Synthesis and Reactivity of Pyrrolo[1,2-*a*]quinoxalines. Crystal Structure and AM1 Calculation

Yves Blache, Alain Gueiffier*, Ahmed Elhakmaoui, Henri Viols, and Jean-Pierre Chapat

Laboratoire de Chimie Organique Pharmaceutique, URA-CNRS 1111,
Faculté de Pharmacie, 15 Avenue Ch. Flahault, 34060 Montpellier, France

Olivier Chavignon and Jean-Claude Teulade

Laboratoire de Chimie Organique Pharmaceutique,
Groupe de Recherche en Pharmacochimie, UFR de Pharmacie,
28 Place Henri Dunant, B.P. 38,
63001 Clermont-Ferrand, France

Gérard Grassy

Centre de Biochimie Structurale, CNRS-UMR 9955, INSERM U-414
Université Montpellier I, Faculté de Pharmacie, 15 Av. Ch. Flahault
34060 Montpellier Cedex, France

Gérard Dauphin

Laboratoire de Chimie Organique Biologique, URA 485 CNRS,
63170 Aubière, France

Alain Carpy

ER-CNRS 61, UFR des Sciences Pharmaceutiques, Place de la Victoire, 33076 Bordeaux, France
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2-Methylquinoxaline reacts with ethyl bromopyruvate giving 2-substituted pyrrolo[1,2-*a*]quinoxalines. The yield of the condensation depends on the functionalization of starting materials, and optimization is obtained with 2-dimethylamino-3-methylquinoxaline (**1c**). Reactivity of the resulting pyrrolo[1,2-*a*]-quinoxalines was investigated and supported by a theoretical approach (AM1 calculation performed with the MOPAC 6.0 software). X-ray analysis of **5** which crystallizes in the monoclinic system, space group $P2_1/n$, with a = 9.095(1), b = 8.972(1), c = 17.749(3) A, β = 96.56(1)°, is also reported.

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Introduction.

7-Trifluoro-4-(4-methyl-1-piperazinyl)-pyrrolo[1,2-*a*]-quinoxaline 1:2 maleate salt, (CGS 12066B) was recently described as a novel selective $5HT_{1B}$ agonist [1]. Following our studies on heterocycles with a bridgehead nitrogen atom, we investigated the synthesis of new derivatives of pyrrolo[1,2-*a*]quinoxaline.

Synthesis of 2-substituted pyrrolo[1,2-*a*]quinoxalines by condensation of methylquinoxaline and α-halocarbonyl compounds was limited by the difffculty of quaternization of quinoxaline [2]. The reactivity of this series was studied only with unsubstituted derivatives. Chlorination with *N*-chlorosuccinimide in sulfuric acid media gave preferentially the 1-chloro derivative, with a small amount of 3-chloro and 1,3-dichloro derivatives. Sulfonation with concentrated sulfuric acid gave only the 3-derivative compound. Nitration with potassium nitrate/sulfuric acid gave a 2:1 mixture of 3- and 1-nitro derivatives [3] whereas the use of 6*M* nitric acid gave only the 3-derivative [4]. Bromination with *N*-bromosuccinimide/sulfuric acid gave the same results as chlorination [5]. No theorical explanation was given to support these results.

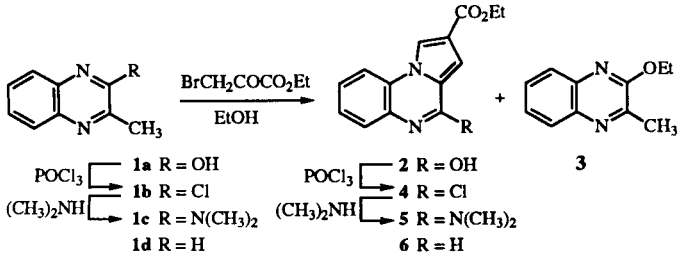
We report here the synthesis and the reactivity of 2-substituted derivatives, and a theoretical approach by AM1 calculation.

Results and Discussion.

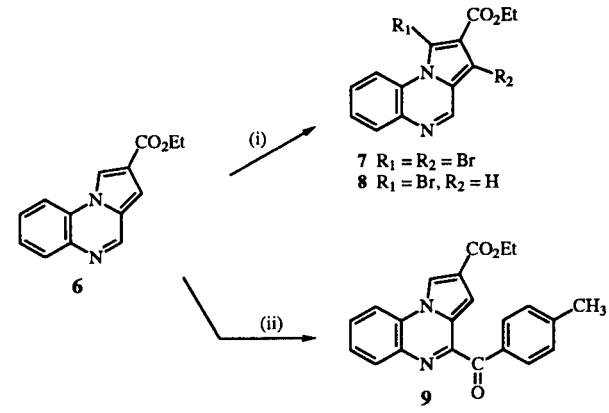
When 3-methylquinoxalin-2-ol (**1a**) was condensed with ethyl bromopyruvate in dry ethanol, ethyl 4-hydroxy-pyrrolo[1,2-*a*]quinoxaline-2-carboxylate (**2**) was isolated. This compound is also obtained admixed with 2-ethoxy-3-methylquinoxaline (**3**) using 2-chloro-3-methylquinoxaline (**1b**) as the starting material. This hydrolysis was reported in the condensation of 2-amino-3-chloroquinoxaline with the same reactant [6]. The chloro derivative **4** was obtained by refluxing **2** in phosphorus oxychloride with an 89% yield. Chlorine substitution was made with dimethylamine to yield ethyl 4-dimethylaminopyrrolo[1,2-*a*]quinoxaline (**5**). In order to optimize the yields of the condensations, we have

investigated the reaction of 3-dimethylamino-2-methylquinoxaline (**1c**) with ethyl bromopyruvate. In this case, **5** was obtained with a 42% yield (Scheme 1).

