Cyclic Amidines. Part XXIV.[1] Cyclisation of *N*-Allyl-*N'*-arylacetamidines to Imidazolines, Dihydroquinazolines, and Dihydrobenzodiazepines

By **Maurice W. Partridge** * and **Alan Smith**, The University, Nottingham NG7 2RD

N-Allyl-*N'*-arylacetamidines have been cyclised, as their hydrochlorides, to 1-aryl-2,5-dimethyl-Δ^2-imidazolines and, in polyphosphoric acid, to 3,4-dihydro-4-ethyl-2-methylquinazolines together with, in certain cases, 4,5-dihydro-2,5-dimethyl-3*H*-1,3-benzodiazepines.

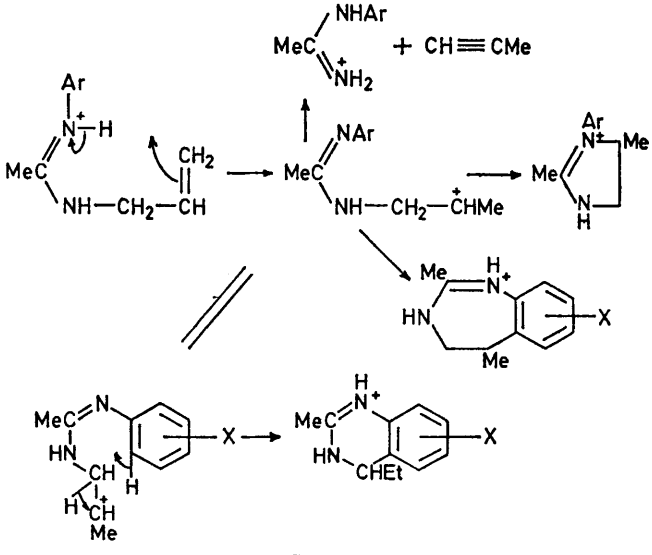
1-ARYL-5-METHYLIMIDAZOLINES have been produced previously [2] from reactions between *N*-allyl amides and arylamine hydrochlorides, or between anilides and allylamine hydrochlorides. In the three examples reported, *N*-allyl-*N'*-arylamidines were suggested as intermediates, although the effective formation of amidines by the interaction of arylamine salts and amides or of anilides and alkylamine salts were not then known reactions. We now describe reactions of *N*-allyl-*N'*-arylacetamidines.

The required *N*-allyl-*N'*-arylacetamidines (Table 1), prepared from *N*-allylacetamide and arylamines *via* *N*-allylacetimidoyl chloride,[3] were converted into their hydrochlorides and heated at 180° to yield 1-aryl-2,5-dimethylimidazolines (Table 2); the 1-phenyl and 1-*p*-tolyl derivatives were also prepared by Clayton's method.[2] *N*-Allyl-*N'*-arylacetamidines and the derived imidazolines are isomeric, but are clearly distinguished by differences in their i.r. and n.m.r. spectra. Direct formation of an imidazoline by the interaction of a nitrile with an allylamine derivative in the presence of aluminium chloride was not realised; only an *N*-allylamidine was formed (Table 3).

The products of cyclisation of *N*-allyl-*N'*-arylacetamidines by polyphosphoric acid depended on the nature of the substituents in the aryl ring. Thus with halogeno-substituents (*o*-bromo-, *p*-bromo-, *p*-chloro-), 4-ethyl-3,4-dihydro-2-methylquinazolines (Table 4) were formed. With *N*-allyl-*N'*-phenylacetamidine and its *o*- and *p*-methyl derivatives, a mixture of a 3,4-dihydroquinazoline and a 4,5-dihydro-2,5-dimethyl-3*H*-1,3-benzodiazepine was formed. The 3,4-dihydroquinazoline was assigned its structure by analogy with the product of debenzylation of 1-benzyl-1,4-dihydroquinazoline, which is a 3,4-dihydroquinazoline.[4]

N-Aryl-*N'*-benzoylethylenediamines have recently been reported [5] to yield 1,2-diarylimidazolines by cyclisation in polyphosphoric acid; dihydrobenzodiazepine formation was, in contrast, not observed in this reaction.

