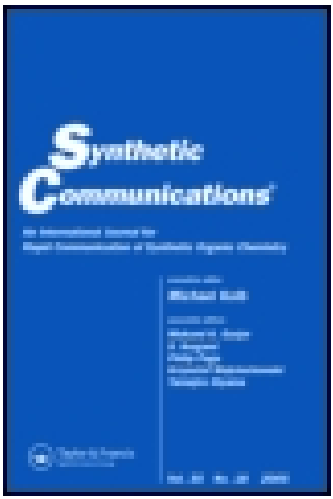


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Polycondensed Heterocycles. VII. A Convenient Synthesis of Pyrrolo[1,2-a]quinoxaline Derivatives by Intramolecular Aromatic Nucleophilic Displacement

G. Campiani [a], V. Nacci [a], F. Corelli [a] & M. Anzini [a]
[a] Dipartimento Farmaco Chimico Tecnologico, Università di Siena, Banchi di Sotto 55, 53100, Siena, Italy
Published online: 23 Sep 2006.

To cite this article: G. Campiani, V. Nacci, F. Corelli & M. Anzini (1991) Polycondensed Heterocycles. VII. A Convenient Synthesis of Pyrrolo[1,2-a]quinoxaline Derivatives by Intramolecular Aromatic Nucleophilic Displacement, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 21:15-16, 1567-1576, DOI: 10.1080/00397919108021054

To link to this article: http://dx.doi.org/10.1080/00397919108021054

SYNTHETIC COMMUNICATIONS, 21(15&16), 1567-1576 (1991)

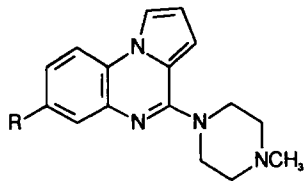
POLYCONDENSED HETEROCYCLES. VII. A CONVENIENT SYNTHESIS OF PYRROLO[1,2-a]QUINOXALINE DERIVATIVES BY INTRAMOLECULAR AROMATIC NUCLEOPHILIC DISPLACEMENT

G. Campiani, V. Nacci*, F. Corelli and M. Anzini

Dipartimento Farmaco Chimico Tecnologico, Università di Siena, Banchi di Sotto 55, 53100 Siena, Italy

Abstract: *4-(4-Methyl-1-piperazinyl)-7-trifluoromethylpyrrolo[1,2-a]quinoxaline (CGS 12066B) and related analogs were prepared in good overall yield through a reaction sequence involving as a key step the intramolecular substitution of aromatic fluoride or nitro groups by a carboxamide moiety.*

4-(4-Methyl-1-piperazinyl)-7-trifluoromethylpyrrolo[1,2-a]quinoxaline **1a** (CGS 12066B) was described in 1987 as a highly selective agonist for the serotonin sensitive receptor subtype 5-HT_{1B}[1]. Although the real selectivity of **1a** for 5-HT_{1B} versus 5-HT_{1A} binding sites has been questioned[2] more recently, yet compound **1a** may prove a useful tool for the identification and the characterization of the putative receptor subtypes.

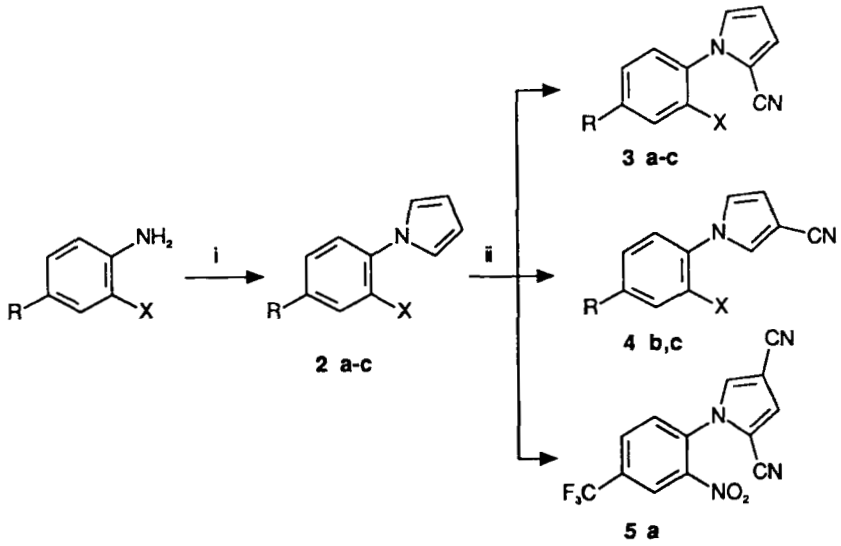


1a : R = CF_3 (CGS12066B)

