o-Nitroaniline derivatives. Part 14.[1,2] Cyclisations leading to benzimidazole *N*-oxides, *N*-hydroxybenzimidazolones and *N*-hydroxyquinoxaline-2,3-diones: a mechanistic borderline

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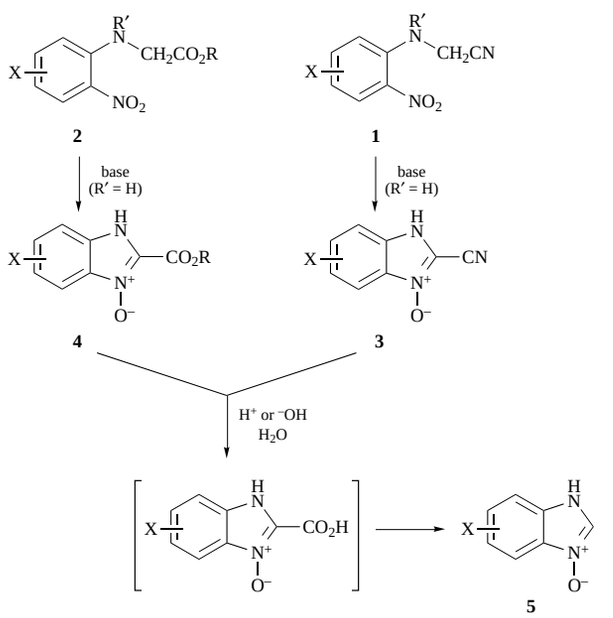
The base-induced cyclisations of *N*-(*o*-nitrophenyl)glycine derivatives (nitriles 9 or esters 13) bearing additional substituents at the other *ortho*-position are anomalous, resembling those involving *N*-(*o*-nitrophenyl)sarcosine analogues. The nitriles are converted into *N*-hydroxybenzimidazolones 10 and the esters into 1-hydroxyquinoxaline-2,3(1*H*,4*H*)diones 14 and 2,2′-diaminoazoxybenzene derivatives 15, instead of, or in addition to, the expected 2-substituted 1*H*-benzimidazole 3-oxides 11 and 16 or the 2-unsubstituted analogues, 17. The possibility that all these reactions proceed through a common 2,1,4-benzoxadiazine intermediate, 18, is explored.

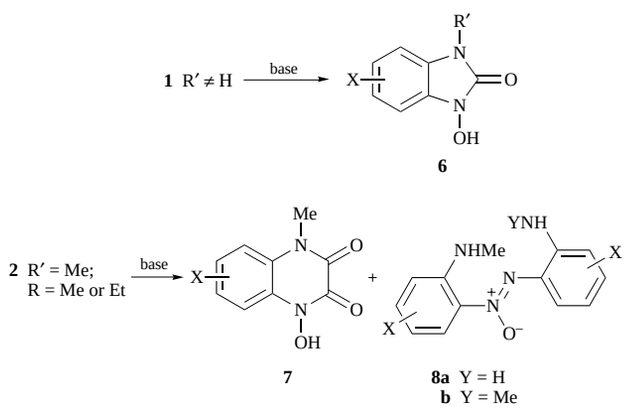
In previous parts of this series[3–5] we have shown that variously substituted *N*-cyanomethyl-*o*-nitroanilines **1** (R′ = H) and *N*-(*o*-nitroaryl)glycine esters **2** (R′ = H) are readily cyclised in basic media to 1*H*-benzimidazole 3-oxides (*N*-hydroxybenzimidazoles) **3** or **4** bearing, respectively, a cyano or an ester function at C-2; hydrolysis of this 2-substituent, in either acid or base, is apparently followed by spontaneous decarboxylation, with the formation of the 2-unsubstituted 1*H*-benzimidazole 3-oxide **5** (Scheme 1). Reactions of the type **1**→**3**



Scheme 1

and **2**→**4** have been explored briefly by a number of other groups.[6–8]

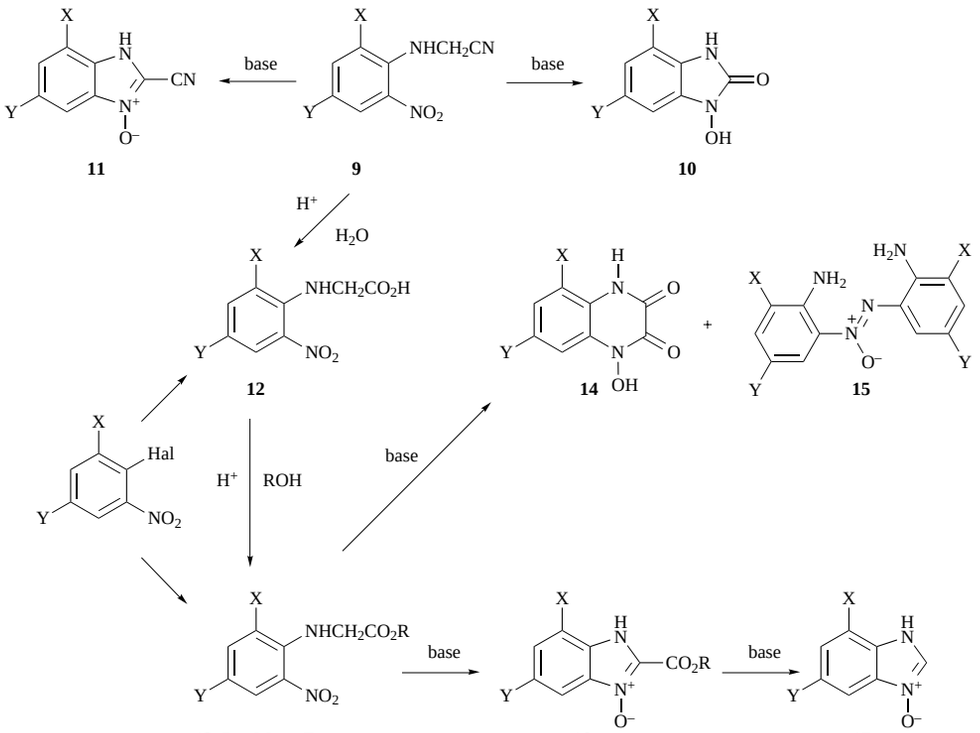
During one of these earlier studies, Livingstone and Tennant[6] had shown that if the amino-nitrogen of the *N*-cyanomethyl-*o*-nitroaniline was tertiary, the product isolated from the cyclisation was not the 1-substituted 2-cyanobenzimidazole 3-oxide but the *N*-hydroxybenzimidazolone **6**. More recently[1,9] our own investigations have shown that the reactions of *N*-(*o*-nitroaryl)sarcosine esters **2** (R′ = Me) with bases also fail to produce benzimidazole *N*-oxides: the heterocyclic products obtained are 1-hydroxy-4-methylquinoxaline-2,3(1*H*,4*H*)-diones **7** and the co-products are azoxybenzene derivatives of the type **8a** or **8b** (Scheme 2).



Scheme 2

Some years ago, attempts by our colleague D. J. Moody[10] to cyclise *N*-cyanomethyl-2,6-dinitroaniline **9a** using potassium carbonate had given an acidic product which was clearly not the expected 2-cyano-7-nitro-1*H*-benzimidazole 3-oxide, but its true structure was not then recognised. Reinvestigation has shown, however, that this main product (39%) is 1-hydroxy-4-nitro-1*H*-benzimidazol-2(3*H*)-one **10a** (Scheme 3). Moreover, *N*-(2,6-dinitrophenyl)glycine ethyl ester **13a** reacts slowly with potassium carbonate to give a mixture containing 1-hydroxy-5-nitroquinoxaline-2,3-(1*H*,4*H*)dione **14a** and showing a peak in the mass spectrum corresponding to the azoxybenzene **15a**. After a reaction time of 20 h, the yield of **14a** was 37%. In neither case was a benzimidazole oxide, **16a** or **17a**, detected.

The reaction of *N*-(2,6-dinitro-4-trifluoromethyl)glycine methyl ester **13b** with triethylamine similarly leads to the hydroxyquinoxalinedione **14b** (38%), together with a small amount of the benzimidazole oxide **17b**. The non-acidic product fraction yields 2,2′-diamino-3,3′-dinitro-5,5′-bis(trifluoromethyl)azoxybenzene **15b** (15%). The reactions of **9a**, **13a** and **13b** with bases thus parallel those of *N*-(*o*-nitroaryl)sarcosine derivatives rather than the nitriles and esters derived from other *N*-(*o*-nitroaryl)glycines. Whereas it is not unprecedented for



		X	Y	R
9-17	**a**	NO_2	H	Et
	b	NO_2	CF_3	Me
	c	Me	H	Et
	d	H	CF_3	Me
	e	H	F	Me

	X	Y	R
f	Cl	CF_3	Me
g	CF_3	NO_2	Me
h	F	F	Me
i	NHAc	H	Et

Scheme 3

Table 1 Products from the reactions of *N*-(*o*-nitroaryl)glycine esters **13** with bases

		Yield (%)				
Compound	Base	**14**	**15**	**16**	**17**	Others
13a	K_2CO_3	37	*a*			
13b	K_2CO_3	39	15	trace		
	$NaHCO_3$					**21b**
13c	K_2CO_3			55		
13d	K_2CO_3				*a*	
13e	Et_3N				24	
	K_2CO_3				72	
13f	Et_3N	*a*	*a*		31	
	K_2CO_3	*a*			*a*	
	$Ba(OH)_2$	*a*	*a*		*a*	**28**
13g	Et_3N	7	*a*	*a*		
	$Ba(OH)_2$	*a*			*a*	
13h	K_2CO_3				85	
13i[b]	K_2CO_3				43	

[a] Detected, but yield not calculable. [b] Data from Part 11.[5]

secondary and tertiary *o*-nitroamines to differ in their reactions and reactivities—the so-called 'tertiary-amino effect' was recognised by Meth-Cohn and Suschitzky[11] many years ago—it was entirely unexpected that the cyclisation of secondary *o*-nitroamines, an apparently general and well-understood reaction, should be totally diverted in this way by the additional ring substituent.

In each of the above cases, the second *ortho*-position in the starting *N*-(*o*-nitroaryl)glycine derivative is also occupied by a nitro substituent. This substituent may of course influence the reactivity of the molecule by means of steric, electronic or hydrogen-bonding effects, or any combination of these. In order to probe these possibilities further, it has been of interest to investigate the reactions of a range of *N*-(*o*-nitro-*o*′-substituted aryl)glycine derivatives in basic media and to compare them with analogues lacking the *o*′-substituent. Several of these starting materials were available to us, having been required in connection with another investigation, but the range is limited by the relative inaccessibility of 1,2,3-trisubstituted benzene derivatives.