N.m.r. spectra of the crude products were used to determine the relative amounts of dihydroquinazoline and benzodiazepine formed; the proportions were not affected by the temperature of cyclisation nor by the quantity of polyphosphoric acid. With no substituent in the aryl ring, the pure dihydroquinazoline was isolated, but with a methyl substituent, the mixed product was separable by chromatography only after oxidation of the



SCHEME

dihydroquinazoline to a quinazoline. Hydrogenation of the isolated quinazoline then furnished the 3,4-dihydro-derivative. Only 4,5-dihydro-2,5,9-trimethyl-3*H*-1,3-benzodiazepine was obtained as a crystalline base.

[1] Part XXIII, D. G. Bloomfield, M. W. Partridge, and H. J. Vipond, *J. Chem. Soc.* (*C*), 1970, 2647.
[2] G. C. Clayton, *Ber.*, 1895, **28**, 1665.
[3] A. J. Hill and M. V. Cox, *J. Amer. Chem. Soc.*, 1926, **48**, 3214.
[4] W. L. F. Armarego, *J. Chem. Soc.*, 1961, 2697.
[5] I. Perillo and S. Lamdan, *J. Heterocyclic Chem.*, 1970, 791.

Elimination of the allyl group from *N*-allyl-*N'*-*p*-nitrophenyl- and *N*-allyl-*N'*-*p*-dimethylaminophenylacetamidines occurred in hot polyphosphoric acid to yield an *N*-aryl amidine, identical with that formed by interaction, in the presence of aluminium chloride, of acetonitrile and *p*-nitroaniline or *p*-amino-*NN*-dimethylaniline, respectively.

We suggest that in the foregoing reactions of *N*-allyl-*N'*-arylacetamidines the amidinium cation yields a carbonium ion; subsequent reactions of this ion to yield the observed products are then dependent on the reaction medium and the nature of the substituents in the aryl ring, according to the illustrated Scheme.

EXPERIMENTAL

Spectra were obtained as follows: i.r., Unicam SP 200 instrument for thin films or KBr discs; n.m.r., Perkin-Elmer R10 or Varian HA100 instrument for solutions in CCl_4 or (for dihydroquinazolines) $CDCl_3$ with $SiMe_4$ standard; u.v., Unicam SP 800 instrument; solutions in ethanol.

N-Allyl-N'-arylacetamidines.—*N*-Allylacetamide (0·1 mol) was dissolved in a cooled solution of phosphorus pentachloride (0·11 mol) in dry benzene (50 ml), and the arylamine (0·1 mol) was added. The mixture was boiled under reflux for 3 h, then evaporated, and the residue was dissolved in the minimum quantity of ethanol. The base, liberated by ammonia, was collected in chloroform, recovered, and distilled or crystallised. Details are summarised in Table 1.

The i.r. and n.m.r. spectra of the *N*-allyl-*N'*-arylacetamidines showed characteristic absorptions at 3460—3420, 3350—3290 (NH), 1640—1620 (C:N), 1000—990 (–CH=), and 928—920 cm^{-1} (=CH_2), and τ 8·2 (Me), 6·1 (CH_2=CH·CH_2), 4·5—5·0 (CH_2=CH·CH_2), and 3·5—4·5 (CH_2=CH·CH_2).

1-Aryl-2,5-dimethylimidazolines.—The *N*-allyl-*N'*-arylacetamidine hydrochloride, prepared from the base and dry hydrogen chloride in ether, was heated at 180—200° for 12 h, then dissolved in dilute hydrochloric acid; the base, liberated by sodium hydroxide, was collected in chloroform, dried, recovered, and distilled. Examples are given in Table 2.

Characteristic i.r. peaks were observed at 1610, 1500—1490 (aromatic ring), 975, and 920 (intensities 2 : 1) cm^{-1}; NH absorptions were absent. The n.m.r. spectra showed signals at τ 5·7—6·7 (3H, m, ABC system, imidazoline ring protons), 8·8 (3H, *J* 6 Hz, 5-Me), and 8·15 (3H, d or ill-defined t, *J* 1·5 and *ca.* 0 Hz, 2-Me); similar long-range coupling has been observed [6] in oxazolines.

