Synthetic Approaches to some Aza-analogues of Benzimidazole *N*-Oxides. Part 1. The Imidazo[4,5-*b*]pyridine Series

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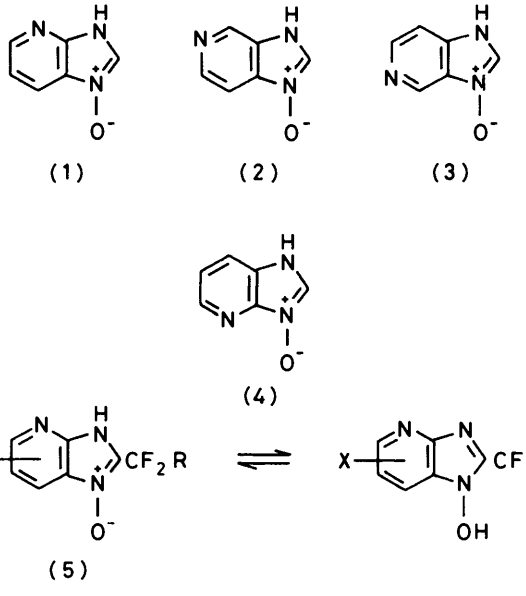
The 3-oxide of 2-*p*-nitrophenylimidazo[4,5-*b*]pyridine (8) may be obtained in good yield by base-induced cyclisation of 2-nitro-3-(*p*-nitrobenzylamino)pyridine (18). It is also obtained in lower yield, along with *p*-nitrobenzoic acid and other cleavage products, by the corresponding reactions of bases with the *N*-ethoxycarbonyl, *N*-methylsulphonyl, and *N*-*p*-tolylsulphonyl derivatives of 2-nitro-3-(*p*-nitrobenzylamino)pyridine [(7), (16), and (15), respectively]. Cleavage is the main reaction when *N*-(2-nitro-3-pyridyl)-*N*-phenacylmethanesulphonamide (17) is treated with bases: phenylglyoxal, or its Schiff base with 3-amino-2-nitropyridine, are possible intermediates in the cleavage process. 3-Nitro-2-(*p*-nitrobenzylamino)pyridine (31) is similarly cyclised in basic media to give the 1-oxide of 2-*p*-nitrophenylimidazo[4,5-*b*]pyridine (32).

Benzimidazole *N*-oxides, although not obtainable by direct oxidation of benzimidazoles, are nevertheless preparable by a wide variety of methods, most of which involve the cyclisation of an appropriately disubstituted benzene derivative.[1] Among the aza-analogues of benzimidazole *N*-oxides, only benzotriazole *N*-oxides are well known,[2] being produced by the action of base on *o*-nitrophenylhydrazines; scarcely anything is known about imidazopyridine 1- and 3-oxides, *i.e.* the ring systems (1)—(4). Imidazo[4,5-*b*]- and -[4,5-*c*]-pyridines undergo *N*-oxidation in the pyridine ring [3] and to the best of our knowledge the only recorded examples of simple 1- or 3-oxides are a group of 3*H*-imidazo[4,5-*b*]pyridine 1-oxides (1-hydroxy-1*H*-imidazo[4,5-*b*]pyridines) of the general formula (5), which are obtainable by partial reduction of the corresponding 2-acylamino-3-nitropyridines.[4]



Previous work in the St. Andrews laboratories [5–7] has been concerned with the formation of benzimidazole *N*-oxides by non-reductive, base-catalysed cyclisation of *o*-nitroaniline derivatives, in particular, the cyclisation of sulphonamides derived from *N*-*p*-nitrobenzyl-, *N*-phenacyl-, and *N*-acetonyl-*o*-nitroanilines. In principle, the cyclisation of the corresponding aminonitropyridine derivatives should provide access to imidazopyridine 1- and 3-oxides, and we now report on our efforts to prepare 1- and 3-oxides of some imidazo-[4,5-*b*]pyridines by such methods.

Analogy with our benzimidazole *N*-oxide syntheses required the use, as starting material, of a sulphonamide derived from 2-amino-3-nitro- or 3-amino-2-nitro-pyridine. However, no such compound had previously been reported in the literature, and so our initial synthetic attempts † began from ethyl *N*-(2-nitro-3-pyridyl)carbamate (6): [8] this is the main product of nitration of ethyl *N*-3-pyridylcarbamate, and is known to undergo alkylation at the exocyclic nitrogen in the presence of base.[8]

The synthetic sequence, shown in Scheme 1, had good precedent in the *o*-nitroaniline series.[6] The simple *p*-nitrobenzylated carbamate (7) was, however, more difficult to obtain than its benzenoid counterpart. It was not isolated by reaction of the carbamate (6) with *p*-nitrobenzyl bromide and sodium ethoxide, the only observed products being the *p*-nitrobenzyloxyimidazopyridine (9) (26%), 3-amino-2-nitropyridine (10%), 2-*p*-nitrophenylimidazo[4,5-*b*]pyridine (10) (2%), and ethyl *p*-nitrobenzyl ether (*ca.* 30%). The *p*-nitrobenzylcarbamate (7) was subsequently prepared, however, from compound (6), *p*-nitrobenzyl bromide, and potassium carbonate, and like its benzenoid analogue it was cyclised to 2-*p*-nitrophenyl-1*H*-imidazo[4,5-*b*]pyridine 3-oxide (8), in 46% yield, by reaction with sodium ethoxide. *p*-Nitrobenzoic acid (27%) was also formed.

Attention was then turned to the sulphonamides of 3-amino-2-nitropyridine. The toluene-*p*-sulphonamide (11) was accessible only *via* 3-amino-2-nitropyridine itself, which in turn had to be prepared *via* the nitrocarbamate (7). Attempts to obtain compound (11) directly by nitration of 3-toluene-*p*-sulphonamidopyridine were unsuccessful; the product of this reaction was a dinitro-compound, tentatively assigned the structure (12).

Nitration of 3-methanesulphonamidopyridine, however, gave a mixture of two mononitro-derivatives, of which the required 3-methanesulphonamido-2-nitropyridine (13) was the major isomer; the minor product was the 5-methanesulphonamido-2-nitro-derivative (14). Conversion of the secondary amides (11) and (13) into their *N*-*p*-nitrobenzyl derivatives, (15) and (16) respectively, and of (13) into its *N*-phenacyl

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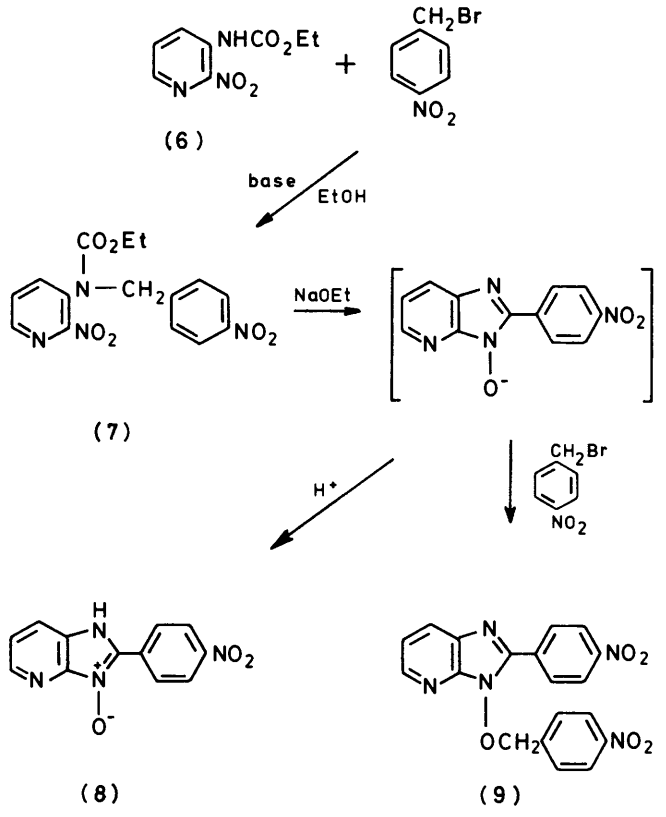
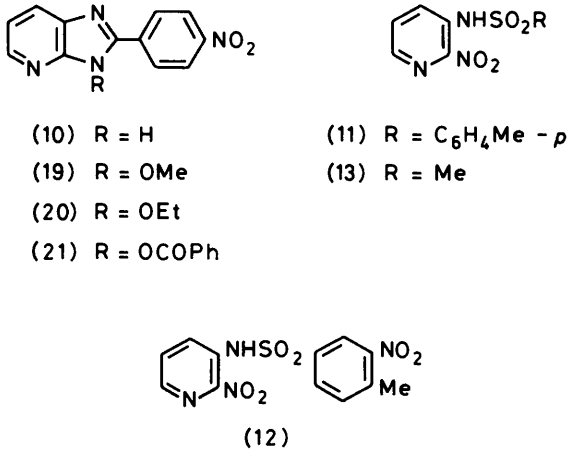


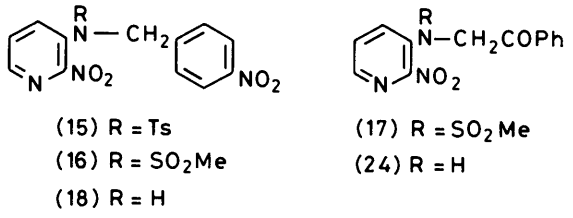
Scheme 1.

