Synthesis of 5,6-Dihydro-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine and 10,11-Dihydro-5*H*,12*H*-pyrrolo[2,1-*c*][1,4]benzodiazocine Derivatives *via* Cyclization of 2-Aminomethylpyrroles

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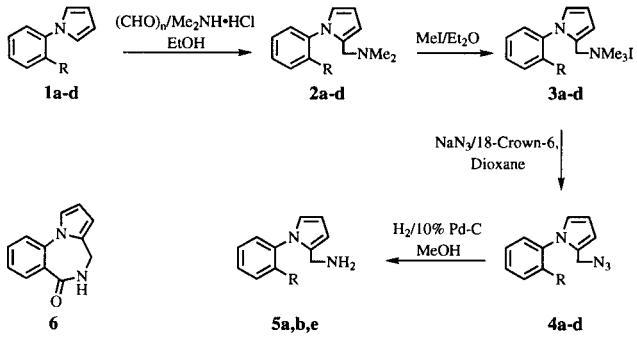
Received February 15, 1994

We have synthesized pyrrolo[1,2-α][1,4]benzodiazepine **6** and pyrrolo[2,1-*c*][1,4]benzodiazocines **12** and **13** from the corresponding 1-arylpyrrole **1d** and 1-benzylpyrroles **7a** and **7b** by routes involving four and five steps, respectively.

J. Heterocyclic Chem., **31**, 1317 (1994).

Fused pyrroles are continuously being investigated due to their significant contributions as therapeutic agents. Pyrrolo[1,2-*a*][1,4]benzodiazepines and pyrrolo[2,1-*c*]-[1,4]benzodiazocines are of potential biological interest because they are related to pharmacologically important compounds such as the 1,4-benzodiazepine CNS agents [1] and the pyrrolo[2,1-*c*][1,4]benzodiazepine antitumour antibiotics [2]. A considerable number of publications have dealt with the synthesis of pyrrolo[1,2-*a*][1,4]benzodiazepines [3a-o]. In contrast, only a few pyrrolo[2,1-*c*]-[1,4]benzodiazocines are known [4a-b]. Recently we reported an efficient synthesis of 2-aminomethylpyrroles. Pyrroles **5a**, **5b** and **5e** were prepared from 1-arylpyrroles **1a-c** by a four step reaction sequence consisting of a Mannich reaction, quaternary salt formation of the Mannich base, displacement of trimethylamine from the quaternary salt by azide anion, and reduction of the azide [5] (Scheme 1). In this paper we have used a similar methodology to synthesise tricycles **6**, **12** and **13** (Schemes 1 and 2).

