Synthesis of [1]Benzofuro[3,2-*g*]pyrrolo[1,2-*a*]quinoxalines and Related Compounds

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As part of our continuing work on the synthesis of condensed polycyclic systems (including evaluation of their biological properties such as their antineoplastic activity), we now describe the synthesis of [1]benzofuro[3,2-*g*]pyrrolo[1,2-*a*]quinoxalines and [1]benzofuro[2,3-*g*]pyrrolo[2,1-*c*][1,2,4]benzotriazine. Other authors[1-6] have shown that 1-arylpyrroles can be used in intramolecular cyclisation reactions. We report examples of the use of 2-nitro-3-(1-pyrrolyl)-dibenzofuran (**2**) in the synthesis of new pentacyclic systems. The starting material, 3-amino-2-nitrodibenzofuran (**1**), is obtained by a five-step synthesis starting from dibenzofuran[7,8,9]. Treatment of 3-amino-2-nitrodibenzofuran (**1**) with 2,5-dimethoxytetrahydrofuran[10,11] affords 2-nitro-3-(1-pyrrolyl)-dibenzofuran (**2**) which is reduced to 2-amino-3-(1-pyrrolyl)-dibenzofuran (**3**) by catalytic hydrogenation. [1]Benzofuro[3,2-*g*]pyrrolo[1,2-*a*]quinoxaline (**5a**) is prepared in high yield by refluxing amino compound **3** with formic acid; the presumable *N*-formyl intermediate is cyclised under these conditions. Treatment of compound **3** with acetic anhydride or benzoyl chloride under standard conditions gives the *N*-acyl derivatives **4b** and **4c**, respectively. These compounds are cyclised to quinoxalines **5b** and **5c** by treatment with boiling phosphoryl chloride. Compound **3** undergoes cyclocondensation with benzaldehyde in ethanol to give the 4-phenyl-4,5-dihydro derivative **6**. Reaction of compound **3** with phosgene in hot toluene affords the 4-oxo-4,5-dihydro derivative **7** which is converted into the 4-chloro derivative **8** by treatment with phosphoryl chloride in pyridine. The Cl-atom of **8** exhibits the expected reactivity towards nucleophilic reagents such as methanolic sodium methoxide and ethanolic sodium ethoxide to give the 4-methoxy (**9a**) and 4-ethoxy derivative (**9d**), respectively. Substitution of the Cl-atom in **8** by

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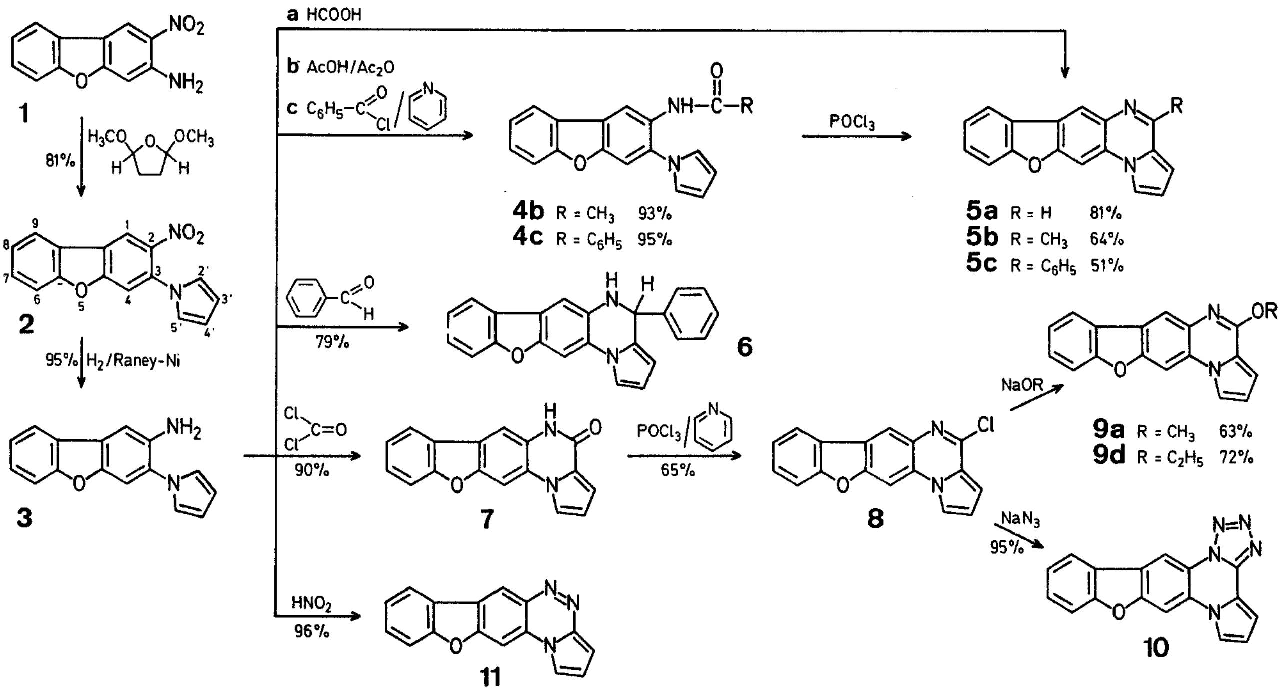