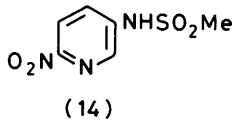


(12)

derivative (17), followed the standard procedures previously used for the corresponding *o*-nitroaniline derivatives.[6,7] Acid hydrolysis of the compound (16) gave 2-nitro-3-(*N*-*p*-nitrobenzylamino)pyridine (18).

The ^{1}H n.m.r. spectra of all these aminonitropyridine derivatives are collected in Table 1. In most cases, as expected, 6-H is the most deshielded of the three pyridine protons, but it is interesting to note the wide variation in the chemical shift of 4-H, according to the nature (and, presumably, the preferred conformation) of the substituents on the adjacent amino-nitrogen. It should also be noted that in the two cases [compounds (6) and (11)] where 4-H is the most deshielded proton, the amino-group is secondary: it can thus engage in hydrogen bonding with the 2-nitro-substituent, and so restrict the conformational possibilities for the ester or arylsulphonyl groups.





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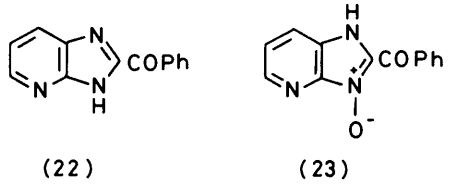


Since the methanesulphonamide (13) was more easily obtainable than the toluene-*p*-sulphonamide (11), most of the cyclisation attempts were carried out on derivatives of the former, *viz.* compounds (16) and (17).

Reaction of the *N*-*p*-nitrobenzyl compound (16) with sodium methoxide gave the *N*-oxide (8) in relatively low yield (23%), together with its reduction product (10) (6%) and *p*-nitrobenzoic acid (65%). Lowering of the reaction temperature did not alter the product ratio significantly, and the use of a milder base (sodium carbonate) produced no significant reaction. On the other hand, diethylamine [which had been largely ineffective in the case of the carbamate (7)] and triethylamine did cyclise (16) to give the *N*-oxide (8) (36 and 16%) and the reduced product (10) (5 and 3%, respectively).

The reactions of the toluene-*p*-sulphonamide (15) with sodium methoxide and with diethylamine gave very similar results. By complete contrast, however, the desulphonylated analogue (18) was cyclised readily, both with sodium methoxide and with diethylamine, to give the *N*-oxide (8) in high yield (93 and 71% respectively).

The *N*-oxide (8) is a high-melting solid which is sparingly soluble in most organic solvents and is difficult to purify: it may be converted, for characterist on purposes, into its *O*-methyl (19), *O*-ethyl (20), *O*-*p*-nitr loenzyl (9), or *O*-benzoyl (21) derivatives.

Attempts to cyclise the *N*-phenacylsulphonamide (17) to an imidazopyridine *N*-oxide were much less successful. Under a variety of basic conditions (Table 2), only complex mixtures were obtained, and the only cyclised product isolated from these was the known [9] 2-benzoylimidazo[4,5-*b*]pyridine (22). When sodium carbonate was used as the base, a small amount of the *N*-oxide (23) may have been present in the acidic fraction (Found: *m/e* 239); however this fraction (a mixture of at least four compounds) resisted attempts at further purification. Additionally, attempts to produce the desulphonylated compound (24) in this series were unsuccessful, the attempted hydrolysis of compound (17) giving only a complex mixture.

When a sulphonamide such as (15), (16), or (17) is treated with a base, cyclisation is, of course, only one of several reaction pathways which may be followed, and the low yields

Table 1. ^{1}H N.m.r. spectra of aminonitropyridines

(a) 3-Amino-2-nitropyridines

Compd.	3-Substituent	Solvent	Chemical shifts (δ) 4-H	5-H	6-H	NH	NCH_2	Other	Coupling constants (Hz) $J_{4,5}$	$J_{5,6}$	$J_{4,6}$	Other
(6)	$NHCO_2Et$	$CDCl_3$	9.10	7.69	8.30	9.56		1.36 (3 H, t) 4.30 (2 H, q)	8.4	4.2	1.6	7.0 (CH_3CH_2)
		C_6D_6	8.83	6.72	7.74	9.40		0.98 (3 H, t) 3.99 (2 H, q)				0.4 (NH, 5-H)
(7)	$N(CO_2Et)CH_2C_6H_4NO_2$-*p*	$CDCl_3$	7.63 [a] (2 H)		8.50 [a]		5.03br s	1.18 (3 H, t) 4.18 (2 H, q) 7.55, 8.20 (4 H, AA′BB′)	*a*	*a*	*a*	7.0 (CH_3CH_2)
		C_6D_6	6.85	6.61	7.85		4.88br s	0.92 (3 H, t) 3.97 (2 H, q) 7.00, 7.85 (AA′BB′)	8.2	4.4	1.6	7.0 (CH_3CH_2)
(11)	NHTs	$CDCl_3$	8.40	7.65	8.33	9.58		2.40 (3 H, s) 7.33, 7.78 (AA′BB′)	8.4	4.4	1.4	
(13)	$NHSO_2Me$	$(CD_3)_2SO$	8.24	7.88	8.46	10.00		3.21 (3 H, s)	8.4	4.4	1.4	
(15)	$NTs{\cdot}CH_2C_6H_4NO_2$-*p*	$(CD_3)_2SO$	7.94	7.80	8.56		4.99 s	2.47 (3 H, s) 7.56 (4 H, s) 7.66, 8.20 (AA′BB′)	8.4	4.2	1.8	
(16)	$N(SO_2Me)CH_2C_6H_4NO_2$-*p*	$(CD_3)_2CO$	8.25	7.80	8.51		5.12 s	3.20 (3 H, s) 7.71, 8.21 (AA′BB′)	8.2	4.6	1.4	
(17)	$N(SO_2Me)CH_2COPh$	$(CD_3)_2SO$	8.51	7.91	8.60		5.43 s	3.28 (3 H, s) 7.64—8.06 (5 H, m)	8.0	4.6	1.6	
(18)	$NHCH_2C_6H_4NO_2$-*p*	$CDCl_3$	7.24	7.46	8.02	*ca.* 8.3 (with Ar–H)	4.76 d	7.59, 8.31 (AA′BB′)	9.0	4.0	1.6	6.0 (CH_2NH)
		$(CD_3)_2SO$	7.40	7.52	7.84	8.50br t	4.81 d	7.66, 8.22 (AA′BB′)				
(25)	$N(SO_2Me)Me$	$(CD_3)_2SO$	8.45	7.91	8.57			3.13 (NMe) 3.31 (SO_2Me)	8.0	4.6	1.5	

Table 1 (*continued*)

(b) 5-Amino-2-nitropyridines

Compd.	5-Substituent	Solvent	Chemical shifts (δ) 3-H	4-H	6-H	NH	N–CH_2	Other	Coupling constants (Hz) $J_{3,4}$	$J_{4,6}$	$J_{3,6}$	Other
	NH_2	$(CD_3)_2SO$	8.04	7.05	7.83	6.76br			8.5	2.5	Not measurable	
(14)	$NHSO_2Me$	$(CD_3)_2SO$	8.41	7.99	8.50	Not observed		3.30 (3 H, s)	9.0	2.6	0.4	
(29)	$N(SO_2Me)CH_2COPh$	CF_3CO_2H	8.51 (2H) [b]		9.04 [b]		5.61 s	3.40 (3 H, s) 7.48—7.74 (3 H, m) 7.96—8.06 (2 H, m)	*b*	*b*	*b*	

