The Nitration of Imidazo[1,5-*a*]pyridines

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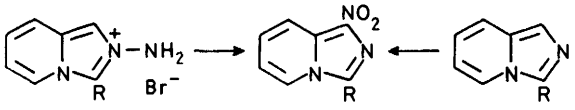
Imidazo[1,5-*a*]pyridines in acetic acid solution are readily nitrated by nitric acid–sulphuric acid, although in some instances treatment of the base hydrogensulphate with nitric acid–acetic acid is preferred. Nitration occurs most readily in the 1-position, but 3-nitration occurs if the 1-position is already substituted.

PREVIOUSLY we reported [1] the formation of 1-nitroimidazo[1,5-*a*]pyridines during the oxidation of 2-aminoimidazo[1,5-*a*]pyridinium bromides (1)—(3) with hot nitric acid. Evidence indicated that the reaction proceeds *via* initial oxidative deamination, followed by nitration in the five-membered ring.

Previous reports,[2,3] however, suggest that imidazo-[1,5-*a*]pyridine (4), although readily nitrated in the 1-position using copper(II) nitrate, is decomposed by nitric



(1) R = H (7) R = H (4) R = H
(2) R = Me (8) R = Me (5) R = Me
(3) R = Ph (9) R = Ph (6) R = Ph
(10) R = NO_2

acid–sulphuric acid even in the cold. This apparent contradiction led us to re-examine the direct nitration of imidazo[1,5-*a*]pyridines.

RESULTS AND DISCUSSION

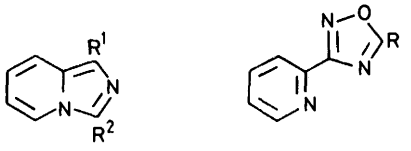
Nitration of the parent base (4) was best accomplished by treating the hydrogensulphate salt with nitric acid–acetic acid giving 1-nitroimidazo[1,5-*a*]pyridine (7).[1,2]

Treatment of acetic acid solutions of the 3-substituted bases (5) and (6) with nitric acid–sulphuric acid gave the corresponding nitro-derivatives (8) and (9) in moderate yields of 34% and 33%, respectively, both products being readily isolated in a pure state. The yield of the 3-methyl-1-nitro-compound (8) compared very favourably with a yield of 3% previously recorded [2] for the nitration of the methyl base (5) using copper(II) nitrate.

Similar nitration of 1-methylimidazo[1,5-*a*]pyridine (15) gave 1-methyl-3-nitroimidazo[1,5-*a*]pyridine (29) in 20% yield.

Reduction of the 3-methyl-1-nitro-compound (8) with zinc dust–acetic acid gave the corresponding amine (13) the structure of which followed from its elemental analysis and from the analysis and mass spectrum of its acetyl derivative (14) (Scheme 1).

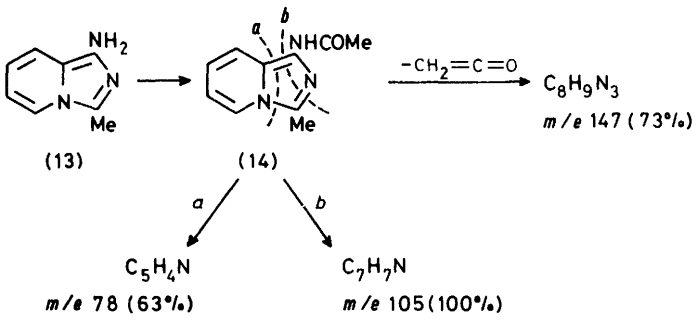
Nitration of the 1-phenyl base (16) gave either the 3-nitro-derivative (18) or the dinitro-derivative (19) depending upon the experimental conditions. Thus treatment of the 1-phenyl base (16) in acetic acid with nitric acid–sulphuric acid gave the dinitro-compound (19); treatment of a solution of the 1-phenyl base hydrogensulphate (17) in acetic acid with 1 equiv. of nitric acid, however, gave the 3-nitro-1-phenyl-base (18). Treatment of the hydrogensulphate salt of the 3-methyl-



R^1	R^2	
(15) Me	H	(11) R = Me
(20) Ph	Me	(12) R = Ph
(21) *p*-$O_2NC_6H_4$	Me	
(29) Me	NO_2	

1-phenyl base (20) with nitric acid–acetic acid gave the 3-methyl-*p*-nitrophenyl compound (21).