1b : R = H

1c : R = F

* To whom correspondence should be addressed



a : R = CF_3 , X = NO_2 ; b : R = H, X = F; c : R = X = F

Key : i, 2,5 · dimethoxytetrahydrofuran, AcOH ; ii, (a) $POCl_3$, DMF; (b) NH_2OH ·HCl, AcONa; (c) Ac_2O

SCHEME 1

Inspection of the literature revealed rather surprisingly that no synthetic procedure for the preparation of **1a** has been described to date, the sole examples of 4-(1-piperazinyl)pyrrolo[1,2-a]quinoxalines being compound **1b** and some of its derivatives chlorinated in the pyrrole ring. These were prepared in 1972 through a high yielding reaction sequence, yet involving the use of a hazardous reagent such as phosgene[3].

Following previous reports of one of us (V.N.) on the chemistry of pyrrolo[1,2-a]quinoxaline derivatives[4] and in connection with a research program on new selective central nervous system agents[5], we resolved on planning a different and safer synthetic approach to 4-(4-methyl-1-piperazinyl)pyrrolo[1,2-a]quinoxalines **1a-c**.

As starting material for our synthesis we chose commercially available anilines bearing a leaving group (F or NO_2) in the 2-position (Scheme 1). These were subjected to Clauson-Kaas reaction[6] with 2,5-dimethoxytetrahydrofuran to give 1-arylpyrroles **2a-c**, which were transformed into 1-aryl-2-cyanopyrroles **3a-c** in 62-81% yield through a one-pot sequence[7] involving formylation, oximation and dehydration.

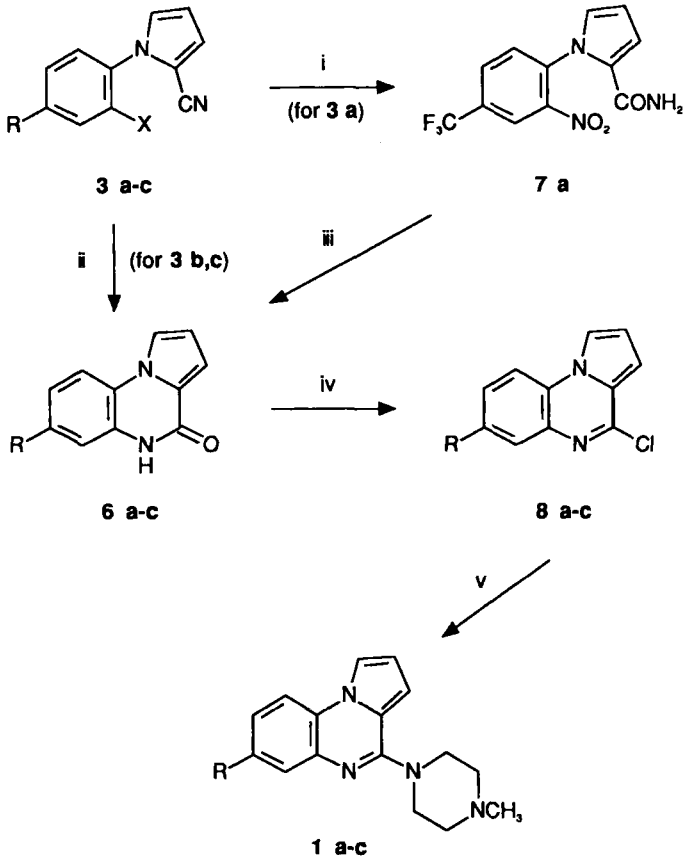
This procedure also furnished little amounts of the isomeric nitriles **4b** and **4c** (5% and 16%, respectively), while in the case of **3a** a by-product was obtained in traces amount, which was assigned structure **5a** by ^{1}H-NMR spectroscopy.

