o-Nitroaniline Derivatives. Part 10.[1] 5- and 6-Amino-1*H*-benzimidazole 3-Oxides

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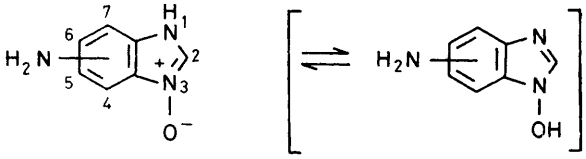
Cyclisation of *N*-(4- or 5-acylamino-2-nitrophenyl)glycine esters in basic media gives alkyl 5- or 6-acylaminobenzimidazole-2-carboxylate *N*-oxides, *e.g.* (**11a**) or (**11b**). Acid hydrolysis of the latter, followed by reaction with ammonia, gives the title compounds (**1b**) and (**1c**), in acceptable yield. The corresponding reaction sequence with 4-acylamino-*N*-cyanomethyl-*o*-nitroanilines also gives (**1b**); where the acyl group is methylsulphonyl, however, the final product is 5-methanesulphonamidobenzimidazole *N*-oxide (**9**). Compound (**1b**) is also obtainable from ethyl 5-nitrobenzimidazole-2-carboxylate *N*-oxide by reduction followed by hydrolysis.

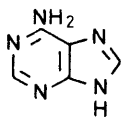
Attempts to cyclise *N*-(*o*-nitrophenyl)glycine derivatives containing a free amino group at the 5-position are unsuccessful. This failure is attributed to mesomeric deactivation of the nitro group by the amino lone pair.

In Part 9[1] we have described a general synthetic route to benzimidazole *N*-oxides which are unsubstituted both at the other nitrogen and at C-2, and we now consider the application of this method to the synthesis of benzimidazole *N*-oxides with an amino substituent in the carbocyclic ring, *viz.* (**1a—d**). These hitherto unknown compounds are of potential biological interest in view of their structural resemblance to the natural purines: thus (**1a**) and (**1d**) are obviously related to adenine (**2**), and (**1b**) and (**1c**) possess some of the functionality of guanine

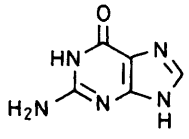


(**1**)

(**1a**) : 4 - NH_2 (**1c**) : 6 - NH_2
(**1b**) : 5 - NH_2 (**1d**) : 7 - NH_2



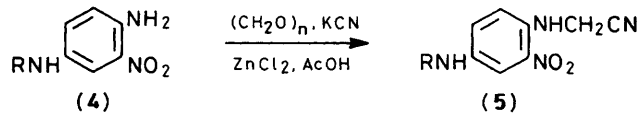
(**2**)



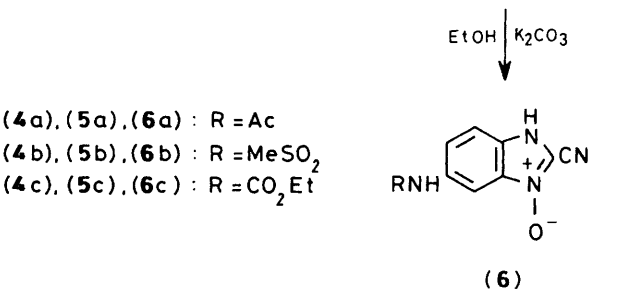
(**3**)

(**3**). The *N*-oxides (**1a—d**) are also of chemical interest in their own right, since they may be expected to react as multifunctional nucleophiles. In this paper we describe the syntheses and characteristics of the 5- and 6-amino compounds (**1b**) and (**1c**).

5-*Amino*-1H-*benzimidazole* 3-*Oxide* (**1b**).—(i) *From* 2-*nitro*-p-*phenylenediamine*. Monoacylation of 2-nitro-*p*-phenylenediamine occurs selectively at the 4-amino group,[2,3] and the acetyl-, methylsulphonyl-, and ethoxycarbonyl protected diamines (**4**) are then cyanomethylated at the other amino group by Dimroth and Aurich's method[4] (*cf.* the preceding paper[1]). Cyclisation of the resulting cyanomethyl compounds (**5**) in ethanolic potassium carbonate[1] gives the 5-acylamino-2-cyanobenzimidazole oxides (**6**) in good yield, and the latter are then hydrolysed in concentrated hydrochloric acid. In



(**4**) (**5**)



(**4a**), (**5a**), (**6a**) : R = Ac
(**4b**), (**5b**), (**6b**) : R = $MeSO_2$
(**4c**), (**5c**), (**6c**) : R = CO_2Et

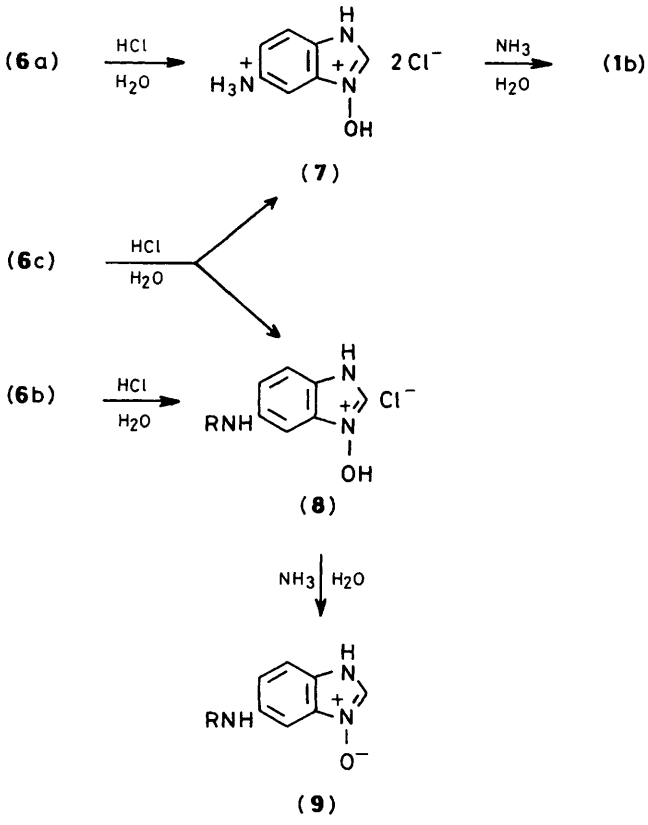
(**6**)

the case of the acetamido compound (**6a**), the hydrolysis product is the dihydrochloride (**7**) of the 5-amino *N*-oxide (**1a**), and the free *N*-oxide is obtained by reaction of the dihydrochloride with ammonia (*cf.* Part 9[1]). The amino-protecting groups in (**6b**) and (**6c**), however, are more resistant to hydrolysis; thus the hydrolysis of (**6b**) gives, *via* the monohydrochloride (**8a**), 5-methanesulphonamidobenzimidazole *N*-oxide (**9a**), and the corresponding hydrolysis of the cyanocarbamate (**6c**) gives a mixture of the dihydrochloride (**7**) and the monohydrochloride (**8b**), and thence the *N*-oxides (**1b**) and (**9b**).

