N-Amination and Subsequent Oxidation of Imidazo[1,2-*a*]pyrimidines

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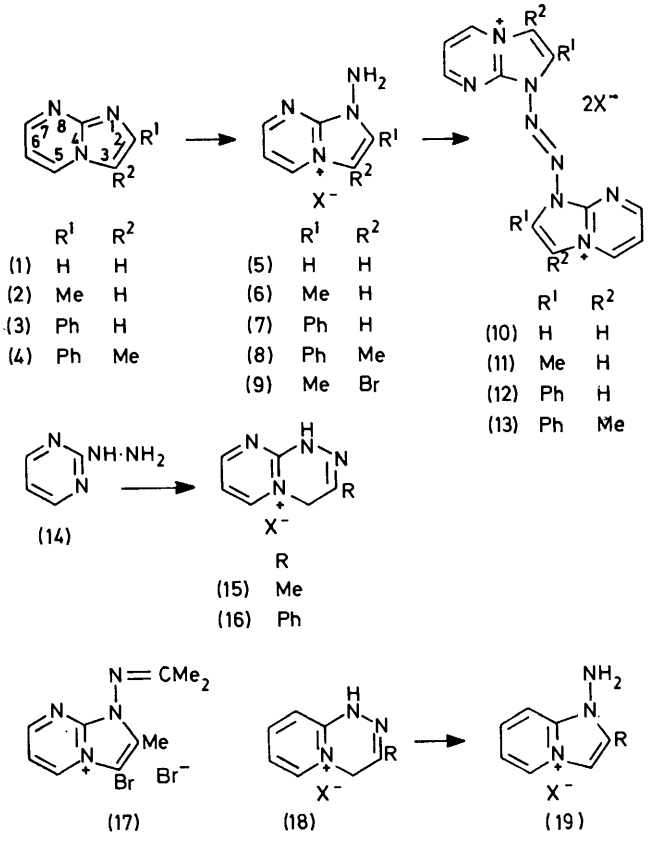
Imidazo[1,2-*a*]pyrimidines are *N*-aminated at N-1 by *O*-*p*-tolylsulphonylhydroxylamine. Subsequent oxidation of the resulting *N*-amino-salts with bromine generally results in the corresponding 1,1′-azoimidazo[1,2-*a*]pyrimidinium salts.

WE were interested in the 1,1′-azoimidazo[1,2-*a*]pyrimidinium salts (10)—(13) as potential short acting, non-depolarising neuromuscular blocking agents, and thought to prepare them by oxidation of the corresponding *N*-amino-salts (5)—(8), in turn obtained by *N*-amination of the imidazopyrimidines (1)—(4), respectively.



An attempt to *N*-aminate 2-methylimidazo[1,2-*a*]-pyrimidine with hydroxylamine-*O*-sulphonic acid was unsuccessful, but treatment of the bases (1)—(4) with *O*-*p*-tolylsulphonylhydroxylamine [1] gave the corresponding *N*-amino-salts (5)—(8) in good yield.

Imidazo[1,2-*a*]pyrimidine undergoes protonation on N-1,[2] and it was anticipated that *N*-amination would likewise occur preferentially at N-1. It has recently been reported,[3] however, that adenine is *N*-aminated by *O*-mesitylsulphonylhydroxylamine at N-3, in the six-membered ring; consequently we considered it necessary to confirm unambiguously the position of *N*-amination of imidazo[1,2-*a*]pyrimidines. Previously it has been shown [4,5] that 1,4-dihydropyrido[1,2-*a*]-*as*-triazinium salts (18) undergo ring contraction in boiling aqueous acid yielding the corresponding 1-aminoimidazo[1,2-*a*]-pyridinium salts (19). We thought to confirm the structure of the *N*-aminoimidazopyrimidinium salts (5)—(9) by similarly obtaining the salts (6) and (7) by ring contraction of the corresponding 1,4-dihydropyrimido-triazinium salts (15) and (16). Treatment of 2-hydrazino-pyrimidine with bromoacetone or phenacyl bromide gave the required triazinium salts (15) and (16), respectively, but attempts to effect ring contraction of the phenyl compound (16) to the *N*-amino-salt (7), even by prolonged heating in 16% hydrobromic acid, were unsuccessful.

Similar treatment of the methyl-substituted triazinium salt (15), however, resulted in ring contraction to the *N*-amino-salt (6), which was identical with a sample prepared by direct *N*-amination of the methyl base (2), thus confirming that *N*-amination of imidazo-[1,2-*a*]pyrimidines occurs at N-1.