Treatment of nitriles **3b** and **3c** (Scheme 2) with potassium hydroxide in ethylene glycol at 145°C or in *tert*-butanol at 80°C, respectively, led directly to the tricyclic lactams **6b,c** in very good yield. This one-pot transformation of nitriles into lactams, involving selective hydrolysis to amides which are able to carry out intramolecular displacement of aromatic fluorine, is unprecedented to the best of our knowledge and offers a quite direct and convenient route to nitrogen-containing polycyclic compounds. On the contrary, compound **3a** was converted by KOH/*tert*-butanol system into the amide **7a**, which however could be smoothly cyclized to **6a** upon treatment with potassium carbonate in N,N-dimethylformamide at 135°C in 55% overall yield from **3a**. Chlorination of lactams **6a-c** was best performed with phosphoryl chloride and chloro derivatives **8a-c** so obtained were reacted with excess of N-methylpiperazine without solvent to give 4-(4-methyl-1-piperazinyl)pyrrolo[1,2-a]quinoxalines **1a-c**.

The synthetic pathway described herein allows the safe preparation of compounds **1a-c** in good overall yield and lends itself to the synthesis of novel related analogs with potential central nervous system activity.

EXPERIMENTAL

Melting points were taken on a Electrothermal 8103 apparatus and are uncorrected. Microanalyses were performed on a Perkin-Elmer 240-C Elemental Analyzer by Dr. G. Corbini and Dr. N. Politi, our Department. Microanalytical data of analyzed elements (C,H,N) were within ± 0.3% of calculated values. IR spectra (neat or nujol mulls) were run on a Perkin-Elmer FT 1600 spectrophotometer: derivatives **3**, **4** and **5** showed a



a : R = CF_3 ; b : R = H ; c : R = F

Key : i, KOH, *t*-BuOH; ii, KOH, *t*-BuOH or $(CH_2OH)_2$; iii, K_2CO_3, DMF; iv, $POCl_3$; v, N-methylpiperazine

SCHEME 2

band at 2210-2220 cm^{-1} accounting for the presence of a cyano group; lactams **6** showed a strong stretching band at 1665-1675 cm^{-1}. ^{1}H-NMR spectra were measured at 200 MHz on a Varian XL-200 instrument using TMS as internal standard. Chemical shifts are expressed in ppm; coupling constants are reported in Hz. Anhydrous sodium sulfate was used to dry organic extracts. Merck silica gel 60 (230-400 mesh) was

used for flash chromatography. All the reactions were carried out under an inert (N_2 or Ar) atmosphere.

Preparation of 1-Arylpyrroles 2a-c: General Procedure. To a solution of the appropriate aniline (65.8 mmol) in glacial acetic acid (36 ml) 2,5-dimethoxytetrahydrofuran (8.5 g, 65.8 mmol) was slowly added. The reaction mixture was refluxed for 1 hr, cooled and evaporated in vacuo to afford an oily residue which was purified by column chromatography (benzene as eluent) in the case of **2a** or by distillation for **2b**[8] and **2c** (bp 60°C/0.1 mmHg).

1-[2-Nitro-4-(trifluoromethyl)phenyl]-1H-pyrrole 2a : ^{1}H-NMR ($CDCl_3$) ∂ 6.40 (t, 2H, J=2.2), 6.80 (t, 2H, J=2.2), 7.61 (d, 1H, J=8.3), 7.89 (dd, 1H, J_{ortho}=8.3, J_{meta}=1.8), 8.10 (d, 1H, J=1.8).

1-(2,4-Difluorophenyl)-1H-pyrrole 2c: ^{1}H-NMR ($CDCl_3$) ∂ 6.36 (m, 2H), 6.90-7.05 (m, 4H), 6.33-7.42 (m, 1H).

