Some Novel Heterocyclic Systems Derived from 7-Amino-2,3-dihydro-8-nitro-1*H*-pyrrolo[1,2-*a*]benzimidazole and the Corresponding Diamine

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The preparation of 7-amino-2,3-dihydro-8-nitro-1*H*-pyrrolo[1,2-*a*]benzimidazole from 1,4-diacetamido-2,3-dinitrobenzene is described. Reaction of this compound with 2,5-dimethoxytetrahydrofuran produces 2,3-dihydro-8-nitro-7-*N*-pyrrolo-1*H*-pyrrolo[1,2-*a*]benzimidazole, which can be cyclised to produce two new heterocyclic ring systems, 9,10-dihydro-8*H*-pyrrolo[1,2-*a*]pyrrolo(1',2':1,2]imidazo[5,4-*f*]quinoxaline and 9,10-dihydro-8*H*-pyrrolo[2,1-*c*]pyrrolo[1',2':1,2]imidazo[4,5-*h*][1,2,4]benzotriazine. The corresponding diamine, 7,8-diamino-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]benzimidazole undergoes a variety of condensation reactions to produce several new heterocyclic systems, for example, with formic acid, 1,7,8,9-tetrahydroimidazo-[4,5-*e*]pyrrolo[2,1-*b*]benzimidazole is formed and with diacetyl, 9,10-dihydro-2,3-dimethyl-8*H*-pyrrolo-[1',2':1,2]imidazo[5,4-*f*]quinoxaline is obtained.

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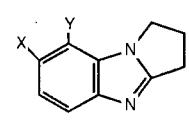
Previous unpublished work within this department has been concerned with the nucleophilic substitution reactions of 1,4-diacetamido- and 1,4-dimethoxy-2,3-dinitrobenzene and has shown that displacement of a nitro group occurs much more readily when bases (especially cyclic bases) rather than anions are employed as nucleophiles. 1,4-Diacetamido-2,3-dinitrobenzene, prepared by the method of Bhalla [1] could therefore be reacted with pyrrolidine to produce 1,4-diacetamido-2-nitro-3-*N*-pyrrolidinobenzene which cyclised with performic acid under the conditions used by Meth-Cohn and Suschitzky [2]. The resulting 7-acetamido-2,3-dihydro-8-nitro-1*H*-pyrrolo-[1,2-*a*]benzimidazole (**1**) was readily hydrolysed by methanolic potassium hydroxide to the corresponding nitroamine **2** which in turn was catalytically reduced to the diamine **3**. This new diamine was characterised by reaction with 9,10-phenanthraquinone.

An aromatic *o*-diamine can undergo a wide variety of condensation reactions resulting in production of various five-, six- and seven-membered heterocyclic systems. 7,8-Diamino-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]benzimidazole (**3**) reacted with formic and acetic acids to produce the corresponding imidazole compounds **4** and **5**, with nitrous acid to produce the triazole **6**, and with selenium dioxide to produce the selenadiazole **7**. Treatment of the diamine **3** with diacetyl and benzil produced the pyrazines, **8** and **9**. No products could be isolated from reaction of the diamine **3** with thionyl chloride, *o*-bromoanil, acetylacetone or cyclohexane-1,3-dione. Failure to react was considered, in most cases, to be due to the only moderate stability of **3** leading to decomposition caused by the prolonged reaction times which sometimes proved necessary.

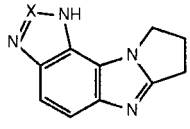
The work of Gross [3] was concerned with the formation of *N*-substituted pyrroles from reaction of aromatic amines



1 X = $NHCOCH_3$ Y = NO_2

2 X = NH_2 Y = NO_2

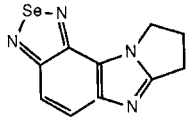
3 X = Y = NH_2



4 X = CH

5 X = C-CH_3

6 X = N



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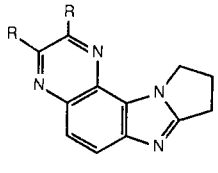
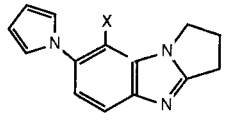