(c) 2-Amino-3-nitropyridines

Compd.	2-Substituent	Solvent	Chemical shifts (δ) 4-H	5-H	6-H	NH	NCH_2	Other	Coupling constants (Hz) $J_{4,5}$	$J_{5,6}$	$J_{4,6}$	Other
(31)	$NHCH_2C_6H_4NO_2$-*p*	$CDCl_3$	8.50	6.76	8.47	8.60br	5.00 d	7.57, 8.24 (AA′BB′)	8.2	4.6	1.6	6.0 (CH_2NH)

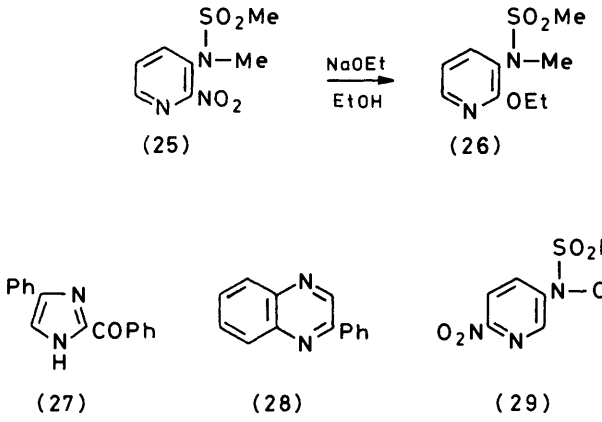
[a] On the spectrum, 4-H and 5-H appear as a doublet and 6-H as a triplet with an apparent coupling constant of 3 Hz. The assignments are based on computer simulation with $J_{4,5}$ 8.2 Hz; $J_{5,6}$ 4.4 Hz; $J_{4,6}$ 1.6 Hz. [b] This is not a first-order spectrum, and the chemical shifts and coupling constants are not measurable directly. The chemical shifts in the Table are based on computer simulation with $J_{3,4}$ 8.5 Hz; $J_{4,6}$ 2.4 Hz; $J_{3,6}$ 0.

Table 2. Products from the reactions of aminonitropyridines with bases

Starting compound	Base	Method [a] (Reaction time)	Extracting solvent	Fraction 1	Fraction 2	Fraction 3a	Fraction 3b	Fraction 4
(7)	NaOEt	A (2 h)	$CHCl_3$	Complex mixture [c] (small amount)		(8) (46%)	*p*-Nitrobenzoic acid (28%)	ANP [d] (7%) + 7 others [c]
	Et_2NH	C (2 h)	$CHCl_3$			(8) (4%)		[Starting material (88%)]
(15)	NaOMe	A (2 h)	$CHCl_3$			(8) (16%)	*p*-Nitrobenzoic acid (72%)	(10) (4%: insol. in $CHCl_3$) + ANP [c] + (19) [c] + 6 others [c]
	Et_2NH	C (2 h)	$CHCl_3$	[Starting material (29%)]		(8) (33%)		(10) (4%) + ANP [c] + 4 others [c]
(16)	NaOMe	1 (2 h)	Et_2O			(8) (23%)	*p*-Nitrobenzoic acid (65%)	(10) (7%) + ANP [b] + methyl *p*-nitrobenzoate [c] + 5 others [b]
	NaOMe	A (Room temp., 2 h)	Et_2O			(8) (20%)	*p*-Nitrobenzoic acid (65%)	(10) (4%) + ANP [c] + methyl *p*-nitrobenzoate [c] + 4 others [c]
	Na_2CO_3	B	Et_2O			(8) (1%)		[Starting material (73%)]
	Et_2NH	C (2 h)	$CHCl_3$	[Starting material (26%)]	(8) (20%)	(8) (4%)		(10) (4%) + starting material (6%) + 8 others [e]
	Et_2NH	C (6 h)	$CHCl_3$		(8) (20%)	(8) (16%)		(10) (5%) + 8 others [c]
	Et_3N	C (2 h)	$CHCl_3$	[Starting material (82%)]	(8) (1%)			Mixture (⩾4 products) [c]
	Et_3N	C (40 h)	$CHCl_3$	[Starting material (26%)]	(8) (16%)			(10) (3%) + complex mixture [c]
(18)	NaOMe	A (6 h)	$CHCl_3$			(8) (93%)		
	Et_2NH	A (6 h)	$CHCl_3$	[Starting material (13%)]	(8) (51%)	(8) (20%)		[Starting material (10%)]

Starting compound	Base	Method [a] (Reaction time)	Extracting solvent	Fraction 1	Fraction 2	Fraction 3	Fraction 4
(17)	NaOEt	A (2 h)	Et_2O		(22) (Trace)	Mixture (⩾5 products) [b]	(22) (7% insol. in Et_2O) + 11 others [b]
	Na_2CO_3	B	Et_2O	[Na_2CO_3]	(22) (*ca.* 2 %)	Mixture (⩾4 products) [b]	(22) (7%) + ⩾9 others [c]
	Et_2NH	C (2 h)	Et_2O		Mixture (⩾5 products) [b]		(22) (4%) + >12 others [c]
	Et_3N	C (2 h)	Et_2O		Mixture (⩾15 products) [b]		(22) (4%) + >10 others [c]
	DBN [d]	C (2 h)	Et_2O			Mixture (>5 products) [b]	Mixture (5 products) [c]
	$NaHCO_3$	B	$CHCl_3$	[$NaHCO_3$]	(22) (Trace)		[Starting material (86%)]
(29)	NaOEt	A (2 h)	Et_2O			Mixture (⩾8 products) [b]	5-Amino-2-nitropyridine (17%) + 7 others [b]

[a] Reactions were carried out at reflux temperature unless otherwise stated. [b] Analysed by h.p.l.c. [c] Analysed by t.l.c. [d] ANP = 3-Amino-2-nitropyridine; DBN = 1,5-diazabicyclo-[4.3.0]non-5-ene.



of cyclised products are presumably due to the intervention of one or more of these other processes.

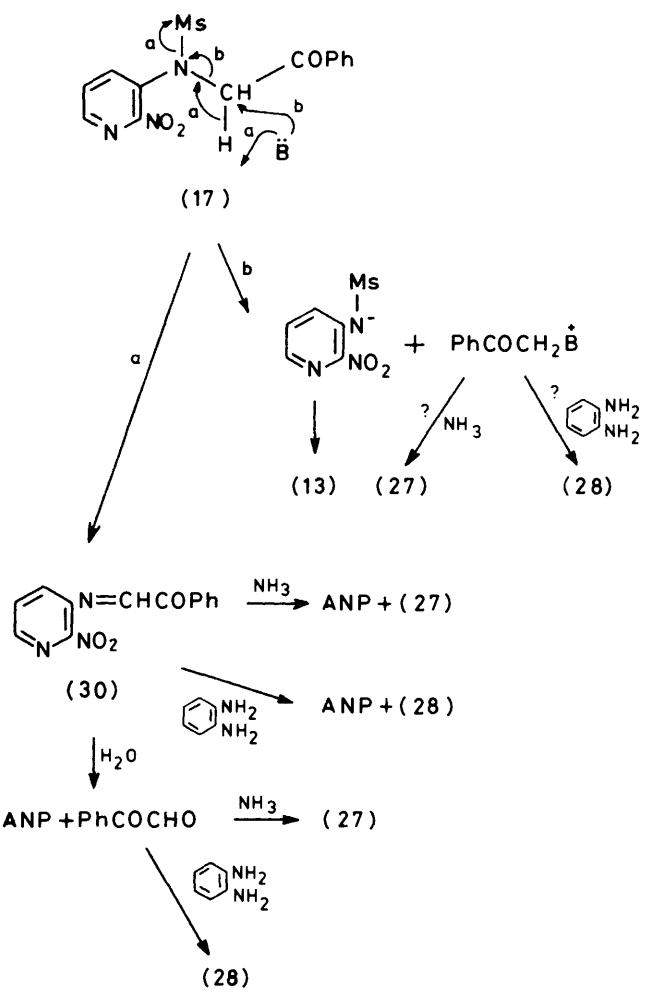
In reactions involving the *p*-nitrobenzyl-sulphonamides (15) and (16) with alkoxides, *p*-nitrobenzoic acid is always a major product. The mechanism by which this is formed, presumably cleavage followed by oxidation, is not obvious, especially since a large proportion of the pyridine-containing moiety is unaccounted for among the products, and since there is apparently no other product formed in appreciable amounts except the *N*-oxide (8). A possible complicating factor may be nucleophilic substitution of the nitro-group from the pyridine ring in (15) or (16): such substitution in 2-nitropyridine derivatives is well known,[10] and we were able to demonstrate it for the nitrosulphonamide (25), which is an obvious relative of (16).