Preparation of 1-Arylpyrrolecarbonitriles 3a-c, 4b,c and 5a: General Procedure. To a cooled (-5°C) mixture of anhydrous N,N-dimethylformamide (1.54 ml, 20 mmol) and anhydrous 1,2-dichloroethane (4.3 ml) a solution of oxalyl chloride (1.7 ml, 20 mmol) in anhydrous 1,2-dichloroethane (2.9 ml) was added dropwise in 20 min. After stirring for 15 min at room temperature and cooling in an ice-water bath, a solution of the proper 1-arylpyrrole **2a-c** (18.2 mmol) in anhydrous 1,2-dichloroethane (3.7 ml) was slowly added. The mixture was allowed to stir at 70°C for 3 hr (**2a**), at room temperature for 30 min (**2b**) and at 35°C for 1 hr (**2c**), then a warm solution of hydroxylamine hydrochloride (1.38 g, 20 mmol) and dry sodium acetate (1.64 g, 20 mmol) in anhydrous N,N-dimethylformamide (3.6 ml) was slowly added. After refluxing for 20 hr, acetic anhydride (8.65 g, 80 mmol) was added dropwise and the solution was refluxed for 4 hr. The cooled mixture was treated with 10% sodium carbonate solution until pH 8, diluted with water (100 ml) and extracted with diethyl ether. The organic layer was washed with brine, dried and evaporated to give an oily residue, which was purified by chromatography (benzene-petroleum ether 60-80°, 10:1) to afford 1-arylpyrrole-2-carbonitriles **3a-c**. Further elution with the same eluting system provided 1-arylpyrrole-3-carbonitriles **4b,c**. In the case of **2a**, a very little amount of the dinitrile **5a** was obtained.

1-[2-Nitro-4-(trifluoromethyl)phenyl]-1H-pyrrole-2-carbonitrile 3a : ^{1}H-NMR ($CDCl_3$) ∂ 6.45 (m, 1H), 6.94 (m, 1H), 7.07 (m, 1H), 7.72 (d, 1H, J=8.2), 8.05 (dd, 1H, J_{ortho}=8.2, J_{meta}=1.6), 8.36 (d, 1H, J=1.6).

1-(2-Fluorophenyl)-1H-pyrrole-2-carbonitrile 3b : ^{1}H-NMR ($CDCl_3$) ∂ 6.37 (m, 1H), 7.03 (m, 2H), 7.00-7.50 (m, 4H).

1-(2,4-Difluorophenyl)-1H-pyrrole-2-carbonitrile 3c : ^{1}H-NMR ($CDCl_3$) ∂ 6.38 (t, 1H, J=6.9), 6.97-7.13 (m, 4H), 7.38-7.49 (m, 1H).

1-(2-Fluorophenyl)-1H-pyrrole-3-carbonitrile 4b : ^{1}H-NMR ($CDCl_3$) ∂ 6.58 (t, 1H, J=4.6), 6.96 (m, 1H), 7.19-7.52 (m, 5H).

1-(2,4-Difluorophenyl)-1H-pyrrole-3-carbonitrile 4c : ^{1}H-NMR ($CDCl_3$) ∂ 6.60 (m, 1H), 6.90-7.25 (m, 3H), 7.30-7.50 (m, 2H).

1-[2-Nitro-4-(trifluoromethyl)phenyl]-1H-pyrrole-2,4-dicarbonitrile 5a : ^{1}H-NMR ($CDCl_3$) ∂ 6.37 (d, 1H, J=4), 7.03 (d, 1H, J=4), 7.71(d, 1H, J=8), 8.10 (dd, 1H, J_{ortho}=8, J_{meta}=1.7), 8.51 (d, 1H, J=1.7).

1-[2-Nitro-4-(trifluoromethyl)phenyl]-1H-pyrrole-2-carboxamide 7a. To a stirred solution of **3a** (0.5 g, 1.77 mmol) in *tert*-butanol (5 ml) 85% potassium hydroxide (0.4 g, 8 mmol) was added. The suspension was heated until the reaction was complete (TLC: silica gel-benzene), then cooled, poured into crushed ice and extracted with chloroform-diethyl ether (1:1). The organic layer was washed with brine, dried and evaporated to give a solid residue, which was purified by chromatography (benzene as eluent) to afford **7a** as a yellow solid. ^{1}H-NMR ($CDCl_3$) ∂ 6.38 (m, 1H), 6.96 (m, 1H), 7.08 (m, 1H), 7.87 (dd, 1H, J_{ortho}=8.9, J_{meta}=1.8), 8.55 (d, 1H, J=1.8), 9.13 (d, 1H, J=8.9), 9.44 (br s, 1H, exch. with D_2O), 11.26 (s, 1H, exch. with D_2O).