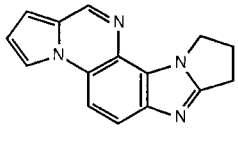
8 R = CH_3

9 R = C_6H_5



10 X = NO_2

11 X = NH_2



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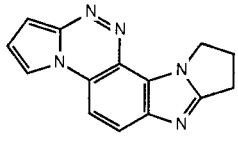

13

with 2,5-dipropoxytetrahydrofuran. The reaction with *o*-phenylenediamine was repeated by Cheeseman and Tuck [4] using 2,5-dimethoxy- or 2,5-diethoxytetrahydrofuran instead of the 2,5-dipropoxy compound and they went on to cyclise the *N*-(2-aminophenyl)pyrrole thus formed to give a pyrroloquinoxaline or a pyrrolobenzotriazine. As an extension of this work, the nitroamine **2** or diamine **3** was used as starting material. Reaction of 7,8-diamino-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]benzimidazole (**3**) with 2,5-dimethoxytetrahydrofuran produced no identifiable product but 7-amino-2,3-dihydro-8-nitro-1*H*-pyrrolo[1,2-*a*]-benzimidazole reacted readily to yield **10** which was catalytically reduced to give the amino derivative **11**. This, on treatment with formic acid, gave 9,10-dihydro-8*H*-pyrrolo[1,2-*a*]pyrrolo[1′,2′:1,2]imidazo[5,4-*f*]quinoxaline (**12**) in 88% yield, whilst treatment with nitrous acid gave, in moderate yield (28%), 9,10-dihydro-8*H*-pyrrolo[2,1-*c*]-pyrrolo[1′,2′:1,2]imidazo[4,5-*h*][1,2,4]benzotriazine (**13**).

In an attempt to produce isomeric forms of **12** and **13**, interchange of the nitro and amino groups **2** was considered. The amino group could not be protected by the formation of a Schiff's base but a phthalimido derivative was obtained from reaction of **2** with phthalic anhydride. However, the nitro group in this molecule could not be reduced.

Other routes to isomeric forms of **12** and **13** are currently under investigation.

EXPERIMENTAL

Melting points were determined with a Reichert hot-stage microscope and are uncorrected. The nmr spectra were recorded with a Jeol C-60 HL spectrometer in the indicated solvents using TMS as an internal standard and unless otherwise indicated were run at room temperature.

Elemental analyses were carried out by CHN Analysis Ltd., South Wigston, Leicestershire.

1,4-Diacetamido-2,3-dinitrobenzene.

This was prepared by Bhalla's modification of the method of Pfeiffer and Case [5] *viz.* the treatment of 1,4-diacetamidobenzene with a mixture of fuming nitric acid and glacial acetic acid. However, when attempts were made to increase the scale of the reaction it was found preferable to use 1,4-diacetamidobenzene prepared by the acetylation of *p*-amino-acetanilide rather than *p*-phenylenediamine since the former gave a much purer product which was considerably easier to nitrate on a larger scale. Typically, 125 g of 1,4-diacetamidobenzene gave 104 g (49%) of 1,4-diacetamido-2,3-dinitrobenzene.

1,4-Diacetamido-2-nitro-3-*N*-pyrrolidinobenzene.

1,4-Diacetamido-2,3-dinitrobenzene (5.0 g, 0.0177 mole) was heated with pyrrolidine (5 ml, 0.60 mole) and chloroform under reflux on a water bath until all the solid had dissolved (15-25 hours). The solution was evaporated under vacuum leaving a black tar. This was boiled with benzene and the solution decanted; on cooling, a dark crystalline mass was obtained. This was recrystallised from benzene (charcoal) to give 1,4-diacetamido-2-nitro-3-*N*-pyrrolidinobenzene (4.2 g, 77%) as yellow crystals, mp 186°; ^{1}H nmr (deuteriochloroform): δ 8.55 (1H, d, J = 10.5 Hz), 8.30 (1H, broad peak, exchanged with deuterium oxide), 7.98 (1H, broad peak, exchanged with deuterium oxide), 7.93 (1H, d, J = 10.5 Hz), 3.16 (4H, t), 2.24, 2.20 (6H, overlapping singlets), 2.02 (4H, t).