reaction with sodium azide affords the tetrazolo compound **10**. Further, compound **3** is converted into [1]benzofuro[2,3-g]pyrrolo[2,1-*c*][1,2,4]benzotriazine (**11**) by treatment with aqueous nitrous acid. Further reactions, chemical properties, and synthesis of other isomers are under investigation.

All melting points are uncorrected and were determined on a block Maquenne apparatus. The I.R. spectra were recorded on a Perkin Elmer 157 G spectrophotometer, the ^{1}H-N.M.R. spectra on a Varian E.M. 360 spectrometer (TMS as internal standard) (except for compounds **5a, b, c, 7, 8, 9a, d, 10, 11** which are insoluble in the standard solvents), and the mass spectra on Varian MAT CH 5 spectrometer.

2-Nitro-3-(1-pyrrolyl)-dibenzofuran (2):

A mixture of 2,5-dimethoxytetrahydrofuran (7.92 g) and 3-amino-2-nitrodibenzofuran (**1**; 13.62 g) in acetic acid (300 ml) is heated at reflux temperature for 1 h and then evaporated in vacuo. The residue is triturated with ether and product **2** isolated by suction; yield: 14.1 g (81%); m.p. 137–138° (from ether).

$C_{16}H_{10}N_2O_3$	calc.	C 69.06	H 3.62	N 10.07
(278.3)	found	69.23	3.49	10.03

I.R. (KBr): ν_{max} = 1630, 1600, 1520, 1330, 1180, 720 cm^{-1}.

^{1}H-N.M.R. (60 MHz, DMSO-d_6): δ = 8.96 (s, 1H, 1-H); 7.96–7.63 (m, 5H, 4-H, 6-H, 7-H, 8-H, 9-H); 7.03 (m, 2H, 2′-H, 5′-H); 6.33 ppm (m, 2H, 3′-H, 4′-H).

2-Amino-3-(1-pyrrolyl)-dibenzofuran (3):

A solution of 2-nitro-3-(1-pyrrolyl)-dibenzofuran (**2**; 4 g) in ethanol (250 ml) is hydrogenated under pressure (50 atm) at 100° over Raney nickel (1 g) for 2 h in a steel bomb. After cooling, Raney nickel is filtered off and ethanol evaporated in vacuo. The residue is triturated with petroleum ether and product **3** isolated by suction. Yield: 3.4 g (95%); m.p. 91–92° (from ether).

$C_{16}H_{12}N_2O$	calc.	C 77.40	H 4.87	N 11.28
(248.3)	found	77.22	4.96	11.25

I.R. (KBr): ν_{max} = 3405, 3320 (NH), 1625, 1600, 1585, 1545, 1175, 855, 745 cm^{-1}.

^{1}H-N.M.R. (60 MHz, DMSO-d_6): δ = 7.96–7.3 (m, 6H, 1-H, 4-H, 6-H, 7-H, 8-H, 9-H); 7.05 (m, 2H, 2′-H, 5′-H); 6.33 (m, 2H, 3′-H, 4′-H); 4.76–4.65 ppm (2H, NH_2).

2-Acetylamino-3-(1-pyrrolyl)-dibenzofuran (4b):

A solution of 2-amino-3-(1-pyrrolyl)-dibenzofuran (**3**; 1 g) in acetic acid (10 ml)/acetic anhydride (2 ml) is stirred at room temperature for 1 h. Ice/water (100 g) is added, the precipitate is isolated by suction, washed thoroughly with water, and dried; yield: 1.1 g (93%); m.p. 254–255° (from acetone).