Scheme 1



Scheme 2



(i) Br_2, AcOH; (ii) *p*-C_6H_4-CHO, KCN, DMSO

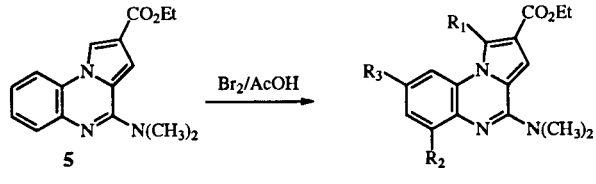
Structural determinations of the tricyclic derivatives **2, 4, 5** and **6** were realized by ^1H and ^{13}C-nmr experiments. For compound **6**, obtained from **1d** in 14% yield, the ^1H-nmr spectrum shows two doublets at δ 7.29 and 8.43 (J = 1.4 Hz) characteristic of a 2-substituted pyrrolic system, a singlet at δ 8.73 for H-4 and an ABXY system for the benzenic nucleus. Assignments of the different signals to H-6 (δ 7.97), H-7 (δ 7.50), H-8 (δ 7.56), and H-9 (δ 7.89) were made according to the ^1H-^1H and ^1H-^{13}C correlations. From these correlations, a complete and unambiguous ^{13}C assignment of **6** was also obtained and used as a reference for the structural elucidation of **5**. Otherwise for this compound, the two ambiguous signals at δ 126.3 and δ 126.8 could be respectively attributed to C-7 and C-6 by performing an HMBC experiment.

An attempt to nitrosate ethyl pyrrolo[1,2-*a*]quinoxaline-2-carboxylate (**6**) with sodium nitrite in hydrochloric acid as reported for pyrrolo[1,2-*a*]quinoline [7] failed. The use of nitrosyl chloride in acetic acid and anhydride, a new method of nitrosation for nitrogen bridgehead heterocycle [8], gave the same result.

Bromination was investigated using bromine in acetic acid media. In these conditions ethyl pyrrolo[1,2-*a*]-quinoxaline-2-carboxylate (**6**) gave the 1,3-dibromo derivative **7** with an 84% yield and a small amount of 1-bromo derivative **8** (Scheme 2). Determination of substitutions on the C-1 and C-3 positions was made from their ^1H-nmr spectra with a singlet at δ 7.38 (H-3) for **8**, and no pyrrolic signals for **7**. In addition, we noted a long range deshielding effect on the signal of H-9 due to the halogen on the C-1 position [9]. Study of the reactivity of compound **6** was achieved by the synthesis of **9** using an aromatic aldehyde [10]. Structural determination of **9** was made by comparison of its ^1H-nmr spectra with (**5** and **6**).

From these results, we have investigated the reactivity of the 4-dimethylamino derivative **5** toward electrophlic reagents. Bromination, in the conditions cited above for **5**, led in this case to a set of four compounds **10, 11, 12, 13** (Scheme 3). The ^1H-nmr of compound **10** shows one singlet at δ 7.35 attributed to H-3 and two doublets at δ 7.72 and 9.26 (J = 2 Hz, respectively H-7 and H-9). This determination is confirmed by ^{13}C-nmr with a quaternary signal for C-1 at δ 104.13. For compound **11**, ^1H-nmr spectra reveals an AMX system indicating a substitution on the C-6 or C-9 position. The disubstitution on C-1 and C-6 positions is finally determined by the presence of the signal at δ 9.21 attributed to H-9 according to the long range deshielding effect previously observed for **8** and **10**. In the two last cases **12,13**, substitution on the C-8 position is confirmed by ^{13}C-nmr with the quaternary signal of C-8 at δ 113.9 for **12** and δ 114.8 for **13**.

Scheme 3



Scheme 4

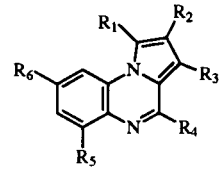


Table 1
Net Charges

	14 [a]	**14** [b]	**6** [a]	**6** [b]	**15** [b]	**8** [b]	**5** [b,c]	
C-1	-0.1226	-0.0500	-0.0431	0.0483	0.0448	-0.0353	-0.0656	
C-2	-0.1824	-0.1733	-0.1823	-0.1644	-0.1338	-0.1312	-0.1621	
C-3	-0.1515	-0.0349	-0.0865	0.0251	-0.0618	0.0114	-0.0553	
C-3a	-0.1191	-0.1820	-0.1302	-0.1931	-0.1768	-0.1805	-0.1690	
C-4	0.0023	0.1554	0.0089	0.1651	0.1637	0.1616	0.3360	
N-5	-0.1365	-0.1443	-0.1336	-0.1400	-0.1369	-0.1305	-0.2211	
C-5a	-0.0335	-0.0081	-0.0258	-0.0108	-0.0100	-0.0153	0.0304	
C-6	-0.0774	-0.1130	-0.0783	-0.1100	-0.1098	-0.1126	-0.1296	
C-7	-0.1421	-0.0829	-0.1353	-0.0822	-0.0807	-0.0802	-0.0759	
C-8	-0.1062	-0.0799	-0.1057	-0.0779	-0.0782	-0.0722	-0.1108	
C-9	-0.1435	-0.1112	-0.1389	-0.1096	-0.1076	-0.1161	-0.0861	
C-9a	0.0258	0.0307	0.0168	0.0310	0.0290	0.0387	-0.0062	
N-10	-0.0482	-0.0307	-0.0449	-0.0338	-0.0243	-0.0206	0.0427	
	5 [b,d]	**5** [b,e]	**17** [b]	**16** [b]	**13** [b]	**11** [b]	**12** [b]	**18** [b]
C-1	-0.0644	-0.0603	-0.1169	-0.0657	-0.0641	-0.1158	-0.1152	-0.0597
C-2	-0.1632	-0.1619	-0.1312	-0.1611	-0.1611	-0.1304	-0.1308	-0.1603
C-3	-0.0450	-0.0234	-0.0640	-0.0574	-0.0572	-0.0614	-0.0611	-0.0550
C-3a	-0.1733	-0.1552	-0.1620	-0.1753	-0.1752	-0.1621	-0.1623	-0.1750
C-4	0.3483	0.3705	0.3334	0.3375	0.3370	0.3349	0.3344	0.3381
N-5	-0.2064	-0.1650	-0.2277	-0.2329	-0.2333	-0.2292	-0.2296	-0.2339
C-5a	-0.0253	0.0074	0.0344	0.0573	0.0406	0.0593	0.0424	0.0648
C-6	-0.1271	-0.1184	-0.1351	-0.1749	-0.1298	-0.1777	-0.1337	-0.1749
C-7	-0.0769	-0.0793	-0.0716	-0.0499	-0.0556	-0.0459	-0.0519	-0.0302
C-8	-0.1086	-0.0995	-0.1146	-0.1170	-0.1538	-0.1169	-0.1537	-0.1574
C-9	-0.0882	-0.0937	-0.0931	-0.0748	-0.0634	-0.0826	-0.0714	-0.0534
C-9a	-0.0035	0.0071	-0.0159	-0.0052	-0.0064	-0.0134	-0.0145	-0.0041
N-10	0.0401	0.0316	0.0649	0.0418	0.0420	0.0619	0.0620	0.0394