The reactions involving the phenacylsulphonamide (17) appear to be even more complicated, judging by the large number of products which were generally detectable. The reaction of (17) with ammonia, however, gave a good yield of 2-benzoyl-4(5)-phenylimidazole (27), identical with the known [11] product of the reaction of phenylglyoxal with ammonia; the reaction of (17) with ammonia in the presence of *o*-phenylenediamine gave as the main product 2-phenylquinoxaline (28), which was identical with that obtained from phenylglyoxal and *o*-phenylenediamine.[12]

2-Phenylquinoxaline was also the major product from the reaction of the sulphonamide (17) with other bases (sodium ethoxide and diethylamine) in the presence of *o*-phenylenediamine. The diamine by itself did not react significantly with the sulphonamide under comparable conditions, and so apparently served in the other cases as a trapping agent for a reaction intermediate (possibly, *although not necessarily*, phenylglyoxal).

Scheme 2 shows a number of possible pathways for the reactions of the sulphonamide (17) with bases. Some of these involve phenylglyoxal as an intermediate, while others do not; none, however, by itself is completely satisfactory to explain all the experimental facts. The first group of pathways (Scheme 2a) involves elimination as the first step, giving the anil (30) as the primary product; further reaction of the anil with nucleophiles, however, would be expected to lead eventually to 3-amino-2-nitropyridine, and this was never detected in sufficient quantity to be considered a major product. [The same was true of the reaction of the isomeric sulphonamide (29) with base, which gave only a low yield of 5-amino-2-nitropyridine.] Scheme 2b, which involves nucleophilic substitution, rather than proton abstraction, at the methylene group of (17), is required to account for the formation of the sulphonamide (13) as a by-product in certain cases.

For comparison purposes, we also prepared 2-*p*-nitrophenyl-3*H*-imidazo[4,5-*b*]pyridine 1-oxide (32) by cyclisation of 3-nitro-2-(*p*-nitrobenzylamino)pyridine (31). Sodium methoxide and diethylamine could both be used to bring about the cyclisation, but the reaction involving the latter was very slow. The *N*-oxide (32) was even less soluble than its isomer (8) in common organic solvents, to the extent that we were unable to obtain its n.m.r. spectrum; however it was convertible, like compound (8), into an *O*-benzoyl derivative (33) with the expected spectroscopic properties (Scheme 3).



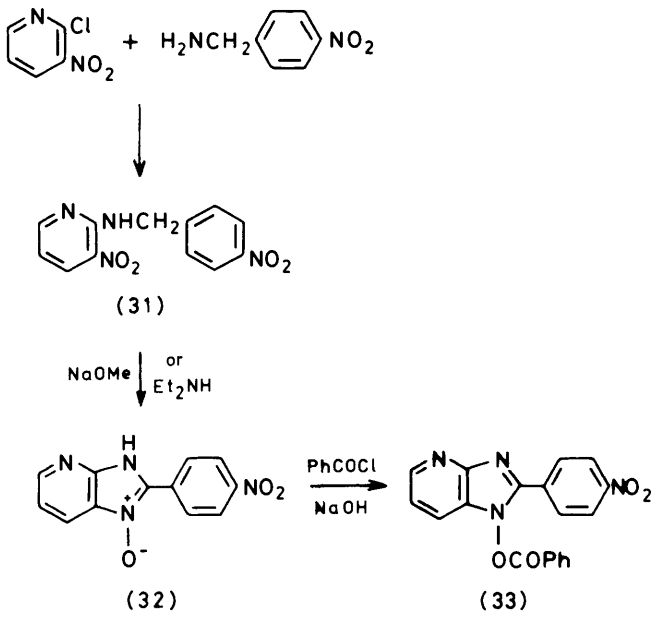
Scheme 2. Ms = CH_3SO_2; ANP = 3-amino-2-nitropyridine

Experiments are continuing in this and the related imidazo-[4,5-*c*]pyridine series, and the results of these will be reported in due course.

Experimental

I.r. spectra were recorded for Nujol mulls. ^{1}H N.m.r. spectra were recorded, with tetramethylsilane as internal reference, on a Bruker WP 80 Fourier Transform spectrometer. High performance liquid chromatography was carried out using a Pye Unicam LC3 system, with a u.v. spectrophotometric detector set at 254 nm. ' Reverse-phase ' conditions were used throughout, with 10 μm silica–ODS as column packing and methanol–water as the solvent system. Ether refers to diethyl ether throughout.

Ethyl *N*-3-pyridylcarbamate, m.p. 87—89 °C (from water) (lit.,[13] 89—90 °C), 3-methanesulphonamidopyridine, m.p. 141—143 °C (from water) (lit.,[14] 140—141 °C), and 3-toluene-



Scheme 3.

p-sulphonamidopyridine, m.p. 187—189 °C (from ethanol) (lit.,[8] 191—192 °C) were prepared by standard procedures (yields 68, 74, and 71%, respectively) from 3-aminopyridine and the appropriate acyl chloride in pyridine.

Ethyl N-(2-*Nitro*-3-*pyridyl*)*carbamate* (6).—Clark-Lewis and Thompson's method [8] was modified as follows.

Fuming nitric acid (*d* 1.5; 58 ml) was added slowly, with stirring, to a solution of ethyl *N*-3-pyridylcarbamate (29 g) in concentrated sulphuric acid (58 ml), so that the temperature of the mixture remained below 10 °C. The reaction flask was then placed in a bath of cold water, and the latter heated *slowly* (during 1 h) to 90 °C and maintained at that temperature for 0.5 h. The mixture was then cooled and poured on to crushed ice; the precipitated nitrocarbamate was filtered off, washed well with ice-cold water, and recrystallised (25 g, 69%) from propan-2-ol. It had m.p. 82—84 °C (lit.,[8] 82—83 °C) and $\nu_{max.}$ 3 350(NH), 1 745(CO), and 1 500br and 1 345 cm^{-1} (NO_2); the n.m.r. spectrum is given in Table 1.

3-*Amino*-2-*nitropyridine*.—This compound had m.p. 195—197 °C (from propan-2-ol) (lit.,[8] 195—196 °C) and was obtained by alkaline hydrolysis (2.5M-sodium hydroxide) of the nitrocarbamate (6), according to the published method.[8]

Reaction of Ethyl N-(2-*Nitro*-3-*pyridyl*)*carbamate* (6) *with* p-*Nitrobenzyl Bromide*.—(*a*) (With B. C. Medcalf and J. M. Richmond). The nitrocarbamate (4.28 g) was added to sodium ethoxide (sodium, 1.08 g, in ethanol, 100 ml) and to the resulting orange-red solution was added *p*-nitrobenzyl bromide (8.8 g). The mixture was heated under reflux for 20 min, then cooled and filtered to give 3-*p*-nitrobenzyloxy-2-*p*-nitrophenyl-3*H*-imidazo[4,5-*b*]pyridine (9) (2.03 g, 26%), m.p. 235—236 °C (from acetic acid), identical with an authentic sample (for preparation, see below).

The reaction mixture was evaporated under reduced pressure and the residue extracted with a little ether. The ether-soluble material gave on distillation an oil (2.48 g) which appeared (by n.m.r.) to consist mainly of ethyl *p*-nitrobenzyl ether and was not further examined. The ether-insoluble residue was then extracted with water: the extract was evaporated to give 3-amino-2-nitropyridine (0.14 g, 10%; purified by sublimation), and the water-insoluble portion was identified as 2-p-*nitrophenyl*-3H-*imidazo*[4,5-b]*pyridine* (10) (0.08 g, 2%), by comparison with an authentic sample (for preparation, see below).