Preparation of Lactams 6b,c: General Procedure. A suspension of **3b,c** (1 mmol) and 85% potassium hydroxide (0.2 g, 4 mmol) in 3 ml of ethylene glycol (**3b**) or *tert*-butanol (**3c**) was heated (see Table), then cooled, poured into crushed ice and extracted with ethyl acetate. The organic layer was washed with brine and dried. Evaporation of the volatiles afforded a residue, which was chromatographed on silica gel (ethyl acetate as eluent) to give **6b,c** as white solids.

Pyrrolo[1,2-a]quinoxalin-4(5H)-one 6b : ^{1}H-NMR (DMSO-d_6) ∂ 6.67 (m, 1H), 7.01 (m, 1H), 7.18-7.28 (m, 3H), 8.03 (d, 1H, J=7.8), 8.16 (m, 1H), 11.25 (s, 1H, exch. with D_2O).

7-Fluoropyrrolo[1,2-a]quinoxalin-4(5H)-one 6c : ^{1}H-NMR (DMSO-d_6) ∂ 6.66 (m, 1H), 7.00-7.11 (m, 3H), 8.04-8.16(m, 2H), 11.32 (s, 1H, exch. with D_2O).

7-(Trifluoromethyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one 6a. A suspension of **7a** (0.51 g, 1.7 mmol) and anhydrous potassium carbonate (0.7 g, 5.1 mmol) in freshly distilled N,N-dimethylformamide (50 ml) was heated until the reaction was complete (TLC: silica gel-benzene), then cooled, diluted with water (150 ml) and extracted with ethyl acetate. The organic layer was washed with brine, dried and evaporated under reduced pressure to afford a residue, which was chromatographed on silica gel. Elution with dichloromethane-benzene (3:1) removed some impurities and further elution with ethyl acetate provided **6a** as a pale yellow solid. ^{1}H-NMR (DMSO-d_6) ∂ 6.72 (m, 1H), 7.08 (m, 1H), 7.43 (d, 1H, J=8.5), 7.63 (dd, 1H, J_{ortho}=8.5, J_{meta}=1.2), 8.41 (d, 1H, J=1.2), 8.47 (s, 1H), 11.57 (s, 1H, exch. with D_2O).

Preparation of 4-Chloropyrrolo[1,2-a]quinoxalines 8a-c: General Procedure. A mixture of the appropriate lactam **6a-c** (0.39 mmol) and phosphoryl chloride (0.37 ml, 4 mmol) was heated for the required time. After cooling the mixture was poured into crushed ice and extracted with dichloromethane. The organic layer was washed with brine, dried and evaporated to afford an oily residue, which was purified by chromatography (chloroform as eluent) to give **8a-c** as white solids.

4-Chloro-7-(trifluoromethyl)pyrrolo[1,2-a]quinoxaline 8a : ^{1}H-NMR ($CDCl_3$) ∂ 6.97 (m, 1H), 7.13 (m, 1H), 7.69 (d, 1H), 7.96-8.11 (superimposed signals, 3H).

4-Chloropyrrolo[1,2-a]quinoxaline 8b : ^{1}H-NMR ($CDCl_3$) ∂ 6.90 (m,1H),7.08 (m, 1H), 7.40-7.60 (m, 2H),7.80-7.94 (m, 2H), 7.98 (m,1H).

4-Chloro-7-fluoropyrrolo[1,2-a]quinoxaline 8c : ^{1}H-NMR ($CDCl_3$) ∂ 6.88 (m, 1H), 7.06 (m, 1H), 7.30 (ddd, 1H, J_{ortho}=8, J_{meta}=3, $J_{orthoF-H}$=9), 7.60 (dd, 1H, J_{meta}=3, $J_{orthoF-H}$=9), 7.83 (dd, 1H, J_{ortho}=8, $J_{metaF-H}$=5), 7.95 (m, 1H).