$C_{18}H_{14}N_2O_2$	calc.	C 74.47	H 4.86	N 9.65
(290.3)	found	74.28	4.85	9.54

I.R. (KBr): ν_{max} = 3240 (NH), 1665 (C O), 1590, 1530, 1485, 1460, 1430, 1060, 740 cm^{-1}.

^{1}H-N.M.R. (60 MHz, DMSO-d_6): δ = 8.06–7.5 (m, 6H, 1-H, 4-H, 6-H, 7-H, 8-H, 9-H); 7.00 (m, 2-H, 2′-H, 5′-H); 6.21 (m, 2H, 3′-H, 4′-H); 1.95 (3H, CH_3); 9.4 ppm (1H, NH).

2-Benzoylamino-3-(1-pyrrolyl)-dibenzofuran (4c):

Benzoyl chloride (0.7 g) is carefully added to a stirred ice-cold solution of 2-amino-3-(1-pyrrolyl)-dibenzofuran (**3**; 1.24 g) in pyridine (10 ml). The mixture is stirred at room temperature for 1 h, and ice-cold water (100 ml) is then added; the precipitate formed is isolated by suction, washed thoroughly with water, and dried; yield: 0.94 g (95%); m.p. 162–163° (from acetone).

$C_{23}H_{16}N_2O_2$	calc.	C 78.39	H 4.58	N 7.95
(352.4)	found	78.26	4.70	7.81

I.R. (KBr): ν_{max} = 3400 (NH), 1660 (C O), 1600, 1170, 750, 710 cm^{-1}.

^{1}H-N.M.R. (60 MHz, DMSO-d_6): δ = 8.43–7.2 (m, 11H, 1-H, 4-H, 6-H, 7-H, 8-H, 9-H, C_6H_5); 7.11 (m, 2H, 2′-H, 5′-H); 6.21 (m, 2H, 3′-H, 4′-H); 10.0 ppm (1H, NH).

[1]Benzofuro[3,2-*g*]pyrrolo[1,2-*a*]quinoxaline (5a):

A mixture of 2-amino-3-(1-pyrrolyl)-dibenzofuran (**3**; 1 g) and 90% formic acid (20 ml) is heated under reflux for 10 min with stirring, and then allowed to cool. Ice/water (100 g) is added followed by the addition of 20% aqueous sodium hydroxide (10 ml). The precipitate is collected by suction, washed with water, and dried; yield: 0.9 g (85%); m.p. 303–304° (from acetone).

$C_{17}H_{10}N_2O$	calc.	C 79.05	H 3.90	N 10.83
(258.26)	found	78.83	4.01	10.64

M.S. (70 eV): m/e = 258 ($M^{+\cdot}$, 100%), 257 (M − H,4), 231 (M − HCN,2), 204 (M − $C_2H_2N_2$,2).

I.R. (KBr): ν_{max} = 1635, 1600, 1580, 1545, 1430, 1330, 1195, 750, 735, 720 cm^{-1}.

4-Methyl[1]benzofuro[3,2-*g*]pyrrolo[1,2-*a*]quinoxaline (5b):

A mixture of 2-acetylamino-3-(1-pyrrolyl)-dibenzofuran (**4b**; 0.5 g) and phosphoryl chloride (10 ml) is heated under reflux with stirring for 15 min and then evaporated in vacuo. Water (100 ml) is added to the residue, followed by the addition of 20% aqueous sodium hydroxide (10 ml). The crude product is isolated by suction, washed with water, dried, and extracted with acetone. The solution is boiled with some charcoal, filtered, and evaporated; yield: 0.3 g (64%); m.p. 221–222° (sublimation in vacuo).

$C_{18}H_{12}N_2O$	calc.	C 79.39	H 4.44	N 10.29
(272.3)	found	79.25	4.55	10.16

M.S. (70 eV): $m/e = 272$ ($M^{+\cdot}$, 100%), 271 (M – H,15), 257 (M – CH_3,1), 245 (M – HCN, 2), 244 (6), 230 (2).

I.R. (KBr): $\nu_{max} = 1630, 1600, 1460, 1165, 1100, 735, 710$ cm^{-1}.