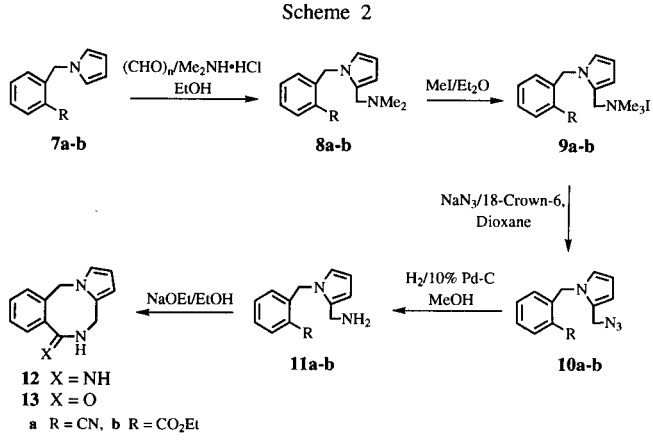
Scheme 1



a R = H, **b** R = CN, **c** R = NO_2, **d** R = CO_2Me, **e** R = NH_2

Pyrroles **1d** [6], **7a** and **7b** [7] were subjected to a Mannich reaction using dimethylamine hydrochloride and paraformaldehyde in refluxing ethanol. These conditions afforded the corresponding 2-dimethylaminomethyl compounds **2d**, **8a** and **8b** in good yields, without contamination by the corresponding 3-isomers. A variation of the Mannich reaction on **7b** by Italian workers [7] had given a 17% yield of the 3-isomer also. In the second step of our synthesis, the Mannich bases **2d**, **8a** and **8b** were converted into their respective quaternary salts **3d**, **9a** and **9b** by stirring in dry diethyl ether with an excess of iodomethane. Although the salt **9b** was previously reported [7] no analytical, physical or spectral data had been given. Displacement of trimethylamine from each of the salts **3d**, **9a** and **9b** by azide anion required heating under reflux in dry dioxan with two equivalents of sodium azide and the presence of a catalytic amount of 18-crown-6. The resulting azides **4d**, **10a** and **10b** were isolated as stable compounds and in yields of 68, 90 and 93%, respectively.

Scheme 2



a R = CN, **b** R = CO_2Et

Catalytic hydrogenation is very efficient in reducing an azido group into amino without affecting ester or aromatic nitrile groups. For our reductions we used 3 atmospheres of hydrogen and 10% palladium on carbon catalyst in methanol. Under these conditions azide **4d** was reduced and cyclized to pyrrolobenzodiazepine **6**. On the other hand, azides **10a** and **10b** were first transformed into the amines **11a** and **11b** and then cyclized into the pyrrolobenzodiazocines **12** and **13** by boiling in an ethanolic solution of sodium ethoxide for 72 and 6 hours, respectively.

The structures of all new compounds were deduced from their analytical and spectral data recorded in Tables I and II.

Table 1

Physical and Analytical Data for Compounds **2d-4d, 8a-11a** and **9b-11b**

Compound	Yield (%)	Mp (°C) or Bp (°C/Torr)	Molecular Formula	Molecular Mass Calcd./Found	Elemental Analyses Calcd./Found C	H	N
2d	83	43-45/12	$C_{15}H_{18}N_2O_2$	258.1368 258.1368			
3d	95	103-105 dec	$C_{16}H_{21}IN_2O_2 \cdot H_2O$		45.94 45.82	5.54 5.63	6.73 6.57
4d	68	32-34/14	$C_{13}H_{12}N_4O_2$	256.0960 256.0960			
8a	60	148-150/25	$C_{15}H_{17}N_3$	239.1422 239.1423			
9a	82	> 200 dec	$C_{16}H_{20}IN_3 \cdot 1/2H_2O$		49.24 49.38	5.42 5.35	10.77 10.65
10a	93	52-53	$C_{13}H_{11}N_5$	237.1014 237.1014			
11a	86	73-75/12	$C_{13}H_{11}N_3$	211.1121 211.1121			
9b	67	168-170 dec	$C_{18}H_{25}IN_2O_2 \cdot 1/2H_2O$		47.48 47.41	6.20 6.18	6.15 6.10
10b	90	55-57/9	$C_{15}H_{16}N_4O_2$	284.1273 284.1273			
11b	88	72-75/10	$C_{15}H_{18}N_2O_2$	258.1368 258.1343			

EXPERIMENTAL

The ir spectra of solids were taken as Nujol mulls and liquids as thin films between sodium chloride discs. Melting points were determined with a Büchi 510 apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 257 spectrophotometer. The nmr spectra were measured at 250 MHz on a Brüker WM 250 spectrometer using tetramethylsilane as internal standard. Mass spectra were obtained with a JEOL JMS-AX505 W machine. Elemental analyses were performed on a Carlo Erba 1106 element analyser. Silica gel (230-400 mesh) was used for flash chromatography and silica gel 60 F_{254} was used for thin layer chromatography.

1-(2-Methoxycarbonylphenyl)pyrrole **1d**, 1-(2-cyanobenzyl)-pyrrole **7a** and 1-(2-ethoxycarbonylbenzyl)pyrrole **7b** were prepared according to the literature methods [6], [4] and [7], respectively.