The reactions of the *N*-(*o*-nitroaryl)glycine esters **13a**–**i** with bases (Table 1) reveal a variety of behaviour according to the presence (or otherwise) of a second *ortho*-substituent and to the nature of that substituent. Where an *o*′-substituent is absent (*i.e.* X = H), the 'normal' cyclisation to the benzimidazole-2-carboxylic ester *N*-oxide **16** or the 2-unsubstituted analogue **17** is invariably observed. Where X ≠ H, the 'normal' cyclisation may be accompanied, or replaced, by the 'abnormal' reaction giving the 1-hydroxyquinoxaline-2,3(1*H*,4*H*)-dione **14** and/or the azoxybenzene derivative **15**. In those cases where several different bases have been used to bring about the reactions, the same products are obtained in each reaction, although the product ratios vary according to the base used and the precise reaction conditions.

One possible effect of the second nitro group in **13a** and **13b** is to bring about an increase in the electron-deficient character of the ring, and thus in the acidity of the amino-hydrogen relative to those in the mono-nitro analogues. This effect appears to have little influence on the course of the cyclisation, however, since the 2,4- and 2,6-dinitro isomers might then be expected to react similarly. The ability of the nitro group to engage in intramolecular hydrogen bonding with the amino-hydrogen appears much more significant: nitro is the only one of the *o*′-substituents so far used which has this capability, and it is the most successful in diverting the 'normal' cyclisation

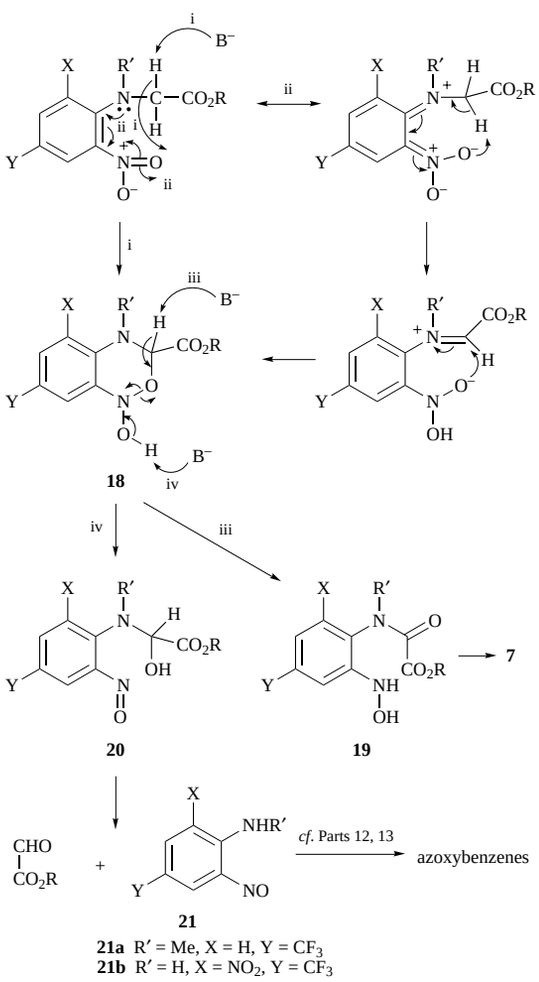
pathway. It seems possible, however, that the steric effect of the *o*′-substituent may also play a part, since chloro and trifluoromethyl partially divert the 'normal' pathway whereas fluoro and methyl (perhaps surprisingly; but see below) do not.

Whereas the nitrile **9a** reacts with base (potassium carbonate) to give the 1-hydroxybenzimidazolone **10a** as the only isolated product, the *o*′-methyl analogue **9c** gives a mixture of the 'normal' benzimidazole *N*-oxide **11c** as well as **10c**, with the former predominating. The reactions of these *o*′-substituted nitriles, like those of the corresponding esters, thus show similarities to those of the tertiary aminonitriles **1** (R′ ≠ H) in addition to, or rather than, those of other analogues containing a secondary amino nitrogen.

The mechanisms of these reactions, both 'abnormal' and 'normal', are now considered in turn.

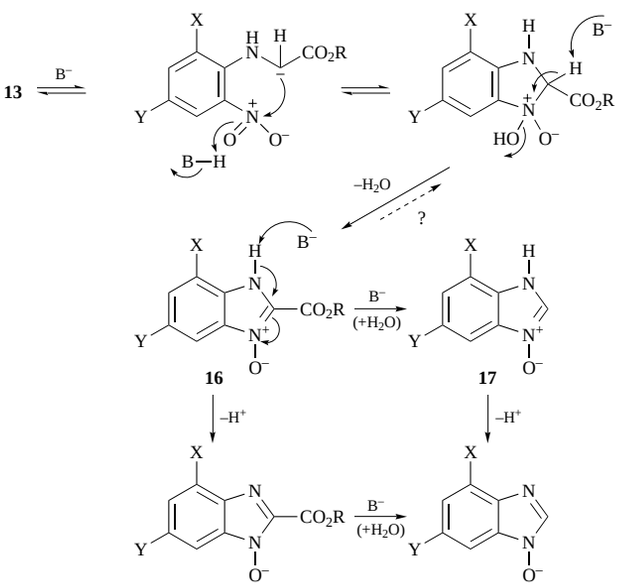
Reactions of the esters

The reactions 2 (R′ ≠ H)→7 + 8 and 13→14 + 15. These two reaction types lead to almost identical classes of product, and it is therefore a reasonable assumption that they follow similar mechanistic pathways. A plausible mechanism for the former has already been set out in Part 13,[1] and this is shown in abbreviated form in Scheme 4. Formation of the *N*-hydroxyquinoxalinedione **7** evidently requires reduction of the nitro group and oxidation of the methylene group of the sarcosine residue. This may be rationalised by initial deprotonation of the methylene group and intramolecular nucleophilic attack on the nitro-group oxygen (pathway **i**), or by abstraction of the methylene proton by an *aci*-nitro oxygen (pathway **ii**). Either pathway leads to the 2,1,4-benzoxadiazine derivative **18**; ring-opening of the latter and recyclisation of the resulting *o*-hydroxyamino ester **19** (pathway **iii**) produces the observed product **7**. Ring-opening of **18** in a different sense (pathway **iv**) leads to an *o*-nitroso alcohol **20**, which is envisaged as a precursor of azoxybenzene derivatives such as **8**; the involvement of nitroso-compounds in these reactions has been proved by the isolation of the *N*-methyl-*o*-nitrosoaniline **21a** from the reaction of the correspondingly substituted sarcosine ester **2** (R′ = Me, X = H, Y = CF_3) with potassium carbonate in ethanol.[1] Isolation of the *o*-nitrosoaniline **21b** from the reaction of **13b** with sodium hydrogen carbonate in methanol now provides evidence in support of a similar mechanism in the 'abnormal' reactions of the *N*-(*o*-nitroaryl)glycine esters **13**.



Scheme 4

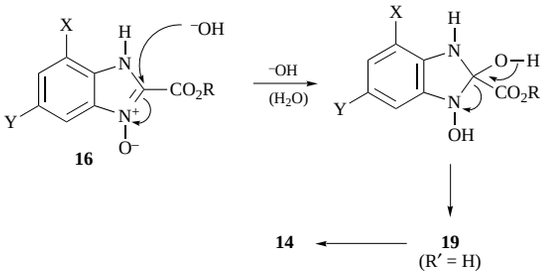
The 'normal' reaction 2 (R′ = H)→4→5 and 13→16→17. The generally accepted mechanism for cyclisations of this type[12] is essentially similar to that of the aldol condensation, with the glycine-derived methylene group furnishing the carbanion and the nitro group serving as the electrophilic component. In this mechanism (Scheme 5) the amino-proton is lost only in the final step, once the cyclisation is complete. (The benzimidazole *N*-oxides **16** and **17** are isolated from the reactions as water-soluble salts.) On this basis it seems surprising that the *o*′-substituent X in **13** should have an appreciable effect on the course of the cyclisation prior to this final step, unless all the preceding steps were completely reversible (which is unlikely, given that one involves elimination of water). The course of the reaction appears to depend, not on the acidity of the methylene protons, but on the accessibility, or otherwise, of the amino-proton towards attack by the base.



Scheme 5

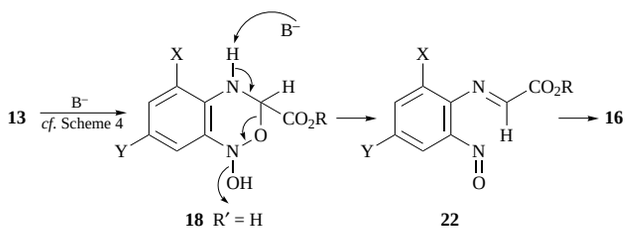
In principle it is of course possible that the benzimidazole *N*-oxide **16** is formed as the primary product *in every case* and that, in the absence of an acidic proton readily accessible to the base, nucleophilic attack at C-2 can then lead to ring opening and recyclisation to the 1-hydroxyquinoxaline-2,3(1*H*,4*H*)-dione **14** (Scheme 6). There is, however, no evidence to suggest that compounds of structure **16**, even where X ≠ H, react further with bases which are also nucleophilic, other than to undergo deprotonation or loss of the ester function (giving **17**); moreover, the intermediacy of **16** does not readily account for the formation of the azoxybenzene co-products **15**.

