Polycyclic Fused Amidines. Part II.[1,2] Synthesis of Dihydroimidazo-fused Systems by Use of 2-Aminoethylammonium Toluene-*p*-sulphonate

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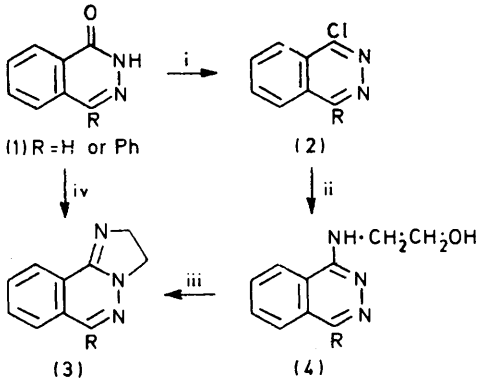
Heating 2-aminoethylammonium tosylate (EDMT) with various aromatic bicyclic amides at 200—250 °C provides a convenient single-stage synthesis of the corresponding dihydroimidazo-compounds. The procedure worked well with phthalazinones (1), quinolones (7), and isoquinolone, but no reaction occurred with analogous monocyclic pyridazones (12) and 2-pyridone. Only low yields of dihydroimidazo-derivatives were obtained from 3,4-dihydroisoquinoline-1(2*H*)-thione (10) and indeno[1,2,3-*de*]phthalazin-3-ones (14). Side reactions dominated the reactions of EDMT with quinoxalinones and benzanilide.

THE usual procedure [3-5] for synthesis of dihydroimidazo-compounds involves the reaction of aromatic heterocyclic amides such as the phthalazinones (1) with phosphoryl

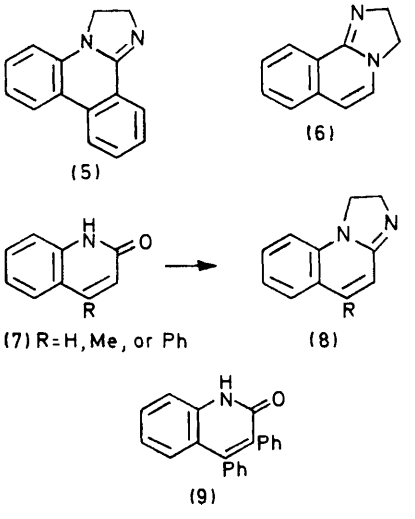


Reagents: i, $POCl_3$; ii, $NH_2{\cdot}CH_2{\cdot}CH_2{\cdot}OH$; iii, $SOCl_2$, then base; iv, $NH_2{\cdot}CH_2{\cdot}CH_2{\cdot}NH_3^+$ *p*-$MeC_6H_4{\cdot}SO_3^-$ (EDMT)

chloride to give the chloro-heterocycles (2). Displacement of the chlorine with 2-amino-ethanol, followed by sequential treatment of the hydroxyalkylamines (4) with thionyl chloride and base provides the dihydroimidazo-systems (3). We have found that certain dihydroimidazo-compounds are readily prepared in one step by heating the corresponding amide with a 2—5 molar excess of 2-aminoethylammonium tosylate (EDMT) at 200—250 °C. Thus the phthalazinone (1; R = H) gave 2,3-dihydroimidazo[2,1-*a*]phthalazine (3; R = H), identical with the compound described by Castle and Takano.[4] The 6-phenyl derivative (3; R = Ph) was similarly prepared and identical with a sample obtained by the route through compound (4; R = Rh). The yield from both approaches was >80%.

Phenanthridone gave >90% yield of the dihydroimidazo-compound (5) on reaction with EDMT.[1] Similarly treatment of isoquinolin-1-one with EDMT at 230 °C gave 2,3-dihydroimidazo[2,1-*a*]isoquinoline (6). The quinolones (7) gave the expected products (8) in *ca.* 40% yield. The diphenylquinolone (9) gave a much lower yield of the fused system, presumably because of steric hindrance.

