o-Nitroaniline Derivatives. Part 9.[1] Benzimidazole *N*-Oxides Unsubstituted at N-1 and C-2

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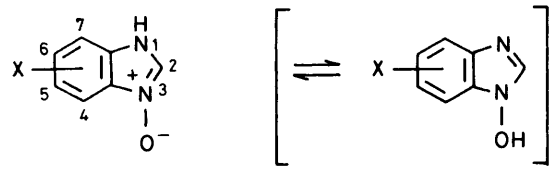
Since previous routes to the title compounds (**1**) have proved unsatisfactory as general methods, a simple new synthesis has been devised. *N*-Cyanomethyl-*o*-nitroanilines (**5**) are cyclised in basic media, giving 2-cyanobenzimidazole *N*-oxides (**12**) in good yield. Hydrolysis of these products with hydrochloric acid gives, directly, the title compounds as their hydrochloride salts (**13**), which may be isolated and purified, and which give the free *N*-oxides (**1**) by treatment with aqueous ammonia followed by evaporation.

o-Nitrophenylglycine esters (**4**) may satisfactorily replace the nitriles (**5**) in certain cases. A modification of this kind in the related nitropyridylglycine series leads to 3*H*-imidazol[4,5-*b*]pyridine 1-oxide (**20**).

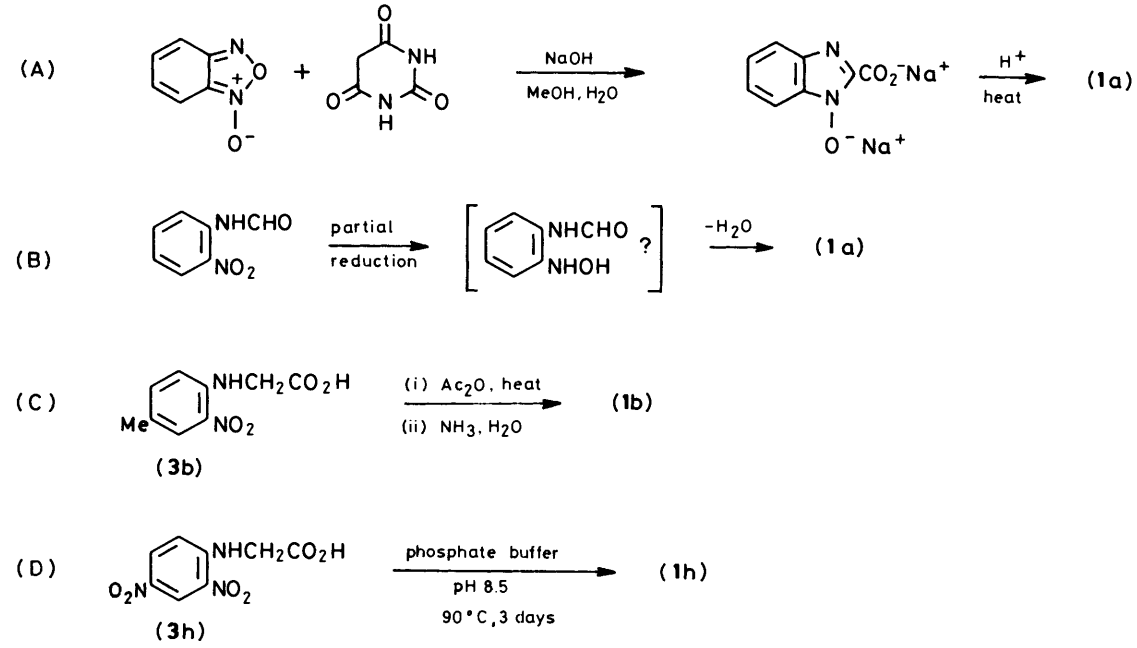
Although benzimidazole *N*-oxide itself [(**1a**); tautomeric with *N*-hydroxybenzimidazole (**2a**)] has been known for many years, and its chemistry extensively investigated,[2] scarcely anything is known about its analogues which bear substituents only in the carbocyclic ring. As part of a study of structural analogues of the natural purines, we have become interested in benzimidazole *N*-oxides with amino and hydroxy substituents, but hitherto no general route to such molecules has been available. In this paper, we describe attempts to develop a useful synthesis of compounds of the general structure (**1**), and in Part 10, which follows, we consider the additional problems associated with the synthesis of 5- and 6-aminobenzimidazole *N*-oxides [X = NH_2 or NHR in (**1**)].



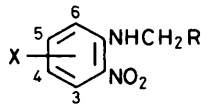
(**1**) (**2**)

	X		X
(**1a**)	H	(**1e**)	6-F
(**1b**)	5-Me	(**1f**)	5-Cl
(**1c**)	5-OMe	(**1g**)	4-NO_2
(**1d**)	5-F	(**1h**)	5-NO_2

Of the previously published routes to the parent compound (**1a**) and its simple analogues (**1b**) and (**1h**) (Scheme 1), reaction A, which is based on benzofuroxan,[3] has not been considered further as a general method. Apart from the fact that substituted benzofuroxans would themselves require to be prepared, monosubstituted benzofuroxans are (in solution, at least) mixtures of tautomers,[4] and might thus be expected to give mixtures of benzimidazole oxides. The generality of reaction D[5] has similarly not been explored; of the *o*-nitrophenylglycine analogues (**3a**—**h**), *N*-(2,4-dinitrophenyl)glycine (**3h**) is not



Scheme 1.



(3) R = CO_2H
(4) R = CO_2Et
(5) R = CN

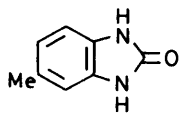
	X
a	H
b	4 - Me
c	4 - OMe
d	4 - Cl
e	4 - F
f	5 - F
g	3 - NO_2
h	4 - NO_2

only the easiest by far to prepare (from a halogeno-2,4-dinitrobenzene), but it is expected to be the easiest to cyclise, by virtue of the second nitro group. (Substituent effects in this type of cyclisation are discussed in Part 10.) The two other methods may now be considered in more detail.

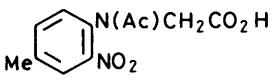
(*B*) *Partial Reduction of* o-*Nitroformanilides.*—Several reducing agents may effect the conversion of *o*-nitroformanilide into (**1a**),[2] but none of these is entirely satisfactory as a general method. Over-reduction, which leads to the parent benzimidazole, is a recurring problem, and other reducible groups in the starting material present obvious difficulties. [2,4-Dinitroformanilide has been successfully reduced to (**1h**) using ammonium sulphide,[6] but the yield is low.] Even the use of sodium borohydride in presence of palladium–charcoal[7]—undoubtedly the cleanest of these reduction methods—is not entirely reliable in this regard, since this combination of reagents is also known[8] to effect complete reduction of nitroarenes (including nitro- and dinitro-anilines) to the corresponding primary amines. There is also likely to be considerable product loss during the work-up (see later).

By following the patented general procedure,[7] we have obtained the parent *N*-oxide (**1a**) and its 5-methyl derivative (**1b**), but only in low yield [10—20%, compared with the patent's claim of 74% for (**1a**)].

(*C*) *Reaction of* o-*Nitrophenylglycine Derivatives with Acetic Anhydride.*—In 1974, Aboulezz and El-Sheikh reported[9] that *N*-(4-methyl-2-nitrophenyl)glycine (**3b**) underwent cyclisation in boiling acetic anhydride. If the reaction was stopped after 8 h and the crude product 'hydrolysed' with aqueous ammonia, the product isolated was the *N*-oxide (**1b**); if the reaction was allowed to proceed for 12 h, the product obtained after 'hydrolysis' was 5-methylbenzimidazolone (**6**). Despite the fact



(**6**)

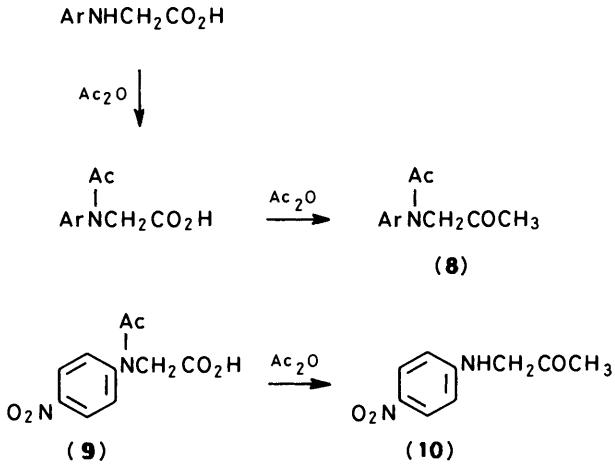


(**7**)

that we found the proposed reaction mechanism unconvincing,* the apparent simplicity of the experimental procedure was obviously attractive.