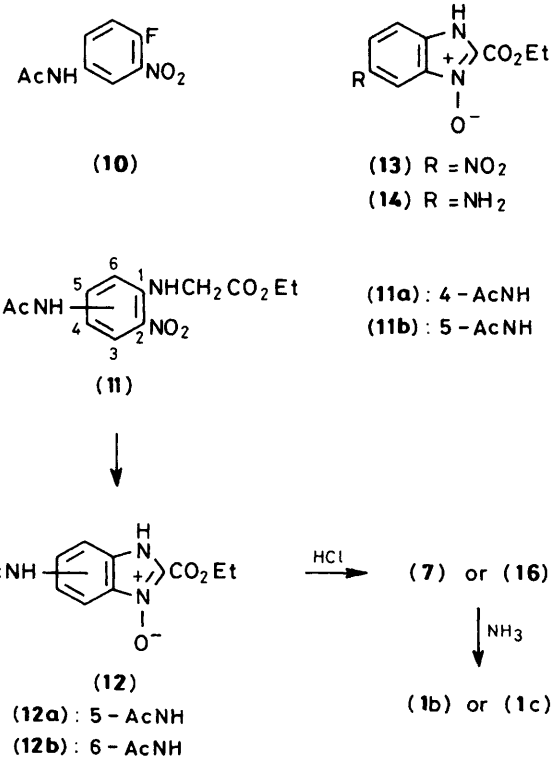
(ii) *From* 4-*fluoro*-3-*nitroaniline*. Although the amino group in this (commercially available) amine deactivates the fluorine towards nucleophilic displacement, the *N*-acetyl derivative (**10**) reacts cleanly with glycine ethyl ester to give the ester (**11a**). This, like the corresponding nitrile (**5a**), is cyclised in base to the benzimidazole oxide (**12a**), and the latter hydrolysed to the dihydrochloride (**7**) and thence to the amino *N*-oxide (**1b**).

(iii) *From* 5-*nitrobenzimidazole* N-*oxide*. The most obvious route to (**1b**), *viz.* the catalytic hydrogenation of 5-nitrobenzimidazole *N*-oxide,[1] presents practical difficulties because of the low solubility of the nitro compound in the usual solvents. However, catalytic hydrogenation of the nitro ester (**13**) proceeds smoothly, and gives the amino ester (**14**) which, although itself not easily purified, is hydrolysable to the dihydrochloride (**7**) and thence to (**1b**).

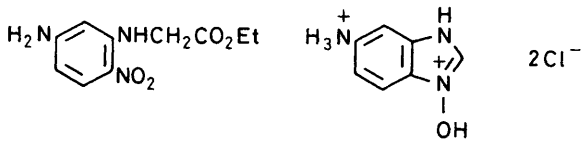
6-*Amino*-1H-*benzimidazole 3-oxide* (**1c**).—3-Fluoro-4-nitroaniline,[5] unlike the 4-fluoro-3-nitro isomer, reacts readily with glycine ethyl ester giving *N*-(5-amino-2-nitrophenyl)glycine



(8a),(9a) : R = SO_2Me ; (8b),(9b) : R = CO_2Et

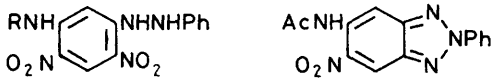


ethyl ester (**15**). Surprisingly, this ester is not cyclised at all in the presence of base, but merely undergoes hydrolysis to the corresponding carboxylic acid. However, the monoacetyl derivative of (**15**), *viz.* (**11b**), is readily cyclised in base to the benzimidazole oxide (**12b**), and hydrolysis of the latter, as described for its isomer (**12a**), leads to the parent *N*-oxide (**1c**).



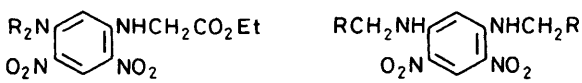
As befits such polar compounds, the *N*-oxides (**1b**) and (**1c**) are appreciably soluble in polar media, and crystallise from water in hydrated form. Presumably as a consequence of the extensive hydrogen bonding, there is no distinct NH stretching absorption in the i.r. spectra; however, the mass spectra show prominent ions for $M^{+\bullet}$, $(M - 16)^+$, and $(M - 29)^+$ (*i.e.* loss of O and CHO),[6] and the ^1H n.m.r. spectra show the characteristic lowfield singlet [1] corresponding to 2-H.

The failure of the glycine ester (**15**) to undergo cyclisation is evidently due to the presence of the primary amino group. The effect of ring substituents on intramolecular condensations involving nitro groups has not been widely or systematically studied: although, for example, we are accumulating evidence that the presence of a second nitro group in the ring may facilitate base-catalysed condensation in certain cases, it is by no means clear, from isolated examples here and there in the literature,[7] to what extent this represents a general trend. The effect of a powerful electron-donor on these condensations is even less well documented. Seventy-five years ago, Fries and Roth [8] reported as 'merkwürdig' (noteworthy, or remarkable) the fact that the aminodinitrodiphenylhydrazine (**17a**) failed to



undergo cyclisation in base, whereas the corresponding acetamido compound (**17b**) was readily cyclised to the benzotriazole (**18**); no explanation was offered for this difference in reactivity, and we are unaware of any other recorded examples in the more recent literature. In the case of the ester (**15**), as in Fries and Roth's experiment, we believe that the mesomeric effect of the *p*-amino group reduces the electrophilicity of the nitro group to such an extent that it is unreactive towards attack by the adjacent nucleophile.

The inhibiting effect of a 5-amino substituent on the cyclisation of an *N*-(*o*-nitrophenyl)glycine derivative is observed even when an additional nitro group is present. Thus, for example, *N*-(5-amino- and 5-dimethylamino-2,4-dinitrophenyl)-glycine ethyl esters (**19a**) and (**19b**) are recovered largely unchanged from treatment with strong base, and attempts to cyclise diaminodinitrobenzene derivatives such as (**20**) and (**21**) in basic media have similarly proved unsuccessful, substantial quantities of starting materials being recovered in each case.



Experimental

I.r. spectra were recorded for Nujol mulls, and ^{1}H n.m.r. spectra were recorded at 80 MHz for solutions in [$^2H_6$]-dimethyl sulphoxide.