A much more attractive mechanistic proposal, which offers an explanation for the base-induced reactions of *all* the *N*-(*o*-nitroaryl)-glycine and -sarcosine esters, is shown below. This is essentially an extension of Scheme 4, with the 2,1,4-benzoxadiazine **18** again as the key intermediate. If compound **18** possesses no amino proton at N-4 (R′ ≠ H), or the 4-proton is



Scheme 6

sterically hindered or intramolecularly hydrogen-bonded, then Scheme 4 is followed. If, however, the amino-proton is readily abstracted (Scheme 7), ring-opening of **18** may ensue, leading

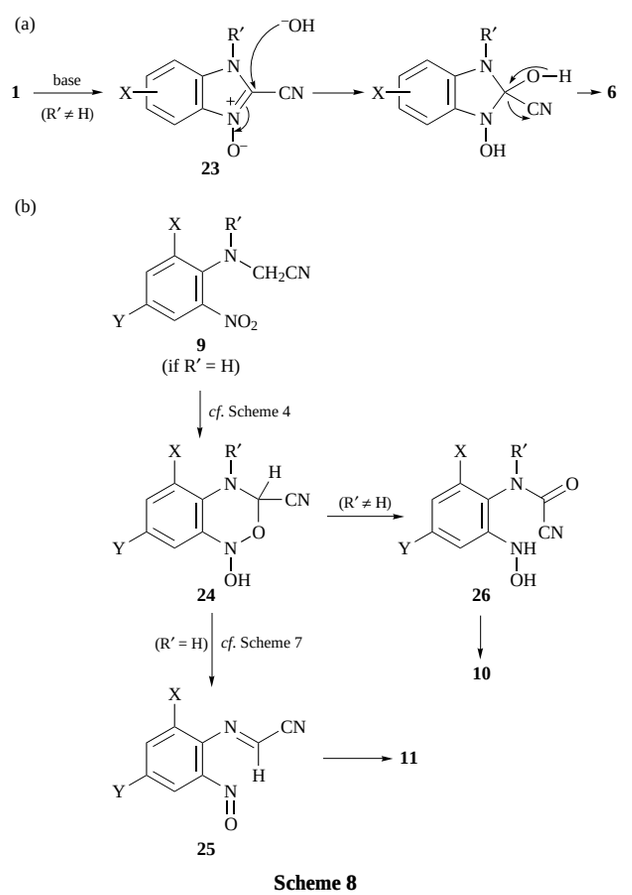


Scheme 7

to the *o*-nitrosoanil **22**; and anils of this type would be expected to undergo spontaneous cyclisation to a benzimidazole *N*-oxide.[13]

Reactions of the nitriles

The above mechanistic argument in respect of the cyclisations of the esters **13** may equally apply to the nitriles **1** or **9**. For the reactions **1** (R′ ≠ H)→**6**, it has been argued[6] that 1-substituted benzimidazole 3-oxides, **23**, are possible intermediates [Scheme 8, route (a)], these then undergoing nucleophilic substitution of



Scheme 8

the cyano group by hydroxide ion. While this is plausible, since compounds such as **23** are known to undergo nucleophilic substitution of the cyano group in aqueous media,[14] no confirmatory evidence is available in this instance. The reaction of **1** (R′ = Me and X = H) with ethanolic potassium carbonate, even in the absence of added water, gives 1-hydroxy-3-methyl-1*H*-benzimidazol-2(3*H*)-one **6** (R′ = Me, X = H) as the sole product, in good yield. In the cyclisations **9**→**10**, a pathway involving the intermediacy of **11** can certainly be ruled out: in the case of **9c**, the cyclisation of which gives both the 2-cyanobenzimidazole *N*-oxide **11c** and the hydroxybenzimidazolone **10c**, the use of an excess of base (potassium carbonate) and a prolonged reaction time does not lead to an increased yield of **10c**; under these conditions compound **11c** is apparently stable as its potassium salt.

Here again, however, it is possible to account for all the observed products in terms of a 2,1,4-benzoxadiazine intermediate, *viz*. **24** [Scheme 8, route (b)]. If this contains a readily abstractable amino-proton, ring opening again would lead to an *o*-nitrosoanil **25** and thence to the benzimidazole *N*-oxide **11**; but if this proton is not easily removed or if N-4 is tertiary, an alternative ring opening (*cf*. Scheme 4) could lead to an *o*-hydroxyamino nitrile **26** which might then undergo recyclisation to the hydroxybenzimidazolone **10**.

It is perhaps appropriate at this stage to consider in general the cyclisations of substituted *o*-nitroanilines to *N*-oxidised benzimidazoles, quinoxalines and other heterocyclic systems, in the light of this possible new mechanism. It has long been recognised that considerable anomalies exist in this area. Some of these nitro-compounds, like those in the present work, are cyclised under remarkably mild conditions, whereas some analogues with methylene protons of apparently comparable acidity require much more severe conditions, or fail to undergo cyclisation altogether; the 'tertiary-amino effect' is also observed in certain cases.[11]

Many years ago, in the earliest systematic review of these reactions, Loudon and Tennant observed[15] that in certain types of cyclisation 'a mobile α-hydrogen appears to compensate for feeble activation at the β-methylene centre of the side-chain', but no convincing rationalisation of this effect has yet been put forward in terms of the 'traditional' mechanism of Scheme 5. The possibility that the new mechanism proposed above may also be followed in the cyclisations of these other *o*-nitroaniline derivatives, and indeed of *o*-nitro aromatic compounds in general, is now receiving our active attention.

Experimental

Recorded infra-red spectra of solids and liquids are those of Nujol mulls and thin films, respectively. The NMR spectra of *N*-(*o*-nitroaryl)amino acid and azoxybenzene derivatives were obtained in deuteriochloroform and those of the cyclised products in [$^2H_6$]dimethyl sulfoxide, unless indicated otherwise. ^{1}H Spectra were obtained at 80, 200 or 300 MHz and ^{13}C spectra at 50.3 or 75.4 MHz, chemical shifts being expressed relative to tetramethylsilane ($\delta_H = \delta_C = 0$); ^{19}F spectra were obtained at 75.3 MHz, the chemical shifts being expressed relative to trichlorofluoromethane ($\delta_F = 0$). Coupling constants, *J*, are expressed in Hz. Mass spectra were obtained under electron impact. 'Ether' refers to diethyl ether and 'petroleum' to the fraction of bp 40–60 °C.

N-Cyanomethyl-*o*-nitroanilines 9

***N*-Cyanomethyl-2,6-dinitroaniline 9a.** To a solution of 1-chloro-2,6-dinitrobenzene (6.0 g, 30 mmol) in dimethyl sulfoxide (7 cm^3) was added sodium hydrogen carbonate (5.0 g, 60 mmol) and aminoacetonitrile hydrochloride (3.0 g, 30 mmol). The mixture was stirred at 80–90 °C until effervescence ceased (*ca*. 20 min), then cooled and poured into ice–water. The brown

precipitate was filtered off, washed with water and recrystallised twice from ethanol (with charcoal), to give the *nitrile* **9a** (3.1 g, 47%), mp 119–120 °C (Found: C, 43.35; H, 2.6; N, 25.3. $C_8H_6N_4O_4$ requires C, 43.25; H, 2.7; N, 25.2%); ν_{max}/cm^{-1} 3320 (N–H), 1520 and 1330 (NO_2); δ_H 4.25 (2H, d, CH_2), 7.15 (1H, t, 4-H), 8.10 (1H, t, NH) and 8.36 (2H, d, 3- and 5-H); $J_{CH_2,NH}$ 7.0, $J_{3,4} = J_{4,5}$ 8.0.

***N*-Cyanomethyl-2-methyl-6-nitroaniline 9c.** A mixture of 2-methyl-6-nitroaniline (2.0 g, 13 mmol), paraformaldehyde (1.17 g, 39 mmol), potassium cyanide (2.54 g, 39 mmol), zinc chloride (6.58 g, 48 mmol) and acetic acid (60 cm^3) containing concentrated sulfuric acid (4 drops) was stirred and heated at 50–55 °C for 7 h, then added to ice–water (300 cm^3). The precipitate was filtered off and recrystallised (twice) from ethanol, to give N,N-*bis*(*cyanomethyl*)-2-*methyl*-6-*nitroaniline* (0.51 g, 17%), mp 113–114 °C (Found: C, 57.7; H, 4.4; N, 24.3. $C_{11}H_{10}N_4O_2$ requires C, 57.4; H, 4.4; N, 24.3%); ν_{max}/cm^{-1} 2245w (C≡N), 1525 and 1340 (NO_2); δ_H 2.43 (3H, s, CH_3), 4.35 (4H, s, 2 × CH_2) and 7.35–7.85 (3H, m, Ar-H). The filtrate from the original recrystallisation was concentrated under reduced pressure to give a yellow solid (0.82 g) which was shown (TLC) to be a mixture of the starting methylnitroaniline and both mono- and bis-cyanomethyl compounds.

Repetition of the experiment using 2-methyl-6-nitroaniline (4.5 g, 30 mmol), paraformaldehyde (2.63 g, 90 mmol), potassium cyanide (5.71 g, 90 mmol), zinc chloride (9.88 g, 73 mmol) and acetic acid (140 cm^3) containing concentrated sulfuric acid (4 drops) gave a solid product which was chromatographed on silica gel (200 g) in petroleum. Elution with ether–petroleum (1:9) gave unreacted amine (1.29 g; 29% recovery) and elution with ether–petroleum (3:7) then gave N-*cyanomethyl*-2-*methyl*-6-*nitroaniline*, **9c** (1.60 g, 29%), mp 75 °C (Found: C, 56.7; H, 4.7; N, 22.1. $C_9H_9N_3O_2$ requires C, 56.5; H, 4.7; N, 22.0%); ν_{max}/cm^{-1} 3325 (N–H), 2240w (C≡N), 1535 and 1330 (NO_2); δ_H 2.39 (3H, s, CH_3), 4.25 2H, d, CH_2), 6.40 (1H, t, NH), 7.08 (1H, t, 4-H), 7.55 (1H, br d, 3-H) and 7.85 (1H, dd, 5-H); $J_{CH_2,NH}$ 7.5, $J_{3,4} = J_{4,5}$ 8, $J_{3,5}$ 1.6. Later fractions contained mixtures of **9c** and the bis-cyanomethyl compound.

***N*-Cyanomethyl-2,4-difluoro-6-nitroaniline 9h.** 2′,4′-Difluoroacetanilide, mp 119–120 °C (from ethanol; lit.,[16] 120.9 °C) was obtained (yield 87%) from 2,4-difluoroaniline and a threefold excess of acetic anhydride at room temperature. Nitration of this amide according to a published method[17] gave 2′,4′-difluoro-6′-nitroacetanilide (yield 83%), mp 132–134 °C (from ethanol; lit,[17] 142–143 °C); $\delta_H[(CD_3)_2CO]$ 2.20 (3H, s, CH_3) and 7.52–7.92 (2H, m, Ar-H); *m/z* 216 (2%), 201, 175, 174, *etc*. Hydrolysis of the acetyl group using concentrated sulfuric acid[16] gave 2,4-difluoro-6-nitroaniline (yield 78%), mp 81–82 °C (from ethanol; lit.,[16] 85.5–86.5 °C); δ_H 5.90 (2H, br, NH_2), 7.00–7.10 (1H, symm. m, 5-H) and 7.50 (1H, dt, 3-H); $J_{3,5} = J_{3,6\text{-}F}$ 3, $J_{3,4\text{-}F}$ 9, $J_{5,4\text{-}F} = J_{5,6\text{-}F}$ 10.