Oxidation of the *N*-amino salts (5), (7), and (8) with bromine afforded the corresponding tetrazenes (10), (12), and (13), respectively, but similar treatment of the methyl-substituted *N*-amino-compound (6) resulted in

TABLE 1

1,4-Dihydropyrimido[1,2-*a*]triazinium salts

Reactants	Product	X	Yield (%)	M.p. (°C)	Cryst. solvent	Found (%) C	H	N	Reqd. (%) C	H	N
(14) [7] (1.26 g) in EtOH (50 ml) + MeCO·CH_2Br (1.57 g) [a]	(15)	Br	50	256—257	MeOH–Et_2O	36.35	4.25	24.4	36.7	4.0	24.5
(14) [7] (1.09 g) in EtOH (50 ml) + PhCO·CH_2Br (1.99 g) [a]	(16)	Br	45	260—262	EtOH	49.2	4.1	19.1	49.5	3.8	19.2
	(16)	$C_6H_2N_3O_7$ [b]		168—170	MeCN	49.2	3.1	22.4	49.2	3.0	22.3

[a] The solution was boiled under reflux for 2 h and then cooled. The product which separated was then filtered off and recrystallized. [b] Picrate.

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TABLE 2

1-Aminoimidazo[1,2-*a*]pyrimidinium salts

Reactants	Product	X	Yield (%)	M.p. (°C)	Cryst. solvent	Found (%) C	Found (%) H	Found (%) N	Reqd. (%) C	Reqd. (%) H	Reqd. (%) N
(1) [a] (0.5 g) in $CHCl_3$ (20 ml) + TSH [b,c]	(5)	$C_7H_7SO_3$ [d]	62	171—173 [e]	MeOH–Et_2O	51.1	4.9	18.2	51.0	4.6	18.3
(2) [g] (0.5 g) in $CHCl_3$ (30 ml) + TSH [f,g]	(6)	$C_7H_7SO_3$ [d]	67	209 [e]	MeOH–Et_2O	52.6	5.0	17.4	52.5	5.0	17.5
(3) [g] (0.5 g) in $CHCl_3$ (30 ml) + TSH [i,j]	(7)	ClO_4	41	203 [e]	H_2O	46.0	4.0	17.7	46.4	3.6	18.0
(4) [k] (1.0 g) in $CHCl_3$ (40 ml) + TSH [l,m]	(8)	$C_7H_7SO_3$ [d]	85	218—219 [e]	MeOH–Et_2O	60.7	5.2	14.05	60.6	5.1	14.1
(15) (1. 31 g) in 16% HBr [h]	(6)	Br	80	238—239	EtOH	36.6	4.2	24.1	36.7	4.0	24.5
(6) [n] (0.5 g) in H_2O (15 ml) + sat.aq.Br_2 (30 ml) [o]	(9) [p]	Br	16	227—228 [e]	MeOH–Et_2O	27.6	2.7	18.1	27.3	2.6	18.2

[a] Prepared by treating 2-aminopyrimidine (1.9 g) with bromoacetaldehyde oxime [5] (2.76 g) and leaving the mixture overnight at room temperature. The resulting gum was thoroughly washed with ether and then dissolved in ethanol (4 ml). The resulting solution was treated with 70% perchloric acid (2 ml) and set aside for 2 h, after which the *imidazo*[1,2-a]*pyrimidine hydroperchlorate* (1.87 g, 78.6%) which had separated was filtered off and recrystallized from ethanol giving needles, m.p. 198—200° (Found: C, 33.0; H, 2.8; N, 19.1. $C_6H_5N_3,HClO_4$ requires C, 32.8; H, 2.75; N, 19.1%). The *hydrobromide* crystallized from methanol–ether and had m.p. 237—239° (decomp.) (Found: C, 36.2; H, 2.95; N, 20.8. $C_6H_5N_3,HBr$ requires, C, 36.0; H, 3.0; N, 21.0%). The free base, obtained by chloroform extraction of a basified solution of the hydroperchlorate salt was purified by vacuum sublimation (110 °C and 0.2 mmHg) and had m.p. 129—130° (lit.,[2] 129—130°) (Found: C, 60.3; H, 4.2; N, 35.2. Calc. for $C_6H_5N_3$: C, 60.5; H, 4.2; N, 35.3%). [b] A solution of *O-p*-tolylsulphonylhydroxylamine [1] in chloroform (30 ml) prepared from ethyl *O-p*-tolylsulphonylacetohydroximate (1.2 g) by the procedure previously described [1] but with extraction of the reagent into chloroform. [c] The mixture was stirred for 1 h after which the product was filtered off and recrystallized. [d] Toluene-*p*-sulphonate. [e] With decomp. [f] As footnote *b* but from ethyl *O-p*-tolylsulphonylacetohydroximate (1.05 g). [g] The mixture was stirred for 0.5 h after which the product was filtered off and recrystallized. [h] The solution was heated on a simmering water-bath for 14 h and then evaporated to dryness, and the residual bromide was recrystallized. [i] As footnote *b* but from ethyl *O-p*-tolylsulphonylacetohydroximate (0.73 g). [j] The mixture was stirred for 0.5 h and then ether (200 ml) was added. The resulting gum was separated and dissolved in methanol (20 ml) and then treated with 70% perchloric acid (20 drops). Ether was then added and the precipitated perchlorate filtered off and recrystallized. [k] Prepared by boiling a solution of 2-aminopyrimidine (10 g) and α-bromopropiophenone (15 g) in methanol (50 ml) under reflux for 24 h. The solution was then evaporated and the residue boiled with acetone. The resulting solid was filtered off and boiled with aqueous 10% sodium carbonate (100 ml). After cooling, the *base* was filtered off, washed with water and then recrystallized from methylated spirits giving yellow needles, m.p. 211° (4.6 g, 31% based on the halogenoketone) (Found: C, 74.2; H, 5.4; N, 20.3. $C_{13}H_{11}N_3$ requires C, 74.6; H, 5.3; N, 20.1%). [l] As footnote *b* but in chloroform (40 ml), and from ethyl *O-p*-tolylsulphonylacetohydroximate (1.35 g). [m] The mixture was stirred for 1 h after which ether (200 ml) was added. The precipitated solid was then filtered off and recrystallized. [n] Toluene-*p*-sulphonate salt. The bromide salt gave similar results. [o] The aqueous bromine was added in bulk and the solution set aside at room temperature for 20 h. The precipitated perbromide was then filtered off and boiled for 2 h in methanol (15 ml) containing 48% HBr (5 drops). Addition of ether precipitated the bromide which was filtered off and recrystallized. [p] When a solution of the bromide (0.03 g) in anhydrous acetone (20 ml) was boiled under reflux for 72 h then filtered to remove starting material and concentrated to 5 ml, the *acetone condensation compound* (17) (0.007 g, 21%) crystallized on cooling and had m.p. 222—225° (decomp.) (Found: C, 33.2; H, 3.7; N, 15.3. $C_{10}H_{12}Br_2N_4,H_2O$ requires C, 32.8; H, 3.85; N, 15.3%).