Anal. Calcd. for $C_{14}H_{18}N_4O_4$: C, 54.90; H, 5.88; N, 18.30. Found: C, 55.0; H, 6.0; N, 18.4.

7-Acetamido-2,3-dihydro-8-nitro-1*H*-pyrrolo[1,2-*a*]benzimidazole (**1**).

To 1,4-diacetamido-2-nitro-3-*N*-pyrrolidinobenzene (20.0 g, 0.065 mole) in a 1 litre round-bottom flask was added formic acid (100 ml, 98%) and hydrogen peroxide (60 ml, 100 vol). The mixture was heated cautiously under a wide-necked condenser on a water bath until a vigorous reaction commenced, at which point the heating was discontinued. After the reaction had subsided (5-10 minutes), the reaction mixture was cooled, poured into water (500 ml) and neutralised with excess sodium carbonate. The yellow-orange precipitate was filtered off, washed well with water and dried, yield 10.8 g (64%). Crystallisation from benzene/petroleum ether (bp 60-80°) gave light yellow needles of compound **1**, mp 211-213°; ^{1}H nmr (deuteriochloroform): δ 10.05 (1H, broad singlet exchanged with deuterium oxide), 8.35 (1H, d, J = 10.5 Hz), 7.87 (1H, d, J = 10.5 Hz), 4.41 (2H, t), 3.4-2.2 (4H, m), 2.30 (3H, s).

Anal. Calcd. for $C_{12}H_{12}N_4O_3$: C, 55.30; H, 4.62; N, 21.54. Found: C, 55.2; H, 4.6; N, 21.5.

7-Amino-2,3-dihydro-8-nitro-1*H*-pyrrolo[1,2-*a*]benzimidazole (**2**).

(Claisens alkali was prepared by dissolving potassium hydroxide (17.6 g) in water (12.6 ml) and diluting to 50 ml with methanol).

7-Acetamido-2,3-dihydro-8-nitro-1*H*-pyrrolo[1,2-*a*]benzimidazole (**1**) (2.0 g, 0.0092 mole) and Claisens alkali (3 ml) were warmed on a steam bath for 15 minutes. Warm water (3 ml) was then added and the mixture digested for a further 15 minutes. After cooling, the mass of deep red crystals was filtered off, washed with water and dried, yield 1.36 g (81%). After being recrystallised several times from methanol, compound **2** was obtained as orange needles, mp 220-221°; ^{1}H nmr (trifluoroacetic acid): δ 7.83 (1H, d, J = 10.5 Hz), 7.26 (1H, d, J = 10.5 Hz), 4.98 (2H, t), 3.50 (2H, t), 1.95 (2H, m).

Anal. Calcd. for $C_{10}H_{10}N_4O_2$: C, 55.05; H, 4.59; N, 25.69. Found: C, 54.9; H, 4.6; N, 25.8.

7,8-Diamino-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]benzimidazole (**3**).

To 7-amino-2,3-dihydro-8-nitro-1*H*-pyrrolo[1,2-*a*]benzimidazole (**2**) (5.0 g, 0.023 mole) in ethanol was added palladium on charcoal (5%, 0.1 g). The solution was then heated to approximately 50° when hydrazine hydrate (5.0 ml) was slowly added. The solution was then refluxed gently with stirring until the red colour had disappeared. If, after 2-3 hours, the colour still remained, further catalyst (0.1 g) was added and the heating continued. The catalyst was filtered from the hot solution which was then cooled to yield small white crystals of compound **3** (2.2 g). On evaporation of the solution a further 1.8 g of less pure material was obtained. Total yield was 4.0 g (93%), mp >150° dec; ^{1}H nmr (DMSO-d_6): δ 6.77 (1H, d, J = 10.0 Hz), 6.55 (1H, d, J = 10.0 Hz), 4.36 (2H, t), 3.60 (4H, broad peak exchanged with deuterium oxide) 2.55 (4H, m).