(*b*) A solution of *p*-nitrobenzyl bromide (1.15 g) in AnalaR acetone (10 ml) was added dropwise, over 10 min, to a refluxing mixture of the nitrocarbamate (6) (1 g) and anhydrous potassium carbonate (1 g) in AnalaR acetone (10 ml). The mixture was then heated under reflux for 6 h, cooled, filtered, and the filtrate concentrated under reduced pressure to give a viscous red oil which eventually crystallised. Recrystallisation from methanol gave 3-(N-*ethoxycarbonyl*-N-p-*nitrobenzyl*-*amino*)-2-*nitropyridine* (7) (1.23 g, 75%), m.p. 70—72 °C (Found: C, 52.2; H, 3.9; N, 16.2. $C_{15}H_{14}N_4O_6$ requires C, 52.0; H, 4.1; N, 16.2%), $\nu_{max.}$ 1 695 cm^{-1} (CO); the n.m.r. spectrum is given in Table 1.

2-p-*Nitrophenylimidazo*[4,5-b]*pyridine* (10).—A mixture of *p*-nitrobenzoic acid (1.67 g), 2,3-diaminopyridine [15] (1.09 g) and polyphosphoric acid (10 ml) was heated, with stirring, at 175 °C for 2 h. The resulting precipitate was filtered off and washed with water. The filtrate was cooled and diluted with water (150 ml) to give a second precipitate which was also filtered off and washed. Neutralisation (solid Na_2CO_3) of this filtrate produced a third precipitate. The precipitates were combined and recrystallised from dimethylformamide to give the mustard-yellow compound (10) (2.07 g, 86%), m.p. >350 °C (Found: C, 60.05; H, 3.15; N, 23.1. $C_{12}H_8N_4O_2$ requires C, 60.0; H, 3.4; N, 23.3%); $\nu_{max.}$ 1 510 and 1 350 cm^{-1} (NO_2); n.m.r. spectrum given in Table 3; *m/e* 240 ($M^{+\cdot}$, 93%), 241 (24), 194 [$(M - NO_2)^+$, 80], 193 (24), *etc.* (base peak at *m/e* 57).

This compound has also been reported recently by Middleton and Wibberley [16] but without spectroscopic data.

2-*Nitro*-3-(N-*toluene*-p-*sulphonamido*)*pyridine* (11).—3-Amino-2-nitropyridine (6 g), toluene-*p*-sulphonyl chloride (10 g), and pyridine (10 ml) were heated together at 100 °C for 2 h; the mixture was cooled and poured into water, and was then allowed to stand at room temperature, with occasional stirring, until crystallisation occurred (2 days). Recrystallisation from propan-2-ol (with charcoal) then gave the *sulphonamide* (11) as orange prisms (5.05 g, 40%), m.p. 99—101 °C (Found: C, 49.1; H, 3.5; N, 14.3. $C_{12}H_{11}N_3O_4S$ requires C, 49.1; H, 3.8; N, 14.3%); $\nu_{max.}$ 3 320 (NH), 1 545 and 1 350 (NO_2), 1 305 and 1 160 cm^{-1} (SO_2); the n.m.r. spectrum is given in Table 1.

Nitration of 3-*Methanesulphonamidopyridine*.—(With J. M. Richmond and G. R. Sneddon). Of several methods tried, the following was found to be most satisfactory. Fuming nitric acid (*d* 1.5; 20 ml) was added dropwise, with stirring, to a cold mixture of 3-methanesulphonamidopyridine (10 g) and concentrated sulphuric acid (10 ml), so that the temperature of the mixture remained below 10 °C. After the addition was complete, the temperature was raised slowly to 60—70 °C and maintained at that level for 2 h. The solution was then cooled and poured on to crushed ice, and the product filtered off, washed with cold water, and dried to give a mixture (6.95 g, 55%) of mononitro-compounds. Fractional crystallisation from methanol gave 3-*methanesulphonamido*-2-*nitropyridine* (13) (4.67 g, 37%), m.p. 146—148 °C (Found: C, 33.1; H, 3.2; N, 19.5. $C_6H_7N_3O_4S$ requires C, 33.2; H, 3.25; N, 19.35%); $\nu_{max.}$ 3 280 (NH), 1 545 and 1 350 (NO_2), and 1 295 and 1 150 cm^{-1} (SO_2); $\lambda_{max.}$ 247 nm (ε 6 630); the n.m.r. spectrum is given in Table 1. The second fraction (1.26 g, 10%) was a mixture of compound (13) (compact pale yellow prisms) and

5-methanesulphonamido-2-nitropyridine (14) (yellow needles). A sample of the latter, separated manually, had m.p. 200—202 °C (Found: C, 33.0; H, 3.3; N, 19.5%); $\nu_{max.}$ 3 250br, 1 530 and 1 350, 1 310 and 1 145 cm^{-1}; $\lambda_{max.}$ 302 nm (ε 11 500); the n.m.r. spectrum is given in Table 1.

This mixed fraction could be used satisfactorily for further experiments (see below), separation being more easily achieved at a later stage.

Nitration of 3-Toluene-p-sulphonamidopyridine.—(With J. M. Richmond). The sulphonamide (1 g) was added slowly, with stirring, to a mixture of fuming nitric acid (2 ml) and concentrated sulphuric acid (2 ml), and the solution was then heated gradually to 100 °C during 1 h, cooled, and added to crushed ice. The precipitate was filtered off and recrystallised from ethanol and water; it had m.p. 125—127 °C and was clearly a dinitro-compound from its mass spectrum (Found: *M*, 338) and analysis (Found: C, 42.6; H, 3.05; N, 16.35. $C_{12}H_{10}N_4O_6S$ requires C, 42.6; H, 3.0; N, 16.6%). Its n.m.r. spectrum contained only a complex multiplet at δ 7.63—8.63, without the obvious AA'BB' pattern of the toluene-*p*-sulphonyl group, and accordingly this compound is tentatively assigned the structure (12).

Even on this small scale, the nitration was difficult to control and the yield of product was extremely low. Various modifications of the reaction conditions were tried without success.

N-p-Nitrobenzyl-N-(2-nitro-3-pyridyl)toluene-p-sulphonamide (15).—2-Nitro-3-toluene-*p*-sulphonamidopyridine (11) (3.65 g) was dissolved in sodium methoxide (sodium, 0.30 g, in methanol, 100 ml). *p*-Nitrobenzyl bromide (3.25 g) was added, and the mixture was heated under reflux for 2 h, then cooled and poured on to crushed ice. The resulting semi-solid mass was recrystallised from propan-2-ol (with charcoal) to give the *nitrobenzylsulphonamide* (15) as colourless crystals (3.50 g, 74%), m.p. 179—181 °C (Found: C, 53.3; H, 4.0; N, 12.9. $C_{19}H_{16}N_4O_6S$ requires C, 53.3; H, 3.8; N, 13.1%); the n.m.r. spectrum is given in Table 1. *N-p-Nitrobenzyl-N-(2-nitro-3-pyridyl)methanesulphonamide* (16) (4.68 g, 66%) was similarly obtained by the corresponding reaction of 3-methanesulphonamido-2-nitropyridine (13) (4.36 g), sodium methoxide (sodium, 0.46 g, in methanol, 100 ml), and *p*-nitrobenzyl bromide (5.18 g). It was recrystallised twice from methanol, m.p. 124—125 °C (Found: C, 44.1; H, 3.15; N, 16.0. $C_{13}H_{12}N_4O_6S$ requires C, 44.3; H, 3.4; N, 15.9%); the n.m.r. spectrum is given in Table 1.

N-(2-Nitro-3-pyridyl)-N-phenacylmethanesulphonamide (17).—3-Methanesulphonamido-2-nitropyridine (13) (1.09 g) was dissolved in sodium methoxide (sodium, 0.115 g, in methanol, 30 ml). The methanol was evaporated under reduced pressure, the residue was redissolved in dimethylformamide (10 ml) and phenacyl bromide (1.2 g) was added. The mixture was stirred at room temperature for 24 h and then poured on to crushed ice, and the product was filtered off and washed with water. The *phenacyl-sulphonamide* (17) (1.34 g, 80%) formed pale yellow plates, m.p. 139—141 °C (from methanol) (Found: C, 49.8; H, 3.7; N, 12.6. $C_{14}H_{13}N_3O_5S$ requires C, 50.15; H, 3.9; N, 12.5%); $\nu_{max.}$ 1 685 (CO), 1 540 (NO_2), 1 335 (NO_2 and SO_2), and 1 160 cm^{-1} (SO_2), the n.m.r. spectrum is given in Table 1.