4-Amino-3-nitroacetanilide (**4a**).—Acetic anhydride (10.2 g, 0.1 mol) was added, with stirring, to a solution of 2-nitro-*p*-phenylenediamine (15.3 g, 0.1 ml) in acetic acid (150 mol) and the mixture set aside overnight. The crystalline product was filtered off, washed with water, and recrystallised from aqueous ethanol. The amide (**4a**) (11.6 g, 59%) had m.p. 187—189 °C (decomp.) (lit.,[2] 189 °C); $\nu_{max.}$ 3 430 (amide NH), 3 280—3 360 (multiplet; NH_2), 1 660 (CO), and 1 510 and 1 335 cm^{-1} (NO_2); δ_H 2.02 (3 H, s, Me), 7.00 (1 H, d, 5-H), 7.29 (2 H, br s, NH_2), 7.53 (1 H, dd, 6-H), 8.37 (1 H, d, 2-H), and 9.87 (1 H, br s, N*H*Ac); $J_{2,6}$ 2.2 Hz and $J_{5,6}$ 9 Hz.

N-(4-Amino-3-nitrophenyl)methanesulphonamide (**4b**).—Methanesulphonyl chloride (11.5 g, 0.1 mol) was added gradually over 3 min to a solution of 2-nitro-*p*-phenylenediamine (15.3 g) in pyridine (70 ml). The temperature of the mixture rose to *ca.* 70 °C; the solution was set aside for 10 min, and then heated under reflux for a further 15 min. The pyridine was evaporated under reduced pressure, and water added to the residue; the sulphonamide (**4b**) was filtered off, and recrystallised from ethanol (with charcoal); yield 14.6 g (63%), m.p. 166—168 °C (lit.,[3] 168—171 °C); $\nu_{max.}$ 3 480, 3 365, 3 240 (NH and NH_2), 1 515 and 1 345 (NO_2), and 1 310 and 1 140 cm^{-1} (SO_2); δ_H 3.00 (3 H, s, Me), 7.20 (1 H, d, 5-H), 7.50 (1 H, dd, 6-H), 7.55 (2 H, s, NH_2), 8.03 (1 H, d, 2-H), 9.60 (1 H, s, N*H*Ms); $J_{2,6}$ 2 Hz and $J_{5,6}$ 9 Hz.

Ethyl N-(4-Amino-3-nitrophenyl)carbamate (**4c**).—Pyridine (16.0 g, 0.2 mol) was added to a solution of 2-nitro-*p*-phenylenediamine (15.3 g) in acetonitrile (100 ml) and the mixture cooled to *ca.* 5 °C. Ethyl chloroformate (10.8 g, 0.1 mol) was added dropwise, with cooling and stirring, over *ca.* 30 min, and the mixture was allowed to warm to room temperature over a further 1 h. The solvent was evaporated under reduced pressure, the oily residue added to ice–water with vigorous stirring, and the solid product filtered off, washed with water, and recrystallised (twice) from aqueous ethanol (with charcoal), to give the carbamate (**4c**) (16.6 g, 74%), m.p. 129—130 °C (lit.,[3] 129—132 °C); $\nu_{max.}$ 3 320 (br, NH and NH_2), 1 680 (CO), and 1 540 and 1 340 cm^{-1} (NO_2); δ_H 1.28 (3 H, t, Me), 4.25 (2 H, q, CH_2), 7.11 (1 H, d, 5-H), 7.40 (2 H, br s, NH_2), 7.65 (1 H, dd, 6-H), 8.40 (1 H, d, 2-H), and 9.70 (1 H, s, N*H*CO_2Et); $J_{2,6}$ 2.2 Hz, $J_{5,6}$ 9.2 Hz, and $J_{CH_3-CH_2}$ 7 Hz.

4-Acetamido-N-cyanomethyl-2-nitroaniline (**5a**).—To 4-amino-3-nitroacetanilide (**4a**) (15 g, 74 mmol) were added, successively, paraformaldehyde (7.41 g, 0.247 mol CH_2O), potassium cyanide (15.34 g, 0.236 mol), zinc chloride (39.3 g, 0.29 mol), and acetic acid (400 ml) containing concentrated sulphuric acid (15 drops). The vigorously stirred mixture was heated to 50 °C over *ca.* 30 min, and kept at this temperature for 6 h. It was then added to crushed ice; the solid product was filtered off and washed well with water. The *nitrile* (**5a**) (14.4 g, 80%) had m.p. 228—229 °C (from acetic acid) (Found: C, 51.3; H, 4.3; N, 24.0. $C_{10}H_{10}N_4O_3$ requires C, 51.3; H, 4.3; N, 23.9%); $\nu_{max.}$ 3 390 and 3 350 (2 × NH), 2 245w (CN), 1 680 (CO), and 1 510 and 1 335 cm^{-1} (NO_2); δ_H 2.07 (3 H, s, Me), 4.60 (2 H, d, CH_2), 7.30 (1 H, d, 6-H), 7.95 (1 H, dd, 5-H), 8.30 (1 H, br t, N*H*CH_2), and 8.70 (1 H, d, 3-H); $J_{3,5}$ 2.8 Hz, $J_{5,6}$ 9.2 Hz, and $J_{CH_2,NH}$ 6 Hz.

N-Cyanomethyl-4-methanesulphonamido-2-nitroaniline (**5b**). This compound, m.p. 169—170 °C (from ethanol), was similarly obtained (yield 82%) from the sulphonamide (**4b**) (21.2 g) (Found: C, 40.1; H, 3.7; N, 20.6. $C_9H_{10}N_4O_4S$ requires C, 40.0; H, 3.7; N, 20.7%); $\nu_{max.}$ 3 370 and 3 270 (2 × NH), 2 250 w (CN), 1 525 and 1 335 (NO_2), 1 310 and 1 140 cm^{-1} (SO_2); δ_H 3.05 (3 H, s, Me), 4.65 (2 H, d, CH_2), 7.35 (1 H, d, 6-H), 7.75 (1 H, dd, 5-H), 8.20 (1 H, d, 3-H), 8.37 (1 H, br t, N*H*CH_2), and 9.5—10.0 (1 H, br, N*H*Ms); $J_{3,5}$ 2.8 Hz, $J_{5,6}$ 9.2 Hz, and $J_{CH_2,NH}$ 6 Hz.