[a] Neutral species. [b] Protonated species. Dihedral angle: [c] 0°, [d] 45°; [e] 90°.

Table 2
π_z Densities

	14 [a]	**14** [b]	**6** [a]	**6** [b]	**15** [b]	**8** [b]	**5** [b,c]	
C-1	0.985	0.9485	1.0246	0.9034	0.9074	0.9984	0.9754	
C-2	1.078	1.0517	1.1732	1.1290	1.1159	1.1131	1.1049	
C-3	1.061	0.9296	1.0057	0.8748	0.9634	0.8814	0.9338	
C-3a	1.146	1.2329	1.1597	1.2470	1.2439	1.2349	1.2804	
C-4	0.908	0.7919	0.9028	0.7802	0.7802	0.7811	0.8092	
N-5	1.140	1.5402	1.1383	1.5329	1.5308	1.5186	1.6561	
C-5a	1.029	1.0830	1.0216	1.0871	1.0852	1.0913	1.0513	
C-6	0.968	1.0029	0.9678	0.9993	0.9986	1.0018	1.0267	
C-7	1.012	0.9412	1.0032	0.9399	0.9378	0.9371	0.9343	
C-8	0.982	0.9373	0.9810	0.9344	0.9338	0.9336	0.9643	
C-9	1.041	1.0015	1.0349	0.9884	0.9968	0.9873	0.9776	
C-9a	1.030	1.0643	1.0430	1.0664	1.0696	1.0650	1.1117	
N-10	1.500	1.4745	1.4919	1.4777	1.4705	1.4818	1.4555	
	5 [b,d]	**5** [b,e]	**17** [b]	**16** [b]	**13** [b]	**11** [b]	**12** [b]	**18** [b]
C-1	0.9722	0.9630	1.0592	0.9767	0.9734	1.0578	1.0542	0.9749
C-2	1.1046	1.0978	1.0901	1.1046	1.1043	1.0888	1.0889	1.1024
C-3	0.9215	0.9009	0.9455	0.9361	0.9355	0.9426	0.9419	0.9331
C-3a	1.2733	1.2412	1.2758	1.2857	1.2866	1.2758	1.2770	1.2862
C4	0.8012	0.7647	0.8185	0.8149	0.8149	0.8177	0.8176	0.8145
N-5	1.6325	1.5609	1.6615	1.6652	1.6689	1.6597	1.6635	1.6663
C-5a	1.0527	1.0616	1.0481	1.0385	1.0389	1.0371	1.0380	1.0291
C-6	1.0228	1.0105	1.0335	1.1011	1.0295	1.1045	1.0321	1.1008
C-7	0.9345	0.9345	0.9294	0.9187	0.9247	0.9132	0.9197	0.9089
C-8	0.9616	0.9504	0.9640	0.9695	1.0331	0.9687	1.0321	1.0365
C-9	0.9794	0.9837	0.9622	0.9641	0.9666	0.9487	0.9515	0.9539
C-9a	1.1083	1.0959	1.1217	1.1147	1.1144	1.1228	1.1226	1.1157
N-10	1.4552	1.4554	1.4453	1.4583	1.4584	1.4496	1.4497	1.4616

[a] Neutral species. [b] Protonated species. Dihedral angle: [c] 0°; [d] 45°; [e] 90°.