2,4-Difluoro-6-nitroaniline (2.61 g, 15 mmol), paraformaldehyde (1.35 g, 45 mmol), zinc chloride (15.54 g, 114 mmol) and potassium cyanide (2.93 g, 45 mmol) were combined and acetic acid (40 cm^3) containing concentrated sulfuric acid (2 drops) was added. The mixture was stirred and heated at 50 °C for 6 h and then kept at room temperature overnight. The mixture was added to ice–water and the product was filtered off and recrystallised from methanol, giving the *nitrile* **9h** (2.88 g, 90%), mp 121–122 °C (Found: C, 44.9; H, 2.2; N, 19.6. $C_8H_5F_2N_3O_2$ requires C, 45.1; H, 2.4; N, 19.7%); $\delta_H[(CD_3)_2CO]$ 4.65 (2H, dd, CH_2), 7.68 (1H, 16 lines, 3-H), 7.75 (1H, br s, NH) and 7.93 (1H, 8 lines, 5-H); δ_F −119.6 (16 lines, 2-F) and −122.0 (8 lines, 4-F); $J_{3,NH}$ 0.4, $J_{CH_2,NH}$ 7.2, $J_{CH_2,2\text{-}F}$ 4, $J_{3,5}$ 3.2, $J_{F,F}$ 2.0, $J_{3,4\text{-}F}$ 9.0, $J_{5,2\text{-}F}$ 2.0, $J_{5,4\text{-}F}$ 8.0, $J_{3,2\text{-}F}$ 13.4.†

† The coupling constants were obtained by computer simulation.

N-(*o*-Nitroaryl)glycines 12

***N*-(2,6-Dinitrophenyl)glycine 12a.** The literature procedure[18] was modified as follows. A solution of glycine (4.15 g, 55 mmol) and sodium hydrogen carbonate (9.25 g, 110 mmol) in water (30 cm^3) was added to a solution of 1-chloro-2,6-dinitrobenzene (10 g, 49 mmol) in methanol (100 cm^3) and the mixture was heated under reflux for 1.5 h and the solvent evaporated. Water (500 cm^3) was added to the residue and the insoluble (copper-coloured) solid was filtered off and treated with dilute hydrochloric acid until the colour had changed to bright yellow. The product was then filtered off and recrystallised from methanol, giving the glycine **12a** (6.78 g, 57%), mp 173–175 °C (lit.,[17] 173 °C); $\delta_H(CDCl_3 + [^2H_6]DMSO)$ 3.71 (2H, d, CH_2), 6.86 (1H, t, 4-H), 8.21 (2H, d, 3- and 5-H) and 9.06 (1H, br s, NH); $J_{CH_2,NH}$ 4.4, $J_{3,4} = J_{4,5}$ 8.2.

***N*-(2-Methyl-6-nitrophenyl)glycine 12c.** *N*-Cyanomethyl-2-methyl-6-nitroaniline **9c** (2.0 g, 10.5 mmol) and concentrated hydrochloric acid (25 cm^3) were heated together under reflux for 1.5 h, and the resulting solution then added to ice–water (150 cm^3). The precipitate was filtered off and recrystallised from ethanol–water, giving the *glycine* **12c** (1.66 g, 76%), mp 137–139 °C (Found: C, 51.8; H, 4.7; N, 13.3. $C_9H_{10}N_2O_4$ requires C, 51.4; H, 4.8; N, 13.3%); ν_{max}/cm^{-1} 1720 (C=O), 1530 and 1325 (NO_2); δ_H 2.36 (3H, s, CH_3), 3.98 (2H, s, CH_2), 6.86 (1H, t, 4-H), 7.43 (1H, br d, 3-H) and 7.80 (1H, dd, 5-H); $J_{3,4}$ 8, $J_{4,5}$ 8.5, $J_{3,5}$ 1.6.

***N*-[2-Nitro-4-(trifluoromethyl)phenyl]glycine 12d.** Potassium carbonate (3.46 g, 25 mmol) and glycine (1.88 g, 25 mmol) were added to a solution of 4-chloro-3-nitrobenzotrifluoride [1-chloro-2-nitro-4-(trifluoromethyl)benzene] (4.51 g, 20 mmol) in ethanol (60 cm^3) and the mixture heated under reflux for 24 h. The resulting solution was acidified (HCl), and the yellow precipitate filtered off, dried and recrystallised from toluene, giving the *glycine* **12d** (3.06 g, 58%), mp 161–162 °C (Found: C, 40.8; H, 2.5; N, 10.45. $C_9H_7F_3N_2O_4$ requires C, 40.9; H, 2.7; N, 10.6%); $\delta_H[(CD_3)_2CO]$ 4.30 (2H, d, CH_2), 7.27 (1H, d, 6-H), 7.80 (1H, dd, 5-H), 8.37–8.50 (1H, m, 3-H), 8.75 (1H, br s, NH) and 9.70 (1H, br s, CO_2H); $J_{CH_2,NH}$ 5, $J_{3,5}$ 2, $J_{5,6}$ 10; *m/z* 264 ($M^{+\bullet}$), 245 and 219 (100%).

***N*-[2,4-Dinitro-6-(trifluoromethyl)phenyl]glycine 12g.** Glycine (2.63 g, 35 mmol) and sodium hydrogen carbonate (5.04 g, 60 mmol) were added to a solution of 2-chloro-3,5-dinitrobenzotrifluoride [2-chloro-1,5-dinitro-3-(trifluoromethyl)-benzene] (8.12 g, 30 mmol) in methanol (150 cm^3). The mixture was heated under reflux for 5 h, then cooled and filtered, and the filtrate concentrated under reduced pressure. The orange residue was stirred with a mixture of dichloromethane (30 cm^3) and hydrochloric acid (5 M; 20 cm^3), then filtered off, washed with water and recrystallised from methanol–water, giving the *glycine* **12g** in almost quantitative yield (9.15 g); mp 161–162 °C (Found: C, 34.8; H, 1.75; N, 13.35. $C_9H_6F_3N_3O_6$ requires C, 35.0; H, 2.0; N, 13.4%); $\delta_H[(CD_3)_2CO]$ 4.25 (2H, s, CH_2), 8.80 (1H, m, 5-H) and 9.27 (1H, d, 3-H); $J_{3,5}$ 3.

***N*-(2,4-Difluoro-6-nitrophenyl)glycine 12h.** The nitrile **9h** (4.10 g, 19 mmol) was heated with acetic acid (90 cm^3) and aqueous sulfuric acid (50% v/v; 220 cm^3) at 100 °C for 2.5 h and the mixture then added to crushed ice. The precipitate was filtered off and recrystallised from ethanol to give the *glycine* **12h** (3.10 g, 70%), mp 156–158 °C (Found: C, 41.2; H, 2.3; N, 11.9. $C_8H_6F_2N_2O_4$ requires C, 41.4; H, 2.6; N, 12.1%) ν_{max}/cm^{-1} 3390 (N–H) and 1710br (C=O); $\delta_H[(CD_3)_2CO]$ 4.45 (2H, d, CH_2), 7.55 (1H, symm. m, 3-H) and 7.87 (1H, symm. m, 5-H); $J_{CH_2,NH}$ 5, $J_{3,5}$ 3.2, $J_{5,F\text{-}4}$ 9.2, $J_{5,F\text{-}2}$ 2.0, $J_{3,F\text{-}4}$ 8.0, $J_{3,F\text{-}2}$ 14.0.

N-(*o*-Nitroaryl)glycine esters 13

***N*-(2,6-Dinitrophenyl)glycine ethyl ester 13a.** A solution of *N*-(2,6-dinitrophenyl)glycine **12a** (2.29 g, 9.5 mmol) in ethanol (60 cm^3) containing concentrated sulfuric acid (1.3 g) was heated under reflux for 4 h, then concentrated under reduced pressure, cooled in ice and the precipitate filtered off and washed with

water. The bright yellow ethyl ester **13a**, mp 86 °C (lit.,[18] 86 °C) was obtained in essentially quantitative yield and was used without further purification; δ_H 1.31 (3H, t, CH_3), 3.78 (2H, s, N-CH_2), 4.28 (2H, q, CH_2CH$_3$), 6.85 (1H, t, 4-H), 8.22 (2H, d, 3- and 5-H) and 9.10 (1H, br s, NH); $J_{CH_3CH_2}$ 7.2, $J_{3,4} = J_{4,5}$ 8.3.

***N*-[2,6-Dinitro-4-(trifluoromethyl)phenyl]glycine methyl ester 13b.** Glycine methyl ester hydrochloride (3.01 g, 24 mmol) and sodium hydrogen carbonate (4.62 g, 55 mmol) were added to a solution of 4-fluoro-3,5-dinitrobenzotrifluoride [1-fluoro-2,6-dinitro-4-(trifluoromethyl)benzene] (5.08 g, 20 mmol) in dry tetrahydrofuran (30 cm^3). The mixture was heated under reflux for 40 min with exclusion of moisture, then filtered and the filtrate evaporated under reduced pressure. The residual oil was triturated with methanol and the crystalline yellow product then washed with a little cold methanol. The *ester* **13b** (3.40 g, 53%) had mp 78–79 °C (from methanol). A second crop (1.21 g, 19%) was obtained by chromatography of the mother-liquor (silica gel; dichloromethane) (Found: C, 37.0; H, 2.35; N, 12.9. $C_{10}H_8F_3N_3O_6$ requires C, 37.2; H, 2.5; N, 13.0%); δ_H[$(CD_3)_2CO$] 3.85 (3H, s, CH_3), 4.05 (2H, d, CH_2), 8.75 (2H, s, 3- and 5-H) and 9.40 (1H, br s, NH); $J_{CH_2,NH}$ 5.