N-Cyanomethyl-4-ethoxycarbonylamino-2-nitroaniline (**5c**). This compound, m.p. 194—195 °C (from acetic acid), was similarly prepared (8 h reaction time) from the carbamate (**4c**) (8.0 g) in 70% yield (Found: C. 50.1; H, 4.5; N, 21.2. $C_{11}H_{12}N_4O_4$ requires C, 50.0; H, 4.6; N, 21.2%); $\nu_{max.}$ 3 400 and 3 355 (2 × NH), 2 230vw (CN), 1 710 (CO), and 1 510 and 1 335 cm^{-1} (NO_2); δ_H 1.30 (3 H, t, Me), 4.25 (2 H, q, C*H*$_2$Me), 4.65 (2 H, d, C*H*$_2$NH), 7.30 (1 H, d, 6-H), 7.90 (1 H, dd, 5-H), 8.30 (1 H, br t, N*H*CH_2), 8.65 (1 H, d, 3-H), and 9.85 (1 H, s, N*H*CO_2Et); $J_{3,5}$ 2.6 Hz, $J_{5,6}$ 9.8 Hz, $J_{CH_2,NH}$ 6 Hz, and J_{Me,CH_2} 7 Hz.

5-Acetamido-2-cyano-1H-benzimidazole 3-Oxide (**6a**).—4-Acetamido-*N*-cyanomethyl-2-nitroaniline (**5a**) (7.0 g, 0.03 mol) was dissolved, as far as possible, in hot ethanol (320 ml). Potassium carbonate (4.1 g, 30 mmol) was added carefully, and the mixture heated under reflux for 45 min. Evaporation of the solvent under reduced pressure gave a solid which was dissolved as far as possible in water (300 ml). The solution was filtered, and the filtrate acidified (conc. HCl) with cooling and stirring. The colourless product was filtered off, washed with water, and recrystallised from aqueous ethanol. The *N-oxide* (**6a**) (4.6 g, 71%) had m.p. 233—234 °C (Found: C, 55.55; H, 3.7; N, 26.0. $C_{10}H_8N_4O_2$ requires C, 55.6; H, 3.7; N, 25.9%); $\nu_{max.}$ 3 320 (NHAc), 2 600br (NH/OH), 2 230 (CN), and 1 630 cm^{-1} (CO); δ_H 2.17 (3 H, s, Me), 7.53 (1 H, dd, 6-H), 7.91 (1 H, d, 7-H), 8.48 (1 H, d, 4-H), 10.40 (1-H, s, N*H*Ac), and 13.0—13.5 (1 H, br s, NH/OH); $J_{4,6}$ 2.0 Hz and $J_{6,7}$ 9.0 Hz.

2-Cyano-5-methanesulphonamido-1H-benzimidazole 3-oxide (**6b**). This compound, m.p. 223—224 °C (decomp.) (from aqueous ethanol), was similarly obtained (reaction time, 1 h; yield, 92%) from the sulphonamidonitrile (**5b**) (11.4 g) (Found: C, 42.8; H, 3.0; N, 22.3. $C_9H_8N_4O_3S$ requires C, 42.85; H, 3.2; N, 22.2%); $\nu_{max.}$ 3 300br (NH), 2 235 (CN), and 1 320 and 1 145 cm^{-1} (SO_2); δ_H 3.15 (3 H, s, Me), 7.45 (1 H, dd, 6-H), 7.65 (1 H, d, 4-H), 7.95 (1 H, d, 7-H), 10.35 (1 H, s, N*H*Ms); $J_{4,6}$ 2.0 Hz and $J_{6,7}$ 9.2 Hz.

2-Cyano-5-ethoxycarbonylamino-1H-benzimidazole 3-oxide (**6c**). This compound, m.p. 215—216 °C (decomp.) (from aqueous ethanol) was similarly obtained (reaction time, 1.5 h; yield, 84%) by cyclisation of the cyanocarbamate (**5c**) (8.3 g) (Found: C, 53.8; H, 4.0; N, 22.7. $C_{11}H_{10}N_4O_3$ requires C, 53.7; H, 4.1; N, 22.75%.) $\nu_{max.}$ 3 220 (NH-CO_2Et), 3 050br (NH/OH), 2 220 (CN), and 1 680 cm^{-1} (CO); δ 1.30 (3 H, t, Me), 4.30 (2 H, q, CH_2), 7.53 (1 H, dd, 6-H), 7.85 (1 H, d, 7-H), 8.12 (1 H, d, 4-H), 10.07 (1 H, s, N*H*-CO_2Et), 12.7—13.5 (1 H, br s, NH/OH); $J_{4,6}$ 2.0 Hz, $J_{6,7}$ 9.2 Hz, and J_{Me,CH_2} 7.0 Hz.

N-(4-Acetamido-2-nitrophenyl)glycine Ethyl Ester (**11a**).—4-Fluoro-3-nitroacetanilide (**10**), m.p. 140—141 °C (from aqueous ethanol, with charcoal; lit.,[9] 139 °C) was prepared in 89% yield by reaction of 4-fluoro-3-nitroaniline (15 g) with acetic anhydride (30 g) at 25 °C, and addition of the mixture to ice–water after 45 min. A suspension of the amide (**10**) (12.5 g, 63 mmol), glycine ethyl ester hydrochloride (9.7 g, 70 mmol), and sodium hydrogen carbonate (10.6 g, 0.126 mol) in dimethyl sulphoxide (40 ml) was stirred for 6 h at 60—65 °C; the mixture was then poured *very slowly*, with vigorous stirring, into ice–water (500 ml), and the red precipitate filtered off. Recrystallisation from ethanol gave the *ester* (**11a**) (8.83 g, 50%) as orange needles, m.p. 164—165 °C (Found: C, 51.5; H, 5.3; N, 14.9. $C_{12}H_{15}N_3O_5$ requires C, 51.2; H, 5.4; N, 14.9%); $\nu_{max.}$ 3 380 (NH), 1 725 and

1 685 (CO), and 1 525 and 1 320 cm^{-1} (NO_2); δ_H 1.23 (3 H, t, $MeCH_2$), 2.03 (3 H, s, *Me*CO), 4.16 (2 H, q, CH_2Me),* 4.20 (2 H, d, CH_2NH),* 6.88 (1 H, d, 6-H), 7.63 (1 H, dd, 5-H), 8.21 (1 H, br t, N*H*CH_2), 8.44 (1 H, d, 3-H), 10.05 (1 H, s, N*H*Ac); $J_{3,5}$ 2 Hz, $J_{5,6}$ 9 Hz, J_{MeCH_2} 7 Hz, and $J_{CH_2,NH}$ 5 Hz.

