Synthesis, Structural and Conformational Study of some Amides Derived from 3,7-Dimethyl-9-amino-3,7-diazabicyclo[3.3.1]nonane-9-carboxamide

M. J. Fernandez, M. S. Toledano and E. Gálvez*

Departamento de Química Orgánica, Universidad de Alcalá,
Madrid Spain

E. Matesanz

Instituto de Ciencia de Materiales (Sede C) C.S.I.C., Serrano 115,
28006 Madrid, Spain

M. Martínez-Ripoll

Instituto "Rocasolano" U.E.I. Cristalografía, C.S.I.C., Serrano 121,
28006 Madrid, Spain

Received September 19, 1991

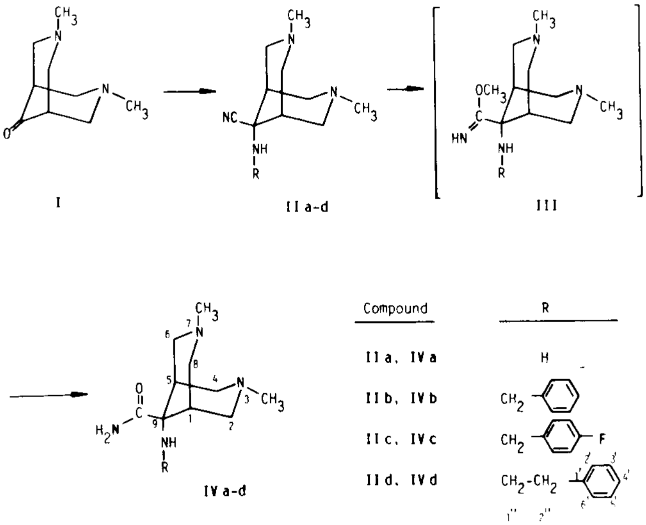
A series of 3,7-dimethyl-9-amino-3,7-diazabicyclo[3.3.1]nonane-9-carbonitrile and 3,7-dimethyl-9-amino-3,7-diazabicyclo[3.3.1]nonane-9-carboxamide *N*-substituted have been synthesized and studied by ^{1}H and ^{13}C nmr spectroscopy and the crystal structure of 3,7-dimethyl-9-benzylamino-3,7-diazabicyclo[3.3.1]nonane-9-carboxamide dihydrochloride (**IVb**•2HCl) has been determined by X-ray diffraction. The compounds studied display in deuteriochloroform, dimethyl sulfoxide-d$_6$ and methanol-d$_4$ the same preferred flattened chair-chair conformation with the methyl groups in equatorial position. The carboxamido group lies in a plane nearly perpendicular to the bispidine skeleton. The conformation and protonation sites of **IVb**•2HCl in the crystal state and in deuterium oxide solution are discussed.

J. Heterocyclic Chem., **29**, 723 (1992).

Introduction.

As a part of a research program related to the synthesis and structural study of new GABA$_B$ receptor antagonists, and in connection with our interest in the preparation and the structural study of bispidine derivatives [1,2], we report in this paper the synthesis and structural analysis carried out with the aid of ^{1}H and ^{13}C nmr spectroscopy of a series of 3,7-dimethyl-9-amino(or aralkylamino)-3,7-diazabicyclo[3.3.1]nonane-9-carboxamides **IVa-d** (Scheme I). In order to determine their preferred conformation both in solution and in the solid state, the crystal structure of compound **IVb**•2HCl has also been determined.

Scheme I



Results and Discussion.

Syntheses.

The schematic synthesis pathway for compounds **IVa-d** is represented in Scheme I. From the reaction of bispidinone **I** [3] with potassium cyanide and the corresponding amine at room temperature, the aminonitrile **II** (*via* ketimine) was obtained. By treating **IIa-d** with methanolic hydrogen chloride, the corresponding imidates **IIIa-d** were obtained, the hydrolysis of **IIIa-d** (which were not isolated) gave the amides **IVa-d**.

Description and Discussion of the Structure of **IVb**•2HCl.

(In this description and in Tables 2-8, numbers corresponding to those given in Figure 1).

Crystal data are shown in Table 1 [4-8]. Two crystallographically independent molecules (**1** and **2**) and four chlorine atoms form the asymmetric unit shown in Figure 1 together with the atomic numbering used in the X-ray analysis. A non-crystallographic symmetry center at -0.16, 0.24, -0.19 relates one part of the asymmetric unit to the other one. In order to compare both crystallographically independent molecules, a half normal probability plot [9] has been made using interatomic distances implying bonds, valence angles and torsional angles. This plot, shown in Figure 2, shows a straight line with zero intercept at -0.02(3), a slope of 2.48(3) and a correlation coefficient of 0.99 when the following distances are excluded: N2-C11, C3-C12, C5-N15, C8-N15, N13-N15, N15-C17, N15-C22 and C16-C22 for each molecule, which are the interatomic distances responsible for the small conformational differences between both molecules.

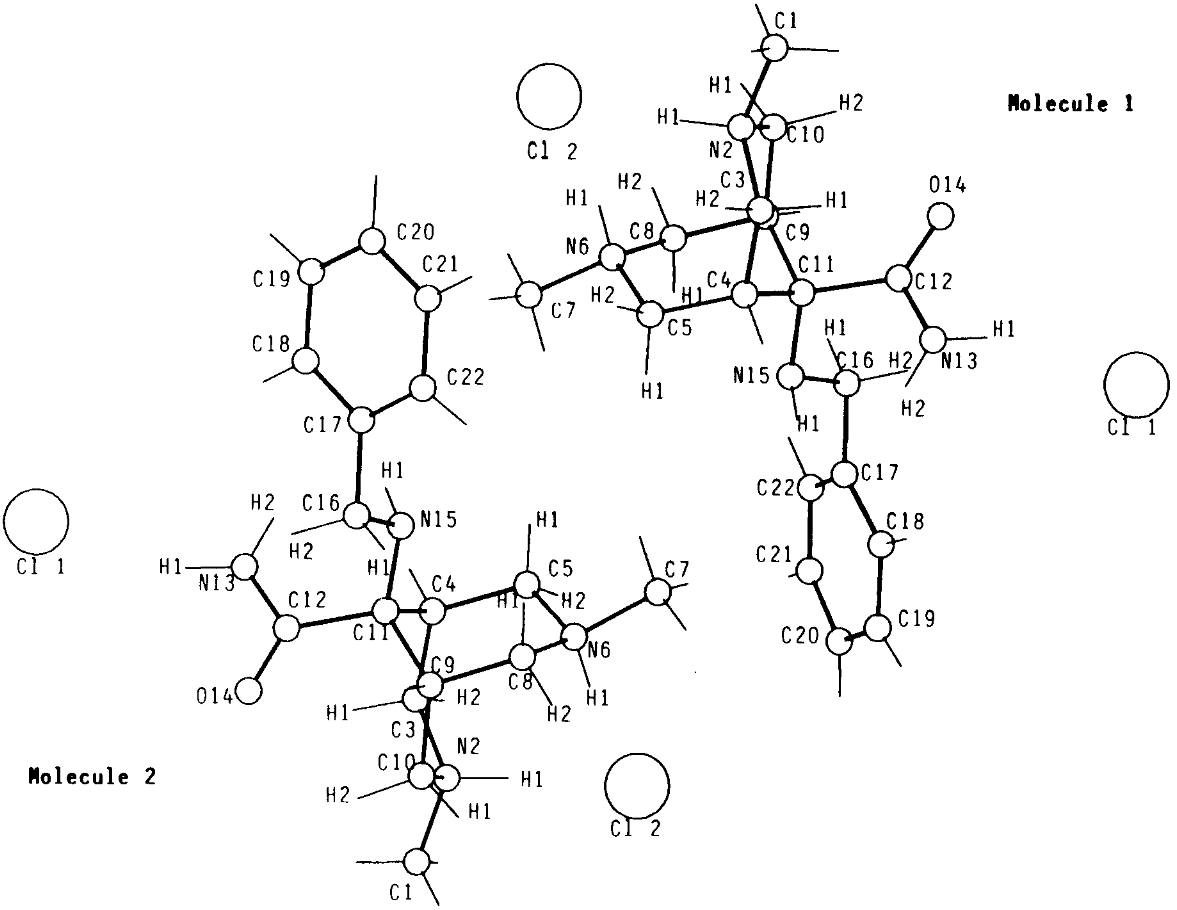


Figure 1. Perspective view and the numbering of the asymmetric unit of compound **IVb** •2HCl.

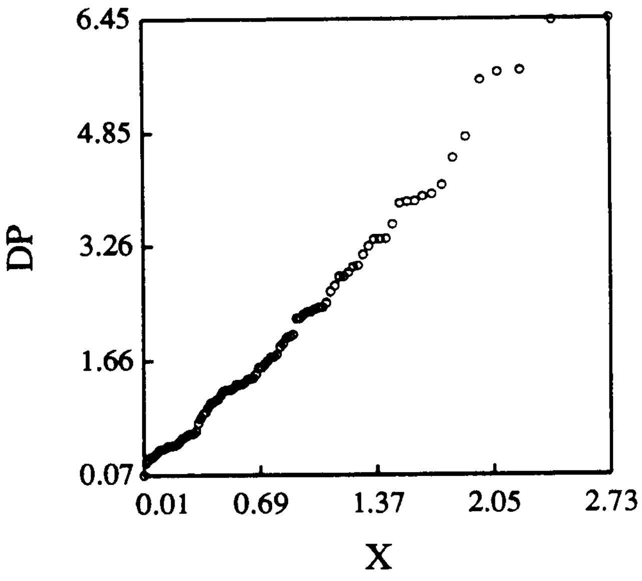


Figure 2

Table 2 contains the final atomic parameters. Tables 3, 4 and 5 show the bond lengths, bond angles and torsional angles, respectively.

The conformation of the piperidine rings can be described by the torsional angles reported in Table 5, and by the ring puckering coordinates [10] given in Table 6. The best least square planes through these piperidine rings (Table 7) show a distorted chair conformation of these rings. This conformation is attributed to the strong steric interaction between the H2 and H5 atoms, which is clearly reflected in the large value of N2...N6 contacts [3.150(3)Å in molecule 1 and 3.125(3)Å in molecule 2]. By comparing the best least square planes in compound **IVb**•2HCl and the N•••N (bispidine contacts) with those obtained in the case of 3,7-dimethyl-3,7-diazabicyclo[3.3.1]nonan-9-ol (**V**) [1], it can be deduced that the N-H•••H-N bispidine steric interaction in **IVb**•2HCl is more severe than lone pair-lone pair interaction in compound **V**.