14,15-Dihydro-13*H*-dibenzo[*a*,*c*]pyrrolo[1′,2′:1,2]imidazo[5,4-*h*]phenazine.

7,8-Diamino-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]benzimidazole (**3**) (6.0 g, 0.032 mole) was heated under reflux with 9,10-phenanthraquinone (5.7 g, 0.032 mole) in ethanol (100 ml). The cooled solution was poured into water (400 ml) and the yellow product filtered off, washed with water and dried, yield 9.3 g (81%). Crystallisation from glacial acetic acid gave 14,15-dihydro-13*H*-dibenzo[*a*,*c*]pyrrolo[1′,2′:1,2]imidazo[5,4-*h*]phenazine as small yellow crystals, mp >306°; ^{1}H nmr (trifluoroacetic acid): δ 9.6-7.8 (10H, m), 5.47 (2H, t), 3.60 (4H, m).

Anal. Calcd. for $C_{24}H_{16}N_4$: C, 80.00; H, 4.44; N, 15.56. Found: C, 79.7; H, 4.4; N, 15.3.

1,7,8,9-Tetrahydroimidazo[4,5-*e*]pyrrolo[2,1-*b*]benzimidazole (**4**).

7,8-Diamino-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]benzimidazole (**3**) (7.0 g, 0.037 mole) was refluxed with formic acid (98%, 25 ml) for one hour. The cooled solution was poured into cold water (100 ml) and neutralised with sodium bicarbonate. The white precipitate was filtered off, washed with water and dried, yield 7.0 g (95%). On recrystallisation from water it gave white needles of the monohydrate of compound **4**, mp 288.5-290° (with sublimation); ^{1}H nmr (perdeuteriomethanol): δ 8.21 (1H, s), 7.60 (1H, d, J

= 10.5 Hz), 7.42 (1H, d, J = 10.5 Hz), 4.43 (2H, t), 2.75 (4H, m).

Anal. Calcd. for $C_{11}H_{10}N_4 \cdot H_2O$: C, 61.09; H, 5.60; N, 25.67. Found: C, 61.3; H, 5.5; N, 25.7.

1,7,8,9-Tetrahydro-2-methylimidazo[4,5-*e*]pyrrolo[2,1-*b*]benzimidazole (**5**).

7,8-Diamino-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]benzimidazole (**3**) (5.0 g, 0.027 mole) was refluxed with glacial acetic acid for 45 minutes. After cooling, the solution was carefully neutralised with ammonia solution. The white precipitate was filtered off, washed with water and recrystallised from water (*ca.* 400 ml) to give compound **5** as white needles, (4.3 g, 75%) mp 270-290° dec; ^{1}H nmr (perdeuteriomethanol): δ 7.55 (1H, d, J = 10.5 Hz), 7.35 (1H, d, J = 10.5 Hz), 4.42 (2H, t), 2.92 (4H, m), 2.64 (3H, s).

Anal. Calcd. for $C_{12}H_{12}N_4$: C, 67.90; H, 5.70; N, 26.40. Found: C, 67.6; H, 5.7; N, 26.6.

1,7,8,9-Tetrahydrotriazolo[4,5-*a*]pyrrolo[2,1-*b*]benzimidazole (**6**).

To a solution of 7,8-diamino-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]benzimidazole (**3**) (6.0 g, 0.032 mole) in a mixture of glacial acetic acid (7.5 ml) and water (15 ml) was added a solution of sodium nitrite (2.15 g) in water (6 ml). The resulting warm solution was cooled and carefully neutralised with dilute ammonia solution. The pale yellow precipitate was filtered off, washed with warm water and dried, yield 5.4 g (84%). After recrystallisation from water compound **6** was obtained as colourless needles, mp 309° dec; ^{1}H nmr (perdeuteriomethanol): δ 80°, 7.93 (1H, d, J = 10.5 Hz), 7.69 (1H, d, J = 10.5 Hz), 4.65 (2H, t), 2.83 (4H, m).