TABLE 3

1,1′-Azoimidazo[1,2-*a*]pyrimidinium salts

Reactants	Product	X	Yield (%)	M.p. (°C)	Cryst. solvent	Found (%) C	Found (%) H	Found (%) N	Reqd. (%) C	Reqd. (%) H	Reqd. (%) N
(5) [a] (0.3 g) in H_2O (15 ml) + sat. aq. Br_2 (60 ml) [b]	(10)	Br	48	245—275 [c]	aq. 48% HBr–Me_2CO	32.9	2.4	25.45	32.5	2.7	25.2 [d]
	(10)	ClO_4 *		288—289 [g]	H_2O	30.8	2.6	23.9	30.85	2.6	24.0
(7) [e] (1.0 g) in H_2O (100 ml) + sat. aq. Br_2 (50 ml) [f]	(12)	Br	49	228 [g]	aq. 48% HBr–Me_2CO	46.9	3.3	18.0	46.9	3.6	18.2 [h]
	(12)	$C_6H_2N_3O_7$ [i]		190—191 [g]	$MeNO_2$–Et_2O	49.5	3.2	22.1	49.4	2.5	22.4
(8) [a] (0.6 g) in H_2O (50 ml) + sat. aq.Br_2 (40 ml) [j]	(13)	Br	45	255 [g]	MeOH–Et_2O	46.4	4.15	16.5	46.0	4.5	16.5 [k]
	(13)	$C_6H_2N_3O_7$		168 [g]	$MeNO_2$–Et_2O	50.4	2.6	22.0	50.6	2.9	21.7

[a] Toluene-*p*-sulphonate salt. [b] The saturated aqueous bromine was added in bulk and the mixture set aside for 1 h. The perbromide was then filtered off, dried, and dissolved in absolute acetone. After a short induction period the bromide separated and was filtered off and recrystallized. [c] Decomposition range. [d] For $1H_2O$. [e] Perchlorate salt. [f] The saturated aqueous bromine was added in bulk and the reaction mixture set aside for 24 h. The perbromide was then filtered off and boiled in absolute acetone. The resulting bromide was then filtered off and recrystallized. [g] With decomp. [h] For $2H_2O$. [i] Picrate salt. [j] As footnote *f* but set aside for 2 h. [k] For $4H_2O$.

* Obtained by treating an aqueous solution of the bromide with 70% perchloric acid.

the brominated *N*-amino-salt (9) instead of the tetrazene (11). Attempts to oxidise compound (9) further were unsuccessful owing to the complete insolubility of its perbromide salt. Treatment of the bromide salt of (9) with acetone resulted in its conversion, in low yield, into the condensation product (17).

The parent imidazo[1,2-*a*]pyrimidine was conveniently and cleanly prepared by treating 2-aminopyrimidine with bromoacetaldehyde oxime,[6] the first formed quaternary pyrimidinium salt being cyclized with perchloric acid.

EXPERIMENTAL

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

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