4-Phenyl[1]benzofuro[3,2-*g*]pyrrolo[1,2-*a*]quinoxaline (5c):

The procedure is analogous to that given for the synthesis of **5b**, using 2-benzoylamino-3-(1-pyrrolyl)-dibenzofuran (**4c**; 0.5 g) as starting material; yield: 0.3 g (51%); m.p. 228–229° (sublimation in vacuo).

$C_{23}H_{14}N_2O$	calc.	C 82.61	H 4.22	N 8.38
(334.3)	found	82.84	4.33	8.27

M.S. (70 eV): $m/e = 334$ ($M^{+\cdot}$, 100%), 333 (M – H, 40), 308 (M – CN, 20), 307 (M – HCN, 4).

I.R. (KBr): $\nu_{max} = 1630, 1600, 1450, 1355, 1165, 740, 690$ cm^{-1}.

4-Phenyl-4,5-dihydro[1]benzofuro[3,2-*g*]pyrrolo[1,2-*a*]quinoxaline (6):

A mixture of 2-amino-3-(1-pyrrolyl)-dibenzofuran (**3**; 1.4 g) and benzaldehyde (0.7 g) in ethanol (250 ml) is refluxed with stirring for 2 h and then evaporated in vacuo. The residue is washed with ether and product **6** isolated by suction; yield 1.5 g (79%); m.p. 214–215° (from ethanol).

$C_{23}H_{16}N_2O$	calc.	C 82.12	H 4.79	N 8.33
(336.3)	found	82.01	4.75	8.27

M.S. (70 eV): $m/e = 336$ ($M^{+\cdot}$, 33%), 335 (M – H, 46), 334 (M – 2H, 100), 259 (M – C_6H_5, 66).

I.R. (KBr): $\nu_{max} = 3345, 3320$ (NH), 1625, 1590, 1475, 1445, 1165, 845, 750, 690 cm^{-1}.

^{1}H-N.M.R. (60 MHz, DMSO-d_6): $\delta = 8.0$–7.3 (m, 12H, 1-H, 6-H, 7-H, 8-H, 9-H, 10-H, 11-H, C_6H_5); 6.73 (1H, NH); 6.26 (1H, 2-H); 5.71 (1H, 3-H); 5.61 ppm (1H, 4-H).

4-Oxo-4,5-dihydro[1]benzofuro[3,2-*g*]pyrrolo[1,2-*a*]quinoxaline (7):

To a solution of 2-amino-3-(1-pyrrolyl)-dibenzofuran (**3**; 5 g) in toluene (5 ml), a 30% solution (100 ml) of phosgene in toluene is added and the mixture refluxed for 30 min. Then, nitrogen is passed through the mixture to remove excess phosgene. The precipitate is isolated by suction and washed with ether; yield: 5 g (90%); m.p. 407–408° (sublimation in vacuo).

$C_{17}H_{10}N_2O_2$	calc.	C 74.44	H 3.68	N 10.21
(274.3)	found	74.48	3.75	10.16

M.S. (70 eV): $m/e = 274$ ($M^{+\cdot}$, 100%), 273 (M – H, 6), 246 (M – CO, 6), 245 (M – CHO, 14), 219 (11).

I.R. (KBr): $\nu_{max} = 1685, 1665$ (C=O), 1490, 1420, 1375, 1180, 1170 cm^{-1}.

4-Chloro[1]benzofuro[3,2-*g*]pyrrolo[1,2-*a*]quinoxaline (8):

A mixture of 4-oxo-4,5-dihydro[1]benzofuro[3,2-*g*]pyrrolo[1,2-*a*]quinoxaline (**7**; 4.5 g), phosphoryl chloride (150 ml), and pyridine (5 ml) is heated at reflux temperature with stirring for 1 h, and then evaporated in vacuo. The residue is isolated by suction, washed thoroughly with water, dried, and extracted with acetonitrile. The solution is decolorised with charcoal and evaporated; yield 3.1 g (65%); m.p. 248–249° (sublimation in vacuo).

$C_{17}H_9ClN_2O$	calc.	C 69.75	H 3.07	N 9.57
(292.7)	found	69.54	3.00	9.71

M.S. (70 eV): $m/e = 292$ ($M^{+\cdot}$, 100%), 291 (M – H, 3), 257 (M – Cl, 9), 231 (3), 230 (9).