Table 1

Experimental Data and Structure Refinement Procedures

Crystal data	
Formula	$C_{17}H_{28}ON_4Cl_2$
Symmetry	Monoclinic, $P2_1/c$
Unit cell determination:	Least-squares fit from 85 reflections (θ<44°)
Unit cell dimensions (Å)	11.1105 (3), 14.2059 (5), 24.587 (1)
(°)	90, 100.076 (3), 90
Packing: V(Å^3), Z	3820.8 (2), 8
Dc (g.cm^{-3}), M, F (000)	1.305, 750.681, 1600
μ(cm^{-1})	31.96
Experimental data	
Technique	Four circle diffractometer: Philips PW1100 Bisecting geometry Graphite oriented monochromator: CuKα ω/2θ scans Detector apertures 1x1°, up θmax. 65°
Number of reflections:	
Measured	6490
Observed	5544 (2σ (I) criterion)
Range of hkl	0 13, 0 16, -28 28, (sinθ/λ)mx. 05877
Solution and refinement	
Solution	Heavy atom method
Refinement	Least Squares on Fobs.
Parameters:	
Number of variables	601
Degrees of freedom	4943
Ratio of freedom	9.22
H atoms	Difference synthesis
Maximum final shift/error	0.78 (z of H1091)
w-scheme	empirical as to give no trends in <wΔ^2F> vs <|Fo|> or <sinθ/λ>
Final ΔF peaks	0.334 e/Å^3
Final R and Rw	0.049, 0.057
Computer and programs	VAX 6000-410, DIRDIF [4], XRAY76 [5], PESOS [6], PARST [7]
Scattering factors	Int. Tables for X-Ray Crystallography [8]
Anomalous dispersion	Int. Tables for X-Ray Crystallography [8]

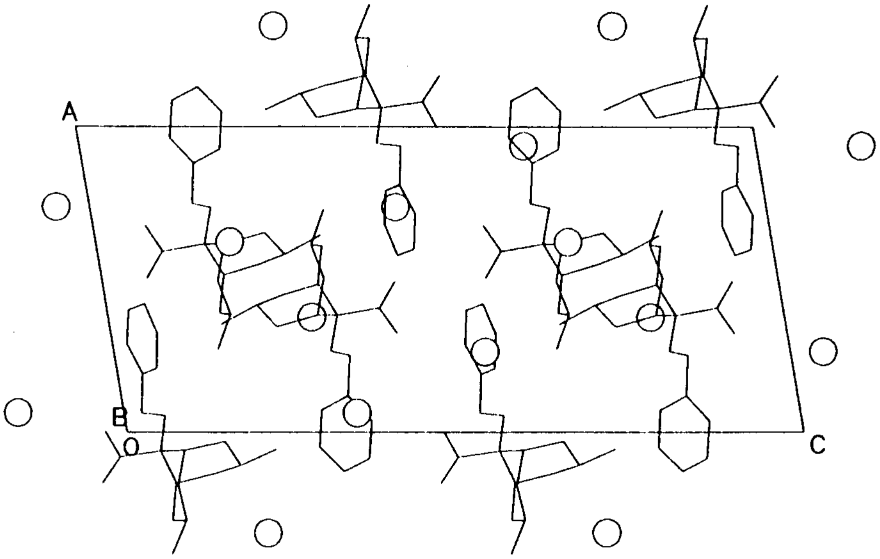


Figure 3. Crystal packing of compound **IVb** •2HCl.

Table 2-A
Atomic Parameters for Non H-Atoms

Coordinates and thermal parameters
as $U_{eq} = (1/6) . \Sigma[U_{ij}.a_i^*.a_j^*.a_i.a_j.\cos(a_i,a_j)].10^4$

Atom	x/a	y/b	z/c	Ueq
C1101	-0.06267 (6)	0.40265 (5)	0.15576 (3)	417 (2)
C1102	0.33119 (6)	0.36927 (5)	-0.18389 (3)	511 (2)
C101	0.4009 (3)	0.4122 (3)	-0.0374 (2)	567 (11)
N102	0.2908 (2)	0.3605 (2)	-0.06624 (9)	386 (7)
C103	0.1765 (2)	0.4147 (2)	-0.0628 (1)	382 (8)
C104	0.0593 (2)	0.3584 (2)	-0.0811 (1)	324 (7)
C105	0.0307 (2)	0.3341 (2)	-0.1425 (1)	363 (8)
N106	0.1097 (2)	0.2576 (2)	-0.16041 (8)	368 (7)
C107	0.0562 (3)	0.2221 (2)	-0.2169 (1)	525 (10)
C108	0.1365 (3)	0.1777 (2)	-0.1201 (1)	417 (9)
C109	0.1685 (2)	0.2102 (2)	-0.0603 (1)	359 (8)
C110	0.2911 (2)	0.2609 (2)	-0.0463 (1)	426 (9)
C111	0.0623 (2)	0.2691 (2)	-0.0455 (1)	324 (7)
C112	0.0830 (2)	0.2956 (2)	0.0167 (1)	377 (8)
N113	-0.0016 (2)	0.3516 (2)	0.0321 (1)	495 (8)
O114	0.1697 (2)	0.2646 (2)	0.04954 (8)	520 (7)
N115	-0.0538 (2)	0.2177 (2)	-0.06100 (8)	356 (6)
C116	-0.0627 (3)	0.1338 (2)	-0.0266 (1)	513 (10)
C117	-0.1896 (2)	0.0934 (2)	-0.0373 (1)	414 (8)
C118	-0.2865 (3)	0.1400 (2)	-0.0215 (2)	638 (13)
C119	-0.4016 (4)	0.1011 (4)	-0.0321 (2)	835 (18)
C120	-0.4208 (4)	0.0141 (4)	-0.0574 (2)	871 (18)
C121	-0.3239 (4)	-0.0341 (4)	-0.0690 (2)	967 (20)
C122	-0.2090 (3)	0.0058 (3)	-0.0598 (2)	719 (14)
C1201	-0.26324 (6)	0.10065 (5)	-0.54981 (3)	502 (2)
C1202	-0.62321 (8)	0.08525 (7)	-0.19850 (3)	644 (3)
C201	-0.7299 (3)	0.0822 (3)	-0.3450 (2)	581 (12)
N202	-0.6132 (2)	0.1274 (2)	-0.3176 (1)	384 (7)
C203	-0.5042 (2)	0.0735 (2)	-0.3289 (1)	413 (9)
C204	-0.3833 (2)	0.1245 (2)	-0.3100 (1)	374 (8)
C205	-0.3464 (3)	0.1369 (2)	-0.2476 (1)	463 (9)
N206	-0.4174 (2)	0.2111 (2)	-0.2231 (1)	482 (8)
C207	-0.3548 (4)	0.2364 (4)	-0.1659 (2)	780 (16)
C208	-0.4452 (3)	0.2976 (2)	-0.2577 (1)	494 (10)
C209	-0.4852 (2)	0.2763 (2)	-0.3187 (1)	395 (8)
C210	-0.6107 (2)	0.2298 (2)	-0.3332 (1)	439 (9)
C211	-0.3829 (2)	0.2198 (2)	-0.3393 (1)	333 (7)
C212	-0.4073 (2)	0.2079 (2)	-0.4027 (1)	398 (8)
N213	-0.3233 (2)	0.1568 (2)	-0.4228 (1)	484 (8)
O214	-0.4947 (2)	0.2441 (2)	-0.43254 (9)	583 (7)
N215	-0.2653 (2)	0.2662 (2)	-0.32102 (9)	352 (6)
C216	-0.2513 (3)	0.3579 (2)	-0.3476 (1)	476 (10)
C217	-0.1188 (2)	0.3855 (2)	-0.3351 (1)	388 (8)
C218	-0.0367 (3)	0.3434 (2)	-0.3639 (1)	437 (9)
C219	0.0869 (3)	0.3624 (2)	-0.3514 (1)	481 (9)
C220	0.1300 (3)	0.4252 (2)	-0.3101 (1)	527 (10)
C221	0.0502 (3)	0.4685 (2)	-0.2810 (1)	514 (10)
C222	-0.0740 (3)	0.4489 (2)	-0.2934 (1)	477 (9)

Table 2-B
Atomic Parameters for Non H-Atoms

Thermal parameters
as $\exp[-2.\pi^2.\Sigma[U_{ij}.a_i^*.a_j^*.h_i.h_j).10^4]$

Atom	U11	U22	U33	U12	U13	U23
C1101	448 (3)	430 (3)	391 (3)	-10 (3)	124 (2)	-33 (3)
C1102	474 (3)	613 (4)	505 (4)	-124 (3)	253 (3)	-25 (3)
C101	388 (15)	644 (21)	646 (21)	-145 (15)	29 (14)	-1 (17)
N102	317 (10)	460 (12)	381 (11)	-68 (9)	63 (9)	15 (9)
C103	400 (14)	338 (13)	412 (14)	-35 (10)	87 (11)	-2 (11)
C104	326 (12)	326 (12)	332 (12)	-10 (10)	94 (9)	7 (9)
C105	379 (13)	392 (13)	328 (12)	-15 (11)	88 (10)	26 (10)
N106	383 (11)	416 (11)	324 (10)	-56 (9)	115 (9)	-28 (9)
C107	659 (20)	559 (18)	365 (14)	-122 (16)	117 (13)	-95 (13)
C108	476 (15)	369 (13)	446 (14)	9 (12)	189 (12)	-18 (11)
C109	367 (13)	350 (12)	375 (13)	21 (10)	108 (10)	44 (10)
C110	340 (13)	461 (15)	482 (15)	28 (11)	85 (11)	56 (12)
C111	315 (12)	340 (12)	331 (12)	-24 (9)	96 (9)	9 (9)
C112	413 (14)	394 (13)	337 (12)	-82 (11)	104 (11)	18 (10)
N113	491 (14)	665 (16)	345 (12)	60 (12)	122 (10)	-75 (11)
O114	534 (12)	664 (13)	349 (10)	46 (10)	38 (9)	31 (9)
N115	351 (11)	400 (11)	327 (10)	-83 (9)	91 (8)	1 (8)
C116	500 (16)	504 (17)	533 (17)	-142 (14)	81 (13)	120 (14)
C117	470 (14)	389 (13)	413 (13)	-70 (11)	159 (11)	2 (11)
C118	656 (21)	465 (17)	871 (25)	-15 (15)	347 (18)	-62 (17)
C119	565 (21)	887 (30)	1165 (35)	145 (21)	461 (23)	253 (27)
C120	569 (23)	1009 (35)	1031 (33)	-351 (24)	124 (21)	84 (26)
C121	820 (30)	810 (29)	1258 (40)	-352 (24)	143 (26)	-494 (28)
C122	616 (20)	657 (21)	921 (27)	-76 (17)	236 (19)	-357 (20)
C1201	501 (4)	545 (4)	474 (3)	-27 (3)	122 (3)	-12 (3)
C1202	597 (4)	797 (5)	578 (4)	-204 (4)	212 (3)	121 (4)
C201	371 (15)	672 (22)	677 (22)	-125 (15)	27 (14)	-26 (17)
N202	296 (10)	435 (12)	429 (12)	-23 (9)	85 (9)	14 (9)
C203	352 (13)	359 (13)	545 (16)	-2 (10)	126 (11)	-3 (12)
C204	317 (12)	338 (12)	493 (14)	51 (10)	145 (11)	32 (11)
C205	359 (14)	566 (17)	467 (15)	18 (12)	84 (11)	123 (13)
N206	380 (12)	704 (16)	382 (12)	-102 (111)	119 (10)	-48 (11)
C207	670 (23)	1226 (38)	426 (18)	-211 (26)	45 (16)	-146 (20)
C208	445 (15)	508 (16)	589 (17)	-24 (13)	256 (13)	-159 (14)
C209	352 (13)	350 (13)	520 (15)	50 (10)	183 (11)	-7 (11)
C210	303 (13)	446 (15)	586 (17)	71 (11)	129 (12)	61 (13)
C211	283 (11)	349 (12)	387 (13)	21 (9)	112 (10)	4 (10)
C212	383 (14)	402 (13)	419 (14)	-4 (11)	100 (11)	9 (11)
N213	484 (13)	603 (15)	386 (12)	68 (11)	131 (11)	-46 (11)
O214	479 (11)	801 (15)	458 (11)	117 (11)	48 (9)	70 (10)
N215	321 (10)	348 (11)	406 (11)	-9 (8)	120 (8)	-12 (9)
C216	437 (15)	366 (14)	648 (19)	-6 (12)	161 (13)	38 (13)
C217	460 (14)	289 (12)	438 (14)	-39 (10)	141 (11)	17 (10)
C218	508 (16)	411 (14)	425 (14)	-67 (12)	172 (12)	-63 (12)
C219	472 (15)	519 (16)	495 (16)	-12 (13)	206 (13)	-25 (13)
C220	461 (16)	560 (17)	570 (17)	-110 (13)	118 (13)	1 (14)
C221	651 (19)	424 (15)	460 (15)	-149 (14)	77 (14)	-94 (13)
C222	616 (18)	351 (14)	504 (16)	-29 (12)	208 (14)	-65 (12)

Table 2-C
Atomic Parameters for H-Atoms

Coordinates and thermal parameters
as exp [$-8.\pi^2.U.(\sin(\theta/\lambda)^2$] fixed to U=0.05