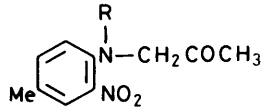
Unfortunately, we have been unable to isolate either the *N*-oxide (**1b**) or the benzimidazolone (**6**) from these reactions. In each case the crude product, both before and after treatment with ammonia, is a complex mixture (by t.l.c.), and the only solid product isolated (from the 12 h reaction) is merely the *N*-acetyl derivative (**7**) of the starting acid. *N*-(*o*-Nitrophenyl)-glycine (**3a**) similarly gives an intractable mixture of products when made to react with acetic anhydride under these conditions. We believe that there must be a serious error or omission in the published experimental procedure, but our attempts to contact the authors of the paper in this connection have so far been unsuccessful.

It is known, however,[10] that other *N*-arylglycines are converted, in boiling acetic anhydride, into α-acetamidoacetone derivatives (**8**) (the Dakin-West reaction), and that this reaction with the *p*-nitrophenyl compound (**9**) leads to the deacetylated amino ketone (**10**) (Scheme 2).† A similar course of events



Scheme 2.

involving compound (**3b**) or (**7**) might be expected to give an *o*-nitroanilinoacetone [(**11**); R = H or Ac], which could conceivably undergo cyclisation and deacetylation in the aqueous ammonia to yield the *N*-oxide (**1b**).



(R = H or Ac)

(**11**)

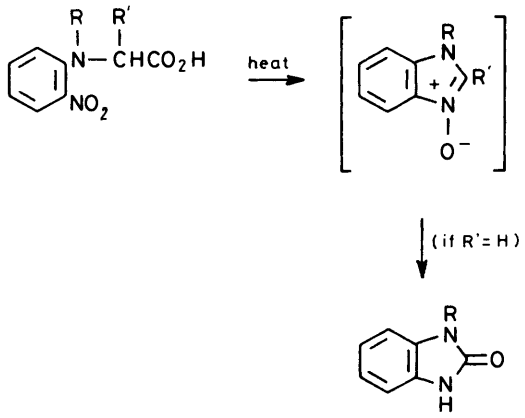
With this last possibility in mind, we have studied the reaction of the glycine (**3b**) with acetic anhydride under milder conditions (1 h at 70 °C; also 1 h at the b.p.), but here again compound (**7**) is the only pure solid isolable from the product mixture. Compound (**7**) is also recovered unchanged after renewed treatment with boiling acetic anhydride for a further 1 h.

A New Route to the N-*Oxides* (**1a—h**).—Since none of these existing procedures provides a satisfactory basis for a general route to the *N*-oxides of type (**1**), we have sought to develop a new and versatile synthesis of such compounds.

In this context, we have reconsidered the thermolysis of *o*-nitrophenylglycine analogues (**3**). Goudie and Preston have shown[11] that the *N*-*o*-nitrophenyl derivatives of glycine and other α-amino acids undergo thermolysis (either in solution or in admixture with sand) to give benzimidazolones, and benzimidazole *N*-oxides have been presumed to be the primary products (Scheme 3). We had hoped that flash vacuum pyrolysis (f.v.p.), in which the very short reaction times and low reactant pressures sometimes permit the isolation of reactive intermediates, might provide a useful route from the acids (**3**) to the *N*-oxides (**1**), and we had in the methyl-substituted glycine

* See ref. 2, pp. 304—305.

† We thank Dr. G. L. Buchanan for bringing these reactions to our attention.

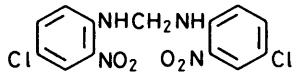


Scheme 3.

(**3b**) an ideal substrate for f.v.p. since the product mixture is easily analysed by ^{1}H n.m.r. F.v.p. of the acid (**3b**) does indeed give the *N*-oxide (**1b**) along with the benzimidazolone (**6**), but the former is never present in sufficient quantity for the method to be synthetically useful.

The successful synthesis of the *N*-oxides (**1a**—**h**), which we now recommend, is based on the previous observation[3] (*cf.* Scheme 1, Reaction A) that benzimidazole-2-carboxylic acid *N*-oxide undergoes particularly facile decarboxylation when heated in a solvent at temperatures as low as 80 °C. The complete reaction sequence is shown in Scheme 4.

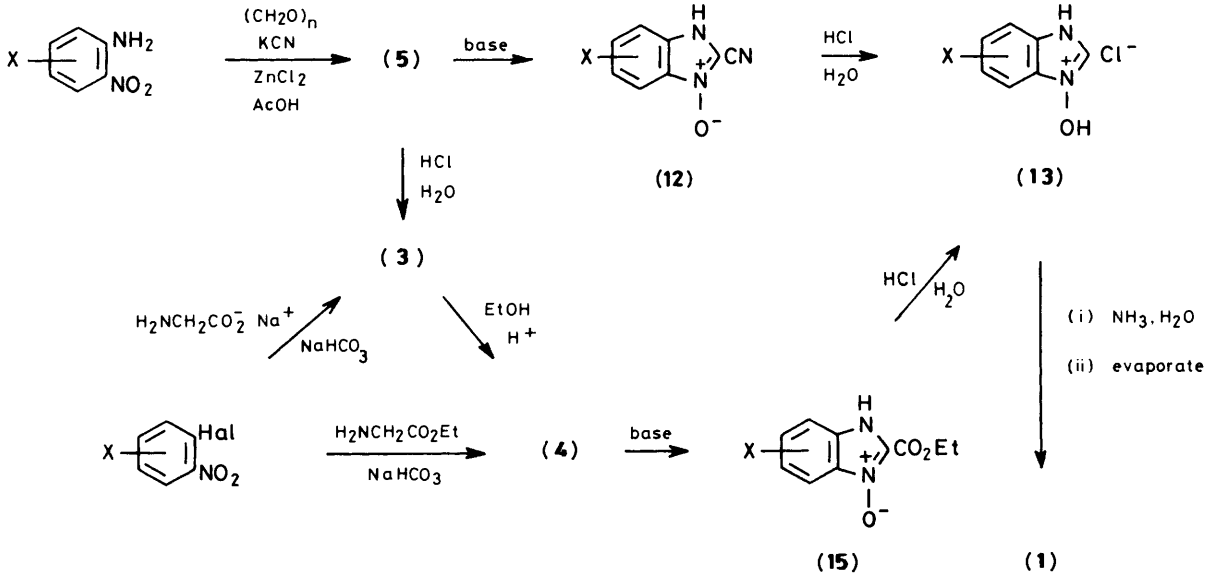
depends critically on the basicity of the amine; thus, for example, reactions involving chloro- and fluoro-nitroanilines require more, and those involving methyl- and methoxy-nitroanilines less, than in the standard procedure for *o*-nitroaniline itself. [In the case of 4-chloro-2-nitroaniline, the use of a smaller quantity of zinc chloride leads to bis(4-chloro-2-nitroanilino)methane (**14**) as the sole product.]



(**14**)

We attribute the success of this synthetic route, in part, to the work-up procedure following the hydrolysis step. Benzimidazole *N*-oxides unsubstituted at the other nitrogen are both weakly basic [the pK_a of protonated (**1a**) being 2.90[14]] and appreciably acidic [the pK_a of (**1a**) being 7.86[14]], and both they and their hydrochlorides are to some extent soluble in water. Our method allows the isolation of the hydrochlorides uncontaminated by inorganic salts; the isolation of the free *N*-oxides by evaporation of their ammonium salts (a method hinted at, although not commented upon, by Aboulezz and El-Sheikh[9]) appears to prevent isomerisation to benzimidazolones, a side-reaction which, under other conditions, may reduce the yield of (**1**).[15]

N-(*o*-Nitrophenyl)glycine esters (**4**) may satisfactorily replace the *N*-cyanomethyl-*o*-nitroanilines (**5**) in the synthesis, although in many cases this modification offers no real advantage, since



Scheme 4.

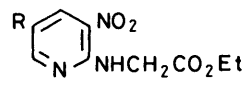
Cyanomethylation of *o*-nitroaniline, as described by Dimroth and Aurich,[12] is an efficient synthetic procedure, and the cyclisation of the cyanomethyl compound (**5a**) also proceeds in high yield, giving 2-cyanobenzimidazole *N*-oxide (**12a**).[13] Hydrolysis of (**12a**) in hot concentrated hydrochloric acid leads directly to the hydrochloride (**13a**) of the parent *N*-oxide (**1a**), and the latter is obtained, in high purity, by dissolving the hydrochloride in aqueous ammonia and evaporating the solution to small volume.

