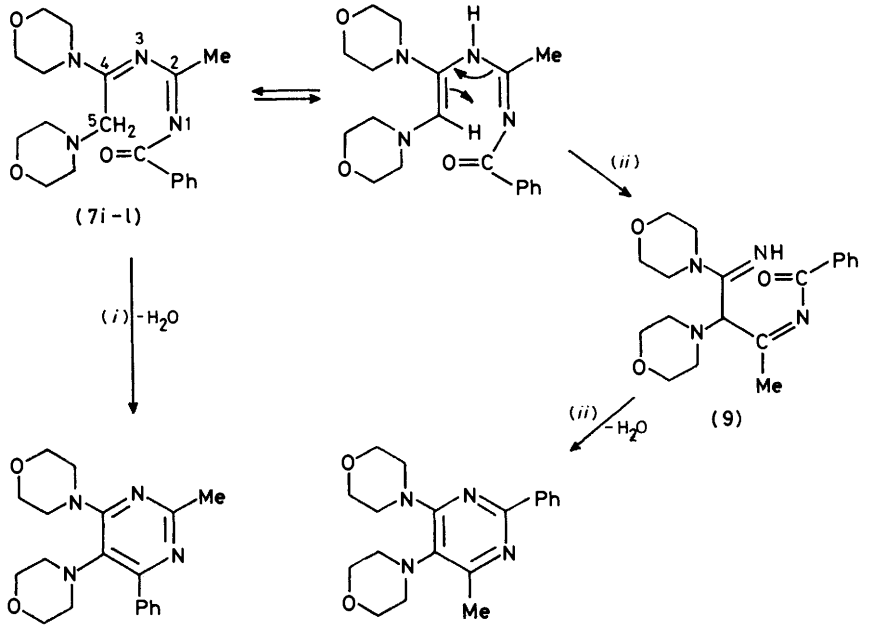
This compound, which was assigned the structure *N*-benzoyl-*N'*-(1,2-dimorpholinoethylidene)benzamidine (7a) on the basis of analytical data and spectral properties, was completely converted into pyrimidine (6a) by boiling in dry xylene for a short time. The formation of intermediate (7) and its subsequent conversion to the pyrimidine derivative could easily be shown for all the imidazolines (6a—e) by carrying out the reaction at 110 °C instead of 135 °C, and by monitoring the conversion by t.l.c.

The formation of an analogous intermediate in the ring expansion of imidazolines (1f—h) to hydroxypyrimidines was assumed by analogy, since no open-chain intermediate could be isolated or detected in these cases.



SCHEME 4

The surprising result obtained from the piperidinoimidazolines (1n) and 1o) probably depends on the better



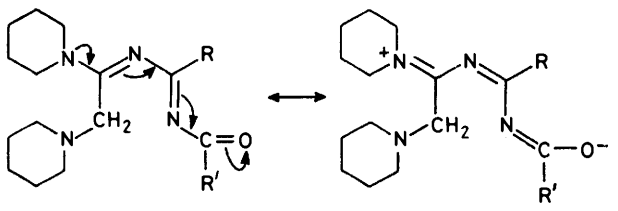
SCHEME 5

For the mechanism followed during the expansion process involving imidazolines (1i—l) we suggest the pathway depicted in Scheme 5. Assuming the prior formation of an open-chain intermediate (7), two mechanisms of cyclization appear to be possible: (*i*) direct electrophilic attack of the carbonyl group at C-5, and (*ii*) a [1,3]sigmatropic shift of C-2 affording an unstable intermediate (9), which subsequently cyclizes to 2-phenyl-4-methylpyrimidine.

delocalization of the nitrogen pair of the piperidino-group on the unsaturated system of the intermediate (7).* Such a delocalization could lower the reactivity of the

* In the reaction involving imidazoline (1o) this intermediate was isolated in the same way as for (7a) and proved to have the expected structure of *N*-(4-chlorobenzoyl)-*N'*-(1,2-piperidinoethylidene)benzamidine (7o).

carbonyl group thus favouring the [1,3] rearrangement and shifting the expansion process towards path (*ii*).