Table 3
Bond Order

	14 [a]	**14** [b]	**6** [a]	**6** [b]	**15** [b]	**8** [b]	**5** [b,c]	
C1-C2	1.504	1.3352	1.4358	1.3084	1.3134	1.2969	1.3953	
C2-C3	1.331	1.5065	1.2836	1.4529	1.4237	1.4472	1.3621	
C3-C3a	1.459	1.2484	1.4908	1.2734	1.2462	1.2848	1.4279	
C3a-C4	1.060	1.3250	1.0504	1.3057	1.3069	1.2858	1.3780	
C4-N5	1.758	1.3917	1.7697	1.4106	1.4116	1.4281	1.3797	
N5-C5a	1.104	1.0186	1.0972	1.0125	1.0136	1.0130	1.3523	
C5a-C6	1.305	1.3226	1.3116	1.3295	1.3294	1.3324	1.4063	
C6-C7	1.484	1.4692	1.4778	1.4619	1.4619	1.4586	1.4061	
C7-C8	1.347	1.3532	1.3529	1.3599	1.3594	1.3625	1.4043	
C8-C9	1.479	1.4659	1.4725	1.4579	1.4576	1.4536	1.4043	
C9-C9a	1.315	1.3269	1.3233	1.3351	1.3353	1.3371	1.4203	
C9a-N10	1.024	0.9981	1.0099	0.9909	0.9887	0.9916	1.3521	
C1-N10	1.180	1.3212	1.2344	1.3430	1.3407	1.2927	1.3506	
C3-N10	1.087	1.0101	1.0704	1.0040	1.0140	1.0163	1.3466	
C5a-C9a	1.299	1.3113	1.3013	1.3099	1.3092	1.3000	1.4060	
	5 [b,d]	**5** [b,e]	**17** [b]	**16** [b]	**13** [b]	**11** [b]	**12** [b]	**18** [b]
C1-C2	1.3952	1.3952	1.3953	1.3953	1.3953	1.3953	1.3953	1.3953
C2-C3	1.3621	1.3621	1.3621	1.3621	1.3621	1.3621	1.3621	1.3621
C3-C3a	1.4279	1.4279	1.4279	1.4279	1.4279	1.4279	1.4279	1.4279
C3a-C4	1.3780	1.3780	1.3780	1.3780	1.3780	1.3780	1.3780	1.3780
C4-N5	1.3797	1.3797	1.3797	1.3797	1.3797	1.3797	1.3797	1.3797
N5-C5a	1.3523	1.3523	1.3523	1.3523	1.3523	1.3523	1.3523	1.3523
C5a-C6	1.4063	1.4062	1.4063	1.4063	1.4063	1.4063	1.4063	1.4063
C6-C7	1.4061	1.4061	1.4061	1.4061	1.4061	1.4061	1.4061	1.4061
C7-C8	1.4043	1.4043	1.4043	1.4043	1.4043	1.4043	1.4043	1.4043
C8-C9	1.4043	1.4043	1.4043	1.4043	1.4043	1.4043	1.4043	1.4043
C9-C9a	1.4203	1.4203	1.4203	1.4203	1.4203	1.4203	1.4203	1.4203
C9a-N10	1.3521	1.3521	1.3521	1.3521	1.3521	1.3521	1.3521	1.3521
C1-N10	1.3506	1.3506	1.3506	1.3506	1.3506	1.3506	1.3506	1.3506
C3a-N10	1.3466	1.3466	1.3466	1.3466	1.3466	1.3466	1.3466	1.3466
C5a-C9a	1.4060	1.4060	1.4060	1.4060	1.4060	1.4060	1.4060	1.4060

[a] Neutral species. [b] Protonated species. Dihedral angle: [c] 0°; [d] 45°; [e] 90°.

Since the two positions of substitutions 1 and 3 for products **6** and **14** and the three positions 1, 6 and 8 for the product **5** are more hindered than the other possible substitution positions, we decided to study the theoritical electron distribution to determine wether the regiospecificity was charge-controlled. Because of the size of the molecules we used a semi empirical approach (MOPAC 6.0-AM1 Hamiltonian). Furthermore, we have also studied the molecular electrostatic potentials and the molecular accessibility since they can be a key factor in the control of the long distance interactions during the approach of the electrophilic bromine reactant. The main electronic characteristics of all the derivatives are shown in Tables 1-3. The net atomic charges are reported in Table 1, the π_z densities in Table 2 and the bond orders in Table 3.

The calculations were performed on neutral and/or N-5 protonated species. In the case of the compound **5**, the study was carried out on the cation given that at experimental conditions, protonated species are the most abundant. To examine the effect on the conjugation between nitrogen and the aromatic moiety, we computed the electronic distribution (net charges, π_z densities and bond orders) of the three rotamers with a dihedral

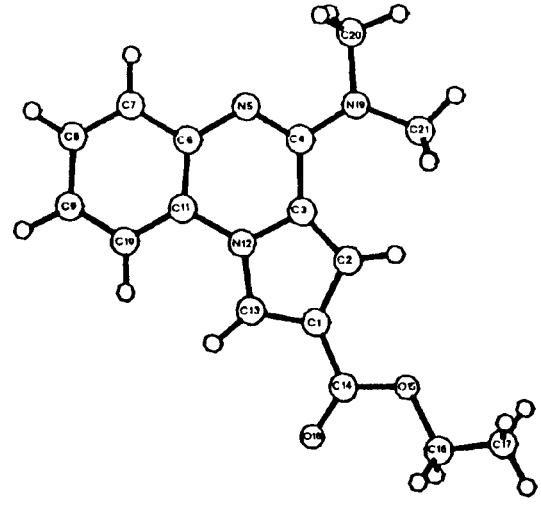


Figure 1. X-Ray numbering.

Table 4

Bond Distances (A) and Angles (°) of **5**

Atom A	Atom B	Atom C	Bond distance (A) A-B	Angle (°) A-B-C
C(2)	C(1)	C(13)	1.413(5)	108.3(3)
C(13)	C(1)	C(14)	1.376(5)	123.1(3)
C(14)	C(1)	C(2)	1.451(5)	128.6(3)
C(1)	C(2)	C(3)		107.4(3)
C(2)	C(3)	C(4)	1.380(5)	137.6(3)
C(2)	C(3)	N(12)		106.7(3)
C(3)	C(4)	N(5)	1.457(5)	122.4(3)
C(3)	C(4)	N(19)		120.1(3)
C(4)	N(5)	C(6)	1.305(5)	119.8(3)
N(5)	C(6)	C(7)	1.382(5)	119.8(3)
C(7)	C(6)	C(11)	1.403(6)	116.5(3)
C(11)	C(6)	N(5)	1.388(5)	123.7(3)
C(6)	C(7)	C(8)		121.8(4)
C(7)	C(8)	C(9)	1.366(7)	120.2(4)
C(8)	C(9)	C(10)	1.397(6)	119.4(4)
C(9)	C(10)	C(11)	1.372(6)	119.7(4)
C(10)	C(11)	C(12)	1.384(5)	122.1(3)
C(6)	C(11)	C(10)		122.4(3)
C(6)	C(11)	N(12)		115.5(3)
C(11)	N(12)	C(13)	1.415(4)	127.1(3)
C(3)	N(12)	C(11)		122.9(3)
C(3)	N(12)	C(13)		110.0(3)
N(12)	C(13)	C(1)	1.357(4)	107.6(3)
C(1)	C(14)	O(18)		124.1(3)
O(15)	C(14)	C(1)	1.323(5)	113.4(3)
O(18)	C(14)	O(15)	1.209(5)	122.6(3)
C(16)	O(15)	C(14)	1.461(6)	117.1(3)
C(17)	C(16)	O(15)	1.377(9)	110.7(5)
C(20)	N(19)	C(4)	1.467(6)	118.2(3)
C(21)	N(19)	C(4)	1.438(6)	126.1(3)