N-Allyl Amidines.—These (Table 3) were formed [7] from reactions of an allylamine or an *N*-substituted allylamine with a cyanide, in the presence of aluminium chloride. Since satisfactory analytical figures were not obtained for these amidines, the picrates were analysed and the bases characterised by their n.m.r. spectra: τ 3·7—4·5 (1H, m, CH_2=C*H*), 4·5—5·2 (2H, m, CH_2=CH), 6·0—6·3 (2H, m, CH_2); for mono-*N*-substituted amidines τ 4·5br (2H, s, NH_2); for di-*N*-substituted amidines τ 3·3—3·8br (1H, s, NH).

Substituted 4-Ethyl-3,4-dihydro-2-methylquinazolines.—(*A*) The *N*-allyl-*N'*-arylacetamidine was stirred in polyphosphoric acid (7 parts by wt.) at 130—170° for 2—7 h and the mixture was poured on crushed ice. The solution was made strongly alkaline (Titan Yellow) with sodium hydroxide and the base was extracted with chloroform, dried, recovered, and crystallised from acetone.

4-Ethyl-3,4-dihydro-2-methylquinazoline was not formed in this way at 117°, whereas at 130° the yield was 40%; with increases in the proportion of polyphosphoric acid to 10 and 44 parts the yields were 65 and 63%, respectively.

(*B*) 4-Ethyl-2,6-dimethyl- and -2,8-dimethylquinazolines (1·86 g) were hydrogenated (3 h) at atmospheric pressure in methanol (50 ml) over palladium–charcoal (10%; 0·2 g). After removal of the catalyst and most of the solvent, the dihydroquinazolines crystallised.

Details of these compounds are given in Table 4. I.r. absorptions were observed at 3200 cm^{-1} (NH). The n.m.r. absorptions were: τ *ca.* 4·0 (1H, s, NH), 5·4 (1H, t, 4-H), 8·0 (3H, s, 2-Me), 8·45 (2H, dt, MeCH_2), and 9·1 (3H, t, CH_3·CH_2).

4-Ethyl-2-methylquinazoline (1·3 g, 86%) was obtained when its 3,4-dihydro-derivative (1·5 g) in aqueous potassium hydroxide (5·5%; 90 ml) was treated at 50° with aqueous potassium ferricyanide (8·3%; 60 ml) and the solution was stirred for 1 h.[8] It was collected in ether after the addition of aqueous potassium hydroxide (33%; 75 ml), dried, recovered, and distilled at 90° and 0·05 mmHg. It had $\lambda_{max.}$ 261 (ε 3200), 268 (3200), and 309 nm (3200), no NH absorption in its i.r. spectrum, and τ 2·0—2·9 (4H, m, aromatic), 6·9 (2H, q, CH_2), 7·25 (3H, s, 2-Me), and 8·65 (3H, t, Me) (Found: C, 76·5; H, 6·8; N, 16·1. $C_{11}H_{12}N_2$ requires C, 76·7; H, 7·0; N, 16·3%).

4-Ethyl-2,8-dimethylquinazoline and 4,5-Dihydro-2,5,9-trimethyl-3H-1,3-benzodiazepine.—*N*-Allyl-*N'*-*o*-tolylacetamidine was heated in polyphosphoric acid as in method (*A*) for 3,4-dihydroquinazolines, and the resulting mixture of bases was oxidised by potassium ferricyanide as described for 4-ethyl-2-methylquinazoline. The crude mixed bases were fractionated in benzene on alumina (type H) to yield, as the first fraction, the *quinazoline* (40%), b.p. 80° at 0·1 mmHg, $\lambda_{max.}$ 275 (ε 2740) and 315 nm (2740), no NH absorption in its i.r. spectrum, τ 2·1—3·0 (3H, m, aromatic), 6·9 (2H, q, CH_2), 7·25 (3H, s, 2-Me), 7·4 (3H, s, 8-Me), and 8·65 (3H, t, Me) (Found: C, 77·0; H, 7·3; N, 15·2. $C_{12}H_{14}N_2$ requires C, 77·4; H, 7·6; N, 15·0%); *picrate*, m.p. 148—149° (from ethanol) (Found: C, 52·0; H, 3·9; N, 16·5. $C_{18}H_{17}N_5O_7$ requires C, 52·05; H, 4·1; N, 16·9%). The second fraction was the *benzodiazepine* (25%), m.p. 126—127° (from acetone), $\lambda_{max.}$ 265 nm (ε 9500), $\nu_{max.}$ 3250 cm^{-1} (NH), τ 2·8—3·3 (3H, m, aromatic), 4·5br (1H, s, NH), 6·3—7·2 (3H, ABC multiplet, ring protons), 7·7 (3H, s, 9-Me), 7·9 (3H, s, 2-Me), and 8·75 (3H, d, *J* 6 Hz, 5-Me) (Found: C, 76·4; H, 8·5; N, 14·7. $C_{12}H_{16}N_2$ requires C, 76·55; H, 8·6; N, 14·9%); *picrate*, m.p. 179—180° (from ethanol) (Found: C, 51·6; H, 4·75; N, 16·7. $C_{18}H_{19}N_5O_7$ requires C, 51·8; H, 4·6; N, 16·8%); *reineckate*, m.p. 155—157° (from water) (Found: C, 37·4; H, 4·6; N, 22·0. $C_{16}H_{23}CrN_8S_4$ requires C, 37·85; H, 4·6; N, 22·1%).