(7n-o)

EXPERIMENTAL

I.r. spectra were recorded in Nujol mulls on a Beckmann Acculub 4 spectrophotometer. N.m.r. spectra were recorded on a Varian A-60 spectrometer at 60 MHz with $SiMe_4$ as internal standard, and mass spectra on a Varian MAT 311-A double focusing mass spectrometer (with a combined FI/FD/EI ion source). The direct-inlet technique was used with a probe temperature of 80—120 °C; the electron energy was 70 eV. T.l.c. was performed on silica gel GF 254.

1-*Acylimidazolines*.—The synthesis of imidazolines (1a—m) has been reported previously;[2] compounds (1n), m.p. 120 °C (from propan-2-ol) and (1o), m.p. 138 °C (from propan-2-ol) are new and were prepared by the same method.

Pyrolysis of 1-*Aroyl*-2-*aryl*-4,5-*diamino*-4,5-*dihydroimidazoles* (1a—e) *and* (1m—o) *to* 2,4-*Diaryl*-5,6-*diaminopyrimidines* (6a—e) *and* (6o—q).—Dihydroimidazoles (1a—e) and (1m—o) (1.0 mmol) were refluxed in dry xylene (30 ml) for the time reported in the Table. The conversion of the starting products was followed by t.l.c. using benzene–tetrahydrofuran (50 : 50) as eluant.

The reaction mixture was then cooled to room temperature and the solvent removed under reduced pressure to give the crude pyrimidine derivative. Crystallization from a suitable solvent then gave pure pyrimidines (6a—e) and (6o—q).

Isolation of N-(1,2-*Dimorpholinoethylidene*)-N′-*benzoylbenzamidines* (7a) *and* (7o).—Dihydroimidazole (1a) (2.0 mmol) was refluxed in dry benzene (30 ml) with an equimolar amount of triethylamine hydrochloride for 22 h. The solvent was removed under reduced pressure, and the crude residue washed with a saturated sodium hydrogencarbonate solution and extracted with diethyl ether. The organic layer was dried over sodium sulphate and solvent removed under reduced pressure. The crude mixture was chromatographed on a silica gel column (ratio SiO_2 : crude product, 40 : 1) using benzene–tetrahydrofuran (50 : 50) as eluant.

N-Benzoyl-*N*′-(1,2-dimorpholinoethylidene)benzamidine (7a) was eluted immediately after pyrimidine (6a), yield 35%, m.p. (from di-isopropyl ether) 137—138 °C (Found: C, 71.4; H, 6.9; N, 13.8. $C_{24}H_{28}N_4O_3$ requires C, 71.25; H, 7.0; N, 13.8%); $\nu_{max.}$ (Nujol): 1 645, 1 638, 1 610, and 1 560 cm^{-1}; $\delta(CDCl_3)$ 2.26 and 3.38 (2 t, CH_2-morpholino), 3.25 (s, CH_2); 3.49 (s, N=C–morpholino), and 7.17—7.68 and 7.83—8.17 (2 m, aromatic).

N-(4-Chlorobenzoyl)-*N*′-(1,2-dipiperidinoethylidene)-benzamidine (7o) was formed from imidazoline (1o) and isolated in the same way as for (7a), yield 40%, m.p. from (di-isopropyl ether) 98 °C (Found: C, 69.5; H, 7.0; N, 12.1. $C_{26}H_{31}ClN_4O$ requires C, 69.2; H, 6.9; N, 12.4%); $\nu_{max.}$ (Nujol): 1 650, 1 610, and 1 575 cm^{-1}; $\delta(CDCl_3)$ 1.26 and 1.52 (2 m, total 12 H, $[CH_2]_3$ of piperidines), 2.2 [m, 4 H, CH_2-N(CH_2)$_2$], 3.1 (s, 2 H, CH_2); 3.45 [m, 4 H, =C–N-(CH_2)$_2$], and 7.1—7.7 and 7.85—8.35 (2 m, aromatic).