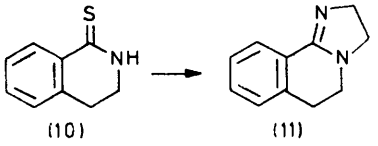
As primary amines, in the presence of acid catalysts, react with amides to give amidines,[6,7] the EDMT annulation reaction presumably proceeds through the α-(2-aminoethylamino)-derivative of the corresponding heterocycle.[1] The sensitivity of the reaction between



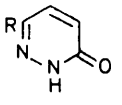
amides and amines to a delicate balance of factors has already been outlined.[6] Similarly, the formation of

[1] Part I, R. F. Cookson and R. E. Rodway, preceding paper.
[2] Preliminary communication, R. F. Cookson and R. E. Rodway, *J.C.S. Chem. Comm.*, 1972, 511; see also R. E. Rodway and R. F. Cookson, B.P. 1,347,493/1974.
[3] O. Bremer, *Annalen*, 1936, **521**, 286; T. Yoshikawa, R. Kiyota, and Y. Urabe, *Yakugaku Zasshi*, 1969, **89**, 767 (*Chem. Abs.*, 1969, **71**, 81,111); M. D. Nair and S. R. Mehta, *Indian J. Chem.*, 1967, **5**, 403.
[4] R. N. Castle and S. Takano, *J. Heterocyclic Chem.*, 1966, **3**, 381.
[5] H. Otomasu, K. Yoshida, and H. Takahashi, *Yakugaku Zasshi*, 1970, **90**, 1391 (*Chem. Abs.*, 1971, **74**, 53,730).
[6] R. I. Fryer, J. V. Earley, G. F. Field, W. Zally, and L. H. Sternbach, *J. Org. Chem.*, 1969, **34**, 1143; J. D. Wilson, C. F. Hobbs, and H. Weingarten, *ibid.*, 1970, **35**, 1542.
[7] J. V. Earley, R. I. Fryer, and L. H. Sternbach, U.S.P. 3,644,335/1972.

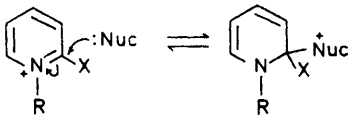
dihydroimidazo-compounds from cyclic amides is influenced markedly by the structures of the amides and amines in the reaction.



(10) (11)



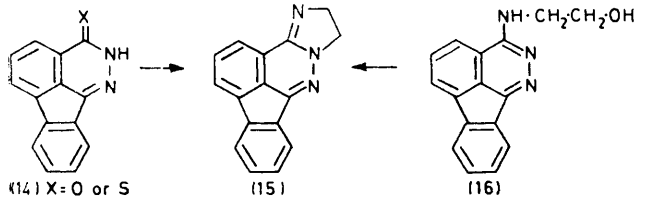
(12) R=Me or Ph



(13) a; R=H, X=O, Nuc=$NH_2CH_2CH_2NH_3^+$
b; R=Me, X=H, Nuc=H_2O

The annulation reaction is favoured if the initial amide is part of an aromatic system. Thus the dihydroisoquinoline-1(2*H*)-thione (10) gave only an 8% yield of the tetrahydro-compound (11), which contrasts with the 56% yield of the dihydro-compound (6) from the aromatic isoquinolone.

Only starting material was recovered when 2-pyridone was treated with EDMT at 200 °C. Similar results were obtained with the pyridazinones (12). The contrasting ease of reaction of the benzologues of 2-pyridone and compounds (13) parallels the ready hydrolysis of, for example, *N*-methylquinolinium chloride, as compared with the relative stability to hydrolysis of *N*-methylpyridinium salts.[8] Both these reactions involve, for the monocyclic systems, complete loss of aromaticity after nucleophilic attack (13). However, in the benzologues



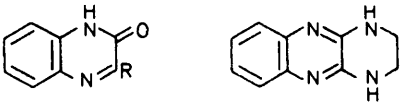
(14) X=O or S (15) (16)

only partial loss of aromatic character occurs, and hence reaction is more favoured for these systems.

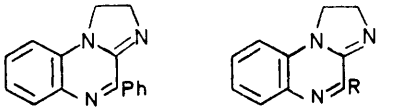
As it is well known that thioamides react more readily with amines than do the corresponding oxo-compounds,[9] the reactivity of the amide–thioamide pair (14) was examined. Even after prolonged heating the indenophthalazone (14; X = O) gave <1% of the dihydroimidazo-compound (15), whereas the thioxo-compound (14; X = S) gave a 7% yield after 16 h at 240 °C. The product (15) was also obtained by way of the amino-compound (16).