4-Ethyl-2,6-dimethylquinazoline and 4,5-Dihydro-2,5,7-trimethyl-3H-1,3-benzodiazepine.—These were similarly prepared from *N*-allyl-*N'*-*p*-tolylacetamidine. The *quinazoline* (41%) had b.p. 100° at 0·01 mmHg, m.p. 50°, $\lambda_{max.}$ 260 (ε 3460), 316 (3460), and 316 nm (3460), no NH absorption

[6] M. A. Weinberger and R. Greenhalgh, *Canad. J. Chem.*, 1963, **41**, 1038.

[7] P. Oxley, M. W. Partridge, and W. F. Short, *J. Chem. Soc.*, 1948, 303.

[8] R. C. Elderfield, T. A. Williamson, W. J. Gensler, and C. B. Kremer, *J. Org. Chem.*, 1947, **12**, 405.

TABLE 1

N-Allyl-*N'*-arylacetamidines

Aryl	Yield (%)	B.p. *T*/°C (mmHg)	M.p. *T*/°C	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
Ph	53	96 (0·2)	58	$C_{11}H_{14}N_2$			15·9			16·1
picrate			145—146	$C_{17}H_{17}N_5O_7$	50·8	4·3	17·5	50·6	4·3	17·4
o-MeC_6H_4	80	85 (0·01)		$C_{12}H_{16}N_2$			14·8			14·9
picrate			155—156	$C_{18}H_{19}N_5O_7$	51·7	4·9	16·5	51·8	4·6	16·8
p-MeC_6H_4	80	102 (0·05)		$C_{12}H_{16}N_2$			14·8			14·9
picrate			123—124	$C_{18}H_{19}N_5O_7$	51·8	4·8	16·8	51·8	4·6	16·8
o-BrC_6H_4	72	84 (2 × 10^{-4})		$C_{11}H_{13}BrN_2$	51·7	4·9		52·2	5·2	
picrate			160—161	$C_{17}H_{16}BrN_5O_7$	42·6	3·5	14·5	42·3	3·3	14·5
p-BrC_6H_4	55	100 (1 × 10^{-4})		$C_{11}H_{13}BrN_2$	51·9	5·0	10·6	52·2	5·2	11·1
picrate			125—126	$C_{17}H_{16}BrN_5O_7$	42·6	3·5	14·0	42·3	3·3	14·5
p-ClC_6H_4	70	123 (0·02)		$C_{11}H_{13}ClN_2$	63·6	6·3	13·1	63·3	6·3	13·4
picrate			116—117	$C_{17}H_{16}ClN_5O_7$	46·2	3·7	15·6	46·6	3·7	16·0
p-$O_2N{\cdot}C_6H_4$	60	120 (2 × 10^{-4})		$C_{11}H_{13}N_3O_2$	60·5	6·0	19·0	60·3	6·0	19·2
picrate			154—155	$C_{17}H_{16}N_6O_9$	45·7	3·6	18·7	45·6	3·6	18·8
p-$Me_2N{\cdot}C_6H_4$	68		79—80	$C_{13}H_{19}N_3$	72·0	8·4	19·7	71·9	8·8	19·3
picrate			164—165	$C_{19}H_{22}N_6O_7$	51·2	4·9	18·4	51·1	5·0	18·8
o-$F_3C{\cdot}C_6H_4$	74	88 (0·04)		$C_{12}H_{13}F_3N_2$	59·3	5·5	11·4	59·5	5·4	11·6
picrate			148—149	$C_{18}H_{16}F_3N_5O_7$	46·0	3·6	14·8	45·9	3·4	14·9
o-FC_6H_4	70		71—72	$C_{11}H_{13}FN_2$			14·6			14·6
picrate			150—151	$C_{17}H_{16}FN_5O_7$	48·5	3·6	16·4	48·5	3·8	16·6
p-$MeOC_6H_4$	71	130 (0·15)		$C_{12}H_{16}N_2O$	70·8	7·4	13·3	70·6	7·9	13·7