When a mixture of 3-methanesulphonamido-2-nitropyridine (13) and its 5-methanesulphonamido-isomer (14) was used in this reaction, the two products were easily separated by extraction with hot methanol. *N-(2-Nitro-5-pyridyl)-N-phenacylmethanesulphonamide* (29), which was almost insoluble in methanol, recrystallised from acetone as colourless leaflets, m.p. 210—212 °C (Found: C, 50.1; H, 3.7; N, 12.95. $C_{14}H_{13}N_3O_5S$ requires C, 50.15; H, 3.9; N, 12.5%); $\nu_{max.}$ 1 690 (CO), 1 525 and 1 340 (NO_2), 1 305 and 1 155 cm^{-1} (SO_2); the n.m.r. spectrum is given in Table 1.

2-Nitro-3-p-nitrobenzylaminopyridine (18).—Concentrated sulphuric acid (14.4 ml) was added dropwise, with stirring, to a cold mixture of *N-p*-nitrobenzyl-*N*-(2-nitro-3-pyridyl)-methanesulphonamide (16) (3.15 g) and acetic acid (7.2 ml), and the mixture was then heated slowly to 100—105 °C and maintained at that temperature for 2 h; it was then cooled and diluted with water (100 ml), and the yellow product filtered off and washed well with water. *2-Nitro-3-p-nitrobenzylaminopyridine* (18) (1.56 g, 64%) had m.p. 163—164 °C (from ethanol) (Found: C, 52 7; H, 3.5; N, 20.6. $C_{12}H_{10}N_4O_4$ requires C, 52.6; H, 3.7; N, 20.4%); $\nu_{max.}$ 3 140 (NH), and 1 500 and 1 340 cm^{-1} (NO_2); the n.m.r. spectrum is given in Table 1.

Attempted Hydrolysis of N-(2-Nitro-3-pyridyl)-N-phenacylmethanesulphonamide (17).—When the above procedure was applied to the sulphonamide (17), the crude product obtained by dilution with water was (by h.p.l.c.) a mixture of at least five compounds, including benzoic acid. Basification (Na_2CO_3) of the aqueous solution and extraction with chloroform gave a mixture of at least nine compounds, one of which (by t.l.c.) was probably 3-amino-2-nitropyridine.

Reactions of the Aminonitropyridine Derivative with Bases. General Procedures.—(A) *With sodium alkoxides.* A solution of the alkoxide (5 mmol) in the corresponding alcohol (30—50 ml) was added slowly to a solution or suspension of the aminonitropyridine (2.5 mmol) in the same alcohol (20 ml). The mixture was then heated under reflux, or stirred at room temperature, for a fixed period, cooled, filtered if necessary (precipitate = fraction 1), and the solvent evaporated under reduced pressure. The residue was extracted with ether–water (1 : 1) or chloroform–water (1 : 1).

(B) *With sodium carbonate.* The aminonitropyridine derivative (2.5 mmol), sodium carbonate (5 mmol) and ethanol (50 ml) were heated together under reflux for 2 h. The mixture was then cooled, filtered if necessary (precipitate = fraction 1), and the ethanol evaporated under reduced pressure. The residue was extracted with ether–water (1 : 1).

(C) *With amines.* The amine (20 mmol) in ethanol (10 ml) was added slowly, with stirring, to a solution or suspension of the aminonitropyridine (10 mmol) in ethanol (80 ml). The mixture was then heated under reflux or stirred at room temperature for a fixed period.* It was then cooled, filtered if necessary (precipitate = fraction 1), and the ethanol and unchanged amine evaporated under reduced pressure. The residue was then extracted with ether–water or chloroform–water (1 : 1).

Isolation Procedures.—Any solid which was insoluble in either the organic or the aqueous layer was filtered off; it was then dissolved, as far as possible, in a large volume of boiling water. Acidification (conc. HCl) gave a precipitate (fraction 2) which was filtered off and recrystallised.

The organic and aqueous extracts were separated and the latter acidified (conc. HCl). The precipitate (fraction 3) was filtered off, dried, and extracted with boiling benzene. The benzene-insoluble portion is designated fraction 3a and the benzene-soluble portion, fraction 3b.

* If the amine was particularly volatile, a second portion of the amine (20 mmol) was added to the mixture after half of the reaction time had elapsed.

The organic extract was dried (Na_2SO_4) and evaporated to give a residue (fraction 4) which was examined, and in certain cases separated, by chromatographic methods.

The results of these experiments are collected in Table 2. 2-p-*Nitrophenyl*-1H-*imidazo*[4,5-b]*pyridine* 3-*oxide* (8), obtained in these reactions, was recrystallised from dimethylformamide. It was pale yellow and decomposed, below its m.p., at *ca.* 330—340 °C (Found: C, 55.8; H, 3.0; N, 21.8. $C_{12}H_8N_4O_3$ requires C, 56.25; H, 3.15; N, 21.9%); $\nu_{max.}$ 1 505 and 1 345 cm^{-1} (NO_2); the n.m.r. spectrum is given in Table 3; *m/e* 256 ($M^{+\cdot}$, 25%), 241 (16), 240 (100), 210 (9), 195 (11), 194 (71), *etc.* [no other intense peaks (>20%) at *m/e* >100].

3-*Methoxy*-3-p-*nitrophenyl*-3H-*imidazo*[4,5-b]*pyridine* (19).—A solution of dimethyl sulphate (1 ml) in methanol (2 ml) was added dropwise, with vigorous stirring, to a warm (60—65 °C) suspension of the *N*-oxide (8) (0.22 g) in 2M-sodium hydroxide (5 ml). After a few minutes, a further portion of 2M-sodium hydroxide (10 ml) and water (10 ml) was added. Stirring at 60—65 °C was continued for 30 min, and the mixture was then cooled and filtered. The solid product was washed well with water and recrystallised from propan-2-ol, to yield the *methoxy-compound* (19) (0.14 g, 60%), m.p. 217—219 °C (Found: C, 57.6; H, 3.6; N, 20.65. $C_{13}H_{10}N_4O_3$ requires C, 57.8; H, 3.7; N, 20.7%); $\nu_{max.}$ 1 520 and 1 345 cm^{-1} (NO_2); the n.m.r. spectrum is given in Table 3; *m/e* 270 ($M^{+\cdot}$, 89%), 271 (15), 254 (12), 240 (54), 239 (10), *etc.* (base peak at *m/e* 194).

The 3-*ethoxy-analogue* (20) (63%), m.p. 149—151 °C (from propan-2-ol) was similarly obtained from the *N*-oxide (8) and diethyl sulphate (Found: C, 59.55; H, 4.05; N, 19.4. $C_{14}H_{12}N_4O_3$ requires C, 59.15; H, 4.25; N, 19.7%); $\nu_{max.}$ 1 520 and 1 350 cm^{-1} (NO_2); the n.m.r. spectrum is given in Table 3; *m/e* 284 ($M^{+\cdot}$, 83%), 285 (17), 255 (55), 240 (12), 239 (83), 193 (90), *etc.* (base peak at *m/e* 150). This compound underwent slight decomposition during recrystallisation, giving 2-*p*-nitrophenylimidazo[4,5-*b*]pyridine (10).

The 3-p-*nitrobenzyloxy-analogue* (9) (41%), m.p. 235—236 °C (from acetic acid) was obtained † by adding equimolar amounts of the *N*-oxide (8) and *p*-nitrobenzyl bromide to sodium ethoxide [1 mol of sodium per mol of (8)], and heating the resultant mixture under reflux for 30 min (Found: C, 58.4; H, 3.3; N, 17.9. $C_{19}H_{13}N_5O_5$ requires C, 58.3; H, 3.35; N, 17.9%); $\nu_{max.}$ 1 510 and 1 320 cm^{-1} (NO_2); the n.m.r. spectrum is given in Table 3; *m/e* 391 ($M^{+\cdot}$, 24%), 374 (13), 240 (19), 194 (17), base peak at *m/e* 136.