This method may be adapted, with only minor modifications, for the synthesis of the *N*-oxides (**1b**—**g**). In the cyanomethylation step, the quantity of Lewis acid (zinc chloride) required

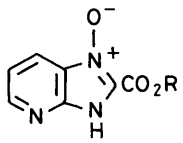
the esters (**4**) are themselves prepared most efficiently from the nitriles (**5**). However, if, in a particular case, an ester is easily obtained (*e.g.* from an *o*-halogenonitrobenzene and glycine ethyl ester), then it may offer a convenient alternative. *N*-(2,4-Dinitrophenyl)glycine ethyl ester (**4h**) is a case in point; its preparation is much simpler than that of the nitrile (**5h**), and its cyclisation to (**15h**) occurs under very mild conditions (piperidine in ethanol). In this particular sequence, the remaining stages are also atypical. The final product (**1h**) is more weakly basic, and much less soluble in water, than the other compounds of the series. It is sufficient in this case to dissolve the hydrochloride (unpurified) in aqueous sodium

hydroxide and make this solution just acid again, whereupon the *N*-oxide is precipitated in good yield.

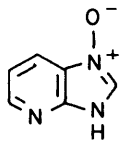
We have attempted to extend this synthetic procedure to obtain some derivatives of 3*H*-imidazo[4,5-*b*]pyridine 1-oxide, since very few representatives of this class have been previously described.[16] *N*-(3-Nitro-2-pyridyl)- and *N*-(3,5-dinitro-2-pyridyl)-glycine ethyl esters (**16**) and (**17**) are easily prepared, but their reactions with base do not parallel those of the corresponding benzene derivatives, (**4a**) and (**4h**). The mono-



(**16**) R = H
(**17**) R = NO_2



(**18**) R = Et
(**19**) R = H



(**20**)

nitro-ester (**16**) is cyclised in ethanolic potassium carbonate to give a mixture of two potassium salts, one soluble and one insoluble in the reaction medium; the former gives, on acidification, the expected imidazopyridine ester (**18**), and the latter, when acidified, gives a thermally labile solid [*possibly* the carboxylic acid (**19**)] which decomposes on warming to give the parent 3*H*-imidazo[4,5-*b*]pyridine 1-oxide (**20**). Interestingly, acid hydrolysis of the ester (**18**) does *not* appear to give a salt of (**20**); this reaction is still receiving our attention.

The dinitropyridylglycine ester (**17**), on the other hand, gives no identifiable product on reaction with potassium carbonate, unchanged starting material (11%) and an intractable black solid (a complex mixture by t.l.c.) being obtained. The reaction of (**17**) with piperidine is similarly unsuccessful; the reason for this failure is unknown.

Experimental

I.r. spectra were recorded for Nujol mulls. ^{1}H N.m.r. spectra were recorded at 80 MHz, and ^{19}F n.m.r. spectra at 75.3 MHz, in [$^2H_6$]dimethyl sulphoxide unless otherwise stated. The ^{19}F chemical shifts are upfield (negative δ) from $CFCl_3$.

Partial Reduction of o-*Nitroformanilides.*—*o*-Nitroformanilide, m.p. 122 °C (from ethanol; lit.,[17] 122 °C) was obtained in 69% yield by heating *o*-nitroaniline (13.8 g) and formic acid (98%; 20 ml) under reflux for 2 h. The product crystallised from the cooled solution. 4-Methyl-2-nitroformanilide, m.p. 124—125 °C (from ethanol; no lit. m.p. quoted[18]), was similarly obtained from 4-methyl-2-nitroaniline; it showed $\nu_{max.}$ 3 260 (NH) and 1 705 and 1 670 cm^{-1} (CO); $\delta_H(CDCl_3)$ 2.42 (3 H, s, Me), 7.60 (1 H, dd, 5-H), 8.10 (1 H, d, 3-H), 8.6—8.9 (2 H, unresolved, 6-H and NH), and 10.0—10.5 (1 H, br, CHO); $J_{3,5}$ 2 Hz and $J_{5,6}$ 8 Hz.

Reduction Procedure.—A solution of sodium borohydride (1.83 g) in water (1.8 ml) was added slowly, with stirring, to a suspension of palladium–charcoal (5%; 1.0 g) in water (15 ml). A solution of the *o*-nitroformanilide (0.02 mol) in pyridine (36 ml) was added to this mixture, at such a rate that the temperature was maintained at 35—40 °C. When the addition was complete (*ca.* 20 min), the mixture was stirred for a further 15 min, the catalyst was filtered off, and the filtrate evaporated under reduced pressure. The residue was dissolved in water (*ca.* 70 ml), acidified (conc. HCl), then concentrated to approximately half volume and neutralised with aqueous ammonia (*d* 0.88) before again being evaporated to dryness under reduced pressure. The residue was extracted with hot ethanol; the extract, when cooled, deposited inorganic material which was filtered off, and the filtrate was further concentrated and cooled to give the *N*-oxide. The yields were variable, but were typically 10—20%. Benzimidazole *N*-oxide itself (**1a**), thus prepared, had m.p. 210—212 °C (from ethanol; lit.,[15] 215 °C), and 5-methylbenzimidazole 3-oxide (**1b**) had m.p. 174—174.5 °C (from ethanol; lit.,[9] 176—178 °C).

N-*Cyanomethyl*-o-*nitroaniline* (**5a**).—The following is adapted from Dimroth and Aurich's procedure.[12]—Acetic acid (125 ml) containing concentrated sulphuric acid (8 drops) was added, with efficient mechanical stirring, to a mixture of *o*-nitroaniline (6.9 g, 0.05 mol), paraformaldehyde (4.5 g, 0.15 mol CH_2O), potassium cyanide (9.75 g, 0.15 mol), and anhydrous zinc chloride (52.5 g, 0.38 mol). The mixture was heated to 50 °C and stirred at this temperature for 8 h. It was then poured into ice–water, and the product filtered off, washed well with water, and recrystallised from ethanol. *N*-Cyanomethyl-*o*-nitroaniline (**5a**) (6.73 g, 76%) had m.p. 136—138 °C (lit.,[12] 139—140.5 °C); $\nu_{max.}$ 3 380 (NH) and 1 510 and 1 340 cm^{-1} (NO_2); δ_H 4.62 (2 H, d, CH_2), 6.92 (1 H, ddd, 4-H), 7.20 (1 H, dd, 6-H), 7.72 (1 H, ddd, 5-H), 8.18 (1 H, dd, 3-H), and 8.32 (1 H, br t, NH); $J_{CH_2,NH}$ 6 Hz, $J_{3,4}$ 8.5 Hz, $J_{4,5}$ 9.5 Hz, $J_{5,6}$ 9 Hz, and $J_{3,5} = J_{4,6}$ 2 Hz.

N-*Cyanomethyl*-4-*methyl*-2-*nitroaniline* (**5b**). This compound, m.p. 146—147 °C (from ethanol), was similarly obtained (7.2 g, 75%) from 4-methyl-2-nitroaniline (7.6 g, 50 mmol), paraformaldehyde (4.5 g), potassium cyanide (9.75 g), and zinc chloride (25 g), in acetic acid (250 ml) and sulphuric acid (4 drops). (The use of a larger proportion of zinc chloride gave increasing proportions of the *N*,*N*-bis-cyanomethyl derivative, as adjudged by n.m.r.) (**5b**) (Found: C, 56.45; H, 4.7; N, 21.95. $C_9H_9N_3O_2$ requires C, 56.5; H, 4.7; N, 22.0%); $\nu_{max.}$ 3 380 (NH), 2 230w (CN), and 1 530 and 1 325 cm^{-1} (NO_2); δ_H 2.30 (3 H, s, Me), 4.65 (2 H, d, CH_2), 7.08 (1 H, d, 6-H), 7.54 (1 H, dd, 5-H), 7.95 (1 H, d, 3-H), and 8.12 (1 H, br t, NH); $J_{CH_2,NH}$ 6 Hz, $J_{3,5}$ 2 Hz, and $J_{5,6}$ 8 Hz.