The location of the nitro-group in the imidazole ring of (18) was based on the observation that its u.v. spectrum was substantially different from that of (21), in which nitration could not have occurred in the five-membered ring. Further, (18), unlike (21), would not form a hydrobromide, an observation consistent with the reduced basicity of (18) consequent upon the direct attachment of the nitro-group to the imidazole ring.



SCHEME 1

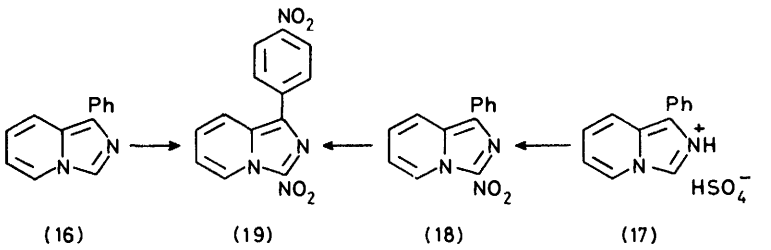
The location of the nitro-group in the 4-position of the benzene ring of (19) followed from its derivation by the further nitration of (18), and from a comparison with the nitric acid oxidation of 2-amino-1-phenylimidazo[1,5-*a*]-pyridinium bromide.[1]

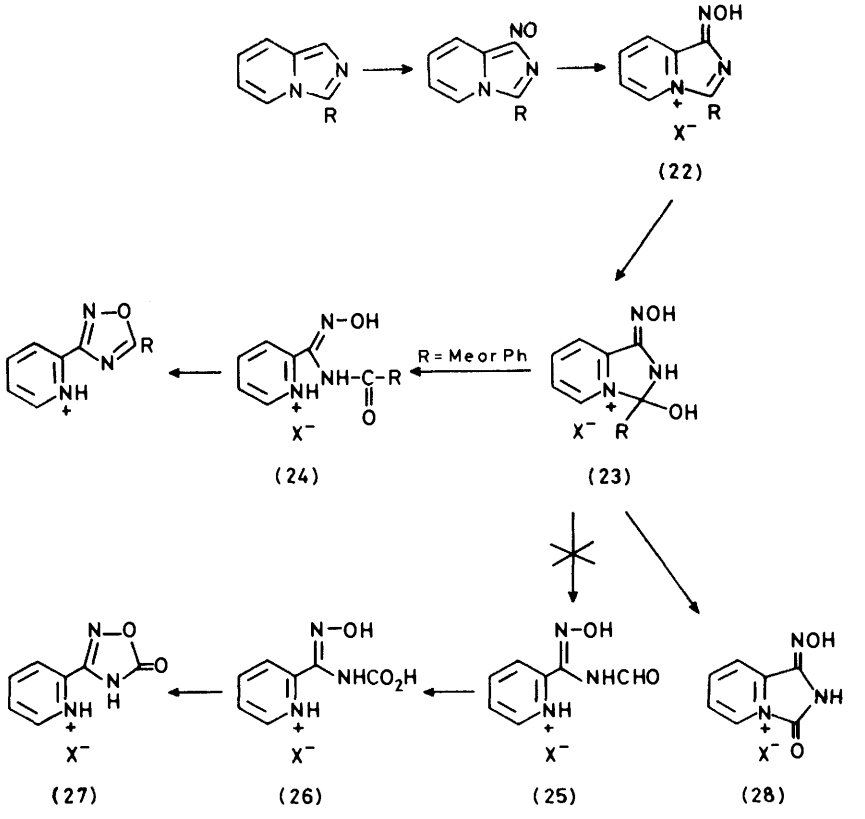
Interestingly, in the nitration of both 3-methyl- and 3-phenyl-imidazo[1,5-*a*]pyridine using nitric acid–sulphuric acid the corresponding 2-(5-substituted-1,2,4-

oxadiazol-3-yl)pyridines (11) and (12) were obtained as by-products.