Anal. Calcd. for $C_{10}H_9N_5 \cdot \frac{1}{2}H_2O$: C, 57.68; H, 4.84; N, 33.64. Found: C, 57.5; H, 4.5; N, 34.0.

8,9-Dihydro-7*H*-pyrrolo[1′,2′:1,2]imidazo[5,4-*e*]benzoselenadiazole (**7**).

7,8-Diamino-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]benzimidazole (**3**) (5.0 g, 0.027 mole) in dilute hydrochloric acid (2*M*, 50 ml) was added with stirring to a solution of selenium dioxide (3.0 g, 0.027 mole) in water (20 ml). The cream precipitate which formed in quantitative yield was filtered off and crystallised from water to give the monohydrate of compound (**7**) as yellow needles, mp 190-270° dec; ^{1}H nmr (DMSO-d_6): 7.81 (1H, d, J = 10.0 Hz), 7.49 (1H, d, J = 10.0 Hz), 7.49 (1H, d, J = 10.0 Hz), 4.46 (2H, t), 2.90 (multiplet overlapped by solvent and water signals).

Anal. Calcd. for $C_{10}H_8N_4Se \cdot H_2O$: C, 42.71; H, 3.58; N, 19.92. Found: C, 42.7; H, 3.0; N, 20.1.

9,10-Dihydro-2,3-dimethyl-8*H*-pyrrolo[1′,2′:1,2]imidazo[5,4-*f*]quinoxaline (**8**).

7,8-Diamino-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]benzimidazole (**3**) (1.2 g, 0.0064 mole) was heated under reflux with diacetyl (0.75 ml, 0.0085 mole) in ethanol (25 ml) for one hour. The cooled solution was poured into water (100 ml) and the resulting white product filtered off, washed with water and dried, yield 1.4 g (93%). Recrystallisation from ethanol gave compound **8** as white needles, mp 185-187° (with sublimation); ^{1}H nmr (DMSO-d_6): δ 7.93 (1H, d, J = 10.5 Hz), 7.69 (1H, d, J = 10.5 Hz), 4.65 (2H, t), 3.10 (4H, m), 2.83 (6H, s).

Anal. Calcd. for $C_{14}H_{14}N_4$: C, 70.59; H, 5.88; N, 23.53. Found: C, 70.5; H, 5.9; N, 23.6.

9,10-Dihydro-2,3-diphenyl-8*H*-pyrrolo[1′,2′:1,2]imidazo[5,4-*f*]quinoxaline (**9**).

7,8-Diamino-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]benzimidazole (**3**) (1.0 g, 0.005 mole) was heated under reflux for 20 minutes with benzil (1.2 g, 0.0057 mole) in ethanol (30 ml). The cooled solution was poured into water and the resulting white precipitate filtered off and crystallised from aqueous acetic acid to give compound **9** as white needles (1.5 g, 78%), mp 265-267°; ^{1}H nmr (DMSO-d_6): δ 160°, 8.10 (1H, d, J = 10.0 Hz), 7.93-7.15 (11H, overlapping signals), 4.70 (2H, t), 3.10 (4H, m).

Anal. Calcd. for $C_{24}H_{18}N_4$: C, 79.56; H, 4.97; N, 15.47. Found: C, 79.6; H, 5.0; N, 15.6.

2,3-Dihydro-8-nitro-7-*N*-pyrrolo-1*H*-pyrrolo[1,2-*a*]benzimidazole (**10**).

7-Amino-2,3-dihydro-8-nitro-1*H*-pyrrolo[1,2-*a*]benzimidazole (**2**) (8.7 g, 0.04 mole) was refluxed with 2,5-dimethoxytetrahydrofuran (5.3 g, 0.04 mole) in glacial acetic acid (50 ml) for 15 minutes. The cooled solution was poured with stirring into cold water (150 ml) whereupon the product was precipitated as a yellow solid which rapidly became red. This solid was filtered off, washed with water and crystallised from methanol (charcoal) to give dark red needles, 8.3 g (78%). After further recrystallisation compound **10** was obtained as yellow needles, mp 186-187°, which darken on exposure to light for several hours; ^{1}H nmr (deuteriochloroform): δ 7.90-6.20 (6H, overlapping signals), 4.70-4.05 (2H, m), 3.35-2.40 (4H, m).