The reaction of EDMT with quinoxalin-2-one (17) resulted in extensive decomposition; the only products isolated were the pyrazinoquinoxaline (19) and benzimidazole. When the 3-position of compound (17) was blocked as in the 3-phenyl compound (18), the main product obtained was the aromatic system (21; R = Ph), formed together with a smaller amount of the known [5] dihydroimidazo[1,2-*a*]quinoxaline (20). The large difference in the acidity constants (pK'; determined in 50% aqueous Methylcellosolve [10]) of the two products (20) (pK' 6.50) and (21; R = Ph); (pK' <2.6) enabled ready separation of the mixture.

The imidazo[1,2-*a*]quinoxalines (21) were obtained by acid-catalysed cyclisation of the products from the reaction of aminoacetaldehyde dimethyl acetal with the corresponding 2-chloroquinoxalines. The low yields obtained by this approach are in line with the poorer yield of imidazo[1,2-*a*]pyrazine reported from the amino-acetal and 2-chloropyrazine.[11] Recently the parent ring



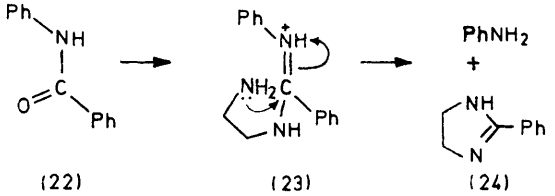
(17) R=H (19)
(18) R=Ph



(20) (21) R=H or Ph

system (21; R = H) has been obtained by other approaches.[12]

An attempt to extend the EDMT annulation reaction to linear secondary amides was unsuccessful. The *trans*-amide benzanilide (22) reacted only slowly with EDMT, forming the monophenylimidazoline (24) and aniline. Steric hindrance would prevent elimination of ammonia from the aminoethylamino-intermediate (23) but would allow the observed expulsion of aniline.



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EXPERIMENTAL

I.r. spectra were recorded with a Perkin-Elmer 157 instrument for Nujol mulls and n.m.r. spectra with a Perkin-Elmer R12 machine operating at 60 MHz. Generally no

[8] A. Albert in ' Physical Methods in Heterocyclic Chemistry,' ed. A. R. Katritzky, Academic Press, London, 1963, vol. I, p. 1.
[9] C. Djerassi and C. R. Scholz, *J. Org. Chem.*, 1948, **13**, 830; G. Forssel, *Ber.*, 1892, **25**, 2132.
[10] R. F. Cookson, *Chem. Rev.*, 1974, **74**, 5.
[11] W. L. F. Armarego, *J. Chem. Soc.*, 1965, 2778.
[12] A. M. Simonov and I. G. Uryukina, *Khim. geterotsikl. Soedinenii*, 1971, **7**, 570 (*Chem. Abs.*, 1972, **76**, 25,242); R. G. R. Bacon and S. D. Hamilton, *J.C.S. Perkin I*, 1974, 1970.

attempt was made to maximise yields. Identity of samples was established by mixed m.p. and i.r. spectral comparisons. Solutions were dried over magnesium sulphate monohydrate. pK' Values were determined in 50% v/v aqueous Methylcellosolve by the method of Albert and Serjeant.[13]

Reaction of Cyclic Amides with EDMT.—General Procedure. An intimate 1 : 2 mixture of the cyclic amide and EDMT was heated in an open flask for several h, cooled, and extracted with hot 5N-hydrochloric acid; any unchanged amide was then filtered off. Basification of the filtrate provided an oil which was taken up in chloroform, washed thoroughly with water, dried, and treated with ethereal hydrogen chloride or, when appropriate, maleic acid. Crystallisation of the salt, or basification of an aqueous solution of the salt, gave the dihydroimidazo-heterocycle (see Table).