TABLE 2

1-Aryl-2,5-dimethylimidazolines

Aryl	Yield (%)	B.p. *T*/°C (mmHg)	M.p. *T*/°C	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
Ph *	66	78 (0·05)								
o-MeC_6H_4	46	72 (0·04)		$C_{12}H_{16}N_2$	76·5	8·3	15·1	76·55	8·6	14·9
picrate			160—161	$C_{18}H_{19}N_5O_7$	52·1	4·7	17·2	51·8	4·6	16·8
p-MeC_6H_4 *	46	75 (0·02)								
picrate			129—130	$C_{18}H_{19}N_5O_7$	51·9	4·6	16·9	51·8	4·6	16·8
o-BrC_6H_4	41	130 (0·01)		$C_{11}H_{13}BrN_2$	52·3	5·2	11·0	52·2	5·2	11·1
picrate			151—152	$C_{17}H_{16}BrN_5O_7$	42·2	3·4	14·4	42·3	3·3	14·5
p-BrC_6H_4	39	104 (0·04)		$C_{11}H_{13}BrN_2$	52·3	5·2	11·0	52·2	5·2	11·1
picrate			140—141	$C_{17}H_{16}BrN_5O_7$	42·2	3·4	14·3	42·3	3·3	14·5
p-ClC_6H_4	25	108 (0·01)		$C_{11}H_{13}ClN_2$	63·1	6·3	13·0	63·3	6·3	13·4
picrate			136—137	$C_{17}H_{16}ClN_5O_7$	46·6	3·6	16·1	46·6	3·7	16·0
p-$O_2N{\cdot}C_6H_4$	35									
picrate			190—191	$C_{17}H_{16}N_6O_9$	45·9	3·5	18·8	45·6	3·6	18·8
o-$F_3C{\cdot}C_6H_4$	66	82 (0·05)		$C_{12}H_{13}F_3N_2$	59·5	5·4	11·8	59·5	5·4	11·6
picrate			184—185	$C_{18}H_{16}F_3N_5O_7$	46·1	3·5	14·4	45·9	3·4	14·9
o-FC_6H_4	77	84 (0·1)		$C_{11}H_{13}FN_2$	68·3	6·8	14·3	68·75	6·8	14·6
picrate			156—157	$C_{17}H_{16}FN_5O_7$	48·3	4·0	16·4	48·5	3·8	16·6

* Identical (m.p. and mixed m.p. and i.r. spectra) with the compounds prepared in 15% yield by Clayton's method.[2]

TABLE 3

N-Allylamidines, $R^1C(:NH)N(CH_2{\cdot}CH{:}CH_2)R^2$

R^1	R^2	Yield (%)	B.p. *T*/°C (mmHg)	M.p. *T*/°C	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
Ph	H	66	108—111 (0·15)								
picrate				157	$C_{16}H_{15}N_5O_7$	49·7	4·0	18·4	49·4	3·9	18·0
Me	H	62	92 (20)								
picrate				105	$C_{11}H_{13}N_5O_7$	40·7	4·1	21·8	40·4	4·0	21·4
Me	Ph	60	130—131 (0·17)								
picrate				141—142	$C_{17}H_{17}N_5O_7$	50·7	4·3	17·6	50·6	4·3	17·4
Ph	Ph	61	130—133 (0·1)								
picrate				170—171	$C_{22}H_{19}N_5O_7$	56·9	4·4	15·1	56·8	4·1	15·1