Anal. Calcd. for $C_{14}H_{12}N_4O_2$: C, 62.69; H, 4.48; N, 20.90. Found: C, 62.6; H, 4.5; N, 20.9.

8-Amino-2,3-dihydro-7-*N*-pyrrolo-1*H*-pyrrolo[1,2-*a*]benzimidazole (**11**).

2,3-Dihydro-8-nitro-7-*N*-pyrrolo-1*H*-pyrrolo[1,2-*a*]benzimidazole (**10**) (1.0 g, 0.0037 mole) in ethanol (25 ml) at 50° was treated with hydrazine hydrate (1 ml) and palladium on charcoal (0.1 g, 5%). The solution was refluxed with stirring until the red colour disappeared (1-2 hours). The solution was filtered hot and evaporated to give a white solid, yield 0.80 g (91%). Crystallisation from aqueous ethanol gave compound (**11**) as off-white needles, mp 166-167°; ^{1}H nmr (deuteriochloroform): δ 7.25-6.20 (6H, overlapping signals), 4.31 (2H, t), 3.65 (2H, broad peak, exchanges with deuterium oxide), 2.65 (4H, m).

Anal. Calcd. for $C_{14}N_{14}N_4$: C, 70.59; H, 5.88; N, 23.53. Found: C, 70.5; H, 5.9; N, 23.4.

9,10-Dihydro-8*H*-pyrrolo[1,2-*a*]pyrrolo[1′,2′:1,2]imidazo[5,4-*f*]quinoxaline (**12**).

8-Amino-2,3-dihydro-7-*N*-pyrrolo-1*H*-pyrrolo[1,2-*a*]benzimidazole (**11**) (5.2 g, 0.022 mole) was refluxed for 10 minutes with formic acid (17 ml, 90%). The cooled solution was poured into water (50 ml). A solution of sodium hydroxide (17.0 g) in water (65 ml) was then added with cooling. Compound **12** was filtered off as an off-white solid (4.8 g, 88%). After recrystallisation from toluene/petroleum ether (bp 100-120°) it gave small white crystals, mp 270°; ^{1}H nmr (deuteriochloroform): δ 8.68 (1H, s), 7.84 (1H, t), 7.74 (1H, d, J = 10.0 Hz), 7.54 (1H, d, J = 10.0 Hz), 6.84, 6.80 (2H, 2 x s), 4.51 (2H, t), 3.85 (4H, m).

Anal. Calcd. for $C_{15}H_{12}N_4$: C, 72.58; H, 4.84; N, 22.58. Found: C, 72.4; H, 4.9; N, 22.7.

9,10-Dihydro-8*H*-pyrrolo[2,1-*c*]pyrrolo[1′,2′:1,2]imidazo[4,5-*h*][1,2,4]benzotriazine (**13**).

8-Amino-2,3-dihydro-7-*N*-pyrrolo[1,2-*a*]benzimidazole (**11**) (2.38 g, 0.01 mole) in hydrochloric acid (15 ml, 20% v/v), cooled in ice, was treated with a solution of sodium nitrite (0.76 g) in water (3 cm^3) added dropwise over 30 minutes to the stirred suspension. On completion of the addition the mixture was allowed to stand for 15 minutes and then made alkaline with a slight excess of dilute sodium hydroxide solution. The dark precipitate was filtered off, washed with water and dried. The crude product was dissolved in chloroform and passed through a neutral alumina column (15 cm x 2 cm), the leading yellow band being collected. After evaporation of the chloroform, the product was crystallised from methanol to give compound **13** (0.7 g, 28%) as yellow needles, mp 292-293°; ^{1}H nmr (deuteriochloroform): δ 8.01-7.01 (5H, overlapping signals), 4.70 (2H, t), 1.0 (4H, m).

Anal. Calcd. for $C_{14}H_{11}N_5$: C, 67.47; H, 4.42; N, 28.11. Found: C, 67.4; H, 4.4; N, 28.2.

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