The *N*-Amination and Subsequent Oxidation by Bromine of Imidazo[1,5-*a*]-pyridines

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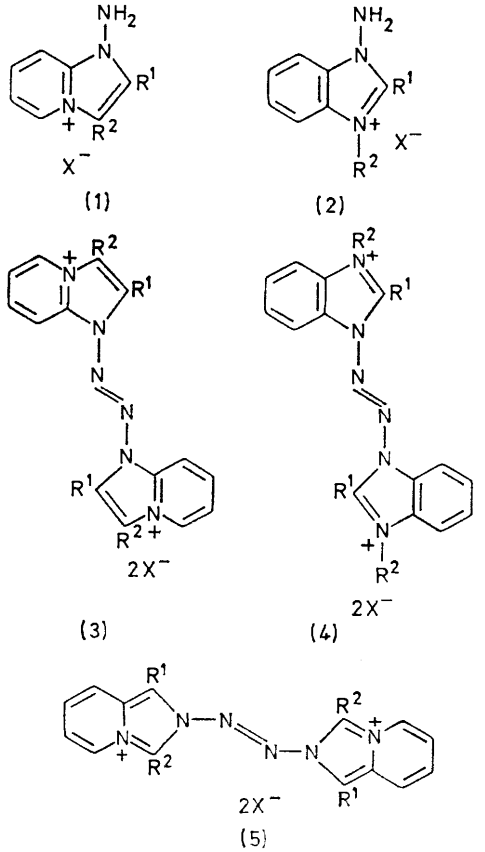
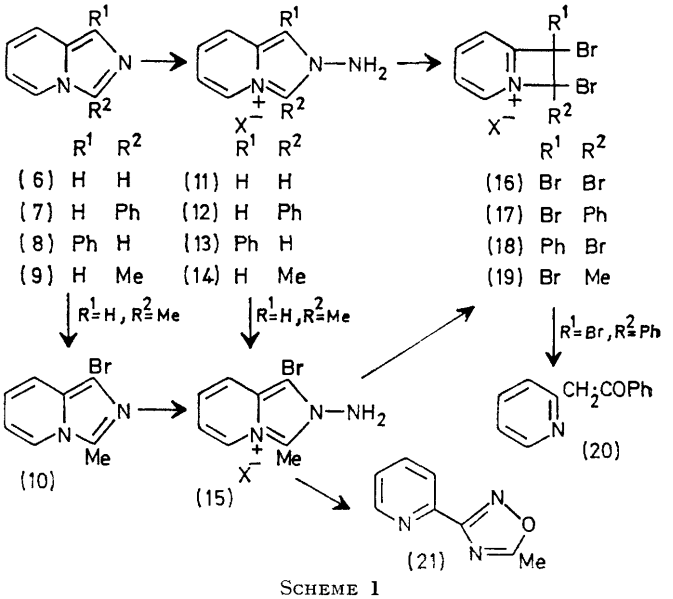
Imidazo[1,5-*a*]pyridines are *N*-aminated by *O*-mesityl- or *O*-*p*-tolyl-sulphonylhydroxylamine and the resulting *N*-amino-compounds are converted by saturated aqueous bromine into brominated 1,2-dihydroazeto[1,2-*a*]pyridinium salts.

1-AMINOIMIDAZO[1,2-*a*]PYRIDINIUM salts (1) and 1-aminobenzimidazolium salts (2) are oxidized [1,2] by



saturated aqueous bromine to the respective diquaternary tetrazenes (3) and (4) which exhibit useful non-depolarising neuromuscular blocking activity. The possibility of the tetrazenes (5) being obtained by oxidation of 2-aminoimidazo[1,5-*a*]pyridinium salts with bromine and showing similar biological activity was, therefore, investigated.

The parent imidazopyridine (6) was *N*-animated in only poor yield by use of hydroxylamine-*O*-sulphonic acid in the procedure described by Gösl and Meuwsen [3]



SCHEME 1

for the *N*-amination of the pyridine, but all the bases (6)—(10) were *N*-aminated in good yield with either *O*-mesityl- [4] or *O*-*p*-tolyl-sulphonylhydroxylamine.[5]

Oxidation of the phenyl-substituted *N*-amino-com-

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[2] D. C. Bishop, E. E. Glover, and K. T. Rowbottom, *J.C.S. Perkin I*, 1973, 842.
[3] R. Gösl and A. Meuwsen, *Chem. Ber.*, 1959, **92**, 2521.
[4] Y. Tamura, J. Minamikawa, Y. Miki, S. Matsugashita, and M. Ikeda, *Tetrahedron Letters*, 1972, 4133.
[5] E. E. Glover and K. T. Rowbottom, *J.C.S. Perkin I*, 1976, 367.

pounds (12) and (13) with saturated aqueous bromine gave, instead of the expected corresponding tetrazenes (5), the tribromo-1,2-dihydroazeto[1,2-*a*]pyridinium bromides, (17) and (18), respectively. The 6,4-fused-ring structure is assigned on the basis of the absence of $\nu(\overset{+}{N}\text{–H})$ i.r. bands, the conversion of the bromide (18) into the corresponding monoperchlorate, and the hydrogenation and subsequent basification of (17) which yielded phenyl 2-pyridylmethyl ketone (20), isolated as the hydrobromide.