N-*Cyanomethyl*-4-*methoxy*-2-*nitroaniline* (**5c**). This compound was prepared (yield, 85%) in the same way as (**5b**), and had m.p. 176—178 °C (from ethanol) (Found: C, 52.1; H, 4.35; N, 20.3. $C_9H_9N_3O_3$ requires C, 52.2; H, 4.4; N, 20.3%); $\nu_{max.}$ 3 375 (NH), 2 240w (CN), and 1 505 and 1 340 cm^{-1} (NO_2); δ_H 3.82 (3 H, s, OMe), 4.59 (2 H, d, CH_2), 7.19 (1 H, d, 6-H), 7.44 (1 H, dd, 5-H), 7.63 (1 H, d, 3-H), and 8.10 (1 H, br t, NH); $J_{CH_2,NH}$ 6.5 Hz, $J_{3,5}$ 2.5 Hz, and $J_{4,5}$ 9 Hz.

4-*Chloro*-N-*cyanomethyl*-2-*nitroaniline* (**5d**). Reaction of 4-chloro-2-nitroaniline (6.85 g, 40 mmol) with paraformaldehyde (3.6 g), potassium cyanide (7.8 g), and zinc chloride (42 g) in acetic acid (100 ml) containing sulphuric acid (4 drops) at 50 °C gave, after 10 h, the *cyanomethyl derivative* (**5d**), m.p. 156—158 °C (from ethanol), in 72% yield (Found: C, 45.3; H, 2.8; N, 19.9. $C_8H_6ClN_3O_2$ requires C, 45.4; H, 2.9; N, 19.9%); $\nu_{max.}$ 3 385 (NH) and 1 510 and 1 335 cm^{-1} (NO_2); δ_H 4.60 (2 H, d, CH_2), 7.23 (1 H, d, 6-H), 7.77 (1 H, dd, 5-H), 8.15 (1 H, d, 3-H), and 8.33 (1 H, br t, NH); $J_{CH_2,NH}$ 6 Hz, $J_{3,5}$ 2 Hz, and $J_{5,6}$ 9 Hz.

Attempts to prepare (**5d**) using the same procedure as for (**5b**) (*i.e.* with a smaller proportion of zinc chloride in a larger volume of solvent) gave only bis(4-chloro-2-nitroanilino)methane (**14**), m.p. 266—268 °C (from dimethylformamide; lit.,[19] 266 °C) in 39% yield (Found: C, 43.5; H, 2.7; N, 15.7. Calc. for

Table 1. Benzimidazole *N*-oxide hydrochlorides (**13**)

Compound	Yield (%) from (**12**)	Yield (%) from (**15**)	M.p. (°C) (recryst. solvent)	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N	Chemical shifts (δ) 2-H	4-H	5-H	6-H	7-H	Other	*J*/Hz
(**13a**)	57	50	199—200 (Pr^iOH)	$C_7H_7ClN_2O$	49.4	4.2	16.5	49.3	4.1	16.4	10.07 s	(7.7—8.1 m)					
(**13b**)	64	85	227—230 (EtOH)	$C_8H_9ClN_2O$	51.9	4.8	15.0	52.05	4.9	15.2	9.80 s	7.63 d		7.42 dd	7.73 d	2.52 Me	8.5 (6,7), *ca.* 1.5 (4,6)
(**13c**)	50	32	215—216 d (EtOH)	$C_8H_9ClN_2O_2$	48.0	4.6	14.0	47.9	4.5	14.0	9.74 s	7.1—7.35 m (with 6-H)		7.1—7.35 m (with 4-H)	7.77 d	3.91 OMe	8 (6,7)
(**13d**)	51		224—226 d (EtOH)	$C_7H_6Cl_2N_2O$	41.2	2.9	13.6	41.0	2.9	13.7	9.81 s	7.96 d		7.63 dd	7.90 d		9 (6,7), 2 (4,6)
(**13e**)	88		240—242 d (HCl)	$C_7H_6ClFN_2O$	44.3	3.1	14.7	44.6	3.2	14.85	9.85 s	7.73 dd		7.46 dt	7.88 dd	δ_F −114.0	9.0 (6,7), 2.0 (4,6), 8.4 (4,F), 9.0 (6,7), 4.4 (7,F)
(**13f**)	79		194—196 (HCl)	$C_7H_6ClFN_2O$	44.8	3.2	15.0	44.6	3.2	14.85	9.78 s	7.90 ddd	7.50 dt		7.73 ddd	δ_F −114.4	9.2 (4,5), 2.4 (5,7), 0.6 (4,7), 9.3 (5,F and 7,F), 4.6 (4,F)
(**13g**)	69		224—225 d (HCl)	$C_7H_6ClN_3O_3$	38.9	2.8	19.5	39.0	2.8	19.5	9.07 s		8.0—8.2 (with 7-H)	7.53 t	8.0—8.2 (with 5-H)		8 (5,6 and 6,7)
(**13h**)		97	*ca.* 240 (HCl)	(Crude product only obtained)							9.62 s	8.55 d		8.30 dd	8.00 d		9 (6,7), 2.5 (4,6)

Table 2. Benzimidazole *N*-oxides (**1**)

Compound	Yield (%)	M.p. (°C) (recryst. solvent)	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N	Chemical shifts (δ) 2-H	4-H	5-H	6-H	7-H	Other	*J*/Hz
(**1a**)	68	*214—216 (EtOH)								8.35 s	(7.1—7.8 m)					
(**1b**)	72	†174—174.5 (EtOH–H_2O)	$C_8H_8N_2O$	64.6	5.45	19.0	64.85	5.4	18.9	8.23 s	7.25 d		7.00 dd	7.45 d	2.40 Me	8 (6,7), *ca.* 1.5 (4,6)
(**1c**)	75	176—177 (H_2O)	$C_8H_8N_2O_2$	58.1	5.0	17.2	58.5	4.9	17.1	8.20 s	6.96 d		6.80 dd	7.50 d	3.82 OMe	8.5 (6,7), 2 (4,6)
(**1d**)	76	224—226 (H_2O)	$C_7H_5ClN_2O$	49.5	2.9	16.3	49.9	3.0	16.6	8.42 s	7.55 d		7.21 dd	7.65 d		8.5 (6,7), 2 (4,6)
(**1e**)	57	227—229 (H_2O)	$C_7H_5FN_2O$	55.1	3.2	18.5	55.3	3.3	18.4	8.38 s	7.30 dd		7.03 ddd	7.65 dd	δ_F −118.7	9.0 (6,7), 2.4 (4,6), 10.0 (6, F), 8.6 (4,F), 4.9 (7,F)
(**1f**)	64	229—231 d (H_2O)	$C_7H_5FN_2O$	55.2	3.0	18.5	55.3	3.3	18.4	8.41 s	7.51 dd	7.14 ddd		7.43 dd	δ_F −121.6	8.8 (4,5), 2.4 (5,7), 9.7 (5,F and 7,F), 5.9 (4,F)
(**1g**)	63	228—230 d (H_2O)	$C_7H_5N_3O_3$	46.7	2.7	23.3	46.9	2.8	23.5	8.57 s		7.9—8.1 m (with 7-H)	7.38 t	7.9—8.1 m (with 5-H)		8 (5,6 and 6,7)
(**1h**)	83	‡274—276 d (EtOH)								8.70 s	8.30 d		8.05 dd	7.75 d		9 (6,7), 2 (4,6)

* Lit.,[15] 215 °C. † Lit.,[9] 176—178 °C. ‡ Lit.,[6] 274 °C (d).

$C_{13}H_{10}Cl_2N_4O_4$: C, 43.7; H, 2.8; N, 15.7%); $\nu_{max.}$ 3 360 cm^{-1} (NH); $\delta_H(CF_3CO_2H)$ 4.07 (2 H, s, CH_2), 5.92 (2 H, br s, 2 × NH), 7.58 (2 H, d, 2 × 6-H), 7.82 (2 H, dd, 2 × 5-H), and 8.39 (2 H, d, 2 × 3-H); $J_{3,5}$ 2.5 Hz and $J_{5,6}$ 8.5 Hz.

N-*Cyanomethyl-4-fluoro-2-nitroaniline* (**5e**). This compound, m.p. 163—164 °C (from ethanol), was obtained in 52% yield by the method described for the chloro analogue (**5d**) (Found: C, 49.55; H, 3.2; N, 21.6. $C_8H_6FN_3O_2$ requires C, 49.2; H, 3.1; N, 21.5%); $\nu_{max.}$ 3 370 (NH), 2 240w (CN), and 1 510 and 1 335 cm^{-1} (NO_2); $\delta_H(CDCl_3)$ 4.57 (2 H, d, CH_2), 7.20 (1 H, dd, 6-H), 7.66 (1 H, ddd, 5-H), 7.92 (1 H, dd, 3-H), and 8.17 (1 H, br s, NH); $\delta_F(CDCl_3)$ −125.5 p.p.m. (8 lines); $J_{CH_2,NH}$ 6 Hz, $J_{3,5}$ 3.0 Hz, $J_{5,6}$ 9.3 Hz, $J_{3,F}$ 8.7 Hz, $J_{5,F}$ 7.0 Hz, and $J_{6,F}$ 4.4 Hz.