The ease of oxidation of imidazo[1,5-*a*]pyridine (4) under nitrating conditions has been previously noted;[2,3] it has also been stated [4] that nitration of readily oxidised compounds can result in simultaneous nitrosation by the nitrous acid produced during the oxidation process. Thus the formation of the oxadiazolylpyridines (11) and (12) as by-products during the nitration of the 3-substituted imidazo[1,5-*a*]pyridines (5) and (6), respectively, may be explained in terms of initial nitrosation followed by rearrangement of the resulting 1-nitroso-imidazo[1,5-*a*]pyridine as shown in Scheme 2; such rearrangements have been described previously.[5]

Further nitration of 1-nitroimidazo[1,5-*a*]pyridine (7) with nitric acid–sulphuric acid–acetic acid gave, in addition to the 1,3-dinitro-compound (10), a by-product, the i.r. spectrum of which showed no bands attributable to a nitro-group. Analytical data for the bromide and hydrogensulphate salts of the by-product indicated a formula of $C_7H_6N_3O_2$ for the cation; the possibility of its being a hydro-salt of 2-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)pyridine (27), formed by oxidation of the ring-opened intermediate (25) followed by re-cyclisation of the resulting carbamic acid (26), was precluded by comparison with an authentic sample prepared from pyridyl-2-carboxamide oxime and ethyl chloroformate. The structure (28) has been assigned to the by-product on the basis of the presence in its u.v. absorption spectrum of a long-wave maximum at 388 nm suggesting the presence of a fused bicyclic system, and the presence in its i.r. spectrum (KBr disc) of bands at 1 755 and 1 700 cm^{-1} attributable to ν(C=O) and ν(C=N); also present was a broad band in the 3 300—2 700 cm^{-1} region attributable to ν(N–H). The formation of (28) may be explained in terms of the oxidation of the intermediate (23, R = H)





SCHEME 2

TABLE 1

Nitrations

Reactants	Product	Yield (%)	M.p. (°C)	Crystallising solvent	Analysis (%) Found C	Found H	Found N	Required C	Required H	Required N
(4) [a] (0.216 g) + HNO_3 (70% w/w) (0.092 g) in AcOH (1.5 cm³) [b]	(7) [c]	21	245—246 [d]	AcOH	50.9	3.3	25.9	51.5	3.1	25.8
(5) [7] (0.5 g) in AcOH (5 cm³) + HNO_3 (70% w/w) (0.3 g) and H_2SO_4 (98% w/w) (0.8 g) in AcOH (3 cm³) [e]	(8)	34	247 [f]	AcOH						
(6) [7] (0.388 g) in AcOH (2 cm³) + HNO_3 (70% w/w) (0.18 g) and H_2SO_4 (98% w/w) (0.4 g) in AcOH (0.5 cm³) [g]	(9)	33	212 [h]	MeCN	65.0	3.6	17.8	65.3	3.8	17.6
(17) [i] (1.27 g) in AcOH (10 cm³) + HNO_3 (70% w/w) (0.391 g) in AcOH (5 cm³) [j]	(18) [k]	24	168	EtOH	64.8	3.8	17.4	65.3	3.8	17.6
(16) [8] (0.552 g) in AcOH (3 cm³) + HNO_3 (70% w/w) (0.27 g) and H_2SO_4 (98% w/w) (0.6 g) in AcOH (1 cm³) [l]	(19) [m]	22	271	MeCN [n]	54.7	2.8	19.4	54.9	2.8	19.7
(18) (0.167 g) + HNO_3 (70% w/w) (0.07 g) and H_2SO_4 (98% w/w) 0.16 g) in AcOH (5 cm³) [o]	(19)	70	270 [p]	MeCN						
(7) (0.34 g) + HNO_3 (70% w/w) (0.19 g) and H_2SO_4(98% w/w) (0.407 g) in AcOH (5 cm³) [q]	(10) [r]	28	278	AcOH [s]	40.8	1.9	26.5	40.4	1.9	26.9
(20) [t] (1.0 g) + HNO_3 (70% w/w) (0.28 g) in AcOH (5 cm³) [u]	(21) [v]	28 [w]	220—221	MeOH–H_2O	66.0	4.4	16.65	66.4	4.4	16.6
(15) [7] (0.396 g) in AcOH (2 cm³) + HNO_3 (70% w/w) (0.271 g) and H_2SO_4 (98% w/w) (0.62 g) in AcOH (3 cm³) [x]	(29) [y]	20	240—242	AcOH [z]	54.05	4.0	23.9	54.0	4.0	23.7