Table 5

Atomic Positions as Fractional Coordinates (x10^4) of **5** with the Estimated Standard Deviations in Parentheses

Atom	x/a(σ)	y/b(σ)	z/c(σ)	B_{eq}/B_i
C(1)	6978(4)	807(4)	-600(2)	4.8(2)
C(2)	5530(4)	1402(4)	-667(2)	4.9(2)
C(3)	5419(4)	2267(4)	-33(2)	4.6(2)
C(4)	4300(4)	3178(4)	271(2)	5.3(2)
N(5)	4567(4)	3913(4)	907(2)	5.8(2)
C(6)	5949(4)	3828(4)	1319(2)	5.4(2)
C(7)	6245(5)	4644(5)	1994(3)	7.0(2)
C(8)	7591(6)	4585(5)	2422(3)	7.1(2)
C(9)	8722(5)	3699(5)	2193(2)	6.3(2)
C(10)	8472(4)	2900(4)	1531(2)	5.4(2)
C(11)	7102(4)	2972(4)	1104(2)	4.8(2)
N(12)	6791(3)	2193(3)	410(2)	4.5(1)
C(13)	7731(4)	1318(4)	67(2)	4.6(1)
C(14)	7623(4)	-204(4)	-1109(2)	5.3(2)
O(15)	6709(3)	-556(3)	-1717(2)	6.5(1)
C(16)	7250(6)	-1611(7)	-2249(3)	8.7(3)
C(17)	6284(8)	-1701(8)	-2904(3)	12.0(4)
O(18)	8873(3)	-678(4)	-1000(2)	7.5(2)
N(19)	2921(3)	3295(4)	-111(2)	6.4(2)
C(20)	1848(5)	4269(6)	203(3)	8.2(3)
C(21)	2369(5)	2485(6)	-784(3)	7.9(3)

N5/C4/N19/C20 (crystallographic numbering) constrained respectively to 0°, 45° and 90°. This conformational study is necessary because the electronic distribution computed with semi-empirical methods is highly dependent on the relative position of the heterocycle and the amino chain. Despite this fact, all these rotamers exhibit a π_z densities in full agreement with the observed bromination positions. For the derivatives **6** and **14** the theoretical results, including MEP's and accessibility surfaces, do not correlate with the observed reactivity; in these cases the transition state of the reaction may be electronically quite different from the ground state starting structure.

Crystallography.

Crystal Data for **5**.

The data are: $C_{16}H_{17}N_3O_2$, mp 179-181°, mol weight 283.33, monoclinic, space group $P2_1/n$, a = 9.095(1)°, b = 8.972(1), c = 17.749(3) A, β = 96.59(1)°, V = 1438.66A^3, Z = 4, D_c = 1.31 g cm^{-3}, T = 293K.

EXPERIMENTAL

General Details.

Melting points were determined on a Kofler hot stage and are uncorrected. Spectral measurements were taken using the following instruments: ^{1}H-nmr spectra were recorded on a Varian EM 360 (60 MHz) or a Brüker MSL 300; ^{13}C-nmr spectra were obtained at 26° with proton noise decoupling at 75.47 MHz with a Brüker MSL 300 instrument. Chemical shifts are expressed relative to internal tetramethylsilane in deuteriochloroform at a concentration of *ca* 5%. Mass spectra were recorded on a LKB 2091 spectrometer at 70 eV [(θ_{source}): 180°]. Compounds were purified by high performance liquid chromatography (hplc), Waters M590 on a preparative silica gel column. Thin layer chromatography (tlc) were performed on 0.25 mm E. Merck precoated neutral alumina plates.

X-ray Crystallography.

The crystal structure of **5** was established by X-ray diffraction. Intensity data up to θ = 65° were collected on a fully automated Enraf-Nonius CAD-4 diffractometer using graphite monochromated CuK_α radiation λ = 1.54178 A of the unique reflections, 1578 with I > 3σ (I) were considered as observed. The intensities were corrected for Lorentz and polarization effects but not for absorption. The structure was solved by routine application of the Multan Program [11]. The positions of the non-hydrogen atoms were refined by block diagonal least-squares with anisotropic thermal parameters. The hydrogen atoms were derived from difference Fourier synthesis and refined with isotropic thermal parameters. The final minimum residual was R = 0.064.

Theoretical Calculations.

We have generated and optimized the molecular structure *in vacuo* of 11 pyrroloquinoxaline derivatives (brominated or not), using the X-ray determination as a starting material. Using the Molecular Advanced Design Software (M.A.D.) [12] we have generated the refined cartesian coordinates of all the neutral

and/or protonated species. We have studied the electron distribution by a semiempirical method (MOPAC 6.0 with AM1 hamiltonian [13] using keyword PRECISE). A complementary study of the electrostatic molecular potential (MEP's) was made by the VSEM method [14] which allows a bi or tridimensional visualization, and the accessibility surface was computed using the Conolly algorithm [15].

2-Chloro-3-methylquinoxaline (**1b**).