5-Fluoro-2-nitroaniline. Hodgson and Nicholson's method[20] was modified as follows. Acetic anhydride (115 ml) was added slowly, with stirring, to *m*-fluoroaniline (50 g) at such a rate that the temperature remained below 40 °C. After addition was complete, the mixture was stirred at 50 °C for 3 h, cooled, and added to ice. The *m*-fluoroacetanilide (56.1 g, 82%) had m.p. 85—87 °C (from propan-2-ol–water; lit.,[20] 85 °C).

A mixture of nitric acid (*d* 1.5; 17 ml) and concentrated sulphuric acid (110 ml) was added dropwise, with stirring, to an ice-cooled solution of *m*-fluoroacetanilide (37.5 g) in concentrated sulphuric acid (110 ml) at such a rate that the temperature of the mixture remained below 5 °C. The addition required *ca.* 2 h; the mixture was then poured onto ice and the precipitate filtered off, washed with water, and dried under suction.

This mixture of nitration products was hydrolysed in ethanolic sulphuric acid, and the fluoronitroanilines separated by steam distillation, as already described.[20] 5-Fluoro-2-nitroaniline (steam-volatile) was obtained in a yield of 19 g (50%) and had m.p. 93—95 °C (from ethanol–water; lit.,[20] 97 °C). The steam-involatile residue, worked up as in the published method, gave 3-fluoro-4-nitroaniline (11.4 g, 30%), m.p. 146—148 °C (from ethanol–water; lit.,[20] 153 °C).

N-*Cyanomethyl-5-fluoro-2-nitroaniline* (**5f**), m.p. 129—131 °C (from ethanol–water), was prepared from 5-fluoro-2-nitroaniline by a procedure similar to that used for (**5d**); the yield was 76% (Found: C, 49.4; H, 3.1; N, 21.1. $C_8H_6FN_3O_2$ requires C, 49.2; H, 3.1; N, 21.5%); $\nu_{max.}$ 3 380 (NH), 2 245w (CN), and 1 505 and 1 340 cm^{-1} (NO_2); δ_H 4.60 (2 H, d, CH_2), 6.73 (1 H, ddd, 4-H), 7.04 (1 H, dd, 6-H), 8.26 (1 H, dd, 3-H), and 8.47 (1 H, br t, NH); δ_F −99.7 p.p.m. (16 lines), $J_{CH_2,NH}$ 6.5 Hz, $J_{3,4}$ 9.5 Hz, $J_{4,6}$ 2.5 Hz, $J_{3,F}$ 6.5 Hz, $J_{4,F}$ 8 Hz, $J_{6,F}$ 12 Hz, and $J_{F,NH}$ 2.2 Hz.

N-*Cyanomethyl-2,3-dinitroaniline* (**5g**). 2,3-Dinitroaniline, m.p. 123–125 °C (from ethanol; lit.,[21] 127 °C) was prepared from *m*-nitroacetanilide by the published procedure.[21]

2,3-Dinitroaniline (4.0 g), paraformaldehyde (1.97 g), potassium cyanide (4.3 g), and zinc chloride (22.9 g) in acetic acid (55 ml) containing sulphuric acid (4 drops) gave, after 20 h at 50 °C, the *cyanomethyl compound* (**5g**), m.p. 183—185 °C (from acetic acid); yield, 3.6 g (74%) (Found: C, 43.3; H, 2.7; N, 25.35. $C_8H_6N_4O_4$ requires C, 43.25; H, 2.7; N, 25.2%); $\nu_{max.}$ 3 385 (NH) and 1 560 and 1 360 cm^{-1} (NO_2); δ_H 4.50 (2 H, d, CH_2), 7.38—7.90 (4 H, m, ArH + NH); $J_{CH_2,NH}$ 6 Hz.

N-*Cyanomethyl-2,4-dinitroaniline* (**5h**). 1-Chloro-2,4-dinitrobenzene (10.2 g), aminoacetonitrile hydrochloride (4.62 g), and sodium hydrogen carbonate (8.4 g) were heated under reflux with ethanol (100 ml) for 2 h. The cooled solution was filtered, and the precipitate was washed with water and recrystallised from acetic acid. The *nitrile* (**5h**) (2.1 g, 19%) had m.p. 162—163 °C (Found: C, 42.9; H, 2.6; N, 25.05. $C_8H_6N_4O_4$ requires C, 43.25; H, 2.7; N, 25.2%); $\nu_{max.}$ 3 330 (NH), 2 240vw (CN), and 1 515 and 1 340 cm^{-1} (NO_2); δ_H 4.72 (2 H, d, CH_2), 7.33 (1 H, d, 6-H), 8.42 (1 H, dd, 5-H), 8.88 (1 H, d, 3-H), 8.98 (1 H, br t, NH); $J_{CH_2,NH}$ 7 Hz, $J_{3,5}$ 2.5 Hz, and $J_{5,6}$ 9 Hz.

N-(o-*Nitrophenyl*)*glycine* (**3a**).—This compound was obtained (3.11 g, 32%) from *o*-fluoronitrobenzene (7 g), glycine (3.38 g), and sodium hydrogen carbonate (19 g) in ethanol (180 ml) and water (100 ml) according to Goudie and Preston's method.[11] The product had m.p. 188—190 °C (decomp.) [from ethanol; lit.,[22] 192—193 °C (decomp.)].

N-(4-*Methyl-2-nitrophenyl*)*glycine* (**3b**). A solution of *N*-cyanomethyl-4-methyl-2-nitroaniline (**5b**) (4 g) in acetic acid (100 ml) and aqueous sulphuric acid (50% v/v; 240 ml) was heated at 100 °C for 2.5 h, then cooled, added to ice, and the precipitate filtered off and washed with water. The acid (**3b**) (2.8 g, 67%) had m.p. 186—188 °C (decomp.) [from propan-2-ol–water; lit.,[22] 189—190 °C (decomp.)]; $\nu_{max.}$ 3 340 (NH) and 1 715 cm^{-1} (CO); δ_H 2.23 (3 H, s, Me), 4.13 (2 H, d, CH_2), 6.83 (1 H, d, 6-H), 7.38 (1 H, dd, 5-H), 7.88 (1 H, d, 3-H), and 8.25 (1 H, br t, NH); $J_{CH_2,NH}$ 5 Hz, $J_{3,5}$ 2 Hz, and $J_{5,6}$ 8 Hz.

N-(4-*Methoxy-2-nitrophenyl*)*glycine* (**3c**), m.p. 188—190 °C (from ethanol), was similarly obtained in 45% yield from the nitrile (**5c**) (Found: C, 47.8; H, 4.4; N, 12.3. $C_9H_{10}N_2O_5$ requires C, 47.8; H, 4.5; N, 12.4%); $\nu_{max.}$ 3 345 (NH) and 1 720 cm^{-1} (CO); δ_H 3.75 (3 H, s, OMe), 4.14 (2 H, d, CH_2), 6.89 (1 H, d, 6-H), 7.27 (1 H, dd, 5-H), 7.51 (1 H, d, 3-H), and 8.20 (1 H, br t, NH); $J_{CH_2,NH}$ 5 Hz, $J_{3,5}$ 2.5 Hz, and $J_{5,6}$ 9 Hz.

N-(o-*Nitroaryl*)*glycine Ethyl Esters* (**4a**—**c**).—These compounds were prepared by saturating an ethanolic solution of the appropriate acid with gaseous hydrogen chloride, and heating the solution under reflux until reaction was complete. The ester (**4a**), m.p. 82—84 °C (from propan-2-ol; lit.,[23] 80 °C) was obtained in 88% yield; the ester (**4b**), m.p. 64—65 °C (from ethanol; lit.,[24] 65 °C) in 83% yield, and the ester (**4c**), m.p. 76—78 °C (from ethanol), in 87% yield; (**4c**) (Found: C, 52.1; H, 5.55; N, 16.0. $C_{11}H_{14}N_2O_5$ requires C, 52.0; H, 5.55; N, 11.0%) $\nu_{max.}$ 3 345 (NH), 1 730 (CO), and 1 510 and 1 345 cm^{-1} (NO_2); $\delta_H(CDCl_3)$ 1.32 (3 H, t, *Me*CH_2), 3.81 (3 H, s, OMe), 4.09 (2 H, s, *CH*$_2$NH), 4.30 (2 H, q, *CH*$_2$-Me), 6.68 (1 H, d, 6-H), 7.17 (1 H, dd, 5-H), and 7.68 (1 H, d, 3-H); J_{Me,CH_2} 7 Hz, $J_{3,5}$ 2.5 Hz, and $J_{5,6}$ 9 Hz.