Atom	x/a	y/b	z/c
H1101	0.395 (4)	0.473 (3)	-0.053 (2)
H1012	0.397 (4)	0.413 (3)	0.003 (2)
H1013	0.462 (4)	0.375 (3)	-0.045 (2)
H1021	0.300 (4)	0.358 (3)	-0.105 (2)
H1031	0.183 (4)	0.435 (3)	-0.024 (2)
H1032	0.178 (4)	0.466 (3)	-0.085 (2)
H1041	-0.010 (4)	0.401 (3)	-0.075 (2)
H1051	-0.054 (4)	0.308 (3)	-0.151 (2)
H1052	0.041 (4)	0.388 (3)	-0.163 (2)
H1061	0.182 (4)	0.284 (3)	-0.164 (2)
H1071	-0.023 (4)	0.189 (3)	-0.213 (2)
H1072	0.049 (4)	0.275 (3)	-0.243 (2)
H1073	0.113 (4)	0.175 (3)	-0.226 (2)
H1081	0.060 (4)	0.138 (3)	-0.125 (2)
H1082	0.207 (4)	0.144 (3)	-0.128 (2)
H1091	0.174 (4)	0.155 (3)	-0.039 (2)
H1101	0.352 (4)	0.228 (3)	-0.062 (2)
H1102	0.314 (4)	0.265 (3)	-0.005 (2)
H1131	0.002 (4)	0.365 (3)	0.067 (2)
H1132	-0.068 (4)	0.374 (3)	0.009 (2)
H1151	-0.115 (4)	0.257 (3)	-0.061 (2)
H1161	-0.001 (4)	0.082 (3)	-0.034 (2)
H1162	-0.044 (4)	0.149 (3)	0.013 (2)
H1181	-0.278 (4)	0.203 (3)	-0.004 (2)
H1191	-0.455 (4)	0.134 (3)	-0.021 (2)
H1201	-0.498 (4)	-0.012 (3)	-0.063 (2)
H1211	-0.332 (4)	-0.100 (3)	-0.083 (2)
H1221	-0.138 (4)	-0.029 (3)	-0.068 (2)
H2011	-0.731 (4)	0.019 (4)	-0.332 (2)
H2012	-0.731 (4)	0.078 (3)	-0.384 (2)
H2013	-0.791 (4)	0.120 (3)	-0.335 (2)
H2021	-0.613 (4)	0.122 (3)	-0.278 (2)
H2031	-0.521 (4)	0.061 (3)	-0.370 (2)
H2032	-0.506 (4)	0.010 (3)	-0.311 (2)
H2041	-0.325 (4)	0.085 (3)	-0.320 (2)
H2051	-0.261 (4)	0.155 (3)	-0.239 (2)
H2052	-0.360 (4)	0.079 (3)	-0.229 (2)
H2061	-0.487 (4)	0.185 (3)	-0.218 (2)
H2071	-0.277 (4)	0.269 (3)	-0.172 (2)
H2072	-0.343 (4)	0.183 (3)	-0.146 (2)
H2073	-0.408 (4)	0.290 (3)	-0.152 (2)
H2081	-0.371 (4)	0.335 (3)	-0.251 (2)
H2082	-0.513 (4)	0.328 (3)	-0.244 (2)
H2091	-0.492 (4)	0.339 (3)	-0.335 (2)
H2101	-0.668 (4)	0.259 (3)	-0.314 (2)
H2102	-0.643 (4)	0.234 (3)	-0.376 (2)
H2131	-0.326 (4)	0.152 (3)	-0.460 (2)
H2132	-0.254 (4)	0.138 (3)	-0.399 (2)
H2151	-0.212 (4)	0.227 (3)	-0.327 (2)
H2161	-0.298 (4)	0.402 (3)	-0.333 (2)
H2162	-0.278 (4)	0.353 (3)	-0.391 (2)
H2181	-0.067 (4)	0.294 (3)	-0.393 (2)
H2191	0.140 (4)	0.329 (3)	-0.373 (2)
H2201	0.222 (4)	0.439 (3)	-0.301 (2)
H2211	0.082 (4)	0.512 (3)	-0.251 (2)
H2221	-0.125 (4)	0.477 (3)	-0.269 (2)

Table 3
Bond Distances (Å)

C101	-H1011	0.94 (4)	C101	-H1012	0.99 (5)
C101	-H1013	0.90 (4)	C101	-H102	1.494 (4)
N102	-H1021	0.96 (4)	N102	-C103	1.500 (3)
N102	-C110	1.498 (3)	C103	-H1031	0.98 (4)
C103	-H1032	0.91 (4)	C103	-C104	1.527 (3)
C104	-H1041	1.01 (4)	C104	-C105	1.528 (3)
C104	-C111	1.538 (3)	C105	-H1051	0.99 (4)
C105	-H1052	0.92 (4)	C105	-N106	1.509 (3)
N106	-H1061	0.90 (4)	N106	-C107	1.498 (3)
N106	-C108	1.501 (3)	C107	-H1071	1.01 (4)
C107	-H1072	0.97 (4)	C107	-H1073	0.97 (4)
C108	-H1081	1.00 (4)	C108	-H1082	0.96 (4)
C108	-C109	1.524 (3)	C109	-H1091	0.94 (4)
C109	-C110	1.525 (3)	C109	-C111	1.541 (3)
C110	-H1101	0.95 (4)	C110	-H1102	1.00 (4)
C111	-C112	1.551 (3)	C111	-N115	1.473 (3)
C112	-N113	1.336 (3)	C112	-O114	1.226 (3)
N113	-H1131	0.86 (5)	N113	-H1132	0.90 (4)
N115	-H1151	0.87 (4)	N115	-C116	1.474 (4)
C116	-H1161	1.05 (4)	C116	-H1162	0.98 (4)
C116	-C117	1.502 (4)	C117	-C118	1.375 (4)
C117	-C122	1.363 (4)	C118	-H1181	0.98 (4)
C118	-C119	1.375 (5)	C119	-H1191	0.84 (5)
C119	-C120	1.384 (7)	C120	-H1201	0.92 (4)
C120	-C121	1.347 (7)	C121	-H1211	0.99 (4)
C121	-C122	1.379 (6)	C122	-H1221	0.98 (4)
C201	-H2011	0.96 (4)	C201	-H2012	0.94 (5)
C201	-H2013	0.93 (4)	C201	-N202	1.497 (3)
N202	-H2021	0.97 (4)	N202	-C203	1.498 (3)
N202	-C210	1.506 (3)	C203	-H2031	1.01 (4)
C203	-H2032	1.00 (4)	C203	-C204	1.525 (3)
C204	-H2041	0.91 (4)	C204	-C205	1.527 (3)
C204	-C211	1.533 (3)	C205	-H2051	0.97 (4)
C205	-H2052	0.97 (4)	C205	-N206	1.504 (4)
N206	-H2061	0.88 (4)	N206	-C207	1.501 (4)
N206	-C208	1.494 (4)	C207	-H2071	1.01 (4)
C207	-H2072	0.89 (4)	C207	-H2073	1.05 (4)
C208	-H2081	0.96 (4)	C208	-H2082	0.97 (4)
C208	-C209	1.518 (4)	C209	-H2091	0.97 (4)
C209	-C210	1.527 (3)	C209	-C211	1.548 (3)
C210	-H2101	0.95 (4)	C210	-H2102	1.04 (4)
C211	-C212	1.543 (3)	C211	-N215	1.462 (3)
C212	-N213	1.343 (4)	C212	-O214	1.223 (3)
N213	-H2131	0.91 (5)	N213	-H2132	0.91 (4)
N215	-H2151	0.84 (4)	N215	-C216	1.476 (3)
C216	-H2161	0.92 (4)	C216	-H2162	1.05 (4)
C216	-C217	1.502 (3)	C217	-C218	1.384 (4)
C217	-C222	1.390 (3)	C218	-H2181	1.00 (4)
C218	-C219	1.381 (4)	C219	-H2191	0.98 (4)
C219	-C220	1.373 (4)	C220	-H2201	1.02 (4)
C220	-C221	1.376 (4)	C221	-H2211	0.98 (4)
C221	-C222	1.388 (4)	C222	-H2221	0.97 (4)

Table 4

Bond Angles (°)

H1013	-C101	-N102	101	(2)	H1012	-C101	-N102	107	(2)
H1012	-C101	-H1013	111	(3)	H1011	-C101	-N102	105	(2)
H1011	-C101	-H1013	117	(3)	H1011	-C101	-H1012	112	(3)
C101	-N102	-C110	110.7	(2)	C101	-N102	-C103	110.6	(2)
C101	-N102	-H1021	105	(2)	C103	-N102	-C110	114.7	(2)
H1021	-N102	-C110	106	(2)	H1021	-N102	-C103	108	(2)
N102	-C103	-C104	113.6	(2)	N102	-C103	-H1032	105	(2)
N102	-C103	-H1031	106	(2)	H1032	-C103	-C104	110	(2)
H1031	-C103	-C104	110	(2)	H1031	-C103	-H1032	109	(3)
C103	-C104	-C111	109.3	(2)	C103	-C104	-C105	115.4	(2)
C103	-C104	-H1041	105	(2)	C105	-C104	-C111	110.8	(2)
H1041	-C104	-C111	110	(2)	H1041	-C104	-C105	104	(2)
C104	-C105	-N106	114.8	(2)	C104	-C105	H1052	108	(2)
C104	-C105	-H1051	108	(2)	H1052	-C105	-N106	107	(2)
H1051	-C105	-N106	104	(2)	H1051	-C105	-H1052	113	(3)
C105	-N106	-C108	114.2	(2)	C105	-N106	-C107	110.8	(2)
C105	-N106	-H1061	107	(2)	C107	-N106	-C108	110.9	(2)
H1061	-N106	-C108	107	(2)	H1061	-N106	-C107	105	(2)
C106	-C107	-H1073	106	(2)	N106	-C107	-H1072	108	(2)
N106	-C107	-H1071	105	(2)	H1072	-C107	-H1073	110	(3)
H1071	-C107	-H1073	108	(3)	H1071	-C107	-H1072	116	(3)
N106	-C108	-C109	113.1	(2)	N106	-C108	-H1082	107	(2)
N106	-C108	-H1081	105	(2)	H1082	-C108	-C109	106	(2)
H1081	-C108	-C109	110	(2)	H1081	-C108	-H1082	113	(3)
C108	-C109	-C111	109.5	(2)	C108	-C109	-C110	114.1	(2)
C108	-C109	-H1091	105	(2)	C110	-C109	-C111	112.4	(2)
H1091	-C109	-C111	107	(2)	H1091	-C109	-C110	107	(2)
N102	-C110	-C109	114.9	(2)	C109	-C110	-H1102	108	(2)
C109	-C110	-H1101	109	(2)	N102	-C110	-H1102	105	(2)
N102	-C110	-H1101	106	(2)	H1101	-C110	-H1102	111	(3)
C104	-C111	-C109	104.7	(2)	C109	-C111	-N115	109.9	(2)
C109	-C111	-C112	112.1	(2)	C104	-C111	-N115	109.3	(1)
C104	-C111	-C112	110.1	(2)	C112	-C111	-N115	110.3	(2)
C111	-C112	-O114	121.7	(2)	C111	-C112	-N113	115.6	(2)
N113	-C112	-O114	122.5	(2)	C112	-N113	-H1132	125	(3)
C112	-N113	-H1131	119	(3)	H1131	-N113	-H1132	114	(4)
C111	-N115	-C116	113.2	(2)	C111	-N115	-H1151	109	(3)
H1151	-N115	-C116	112	(3)	N115	-C116	-C117	111.3	(2)
N115	-C116	-H1162	111	(2)	N115	-C116	-H1161	110	(2)
H1162	-C116	-C117	106	(2)	H1161	-C116	-C117	108	(2)
H1161	-C116	-H1162	107	(3)	C116	-C117	-C122	119.7	(2)
C116	-C117	-C118	121.5	(2)	C118	-C117	-C122	118.5	(3)
C117	-C118	-C119	120.0	(3)	C117	-C118	-H1181	122	(2)
H1181	-C118	-C119	117	(2)	C118	-C119	-C120	120.5	(4)
C118	-C119	-H1191	113	(3)	H1191	-C119	-C120	125	(3)
C119	-C120	-C121	118.9	(4)	C119	-C120	-H1201	119	(2)
H1201	-C120	-C121	121	(2)	C120	-C121	-C122	120.4	(4)
C120	-C121	-H1211	121	(2)	H1211	-C121	-C122	117	(2)
C117	-C122	-C121	121.2	(3)	C121	-C122	-H1221	120	(2)
C117	-C122	-H1221	117	(2)	H2013	-C201	-N202	104	(2)
H2012	-C201	-N202	109	(2)	H2012	-C201	-H2013	113	(3)
H2011	-C201	-N202	108	(2)	H2011	-C201	-H2013	113	(3)
H2011	-C201	-H2012	106	(3)	C201	-N202	-C210	110.6	(2)
C201	-N202	-C203	111.1	(2)	C201	-N202	-H2021	105	(2)
C203	-N202	-C210	113.3	(2)	H2021	-N202	-C210	109	(2)
H2021	-N202	-C203	106	(2)	N202	-C203	-C204	113.4	(2)
N202	-C203	-H2032	107	(2)	N202	-C203	-H2031	105	(2)
H2032	-C203	-C204	112	(2)	H2031	-C203	-C204	112	(2)
H2031	-C203	-H2032	105	(3)	C203	-C204	-C211	110.5	(2)