We suggest that the reaction occurs *via* initial bromination at the free position of the imidazole ring, followed by oxidation of the amino-function, yielding the aminonitrene (22). The 1,4-addition of bromine in the five-membered ring followed by loss of nitrogen then gives the tribromo-1,2-dihydroazetopyridinium bromides, as shown in Scheme 2. Evidence for the initial electrophilic bromination stage was obtained by the isolation of the bromo-substituted *N*-amino-salt (15) when 2-amino-3-methylimidazo[1,5-*a*]pyridinium bromide (14) was treated with saturated aqueous bromine; compound (15) was also obtained by *N*-amination of 1-bromo-3-methylimidazo[1,5-*a*]pyridine (10). Deamination of the

TABLE 1

N-Amino-salts

Reactants		Product X	Yield (%)	M.p. (°C)	Cryst. solvent	Found (%) C	H	N	Required (%) C	H	N
(6)[7] (2.3 g) + $NH_2{\cdot}O{\cdot}SO_3H$[8] (0.68 g) in H_2O (4.1 ml) [a]	(11)	I	0.4	204—205 [b]	EtOH	32.1	3.2	15.9	32.2	3.1	16.1
(6)[7] (5.5 g) in $CHCl_3$ (20 ml) + TSH [c] (200 ml) [d,e]	(11)	$C_7H_7SO_3$ [f]		214—215	MeOH–Et_2O	55.1	5.2	13.6	55.1	4.95	13.8
	(11)	Br [g]	75 [h]	219—221	MeOH–Et_2O	39.3	3.8	19.6	39.3	3.8	19.6
(6)[7] (0.214 g) in CH_2Cl_2 (2 ml) + MSH [i] (0.39 g) in CH_2Cl_2(1.5 ml) [j]	(11)	$C_9H_{11}SO_3$ [k]	95	186—188	MeOH–Et_2O	57.8	6.0	12.4	57.65	5.75	12.6
	(11)	$C_6H_2N_3O_7$ [l]		198—201	EtOH	42.9	2.9	22.7	43.1	2.8	23.2
(9)[7] (2 g) in $CHCl_3$ (min. vol.) + TSH [c] (64 ml) [d,m]	(14) [n]	Br	58	221	MeOH–Et_2O	41.8	4.6	18.2	42.1	4.4	18.4
(10) [o] in $CHCl_3$ (10 ml) + TSH [c] (40 ml) [d,p]	(15)	Br	36 [q]	223	MeOH	31.5	2.8	13.6	31.3	3.0	13.7
(14) [r] (1 g) in H_2O (4 ml) + sat. aq. Br_2 (100 ml) [s]	(15)	Br	23	223	MeOH	31.7	2.8	13.9	31.3	3.0	13.7
(8)[9] (10 g) in CH_2Cl_2 (min. vol) + TSH [c] (200 ml) [t,u]	(13)	Br	73 [h]	217	MeOH–Et_2O	53.9	4.45	14.3	53.8	4.2	14.5
(8)[9] (0.9 g) in CH_2Cl_2 (0.5 ml) + MSH [i] (0.1 g) in CH_2Cl_2 (0.5 ml) [j]	(13)	$C_9H_{11}SO_3$ [k]	85	265—266	MeOH	64.65	5.8	10.1	64.5	5.7	10.3
(7)[7] (5.2 g) in $CHCl_3$ (min. vol.) + TSH [c] (104 ml) [d,v]	(12)	$C_7H_7SO_3$ [f]	73	139—140	MeOH–Et_2O	62.7	5.1	11.0	63.0	5.0	11.0
	(12)	Br [w]		208	EtOH–Et_2O	53.9	4.2	14.6	53.8	4.2	14.5
(7)[7] (0.09 g) in CH_2Cl_2 (0.5 ml) + MSH [i] (0.1 g) in CH_2Cl_2 (0.5 ml) [j]	(12)	$C_9H_{11}SO_3$ [k]	90	200—202	EtOH–Et_2O	64.2	5.9	10.2	64.5	5.7	10.3