3-Methylquinoxalin-2-ol (15 g, 0.09 mole) was suspended in phosphorus oxychloride (100 ml) and refluxed for 1 hour. Phosphorus oxychloride was distilled off and the dark residue poured into ice. The solution was basified with sodium carbonate, extracted with dichloromethane. After drying, the solvent was removed *in vacuo* and the residue submitted to chromatography on silica gel. Elution with dichloromethane gave 11.3 g (68%) of **1b** as white plates, mp 80-82° [lit [16] 84-86°].

2-Dimethylamino-3-methylquinoxaline (**1c**).

To 10 ml of dimethylamine (40% in water) was added 3.2 g (0.02 mole) of **1b** and the suspension refluxed for 30 minutes. After cooling, the solution was extracted with methylene chloride. The organic layers were dried (sodium sulfate), concentrated *in vacuo* and chromatographed on silica gel. Elution with dichloromethane gave 3 g (88%) of (**1c**), mp 177-179°, ^{1}H-nmr (deuteriochloroform): (60 MHz) δ 2.75 (3H, s, CH_3), 3.06 (6H, s, $N(CH_3)_2$), 7.50 (2H, m), 7.83 (2H, m).

Anal. Calcd. for $C_{11}H_{13}N_3$: C, 70.56; H, 7.00; N, 22.44. Found: C, 70.42; H, 7.12; N, 22.46.

Ethyl 4-Hydroxypyrrolo[1,2-*a*]quinoxaline-2-carboxylate (**2**) and 2-Ethoxy-3-methylquinoxaline (**3**).

2-Chloro-3-methylquinoxaline (**1b**) (1.5 g, 8.4 mmoles) and ethyl bromopyruvate (2.2 g, 11.3 mmoles) were refluxed for 8 hours in dry ethanol. After cooling the precipitate was filtered to give 500 mg of ethyl 4-hydroxypyrrolo[1,2-*a*]quinoxaline-2-carboxylate (**2**) (26%), mp >260°; ir: (potassium bromide), cm^{-1}: 3440 (OH), 1670 (C=O) and 1280 (C-O-C); ms: 256 (M^+, 100).

Anal. Calcd. for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93. Found: C, 65.44; H, 4.60; N, 10.84.

The filtrate was evaporated to dryness and the residue solubilized in water. The solution was made alkaline with sodium carbonate, extracted with methylene chloride. After drying, the residue was evaporated to dryness and the residual oil chromatographed on neutral alumina. Elution with methylene chloride gave 200 mg of 2-ethoxy-3-methylquinoxaline (**3**) (13%), mp 56-58°; ^{1}H nmr (deuteriochloroform): (60 MHz) δ 1.47 (3H, t, CH_2-CH_3), 2.62 (3H, s, CH_3), 4.53 (2H, q, CH_2-CH_3), 7.53 (2H, m), 7.93 (2H, m), [lit [17]: 55-57°].

Ethyl 4-chloropyrrolo[1,2-*a*]quinoxaline-2-carboxylate (**4**).

Compound **2** (0.5 g, 2 mmoles) was refluxed for 1hour in phosphorus oxychloride (5 ml). After cooling the solution was poured into ice, and the solution made alkaline with sodium carbonate. After extraction with dichlormethane, drying and evaporation in vacuo, the residue was chromatographed on silica gel. Elution with dichloromethane gave 0.48 g of **3** (89%), mp 162-164°, ^{1}H-nmr (deuteriochloroform): (60 MHz) δ 1.42 (3H, t, CH_2-CH_3), 4.43 (2H, q, CH_2-CH_3), 7.10 (d, $J_{1,3}$ = 1.5 Hz, H-3), 7.57 (2H, m), 7.90 (2H, m), 8.47 (d, H-1).

Anal. Calcd. for $C_{14}H_{11}ClN_2O_2$: C, 61.21; H, 4.04; N, 10.20. Found: C, 61.37; H, 4.12; N, 10.03.

Ethyl 4-Dimethylaminopyrrolo[1,2-*a*]quinoxaline-2-carboxylate (**5**).

Method A.

To a solution of 3 g (0.016 mole) of **1c** in dry ethanol (50 ml) was added 4.4 g (0.02 mole) of ethyl bromopyruvate. The mixture was refluxed for 8 hours. After filtration, the solid was suspended in water, made alkaline with sodium carbonate and extracted with dichloromethane. After drying, the organic layers were evaporated to give 1.9 g (42%) of **5** as yellow plates, mp 179-181°; ms: 283 (M^+, 51), 268 (M^+ -CH_3, 24), 254 (M^+ -C_2H_5, 56), 240 (34), 226 (24), 212 (20), 195 (13), 181 (4), 167 (27), 149 (100); ^{1}H-nmr (deuteriochloroform): (300 MHz) δ 1.42 (3H, t, CH_2-CH_3), 3.41 (6H, s, $N(CH_3)_2$), 4.32 (2H, q, CH_2-CH_3), 7.16 (ps t, $J_{7,8} = J_{6,7}$ = 8 Hz, $J_{7,9}$ = 1.5 Hz, H-7), 7.29 (d, $J_{1,3}$ = 1.5 Hz, H-3), 7.31 (ps t, $J_{8,9}$ = 8 Hz, H-8), 7.57 (dd, $J_{6,8}$ = 1.5 Hz, H-6), 7.66 (dd, H-9), 8.28 (d, H-1); ^{13}C-nmr (deuteriochloroform): (75.4 MHz) δ 14.6 (CH_2-CH_3), 40.4 ($N(CH_3)_2$), 60.5 (CH_2-CH_3), 109.3 (C-3), 113.4 (C-9), 117.6 (C-1), 118.9 (C-3a), 120.4 (C-2), 122.9 (C-8), 124.3 (C-9a), 126.3 (C-7), 126.8 (C-6), 137.3 (C-5a), 151.8 (C-4), 164.5 (C=O).

Anal. Calcd. for $C_{16}H_{17}N_3O_2$: C, 67.83; H, 6.05; N, 14.83. Found: C, 68.01; H, 5.87; N, 14.94.

Method B.