N-(2,4-*Dinitrophenyl*)*glycine Ethyl Ester* (**4h**).—Glycine ethyl ester hydrochloride (14.0 g, 0.1 mol) and sodium hydrogen carbonate (16.8 g, 0.2 mol) were added successively to a solution of 1-chloro-2,4-dinitrobenzene (20.3 g, 0.1 mol) in ethanol (200 ml); the mixture was heated under reflux for 2 h and then added to ice–water. The product was filtered off, washed with ethanol and with water, and recrystallised from acetic acid to give the ester (**4h**) (20.9 g, 78%), m.p. 142—144 °C (lit.,[25] 144 °C).

Reaction of N-(4-*Methyl-2-nitrophenyl*)*glycine* (**3b**) *with Acetic Anhydride*.—(a) N-*Acetyl*-N-(4-*methyl-2-nitrophenyl*)-*glycine* (**7**). *N*-(4-Methyl-2-nitrophenyl)glycine (**3b**) (1.8 g, 8.6 mmol) was dissolved, with stirring, in warm (70 °C) acetic anhydride (20 ml). When solution was complete the mixture was kept at 70 °C for 1 h, during which time the colour changed from orange to yellow; it was then diluted with water (100 ml), vigorously stirred until homogeneous, set aside overnight, concentrated under reduced pressure (to *ca.* 30 ml), and the product filtered off. N-*Acetyl*-N-(4-*methyl-2-nitrophenyl*)*glycine* (**7**) (1.31 g, 61%) had m.p. 148—150 °C (from water) (Found: C, 52.2; H, 4.8; N, 11.1. $C_{11}H_{12}N_2O_3$ requires C, 52.4; H, 4.8; N, 11.1%); $\nu_{max.}$ 1 730 (CO, acid), 1 630 (CO, amide), and 1 530 and 1 360 cm^{-1} (NO_2); δ_H 1.75 (3 H, s, *Me*CO), 2.45 (3 H, s, *Me*-Ar), 3.89 and 4.49 (2 H, AB quartet,* *J* 17 Hz, CH_2), and 7.6—8.0 (3 H, m, Ar-H).

* The non-equivalence of methylene protons in this type of molecule has been discussed in Part 5.[26]

Repetition of this experiment at the b.p. (140 °C) of acetic anhydride, followed by removal of the latter by distillation at reduced pressure, also gave (**7**) as the only isolable product, albeit in lower yield (29%). Compound (**7**) was recovered, almost quantitatively, after further treatment with boiling acetic anhydride for 1 h.

(b) *The procedure of Aboulezz and El-Sheikh.*[9] The glycine (**3b**) (1.3 g) was heated under reflux with acetic anhydride (12 ml) for 12 h. After removal of the acetic anhydride under reduced pressure, the black sticky residue was heated under reflux with aqueous ammonia (25%; 10 ml) for 1 h. No precipitation occurred on evaporation of the ammonia under reduced pressure (in contradiction of the published claims). The tarry product was vigorously stirred with water (20 ml) for 10 min, and the aqueous layer (which contained a little suspended solid) was decanted off, filtered, and acidified (HCl) to give a yellow semisolid (0.15 g), found by n.m.r. to be mainly the *N*-acetylglycine (**7**).

Repetition of the above procedure, with reduction of the initial reaction period to 8 h, gave black tarry material from which no solid product could be isolated.

5-*Methylbenzimidazol-2-one* (**6**).—Urea (3.0 g, 50 mmol) was added to a solution of 3,4-diaminotoluene (6.1 g, 50 mmol) in pentan-1-ol (20 ml) and the mixture was heated under reflux until evolution of ammonia ceased (*ca.* 2 h). The colourless product obtained on cooling was filtered off and washed with cold ethanol. The benzimidazolone (**6**) (2.8 g, 38%) had m.p. 297—300 °C (from ethanol) (lit.,[27] 299—300 °C); $\nu_{max.}$ 3 100 (NH) and 1 740 cm^{-1} (CO); δ_H 2.25 (3 H, s, Me), 6.75 (3 H, approx. s, ArH), and 10.42 (2 H, br s, 2 × NH).

Flash Vacuum Pyrolysis (*f.v.p.*) *Experiments.*—The substrates to be pyrolysed were volatilised under low pressures (typically 10^{-1} to 10^{-2} mmHg) and the vapour passed through a horizontal quartz tube (300 mm long × 25 mm i.d.) externally heated to 600—770 °C. The solid products collected near the furnace outlet and their m.p.s, i.r. and ^1H n.m.r. spectra were examined.

F.v.p. of N-(4-*Methyl-2-nitrophenyl*)*glycine* (**3b**). (a) *At* 750 °C. The glycine (0.2 g) was volatilised at 130—140 °C/7—9 × 10^{-2} mmHg. Upon pyrolysis, a colourless solid (0.035 g), m.p. 296—300 °C, was obtained; this was identical spectroscopically with 5-methylbenzimidazol-2-one (**6**); yield 18%.

(b) *At* 700 °C. The glycine (0.18 g), volatilised at 120—140 °C/1—2 × 10^{-2} mmHg, gave on pyrolysis a pale orange solid (0.05 g) which was analysed by ^1H n.m.r. This showed that the product was a mixture of the unchanged glycine, the *N*-oxide (**1b**), and the benzimidazolone (**6**), in the appropriate ratio 1:0.8:1.

(c) *At* 650 °C. The glycine (0.30 g), volatilised at 120—130 °C/1—2 × 10^{-2} mmHg, gave on pyrolysis an orange solid (0.15 g; m.p. 135—142 °C) which was shown by ^1H n.m.r. to consist of the same three compounds as in (b), the approximate ratio being (**3b**):(**1b**):(**6**) = 3:1:1.1.

F.v.p. of the N-*oxide* (**1b**).—The *N*-oxide (0.09 g) was volatilised at 120—125 °C/5—7 × 10^{-2} mmHg, and pyrolysed at 750 °C to give 5-methylbenzimidazol-2-one (0.035 g, 39%), m.p. 296—298 °C.

Cyclisation of N-*Cyanomethyl*-o-*nitroanilines* (**5**): 2-*Cyanobenzimidazole* N-*Oxides* (**12**).—*The parent compound* (**12a**) (*cf.* ref. 13). Potassium carbonate (1.22 g) was added to a suspension of *N*-cyanomethyl-*o*-nitroaniline (**5a**) (3.08 g) in hot ethanol (170 ml), and the mixture heated under reflux for 4 h. The solvent was distilled off under reduced pressure, and the residue dissolved, as far as possible, in water. The mixture was filtered, and the filtrate acidified (HCl) to give the pale yellow N-*oxide* (**12a**). It had m.p. 232—234 °C (decomp.) (from ethanol–water; lit.,[13] 232 °C, 240—241 °C); $\nu_{max.}$ 2 240 cm^{-1} (CN); δ_H 7.30—8.0 (unresolved multiplet); yield 1.48 g (54%).

2-*Cyano*-5-*methyl*-1H-*benzimidazole* 3-*oxide* (**12b**). This compound, m.p. 236 °C (from dimethylformamide–water), was similarly obtained (reaction time 9 h) from *N*-cyanomethyl-4-methyl-2-nitroaniline (**5b**) (2.5 g) and potassium carbonate (1.92 g) in ethanol (140 ml); yield 1.20 g (53%) (Found: C, 62.1: H, 4.0; N, 24.1. $C_9H_7N_3O$ requires C, 62.4; H, 4.1; N, 24.3%); $\nu_{max.}$ 2 235 cm^{-1} (CN); δ_H 2.48 (3 H, s, Me), 7.22 (1 H, br d, 6-H), 7.38 (1 H, br s, 4-H), and 7.67 (1 H, d, 7-H); $J_{6,7}$ 8.5 Hz and $J_{4,6}$ not measurable (peaks broadened by Me).

2-*Cyano*-5-*methoxy*-1H-*benzimidazole* 3-*oxide* (**12c**). This compound was similarly obtained (reaction time 4.5 h; yield 51%) from the nitrile (**5c**) (2.5 g) and potassium carbonate (1.77 g) in ethanol (130 ml), and had m.p. 276—277 °C (from dimethylformamide–water) (Found: C, 57.45; H, 3.65; N, 22.3. $C_9H_7N_3O_2$ requires C, 57.1; H, 3.7; N, 22.2%); $\nu_{max.}$ 2 230 cm^{-1} (CN); δ_H 3.90 (3 H, s, OMe), 6.9—7.1 (2 H, m, 4- and 6-H), 7.6—7.75 (1 H, m, 7-H), and 12.9 (1 H, v br, NH/OH).