[a] The solution was heated to 90 °C for 20 min and then cooled before treatment with potassium carbonate (0.96 g). After evaporation of the water the residue was treated with ethanol (8 ml) and the resulting solution filtered, and then treated with concentrated hydroiodic acid (0.94 ml). After 1 h at −20 °C the solid which had separated was filtered off and recrystallized. [b] With decomp. [c] O-*p*-Tolylsulphonylhydroxylamine.[5] [d] 5% (w/v) Solution in chloroform. [e] The TSH solution was added in bulk and the reaction mixture stirred for 0.5 h. Ether was then added to complete precipitation of the product, which was filtered off and recrystallized. [f] Toluene-*p*-sulphonate. [g] Prepared by addition of ether to a solution of the toluene-*p*-sulphonate in methanol–48% hydrobromic acid. [h] Overall yield based on the starting imidazopyridine. [i] *O*-Mesitylsulphonylhydroxylamine.[4] [j] The reaction mixture was set aside for 5 min and then ether was added. The precipitated product was filtered off and recrystallized. [k] Mesitylenesulphonate. [l] Picrate. [m] The reaction mixture was stirred for 1 h and ether was added to precipitate completely the toluene-*p*-sulphonate salt, m.p. 165° (from methanol–ether). The toluene-*p*-sulphonate salt was then converted into the bromide by dissolution in ethanol–48% hydrobromic acid followed by addition of ether. [n] Deamination of this compound by treatment with nitrous acid followed by phosphinous acid resulted in simultaneous nitrosation and rearrangement giving 5-methyl-3-(2-pyridyl)-1,2,4-oxadiazole (21), m.p. 89° (from ether) (lit.,[6] 88—89°) (Found: C, 59.4; H, 4.3; N, 26.3. Calc. for $C_8H_7N_3O$: C, 59.6; H, 4.4; N, 26.1%). [o] Obtained by basifying an aqueous solution of the hydrobromide of (10) (1.7 g) and extracting the liberated base into ether. The hydrobromide of (10) was prepared in 75% yield by treating (9) with bromine in methanol solution. Addition of ether precipitated the *hydrobromide*, m.p. 179° (decomp.) (from methanol–ether) (Found: C, 33.1; H, 3.2; N, 9.5. $C_8H_7BrN_2$,HBr requires C, 32.9; H, 2.8; N, 9.6%). The free *base* (10), purified by vacuum sublimation, had m.p. 96° (Found: C, 45.8; H, 3.4; N, 13.3. $C_8H_6BrN_2$ requires C, 45.5; H, 3.3; N, 13.3%). [p] The reaction mixture was stirred for 1 h and ether was added to precipitate completely the toluene-*p*-sulphonate salt, m.p. 216° (decomp.) (from methanol–ether). The salt was then converted into the bromide by dissolution in methanol–48% hydrobromic acid followed by addition of ether. [q] Overall yield based on the starting hydrobromide of (10). [r] Bromide salt. [s] The aqueous bromine was added in bulk and the mixture stirred for 2 min. The product was then filtered off and washed with water before recrystallization. [t] 5% (w/v) Solution in methylene chloride. [u] The reaction mixture was stirred for 1 h and ether was added to precipitate completely the toluene-*p*-sulphonate salt, m.p. 164° (from methanol–ether). The salt was then converted into the bromide by dissolution in methanol–48% hydrobromic acid followed by addition of ether. [v] As in *e* but with stirring for 1 h. [w] Prepared by dissolving the toluene-*p*-sulphonate salt in ethanol–48% hydrobromic acid and adding ether, or by ion exchange on Amberlite IRA400(Br^-).

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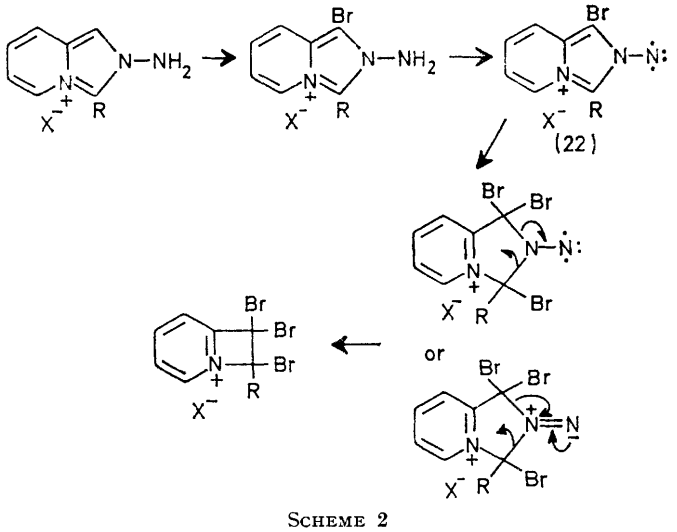
TABLE 2