Reactions of cyclic amides with 2-aminoethylammonium tosylate

Starting material	Scale (mol)	Reaction time (h)	Temp. (°C)	Cryst. solvent	Product	Yield (%)	M.p. (°C)	Found (%) C	H	N	Formula	Required (%) C	H	N
Phthalazin-1-one	0.14	6	220	EtOH	(3; R = H)	20	337—339 [a]	57.5	5.0	20.6 [b]	$C_{10}H_9N_2$,HCl	57.8	4.8	20.3
4-Phenylphthalazin-1-one	0.10	20	240	C_6H_6	(3; R = Ph)	42	156—157	77.4	5.3	17.1	$C_{16}H_{12}N_2$	77.5	5.3	17.0
Isoquinolin-1-one	0.09	17	245	Pr^{i}OH	(6)	26 [c]	303—307	63.8	5.4	13.4 [d]	$C_{11}H_{10}N_2$,HCl	63.9	5.3	13.6
Quinolin-2-one	0.06	6	240	Pr^{i}OH	(8; R = H)	37	282—283	62.8	4.9	9.8	$C_{15}H_{14}N_2O_2$ [e]	62.9	4.9	9.8
4-Methylquinolin-2-one	0.10	7	230	EtOH	(8; R = Me)	43	*ca.* 335	65.2	6.0	13.0 [f]	$C_{13}H_{13}N_2$,HCl	65.3	5.9	12.7
4-Phenylquinolin-2-one	0.10	18	235	Pr^{i}OH–Et_2O	(8; R = Ph)	41	327—334	72.1	5.4	9.9	$C_{17}H_{14}N_2$,HCl	72.2	5.3	9.9
3,4-Diphenylquinolin-2-one	0.06	18	260	EtOH		10	241—244	85.9	5.9	8.7	$C_{23}H_{18}N_2$	85.7	5.6	8.7
3,4-Dihydroisoquinoline-1(2*H*)-thione	0.07	4	220	Pr^{i}OH	(11)	8	221—223 [g]	53.9	6.7	11.3	$C_{11}H_{13}N_2$,HCl,$2H_2O$	53.9	7.0	11.4
Indeno[1,2,3-*de*]phthalazin-3-one	0.1	30	250	C_6H_6	(15)	0.4	173—174				$C_{16}H_{11}N_3$			
Indeno[1,2,3-*de*]phthalazine-3-thione	0.05	16	240	H_2O–EtOH	(15)	7	>360 (decomp.)	68.1	4.5	14.6	$C_{16}H_{11}N_3$,HCl	68.2	4.3	14.9

[a] Base, m.p. 105—107° (lit.,[4] 103—104°); ref. 4 mentions a dihydrochloride, m.p. 335—336°. [b] Found: Cl, 16.9. Calc.: Cl, 17.1%. [c] Yield of crude base, 56%. [d] Found: Cl, 17.1. Required: Cl, 17.2%. [e] Hydrogen maleate, $C_{11}H_{10}N_2,C_4H_4O_4$. [f] Found: Cl, 16.0. Required: Cl, 16.1%. [g] Lit. m.p. 220—222° (M. W. Gittos, J. W. James and J. P. Verge, U.S.P., 3,652,570/1972). [h] Found: Cl, 14.2. Required: Cl, 14.5%. [i] Found: Cl, 12.1. Required: Cl, 12.6%.

Quinoxalin-2-one. An intimate mixture of quinoxalin-2-one (10 g, 0.068 mol) and EDMT (40 g, 0.172 mol) was heated at 180—190 °C for 5 h. The cooled mixture was dissolved in 5N-hydrochloric acid (300 ml) and the solution was washed with ether. Basification of the aqueous layer gave an oil which was taken up in methylene chloride; the solution was washed, dried, and evaporated to dryness. The solid obtained (2.7 g) was crystallised from industrial methylated spirits (250 ml) to give 1,2,3,4-tetrahydropyrazino[2,3-*b*]quinoxaline (19) (0.3 g), m.p. 317—318° (lit.,[14] >350°) (Found: C, 64.3; H, 5.6; N, 29.9. Calc. for $C_{10}H_{10}N_4$: C, 64.5; H, 5.4; N, 30.1%). Evaporation of the mother liquors from the crystallisation gave a residue which was treated with chloroform. A further 0.6 g of the tetrahydropyrazinoquinoxaline (m.p. 315—318°) was filtered off. The chloroform solution was treated with ethereal hydrogen chloride and an excess of dry ether, and the precipitate was collected and dissolved in water. The aqueous solution was washed with chloroform and then basified. Extraction with ether gave a solid which was recrystallised twice from benzene to give benzimidazole (0.3 g), m.p. 170—172° (lit.,[15] 170°) (Found: C, 71.3; H, 5.3; N, 23.8. Calc. for $C_7H_6N_2$: C, 71.2; H, 5.1; N, 23.7%).