Compound **4** (150 mg, 0.5 mmole) was suspended in dimethylamine (1.5 ml of a 40% solution in water) and refluxed for 2 hours. Treatment as above gave 120 mg (80%) of (**5**).

Ethyl Pyrrolo[1,2-*a*]quinoxaline-2-carboxylate (**6**).

Ten g of 2-methylquinoxaline (0.07 mole) and 12.9 g (0.1 mole) of ethyl bromopyruvate in 100 ml of dry ethanol were refluxed for 24 hours. The solvent was removed *in vacuo* and the residue treated with water. The solution was basified with sodium carbonate and extracted with dichloromethane. The organic layers were dried, evaporated *in vacuo* and the residue submitted to chromatography on neutral alumina. Elution with methylene chloride gave 2.4 g (14%) of **6**, mp 145-148°, ^{1}H-nmr (deuteriochloroform): (300 MHz) δ 1.40 (3H, t, CH_2-CH_3), 4.38 (2H, q, CH_2-CH_3), 7.29 (d, $J_{1,3}$ = 1.4 Hz, H-3), 7.50 (ps t, $J_{7,8}$ = 8.6 Hz, $J_{7,9}$ = 1.7 Hz, H-7), 7.56 (ps t, $J_{8,9}$ = 8.9 Hz, $J_{6,8}$ = 1.9 Hz, H-8), 7.89 (dd, H-9), 7.97 (dd, H-6, $J_{6,7}$ = 8.6 Hz), 8.43 (d, H-1), 8.73 (s, H-4); ^{13}C-nmr (75.4 MHz) δ 14.5 (CH_2-CH_3), 60.7 (CH_2-CH_3), 108.5 (C-3), 114.1 (C-9), 117.4 (C-1), 120.9 (C-2), 126.4 (C-3a), 126.5 (C-7), 127.4 (C-9a), 128.5 (C-8), 130.3 (C-6), 135.9 (C-5a), 146.4 (C-4), 164.1 (CO).

Anal. Calcd. for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 69.82; H, 5.12; N, 11.57.

Bromination of **6**.

Compound **6** (0.5 g, 2 mmoles) dissolved in acetic acid was treated with bromine (0.24 ml, 4 mmoles). The mixture was stirred for 1 hour at 20° and the suspension was filtered. The precipitate was dissolved in water, made basic with sodium carbonate and extracted with dichloromethane. After drying (sodium sulfate), evaporation *in vacuo*, the residue was chromatographed on silica gel. Elution with dichloromethane gave 0.70 g of **7** as ethyl 1,3-dibromopyrrolo[1,2-*a*]quinoxaline-2-carboxylate (84%), mp 120-122°, ms: 400 (M^+ +4, 52), 398 (M^+ +2, 100), 396 (M^+, 51), 368 (M^+ -C_2H_4, 34), 351 (M^+ -OC_2H_5, 21), 323 (M^+ -CO_2H_5), 273 (52); ^{1}H-nmr (deuteriochloroform): (60

MHz) δ 1.46 (3H, t, CH_2-CH_3), 4.50 (2H, q, CH_2-CH_3), 7.53 (2H, m, H-7,8), 7.97 (m, H-6), 8.83 (s, H-4), 9.40 (m, H-9).

Anal. Calcd. for $C_{14}H_{10}Br_2N_2O_2$: C, 42.24; H, 2.53; N, 7.04. Found: C, 42.10; H, 2.66; N, 7.16.

Further elution gave **8** 0.04 g (6%) as ethyl 1-bromopyrrolo-[1,2-*a*]quinoxaline-2-carboxylate, mp 97-99°, ms: 320 (M^+ +2, 60), 318 (M^+, 62), 290 (M^+ -C_2H_4, 27), 273 (M^+ -OC_2H_5, 35), 245 (M^+ -CO_2H_5, 11), 195 (54), 167 (49); ^{1}H-nmr (deuteriochloroform): (60 MHz) δ 1.42 (3H, t, CH_2-CH_3), 4.40 (2H, q, CH_2-CH_3), 7.38 (s, H-3), 7.53 (2H, m, H-7,8), 7.98 (m, H-6), 8.70 (s, H-4), 9.78 (m, H-9).

Anal. Calcd. for $C_{14}H_{11}BrN_2O_2$: C, 52.69; H, 3.47; N, 8.78. Found: C, 52.77; H, 3.63; N, 8.66.

Ethyl 4-(4-Methylbenzoyl)pyrrolo[1,2-*a*]quinoxaline-2-carboxylate (**9**).

Potassium cyanide (1 g, 15.3 mmoles) was added to a solution of **6** (1 g, 4 mmoles) and 1 g (8.3 mmoles) of 4-methylbenzaldehyde in DMF (8 ml). The mixture was heated at 80° for 12 hours. After cooling, the solution was acidified with 1*N* hydrochloric acid, stirred overnight and extracted with dichloromethane. The organic layers were dried over calcium chloride, concentrated *in vacuo* and chromatographed on neutral alumina. Elution with dichloromethane led to **9** as white plates (12%), mp 186-188°; ^{1}H-nmr (deuteriochloroform): (300 MHz) δ 1.41 (3H, t, CH_2-CH_3), 2.18 (3H, s, CH_3), 4.48 (2H, q, CH_2-CH_3), 7.32 (d, J = 8 Hz, H-3',5'), 7.55 (td, $J_{6,7} = J_{7,8} = 7.5$ Hz, $J_{7,9} = 0.7$ Hz, H-7), 7.58 (d, $J_{1,3} = 1.3$ Hz, H-3), 7.67 (td, $J_{8,9} = 7.5$ Hz, $J_{6,8} = 1.2$ Hz, H-8), 7.97 (dd, H-9), 8.05 (dd, H-6), 8.54 (d, H-1); ^{13}C-nmr (deuteriochloroform): (75.4 MHz) δ 14.5 (CH_2-CH_3), 21.9 (CH_3), 60.8 (CH_2-CH_3), 109.1 (C-3), 114.2 (C-9), 117.8 (C-1), 121.5 (C-2), 1254.5 (C-3a), 126.7 (C-7), 127.4 (C-9a), 129.3 (C-3',5'), 131.2 (C-2',6'), 135.4 (C-5a), 145.1 (C-4'), 151.0 (C-4), 164.2 (C=O), 191.3 (C=O).