Table 4 (Continued)

Bond Angles (°)

C203	-C204	-C205	115.3 (2)	C203	-C204	-H2041	104 (2)
C205	-C204	-C211	110.3 (2)	H2041	-C204	-C211	110 (2)
H2041	-C204	-C205	105 (2)	C204	-C205	-N206	114.5 (2)
C204	-C205	-H2052	110 (2)	C204	-C205	-H2051	108 (2)
H2052	-C205	-N206	105 (2)	H2051	-C205	-N206	107 (2)
H2051	-C205	-H2052	110 (3)	C205	-N206	-C208	114.7 (2)
C205	-N206	-C207	110.6 (2)	C205	-N206	-H2061	107 (2)
C207	-N206	-C208	110.6 (3)	H2061	-N206	-C208	108 (2)
H2061	-N206	-C207	103 (2)	N206	-C207	-H2073	106 (2)
N206	-C207	-H2072	107 (3)	N206	-C207	-H2071	103 (2)
H2072	-C207	-H2073	118 (4)	H2071	-C207	-H2073	105 (3)
H2071	-C207	-H2072	114 (4)	N206	-C208	-C209	113.1 (2)
N206	-C208	-H2082	104 (2)	N206	-C208	-H2081	105 (2)
H2082	-C208	-C209	108 (2)	H2081	-C208	-C209	111 (2)
H2081	-C208	-H2082	113 (3)	C208	-C209	-C211	108.8 (2)
C208	-C209	-C210	114.5 (2)	C208	-C209	-H2091	102 (2)
C210	-C209	-C211	113.0 (2)	H2091	-C209	-C211	110 (2)
H2091	-C209	-C210	107 (2)	N202	-C210	-C209	114.4 (2)
C209	-C210	-H2102	110 (2)	C209	-C210	-H2101	111 (2)
N202	-C210	-H2102	107 (2)	N202	-C210	-H2101	104 (2)
H2101	-C210	-H2102	109 (3)	C204	-C211	-C209	103.8 (2)
C209	-C211	-N215	109.4 (2)	C209	-C211	-C212	112.2 (2)
C204	-C211	-N215	109.2 (2)	C204	-C211	-C212	111.3 (2)
C212	-C211	-N215	110.5 (2)	C211	-C212	-O214	122.6 (2)
C211	-C212	-N213	114.8 (2)	N213	-C212	-O214	122.4 (2)
C212	-N213	-H2132	118 (2)	C212	-N213	-H2131	120 (2)
H2131	-N213	-H2132	119 (4)	C211	-N215	-C216	114.8 (2)
C211	-N215	-H2151	105 (3)	H2151	-N215	-C215	111 (3)
N215	-C216	-C217	108.4 (2)	N215	-C216	-H2162	110 (2)
N215	-C216	-H2161	108 (2)	H2162	-C216	-C217	108 (2)
H2161	-C216	-C217	110 (2)	H2161	-C216	-H2162	110 (3)
C216	-C217	-C222	122.0 (2)	C216	-C217	-C218	119.5 (2)
C218	-C217	-C222	118.3 (2)	C217	-C218	-C219	121.3 (2)
C217	-C218	-H2181	119 (2)	H2181	-C218	-C219	119 (2)
C218	-C219	-C220	119.7 (2)	C218	-C219	-H2191	116 (2)
H2191	-C219	-C220	123 (2)	C219	-C220	-C221	120.1 (3)
C219	-C220	-H2201	119 (2)	H2201	-C220	-C221	120 (2)
C220	-C221	-C222	120.1 (2)	C220	-C221	-H2211	119 (2)
H2211	-C221	-C222	119 (2)	C217	-C222	-C221	120.3 (2)
C221	-C222	-H2221	116 (2)	C217	-C222	-H2221	122 (2)

The amido group lies in a plane nearly perpendicular to the C3-C4-C9-C10 plane. The N15 lone pair also lies in a plane nearly perpendicular to C4-C5-C8-C9 plane.

The crystal packing is mainly due to the hydrogen contacts of the type shown in Table 8, all of them implying the chlorine atoms and forming infinite chains (Figure 3).

NMR Spectra.

Spectral Analysis of Compounds **IIa-d**.

^{1}H-nmr (300 MHz) and ^{13}C-nmr (75 MHz) spectroscopy was used to provide the required information. The assignment of proton and carbon resonances was made on the basis of literature data for related systems [1-3,11]. In order to help the assignments, double resonance experiments (DR) for all of the compounds studied, homonuclear 2D COSY-45 spectrum [12,13] and heteronuclear ^{1}H-^{13}C XHCORD spectrum [14,15] for compound **IIa** were obtained.

^{1}H-NMR Spectra in Deuteriochloroform.

The H1(5), H6(8)eq and H6(8)ax signals appears well differentiated. The H1(5) signal appear in all cases as a wide singlet (W½ ≅ 8Hz). The H6(8)eq signal corresponds to protons gauche to the nitrogen electron pair [1,2]. The

Table 5

Torsion Angles (°)

H1021	-N102	-C110	-H1101	40	(3)
H1021	-N102	-C110	-H1102	158	(3)
H1021	-N102	-C103	-H1032	-45	(4)
H1032	-C103	-C014	-H1041	-64	(4)
H1041	-C104	-C105	-H1051	-53	(3)
H1051	-C105	-N106	-H1061	162	(4)
H1061	-N106	-C108	-H1081	-163	(4)
H1061	-N106	-C108	-H1082	-42	(4)
H1082	-C108	-C109	-H1091	-67	(4)
H1091	-C109	-C110	-H1101	72	(4)
H1021	-N102	-C103	-H1031	-161	(3)
H1031	-C103	-C105	-H1041	57	(3)
H1041	-C104	-C105	-H1052	69	(3)
H1052	-C105	-N106	-H1061	41	(4)
N115	-C111	-C112	-O114	116.8	(2)
C111	-C112	-N113	-H1131	174	(3)
O114	-C112	-N113	-H1132	-177	(3)
C111	-N115	-C116	-H1161	-68	(2)
C111	-N115	-C116	-C117	170.2	(2)
H1151	-N115	-C116	-H1162	-73	(4)
N115	-C116	-C117	-C118	-69.0	(3)
H1162	-C116	-C117	-C118	52	(2)
H1162	-C116	-C117	-C122	-122	(2)
C116	-C117	-C122	-H1221	0	(2)
C116	-C117	-C118	-H1181	2	(3)
H2021	-N202	-C210	-H2101	-43	(3)
H2021	-N202	-C210	-H2102	-159	(3)
H2021	-N202	-C203	-H2032	49	(3)
H2032	-C203	-C204	-H2041	59	(4)
H2041	-C204	-C205	-H2051	50	(4)
H2051	-C205	-N206	-H2061	-157	(4)
H2061	-N206	-C208	-H2081	160	(4)
H2061	-N206	-C208	-H2082	40	(4)
N115	-C111	-C112	-N113	-61.0	(2)
C111	-C112	-N113	-H1132	0	(3)
O114	-C112	-N113	-H1131	-3	(3)
H1151	-N115	-C116	-H1161	166	(4)
H1151	-N115	-C116	-C117	45	(3)
N115	-C116	-C117	-C122	115.2	(3)
H1161	-C116	-C117	-C118	168	(2)
H1161	-C116	-C117	-C122	-7	(2)
H2021	-N202	-C203	-H2031	161	(3)
H2031	-C203	-C204	-H2041	-58	(4)
H2041	-C204	-C205	-H2052	-70	(4)
H2052	-C205	-N206	-H2061	-39	(4)
H2061	-N206	-C207	-H2071	-177	(4)
H2091	-C209	-C210	-H2101	-69	(4)
C212	-C211	-N215	-H2151	-68	(4)
C212	-C211	-N215	-H2151	-68	(3)
N215	-C211	-C212	-O214	-118.7	(2)
C211	-C212	-N213	-H2131	-173	(3)
O214	-C212	-N213	-H2132	171	(3)
C211	-N215	-C216	-H2161	73	(3)
C211	-N215	-C216	-C217	-166.8	(2)
H2151	-N215	-C216	-H2162	72	(4)
N215	-C216	-C217	-C218	77.3	(3)
H2162	-C216	-C217	-C218	-43	(2)
H2162	-C216	-C217	-C222	140	(2)
C216	-C217	-C222	-H2221	1	(3)
C216	-C217	-C218	-H2181	0	(2)
H2081	-C208	-C209	-H2091	-56	(3)
H2091	-C208	-C210	-H2102	51	(3)
C204	-C211	-N215	-C216	178.1	(2)
C204	-C211	-C212	-N213	-61.9	(3)
C212	-C211	-N215	-C216	55.3	(2)
N215	-C211	-C212	-N213	59.6	(3)
C211	-C212	-C213	-H2132	-6	(3)
O214	-C212	-N213	-H2131	5	(3)
C211	-N215	-C216	-H2162	-47	(2)
H2151	-N215	-C216	-H2161	-166	(4)
N215	-C216	-C217	-C222	-99.2	(3)
H2161	-C216	-C217	-C218	-163	(3)
H2161	-C216	-C217	-C222	19	(3)

Table 6

Conformational Parameters

Ring	Asymmetry Parameters		
	Q_T	$\phi 2$	$\theta 2$
C103-C104-C109-C110-N102-C111	0.572 (2)	163 (1)	21.3 (3)
C105-C108-C109-C104-N106-C111	0.585 (3)	187.1 (1)	19.9 (3)
C203-C204-C209-C210-N202-C211	0.573 (3)	-18 (2)	162.5 (1)
C205-C208-C209-C204-N206-C211	0.598 (3)	-11 (2)	158.4 (2)

H6(8)ax signal appears at higher field due to the σ-electron delocalization of the nitrogen lone pair in trans-coplanar C-H bonds [1,2,16]. The resonance signal of H2(4)ax in **IIa-c** is downfield relative to the same absorption of H6(8)ax ($\Delta\delta \cong 0.12$ ppm). This deshielding is due to (i) the field effect exerted by the lone pair of the exocyclic-*N* and (ii) the diminished *trans*-coplanarity with respect to the *N*-lone pair (see above).

In order to clarify the assignment of the signals and to deduce the proton magnetic parameters, homonuclear 2D COSY spectrum for **IIa** was performed. The contour plot of the 300 MHz proton COSY spectrum is shown in Figure 4.