TABLE : Elemental Analyses of compound 1-4 and 6-8 -

COMPD.	MOLECULAR FORMULA	C	H	N	CALCD. FOUND
1a	$C_{17}H_{17}F_3N_4$	61.07	5.12	16.76	
		61.24	5.01	16.67	
1b	$C_{16}H_{18}N_4$	72.16	6.81	21.04	
		72.10	6.78	21.11	
1c	$C_{16}H_{17}FN_4$	67.58	6.02	19.70	
		67.62	6.28	19.34	
2a	$C_{11}H_7F_3N_2O_2$	51.57	2.75	10.93	
		51.73	2.77	10.86	
2c	$C_{10}H_7F_2N$	67.04	3.93	7.81	
		67.26	4.11	7.97	
3a	$C_{12}H_6F_3N_3O_2$	51.25	2.15	14.94	
		51.29	2.13	14.99	
3b	$C_{11}H_7FN_2$	70.96	4.17	15.04	
		70.84	4.09	15.12	
3c	$C_{11}H_6F_2N_2$	64.71	2.96	13.72	
		64.72	2.89	13.68	
4b	$C_{11}H_7FN_2$	70.96	4.17	15.04	
		71.12	4.29	15.32	
4c	$C_{11}H_6F_2N_2$	64.71	2.96	13.72	
		64.78	3.08	13.68	
6a	$C_{12}H_7F_3N_2O$	57.15	2.79	11.11	
		56.96	2.75	11.06	
6b	$C_{11}H_8N_2O$	71.72	4.37	15.21	
		72.08	4.28	15.32	
6c	$C_{11}H_7FN_2O$	65.34	3.49	13.85	
		65.10	3.46	13.68	
7a	$C_{12}H_8F_3N_3O_2$	48.10	2.69	14.04	
		48.41	2.75	13.90	
8a	$C_{12}H_6ClF_3N_2$	53.28	2.23	10.35	
		53.24	2.16	10.42	
8b	$C_{11}H_7ClN_2$	65.20	3.48	13.82	
		65.38	3.56	13.76	
8c	$C_{11}H_6ClFN_2$	59.91	2.74	12.70	
		60.09	2.81	12.54	

TABLE . Chemical and Physical Data of compounds 1-4 and 6-8

Compd.[a]	X	Reaction time (hr)	Reaction temp.(°C)	Yield[b] (%)	M.p. (°C)	Recryst. solv.[c]	Molecular Formula (M. W.)
1a	-	6	130	93	158-9	A	$C_{17}H_{17}F_3N_4$ (334.3)
1b	-	6	130	95	oil	-	$C_{16}H_{18}N_4$ (266.3)
1c	-	6	130	87	81-2	B	$C_{16}H_{17}FN_4$ (284.3)
2a	NO_2	1	115	92	oil	-	$C_{11}H_7F_3N_2O_2$ (256.1)
2c	F	1	115	72	oil	-	$C_{10}H_7F_2N$ (179.1)
3a	NO_2	24	reflux	81	74-5	B	$C_{12}H_8F_3N_3O_2$ (281.1)
3b	F	24	reflux	62	65-6	C	$C_{11}H_7FN_2$ (186.1)
3c	F	24	reflux	72	72-4	B	$C_{11}H_6F_2N_2$ (204.1)
4b	F	24	reflux	5	94-5	A	$C_{11}H_7FN_2$ (186.1)
4c	F	24	reflux	16	109-10	A	$C_{11}H_6F_2N_2$ (204.1)
6a	-	1.5	135	84	267-8	D	$C_{12}H_7F_3N_2O$ (252.1)
6b	-	4	145	93	277-8[d]	E	$C_{11}H_8N_2O$ (184.2)
6c	-	2	80	83	287-8	F	$C_{11}H_7FN_2O$ (202.1)
7a	NO_2	1	80	66	267-9	G	$C_{12}H_8F_3N_3O_2$ (283.1)
8a	-	4	120	72	111-3	B	$C_{12}H_6ClF_3N_2$ (270.5)
8b	-	4	130	97	166-7[e]	A	$C_{11}H_7ClN_2$ (202.6)
8c	-	3.5	130	87	194-5	A	$C_{11}H_6ClFN_2$ (220.5)

a: For compound 2b see Ref.8.
b: Yields refer to isolated and purified materials.
c: A = cyclohexane; B = n-hexane; C = light petroleum ether; D = n-hexane-ethyl acetate; E = benzene; F = ethyl acetate; G = cyclohexane-benzene.
d: Lit.[3]: 276-8°C.
e: Lit.[3]: 170-1°C.