3-*Benzoyloxy*-2-p-*nitrophenyl*-3H-*imidazo*[4,5-b]*pyridine* (21).—Benzoyl chloride (2 ml) was added dropwise to a well-stirred suspension of the *N*-oxide (8) (0.3 g) in 2M-sodium hydroxide (12 ml) and dimethylformamide (8 ml). Stirring was continued until the orange-red colour disappeared, and the yellow solid was filtered off and washed well with water. The *benzoate* (21), m.p. 246—248 °C (from toluene), was obtained in almost quantitative yield (Found: C, 63.2; H, 3.1; N, 15.5. $C_{19}H_{12}N_4O_4$ requires C, 63.3; H, 3.4; N, 15.5%); $\nu_{max.}$ 1 780 (CO), and 1 515 and 1 345 cm^{-1} (NO_2); the n.m.r. spectrum is given in Table 3; *m/e* 360 ($M^{+\cdot}$, 1%), 240 (3), 194 (3), 193 (3), 150 (2), 105 (100), *etc.*

2-*Benzoylimidazo*[4,5-b]*pyridine* (22).—A solution of 2,3-diaminopyridine [15] (1 g) and phenylacetic acid (1.41 g) in ethanol (10 ml) was heated under reflux for 15 min. The ethanol was then evaporated under reduced pressure and the residue heated at 190 °C for 1 h. The melt crystallised when cooled, and was recrystallised three times from ethanol (with charcoal) to give 2-benzylimidazo[4,5-*b*]pyridine (0.73 g, 38%), m.p. 188—191 °C (lit.,[9] 192—194 °C). This was then oxidised by manganese dioxide in dioxan [9] to give 2-benzoylimidazo-[4,5-*b*]pyridine (22) (0.57 g, 27%), m.p. 259—260 °C (with phase change at 240—244 °C) (from propan-1-ol) (lit.,[9] 263—264 °C) (Found: C, 70.0; H, 4.0; N, 18.5. Calc. for $C_{13}H_9N_3O$: C, 69.95; H, 4.1; N, 18.8%); $\nu_{max.}$ 1 640 cm^{-1} (CO); the n.m.r. spectrum is given in Table 3; *m/e* 223 ($M^{+\cdot}$, 20%), 195 (60), 105 (79), 77 (100), *etc.*

N-*Methyl*-N-(2-*nitro*-3-*pyridyl*)*methanesulphonamide* (25).—3-Methanesulphonamido-2-nitropyridine (13) (1.08 g) was dissolved in sodium methoxide (sodium, 0.115 g, in methanol, 30 ml). The methanol was evaporated under reduced pressure, and the residue was dissolved in dimethylformamide (10 ml); iodomethane (0.71 g) was added and the mixture was stirred at room temperature for 24 h. It was then poured on to crushed ice and the product filtered, washed with water, and recrystallised from methanol. N-*Methyl*-N-(2-*nitro*-3-*pyridyl*)-*methanesulphonamide* (25) (0.81 g, 70%) was obtained as colourless leaflets, m.p. 129—131 °C (Found: C, 36.1; H, 3.8; N, 18.2. $C_7H_9N_3O_4S$ requires C, 36.4; H, 3.9; N, 18.2%); $\nu_{max.}$ 1 540, 1345 (NO_2), and 1 320 and 1 145br cm^{-1} (SO_2); the n.m.r. spectrum is given in Table 1.

N-(2-*Ethoxy*-3-*pyridyl*)-N-*methylmethanesulphonamide* (26).—The nitrosulphonamide (25) (0.46 g) was dissolved in sodium ethoxide (sodium, 0.092 g, in ethanol, 30 ml). The solution was heated under reflux for 2 h; the solvent was then evaporated under reduced pressure, and the residue extracted with ether–water (1 : 1). The ether layer was separated, dried (Na_2SO_4), and evaporated, giving the *ethoxy-sulphonamide* (26) (0.26 g, 57%), m.p. 102—104 °C (from methanol) (Found: C, 47.0; H, 6.2; N, 12.0. $C_9H_{14}N_2O_3S$ requires C, 46.9; H, 6.1; N, 12.2%); $\nu_{max.}$ 1 325br and 1 160br cm^{-1} (SO_2); δ [$(CD_3)_2SO$] 1.36 (3 H, t, CH_3CH_2), 3.02 (3 H, s, CH_3N), 3.16 (3 H, s, CH_3SO_2), 4.40 (2 H, q, CH_3CH_2), 7.00 (1 H, dd, 5-H), 7.68 (1 H, dd, 4-H), and 8.12 (1 H, dd, 6-H); $J_{4,5}$ 7.8 Hz, $J_{5,6}$ 5.0 Hz, $J_{4,6}$ 1.8 Hz, $J_{CH_3CH_2}$ 7.0 Hz.

Reaction of N-(2-*Nitro*-3-*pyridyl*)-N-*phenacylmethanesulphonamide* (17) *with Ammonia*.—(*a*) Aqueous ammonia [*d* 0.88; 1.24 g (= 0.43 g NH_3)] diluted with ethanol (20 ml) was added dropwise, with stirring, to the sulphonamide (17) (0.84 g) in ethanol (30 ml), and the (red) mixture was allowed to stand at room temperature for 5 days. [After 2 days a second portion of ammonia (1.24 g) in ethanol (20 ml) was added.] A small precipitate (0.06 g), which was filtered off, was shown (h.p.l.c.) to be a complex mixture and was not further examined. The ammoniacal filtrate was evaporated under reduced pressure and the residue extracted with chloroform–water (1 : 1).

The organic layer was dried (Na_2SO_4) and evaporated to smaller volume to give an extract (a); it was then chromatographed on silica, with chloroform–carbon tetrachloride (3 : 1) as eluant. The composition of the eluate was monitored by h.p.l.c. and the mixed fractions were re-chromatographed. Thus was obtained, as the main product, 2-benzoyl-4(5)-phenylimidazole (27) (0.15 g, 48%), m.p. 193—194 °C (lit.,[11] 197—198 °C, [17] 192—194 °C), identical (i.r., m.s., h.p.l.c.) with an authentic sample prepared from phenylglyoxal hydrate and ammonia.[11] The most polar fraction, eluted with methanol, contained a trace (*ca.* 1%) of 3-methanesulphonamido-2-nitropyridine (13), identical by i.r. and h.p.l.c. with an authentic sample; compound (13) was also detected (by h.p.l.c.) as a component of other fractions. The aqueous layer on acidification (HCl) and evaporation yielded only a small amount of a complex mixture, one component of which (by h.p.l.c.) was apparently 3-amino-2-nitropyridine.

† By J. M. Richmond.

Table 3. ^{1}H N.m.r. spectra of imidazo[4,5-*b*]pyridines

(*a*) 2-p-Nitrophenyl derivative

Compd.	Substituents	Solvent	Chemical shifts (δ) 5-H	6-H	7-H	2-$C_6H_4NO_2$ (AA'BB')	Other	Coupling constants (Hz) $J_{5,6}$	$J_{6,7}$	$J_{5,7}$	Others
(10)		$(CD_3)_2SO$	8.39	7.26	8.06	8.44 (s)		5.0	8.0	1.6	
(8)	3-Oxide	$(CD_3)_2SO$	8.33—8.61 (with C_6H_4)	7.35	8.14	8.33—8.61 (with 5-H)		4.6	8.0	1.5	
(9)	3-($OCH_2C_6H_4NO_2$-*p*)	$(CD_3)_2SO$	8.72	7.61	8.38	8.45 (almost a singlet)	5.74 (2 H, s) 7.70, 8.24 (AA'BB')	4.8	8.2	1.4	
(19)	3-OCH_3	$(CD_3)_2SO$	8.56	7.47	8.26	8.52 (s)	4.30 (3 H, s)	4.8	8.2	1.4	
(20)	3-OCH_2CH_3	$CDCl_3$	8.37—8.63 (with C_6H_4)	7.35	8.14	8.37—8.63 (with 5-H)	1.43 (3 H, t) 4.53 (2 H, q)	4.8	8.2	1.4	7.0 (CH_3CH_2)
(21)	3-$OCOC_6H_5$	$CDCl_3$	8.54	7.43	8.25	8.26—8.36 (with *o*-protons of COPh)	7.56—7.84 (3 H, m) 8.26—8.36 (2 H, m) (with $C_6H_4NO_2$)	5.0	8.2	1.4	
(33)	1-$OCOC_6H_5$	$CDCl_3$	8.72	7.35	7.72	8.33 (s)	7.50—7.85 (3 H, m) 8.22 (2 H, m)	4.8	8.2	1.6	

(*b*) 2-Benzoyl derivative

							2-COPh				
(22)	2-COPh	CF_3CO_2H	8.91	8.07	8.98		7.54—7.86 (3 H, m) 8.42 (2 H, approx. d)	*ca.* 6	*ca.* 8	Very small	

(*b*) In a second experiment, the chloroform extract (a) was analysed quantitatively by h.p.l.c., and the yield of compound (27) was estimated to be 66%.