The cross-connectivity patterns were analyzed taking into account that the wide singlet at 1.95 ppm can be unambiguously assigned to bridghead H1(5) protons. By considering the correlations, the following can be established: (i) The doublet of doublets centered at 3.08 ppm due to two protons with a correlation with H1(5) and a stronger correlation with the signal centered at 2.70 ppm (two protons), must correspond to H6(8)eq, and the signal at 2.70 ppm correspond to H6(8)ax, (ii) the doublet of doublets of doublets centered at 2.86 ppm due to two protons with a correlation with H1(5) and a stronger correlation with the doublet of doublets at 2.79 ppm (two protons) must correspond to H2(4)ax and the signal at 2.79 ppm correspond to H2(4)eq, in this signal a smaller cross-peak with H1(5) is

Table 7

Least Squares Planes Through the Six-Membered Rings

	*C x 03	*C x 04	*C x 09	*C x 10	N x 02	*C x 11	*C x 05	*C x 08	*C x 09	*C x 04	N x 06	*C x 11
x = 1	-0.033 (3)	0.024 (2)	-0.029 (2)	0.039 (3)	0.477 (2)	-0.790 (2)	0.023 (2)	-0.029 (3)	0.022 (2)	-0.020 (2)	0.488 (2)	-0.795 (2)
x = 2	0.031 (3)	-0.023 (2)	0.027 (3)	-0.031 (3)	-0.516 (2)	0.783 (2)	-0.025 (3)	0.028 (3)	-0.020 (2)	0.020 (2)	-0.480 (2)	0.820 (2)

* = Atoms defining the plane.

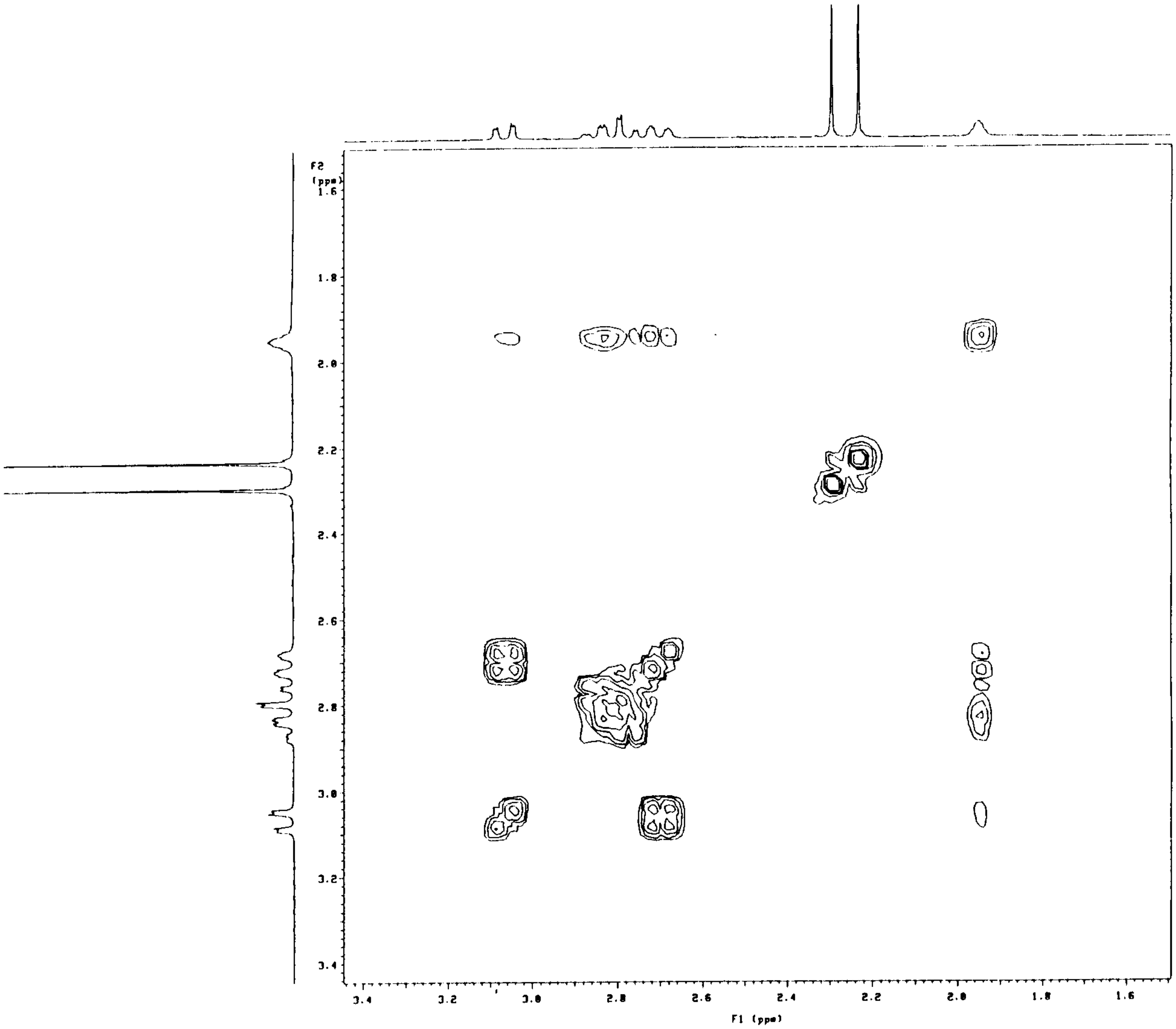


Figure 4. Contour plot of the 300 MHz COSY spectrum of **IIa** in deuteriochloroform.

observed, that is in agreement with the small value for ^{3}J H2(4)eq-H1(5).

To assist of the ^{1}H assignments, double resonance (DR) experiments were performed for **IIa-d** (in deuteriochloroform at 300 MHz). Compound **IIa**: On saturating the signal at 3.08 ppm, the doublet of doublets of doublets at 2.70 ppm coalesces to a wide singlet; by saturation the signal at 1.95 ppm [H1(5)], the signals at 3.08 ppm (dd), 2.86 ppm (ddd), 2.79 ppm (dd) and 2.70 ppm (ddd) become a doublet, a doublet of doublets (W coupling), a doublet, and a doublet of doublets (W coupling) respectively.

Bearing in mind the above considerations, the analysis

Table 8
Hydrogen Contacts (Å, °)

X-H...Y	X-H	X...Y	H...Y	<X-H...Y
N102-H1021...C1102	0.97 (5)	3.006 (2)	2.04 (5)	171 (4)
N106-H1061...C1102	0.90 (5)	3.067 (2)	2.18 (5)	167 (4)
N113-H1131...C1101	0.86 (5)	3.310 (3)	2.48 (5)	161 (4)
N113-H1132...C1201 (ii)	0.90 (4)	3.293 (3)	2.40 (4)	167 (4)
N115-H1151...C1201 (i)	0.87 (4)	3.522 (2)	2.66 (4)	167 (3)
N202-H2021...C1202	0.97 (5)	3.010 (3)	2.05 (5)	170 (4)
N206-H2061...C1202	0.88 (5)	3.046 (3)	2.19 (5)	162 (4)
N213-H2131...C1201	0.92 (5)	3.379 (3)	2.51 (5)	158 (4)
N213-H2132...C1101 (iii)	0.91 (4)	3.297 (3)	2.38 (4)	174 (4)
N215-H2151...C1101 (iii)	0.84 (5)	3.406 (2)	2.56 (5)	175 (4)

(i) 1+X, 1/2-Y, 1/2+Z. (ii) X, 1/2-Y, 1/2+Z. (iii) X, 1/2-Y, -1/2+Z.

of the spectra leads to the establishment of the protonic parameters given in Tables 9 and 10.

^{1}H NMR in DMSO-d_6 Solution.

In order to clarify the assignment of the signals and to deduce the proton magnetic parameters, (Tables 9, 10) double resonance experiments for **IIa-d** were performed.

^{13}C NMR Spectra in Deuteriochloroform and DMSO-d_6 Solutions.

The ^{13}C nmr chemical shifts of compound **IIa-d** are given together with the signals assignments in Table 11. Signal multiplicity were obtained from DEPT experiments. To strenghten the δ C assignments, the heteronuclear ^{1}H-^{13}C correlation spectrum of compound **IIa** has been recorded (Figure 5).

Table 9
^{1}H Chemical Shifts of Compounds **IIa-d**

	IIa		**IIb**		**IIc**		**IId**	
δ (ppm) [a]	$CDCl_3$	DMSO	$CDCl_3$	DMSO	$CDCl_3$	DMSO	$CDCl_3$	DMSO
H 1 (5)	1.95 (brs)	1.88 (brs)	1.98 (brs)	2.05 (brs)	2.03 (brs)	2.07 (brs)	1.93 (brs)	1.96 (brs)
H 2 (4) eq	2.79 (dd)	2.53 (dd)	2.80 (s)	2.54 (d)	2.82 (s)	2.53 (d)	2.72 (dd) [b]	2.45 (m)
H 2 (4) ax	2.86 (ddd)	2.77 (ddd)	2.80 (s)	2.71 (d)	2.82 (s)	2.68 (d)	2.61 (ddd) [c]	2.45 (m)
H 6 (8) eq	3.08 (dd)	2.88 (dd)	3.09 (d)	2.93 (d)	3.13 (d)	2.91 (d)	3.07 (dd)	2.87 (d)
H 6 (8) ax	2.70 (ddd) [b]	2.47 (ddd) [b]	2.68 (d)	2.49 (d)	2.73 (d)	2.47 (m)	2.66 (dm) [c]	2.45 (m)
CH_3	2.25 (s)	2.05 (s)	2.23 (s)	2.09 (s)	2.26 (s)	2.04 (s)	2.15 (s)	1.91 (s)
CH_3	2.30 (s)	2.09 (s)	2.27 (s)	2.11 (s)	2.32 (s)	2.09 (s)	2.28 (s)	2.09 (s)
H 2' (6')			7.29 (m)	7.31 (m)	7.37 (m)	7.41 (m)	7.28 (m)	7.27 (m)
H 3' (5')			7.29 (m)	7.31 (m)	7.37 (m)	7.16 (m)	7.28 (m)	7.27 (m)
NH	1.85 (brs)		1.87 (brs)	3.08 (t)	1.30 (ta)	3.10 (t)		
H 1"			3.80 (s)	3.70 (d)	3.82 (da)	3.66 (d)	2.95 (m)	2.74 (m)
H 2"							2.85 (m)	2.74 (m)

[a] Abbreviations: br, broad; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; m, multiplet; s, singlet; t, triplet. δ values were deduced by first order analysis of the spectra; error + 0.05 ppm. [b] Signals of low resolution. [c] Signals are partially overlapped.

Table 10
Coupling Constants Deduced from the Analysis of the ^{1}H NMR Spectra of Compounds **IIa-d**

	IIa		**IIb**		**IIc**		**IId**
J (Hz) [a]	$CDCl_3$	DMSO	$CDCl_3$	DMSO	$CDCl_3$	DMSO	$CDCl_3$
H2 (4) ax-H2 (4) eq	11.2	10.74		10.9		10.9	11.2
H2 (4) eq-H1 (5)	2.4	2.2					2.2
H2 (4) ax-H1 (5)	3.9	3.1					3.4
H2 (4) ax-H6 (8) ax	1.4						1.7
H6 (8) ax-H6 (8) eq	12.5	11.72	12.2	11.9	12.2	12.1	12.4
H6 (8) eq-H1 (5)	2.6	2.44					2.5
H6 (8) ax-H1 (5)	2.7	2.44					
H1"-NH				7.3		7.4	
H2' (6')-H3' (5')					8.5	8.5	
H2' (6')-F					5.5	5.8	
H3' (5')-F					8.6	8.6	

[a] Values deduced from the first order analysis of the corresponding system protons. Error ± 0.2 Hz.