Preparation of 4-(4-Methyl-1-piperazinyl)pyrrolo[1,2-a]quinoxalines 1a-c: General Procedure. A stirred mixture of the proper **8a-c** (0.77 mmol) and 1-methylpiperazine (0.6 ml, 5.38 mmol) was heated for the required time. After cooling, the mixture was diluted with water and extracted with diethyl ether. The organic layer was washed with brine, dried and evaporated to afford a residue, which was chromatographed (ethyl acetate as eluent) to yield **1a-c**.

4-(4-Methyl-1-piperazinyl)-7-(trifluoromethyl)pyrrolo[1,2-a]quinoxaline 1a : ^{1}H-NMR ($CDCl_3$) ∂ 2.38 (s, 3H), 2.61 (t, 4H, J=4.9), 3.92 (t, 4H, J=4.9), 6.79 (m, 1H), 6.84 (m, 1H), 7.52 (dd, 1H, J_{ortho}=9, J_{meta}=2.8), 7.68 (d, 1H, J_{ortho}=9), 7.85 (m, 1H), 7.94 (d, 1H, J_{meta}=2.8).

4-(4-Methyl-1-piperazinyl)pyrrolo[1,2-a]quinoxaline 1b : ^{1}H-NMR ($CDCl_3$) ∂ 2.37 (s, 3H), 2.61 (t, 4H, J=4.9), 3.82 (t, 4H, J=4.9), 6.76 (m, 2H), 7.22-7.37 (m, 2H), 7.64-7.77 (m, 2H), 7.81 (m, 1H).

7-Fluoro-4-(4-methyl-1-piperazinyl)pyrrolo[1,2-a]quinoxaline 1c : ^{1}H-NMR ($CDCl_3$) ∂ 2.36 (s, 3H), 2.59 (t, 4H, J=5), 3.85 (t, 4H, J=5), 6.76 (m, 2H), 6.97 (td, 1H, J_{ortho}=9, J_{meta}=2.8, $J_{orthoF-H}$=10), 7.32 (dd, 1H, J_{meta}=2.8, $J_{orthoF-H}$=10), 7.65 (dd, 1H, J_{ortho}=9, $J_{metaF-H}$=5.2), 7.78 (m, 1H).

Acknowledgements. Authors are indebted to Italian MURST and C.N.R. for supporting this research with grants.

REFERENCES

1. Neale, R. F., Fallon, S. L., Boyar, W. C., Wasley, J. W. F., Martin, L. L., Stone, G. A., Glaeser, B. S., Sinton, C. M., and Williams, M., *Eur. J. Pharmacol.*, **1987**, *136*, 1.

2. Schoeffter, P., and Hoyer, D., *Naunyn-Schmiedeberg's Arch. Pharmacol.*, **1989**, *339*, 675.

3. Nagarajan, K., Ranga Rao, V., and Venkateswarlu, A., *Indian J. Chem.*, **1972**, *10*, 344.

4. (a) Artico, M., De Martino, G., and Nacci, V., *Ann. Chem. (Rome)*, **1967**, *57*, 1431. (b) Artico, M., Nacci, V., and De Martino, G., *ibidem*, **1968**, *58*, 136.

5. (a) Nacci, V., Fiorini, I., Garofalo, A., and Cagnotto, A., *Il Farmaco, Ed. Sci.*, **1990**, *45*, 545. (b) Massa, S., Artico, M., Mai, A., Corelli, F., Pantaleoni, G. C., Giorgi, R., Ottaviani, D., and Cagnotto, A., *ibidem*, **1990**, *45*, 1265.

6. Clauson-Kaas, N., and Tyle, Z., *Acta Chem. Scand.*, **1952**, *6*, 667.

7. Barnett, G. H., Anderson, H. J., and Loader, C. E., *Can. J. Chem.*, **1980**, *58*, 409.

8. Nacci, V., Campiani, G., and Garofalo, A., *Synth. Commun.*, **1990**, *20*, 3019.

(Received in UK 15 April, 1991)