[a] The hydrogensulphate salt was used; it was prepared by dissolving the base [7] in acetic acid and adding concentrated sulphuric acid followed by diethyl ether. The precipitated *hydrogensulphate* crystallised from methanol–diethyl ether as colourless plates, m.p. 188—190 °C (Found: C, 38.9; H, 3.8; N, 12.9. $C_7H_6N_2$, H_2SO_4 requires C, 38.9; H, 3.7; N, 13.0%). [b] The mixture was heated in a boiling water-bath. After about 0.5 min a vigorous reaction occurred giving a red solution which was immediately cooled in ice and treated with diethyl ether. The gummy solid which precipitated was separated and triturated with ethanol, to give the mono-nitro-compound which was filtered off and recrystallised. [c] $\lambda_{max.}$ (MeOH) 211, 230 (sh), 261 (sh), 272 (sh), and 383 nm (log ε 3.97, 3.945, 3.37, 3.32 and 4.19). [d] Lit.[2] m.p. 244—245 °C. [e] The reaction mixture was allowed to stand at room temperature; it rapidly became deep green before turning yellow after about 3 min. Diethyl ether was then added and the solution cooled on ice. The gum which separated was separated from the mother-liquors by decantation and triturated with ethanol. The nitro-compound which separated was filtered off and recrystallised; treatment of the filtrate with diethyl ether gave a gum which was separated, basified, and extracted with diethyl ether. Evaporation of the dried extract followed by recrystallisation of the residue from di-isopropyl ether gave 2-(5-methyl-1,2,4-oxadiazol-3-yl)pyridine (**11**) (0.069 g, 11%) m.p. 87—88 °C (lit.[5] m.p. 88—89 °C) (Found: C, 59.2; H, 4.2; N, 25.8; Calc. for $C_8H_7N_3O$: C, 59.6; H, 4.4; N, 26.1%). [f] Lit.[1,2] m.p. 274, 271.5 °C. [g] The mixed acids were added dropwise over a period of 5 min to the solution of the base and the reaction mixture stirred a further 5 min at room temperature. Addition of ethanol (15 cm³) completed the separation of the *nitro-compound* which was filtered off and recrystallised. Evaporation of the filtrate to dryness followed by treatment of the residue with concentrated (48% w/w) hydrobromic acid followed by ethanol and diethyl ether gave 2-(5-*phenyl*-1,2,4-*oxadiazol*-3-*yl*)*pyridine hydrobromide* (3.5%) which was recrystallised from methanol–ether and had m.p. 186 °C (Found: C, 51.55; H, 3.3; N, 13.8; $C_{13}H_9N_3O$·HBr requires C, 51.3; N, 3.3; N, 13.8%). The hydrobromide was identical with a sample prepared from the oxadiazolylpyridine (**12**) obtained using the procedure previously described.[5] [h] Lit.[1] m.p. 215 °C. [i] Prepared by dissolving the base (**16**) [6] (1 g) in acetic acid (10 cm³) and adding 98% sulphuric acid (0.6 g). Addition of diethyl ether precipitated the *hydrogensulphate* (0.79 g, 52%) which was recrystallised from methanol and had m.p. 225 °C (Found: C, 53.4; H, 3.95; N, 9.4. $C_{13}H_{10}N_2$, H_2SO_4 requires C, 53.4; H, 4.1; N, 9.6%). [j] The cooled solutions were mixed and stirred at 13—15 °C for 3.5 min. Ethanol (25 cm³) was then added, the reaction mixture stirred vigorously and the product filtered off and recrystallised. [k] $\lambda_{max.