1,2-Dihydroazeto[1,2-*a*]pyridinium salts

Reactants	Product	X	Yield (%)	M.p. (°C)	Cryst. solvent	Found (%) C	H	N	Required (%) C	H	N
(11) [a] (0.4 g) in H_2O (2 ml) + sat. aq. Br_2 (75 ml) [b,c]	(16)	Br	22	156—158	Me_2CO–48% aq. HBr	16.9	1.1	2.8	16.8	0.8	2.8
(15) [a] (0.2 g) in 50% aq. MeOH (5 ml) + sat. aq. Br_2 (30 ml) [b,d]	(19)	Br	17	142—143	MeOH–Et_2O	22.2	1.8	3.35	22.0	1.6	3.2
(13) [a] (0.5 g) in H_2O (2 ml) + sat. aq. Br_2 (75 ml) [b,d]	(18)	Br	53	187—188	MeOH–Et_2O	31.4	2.4	2.8	31.3	1.8	2.8
	(18)	ClO_4 [e]		177—178	MeOH–Et_2O	30.5	2.1	2.7	30.1	1.75	2.7
(12) [f] (0.25 g) in H_2O (5 ml) + sat. aq. Br_2 (30 ml) [b,c]	(17) [g]	Br	66	104	MeOH–Et_2O	31.5	2.0	2.5	31.3	1.8	2.8
(12) [a] (0.5 g) in H_2O (5 ml) + sat. aq. Br_2 (75 ml) [b,d]	(17) [g]	Br	75	107—108	MeOH–Et_2O						

[a] Bromide salt. [b] Added in bulk. [c] The reaction mixture was stirred for 0.5 h, after which the red solid which had separated was filtered off, washed with water, and dissolved in absolute acetone. The solution was then boiled and the product which separated filtered off. [d] The reaction mixture was stirred for 0.5 h, after which the liquid was decanted from the red oil which had separated. After washing with water the oil was dissolved in absolute acetone and the solution boiled under reflux until the product precipitated. [e] Obtained by adding ether to a solution of the bromide in methanol–60% perchloric acid. [f] Toluene-*p*-sulphonate salt. [g] Hydrogenation of the bromide (0.5 g) in ethanol (75 ml) over 10% palladium–charcoal (0.15 g) until uptake ceased followed by filtration, basification, extraction of the filtrate with ether, and evaporation of the dried extract gave a gum which was dissolved in ethanol–48% hydrobromic acid. Addition of ether gave phenyl 2-pyridylmethyl ketone hydrobromide (0.04 g, 15%), m.p. 157—158° (from ethanol–ether) (lit.,[10] 156—157°) (Found: C, 56.1; H, 4.3; N, 5.1. Calc. for $C_{13}H_{11}NO,HBr$: C, 56.1; H, 4.35; N, 5.0%). identical with a sample prepared from the authentic ketone.[11]

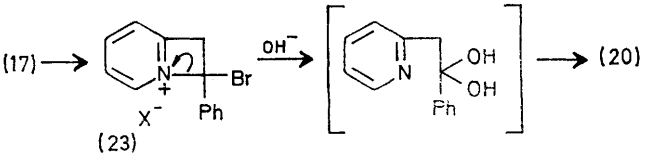
N-amino-salt (15) with nitrous acid gave the pyridyloxadiazole (21), which has been shown previously [6] to be the



SCHEME 2

product of nitrosation of 3-methylimidazo[1,5-*a*]pyridine. Further treatment of compound (15) with aqueous bromine gave the corresponding tribromodihydroazetopyridinium salt (19). Hydrogenation of the tribromo-2-phenyldihydroazetopyridinium salt (17) over palladium–charcoal resulted in the uptake of *ca.* 2 mol. equiv. of hydrogen, and subsequent basification gave phenyl 2-pyridylmethyl ketone, presumably *via* the intermediate monobromo-compound (23) as shown in Scheme 3.

Oxidation of the *N*-amino-salt (11) derived from the parent imidazopyridine (6) gave 1,1,2,2-tetrabromo-1,2-dihydroazeto[1,2-*a*]pyridinium bromide (16), probably



SCHEME 3

via initial electrophilic brominations at both the free positions of the five-membered ring.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus.

We thank Allen and Hanburys for a maintenance grant (to K. D. V.).

[5/2185 *Received*, 10*th November*, 1975]

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