***N*-(2-Methyl-6-nitrophenyl)glycine ethyl ester 13c.** Dry hydrogen chloride (1.1 g) was bubbled into a solution of the glycine **12c** (1.0 g, 4.8 mmol) in ethanol (50 cm^3) and the mixture was then heated under reflux for 4 h. The solvent was evaporated under reduced pressure, the residue was chromatographed on silica gel with ether as eluent to give the *ester* **13c** (0.90 g, 79%), mp 51–52 °C (from ethanol), induced to crystallise by cooling in ice and scratching (Found: C, 55.9; H, 6.0; N, 11.85. $C_{11}H_{14}N_2O_4$ requires C, 55.5; H, 5.9; N, 11.8%); ν_{max}/cm^{-1} 3355 (N–H), 1730 (C=O), 1535 and 1340 (NO_2); δ_H 1.16 (3H, t, CH_3CH$_2$), 2.35 (3H, s, CH_3Ar), 4.02 (2H, d, CH_2NH), 4.06 (2H, q, CH_2CH$_3$), 6.88 (2H, br t, NH and 4-H), 7.42 (1H, br d, 3-H) and 7.77 (1H, dd, 5-H); J_{CH_3,CH_2} 6.3, $J_{CH_2,NH}$ 6.3, $J_{3,4}$ 7.5, $J_{4,5}$ 8.5, $J_{3,5}$ 1.3.

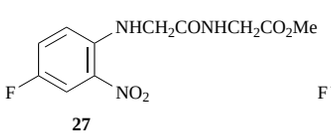
***N*-[2-Nitro-4-(trifluoromethyl)phenyl]glycine methyl ester 13d.** Prepared similarly to **13c** (reaction time 5 h); in this case chromatography was unnecessary. Yield 94%, mp 129–130 °C (from methanol) (Found: C, 43.1; H, 3.1; N, 10.0. $C_{10}H_9F_3N_2O_4$ requires C, 43.2; H, 3.3; N, 10.1%); δ_H 3.90 (3H, s, CH_3), 4.20 2H, d, CH_2), 6.90 (1H, d, 6-H), 7.75 (1H, dd, 5-H), 8.60 (1H, d, 3-H) and 8.75 (1H, br s, NH); $J_{CH_2,NH}$ 6, $J_{3,5}$ 2, $J_{5,6}$ 9.

***N*-(4-Fluoro-2-nitrophenyl)glycine methyl ester 13e.** (a) 1,4-Difluoro-2-nitrobenzene (0.94 g, 6 mmol), glycine methyl ester hydrochloride (0.82 g, 6.5 mmol), triethylamine (1.52 g, 15 mmol) and tetrahydrofuran (40 cm^3) were heated together under reflux for 13 h. Further portions of the ester (0.75 g, 6 mmol) and triethylamine (0.66 g, 6.5 mmol) were added, heating was continued for a further 6 h and the mixture was then filtered and the filtrate evaporated to dryness. The residue was treated with dilute (5 M) hydrochloric acid and filtered off, giving the *ester* **13e** (0.74 g, 54%), mp 107–108 °C (from methanol) (Found: C, 47.3; H, 3.8; N, 12.3. $C_9H_9FN_2O_4$ requires C, 47.4; H, 4.0; N, 12.3%); δ_H 3.90 (3H, s, CH_3), 4.28 (2H, d, CH_2), 6.78 (1H, dd, 6-H), 7.30 (1H, 8 lines, 5-H), 8.05 (1H, dd, 3-H) and 8.38 (1H, br s, NH); δ_F −99.4 (8 lines); $J_{CH_2,NH}$ 7, $J_{3,5}$ 3, $J_{5,6}$ 9, $J_{3,F}$ 7, $J_{5,F}$ 11, $J_{6,F}$ 4.

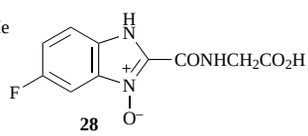
(b) The above reaction was repeated, using 1,4-difluoro-2-nitrobenzene (4.77 g, 30 mmol), glycine methyl ester hydrochloride (7.53 g, 60 mmol), triethylamine (10.1 g, 100 mmol) and dry tetrahydrofuran (150 cm^3), and adding further portions of ester and base at 6-hourly intervals (total ester used, 25.11 g, 200 mmol; total triethylamine used, 29.12 g, 288 mmol). After 40 h, unchanged difluoronitrobenzene was still present (TLC); after a further 30 h under reflux this compound was still detectable. The mixture was filtered, the filtrate evaporated to dryness and the residue taken up as far as possible in a mixture of ether (50 cm^3) and hydrochloric acid (5 M; 20 cm^3).

The orange solid which was soluble in neither layer was filtered off, recrystallised from methanol and the crude solid purified further by chromatography on silica gel (eluent, petroleum–dichloromethane) giving as the main product the ester **13e** (2.07 g, 30%), mp 107–108 °C, and a more polar fraction identified as [N-(4-*fluoro*-2-*nitrophenyl*)*glycyl*]*glycine methyl ester* **27** (0.13 g, 1.3%), mp 152 °C (from methanol) (Found: C, 46.1; H, 3.8; N, 15.0. $C_{11}H_{12}FN_3O_5$ requires C, 46.3; H, 4.2; N, 14.7%); δ_H[$(CD_3)_2CO$] 3.65 (3H, s, CH_3), 3.91 (2H, d, CH_2), 4.10 (2H, d, CH_2), 6.88 (1H, dd, 6-H), 7.52 (1H, 8 lines, 5-H), 7.87 (1H, dd, 3-H), 8.36 (1H, br t, NH) and 8.51 (1H, br t, NH); $J_{CH_2,NH}$ 6, $J_{3,5}$ 3, $J_{5,6}$ 9, $J_{3,F}$ 9, $J_{5,F}$ 11, $J_{6,F}$ 5; δ_C 40.7 (CH_2), 45.7 (CH_2), 51.8 (CH_3), 111.1 (d, *J* 27, C-3), 116.6 (d, *J* 6, C-6), 125.1 (d, *J* 24, C-5), 130.4 (d, *J* 9, C-4), 141.9 (d, *J* 8, C-1), 152.1 (d, *J* 236, C-4), 169.1 (d, *J* 3, amide CO) and 170.2 (ester CO).

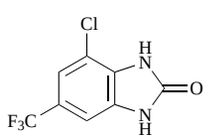
The original acidic extract was neutralised (3 M NaOH) and extracted several times with dichloromethane. During each extraction a brown solid formed at the interface: this was filtered off (total yield, 0.17 g), and a further crop (0.40 g) was produced when the solution was then left overnight. ^{19}F NMR spectroscopy of this solid indicated the presence of three fluorine-containing products and the ^{1}H and ^{13}C NMR spectra suggested that the main component (with δ_F −119.9) was probably N-[(5-*fluoro*-3-*oxido*-1H-*benzimidazol*-2-*yl*)*carbonyl*]*glycine*, **28**; δ_H 4.05 (2H, d, CH_2), 7.24 (1H, dt, 6-H), 7.43 (1H, dd, 4-H) and 7.75 (1H, dd, 7-H); δ_C 40.8 (CH_2), 96.8 (d, *J* 27, C-4), 112.8 (d, *J* 26, C-6), 120.7 (d, *J* 9, C-7), 132.9 and 133.0 (C-3a and 7a), 157.1 (C-2), 158.6 (d, *J* 240, C-5) and 170.5 (CO). (The second CO resonance was not observed: it may coincide with that of C-2 or C-5.) δ_F −119.9 (8 lines); $J_{CH_2,NH}$ 6, $J_{4,6}$ 3, $J_{6,7} = J_{4,F} \approx J_{6,F}$ *ca.* 9, $J_{7,F}$ 5.



27



28



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***N*-[2-Chloro-6-nitro-4-(trifluoromethyl)phenyl]glycine methyl ester 13f.** 3-Chloro-4-fluoro-5-nitrobenzotrifluoride [1-chloro-2-fluoro-3-nitro-5-(trifluoromethyl)benzene] (2.46 g, 10 mmol), glycine methyl ester hydrochloride (1.26 g, 10 mmol), sodium hydrogen carbonate (1.68 g, 20 mmol) and methanol (30 cm^3) were heated together under reflux for 2 h. The solution was allowed to cool overnight to 4 °C, and was then added to ice–water; the *ester* **13f** (2.89 g, 93%) was then filtered off and had mp 48–49.5 °C (from methanol) (Found: C, 38.1; H, 2.3; N, 8.8. $C_{10}H_8ClF_3N_2O_4$ requires C, 38.4; H, 2.6; N, 9.0%); δ_H 3.80 (3H, s, CH_3), 4.25 (2H, d, CH_2), 7.95 (1H, br s, NH), 7.97 (1H, d, 5-H) and 8.22 (1H, d, 3-H); δ_F −62.9; $J_{3,5}$ 2.

Attempts to prepare this ester using other bases gave product mixtures, which resulted from further reaction of the ester with the base; these are considered below.

***N*-[2,4-Dinitro-6-(trifluoromethyl)phenyl]glycine methyl ester 13g.** Mp 77–78 °C (from methanol). Obtained by the method described for **13c** (reaction time, 7 h; eluent, dichloromethane; yield 63%) (Found: C, 37.2; H, 2.4; N, 13.0. $C_{10}H_8F_3N_3O_6$ requires C, 37.2; H, 2.5; N, 13.0%); δ_H[$(CD_3)_2CO$] 3.82 (3H, s, CH_3), 4.25 (2H, d, CH_2), 8.20 (1H, br s, NH), 8.75 (1H, d, 5-H) and 9.10 (1H, d, 3-H); $J_{CH_2,NH}$ 5, $J_{3,5}$ 2.

***N*-(2,4-Difluoro-6-nitrophenyl)glycine methyl ester 13h.** Mp 73–74 °C (from methanol). Obtained as for **13c** (reaction time, 3.5 h; product isolated by addition of the reaction mixture to ice; yield 88%) (Found: C, 44.0; H, 3.1; N, 11.4. $C_9H_8F_2N_2O_4$ requires C, 43.9; H, 3.3; N, 11.4%); δ_H[$(CD_3)_2CO$] 3.80 (3H, s,

Table 2 ^{13}C NMR spectra of benzimidazole *N*-oxides **16** and **17**

	Chemical shift (δ)										
Cpd.	C-2	C-3a	C-4	C-5	C-6	C-7	C-7a	Me	CF_3	CO	CH_2
16b	142.6	125.1	114.9q	123.0[a]	116.8	135.1	131.7	53.2	123.0[a]	157.4	
16c(?)	137.7	131.4	108.2	125.9[b]	123.8[b]	133.2	137.1	14.5 16.2		158.8	62.0
17d	142.6	130.9[b]	106.8q	123.0q	118.2q	120.8	141.2[b]	—	124.9q		
17e	140.9	131.7d	95.6d	159.1d	110.0d	120.9d	135.6	—	—		
17f	143.1	132.1	106.3q	124.0q	117.7q	124.8	138.1	—	124.0q		
17h	141.1	133.8	92.0dd	158.0dd	96.7dd	152.7dd	124.5d	—	—		

***J*(C-F)**/Hz:	**17d**:		**17e**:		**17f**:		**17h**:	
	C-4	4	C-3a	14	C-4	4	C-3a	16,11
	C-5	32	C-4	28	C-5	33	C-4	28, 4
	C-6	3	C-5	238	C-6	3	C-5	239, 11
	CF_3	271	C-6	25	CF_3	272	C-6	30, 22
			C-7	10			C-7	254,15
							C-7a	18

[a] Approximate shifts (very weak signals). [b] Provisional assignments.