General Procedure for the Preparation of 2-Dimethylamino-methyl-1-(2-methoxycarbonylphenyl)pyrrole **2d**, 2-Dimethyl-aminomethyl-1-(2-cyanobenzyl)pyrrole **8a** and 2-Dimethyl-aminomethyl-1-(2-ethoxycarbonylbenzyl)pyrrole **8b**.

A mixture of the appropriate 1-substituted pyrrole **1d**, **7a** or **7b** (30 mmoles) dimethylamine hydrochloride (90 mmoles) and paraformaldehyde (6 g) in absolute ethanol (150 ml), was heated under reflux for 12 hours under argon. The solvent was evaporated *in vacuo* and water (60 ml) was added to the residual oil. The resulting solution was basified to *p*H 8 with 1*N*-sodium hydroxide, extracted with dichloromethane (3 x 20 ml), washed with brine (3 x 20 ml), dried over anhydrous sodium sulphate, filtered, and the solvent evaporated off. The oily residue was purified by flash chromatography with ethyl acetate:petroleum ether (bp 40-60°) (1:1) and then with ethyl acetate as eluents. Evaporation of the appropriate eluents afforded the title compounds (Tables I and II).

Pyrrole **8b** was in all respects identical to an authentic sample [7].

General Procedure for the Preparation of Methiodides **3d**, **9a** and **9b**.

To a stirred solution of the appropriate pyrrole **2d**, **8a** or **8b** (20 mmoles) in dry diethyl ether (150 ml) under argon, was added dropwise methyl iodide (100 mmoles). The reaction mixture was left stirring at room temperature for 16 hours. The insoluble methiodide was filtered off under a stream of argon, washed several times with dry diethyl ether and then purified by suspending in dry diethyl ether, stirring for a few minutes, collecting as above, and then drying. The methiodides **3d**, **9a** and **9b** prepared in this manner were analytically pure (Tables I and II).

General Procedure for the Preparation of 2-Azidomethyl-1-(2-methoxycarbonylphenyl)pyrrole **4d**, 2-Azidomethyl-1-(2-cyanobenzyl)pyrrole **10a** and 2-Azidomethyl-1-(2-ethoxycarbonylbenzyl)pyrrole **10b**.

A mixture of the appropriate methiodide **3d**, **9a** or **9b** (12.5 mmoles), sodium azide (25 mmoles) and a catalytic amount of 18-crown-6 in dry dioxan (150 ml) were refluxed for 16 hours under argon. The reaction mixture was filtered and the solvent evaporated *in vacuo* to afford a residue. The products **4d**, **10a** or **10b** were purified by flash chromatography. For **4d**, ethyl acetate:petroleum ether (40-60°) (1:4) was used as eluent, whereas for **10a** and **10b**, ethyl acetate:petroleum ether (40-60°) (1:8) was used as eluent (Tables I and II).

5,6-Dihydro-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine **6**.