5-*Chloro*-2-*cyano*-1H-*benzimidazole* 3-*oxide* (**12d**). The nitrile (**5d**) (1 g) and potassium carbonate (0.29 g) in ethanol (60 ml) were stirred for 2 h at 50 °C, the ethanol distilled off, and the residue dissolved, as far as possible, in water. The insoluble portion was identified as 2-(4-*chloro*-2-*nitroanilino*)*acetamide* (0.27 g, 23%), m.p. 211—213 °C (from methanol) (Found: C, 41.8; H, 3.5; N, 18.3. $C_8H_8ClN_3O_3$ requires C, 41.85; H, 3.5; N, 18.3%); $\nu_{max.}$ 3 390 and 3 145 (NH), 1 660 (CO), and 1 505 and 1 340 cm^{-1} (NO_2); δ_H 3.98 (2 H, d, CH_2), 6.81 (1 H, d, 6-H), 7.25 (1 H, br s, amide NH), 7.60 (2 H, overlapping dd and br s, 5-H and amide NH), 8.06 (1 H, d, 3-H), and 8.47 (1 H, br t, *NH*-CH_2); $J_{CH_2,NH}$ 6 Hz, $J_{3,5}$ 2.5 Hz, and $J_{5,6}$ 9 Hz. The water-soluble portion, when acidified (HCl), gave the N-*oxide* (**12d**) (0.48 g, 58%), m.p. 216—218 °C (from aqueous dimethylformamide) (Found: C, 49.3; H, 2.0; N, 21.5. $C_8H_4ClN_3O$ requires C, 49.6; H, 2.1; N, 21.7%); $\nu_{max.}$ 2 220 cm^{-1} (CN); δ_H 7.43 (1 H, dd, 6-H), and 7.7—7.9 (2 H, m, 4- and 7-H); $J_{4,6}$ 2.5 Hz and $J_{6,7}$ 8 Hz.

2-*Cyano*-5-*fluoro*-1H-*benzimidazole* 3-*oxide* (**12e**). This compound, m.p. 231—232 °C (decomp.) (from aqueous methanol) was obtained (reaction time 1.5 h; yield 71%) from the nitrile (**5e**) (3.4 g) and potassium carbonate (1.22 g) in ethanol (170 ml) by the standard method (Found: C, 54.6; H, 2.3; N, 24.1. $C_8H_4FN_3O$ requires C, 54.25; H, 2.3; N, 23.7%); $\nu_{max.}$ 2 230 cm^{-1} (CN); δ_H 7.28 (1 H, ddd, 6-H), 7.53 (1 H, ddd, 4-H), 7.86 (1 H, ddd, 7-H), and 13.0 (1 H, br, NH/OH); δ_F −112.8 p.p.m. (8 lines); $J_{4,6}$ 2.6 Hz, $J_{6,7}$ 9.1 Hz, $J_{4,7}$ 0.6 Hz, $J_{4,F}$ 8.4 Hz, $J_{6,F}$ 9.8 Hz, and $J_{7,F}$ 4.8 Hz.

The above procedure with piperidine (1 mol equiv.) instead of potassium carbonate gave (**12e**) in 46% yield.

2-*Cyano*-6-*fluoro*-1H-*benzimidazole* 3-*oxide* (**12f**). This compound was prepared in the same way as (**12e**); the yield was 70%. It had m.p. 233—235 °C (decomp.) (from aqueous dimethylformamide) (Found: C, 54.1; H, 2.3; N, 23.25. $C_8H_4FN_3O$ requires C, 54.2; H, 2.3; N, 23.7%); $\nu_{max.}$ 2 235 cm^{-1} (CN); δ_H 7.3—7.85 (unresolved multiplet); δ_F −117.3 p.p.m. (dt); $J_{4,F}$ 5 Hz and $J_{5,F} = J_{7,F}$ 9.5 Hz.

2-*Cyano*-4-*nitro*-1H-*benzimidazole* 3-*oxide* (**12g**). This compound, m.p. 203—206 °C (decomp.) (from aqueous ethanol with charcoal) was obtained (reaction time 2 h; yield 34%) from the nitrile (**5g**) (2.2 g) and potassium carbonate (1.38 g) in ethanol (120 ml) at 50 °C (Found: C, 47.45; H, 1.9; N, 27.6. $C_8H_4N_4O_3$ requires C, 47.1; H, 2.0; N, 27.4%); $\nu_{max.}$ 2 240 (CN) and 1 520 and 1 335 cm^{-1} (NO_2); δ_H 7.75 (1 H, dd, *J* 8.6 and 7.8 Hz, 6-H) and 8.3—8.55 (2 H, unresolved, 5- and 7-H).

Attempts to prepare the 5-nitro isomer (**12h**) were unsuccessful, only dark red resinous material being obtained.

Cyclisation of N-o-*Nitrophenylglycine Esters* (**4**): *Ethyl Benzimidazole-2-carboxylate* N-*Oxides* (**15**).—*The parent compound* (**15a**). An ice-cold solution of *N-o*-nitrophenylglycine ethyl ester (**4a**) (2.1 g) in ethanol (250 ml) was treated, dropwise with stirring, with a solution of sodium ethoxide (from sodium, 0.21 g; 1 mol equiv.) in ethanol (20 ml) so that the temperature did not exceed 5 °C. The mixture was stirred overnight, after which the solvent was evaporated under reduced pressure and the residue partitioned between ether and water. Acidification (HCl) of the aqueous layer gave the *N*-oxide (**15a**) (0.60 g, 31%), m.p. 168—170 °C (from toluene–ethanol; lit.,[28] 166—167 °C).

Ethyl 5-methyl-1H-*benzimidazole-2-carboxylate 3-oxide* (**15b**). This compound was similarly obtained from the ester (**4b**) (2.5 g) in ethanol (90 ml) and dimethylformamide (5 ml), and a solution of sodium ethoxide (from sodium, 0.23 g) in ethanol (20 ml). The reaction mixture was stirred for only 2 h; the yield was 1.0 g (46%). The *ester* (**15b**) had m.p. 144—145 °C (from ethanol) and showed $\nu_{max.}$ 1 720 cm^{-1} (CO); δ_H 1.38 (3 H, t, *Me*CH_2), 2.50 (3 H, s, *Me*Ar), 4.50 (2 H, q, CH_2Me), 7.30 (1 H, dd, 6-H), 7.51 (1 H, d, 4-H), and 7.80 (1 H, d, 7-H); J_{MeCH_2} 6 Hz, $J_{6,7}$ 8 Hz, $J_{4,6}$ not measurable [*cf.* compound (**12b**)] (Found: C, 59.6; H, 5.4; N, 12.8. $C_{11}H_{12}N_2O_3$ requires C, 60.0; H, 5.5; N, 12.7%).

Ethyl 5-methoxy-1H-*benzimidazole-2-carboxylate 3-oxide* (**15c**). This compound was obtained in 68% yield by the corresponding reaction of the ester (**4c**). It had m.p. 98—99 °C (from aqueous dimethylformamide) (Found: C, 51.7; H, 5.5; N, 11.0. $C_{11}H_{12}N_2O_4 \cdot H_2O$ requires C, 52.0; H, 5.55; N, 11.0%); $\nu_{max.}$ 1 700 cm^{-1} (CO); δ_H 1.35 (3 H, t, *Me*CH_2), 3.85 (3 H, s, *Me*O), 4.39 (2 H, q, CH_2Me), 6.8—7.0 (2 H, m, 4- and 6-H), and 7.65 (1 H, m, 7-H); J_{MeCH_2} 7 Hz.

Ethyl 5-nitro-1H-*benzimidazole-2-carboxylate 3-oxide* (**15h**). Piperidine (14 g; *ca.* 2.1 mol equiv.) was added to a solution of *N*-(2,4-dinitrophenyl)glycine ethyl ester (**4h**) (20.8 g) in warm ethanol (800 ml). The mixture was boiled for 2 h, after which the solvent was distilled off under reduced pressure and the residue dissolved in water and the solution acidified (HCl). The precipitated N-*oxide* (**15h**) (10.8 g, 56%) had m.p. 209—210 °C (from ethanol) (Found: C, 47.8; H, 3.6; N, 16.7. $C_{10}H_9N_3O_5$ requires C, 47.8; H, 3.6; N, 16.7%); $\nu_{max.}$ 1 715 (CO) and 1 540 and 1 340 cm^{-1} (NO_2); δ_H 1.40 (3 H, t, *Me*CH_2), 4.50 (2 H, q, CH_2Me), 8.07 (1 H, d, 7-H), 8.30 (1 H, dd, 6-H), and 8.55 (1 H, d, 4-H); J_{MeCH_2} 6 Hz, $J_{4,6}$ 2 Hz, and $J_{6,7}$ 9 Hz.