I.R. (KBr): $\nu_{max} = 1600, 1575, 1455, 1430, 1335, 1170, 745, 730$ cm^{-1}.

4-Methoxy[1]benzofuro[3,2-*g*]pyrrolo[1,2-*a*]quinoxaline (9a):

4-Chloro[1]benzofuro[3,2-*g*]pyrrolo[1,2-*a*]quinoxaline (**8**; 0.4 g) in a solution of sodium methoxide in methanol (0.2 g of sodium and 50 ml of methanol) is heated at reflux temperature for 7 h and then evaporated in vacuo. Water is added to the residue and the precipitate is isolated by suction and dried; yield: 0.25 g (63%); m.p. 212–213° (sublimation in vacuo).

$C_{18}H_{12}N_2O_2$	calc.	C 74.99	H 4.20	N 9.72
(288.2)	found	74.79	4.29	9.61

M.S. (70 eV): $m/e = 288$ ($M^{+\cdot}$, 100%), 287 (M – H, 47), 273 (M – CH_3, 4), 259 (M – CHO, 38), 258 (23), 245 (19).

I.R. (KBr): $\nu_{max} = 1640, 1610, 1530, 1465, 1440, 1245, 735, 710$ cm^{-1}.

4-Ethoxy[1]benzofuro[3,2-*g*]pyrrolo[1,2-*a*]quinoxaline (9d):

The procedure is analogous to that given for the synthesis of **9a**, using compound **8** (0.4 g) as starting material and ethanolic sodium ethoxide as reagent; yield: 0.3 g (72%); m.p. 172–173° (sublimation in vacuo).

$C_{19}H_{14}N_2O_2$	calc.	C 75.48	H 4.67	N 9.27
(302.3)	found	75.30	4.71	9.34

M.S. (70 eV): $m/e = 302$ ($M^{+\cdot}$, 100%), 301 (M – H, 6), 287 (M – CH_3, 38), 273 (M – C_2H_5, 12).

I.R. (KBr): $\nu_{max} = 1645. 1615, 1575, 1470, 1435, 1245, 1175, 750, 720$ cm^{-1}.

[1]Benzofuro[3,2-*g*]pyrrolo[1,2-*a*]tetrazolo[*c*]quinoxaline (10):

A mixture of 4-chloro[1]benzofuro[3,2-*g*]pyrrolo[1,2-*a*]quinoxaline (**8**; 0.6 g) and sodium azide (0.6 g) in 90% aqueous ethanol (150 ml) is heated under reflux for 4 h and then allowed to cool. The precipitate is isolated by suction and dried; yield: 0.58 g (95%); m.p. 318–319° (sublimation in vacuo).

$C_{17}H_9N_5O$	calc.	C 68.22	H 3.03	N 23.40
(299.2)	found	68.38	3.00	23.43

M.S. (70 eV): $m/e = 299$ ($M^{+\cdot}$, 3%), 298 (M – H, 13), 273 (M – CN, 32), 272 (M – HCN, 100), 271 (M – N_2, 14), 270 (30).

I.R. (KBr): $\nu_{max} = 1625, 1600, 1480, 1465, 1440, 1180, 630, 620$ cm^{-1}.

[1]Benzofuro[2,3-*g*]pyrrolo[2,1-*c*][1,2,4]benzotriazine (11):

2 Normal hydrochloric acid (5 ml) is added carefully at 40° to a stirred solution of 2-amino-3-(1-pyrrolyl)-dibenzofuran (**3**; 0.5 g) and sodium nitrite (0.5 g) in 80% aqueous ethanol (50 ml). The mixture is stirred at room temperature for 1 h and then water (50 ml) is added. The precipitate is collected by suction, washed with water, and dried; yield: 0.5 g (96%); m.p. 344–345° (sublimation in vacuo).

$C_{16}H_9N_3O$	calc.	C 74.12	H 3.50	N 16.21
(259.2)	found	73.96	3.57	16.30

M.S. (70 eV): $m/e = 259$ ($M^{+\cdot}$, 100%), 231 (M – N_2, 3), 230 (14), 203 (7).

I.R. (KBr): $\nu_{max} = 1625, 1600, 1570, 1430, 1300, 1180, 740$ cm^{-1}.

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