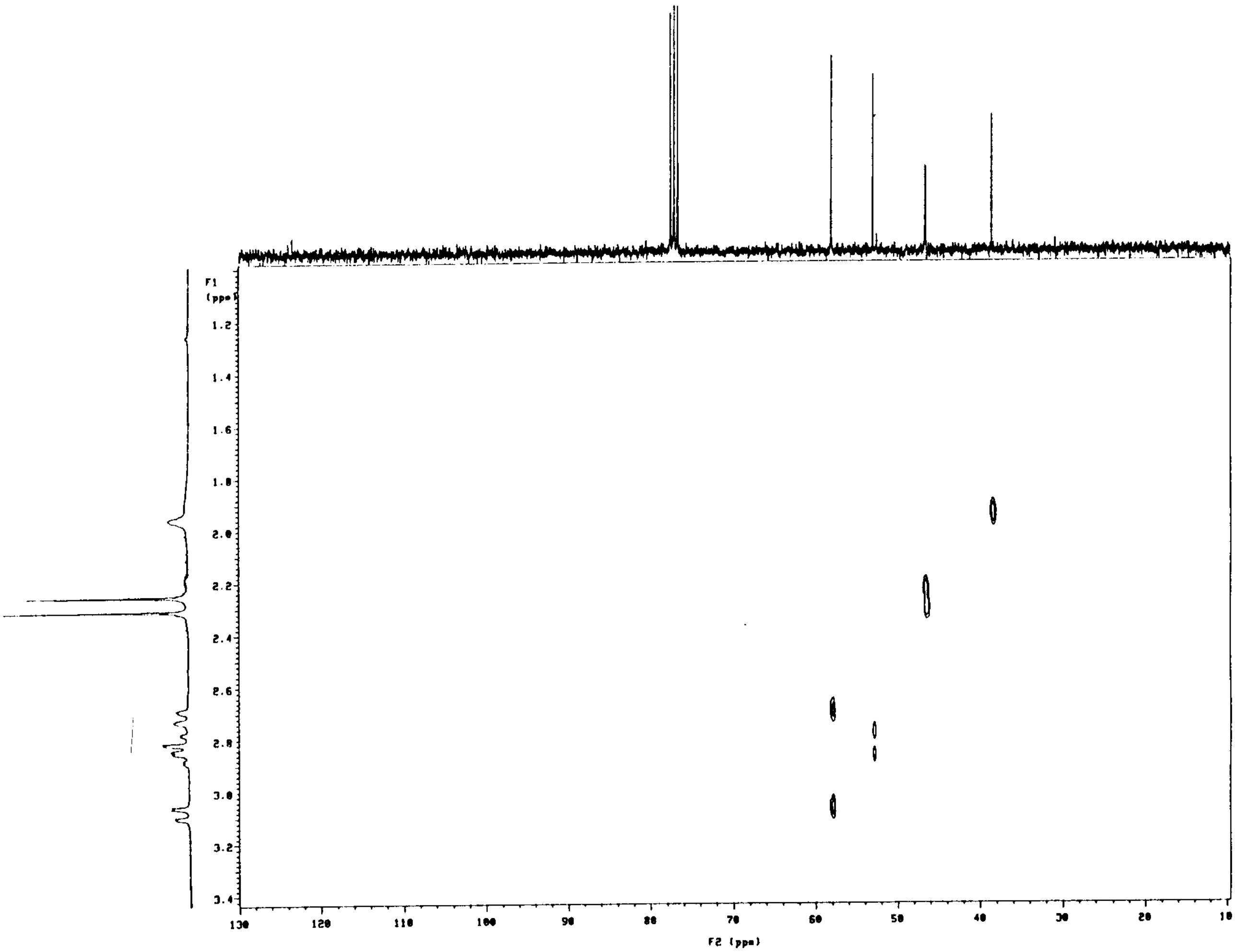


Figure 5. Proton-Carbon shift correlation spectrum (XHCORD) of **IIa** in deuteriochloroform.

Table 11

Carbon-13 Chemical Shifts of Compounds **IIa-d**

	IIa		**IIb**	**IIc** [c]	**IId**	
δ (ppm) [a]	$CDCl_3$	DMSO	$CDCl_3$	$CDCl_3$	$CDCl_3$	DMSO
C 1 (5)	38.53	37.50	37.74	37.00	36.69	35.43
C 2 (4)	52.97	52.38	53.06	53.33	52.96	52.22
C 6 (8)	58.01	57.25	57.75	57.98	57.72	57.04
C 9	52.48	51.86	58.28	58.52	57.96	57.56
CH_3	46.50	45.21	46.53	46.71	46.52	45.33
CH_3	46.60	45.25	46.78	46.94	46.64	45.39
CN	123.40	123.84	120.90	121.03	120.79	121.13
C 1'			138.81	134.92	139.26	140.32
C 2' (6')			128.38 [b]	130.17	128.51 [b]	128.06 [b]
C 3' (5')			128.48 [b]	115.65	128.79 [b]	128.81 [b]
C 4'			127.53	162.50	126.42	125.84
C 1"			47.39	47.07	43.70	43.91
C 2"					36.13	35.67

[a] Directly measured on the spectra; error ± 0.05 ppm. [b] These values may be interchanged. [c] Coupling constants observed: J Cl'-F 3.0 Hz, J C2' (6')-F 8.4 Hz, J C3' (5')-F 21.2 Hz and J C4'-F 250.0 Hz.

Conformational Study of Compounds **IIa-d** in Deuteriochloroform and DMSO-d_6 Solutions.

Among the more significant data, the range of values of =8 Hz observed for W½ of H1(5) in the ^{1}H nmr spectra of the titled compounds is in good agreement with previously reported values for a slightly flattened chair-chair conformation in related bicyclic systems with the *N*-substituents in the equatorial position [1,2,16]. Moreover, in the case of compounds **IIa** and **IId** the piperidine ring with the amino group axial is more flattened in order to relieve the syn-diaxial effect on the H2(4)ax, this fact is being corroborated because ^{3}JH2(4)ax-H1(5) is greater than ^{3}J H2(4)eq-H1(5), and consequently the dihedral angle H2(4)eq-C-C-H1(5) is greater than H2(4)ax-C-C-H1(5) (this fact can be also supposed for compounds **IIb,c** in which, the H2(4)ax and H2(4)eq signals coalesce in a singlet). These facts are also more consistent with a chair-chair flattened conformation than with a chair boat conformation since the latter form should not only give a value of *ca.* 10 Hz for ^{3}J H2(4)-H1(5) but also the signal corresponding to H1(5) should appear as an apparent doublet, a common feature in previously reported systems that adopt the chair-boat conformation [1]. In summary, several points of evidence lead to establish that compounds **IIa-d** adopt in deuteriochloroform and DMSO-d_6 solution a flattened chair-chair conformation with the *N*-substituents in equatorial position.

Spectral Analysis of Compounds **IVa-d**.

^{1}H nmr (300 MHz) and ^{13}C nmr (75 MHz) spectroscopy was used to provide the required information. The assignments of proton and carbon resonance was made on the basis of literature data for related systems [1,2,16] and our previous results for compounds **IIa-d**. In order to clarify the assignment of the signals and to deduce the proton magnetic parameters (Tables 12,13) double resonance experiments (DR) for **IVa-d** in deuteriochloroform, DMSO-d_6 and perdeuteriomethanol were performed. The ^{13}C nmr chemical shifts of compounds **IVa-d** are given together signal assignments in Table 14. Signal mutliplicity obtained from DEPT and the results obtained for compounds **IIa-d** were taken into consideration. To strenghten the δ C assignments, the heteronuclear ^{1}H-^{13}C correlated (XHCORD) spectra of compounds **IVa** (DMSO-d_6) and **IVd** (DMSO-d_6 and deuteriochloroform) have been recorded (Figures 6, 7 and 8).

Conformational Study of Compounds **IVa-d**.

In the case of compounds **IVa-d** in deuteriochloroform, DMSO-d_6 and perdeuteriomethanol solution, we propose for the bicyclic system a preferred conformation similar to that observed for compounds **IIa-d**, *i.e.*: a flattened chair-chair conformation with the *N*-substituents in equatorial

Table 12

^{1}H Chemical Shifts of Compounds **IVa-d**

	IVa			**IVb**			**IVc**			**IVd**		
δ (ppm) [a]	DMSO	$CDCl_3$	CD_3OD	DMSO	$CDCl_3$	CD_3OD	DMSO	$CDCl_3$	CD_3OD	DMSO	$CDCl_3$	CD_3OD
H 1 (5)	2.07 (brs)	2.06 (brs)	2.11 (brs)	2.21 (brs)	2.24 (brs)	2.21 (brs)	2.40 (brs)	2.54 (brs)	2.48 (brs)	2.08 (brs)	2.06 (brs)	2.08 (brs)
H 2 (4) eq	2.47 (dd) [b]	2.62 (m)	2.81 (dd)	2.56 (dd) [b]	2.81 (d)	2.87 (dd) [b]	2.91 (d)	3.05 (m)	3.22 (d)	2.47 (m)	2.74 (m)	2.79 (d)
H 2 (4) ax	2.54 (dd)	2.62 (m)	2.54 (ddd)	2.56 (dd) [b]	2.72 (d)	2.54 (dd)	2.91 (d)	3.05 (m)	2.73 (d)	2.47 (m)	2.64 (dd)	2.67 (m)
H 6 (8) eq	2.40 (dd) [b]	2.62 (m)	2.74 (dd)	2.41 (dd) [b]	2.70 (d)	2.71 (dd) [b]	2.61 (d)	2.82 (dd)	3.32 (d)	2.25 (d)	2.59 (dd)	2.56 (d)
H 6 (8) ax	2.75 (dd) [b]	2.62 (m)	2.94 (ddd)	2.78 (dd)	2.81 (d)	3.04 (dd)	3.15 (d)	3.00 (d)	3.61 (d)	2.50 (m)	2.39 (dd)	2.45 (d)
CH_3	1.99 (s)	2.10 (s)	2.11 (s)	2.00 (s)	2.19 (s)	2.13 (s)	2.17 (s)	2.30 (s)	2.35 (s)	1.94 (s)	2.05 (s)	2.08 (s)
CH_3	2.15 (s)	2.20 (s)	2.26 (s)	2.13 (s)	2.28 (s)	2.24 (s)	2.40 (s)	2.46 (s)	2.69 (s)	1.97 (s)	2.15 (s)	2.03 (s)
H 2 (6')				7.30 (m)	7.28 (m)	7.27 (m)	7.39 (m)			7.20 (m)	7.24 (m)	7.21 (m)
H 3' (5')				7.30 (m)	7.28 (m)	7.27 (m)	7.14 (m)			7.20 (m)	7.24 (m)	7.21 (m)
NH		1.80 (br)		1.74 (t)			2.46 (t)	3.57 (s)		1.34 (t)		
H 1"				3.44 (d)	3.59 (s)	3.53 (s)	3.45 (d)		3.54 (s)	2.50 (m)	2.72 (m)	2.71 (m)
H 2"										2.62 (m)	2.72 (m)	2.62 (m)
NH_2	6.7 (br)	5.50 (br)		6.88 (br)	5.75 (br)		7.2 (br)			6.78 (br)	5.7 (brs)	

[a] Abbreviations: br, broad; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; m, multiplet; s, singlet; t, triplet. δ values were deduced by first order analysis of the spectra; error ± 0.05 ppm. [b] Signals of low resolution.