Benzimidazole N-*Oxides* (**1**): *General Procedure*.—The nitrile (**12**) or ester (**15**) was heated under reflux with concentrated hydrochloric acid (20—25 ml per g of substrate) for 4 h. The *N*-oxide hydrochloride (**13**) crystallised from the cooled solution, and was purified by recrystallisation as shown in Table 1. The hydrochloride was then dissolved in aqueous ammonia (*d* 0.88; *ca.* 40 ml per g of hydrochloride), and the solution concentrated under reduced pressure at 50 °C until crystallisation commenced. The mixture was then cooled and the *N*-oxide filtered off.

The properties of the hydrochlorides and of the free *N*-oxides are collected in Tables 1 and 2.

In the 5-nitro series [(**15**)→(**13h**)→(**1h**)], the hydrochloride (**13h**), m.p. *ca.* 240 °C, partially decomposed on attempted recrystallisation (from HCl); the crude salt was dissolved directly in 5M sodium hydroxide, and the *N*-oxide precipitated by reacidification.

N-(3-*Nitro*-2-*pyridyl*)*glycine Ethyl Ester* (**16**).—The following is more efficient than the previously published method.[29] Sodium glycinate (11.6 g, 0.12 mol) in water (50 ml) was added to a suspension of 2-chloro-3-nitropyridine (10 g, 60 mmol) and potassium carbonate (9g, 60 mmol) in ethanol (250 ml). The mixture was heated under reflux for 3.5 h and then cooled to 0 °C and the yellow product filtered off; a second crop was obtained by addition of ethanol to the filtrate. The combined precipitates were dissolved in water, and the solution acidified (HCl) to give *N*-(3-nitro-2-pyridyl)glycine (11.0 g, 89%), m.p. 170 °C (decomp.) (from ethanol–water; lit.,[30] 175—176 °C).

The glycine (8.0 g) was heated for 6 h under reflux in ethanol (100 ml) containing concentrated sulphuric acid (2 g). The solution was then concentrated under reduced pressure to *ca.* 25 ml, added to ice–water and the mixture set aside at 5 °C for 2 h. The crude ester was filtered off and purified by chromatography (in ether solution) through a short column of silica. *N*-(3-Nitro-2-pyridyl)glycine ethyl ester (**16**) (8.39 g, 92%) had m.p. 40—41 °C (lit.,[29] b.p. 143 °C/0.25 mmHg; not reported as a solid) (Found: C, 48.1; H, 4.9; N, 18.8. Calc. for $C_9H_{11}N_3O_4$: C, 48.0; H, 4.9; N, 18.7%); $\nu_{max.}$ 3 360 (NH), 1 720 (CO), and 1 555 and 1 335 cm^{-1} (NO_2); δ_H($CDCl_3$) 1.30 (3 H, t, Me), 4.33 (2 H, q, CH_2Me), 4.46 (2 H, d, CH_2NH), 6.86 (1 H, dd, 5-H), 8.5—8.7 (3 H, m, 4- and 6-H, and NH); J_{CH_3,CH_2} 7 Hz, $J_{CH_2,NH}$ 6 Hz, $J_{4,5}$ 8 Hz, and $J_{5,6}$ 5.1 Hz.

N-(3,5-*Dinitro*-2-*pyridyl*)*glycine Ethyl Ester* (**17**).—The literature method[31] was improved as follows. Glycine ethyl ester hydrochloride (1.40 g, 0.01 mol) was added portionwise to a solution of 2-chloro-3,5-dinitropyridine (2.03 g, 0.01 mol) and triethylamine (2.0 g, 20 mmol) in ethanol (50 ml). Crystallisation of the product began almost immediately; after 5 min, it was filtered off and recrystallised from ethanol. The ester (**17**) (2.29 g, 84%) had m.p. 95 °C (lit.,[31] 89 °C); $\nu_{max.}$ 3 355 (NH), 1 720 (CO), and 1 540 and 1 335 cm^{-1} (NO_2); δ_H 1.21 (3 H, t, Me), 4.16 (2 H, q, CH_2Me), 4.41 (2 H, d, CH_2NH), 9.02 (1 H, d) and 9.24 (1 H, d) (4- and 6-H), and 9.49 (1 H, br t, NH); J_{CH_3,CH_2} 7 Hz, $J_{CH_2,NH}$ 6 Hz, and $J_{4,6}$ 2.5 Hz.

Cyclisation of the Ester (**16**).—The ester (**16**) (8.0 g, 36 mmol), potassium carbonate (5.1 g, 37 mmol), and ethanol (190 ml) were heated together, under reflux, for 5 h. The cooled mixture was filtered and the precipitate washed with a little ethanol; it was then dissolved in water, and the solution decolourised with charcoal and acidified (HCl). The resulting solid was collected, redissolved in boiling water (gas was evolved), and the solution evaporated to dryness under reduced pressure. The sticky residue was washed with a little ether and recrystallised from ethanol to give 3H-*imidazo*[4,5-b]*pyridine* 1-*oxide* (**20**) (0.85 g, 18%), m.p. 173—175 °C (Found: C, 53.25; H, 3.6; N, 31.05. $C_6H_5N_3O$ requires C, 53.3; H, 3.7; N, 31.1%); $\nu_{max.}$ 2 200—2 500br cm^{-1} (NH/OH); δ_H 7.33 (1 H, dd, 6-H), 8.00 (1 H, dd, 7-H), 8.46 (1 H, dd, 5-H), 8.63 (1 H, s, 2-H), and 12.0 (1 H, br s, NH/OH); $J_{6,7}$ 8.3 Hz, $J_{5,7}$ 1.5 Hz, and $J_{5,6}$ 4.4 Hz; *m/z* 135 ($M^{+\bullet}$), 119.

The ethanolic reaction mother-liquor was evaporated to dryness under reduced pressure and the residue dissolved in water. The solution was acidified (HCl) to pH 3—4, saturated with sodium chloride, and extracted repeatedly with dichloromethane. The extract was dried (Na_2SO_4) and evaporated, and the residue washed with a little ether and recrystallised from propan-2-ol. *Ethyl* 3H-*imidazo*[4,5-b]*pyridine-2-carboxylate* 1-*oxide* (**18**) (2.22 g, 30%) had m.p. 150 °C (Found: C, 52.35; H, 4.5; N, 20.5. $C_9H_9N_3O_3$ requires C, 52.2; H, 4.4; N, 20.3%); $\nu_{max.}$ 2 300—2 700 (br, NH/OH) and 1 730 cm^{-1} (CO); δ_H (1.40 (3 H, t, Me), 4.46 (2 H, q, CH_2), 7.46 (1 H, dd, 6-H), 8.09 (1 H, dd, 7-H), 9.11 (1 H, dd, 5-H), and 12.5 (1 H, br s, NH/OH); J_{MeCH_2} 8 Hz, $J_{6,7}$ 8 Hz, $J_{5,6}$ 4.6 Hz, and $J_{5,7}$ 1.8 Hz; *m/z* 207 ($M^{+\bullet}$), 191, 163, and 161 (M − EtOH)$^{+\bullet}$, 135 and 119.

Reaction of the Ester (**17**) *with Bases*.—Potassium carbonate (1.28 g; 1 mol equiv.) was added portionwise to a stirred solution of the dinitro ester (**17**) (2.5 g) in ethanol (100 ml) and dimethylformamide (17 ml). After 3 h more ethanol (100 ml) was

added and the mixture filtered. The precipitate, on dissolution in water followed by acidification (HCl), gave only a trace of black solid. The filtrate was evaporated to dryness and the residue partitioned between dichloromethane and water; the dried (Na_2SO_4) organic layer gave, on evaporation, unchanged starting material (0.28 g, 11%). The (black) aqueous layer on acidification gave a black solid (1.56 g) which (by t.l.c.) contained more unchanged starting material but was mostly highly polar and tarry.

The reaction of (**17**) with piperidine [as described for the dinitrophenyl analogue (**4h**)] similarly gave a black intractable tarry solid.

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