CH_3), 4.45 (2H, dd, CH_2), 7.50 (1H, symm. m, 3-H), 7.85 (1H, symm. m, 5-H) and 8.00 (1H br s, NH); δ_F −121.1 (m, 2-F) and −124.9 (m, 4-F); $J_{CH_2,NH}$ 6.0, $J_{CH_2,F\text{-}2}$ 5.2, $J_{NH,F\text{-}2}$ 2.3, $J_{F,F}$ 1.0, $J_{5,F\text{-}4}$ 9.4, $J_{5,F\text{-}2}$ 2.0, $J_{3,F\text{-}4}$ 8.0, $J_{3,F\text{-}2}$ 14.0.‡

Reactions of *N*-cyanomethyl-*o*-nitroanilines with bases

***N*-Cyanomethyl-*N*-methyl-2-nitroaniline (1: R′ = Me, X = H) with potassium carbonate.** *N*-Cyanomethyl-*N*-methyl-2-nitroaniline (**1**: R′ = Me, X = H) was obtained as a viscous liquid, bp (Kugelrohr) 125 °C/0.05 mmHg (no bp reported in the literature[6]) by reaction of *N*-methyl-*o*-nitroaniline with paraformaldehyde, potassium cyanide and zinc chloride in acetic acid, following the procedure already described[3] for *o*-nitroaniline; δ_H 3.93 (3H, s, CH_3), 4.06 (2H, s, CH_2) and 7.10–7.83 (4H, m, Ar-H).

N-Cyanomethyl-*N*-methyl-2-nitroaniline (1.0 g, 5.2 mmol), potassium carbonate (0.72 g, 5.2 mmol) and ethanol (15 cm^3) were stirred together at room temperature for 30 min, then heated under reflux for 3 h. The solvent was evaporated under reduced pressure, the residue was partitioned between ether and water, and the aqueous layer acidified (HCl), to give 1-hydroxy-3-methyl-1*H*-benzimidazol-2(3*H*)-one **6** (R′ = Me, X = H) (0.50 g, 59%), mp 198–200 °C (from water; lit.,[6] 203 °C); ν_{max}/cm^{-1} 1685 (C=O); δ_C 27.0 (CH_3), 106.4 and 107.9 (C-4 and C-7), 120.8 and 121.2 (C-5 and C-6), 126.4 and 128.5 (C-3a and C-7a) and 151.6 (C-2).

***N*-Cyanomethyl-2,6-dinitroaniline 9a with potassium carbonate.** A mixture of the cyanomethyl compound **9a** (2.0 g, 9 mmol), potassium carbonate (1.24 g, 9 mmol) and ethanol (100 cm^3) was heated under reflux for 30 min and then cooled. The precipitate was filtered off and dissolved as far as possible in boiling water; the suspension was filtered hot, the filtrate acidified (conc. HCl) and the solid product filtered off and recrystallised from dimethylformamide–water (with charcoal) to give 1-*hydroxy*-4-*nitro*-1H-*benzimidazol*-2(3H)-*one* **10a** (0.69 g, 39%), mp 275 °C (decomp.) (Found: C, 43.0; H, 2.4; N, 21.5. $C_7H_5N_3O_4$ requires C, 43.1; H, 2.6; N, 21.5%); ν_{max}/cm^{-1} 3200br (O–H), 1735 (C=O), 1520 and 1310 (NO_2); δ_H 7.20 (1 H, t, H-6), 7.43 (1H, dd, H-7), 7.80 (1H, dd, H-5) and 11.63 (1H, br s, OH); δ_C 112.0 (C-7), 115.8 (C-5), 120.88 (C-6) and 120.94 (C-3a), 130.6 and 131.9 (C-4 and C-7a) and 151.6 (C-2).

***N*-Cyanomethyl-2-methyl-6-nitroaniline 9c with potassium carbonate.** (a) Compound **9c** (0.30 g, 1.6 mmol), potassium carbonate (0.22 g, 1.6 mmol) and ethanol (10 cm^3) were heated together under reflux for 2 h and the mixture then cooled and filtered. The precipitate was dissolved in water and reprecipitated using hydrochloric acid, giving 1-hydroxy-4-methyl-1*H*-benzimidazol-2(3*H*)-one **10c** (0.015 g, 6%), mp 240 °C (decomp.) (lit.,[19] 254–257 °C), spectroscopically identical with an authentic sample; ν_{max}/cm^{-1} 1710; δ_C 15.7 (CH_3), 103.8 (C-7), 118.8 (C-4), 120.8 and 122.0 (C-5 and 6), 123.4 (C-3a), 129.2 (C-7a) and 152.1 (C-2).

The original reaction filtrate was evaporated to dryness and the residue partitioned between ether and water. Acidification (HCl) of the aqueous layer gave 2-*cyano*-7-*methyl*-1H-*benzimidazole* 3-*oxide* **11c** (0.17 g, 63%), mp 228–229 °C (from ethanol–water) (Found: C, 62.2; H, 4.0; N, 24.3. $C_9H_7N_3O$ requires C, 62.4; H, 4.1; N, 24.3%); ν_{max}/cm^{-1} 2240 (C≡N); δ_H 2.58 (3H, s, CH_3) and 7.14–7.54 (3H, m, Ar-H).

(b) Repetition of procedure (a) with a reaction time of 6 h gave the *N*-oxide **11c** (0.13 g, 48%) and a second crop of crystals (0.01 g; mp *ca.* 190 °C) which consisted of a mixture of **10c** and **11c**.

(c) Repetition of procedure (a) using the cyanomethyl compound **9c** (0.20 g) and an excess of potassium carbonate (0.29 g, 2.1 mmol) in ethanol (6.5 cm^3) led to the *N*-oxide **11c** (44%) as the only isolated product.

Reactions of *N*-(*o*-nitroaryl)glycine esters 13 with bases

***N*-(2,6-Dinitrophenyl)glycine ethyl ester 13a with potassium carbonate.** Potassium carbonate (1.02 g, 7.4 mmol) was added portionwise to a well-stirred solution of the ester **13a** (2.0 g, 7.4 mmol) in ethanol (80 cm^3) and dimethylformamide (10 cm^3). Stirring was continued at room temperature for 2.5 h; the mixture was then filtered, the precipitate dissolved in water and the black tarry material formed was removed by refiltration. The filtrate was acidified (HCl) and the solid product (0.04 g) filtered off. Saturation of the solution with sodium chloride and extraction with dichloromethane gave a further 0.04 g of product. Recrystallisation of the combined solids from ethanol yielded 1-*hydroxy*-5-*nitroquinoxaline*-2,3(1H,4H)-*dione* **14a** (0.05 g, 3%).

The reaction mother-liquor was evaporated to dryness and partitioned between water and dichloromethane. The red–brown solid (0.37 g) which was insoluble in both phases was a complex mixture (by TLC), but gave a mass spectrum with an apparent molecular ion (found: *m/z* 318.0723) corresponding to 2,2′-diamino-3,3′-dinitroazoxybenzene **15a** ($C_{12}H_{10}N_6O_5$ requires *M*, 318.0713). Concentration of the dried (Na_2SO_4) organic layer gave a dark oil (0.42 g) containing at least 7 components (by TLC). Acidification of the aqueous layer gave a further crop of (impure) 1-hydroxy-5-nitroquinoxaline-2,3(1*H*,4*H*)-dione **14a** (0.09 g, 5%).

When the reaction time was extended to 20 h and the extraction carried out using ethyl acetate instead of dichloromethane, the yield of compound **14a** was increased to 37%.

‡ The ^{1}H and ^{19}F NMR assignments and coupling constants were verified by computer simulation.

Table 3 ^{13}C NMR spectra of 1-hydroxyquinoxaline-2,3-diones **14**

	Chemical shift (δ)								
Cpd.	C-2	C-3	C-4a	C-5	C-6	C-7	C-8	C-8a	CF_3
14a	154.9	151.3	119.8	135.3	119.4[a]	123.6	121.0[a]	130.3	—
14b	154.2	150.6	122.4	134.8	117.0q	122.9q	114.1q	130.9	123.0q
14f	154.9	151.0	129.2	119.3	120.8q	123.8q	108.3q	124.4	123.3q
14g	155.1	151.1	130.5[a]	116.4q	117.5q	143.3	112.9	127.5[a]	123.6q

***J*(C-F)**/Hz:	**14b**:		**14f**:		**14g**:	
	C-6	3	C-6	4	C-4a	0
	C-7	35	C-7	33	C-5	33
	C-8	4	C-8	3	C-6	6
	CF_3	272	CF_3	272	CF_3	272

[a] Provisional assignments.

Table 4 ^{13}C NMR spectra of azoxybenzene derivatives **15**

	Chemical shift (δ)													
Cpd.	C-1	C-1′	C-2	C-2′	C-3	C-3′	C-4[a]	C-4′[a]	C-5[a]	C-5′[a]	C-6	C-6′	CF_3[a]	CF_3′[a]
15b	131.2	131.8	144.3	141.5	133.0	137.3	124.0q	124.5q	*b*	*b*	128.2q	126.3q	123.70q	123.73q
15g	128.3	133.6	147.6	144.6	113.3q	111.1q	124.1q	125.2q	133.8	134.1	125.9	121.5	122.9q	123.0q

***J*(C-F)**/Hz:	**15b**:		**15g**:	
	C-4	3	C-3	32
	C-4′	4	C-3′	32
	C-6	4	C-4	5
	C-6′	4	C-4′	5
	CF_3	271	CF_3	271

[a] Provisional assignments. [b] Not detected (very weak signal).