Table II
IR, MS and PMR of Compounds **2d-4d, 8a-11a** and **9b-11b**

Compound	IR (cm^{-1})	MS m/z (%)	PMR (δ ppm)
2d	1740 (C=O)	258 (M^+, 65.6), 243 (10.7), 214 (100), 184 (25.3), 168 (5.4), 154 (14), 113 (5.2), 77 (4.9), 58 (12.5)	2.05 (s, 6H, NMe_2), 3.11 (s, 2H, CH_2), 3.65 (s, 3H, Me), 6.17 (dd, 1H, 4-H), 6.21 (dd, 1H, 3-H), 6.67 (dd, 1H, 5-H), 7.45-7.59 and 7.89-7.91 (m, 4H, benzenoid)
3d	1770 (C=O)	401 (M^+ +1, 1.6), 374 (2.0), 332 (2.5), 254 (2.2), 199 (6.6), 154 (7.3), 142 (38.2), 130 (66.5), 84 (35.7), 58 (100)	2.88 (s, 9H, NMe_3I), 3.37 (s, 2H, CH_2), 3.66 (s, 3H, Me), 6.32 (dd, 1H, 4-H), 6.64 (dd, 1H, 3-H), 6.96 (dd, 1H, 5-H), 7.52-8.04 (m, 4H, benzenoid)
4d	2110 (N_3), 1730 (C=O)	256 (M^+, 8.3), 227 (8.0) 214 (100), 169 (94.9), 154 (25.8), 140 (9.8), 115 (11.2), 91 (5.8), 77 (16.1)	3.68 (s, 3H, Me), 4.08 (s, 2H, CH_2), 6.25 (dd, 1H, 4-H), 6.36 (dd, 1H, 3-H), 6.74 (dd, 1H, 5-H), 7.39-7.64 and 7.95-7.97 (m, 4H, benzenoid)
8a	2220 (CN)	239 (M^+, 24), 195 (100), 116 (64), 89 (11.2), 58 (5.1)	2.10 (s, 6H, NMe_2), 3.22 (s, 2H, CH_2NMe_2), 5.46 (s, 2H, $PhCH_2$), 6.07 (dd, 1H, 4-H), 6.14 (dd, 1H, 3-H), 6.67 (dd, 1H, 5-H), 6.76-6.78 and 7.31-7.67 (m, 4H, benzenoid)
9a	2220 (CN)	383 (M^+ +2, 0.5), 239 (15.4), 195 (100), 116 (50.9), 89 (8.9), 51 (29)	3.03 (s, 9H, NMe_3I), 4.59 (s, 2H, CH_2NMe_3I), 5.55 (s, 2H, $PhCH_2$), 6.27 (dd, 1H, 4-H), 6.53 (dd, 1H, 3-H), 6.94 (dd, 1H, 5-H), 7.48-7.50, 7.63-7.65 and 7.90-7.92 (m, 4H, benzenoid)
10a	2220 (CN) 2100 (N_3)	237 (M^+, 14.4), 209 (7.3), 195 (100), 181 (7.1), 116 (47.3), 89 (13.8), 51 (9.9)	4.20 (s, 2H, CH_2N_3), 5.35 (s, 2H, $PhCH_2$), 6.21 (dd, 1H, 4-H), 6.29 (dd, 1H, 3-H), 6.75 (dd, 1H, 5-H), 7.36-7.38, 7.50-7.54 and 7.68-7.70 (m, 4H, benzenoid)
11a	3320 (NH_2), 2220 (CN)	211 (M^+, 4.0), 195 (100), 183 (2.1), 116 (2.8), 89 (1.1)	2.43 (br s, 1H, NH_2), 3.78 (s, 2H, CH_2NH_2), 5.41 (s, 2H, $PhCH_2$), 6.17 (dd, 1H, 4-H), 6.64-6.65 (m, 2H, 3-H and 5-H), 7.34-7.38, 7.47-7.52 and 7.66-7.68 (m 4H, benzenoid)
9b	1730 (C=O)	429 (M^+ +1, 1.2), 402 (1.8), 286 (12.4), 243 (100), 198 (27.3), 119 (41.5), 58 (12.5)	1.32 (t, 3H, $CO_2CH_2CH_3$), 3.00 (s, 9H, NMe_3I), 4.31 (q, 2H, $CO_2CH_2CH_3$),4.50 (s, 2H, CH_2NMe_3I), 5.64 (s, 2H, $PhCH_2$), 6.24-6.26 (m, 2H, 3-H and 4-H), 6.51 (dd, 1H, 5-H), 6.89-6.97, 7.42-7.51 and 7.95-7.96 (m, 4H, benzenoid)
10b	2120 (N_3), 1730 (C=O)	284 (M^+, 24.6), 256 (8.2), 242 (95), 184 (13.1), 168 (16.9), 135 (100), 77 (17.5)	1.42 (t, 3H, $CO_2CH_2CH_3$), 4.15 (s, 2H, CH_2N_3), 4.39 (q, 2H, $CO_2CH_2CH_3$), 5.57 (s, 2H, $PhCH_2$), 6.20 (dd, 1H, 4-H), 6.29 (dd, 1H, 3-H), 6.37-6.41 (m, 1H, benzenoid), 6.73 (dd, 1H, 5-H), 7.29-7.44 (m, 2H, benzenoid), 8.02-8.06 (m, 1H, benzenoid)
11b	3350 (NH_2) 1730 (C=O)	258 (M^+, 48.9), 241 (31.6), 213 (9.4), 184 (29.1), 168 (91.1), 135 (100), 95 (98.2), 77 (22.7), 51 (23.1)	1.42 (t, 3H, $CO_2CH_2CH_3$), 1.90 (br s, 2H, NH_2), 3.68 (s, 2H, CH_2NH_2), 4.38 (q, 2H, $CO_2CH_2CH_3$), 5.56 (s, 2H, $PhCH_2$), 6.12 (dd, 1H, 4-H), 6.17 (dd, 1H, 3-H), 6.35-6.41 (m, 1H, benzenoid), 6.63 (dd, 1H, 5-H), 7.23-7.41 (m, 2H, benzenoid), 7.92-8.04 (m, 1H, benzenoid)