N-(5-*Amino*-2-*nitrophenyl*)*glycine Ethyl Ester* (**15**).—3-Fluoro-4-nitroaniline[1,5] (3.4 g, 22 mmol), glycine ethyl ester hydrochloride (4.2 g, 30 mmol), and sodium hydrogen carbonate (3.7 g, 44 mmol) were stirred in dimethyl sulphoxide (15 ml) for 4 h at 90—100 °C. The orange suspension was cooled and added to ice–water (200 ml), and the precipitate filtered off and recrystallised from aqueous ethanol to give the *ester* (**15**) (4.43 g, 85%), m.p. 123—127 °C (Found: C, 50.2; H, 5.5; N, 17.8. $C_{10}H_{13}N_3O_4$ requires C, 50.2; H, 5.5; N, 17.6%); $\nu_{max.}$ 3 580, 3 460, 3 330, and 3 220 (NH), 1 730 (CO), and 1 560 and 1 310 cm^{-1} (NO_2); δ_H 1.25 (3 H, t, Me), 4.09 (2 H, d, CH_2NH), 4.20 (2 H, q, CH_2Me), 5.69 (1 H, d, 6-H), 6.04 (1 H, dd, 4-H), 6.53 (2 H, br s, NH_2), 7.81 (1 H, d, 3-H), and 8.60 (1 H, t, N*H*CH_2); $J_{3,4}$ 9 Hz, $J_{4,6}$ 2 Hz, J_{CH_2Me} 7 Hz, and $J_{CH_2,NH}$ 5 Hz.

N-(5-*Amino*-2-*nitrophenyl*)*glycine*. (*a*) The foregoing ester (**15**) (0.24 g, 1.0 mmol), potassium carbonate (0.16 g, 1.1 mmol), and ethanol (15 ml) were heated together under reflux for 1 h. The yellow precipitate was filtered off and dissolved in water; acidification (HCl) gave the free acid (0.13 g, 62%).

(*b*)[10] 3-Fluoro-4-nitroaniline (0.75 g, 4.8 mmol), glycine (0.38 g. 5.1 mmol), sodium hydrogen carbonate (4.0 g), ethanol (30 ml), and water (10 ml) were heated together under reflux for 3 h. The solution was then concentrated under reduced pressure to *ca.* 10 ml, and acidified (HCl) to precipitate the acid (0.40 g, 40%).

N-(5-*Amino*-2-*nitrophenyl*)*glycine* had m.p. 210—214 °C (from aqueous ethanol) (Found: C, 45.6; H, 4.35; N, 19.6. $C_8H_9N_3O_4$ requires C, 45.5; H, 4.3; N, 19.9%); $\nu_{max.}$ 3 480 and 3 380 (NH), 1 725 (CO), and 1 555 and *ca.* 1 300 cm^{-1} (NO_2); δ_H 4.00 (2 H, d, CH_2), 5.70 (1 H, d, 6-H), 6.03 (1 H, dd, 4-H), 6.55 (2 H, br s, NH_2), 7.84 (1 H, d, 3-H), 8.59 (1 H, br t, N*H*CH_2); $J_{3,4}$ 9 Hz, $J_{4,6}$ 2 Hz, and $J_{CH_2,NH}$ 5 Hz.

N-(5-*Acetamido*-2-*nitrophenyl*)*glycine ethyl ester* (**11b**). This compound, m.p. 210—212 °C (from ethanol), was prepared by acetylation of the 5-amino analogue (**15**) (4 g) with acetic anhydride (8 g) at 100 °C for 30 min; it was isolated by adding the reaction mixture to ice–water (150 ml); yield, 3.89 g (83%) (Found: C, 51.4; H, 5.3; N, 14.9. $C_{12}H_{15}N_3O_5$ requires C, 51.2; H, 5.4; N, 14.9%); $\nu_{max.}$ 3 360, 3 340, 3 310sh (NH), 1 745 and 1 695 (CO), and 1 550 and 1 320 cm^{-1} (NO_2); δ_H 1.25 (3 H, t, *Me*-CH_2), 2.11 (3 H, s, *Me*CO), 4.15 (2 H, d, CH_2NH),* 4.19 (2 H, q, CH_2Me),* 6.86 (1 H, dd, 4-H), 7.29 (1 H, d, 6-H), 8.06 (1 H, d, 3-H), 8.49 (1 H, br t, N*H*CH_2), and 10.28 (1 H, s, N*H*Ac); $J_{3,4}$ 9 Hz, $J_{4,6}$ 2 Hz, $J_{CH_2,NH}$ 6 Hz, and J_{CH_2Me} 7 Hz.

Ethyl 5-*Acetamido*-1H-*benzimidazole*-2-*carboxylate* 3-*Oxide* (**12a**).—*N*-(4-Acetamido-2-nitrophenyl)glycine ethyl ester (**11a**) (8 g, 28 mmol), potassium carbonate (3.93 g, 28 mmol), and ethanol (300 ml) were heated together under reflux for 2 h (a precipitate was formed). The solvent was evaporated under reduced pressure, and the residue partitioned between water and dichloromethane; the aqueous layer was acidified (HCl) and the N-*oxide* (**12a**) filtered off. It had m.p. 133—134 °C (from aqueous ethanol); the yield was 4.84 g (61%) (Found: C, 51.2; H, 5.3; N, 15.0. $C_{12}H_{13}N_3O_4 \cdot H_2O$ requires C, 51.2; H, 5.4; N, 14.9%); $\nu_{max.}$ 3 360 (N*H*Ac), 3 300br (H_2O?), 2 650br (NH/OH), and 1 720 and 1 655 cm^{-1} (CO); δ_H 1.35 (3 H, t, *Me*CH_2), 2.10 (3 H, s, *Me*CO), 4.39 (2 H, q, CH_2), 7.26 (1 H, dd, 6-H), 7.64 (1 H, d, 7-H), 8.15 (1 H, d, 4-H), 10.15 (1 H, s, N*H*Ac), and 12.05 (1 H, br s, NH/OH); $J_{4,6}$ 2 Hz, $J_{6,7}$ 9 Hz, and $J_{CH_3CH_2}$ 7 Hz.

Ethyl 6-*acetamido*-1H-*benzimidazole*-2-*carboxylate* 3-*oxide* (**12b**). This compound, m.p. 198—200 °C (from dimethylformamide–water), was similarly obtained from the 5-acetamido analogue (**11b**) (3.5 g, 12 mmol) and potassium carbonate (1.72 g, 12 mmol) in ethanol (100 ml); yield 2.34 g (67%) (Found: C, 51.2; H, 5.3; N, 15.3. $C_{12}H_{13}N_3O_4 \cdot H_2O$ requires C, 51.2; H, 5.4; N, 14.9%); $\nu_{max.}$ 3 110—3 280br (N*H*Ac, NH/OH), and 1 705 and 1 660 cm^{-1} (CO); δ_H 1.36 (3 H, t, *Me*CH_2), 2.08 (3 H, s, *Me*CO), 4.40 (2 H, q, CH_2), 7.35—7.5 (2 H, m)† and 7.9—8.1 (1 H, m, ArH),† 10.01 (1 H, s, N*H*Ac), and 12.13 (1 H, br s, NH/OH).