3-*Phenylquinoxalin-2-one.* A finely ground mixture of 3-phenylquinoxalin-2-one (9.3 g, 0.042 mol) and EDMT (19.4 g, 0.084 mol) was heated in an open flask at 200 °C for 19 h. The cooled mixture was treated with 5N-hydrochloric acid (250 ml) and filtered. Basification of the filtrate followed by extraction with ether gave a solid (4.8 g) which was shown by n.m.r. analysis to be a mixture of compounds (20) (17%) and (21; R = Ph) (83%). A portion (2 g) was dissolved in 5N-hydrochloric acid (50 ml) and the solution was basified to pH 3. The precipitate was dissolved in chloroform and washed thoroughly with water (pH 5). Evaporation of the dried solution gave a solid which was crystallised from industrial methylated spirits to give 4-*phenylimidazo*[1,2-a]*quinoxaline* (21; R = Ph) (1.4 g), m.p. 153° (Found: C, 78.2; H, 4.5; N, 17.0. $C_{16}H_{11}N_3$ requires C, 78.4; H, 4.5; N, 17.1%); δ ($CDCl_3$) 7.4—8.35 (9 H, m) and 8.6—8.85 (2 H, m); p$K' < 2.6$ (too low to be determined by titration). The filtered aqueous solution (pH 3) was adjusted to pH 5 and washed with ether. The washings were discarded and the aqueous layer was basified to pH 13. Extraction with ether gave crude 1,2-dihydro-4-phenylimidazo[2,1-*a*]quinoxaline (20) as a gum (0.3 g); δ ($CDCl_3$) 4.0—4.3 (4 H, m), 6.6—7.8 (7 H, m) and 8.3—8.5 (2 H, m). The gum was dissolved in chloroform and treated with ethereal hydrogen chloride and an excess of dry ether. The precipitate was crystallised from propan-2-ol to give the hydrochloride (0.1 g), m.p. 268—270° (Found C, 67.6; H, 4.9; N, 14.7. Calc. for $C_{16}H_{13}N_3$,HCl: C, 67.7; H, 4.9; N, 14.8%); pK' 6.50 ± 0.02.

1-(2-*Hydroxyethylamino*)-4-*phenylphthalazine.*—A solution of 2-chloro-4-phenylphthalazine [16] (24 g, 0.1 mol) and 2-aminoethanol (30.5 g, 0.5 mol) in dry dioxan (150 ml) was heated under reflux for 19 h. Evaporation yielded an oil which was treated with water to give a solid. Crystallisation from industrial methylated spirits gave 1-(2-*hydroxyethylamino*)-4-*phenylphthalazine monohydrate* (23.8 g, 84%), m.p. 157—169° (Found: C, 68.0; H, 6.0; N, 14.8. $C_{16}H_{15}N_3O,H_2O$ requires C, 67.8; H, 6.0; N, 14.8%).

2,3-*Dihydro*-6-*phenylimidazo*[2,1-a]*phthalazine* (3; R = Ph).—Phosphoryl chloride (5 ml) was added cautiously to 1-(2-hydroxyethylamino)-4-phenylphthalazine monohydrate (3 g, 0.01 mol). When the reaction had subsided the mixture was heated under reflux for 0.5 h. The residue obtained on evaporation of the phosphoryl chloride was taken up in chloroform (150 ml) and the solution was stirred with chilled ammonium hydroxide solution and then with saturated potassium carbonate solution. Evaporation of the washed and dried chloroform layer gave a solid (2.6 g, 99%), m.p. 145—147°, which on crystallisation from aqueous industrial methylated spirits afforded 2,3-*dihydro*-6-*phenylimidazo*[2,1-a]*phthalazine* (1.2 g, 48%), m.p. 158—159° (Found: C, 77.4; H, 5.4; N, 17.2. $C_{16}H_{13}N_3$ requires

[13] A. Albert and E. P. Serjeant, ' Determination of Ionization Constants,' 2nd edn., Chapman and Hall, London, 1971.

[14] R. A. Ogg, jun., and F. W. Bergstrom, *J. Amer. Chem. Soc.*, 1931, **53**, 1846.

[15] M. A. Phillips, *J. Chem. Soc.*, 1928, 2393.

[16] M. Hartmann and J. Druey, U.S.P. 2,484,029/1949 (*Chem. Abs.*, 1950, **44**, 4046f).

C, 77.7; H, 5.3; N, 17.0%), identical with the product from the reaction between 4-phenylphthalazin-1-one and EDMT.