}$ (MeOH) 207.5, 229, 280, 342, and 436 nm (log ε 4.245, 4.09, 4.23, 3.69, and 4.19). [l] The mixed acids were added dropwise to the solution of the base over 15 min, the reaction mixture being maintained at 15—16 °C. After stirring for a further 5 min the reaction mixture was diluted with water and the precipitated dinitro-compound filtered off and recrystallised. [m] $\lambda_{max.}$ (MeOH) 233, 252 (sh), 368, and 430 nm (log ε 4.015, 3.95, 4.16, and 4.25). [n] With decolourising charcoal. [o] The reaction mixture was heated for 2 min at 77—80 °C, after which it was cooled and treated with diethyl ether. The gum which precipitated was separated off and boiled with ethanol (10 cm³). The dinitro-compound was then filtered off and recrystallised. [p] The i.r. spectrum was identical with that of the previous sample and a mixed m.p. showed no depression. [q] The mononitro-compound was treated with nitric acid–sulphuric acid–acetic acid and heated at 64 °C for 2 min. The mixture was then cooled and treated with diethyl ether; the gum which precipitated was separated off and warmed with ethanol (10 cm³) giving the yellow dinitro-compound which was filtered off. The filtrate was then again treated with diethyl ether giving 1-*hydroxyimino*-3-*oxo*-1,2,3-*trihydroimidazo*[1,5-*a*]*pyridinium hydrogensulphate* (**28**, X = HSO_4) (0.114 g, 21%) which was recrystallised from methanol and had m.p. 225 °C (Found: C, 31.8; H, 2.45; N, 15.8. $C_7H_7N_3O_6S$ requires C, 32.2; H, 2.7; N, 16.1%), $\lambda_{max.}$ (MeOH) 268 and 388 nm (log ε 3.96 and 3.70). The *bromide* (**28**, X = Br) prepared by dissolving the hydrogensulphate in (48% w/w) hydrobromic acid followed by the addition of methanol and diethyl ether, and was recrystallised from (48% w/w) hydrobromic acid–methanol–diethyl ether, m.p. 260—262 °C (Found: C, 34.4; H, 2.9; N, 17.2. $C_7H_6BrN_3O_2$ requires C, 34.45; H, 2.5; N, 17.2%). [r] $\lambda_{max.}$ (MeOH) 207, 239, 334 (sh), 347, and 383 nm (log ε 3.96, 3.97, 4.02, 4.15, and 4.08). [s] Or by vacuum sublimation at 140—150 °C and 0.1 mmHg. [t] The hydrogensulphate salt monohydrate was used. [u] The solution was heated in a boiling water-bath until the initial effervescence subsided. Addition of diethyl ether to the cooled reaction mixture precipitated a gum which was separated off and dissolved in methanol (20 cm³) containing 48% hydrobromic acid (5 drops). Addition of diethyl ether precipitated 3-methyl-1-(4-nitrophenyl)-imidazo[1,5-*a*]pyridine hydrobromide monohydrate (0.305 g, 28%) which was recrystallised from hydrobromic acid (48% w/w)–methanol–diethyl ether, m.p. 245 °C (decomp.) (Found: C, 47.8; H, 3.9; N, 12.0. $C_{14}H_{11}N_3O_2$, HBr, H_2O requires C, 47.7; H, 4.0; N, 11.9%). The *free base* (**21**) was obtained by basifying an aqueous methanolic solution of the hydrobromide. [v] $\lambda_{max.}$ (MeOH) 207, 223.5, 288 (sh), and 420 nm (log ε 4.32, 4.26, 3.59, and 4.275). [w] Based on the initially isolated hydrobromide. [x] The mixed acids were added dropwise over a period of 15 min to the stirred suspension of the base at 15—16 °C. The reaction mixture was then stirred for a further 5 min at 15 °C before the addition of an equal volume of water; the product which precipitated was then filtered off and purified. [y] $\lambda_{max.}$ (MeOH) 208, 255, 261, 332, and 425 nm (log ε 4.07, 3.85, 3.85, 30.1, and 4.15). [z] After initial vacuum sublimation.