(*c*) In a third experiment, the reaction was carried out at reflux temperature for 2 h instead of room temperature for 5 days. Analysis of the chloroform layer (a) by h.p.l.c. indicated the yield of sulphonamide (13) to be 23%. Isolation of the products was achieved (i) by fractional extraction with chloroform, giving the imidazole (27) (19%) as the residue; (ii) by chromatography of the chloroform extract on a silica column [eluting solvent, chloroform–tetrahydrofuran (1 : 1)] and twice on a preparative t.l.c. plate (solvent, chloroform). The imidazole (27) (39%) and the sulphonamide (13) (7%) were thus obtained pure.

Reactions of the Sulphonamide (17) *with Bases in Presence of* o-*Phenylenediamine.*—(*a*) *With ammonia.* Aqueous ammonia (*d* 0.88; 1.24 g) was added to a mixture of the sulphonamide (17) (0.84 g) and *o*-phenylenediamine (0.27 g, 1 mol equiv.) in ethanol, as described in the preceding section, paragraph (*a*). The mixture was heated under reflux for 2 h, the ammonia and solvent were evaporated under reduced pressure, and the residue was extracted with hot light petroleum (b.p. 40—60 °C). Evaporation of the petroleum gave 2-phenylquinoxaline (28) (0.21 g, 41%), m.p. 77—78 °C (lit.,[12] 78 °C), identical (i.r., n.m.r., m.s., h.p.l.c.) with an authentic sample.[12] The petroleum-insoluble product was extracted into chloroform–water (1 : 1), and the organic layer separated, dried (Na_2SO_4) and reduced to a small volume. Chromatography (twice) on silica, with ether as eluant, gave 2-phenylquinoxaline (0.24 g, 47%) and 3-methanesulphonamido-2-nitropyridine (13) (0.08 g, 14%). The aqueous extract was shown by h.p.l.c. to contain a mixture, one component of which was 3-amino-2-nitropyridine; however the latter was present in only small quantities and was not isolated.

(*b*) *With diethylamine.* Repetition of the above, with diethylamine (0.37 g) in place of ammonia, gave a crude product which was extracted directly into chloroform–water and the chloroform extract chromatographed on silica. 2-Phenylquinoxaline (0.42 g, 81%) was thus obtained. The sulphonamide (13) and 3-amino-2-nitropyridine were not detected.

(*c*) *With sodium ethoxide.* Repetition of the above with sodium ethoxide (sodium, 0.115 g) as base gave 2-phenylquinoxaline (0.36 g, 70%). Once again the sulphonamide (13) and 3-amino-2-nitropyridine were not detected.

(*d*) *With* o-*phenylenediamine alone.* This gave unchanged starting sulphonamide (74%) and a mixture of at least 10 compounds including (by t.l.c.) *o*-phenylenediamine and 2-phenylquinoxaline.

Reaction of N-(2-*Nitro*-5-*pyridyl*)-N-*phenacylmethanesulphonamide* (29) *with Sodium Ethoxide.*—This reaction, according to procedure A (Table 2), gave as the only identifiable product 5-amino-2-nitropyridine (0.06 g, 17%), m.p. 224—226 °C (decomp.) (from benzene) [lit.,[18] 234—235 °C (decomp.)]; $\nu_{max.}$ 3 440, 3 320, 3 220 (NH_2), 1 515 (w) and 1 350 cm^{-1} (NO_2); the n.m.r. spectrum is given in Table 1.

p-*Nitrobenzylamine.*—This compound was prepared by a modification of the Gabriel synthesis. *p*-Nitrobenzyl chloride (17.1 g), potassium phthalimide (18.5 g), and dimethylformamide (275 ml) were stirred at room temperature for 1 h. The mixture was then added to water (600 ml) and *N*-*p*-nitrobenzylphthalimide filtered off (17 g, 60%), m.p. 173—175 °C (from ethanol) (lit.,[19] 174—175 °C). This imide (14.1 g), hydrazine hydrate (11 ml), and ethanol (875 ml) were heated together, under reflux, overnight; the ethanol was distilled off, water (1.5 l) was added to the residue, and the mixture acidified (acetic acid). Phthalazine-1,4-dione was filtered off and the filtrate concentrated under reduced pressure to give *p*-nitrobenzylammonium acetate (8.26 g, 78%), m.p. 157—158 °C (from ethanol); δ (D_2O) 1.95 (3 H, s), 4.40 (2 H, s), and 7.72, 8.28 (4 H, AA′BB′). This salt (6.8 g) was dissolved in water (100 ml) and the solution basified (NaOH). The *p*-nitrobenzylamine was extracted with ether and concentration of the extract gave the amine (4.66 g, 96%), m.p. *ca.* room temperature (20 °C).

3-*Nitro*-2-(p-*nitrobenzylamino*)*pyridine* (31).—A solution of 2-chloro-3-nitropyridine (2.87 g) and *p*-nitrobenzylamine (4.37 g) in redistilled dimethyl sulphoxide (20 g) was heated at 50 °C for 18 h. It was then cooled and diluted with water, and the precipitate filtered off, washed with water, and recrystallised from ethanol, giving the *nitro-amine* (31) (2.94 g, 59%), m.p. 150—152 °C (Found: C, 52.3; H, 3.4; N, 20.5. $C_{12}H_{10}N_4O_4$ requires C, 52.6; H, 3.7; N, 20.4%); $\nu_{max.}$ 3 410 (NH), and 1 505 and 1 340 cm^{-1} (NO_2); the n.m.r. spectrum is given in Table 1.

2-p-*Nitrophenyl*-3H-*imidazo*[4,5-b]*pyridine* 1-*Oxide* (32).—Cyclisation of 3-nitro-2-(*p*-nitrobenzylamino)pyridine (31), using either sodium methoxide (method A: 6 h reflux) or diethylamine (method C: 6 h reflux) gave the *N*-oxide (32) in yields of 92 and 17% respectively. [In the latter case, unchanged nitroamine (31) was recovered in 77% yield.]

The N-*oxide* (32) had m.p. 328—331 °C (decomp.) (from dimethylformamide) (Found: C, 56.1; H, 3.1; N, 21.75. $C_{12}H_8N_4O_3$ requires C, 56.25; H, 3.15; N, 21.9%); $\nu_{max.}$ 1 510, 1 350 or 1 340 (NO_2); *m/e* 256 ($M^{+\cdot}$, 7%), 240 (100), 210 (20), 195 (10), 194 (63), *etc.* N.m.r. spectrum was not available because of low solubility.

The *N*-oxide was converted into the O-*benzoyl derivative* (33) (40%) by reaction with benzoyl chloride, aqueous sodium hydroxide, and dimethylformamide, as described for the preparation of its isomer (21), but with half of the stated quantities of these reagents and solvents. The *benzoate* had m.p. 205—207 °C (from toluene) (Found: C, 63.25; H, 3.05; N, 15.7. $C_{19}H_{12}N_4O_4$ requires C, 63.3; H, 3.4; N, 15.55%); $\nu_{max.}$ 1 780 (CO), 1 520br and 1 350 cm^{-1} (NO_2); the n.m.r. spectrum is given in Table 3; *m/e* 240 [$(M - PhCO_2 + H)^+$, 35%], 194 (21), 122 (29), 105 (100).

Acknowledgements

We thank Mrs. S. Smith for the microanalyses, Dr. R. K. Mackie and Mrs. M. Smith for the n.m.r. spectra (including the computer simulations), Mr. C. Millar for the mass spectra, and the S.R.C. and the Wellcome Research Laboratories for a CASE Studentship to A. F. A.

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Received 26*th April* 1982; *Paper* 2/677