5,6-Dihydroimidazo[2,1-a]*indeno*[1,2,3-de]*phthalazine* (15).—3-(2-Hydroxyethylamino)indeno[1,2,3-*de*]phthalazine [17] (12.6 g, 0.048 mol) in phosphoryl chloride (100 ml) was heated under reflux for 2½ h. The cooled solution was poured onto ice and ammonium hydroxide solution, and the mixture was basified to pH 12 with saturated potassium carbonate solution and extracted with chloroform. Evaporation of the washed and dried extracts gave a yellow solid (10 g) which was taken up in chloroform and treated with ethereal hydrogen chloride (15 ml) and an excess of dry ether. The precipitate was collected, dried, and treated with water (500 ml). Basification of the filtered solution with potassium carbonate solution gave a yellow solid which was crystallised from benzene to yield yellow crystals of *5,6-dihydroimidazo*[2,1-a]*indeno*[1,2,3-de]*phthalazine* (4.2 g, 36%), m.p. 176—178° (Found C, 78.2; H, 4.6; N, 17.2. $C_{16}H_{11}N_3$ requires C, 78.4; H, 4.5; N, 17.1%); δ ($CDCl_3$) 4.11 (4 H, s, H-5 and -6) and 7.20—8.25 (7 H, m, aromatic), identical with that obtained from indeno[1,2,3-*de*]phthalazin-3-one and EDMT.

Imidazo[1,2-a]*quinoxaline* (21; R = H).—2-Chloroquinoxaline (16 g, 0.097 mol) in bis-(2-methoxyethyl) ether (100 ml) was heated under reflux with aminoacetaldehyde dimethyl acetal (30.4 g, 0.29 mol) for 8 h. Treatment with water followed by extraction with ether gave an oil (16.3 g) which was boiled with 5N-hydrochloric acid for 2 h. Basification with potassium carbonate solution gave a solid which was dissolved in chloroform, and treated with ethereal hydrogen chloride and an excess of dry ether. The solid obtained was crystallised from a mixture of industrial methylated spirits (charcoal) and ether to give white crystals of imidazo[1,2-*a*]quinoxaline hydrochloride (2.6 g, 13%), m.p. 267—269° (Found C, 58.4; H, 4.0; Cl, 17.0; N, 20.2. Calc. for $C_{10}H_7N_3$,HCl: C, 58.4; H, 3.9; Cl, 17.3; N, 20.4%).

4-Phenylimidazo[1,2-a]*quinoxaline* (21; R = Ph).—A solution of 2-chloro-3-phenylquinoxaline (18.4 g, 0.76 mol) and aminoacetaldehyde dimethyl acetal (23 g, 0.22 mol) in bis-(2-methoxyethyl) ether (150 ml) was heated under reflux for 16 h, then poured into water. Extraction with ether gave an oil which was boiled with 5N-hydrochloric acid for 2 h. Basification of the filtered solution gave a solid which was crystallised from industrial methylated spirits (charcoal) to give *4-phenylimidazo*[1,2-a]*quinoxaline* (2.7 g, 14.5%), m.p. 154—157° (Found: C, 78.5; H, 4.6; N, 16.8. $C_{16}H_{11}N_3$ requires C, 78.4; H, 4.5; N, 17.1%).

Reaction of Benzanilide with EDMT.—An intimate mixture of benzanilide (8 g, 0.041 mol) and EDMT (20 g, 0.086 mol) was heated at 260 °C for 24 h, cooled, and extracted with hot 5N-hydrochloric acid (*ca.* 250 ml); the cooled extract was then filtered and basified to pH 10. The precipitate was washed, dried, and taken up in chloroform (25 ml). Treatment of the solution with ethereal hydrogen chloride and an excess of dry ether gave an oil which was separated and taken up in water. Basification of the aqueous solution gave a white solid which on crystallisation from a small volume of benzene gave white crystals of 2-phenylimidazoline (1.2 g, 20%), m.p. 94—96° (lit.,[18] 101°) (Found C, 73.9; H, 7.0; N, 19.5. Calc. for $C_9H_{10}N_2$: C, 74.0; H, 6.9; N, 19.2%).

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[17] R. E. Rodway and R. G. Simmonds, B.P. 1,341,698/1973.
[18] P. Oxley and W. F. Short, *J. Chem. Soc.*, 1947, 497.