Ethyl 5-*Amino*-1H-*benzimidazole*-2-*carboxylate* 3-*Oxide* (**14**).—A solution of ethyl 5-nitro-1*H*-benzimidazole-2-carboxylate 3-oxide (**13**)[1] (1.0 g) in ethanol (250 ml) was hydrogenated in presence of 5% palladium–charcoal (0.3 g). When the uptake of hydrogen was complete (15—20 min), the catalyst was filtered off and the filtrate concentrated under reduced pressure. The buff residue was recrystallised from ethyl acetate to give the *amino ester* (**14**) (0.55 g, 63%), m.p. 156—159 °C (Found: C, 54.8; H, 5.1; N, 18.5. $C_{10}H_{11}N_3O_3$ requires C, 54.3; H, 5.0; N, 19.0%); $\nu_{max.}$ 3 485 and 3 370 (NH_2), 2 600br (NH/OH), and 1 700 cm^{-1} (CO); δ_H 1.35 (3 H, t, Me), 4.38 (2 H, q, CH_2), 6.60 (1 H, d, 4-H), 6.72 (1 H, dd, 6-H), and 7.42 (1 H, d, 7-H); $J_{4,6}$ 2 Hz, $J_{6,7}$ 9 Hz, and J_{MeCH_2} 7.5 Hz; *m*/*z* 221 ($M^{+\cdot}$, 95%), 205 (32%), 175 (55%), 160 (40%), 159 (69%), 133 (45%), 132 (91%), 131 (100%), *etc.* Although a completely pure sample was not obtained, the amino ester appeared to darken on storage, and so was used immediately without further purification.

5-*Amino*-1H-*benzimidazole* 3-*Oxide Dihydrochloride* (**7**).—(a) *From the acetamido-ester* (**12a**). The ester (**12a**) (3 g, 10 mmol) and concentrated hydrochloric acid (25 ml) were heated together under reflux for 1.5 h. The colourless dihydrochloride (**7**) (1.86 g, 74%) crystallised from the cooled solution.

(b) *From the acetamido nitrile* (**6a**). The nitrile (2 g, 9 mmol) was similarly hydrolysed to give compound (**7**) (1.45 g, 71%).

(c) *From the amino ester* (**14**). The crude amino ester (0.2 g) and concentrated hydrochloric acid (10 ml) were heated together under reflux for 1 h. Cooling gave compound (**7**) (0.090 g), and concentration of the mother-liquor gave a further crop (0.070 g; total yield 80%).

The *dihydrochloride* (**7**) had m.p. 238 °C (decomp.) (from conc. HCl) (Found: C, 37.5; H, 4.1; N, 18.9. $C_7H_7N_3O \cdot 2HCl$ requires C, 37.9; H, 4.1; N, 18.9%); $\nu_{max.}$ 2 600 (v br; NH and OH); δ_H 7.51 (1 H, dd, 6-H), 7.79 (1 H, d, 4-H), 7.94 (1 H, d, 7-H), 9.90 (1 H, s, 2-H), and 10.63 (5 H, br s, $\overset{+}{N}H_3$, $\overset{+}{N}H$, OH); $J_{4,6}$ 2 Hz and $J_{6,7}$ 8.5 Hz.

5-*Amino*-1H-*benzimidazole* 3-*Oxide* (**1b**).—The dihydrochloride (**7**) (1.4 g, 6 mmol) was dissolved in aqueous ammonia (*d* 0.88; 10 ml) and the solution was immediately evaporated to dryness under reduced pressure. The residue was washed with a little water, filtered off, and recrystallised from water to give the colourless N-*oxide* (**1b**) (0.6 g, 57%), m.p. 97—98 °C (Found: C, 50.0; H, 5.5; N, 25.5. $C_7H_7N_3O \cdot H_2O$ requires C, 50.3; H, 5.4; N, 25.1%); $\nu_{max.}$ 3 430sh, 3 310, 3 320sh, 3 140, and 3 080 cm^{-1} (all broad); δ_H 5.65 (br s, $NH_2 + H_2O$), 6.45—6.63 (2 H, m),† 7.15—7.33 (1 H, m),† and 8.00 (1 H, s, 2-H); *m*/*z* 149 ($M^{+\cdot}$, 60%), 133 (100%), 132 (87%), 120 (20%), 106 (20%), and 105 (67%), *etc.*

5-*Methanesulphonamido*-1H-*benzimidazole* 3-*Oxide* (**9a**).—The sulphonamido nitrile (**6b**) (2 g) was hydrolysed with

* Overlapping signals.

† Not first-order spectrum.

concentrated hydrochloric acid as described above for compound (**12a**). No crystalline product was obtained on cooling the solution; the acid was distilled off under reduced pressure and the residue washed with warm ethanol (30 ml). The *hydrochloride* (**8a**) (1.18 g, 57%) showed $\nu_{max.}$ 3 100br (*NH*Ms), 2 625br (NH/OH), and 1 320 and 1 140 cm^{-1} (SO_2); δ_H 3.10 (3 H, s, Me), 7.48 (1 H, dd, 6-H), 7.69 (1 H, d, 4-H), 7.86 (1 H, d, 7-H), 9.82 (1 H, s, 2-H), and 10.32 (1 H, s, N*H*Ms). A sample recrystallised from a large volume of ethanol had m.p. 211—212 °C (Found: C, 36.5; H, 3.8; N, 15.95. $C_8H_9N_3O_3S$·HCl requires C, 36.4; H, 3.8; N, 15.9%). Reaction of the hydrochloride with ammonia, as described in the preceding paragraph, gave the *sulphonamido* N-*oxide* (**9a**), m.p. 220—222 °C (from ethanol) (Found: C, 42.6; H, 3.9; N, 18.6. $C_8H_9N_3O_3S$ requires C, 42.3; H, 4.0; N, 18.5%); $\nu_{max.}$ 3 215 (*NH*Ms), and 1 320 and 1 145 cm^{-1} (SO_2); δ_H 2.95 (3 H, s, Me), 7.09 (1 H, dd, 6-H), 7.39 (1 H, d, 4-H), 7.59 (1 H, d, 7-H), 8.31 (1 H, s, 2-H), 9.70 (1 H, s, N*H*Ms), 11.88 (1 H, br s, NH/OH); $J_{4,6}$ 2 Hz and $J_{6,7}$ 9 Hz.