Spectra of compounds **2d**, **4d**, **8a**, **10a**, **10b** and **11b** were measured in deuteriochloroform; spectra of compounds **3d**, **9a** and **9b** were measured in DMSO-d_6.

2-Azidomethyl-1-(2-methoxycarbonylphenyl)pyrrole **4d** (1 g, 3.9 mmoles) was dissolved in absolute methanol (50 ml) containing 10% palladium on carbon (0.05 g). The mixture was hydrogenated at 3 atmospheres for 6 hours, until no hydrogen was absorbed. The catalyst was filtered off and the solvent evaporated *in vacuo* to give a solid which was recrystallized from toluene to give 0.66 g (86%) of **6**, mp 163-165°; ir: ν 3200 cm^{-1} (NH), 1670 (C=O); pmr (dimethyl sulphoxide-d_6): δ 4.06 (s, 2H, CH_2), 6.12 (dd, 1H, 2-H), 6.23 (dd, 1H, 3-H), 7.25 (dd, 1H, 1-H), 7.37-7.85 (m, 4H, benzenoid), 8.69 (t, 1H, NH, deuterium oxide-exchangeable); cmr: δ 36.1 (4-C), 106.4 (2-C), 109.8 (3-C), 120.3 (3a-C), 122.5 (1-C), 125.6, 127.6, 131.4, 132.4, 132.7, 136.3, 168.2 (C=O) [8]; ms: 198 (M^+, 100), 170 (31.6), 154 (15.8), 115 (7.2), 77 (8.1).

Anal. Calcd. for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.08; N, 14.14. Found: C, 72.52; H, 5.25; N, 13.88.

General Procedure for the Reduction of Azides **10a** or **10b.**

The azide **10a** or **10b** (8 mmoles) was dissolved in absolute methanol (50 ml) and hydrogenated at 3 atmospheres for 6 or 12 hours in the presence of 10% palladium on carbon catalyst (0.1 g). The catalyst was filtered off and the solvent evaporated *in vacuo*. The residual oil was purified by flash chromatography using ethyl acetate and then methanol as eluents to afford amines **11a** or **11b** (Tables I and II).