Table 13

Coupling Constants Deduced from the Analysis of the ^1H NMR Spectra of Compounds **IVa-d**

	IVa		**IVb**			**IVc**			**IVd**	
J (Hz)	DMSO	CD_3OD	DMSO	$CDCl_3$	CD_3OD	DMSO	$CDCl_3$	CD_3OD	$CDCl_3$	CD_3OD
H2 (4) ax-H2 (4) eq	11.0	11.9		11.0	11.2			11.5	11.5	12.3
H2 (4) eq-H1 (5)					1.9					2.2
H2 (4) ax-H1 (5)	6.3	4.0			3.0				4.6	
H2 (4) ax-H6 (8) ax		1.5						2.4		
H6 (8) ax-H6 (8) eq	10.6	11.5	10.5	11.1	10.8	11.7	11.5	11.9	11.5	11.6
H6 (8) eq-H1 (5)					1.2		3.4		2.3	1.2
H6 (8) ax-H1 (5)		2.9	1.9		2.4				3.2	
H1"-NH			7.6			7.1				
H2' (6')-H3' (5')						8.8				
H2' (6')-F						5.7				
H3' (5')-F						8.9				

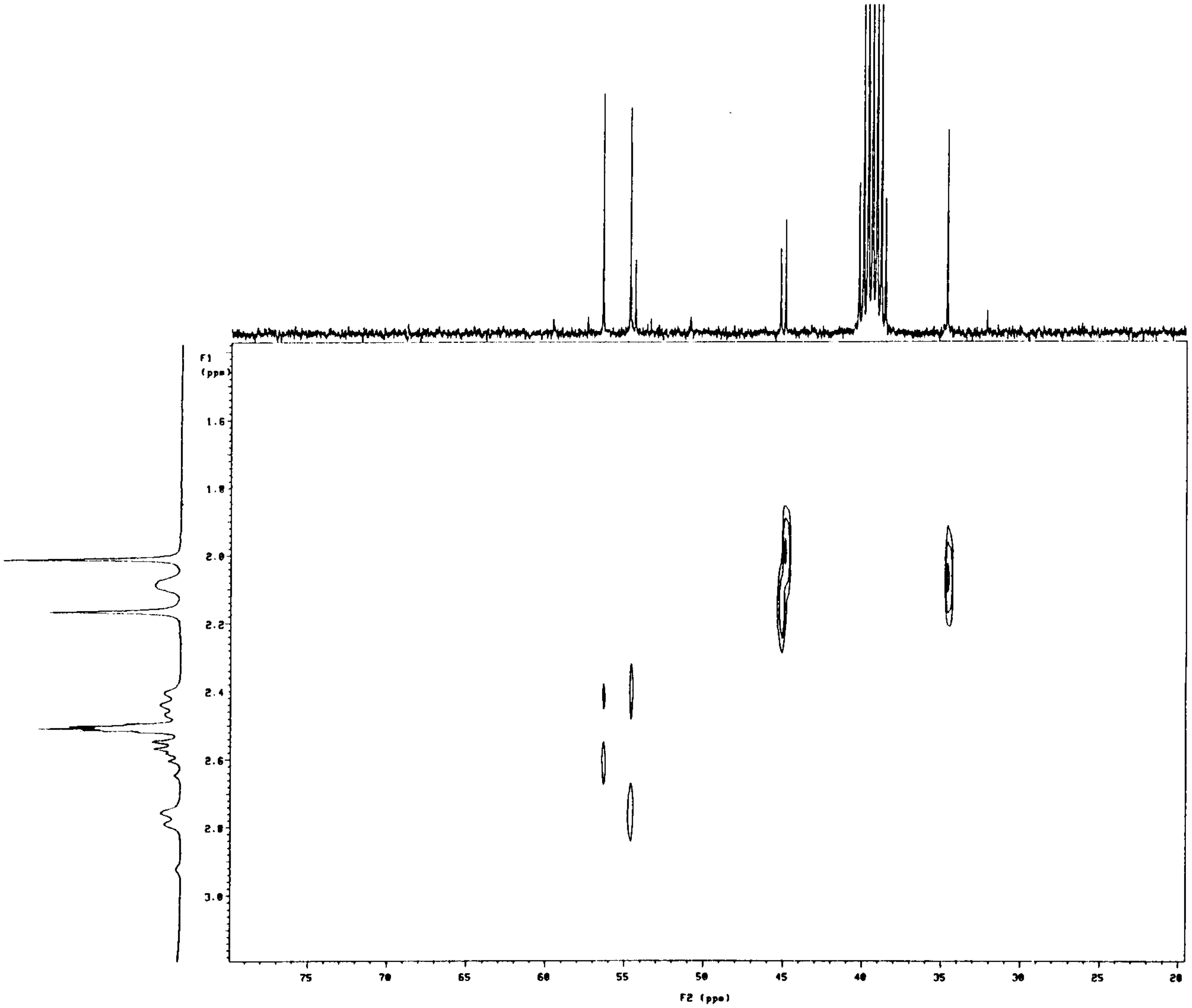


Figure 6. Proton-Carbon shift correlation spectrum (XHCORD) of **IVa** in DMSO.

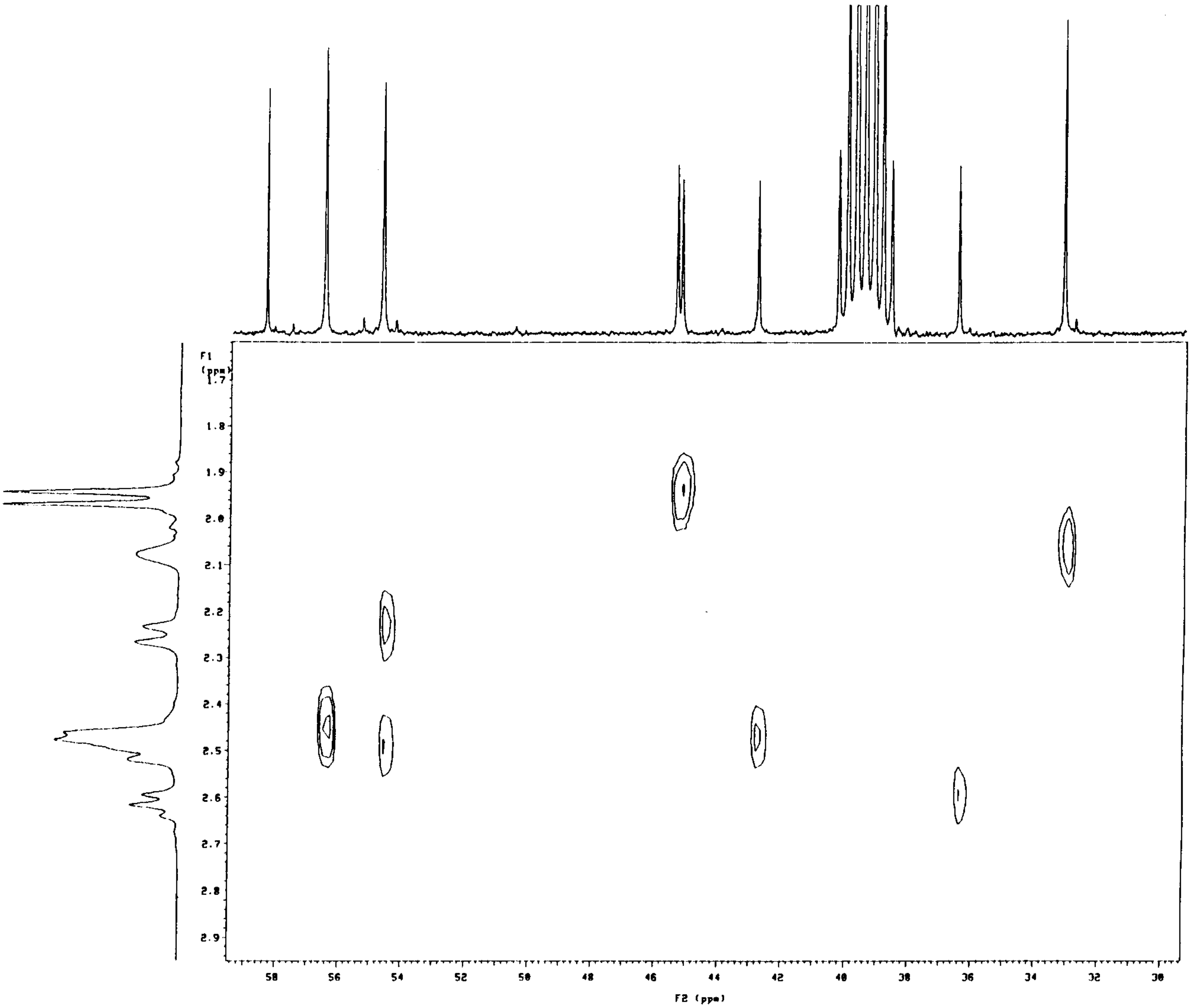


Figure 7. Proton-Carbon shift correlation spectrum (XHCORD) of **IVd** in DMSO.

position; furthermore, the piperidine ring with the amino group axial seems to be more flattened in order to avoid the syn-diaxial effect on H2(4)ax. These conclusions are substantiated by similar arguments as those exposed for compounds **IIa-d**.

For compounds **IVa-d**, the H6(8)ax signal appears at lower field than H6(8)eq signal. This fact is attributed to the field effect exerted by the carbonyl group on H6(8)ax. By consequence, it can be supposed that for compounds **IVa-d** the amino carbonyl group adopts a preferred conformation in which the carboxamide plane is perpendicular with respect to the C1-C2-C4-C5 plane (Scheme I) with the carbonyl group in trans position with respect to the amino group.

Compound **IVb**•2HCl.

In Table 15 we summarize the ^{1}H chemical shifts of *N*,*N'*-dimethylbispidine perchlorate in deuterium oxide, *N*,*N*-dimethylbispidine in trifluoroacetic acid [3] and compound **IVb**•2HCl in deuterium oxide. For *N*,*N'*-dimethylbispidine perchlorate, Douglass *et al.* [3] proposed an adamantane like structure (Figure 9a).

Support for this structure was derived from the position of the *N*-methyl resonance. The observed shift is some 0.6 ppm further upfield than is commonly found when the nitrogen atom carries a full positive charge (as it happens on dissolving bispidine in trifluoroacetic acid [3]). However, the same authors admit that his fact does not

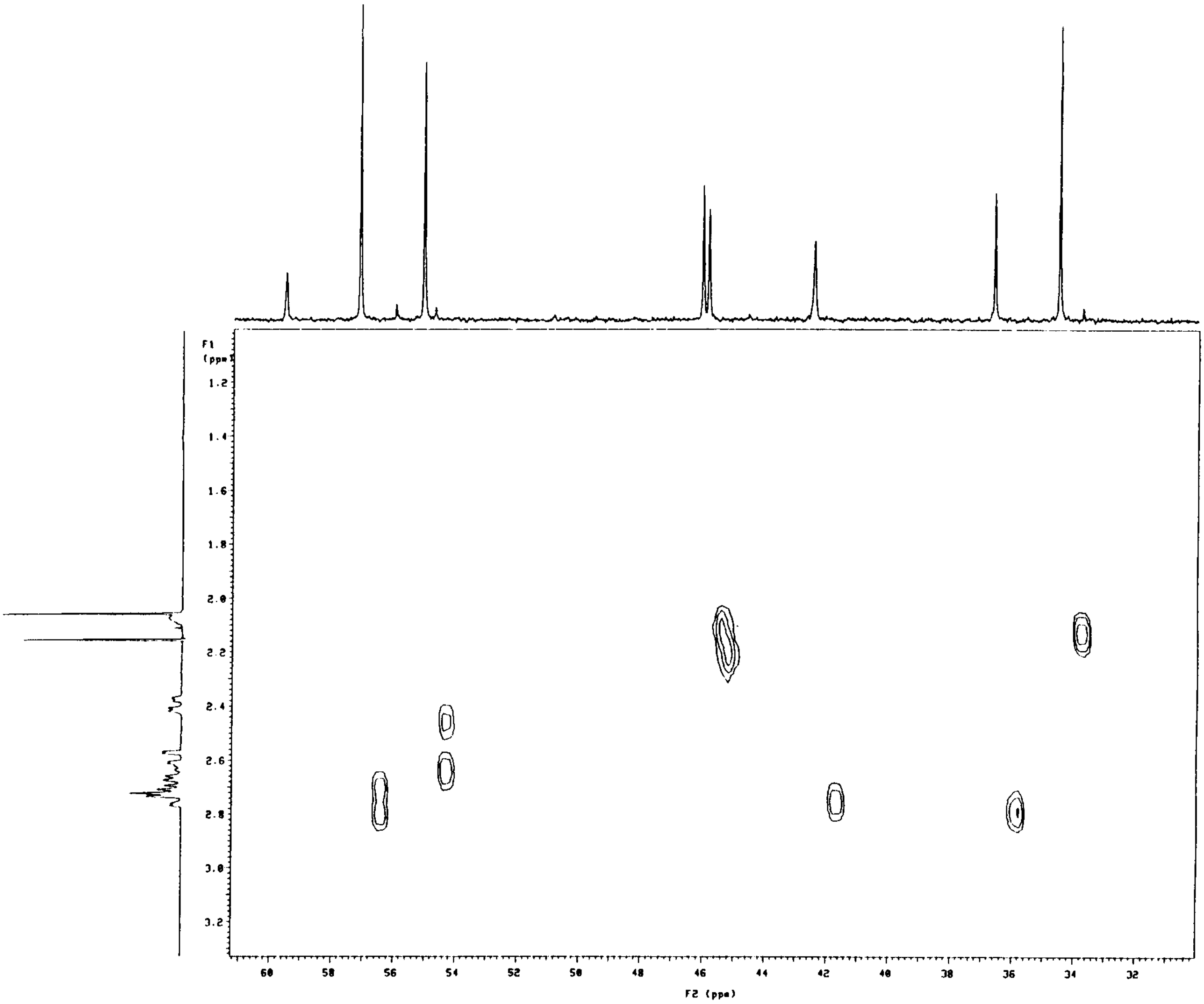


Figure 8. Proton-Carbon shift correlation spectrum (XHCORD) of **IVd** in deuteriochloroform.