Hydrolysis of the Cyano Carbamate (**6c**).—Compound (**6c**) (5.0 g) and concentrated hydrochloric acid (50 ml) were heated together under reflux for 2.5 h. 5-*Ethoxycarbonylamino*-1H-*benzimidazole* 3-*oxide hydrochloride* (**8b**) crystallised from the cooled solution. Recrystallised from ethanol, it had m.p. 210—211 °C (decomp.); yield 2.20 g (42%) (Found: C, 46.8; H. 4.7; N, 16.2. $C_{10}H_{11}N_3O_3$·HCl requires C, 46.6; H, 4.7; N, 16.3%); $\nu_{max.}$ 3 280, 3 200, 3 130 (NH), 2 600br ($\overset{+}{N}H$, OH), and 1 720 cm^{-1} (CO); δ_H 1.29 (3 H, t, Me), 4.19 (2 H, q, CH_2), 7.58 (1 H, dd, 6-H), 7.78 (1 H, d, 7-H), 8.11 (1 H, d, 4-H), 9.83 (1 H, s, 2-H), 10.13 (1 H, s, N*H*CO_2Et), and 12.78 (2 H, br s, NH/OH); $J_{4,6}$ 2 Hz, $J_{6,7}$ 9 Hz, and J_{MeCH_2} 7 Hz.

The reaction mother-liquor was concentrated under reduced pressure to *ca.* 10 ml, and cooled in ice. 5-Amino-1*H*-benzimidazole 3-oxide dihydrochloride (**7**) (1.57 g, 35%) crystallised out and was identified by comparison with an authentic sample.

Increasing the reaction time to 7 h increased the product ratio (**7**): (**8b**) but some decomposition also occurred and the products were therefore less easily isolated. A black tarry residue was also obtained.

5-*Ethoxycarbonylamino*-1H-*benzimidazole* 3-*Oxide* (**9b**).—The hydrochloride (**8b**) (1 g) was dissolved in aqueous ammonia (*d* 0.88; 10 ml), the solution was concentrated under reduced pressure until precipitation commenced, and the mixture was then cooled in ice and the product filtered off and washed with a little water. The N-*oxide* (**9b**) (0.44 g, 51%) had m.p. 205 °C (decomp.) (from ethanol) (Found: C, 54.3; H, 5.0; N, 18.8. $C_{10}H_{11}N_3O_3$ requires C, 54.3; H, 5.0; N, 19.0%) $\nu_{max.}$ 3 310 (NH), 2 300 br (NH/OH), and 1 700 cm^{-1} (CO); δ_H 1.28 (3 H, t, Me), 4.18 (2 H, q, CH_2), 7.22 (1 H, dd, 6-H), 7.54 (1 H, d, 7-H), 7.86 (1-H, d, 4-H), 8.28 (1 H, s, 2-H), and 9.71 (1 H, s, N*H*CO_2Et); $J_{4,6}$ 2 Hz, $J_{6,7}$ 8.5 Hz, and J_{MeCH_2} 7 Hz.

6-*Amino*-1H-*benzimidazole* 3-*Oxide* (**1c**).—The acetamido ester (**12b**) (4.3 g, 15 mmol) and concentrated hydrochloric acid (70 ml) were heated together under reflux for 3 h. The solution was evaporated to dryness under reduced pressure to give the *dihydrochloride* (**16**) (1.93 g, 57%), m.p. 255 °C (decomp.) (from hydrochloric acid, with charcoal) (Found: C, 37.8; H, 4.4; N, 19.2. $C_7H_7N_3O$·2HCl requires C, 37.9; H, 4.1; N, 18.9%); $\nu_{max.}$ 2 580 cm^{-1} (v br); δ_H 7.6—7.75 (1 H, m),* 7.9—8.13 (2 H, m),* 9.3 (br s, $\overset{+}{N}H$, OH, $\overset{+}{N}H_3$), and 9.96 (1 H, s, 2-H). The dihydrochloride (1.5 g) was added in small portions to aqueous ammonia (*d* 0.88; 15 ml) at 0—5 °C; the solution was evaporated to dryness under reduced pressure, and the residue washed with ice-cold water (20 ml). The buff N-*oxide* (**1c**) (0.86 g, 68%) had m.p. 185 °C (decomp.) (from water) (Found: C, 45.7; H, 5.9; N, 22.8. $C_7H_7N_3O$·2H_2O requires C, 45.4; H, 6.0; N, 22.7%); $\nu_{max.}$ 3 360, 3 160br, and 3 080 cm^{-1}; δ_H 4.8 (br s, NH_2, H_2O), 6.63—6.85 (2 H, m),* 7.15—7.35 (1 H, m),* and 8.20 (1 H, s, 2-H); *m/z* 149 ($M^{+\bullet}$, 67%), 133 (100%), 132 (47%), 121 (13%), 120 (13%), 106 (20%), and 105 (33%), *etc.*

1,5-*Dichloro*-2,4-*dinitrobenzene*.—This compound, m.p. 99—101 °C (from ethanol; lit.,[11] 103—104 °C), was prepared in 59% yield by nitration of *m*-dichlorobenzene.[11]

N-(5-*Amino*-2,4-*dinitrophenyl*)*glycine Ethyl Ester* (**19a**).—Aqueous ammonia (*d* 0.88; 200 ml) was added to 1,5-dichloro-2,4-dinitrobenzene (30 g) in ethanol (300 ml), and the mixture heated under reflux for 3 h. The yellow crystalline product was filtered off, washed with water and a little cold ethanol, and recrystallised from ethanol to give 5-chloro-2,4-dinitroaniline (19 g, 69%), m.p. 172—174 °C (lit.,[8] 178 °C). To a warm (60 °C) solution of this amine (10 g, 46 mmol) in dimethyl sulphoxide (40 ml) were added, with stirring, sodium hydrogen carbonate (7.7 g, 92 mmol) and glycine ethyl ester hydrochloride (6.5 g, 46 mmol). Stirring was continued while the mixture was heated to 100—110 °C over 20 min, and kept at this temperature until effervescence ceased (a further 20 min). When cooled, the mixture set solid; water was added, and the product filtered off, washed with water, and recrystallised from acetic acid. The *ester* (**19a**) had m.p. 179—180 °C; yield 8.8 g (67%) (Found: C, 42.6; H, 4.3; N, 19.8. $C_{10}H_{12}N_4O_6$ requires C, 42.3; H, 4.3; N, 19.7%); $\nu_{max.}$ 3 460 and 3 330 (NH), 1 735 (CO), and 1 510 and 1 315 cm^{-1} (NO_2); δ_H 1.25 (3 H, t, Me), 4.20 (2 H, d, CH_2NH),† 4.26 (2 H, q, CH_2Me),† 6.10 (1 H, s, 6-H), 7.90 (2 H, br s, NH_2), 8.60 (1 H, t, N*H*-CH_2), and 9.08 (1 H, s, 3-H); J_{MeCH_2} 7 Hz and J_{CH_2NH} 6 Hz.