Compound **14a** had mp 231–232 °C (from ethanol) (Found: C, 42.9; H, 2.2; N, 18.85. $C_8H_5N_3O_5$ requires C, 43.0; H, 2.3; N, 18.8%); ν_{max}/cm^{-1} 3290, 3260, 3180 (N–H, O–H), 1700br (C=O), 1530 and 1310 (NO_2); δ_H 7.39 (1H, t, 7-H), 7.85 and 7.98 (2H, 2 × dd, 6- and 8-H), 11.2 and 12.1 (2H, br s, NH and OH); $J_{6,7} = J_{7,8}$ 8.0, $J_{6,8}$ 1.5; δ_C: see Table 3.

***N*-[2,6-Dinitro-4-(trifluoromethyl)phenyl]glycine methyl ester 13b.** (*a*) *With triethylamine.*—Triethylamine (0.61 g, 6 mmol) was added to a solution of the ester **13b** (1.94 g, 6 mmol) in toluene (30 cm^3) and the mixture stirred at room temperature for 4.5 h. The solution was then concentrated under reduced pressure, the oily residue partitioned between dichloromethane and water and the aqueous layer acidified (5 M HCl). The precipitate was filtered off and washed with a little dichloromethane, to give crude 1-*hydroxy*-5-*nitro*-7-*trifluoromethyl*-*quinoxaline*-2,3(1H, 4H)-*dione* **14b** (0.22 g, 13%). The combined dichloromethane solutions were extracted with water and the extract acidified to give a further crop (0.45 g, 26%) of this product, mp 247 °C (decomp.) (from methanol) (Found: C, 36.8; H, 1.2; N, 14.3. $C_9H_4F_3N_3O_5$ requires C, 37.1; H, 1.4; N, 14.4%); ν_{max}/cm^{-1} 3100–3240w (NH and OH), 1760br and 1690w (C=O); δ_H 8.28 (1H, d, 8-H), 8.40 (1H, d, 6-H) and 11.50 (2H, br s, NH and OH); $J_{6,8}$ 2; δ_C: see Table 3; *m/z* 291 ($M^{+\bullet}$), 275, 273, 257, 247, 236, *etc.*

The remaining dichloromethane solution was extracted with saturated aqueous sodium hydrogen carbonate; the extract was then acidified and the product re-extracted with dichloromethane. This extract when dried (Na_2SO_4) and concentrated gave a small amount of solid which was considered to be a mixture of the hydroxyquinoxalinedione **14b** and *methyl* 7-*nitro*-5-*trifluoromethyl*-1H-*benzimidazole*-2-*carboxylate* 3-*oxide* **16b**. Resonances at δ_H 4.0, 8.0 and 8.75, δ_C as in Table 2 and *m/z* 305 ($M^{+\bullet}$) and 289 could all be attributed to the latter compound.

The dichloromethane solution remaining after successive extractions was a complex mixture (by TLC). After drying and concentration the residue was triturated with a little dichloromethane, giving 2,2′-*diamino*-3,3′-*dinitro*-5,5′-*bis*(*trifluoromethyl*)*azoxybenzene* **15b** (0.25 g, 15%), mp 193 °C (from ethanol) (Found: C, 37.1; H, 1.5; N, 18.4. $C_{14}H_8F_6N_6O_5$ requires C, 37.1; H, 1.8; N, 18.5%); δ_H 8.30 (4 H, br s, 2 × NH_2), 8.36 and 8.51 (each 1H, d, 4- and 4′-H), 8.54 (1H, d, 6-H) and 9.04 (1H, d, 6′-H);§ $J_{3,5} = J_{3',5}$ 2; δ_C: see Table 4; *m/z* 454 ($M^{+\bullet}$, 100%), 438, 435, *etc*.

(*b*) *With sodium hydrogen carbonate.*—Sodium hydrogen carbonate (0.34 g, 4 mmol) was added to a solution of the ester **13b** (1.30 g, 4 mmol) in methanol (30 cm^3). The mixture was stirred at room temperature for 2.5 h then filtered and the residue washed with methanol. The filtrate was evaporated under reduced pressure and the dark oily residue washed with an ether–petroleum mixture (1:1; 10 cm^3). The resulting solid was filtered off, washed several times with further portions of the ether–petroleum mixture and finally with dichloromethane, before being sublimed *in vacuo*, to give dark green needles, mp 98–99 °C, which were identified as 2-*nitro*-6-*nitroso*-4-*trifluoromethylaniline* **21b** (Found M^+, 235.0199. $C_7H_4F_3N_3O_3$ requires *M*, 235.0205) mixed with a little 2,6-dinitro-4-trifluoromethylaniline (*m/z* 251; no peak at *m/z* 235). The involatile residue consisted (by ^{1}H NMR spectroscopy) of unreacted ester **13b** and the azoxybenzene derivative **15b**.

The solid filtered off from the original reaction mixture was dissolved in the minimum of water. Acidification (HCl) gave a precipitate of the hydroxyquinoxalinedione **14b** (0.10 g); a second crop (0.03 g; total 11%) was obtained from the aqueous filtrate as described under (a), above.

***N*-(2-Methyl-6-nitrophenyl)glycine ethyl ester 13c with potassium carbonate.** A suspension of the ester **13c** (0.55 g, 2.3 mmol) and potassium carbonate (0.32 g, 2.3 mmol) in ethanol (15 cm^3) was stirred at 60 °C for 5 h, then cooled and concentrated under reduced pressure. The residue was partitioned between ether and water, the aqueous layer was separated, the pH adjusted to *ca.* 7 using dilute hydrochloric acid and then the solid product was filtered off and washed with a little water to give *ethyl* 7-*methyl*-1H-*benzimidazole*-2-*carboxylate* 3-*oxide* **16c** (0.28 g, 55%), mp 170–172 °C (from ethanol–water) (Found: C, 59.7; H, 5.5; N, 12.6. $C_{11}H_{12}N_2O_3$ requires C, 60.0; H, 5.5; N, 12.7%);

§ Provisional assignments.

ν_{max}/cm^{-1} 1730 (C=O); δ_H 1.40 (3H, t, CH_3CH$_2$), 2.59 (3H, s, CH_3Ar), 4.45 (2H, q, CH$_2$), 7.06–7.45 (3H, m, Ar-H) and 12.18 (1H, s, NH or OH).

***N*-[2-Nitro-4-(trifluoromethyl)phenyl]glycine methyl ester 13d with potassium carbonate.** A mixture of the ester **13d** (1.50 g, 5.4 mmol) and potassium carbonate (1.52 g, 11 mmol) in methanol (30 cm^3) was heated under reflux for 1.5 h. The solvent was then evaporated under reduced pressure, the residue partitioned between dichloromethane and water and the aqueous layer carefully acidified (5 M HCl) to give a solid which was filtered off and washed with chloroform. The product (0.97 g) was tentatively identified as 5-trifluoromethyl-1*H*-benzimidazole-2-carboxylic acid 3-oxide [ν_{max}/cm^{-1} 3000–3700br (O–H), 1650 (C=O)]. This was recrystallised several times from dilute hydrochloric acid and finally from ethanol–water, to give 5-*trifluoromethyl*-1H-*benzimidazole* 3-*oxide* **17d**, mp 196 °C (Found: C, 47.85; H, 2.4; N, 13.9. $C_8H_5F_3N_2O$ requires C, 47.5; H, 2.5; N, 13.9%); ν_{max}/cm^{-1} 3140 (N–H); δ_H 7.54 (1H, dd, 6-H), 7.86–7.95 (2H, m, 4- and 7-H) and 8.75 (1H, s, 2-H); $J_{4,6}$ 1.2, $J_{6,7}$ 8.3; δ_F −59.0; δ_C: see Table 2.

***N*-(4-Fluoro-2-nitrophenyl)glycine methyl ester 13e.** (*a*) *With triethylamine.*—The ester **13e** (1.44 g, 6.3 mmol), triethylamine (1.52 g, 15 mmol) and methanol (40 cm^3) were heated together under reflux for 6 h. The solvent and excess triethylamine were then removed under reduced pressure and the residue partitioned between ether and water. The ether layer was washed with a little 5 M hydrochloric acid and the aqueous layer acidified using the same reagent; the combined acidic fractions were carefully basified (NaOH) and reacidified (5 M HCl); 5-fluoro-1*H*-benzimidazole 3-oxide, **17e** (0.23 g, 24%), mp 225–227 °C (from water; lit.,[3] 227–229 °C), spectroscopically identical with an authentic sample, was obtained.

(*b*) *With potassium carbonate.*—Potassium carbonate (2.76 g, 20 mmol) was added to a solution of the ester **13e** (2.10 g, 9 mmol) in methanol (50 cm^3), causing a colour change from yellow to red. The mixture was heated under reflux for 3 h, the solvent evaporated under reduced pressure and the residue partitioned between dichloromethane and water. The aqueous layer was acidified (5 M HCl) and the product filtered off and washed with chloroform, to give 5-fluoro-1*H*-benzimidazole 3-oxide **17e** (1.01 g, 72%), mp 225–227 °C, identical with the product obtained in (a), above. δ_C: see Table 2.

***N*-[2-Chloro-6-nitro-4-(trifluoromethyl)phenyl]glycine methyl ester 13f.** (*a*) *With triethylamine.*—Attempts to prepare the ester **13f** by addition of glycine methyl ester hydrochloride (1.56 g, 12.5 mmol) in portions to a solution of 3-chloro-4-fluoro-5-nitrobenzotrifluoride (2.46 g, 10 mmol) and triethylamine (2.02 g, 20 mmol) in methanol (30 cm^3) at room temperature gave after 1.8 h a product mixture containing not only the ester **13f** (2.80 g, 89%) but also a small amount of solid acidic material which (by MS) appeared to contain both 7-*chloro*-5-*trifluoromethyl*-1H-*benzimidazole* 3-*oxide* **17f** and 5-*chloro*-1-*hydroxy*-7-*trifluoromethylquinoxaline*-2,3(1H,4H)-*dione* **14f** (*m/z* 236 and 280 respectively; see below).