General Procedure for Cyclization of Amines **11a** or **11b.**

The amines **11a** or **11b** (5 mmoles) were dissolved in a solu-

tion of sodium (0.4 g, 18 g-atoms) in dry ethanol (70 ml) and the mixture heated under reflux for 72 and 6 hours, respectively. Evaporation of the solvent gave a semi-solid which was suspended in water (30 ml) and then extracted with dichloromethane (3 x 15 ml). The organic extracts were dried over sodium sulphate, filtered and evaporated to give an oily residue which was triturated with diethyl ether. The solid which separated was collected and dried to give **12** or **13** in 88 and 60% yields, respectively.

10,11-Dihydro-10-imino-5*H*,12*H*-pyrrolo[2,1-*c*][1,4]benzodiazocine **12**.

This compound was obtained as off white microcrystals (toluene), mp 128-130°; ir: ν 3370 and 3170 cm^{-1} (imine NH and NH), 1670 (C=N); pmr (dimethyl sulphoxide-d_6): δ 3.51 (s, 2H, 12-CH_2), 5.36 (s, 2H, 5-CH_2), 5.96 (2dd, each 1H, 1-H and 2-H), 6.46 (d, 1H, imine NH, deuterium oxide-exchangeable), 6.69 (dd, 1H, 3-H), 7.27-7.34 and 7.49-7.51 (m, 4H, benzenoid), 7.94 (t, 1H, 11-NH, deuterium oxide-exchangeable); cmr: δ 37.29 (12-C), 47.2 (5-C), 106.5 (2-C), 106.5 (1-C), 129.7 (3-C), 126.3, 126.6, 127.3, 129.9, 134.0, 134.4, 137.6 (12a-C), 170.2 (C=O) [9]; ms: m/z 212 (M^+ +1, 22.8), 184 (12.3), 168 (17.3), 133 (35.6), 116 (21.9), 95 (100), 51 (41.6).

Anal. Calcd. for $C_{13}H_{13}N_3$: C, 73.91; H, 6.20; N, 19.89. Found: C, 73.78; H, 6.47; N, 19.66.

10,11-Dihydro-10-oxo-5*H*,12*H*-pyrrolo[2,1-*c*][1,4]benzodiazocine **13**.

This compound was obtained as pale yellow microcrystals (toluene), mp 185-187°; ir: ν 3210 cm^{-1} (NH), 1660 (C=O); pmr (dimethyl sulphoxide-d_6): δ 3.90 (d, 2H, 12-CH_2), 5.02 (s, 2H, 5-CH_2), 5.83 (dd, 1H, 2-H), 5.89 (dd, 1H, 1-H), 6.87 (dd, 1H, 3-H), 7.43-7.57 (m, 4H, benzenoid), 8.42 (t, 1H, 11-NH, deuterium oxide-exchangeable); cmr: δ 36.1 (12-C), 49.8 (5-C), 105.6 (2-C), 107.5 (1-C), 123.2 (3-C), 126.7, 127.7, 129.1, 130.1, 130.5, 131.3, 137.2 (12a-C), 172.0 (C=O) [10]; ms: m/z 212 (M^+, 100), 183 (21.1), 168 (28.8), 155 (10.6) 133 (7.9), 118 (14.2), 91 (29), 80 (28.1).

Anal. Calcd. for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.38; H, 5.71; N, 12.93.

Acknowledgements.

The authors wish to thank the Research Committee of the University of Ioannina for financial support, J. Cobb for nmr measurements, A. Cakebread and R. Tye for mass spectra, and, W. Baldeo and L. Randall for elemental analyses which were obtained on machines funded by the University of London Intercollegiate Research Services Scheme.

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[8] Values 127.6 and 136.3 are the two quaternary benzenoid carbons, 125.6, 131.4, 132.4 and 132.7 are the four protonated benzenoid carbons.

[9] Values 126.3, 126.6, 127.3 and 129.9 are the four protonated benzenoid carbons, 134.0 and 134.4 are the two quaternary benzenoid carbons.

[10] Values 126.7, 129.1, 130.1 and 130.5 are the four protonated benzenoid carbons, 127.7 and 131.3 are the two quaternary benzenoid carbons.