Anal. Calcd. for $C_{22}H_{18}N_2O_3$: C, 73.73; H, 5.06; N, 7.82. Found: C, 73.56; H, 5.09; N, 7.93.

Bromination of **5**.

Compound **5** (0.5 g, 1.76 mmoles) was dissolved in acetic acid and bromine (0.2 ml, 0.56 g, 3.5 mmoles) was added. The mixture was stirred for 1 hour. Workup as above gave ethyl 4-dimethylamino-1,6,8-tribromopyrrolo[1,2-*a*]quinoxaline-2-carboxylate (**10**) (3%) which could not be crystallized; ^{1}H-nmr (deuteriochloroform): (300 MHz) δ 1.42 (3H, t, CH_2-CH_3), 3.45 (6H, s, $N(CH_3)_2$), 4.39 (2H, q, CH_2-CH_3), 7.35 (s, H-3), 7.72 (d, $J_{7,9} = 2$ Hz, H-7), 9.26 (d, H-9); ^{13}C-nmr (deuteriochloroform): (75.4 MHz) δ 14.4 (CH_2-CH_3), 40.6 ($N(CH_3)_2$), 60.9 (CH_2-CH_3), 104.1 (C-1), 111.2 (C-3), 112.4 (C-8), 118.5 (C-9), 119.8 (C-3a), 121.5 (C-2 or C-6)), 122.0 (C-2 or C-6), 126.5 (C-9a), 132.8 (C-7), 135.8 (C-5a), 150.9 (C-4), 162.7 (C=O).

Anal. Calcd. for $C_{16}H_{14}Br_3N_3O_2$: C, 36.96; H, 2.71; N, 8.08. Found: C, 36.80; H, 2.60; N, 7.96.

Further elution gave (**11**) as ethyl 4-dimethylamino-1,6-dibromopyrrolo[1,2-*a*]quinoxaline-2-carboxylate (2%) as a yellow oil; ^{1}H-nmr (deuteriochloroform): (300 MHz) δ 1.41 (3H, t, CH_2-CH_3), 3.46 (6H, s, $N(CH_3)_2$), 4.41 (2H, q, CH_2-CH_3), 7.01 (t, $J_{7,8} = J_{8,9} = 8$ Hz, H-8), 7.47 (s, H-3), 7.70 (d, $J_{7,9} = 1.5$ Hz, H-7), 9.21 (d, H-9).

Anal. Calcd. for $C_{16}H_{15}Br_2N_3O_2$: C, 43.57 H, 3.43; N, 9.53. Found: C, 43.69; H, 3.56; N, 9.41.

Further elution gave **12** as ethyl 4-dimethylamino-1,8-dibromopyrrolo[1,2-*a*]quinoxaline-2-carboxylate (51%), mp 179-181°, ms: 445 (M^+ +4, 9), 443 (M^+ +2, 17), 441 (M^+, 11); ^{1}H-nmr (deuteriochloroform): (300 MHz) δ 1.43 (3H, t, CH_2-CH_3), 3.35 (6H, s, $N(CH_3)_2$), 4.40 (2H, q, CH_2-CH_3), 7.41 (s, H-3), 7.45 (2H, m, H-6,7), 9.40 (p s, H-9); ^{13}C-nmr (deuteriochloroform): (75.4 MHz) δ 14.5 (CH_2-CH_3), 40.6 ($N(CH_3)_2$), 60.9 (CH_2-CH_3), 103.6 (C-1), 110.9 (C-3), 113.9 (C-8), 119.1 (C-3a), 119.2 (C-9), 121.9 (C-2), 126.6 (C-9a), 128.2 (C-6), 129.8 (C-7), 137.8 (C-5a), 152.0 (C-4), 163.1 (C=O).

Anal. Calcd. for $C_{16}H_{15}Br_2N_3O_2$: C, 43.57; H, 3.43; N, 9.53. Found: C, 43.50; H, 3.60; N, 9.47.

Further elution gave **13** as ethyl 4-dimethylamino-8-bromopyrrolo[1,2-*a*]quinoxaline-2-carboxylate, mp 187-189°; ms: 363 (M^+ +2, 95), 361 (M^+, 95), 348-346 (M^+ -CH_3, 42-44), 332 (M^+ -C_2H_5, 66), 318 (50), 304 (26), 290 (22), 273 (14), 248 (11), 167 (32), 149 (100); ^{1}H-nmr (deuteriochloroform): (300 MHz) δ 1.41 (3H, t, CH_2-CH_3), 3.37 (6H, s, $N(CH_3)_2$), 4.37 (2H, q, CH_2-CH_3), 7.26 (d, $J_{1,3} = 2$ Hz, H-3), 7.37 (2H, m, H-6,7), 7.75 (p.s, H-9), 8.16 (d, H-1); ^{13}C-nmr (deuteriochloroform): (75.4 MHz) δ 14.5 (CH_2-CH_3), 40.3 ($N(CH_3)_2$), 60.3 (CH_2-CH_3), 109.6 (C-3), 114.8 (C-8), 116.4 (C-1 or C-9), 117.7 (C-1 or C-9), 119.3 (C-3a), 120.0 (C-2), 125.0 (C-9a), 128.0 (C-7), 129.3 (C-6), 136.3 (C-5a), 151.6 (C-4), 164.2 (C=O).

Anal. Calcd. for $C_{16}H_{16}BrN_3O_2$: C, 53.05; H, 4.45; N, 11.60. Found: C, 52.82; H, 4.56; N, 11.72.

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