Table 2

Syntheses

Reactants	Product	Yield (%)	M.p. (°C)	Crystallising solvent	Analysis (%) Found C	Found H	Found N	Required C	Required C	Required N
(Phenyl-2-pyridylmethyl)amine dihydrochloride [g] (15 g) + AcOH (70 cm³) [a]	*N*-(phenyl-2-pyridylmethyl)-acetamide	40	107	Et_2O	74.2	6.2	12.4	74.3	6.2	12.4
(Phenyl-2-pyridylmethyl)amine dihydrochloride [g] (41 g) + Ac_2O (50 cm³) [b]	(20)-hydrogensulphate salt	79	238	MeOH	51.7	4.5	8.6	51.85	5.0	8.6 [c]
N-(Phenyl-2-pyridylmethyl)-acetamide (4 g) + $POCl_3$ (8 cm³) in benzene (25 cm³) [d]	(20)-hydrobromide salt	35	264—266$_1$	MeOH–Et_2O	58.0	4.5	9.7	58.15	4.5	9.7
Pyridine-2-carboxamide oxime (1.37 g) in toluene (10 cm³) + ethyl chloroformate (1.09 g) in toluene (20 cm³) [e]	pyridine-2-carboxamide oxime ethoxycarbonyl ether	62 [f]	100.5	PhMe	51.3	5.2	20.2	51.7	5.3	20.1
Pyridine-2-carboxamide oxime (1.37 g) in toluene (10 cm³) + ethyl chloroformate (1.085 g) toluene (20 cm³) [g]	2-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-pyridine [h]	10	204	PhMe	52.0	3.0	26.1	51.5	3.1	25.8
	2-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-pyridine hydrobromide [i]	56	203—207 (decomp)	EtOH–Et_2O	34.1	2.8	17.2	34.45	2.5	17.2

[a] The mixture was boiled under reflux for 18 h. It was then cooled and the acetic acid evaporated off under reduced pressure. The residue was basified and the liberated base extracted into diethyl ether. Evaporation of the dried extract gave the *substituted acetamide*. [b] The mixture was boiled under reflux for 1 h. The acetic anhydride was then evaporated off under reduced pressure and the residue basified. The liberated base was extracted into diethyl ether and the dried extract evaporated. The oily residue was dissolved in methanol and treated with a solution of 98% w/w sulphuric acid (20 g) in methanol (100 cm³). Addition of diethyl ether precipitated the *hydrogensulphate* which was filtered off and recrystallised. [c] For the monohydrate. [d] The mixture was boiled under reflux for 17 h and then the benzene evaporated off under reduced pressure. The residue was basified and the liberated base extracted into diethyl ether. Evaporation of the dried extract gave the base which was converted into the *hydrobromide* by treatment with ethanol–hydrobromic acid (48 w/w %) followed by diethyl ether. [e] The ethyl chloroformate solution was added to the boiling solution of the carboxamide oxime and the mixture boiled under reflux for a further 0.5 h. The mixture was then filtered whilst still hot giving pyridine-2-carboxamide oxime hydrochloride (0.74 g). Evaporation of the filtrate gave the *amino-ester* (1.1 g) which was recrystallised. [f] Based on unrecovered pyridine-2-carboxamide oxime. [g] The ethyl chloroformate solution was added to the boiling solution of the carboxamide oxime and the mixture boiled under reflux for 18 h. The mixture was filtered whilst still hot and the filtrate then cooled. The solid which separated was evaporated off and digested with toluene (15 cm³) at 55 °C. The residue was filtered off and recrystallised. [h] λ_{max} (MeOH) 220, 272, and 279 (sh) nm (log ε 3.87, 3.79, and 3.66). [i] Prepared by treating the base with ethanol–hydrobromic acid (48% w/w) followed by diethyl ether.

in preference to its ring-opening and subsequent recyclisation, as occurs for the methyl and phenyl analogues (24) as shown in Scheme 2.

The mechanistic route suggested for the conversion of the 1-nitro-base (7) into the quaternary salt (22) requires the initial replacement of the nitro- by a nitroso-group *via* the agency of nitrous acid produced in a competing oxidation process. Replacement of a 1-substituent in imidazo[1,5-*a*]pyridines has previously been noted;[1,6] thus 1-bromo-3-methylimidazo[1,5-*a*]pyridine is converted into the oxadiazolypyridine (11) or 3-methyl-1-nitroimidazo[1,5-*a*]pyridine (8) by nitrous acid and nitric acid, respectively.

EXPERIMENTAL

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

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