N-(5-N,N-*Dimethylamino*-2,4-*dinitrophenyl*)*glycine ethyl ester* (**19b**). This compound was similarly obtained. 5-Chloro-*N*,*N*-dimethyl-2,4-dinitroaniline, m.p. 119—123 °C (from ethanol; lit.,[12] 129 °C) was prepared in 85% yield from 1,5-dichloro-2,4-dinitrobenzene and dimethylamine[12] and was converted into the ester (**19b**) in 42% yield by reaction with sodium hydrogen carbonate and glycine ethyl ester hydrochloride in dimethyl sulphoxide, initially for 30 min at 80 °C followed by 10 min at 95 °C. The *ester* (**19b**) had m.p. 190—191 °C (from acetic acid) (Found: C, 46.1; H, 5.0; N, 17.8. $C_{12}H_{16}N_4O_6$ requires C, 46.15; H, 5.2; N, 17.8%); $\nu_{max.}$ 3 340 (NH), 1 730 (CO), and 1 510 and 1 335 cm^{-1} (NO_2); δ_H 1.24 (3 H, t, *Me*CH_2), 2.93 (6 H, s, Me_2N), 4.22 (2 H, q, CH_2Me),† 4.32 (2 H, d, CH_2NH),† 5.92 (1 H, s, 6-H), and 8.66 (1 H, s, 3-H and 1 H, br t, NH);‡ J_{MeCH_2} 7 Hz and $J_{CH_2,NH}$ 5 Hz.

N,N-(4,6-*Dinitro*-1,3-*phenylene*)*bisglycine Diethyl Ester* (**20**).—To a solution of 1,5-dichloro-2,4-dinitrobenzene (9 g, 39 mmol) in dimethyl sulphoxide (45 ml) were added sodium hydrogen carbonate (13.1 g, 0.156 mol) and glycine ethyl ester hydrochloride (10.9 g, 78 mmol). The mixture was stirred and heated at 60 °C until effervescence had almost ceased (*ca.* 35 min); it was then heated to 90 °C and maintained at this temperature until no more carbon dioxide was evolved (a further 20 min). The mixture was then cooled, diluted with water, and filtered. The solid product was recrystallised from acetic acid to give the *diester* (**20**) (10.7 g, 76%) as bright yellow needles, m.p. 190—191 °C (Found: C, 45.5; H, 4.8; N, 15.1. $C_{14}H_{18}N_4O_8$ requires C, 45.4; H, 4.9; N, 15.1%); $\nu_{max.}$ 3 350

* Not first-order spectrum.

† Overlapping signals.

‡ Coincident chemical shifts.

(NH), 1 715 (CO), and 1 535 and 1 350 cm^{-1} (NO_2); δ 1.28 (6 H, t, 2 × Me), 4.22 (4 H, q, 2 × CH_2Me),* 4.30 (4 H, d, 2 × CH_2NH),* 5.74 (1 H, s, 2-H), 8.67 (2 H, br t, 2 × NH), and 8.98 (1 H, s, 5-H); J_{MeCH_2} 7 Hz and $J_{CH_2,NH}$ 5 Hz.

N,N′-*Biscyanomethyl*-4,6-*dinitrobenzene*-1,3-*diamine* (**21**).—Sodium carbonate (5.7 g, 68 mmol) and powdered aminoacetonitrile hydrochloride (3.15 g, 34 mmol) were added to a solution of 1,5-dichloro-2,4-dinitrobenzene (4.0 g, 17 mmol) in dimethyl sulphoxide (20 ml). The mixture was stirred and heated at 80—90 °C until effervescence ceased (*ca.* 40 min) and was then poured into ice–water (200 ml). The solid product was filtered off, washed with ethanol, and recrystallised from dimethylformamide–acetic acid (1:1) to give the *dinitrile* (**21**) (2.70 g, 58%), m.p. 274—276 °C (Found: C, 43.6; H, 2.9; N, 30.5. $C_{10}H_8N_6O_4$ requires C, 43.5; H, 2.9; N, 30.4%); $\nu_{max.}$ 3 340 (NH), 2 240w (CN), and 1 530 and 1 320 cm^{-1} (NO_2); δ_H 4.80 (4 H, d, 2 × CH_2), 6.30 (1 H, s, 2-H), 9.00 (2 H, t, 2 × NH), and 9.18 (1 H, s, 5-H); $J_{CH_2,NH}$ 7 Hz.

Attempted Cyclisations of Compounds (**19**)—(**21**).—(a) (**19a**) *With sodium ethoxide.* The ester (**19a**) (3 g, 10.5 mmol) in dimethylformamide (10 ml) was added slowly, with stirring, to a solution of sodium ethoxide (from sodium, 0.25 g, 10.8 mmol) in ethanol (200 ml). Precipitation of a yellow solid began almost immediately; when addition of the ester was complete, the mixture was stirred for 30 min, and the solid (2.1 g) filtered off and washed with ethanol. It was dissolved in water, and the solution acidified (HCl) to give only the starting ester (1.7 g), identical with an authentic sample.

(b) (**19b**) *With sodium ethoxide.* The dimethylamino ester (**19b**) (1 g, 2.8 mmol) in dimethylformamide (50 ml) and ethanol (25 ml) was treated dropwise, over 10 min, with sodium ethoxide solution [from sodium (0.074 g, 3.2 mmol) and ethanol (10 ml)]. The mixture was set aside overnight, then diluted with water (400 ml) and filtered; the filtrate was acidified (HCl), giving unchanged starting material (0.80 g).

(c) (**20**) *With sodium ethoxide.* The ethoxide solution [from sodium (0.23 g) and ethanol (10 ml)] was added dropwise over 10 min to a stirred solution of the diester (**20**) (3.52 g, 9.5 mmol) in dimethylformamide (50 ml) at 5—10 °C. The dark red solution was stirred at this temperature for 15 min after which it was evaporated under reduced pressure at 60 °C and the residue dissolved in water. Acidification (HCl) gave the starting diester (**20**) (2.0 g), identical with an authentic sample.

(d) (**21**) *With sodium hydride.* Sodium hydride (50% dispersion in oil; 0.36 g, 7.5 mmol) in dry dimethyl sulphoxide (5 ml) was added dropwise, with stirring and cooling, to the dinitrile (**21**) (1.0 g, 3.6 mmol) in the same solvent (10 ml) so that the temperature was maintained at 20—25 °C. When addition was complete (10 min) the dark red solution was kept at room temperature for a further 45 min and then added to ice–water (100 ml). The sticky black precipitate was filtered off, washed with water and ethanol, and recrystallised from aqueous dimethylformamide, to give the starting dinitrile (**21**) (0.27 g) as the only isolated product.

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