A solution of the ester **13f** (1.56 g, 5 mmol) and triethylamine (0.56 g, 5.5 mmol) in toluene (20 cm^3) was stirred at room temperature for 2 h, then at 75 °C for 1 h and finally at 80–90 °C for 4 h; it was then concentrated under reduced pressure and the residue was taken up as far as possible in ether containing a little methanol and extracted with 1 M hydrochloric acid. The aqueous layer was filtered, giving an orange solid which was identified (IR, ^{1}H NMR and mass spectroscopy) as a mixture of unreacted ester **13f** and the quinoxalinedione **14f**. The ether layer was extracted with 3 M sodium hydroxide and this extract acidified, giving (upon re-extraction with ether) 7-chloro-5-trifluoromethyl-1*H*-benzimidazole 3-oxide, **17f** (0.36 g, 31%). The original ether–methanol extract was dried and evaporated to give a complex mixture, the major component of which was identified (^{1}H NMR) as 2,2′-*diamino*-3,3′-*dichloro*-5,5′-*bis*(*trifluoromethyl*)*azoxybenzene* **15f**. The latter was purified by sublimation at reduced pressure, but could not be obtained in analytically pure form; the sublimate had mp 171–175 °C.

(*b*) *With potassium carbonate.*—The ester **13f** (0.63 g, 2 mmol), potassium carbonate (0.28 g, 2 mmol) and methanol (20 cm^3) were heated together under reflux for 5.5 h. Filtration of the cooled mixture gave a solid which was dissolved in water, decolourised with charcoal and acidified. The solid product (0.01 g) was identified (MS) as a mixture of the quinoxalinedione **14f** and the benzimidazole oxide **17f**. The mother-liquor contained an unresolvable mixture.

(*c*) *With barium hydroxide.*—(i) Attempts to prepare the ester **13f** from 3-chloro-4-fluoro-5-nitrobenzotrifluoride (2.44 g, 10 mmol), glycine methyl ester hydrochloride (1.38 g, 11 mmol) and barium hydroxide (6.94 g, 22 mmol) in tetrahydrofuran (30 cm^3) showed incomplete reaction after 18 h at room temperature; additional ester (20 mmol) and barium hydroxide (40 mmol) were then added. After a further 3 h, the solvent was evaporated and the residue worked up in the usual way. The acidic fraction (1.04 g) consisted of the benzimidazole *N*-oxide **17f** contaminated by a small amount of the hydroxyquinoxalinedione **14f**; the latter was extracted from the mixture with boiling water. The non-acidic fraction consisted of slightly impure ester **13f** (1.01 g, 32%).

(ii) The ester **13f** (1.56 g, 5 mmol), barium hydroxide (1.89 g, 6 mmol) and dry tetrahydrofuran (20 cm^3) were stirred together at room temperature for 19 h and the solvent was then evaporated. The non-acidic fraction (0.17 g) was a complex mixture (TLC), but consisted mainly of unchanged ester **13f** and the azoxybenzene **15f**. The chloroform-insoluble part of the acidic fraction (0.28 g) was analysed by IR, NMR and mass spectroscopy; it contained the benzimidazole *N*-oxide **17f** (0.15 g, 13%), the hydroxyquinoxalinedione **14f** (0.02 g, 1%) and a third component tentatively identified as 4-chloro-6-trifluoromethyl-1*H*-benzimidazol-2(3*H*)-one, **29**; δ_C 101.7 (q, *J* 3, C-4), 113.9 (C-7), 117.85 (q, *J* 5, C-6), 117.94 (C-3a), 123.3 (q, *J* 32, C-5), 124.0 (q, *J* 272, CF_3), 130.6 (C-7a) and 151.7 (CO). The formation of compound **29** is conceivable through prolonged exposure of the benzimidazole *N*-oxide **17f** to aqueous alkali.

7-Chloro-5-trifluoromethyl-1*H*-benzimidazole 3-oxide **17f** has mp 217–218 °C (from ethanol) (Found: C, 40.5; H, 1.5; N, 11.7. $C_8H_4ClF_3N_2O$ requires C, 40.6; H, 1.7; N, 11.8%); δ_H 7.75 (1H, d, 6-H), 7.95 (1H, d, 4-H) and 8.85 (1H, s, 2-H); $J_{4,6}$ 1.5; δ_C: see Table 2; δ_F −59.3; *m/z* 236/8 ($M^{+\cdot}$), 220/2, 217/9, 201, 193, 187, 181, *etc.*

5-Chloro-1-hydroxy-7-trifluoromethylquinoxaline-2,3-(1*H*,4*H*)-dione **14f** has mp 247–249 °C (from dilute HCl) (Found: C, 38.3; H, 1.2; N, 9.8. $C_9H_4ClF_3N_2O_3$ requires C, 38.5; H, 1.4; N, 10.0%); ν_{max}/cm^{-1} 3000–3300br (NH and OH), 1750 and 1670 (CO); δ_H 7.64 (1H, d, 8-H), 7.68 (1H, d, 6-H) and 11.95 (*ca.* 2H, br s, NH and OH); $J_{6,8}$ 1.5; δ_C: see Table 3; δ_F −60.5; *m/z* 280/2 ($M^{+\cdot}$), 261, 252, 235, 216, 208, 173 (100%), *etc.*

2,2′-Diamino-3,3′-dichloro-5,5′-bis(trifluoromethyl)azoxybenzene **15f** was not obtained analytically pure, but the impure compound had mp 170–172 °C and showed δ_H 5.20 and 6.45 (each 2H, br s, NH$_2$), 7.65 (1H, d, 4′-H), 7.85 (1H, d, 4-H), 8.31 (1H, d, 6-H) and 9.08 (1H, d, 6′-H)¶; *J ca.* 2; *m/z* 432/4/6 ($M^{+\cdot}$), 416/8/20, 224/6, 209/11, 208, 194 (100%)/196, *etc.*

***N*-[2,4-Dinitro-6-(trifluoromethyl)phenyl]glycine methyl ester 13g.** (*a*) *With triethylamine.*—A solution of the ester (1.62 g, 5 mmol) and triethylamine (0.51 g, 5 mmol) in toluene (30 cm^3) was stirred at room temperature for 4.5 h, and the solid product filtered off, dissolved as far as possible in a mixture of dichloromethane and water and the mixture re-filtered. The insoluble portion was identified as (slightly impure) 2,2′-*diamino*-5,5′-

¶ Decoupling was carried out to confirm the assignments.

dinitro-3,3′-*bis*(*trifluoromethyl*)*azoxybenzene* **15g** (0.13 g), mp 292–293 °C (from ethanol). A second crop (0.06 g; total yield, 17%) was obtained from the dichloromethane layer by renewed washing with water (Found: C, 36.6; H, 1.5; N, 18.1. $C_{14}H_8F_6N_6O_5$ requires C, 37.0; H, 1.8; N, 18.5%); ν_{max}/cm^{-1} 3500w, 3400w and 3320w (NH_2); δ_H 7.20 (2H, br s, NH_2), 7.67 (2H, br s, NH_2), 8.30 (1H, d, 4′-H‖), 8.42 (1H, d, 4-H‖), 8.92 (1H, d, 6-H) and 9.48 (1H, d, 6′-H); $J_{3,5} = J_{3',5'}$ 2; δ_C: see Table 4; *m/z* 454 ($M^{+\cdot}$, 100%), 438, *etc.*

The aqueous layer from the original partition was carefully acidified (5 M HCl) and the colourless crystalline product filtered off to give 1-*hydroxy*-7-*nitro*-5-*trifluoromethylquinoxaline*-2,3(1H,4H)-*dione* **14g** (0.10 g, 7%), mp 244–245 °C (from water) (Found: C, 35.1; H, 1.7; N, 13.7. $C_9H_4F_3N_3O_5{\cdot}H_2O$ requires C, 35.0; H, 2.0; N, 13.6%); ν_{max}/cm^{-1} 3000–3600br (OH), 3110 (NH), 1730 and 1680s (C=O); δ_H[$(CD_3)_2CO$] 6.75 (1H, br s, NH), 8.55 (1H, d, 8-H) and 8.81 (1H, d, 6-H); $J_{6,8}$ 3; δ_C: see Table 3; *m/z* 291 ($M^{+\cdot}$), 275, 263, 247, *etc.*

The aqueous solution obtained from washing of the dichloromethane extract was, in turn, carefully acidified to give a solid (0.20 g) which was identified as a mixture of *methyl* 5-*nitro*-7-*trifluoromethyl*-1H-*benzimidazole*-2-*carboxylate* 3-*oxide* **16g** [*m/z* 305 (intensity 41%)] and the hydroxyquinoxalinedione **14g** [*m/z* 291 (intensity 22%)]. Saturation of the remaining solution with sodium chloride, extraction with ethyl acetate and addition of dichloromethane precipitated a further crop (0.02 g) of compound **14g**.

(*b*) *With barium hydroxide.*—Barium hydroxide (1.58 g, 5 mmol) was added to a solution of the ester **13g** (1.62 g, 5 mmol) in tetrahydrofuran (30 cm^3) and the mixture stirred at room temperature for 35 min. The supernatant liquid was carefully decanted off and the residue washed several times with ether; the washings were added to the reaction mother-liquor.

The ester **13g** (37%) was recovered unchanged from the mother-liquor, but attempts to separate the complex mixture of other products were unsuccessful. ^{1}H NMR and mass spectral evidence indicated the presence of the hydroxyquinoxalinedione **14g** and the 2-*unsubstituted* 5-nitro-7-trifluoromethylbenzimidazole oxide **17g**, but neither could be isolated in pure form.

***N*-(2,4-Difluoro-6-nitrophenyl)glycine methyl ester 13h with potassium carbonate.** The ester **13h** (0.40 g, 1.6 mmol), potassium carbonate (0.22 g, 1.6 mmol) and methanol (15 cm^3) were stirred together at room temperature for 18 h and the mixture was then heated under reflux for 5 h and cooled. The colourless precipitate was filtered off and dissolved in water; acidification of this solution gave 5,7-*difluoro*-1H-*benzimidazole* 3-*oxide* **17h** (0.23 g, 85%), mp 210–211 °C (from water) (Found: C, 49.4; H, 2.4; N, 16.4. $C_7H_4F_2N_2O$ requires C, 49.4; H, 2.4; N, 16.5%); ν_{max}/cm^{-1} 3660w (NH or OH) and 1700br (C=O); δ_H 6.94 (1H, dt, 6-H), 7.03 (1H, dd, 4-H) and 8.28 (1H, s, 2-H); $J_{4,6}$ 2.0, $J_{4,F\text{-}5}$ 8.0, $J_{6,F\text{-}5} = J_{6,F\text{-}7}$ 11.0, $J_{4,F\text{-}7}$ not measurable; δ_C: see Table 2.

‖ Provisional assignments.

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