Pyrolysis of 1-*Aroyl*-2-*methyl*-4,5-*dimorpholino*-4,5-*dihydroimidazoles* (1i—l) *to* 2-*Methyl*-4-*aryl*-5,6-*dimorpholinopyrimidines* (6g, i, k, m) *and* 2-*Aryl*-4-*methyl*-5,6-*dimorpholinopyrimidines* (6h, j, l, n).—Dihydroimidazoles (1i—l) (1.5 mmol) were refluxed in dry xylene (30 ml) for the time shown in the Table. The reaction course was followed by t.l.c., using benzene–tetrahydrofurane (50 : 50) as eluant. The reaction mixture was cooled to room temperature and the solvent removed under reduced pressure. The oily residue was chromatographed on a silica gel column (ratio SiO_2 : crude mixture, 40 : 1) using diethyl ether as eluant. The head fractions were collected and solvent removed *in vacuo*, yielding a mixture of the isomeric pair of pyrimidines, which was purified by crystallization from the solvent reported in the Table.

A mixture of (6i) and (6j) (1 g, *ca.* 50 : 50) was rechromatographed on a column containing 100 g of SiO_2, using diethyl ether–light petroleum (80 : 20) as eluant, to yield pure (6i); *m/e* 358 (94%, M^+), 327 (21), 269 (17), 255 (21), 243 (25), 242 (38), 241 (40), 216 (19), 122 (80), 121 (100), 95 (22), 66 (29), and 42 (50); and (6j), *m/e* 358 (M^+, 100%), 327 (31), 269 (15), 255 (18), 243 (22), 242 (35), 241 (36), 216 (22), 122 (36), 121 (43), 56 (26), 55 (36), and 42 (72).

Pyrolysis of 1-*Acetyl*-2-*phenyl*-4,5-*dimorpholino*-4,5-*dihydroimidazole* (1p) *to* 2-*Methyl*-4-*phenyl*-5,6-*dimorpholinopyrimidine* (6g) *and* 2-*Phenyl*-4-*methyl*-5,6-*dimorpholinopyrimidine* (6h).—Dihydroimidazole (1p) (3.5 mmol) was refluxed in dry xylene (20 ml) with an equimolar amount of triethylamine hydrochloride until no more starting product was detectable by t.l.c. (24 h), using diethyl ether–ethanol (90 : 10) as eluant. The reaction mixture was washed with a saturated sodium hydrogencarbonate solution; the organic layer was dried over sodium sulphate and solvent removed under reduced pressure. The crude residue was chromatographed on a silica gel column (ratio SiO_2 : crude mixture, 60 : 1) using diethyl ether–ethanol (95 : 5) as eluant.

The mixture of the two isomers (0.48 g) thus isolated was crystallized several times from di-isopropyl ether affording pure (6g), m.p. 158 °C. The mother-liquors from the crystallization were evaporated, and the residue crystallized with pentane. The cream solid thus obtained had m.p. 100—110 °C and proved to be a mixture of (6h) (80%) and (6g) (20%).

Pyrolysis of 1-*Alkoxycarbonyl*-2-*phenyl*-4,5-*dimorpholino*-4,5-*dihydro-imidazoles* (1f—h) *to* 2-*Phenyl*-4-*hydroxy*-5,6-*dimorpholinopyrimidine* (6f).—Dihydroimidazoles (1f—h) (2.0 mmol) were refluxed for the time reported in the Table in dry xylene (20 ml) in the presence of an equimolar amount of triethylamine hydrochloride. The reaction course was followed by t.l.c., using ethyl acetate–ethanol (90 : 10) as eluant. The reaction mixture was cooled and the solvent removed under reduced pressure; the crude residue was washed with water and extracted twice with diethyl ether. The organic layer was dried over sodium sulphate and solvent removed under reduced pressure.

Pyrimidine (6f) was purified by column chromatography on silica gel (SiO_2 : crude mixture, 40 : 1) using ethyl acetate–ethanol (95 : 5) as eluant, and subsequently by crystallization from ethanol; *m/e* 342 (100%, M^+), 325 (15),

311 (25), 309 (19), 283 (18), 239 (12), 226 (23), 225 (19), and 104 (26).

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