TABLE 4

Substituted 4-ethyl-3,4-dihydro-2-methylquinazolines

Substituent	Method	Yield (%)	M.p. *T*/°C	$\lambda_{max.}$/nm (ε)	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
	A	75	131—132	284 (6900)	$C_{11}H_{14}N_2$	76·1	7·8	15·9	75·8	8·1	16·1
8-Br	A	71	128—129	294 (7300)	$C_{11}H_{13}BrN_2$	52·0	5·2	10·8	52·2	5·2	11·1
6-Br	A	69	127—128	293 (9800)	$C_{11}H_{13}BrN_2$	52·5	5·2	10·7	52·2	5·2	11·1
6-Cl	A	58	128—129	293 (9600)	$C_{11}H_{13}ClN_2$	63·8	6·1	13·2	63·3	6·3	13·1
8-Me	B	98	122—124	267 (8100)	$C_{12}H_{16}N_2$	76·8	8·5	14·5	76·6	8·6	14·9
6-Me	B	98	144—145	285 (8400)	$C_{12}H_{16}N_2$	76·5	8·1	14·8	76·6	8·6	14·9

in its i.r. spectrum, τ 2·15—2·7 (m, aromatic), 6·9 (2H, q, CH_2), 7·25 (3H, s, 2-Me), 7·5 (3H, s, 6-Me), and 8·6 (3H, t, Me) (Found: C, 77·4; H, 7·8; N, 15·0. $C_{12}H_{14}N_2$ requires C, 77·4; H, 7·6; N, 15·0%). The *benzodiazepine* (22·5%) showed $\nu_{max.}$ 3250 cm^{-1} (NH), τ 2·9—3·4 (3H, m, aromatic), 4·1br (1H, s, NH), 6·2—7·0 (3H, ABC multiplet, ring protons), 7·75 (3H, s, 7-Me), 7·9 (3H, s, 2-Me), and 8·75 (3H, d, 5-Me); *reineckate*, m.p. 173—175° (from water) (Found: C, 37·9; H, 4·6; N, 22·4. $C_{16}H_{23}CrN_8S_4$ requires C, 37·85; H, 4·6; N, 22·1%).

N-p-*Dimethylaminophenylacetamidine*, m.p. 114—115° (from acetone), was prepared [7] (74%) by interaction of equimolecular quantities of *p*-amino-*NN*-dimethylaniline, acetonitrile, and aluminium chloride at 160° for 1 h. For isolation, the cooled melt was dissolved in dilute hydrochloric acid, excess of sodium hydroxide was added, and the amidine was collected in chloroform; $\nu_{max.}$ 3500 and 3350 (NH_2) and 2800 cm^{-1} (NMe), τ 3·3 (4H, s, ring protons), 5·4br (2H, s, NH_2), 7·15 (6H, s, NMe_2), and 8·0 (3H, s, CMe) (Found: C, 67·8; H, 8·4; N, 23·8. $C_{10}H_{15}N_3$ requires C, 67·8; H, 8·5; N, 23·7%).

The same compound was formed (52%) when *N*-allyl-*N'*-(*p*-amino-*NN*-dimethylaminophenyl)acetamidine was heated in polyphosphoric acid at 145° for 2 h.

N-p-*Nitrophenylacetamidine*, m.p. 159—160°, was likewise formed from *p*-nitroaniline, acetonitrile, and aluminium chloride (yield 70%) and from *N*-allyl-*N'*-*p*-nitrophenylacetamidine and polyphosphoric acid (yield 32%) (Found: C, 53·5; H, 5·2; N, 23·9. $C_8H_9N_3O_2$ requires C, 53·6; H, 5·1; N, 23·5%); *picrate*, m.p. 175—176° (Found: C, 41·4; H, 3·1; N, 20·1. $C_{14}H_{12}N_6O_9$ requires C, 41·2; H, 3·0; N, 20·6%).

We acknowledge with thanks a N.A.T.O. Fellowship (to A. S.).

[2/2029 *Received*, 30*th August*, 1972]