Table 14

Carbon-13 Chemical Shifts of Compounds **IVa-d**

	IVa		**IVb**	**IVc**	**IVd**	
δ (ppm) [a]	DMSO	$CDCl_3$	DMSO	DMSO	DMSO	$CDCl_3$
C 1 (5)	34.87	36.21	33.32	32.80	33.19	34.56
C 2 (4)	56.51	56.54	56.58	56.58	56.52	57.16
C 6 (8)	54.78	55.13	54.94	54.62	54.68	55.09
C 9	54.54	55.69	58.85	58.57	58.37	59.54
CH_3	45.06	45.08	45.33	44.63	45.24	45.89
CH_3	45.39	45.95	45.71	44.75	45.39	46.09
C=O	177.86	178.60	174.72	174.05	174.63	176.18
C 1'			141.09	136.72	140.54	139.89
C 2' (6')			127.82 [b]	129.75	128.03 [b]	128.34 [b]
C 3' (5')			128.12 [b]	114.81	128.72 [b]	128.85 [b]
C 4'			126.56	161.08	125.71	126.16
C 1"			45.33	44.63	42.86	42.47
C 2"					36.52	36.65

[a] Directly measured on the spectra; error ± 0.05 ppm. [b] These values may be interchanged. [c] Coupling constants observed: J C1'-F 3.0 Hz, J C2' (6')-F 8 Hz, J C3' (5')-F 20.6 Hz and J C4'-F 250 Hz.

Table 15

^{1}H Chemical Shifts (δ, ppm) of Salts of Compounds **IVb** and of N,N-Dimethylbispidine

Compound	Solvent	H1 (5)	H2 (4) ax	H2 (4) eq	H6 (8) ax	H6 (8) eq	N3-CH$_3$	N7-CH$_3$
IVb•2HCl	D_2O	2.59	2.88	3.36	3.43	3.28	2.43	2.56
VI•HClO$_4$	D_2O	2.32	2.92	3.50	2.92	3.50	2.42	2.42
VI	CF_3CO_2H	2.68	3.42	3.97	3.42	3.97	3.07	3.07

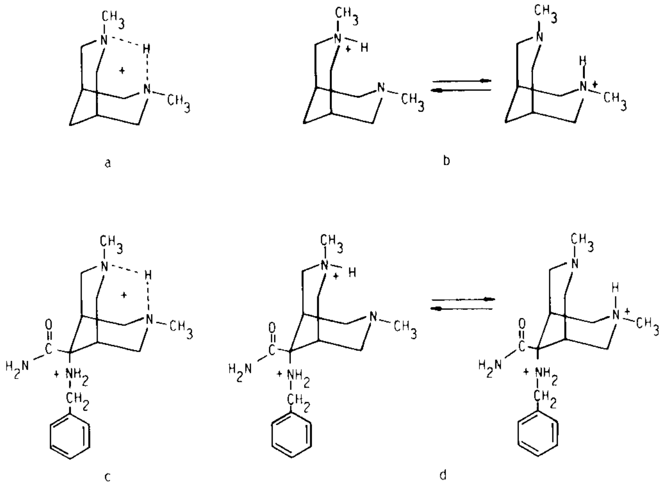


Figure 9.

constitute proof for said adamantane like structure for this cation, since rapid exchange intra or intermolecularly will give an average effect for the N-methyl an the N^+-methyl signals (Figure 9b).

The observed chemical shifts of the N3-CH$_3$ and N7-CH$_3$ protons of **IVb**•2HCl in deuterium oxide clearly suggest that both nitrogen atoms carry between them a positive charge. These values can be applied to both an adamantane like structure (Figure 9c) or a monoprotonated compound where rapid exchange would give an average effect for N3-CH$_3$ and N7-CH$_3$ (Figure 9d). The chemical shifts of the bispidine skeleton protons in **IVb**•2HCl are consistent with nitrogen atoms so charged. These protons have a very close chemical shifts with respect to the relative protons in N,N'-dimethylbispidine perchloriate (Table 15). The remarkable downfield shift of the H6(8)ax proton in comparison to the relative protons in N,N'-dimethylbispidine perchlorate (= 0.5 ppm) can be attributed to the additional effect due to the magnetic anisotropy of the carbonyl group.

Table 16

Analytical data

Compound	Formula	Found (%) (Calcd.) C	H	N
IIa	$C_{10}H_{18}N_4$	61.80	9.34	28.86
		(61.82	9.34	28.84)
IIb	$C_{17}H_{24}N_4$	71.82	8.54	19.64
		(71.79	8.51	19.70)
IIc	$C_{17}H_{23}N_4F$	(67.37	7.60	18.64)
		(67.52	7.67	18.53)
IId	$C_{18}H_{26}N_4$	72.40	8.75	18.85
		(72.44	8.78	18.77)
IVa	$C_{10}H_{20}N_4O$	56.45	9.60	26.38
		(56.58)	9.50	26.39)
IVb	$C_{17}H_{26}N_4O$	67.71	8.65	18.45
		(67.52	8.67	18.53)
IVc	$C_{17}H_{25}N_4OF$	63.66	7.82	17.56
		(63.73	7.86	17.49)
IVd	$C_{18}H_{28}N_4O$	68.31	8.95	17.64
		(68.32	8.92	17.70)

According to what we have stated up to now, compound **IVb**•2HCl in deuterium oxide solution has a hybrid ionic structure (Figure 9c, d).

The main difference between the crystal and solution (deuterium oxide states for compound **IVb**•2HCl is that in the crystal lattice, the N-bispidine atoms are protonated and the N-benzylamine nitrogen remains unprotonanted. These facts seem to be governed by the strong hydrogen contacts between the N-H$^{\delta+}$ bispidine protons and the chloride atoms. In deuterium oxide, solution, by the contrary, the molecule prefers to adopt a monoprotonated adamantane like bispidine skeleton and by this way, the steric repulsion between the N-piperidine protons can be relieved.

EXPERIMENTAL

The crystal structure of compound **IVb**•2HCl has been determined from single-crystal X-ray data by Patterson methods (see Table 1).

All melting points were taken in open capillary tubes and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 883 spectrophotometer. The nmr spectra were performed on a Varian UNITY-300 spectrometer. The ^{1}H nmr spectra were obtained at 300 MHz using spectral width of 4000 Hz and acquisition time of 3.0 s over 64 transients. LB = -8.0, GF = 0.6 and GFS = 0.2 were used for resolution enhancement. Conventional irradiation was used for the double resonance experiments. The ^{13}C nmr spectra were recorded at 75 MHz. The spectral parameters included spectral width of 16500 Hz, acquisition time of 1.0 s, delay time of 1.0 s and pulse width of 4 μs. The homonuclear (COSY 45°) and heteronuclear (XHCORD) shift correlation experiments were performed by using standard Varian pulse sequences. The elemental analyses were made in a Perkin-Elmer Elemental Analyzer model 240 B.

The mass spectra were recorded on a Hewlett-Packard 5890 spectrometer at 70 eV using a direct insertion probe.

Synthesis of the Aminonitriles **IIb-d**. General Procedure.

To a stirred solution of potassium cyanide (0.012 mole) and the corresponding amine hydrochloride (0.012 mole) in water (8.5 ml) was added a solution of **I** (0.012 mole) [3] in methanol (8.5 ml). The resulting solution was stirred for three days at room temperature.

In the case of compounds **IIb,c** the white solid obtained was filtered, washed with water and maintained for 24 hours at vacuum. These compounds were purified by crystllization from hexane/methylene chloride.

In the case of compound **IId**, the resulting mixture was extracted with methylene chloride (3 x 100 ml), the organic layer was dried (magnesium sulfate), filtered and concentrated under reduced pressure, and an oil was obtained.

3,7-Dimethyl-9-benzylamino-3,7-diazabicyclo[3.3.1]nonane-9-carbonitrile (**IIb**).

This compound was obtained in 59% yield, mp 94-96°; ir (potassium bromide): CN, 2215 cm^{-1}; ^{1}H nmr: (see Tables 9 and 10); ^{13}C (see Table 11); ms: m/z 284 (M^{+}, 6%), 256 (3), 213 (4), 199 (6), 179 (10), 119 (11), 91 (96), 83 (69), 82 (52), 58 (100).

3,7-Dimethyl-9-p-fluorobenzylamino-3,7-diazabicyclo[3.3.1]nonane-9-carbonitrile (**IIc**).

This compound was obtained in 50% yield, mp 77-78°; ir (potassium bromide): CN, 2214 cm^{-1}; ^{1}H nmr: (see Tables 9 and 10); ^{13}C nmr (see Table 11); ms: m/z 302 (M^{+}, 6%), 374 (3), 231 (4), 217 (6), 179 (9), 119 (10), 109 (97), 83 (97), 82 (59), 58 (100).

3,7-Dimethyl-9-phenethylamino-3,7-diazabicyclo[3.3.1]nonane-9-carbonitrile (**IId**).

This compound was obtained in 93% yield, bp 215° at 0.5 mm Hg; ir (film): CN, 2215 cm^{-1} ^{1}H nmr: (see Tables 9 and 10); ^{13}C nmr: (see Table 11); ms: m/z 298 (M^{+}, 4%), 270 (3), 227 (4), 213 (6), 179 (3), 119 (6), 83 (41), 82 (27), 58 (100).

3,7-Dimethyl-9-amino-3,7-diazabicyclo[3.3.1]nonane-9-carbonitrile (**IIa**).

A solution of **I** (0.008 mole), potassium cyanide (0.008 mole) and ammonium chloride (0.008 mole) in 1,4-dioxane: water (35:1, 24 ml) was stirred for seven days at room temperature, then, water was added until solution of the oil that separated. The resulting solution was cooled (ice bath), basified (potassium hydroxide) and extracted with methylene chloride (3 x 80 ml). The organic layer was washed with water, dried (anhydrous magnesium sulfate) and concentrated under reduced pressure. An oil was obtained that precipitates on cooling and which was recristallized from hexane/methylene chloride. The title compound was obtained in 79% yield, mp 178-179° dec; ir (potassium bromide): CN, 2220 cm^{-1}; ^{1}H nmr: (see Tables 9 and 10); ^{13}C nmr: (see Table 11); ms: m/z 194 (M^{+}, 26%), 168 (6), 124 (17), 109 (27), 119 (35), 82 (84), 58 (100).

Synthesis of the Amides **IVa-d**. General Procedure.

Anhydrous hydrogen chloride was bubbled into a solution of the corresponding aminonitrile (0.004 mole) in methanol (35 ml) until saturation with external cooling and magnetic stirring. Then, the solution was stirred overnight at room temperature, heated under reflux for 90 minutes and cooled. The white solid that separated was recrystallized in methanol-2-propanol, **IVb-d**·2HCl, or 2-propanol-water, **IVa**·2HCl. Then this dihydrochloride was dissolved in water (minimal quantity), the solution was cooled in an ice bath and basified with concentrated solution of potassium hydroxide, and the amide precipitated as a white solid, that was filtered and maintained in a desiccator under vacuum for 24 hours and then crystallized from methanol/diethyl ether.

3,7-Dimethyl-9-amino-3,7-diazabicyclo[3.3.1]nonane-9-carboxamide (**IVa**).

This compound was obtained in 14% yield, mp 173-174° dec; ir (potassium bromide): C=O, 1678 cm^{-1}; ^{1}H nmr: (see Tables 12 and 13); ^{13}C nmr: (see Table 14); ms: m/z 212 (M^{+}, 21), 168 (7), 137 (25), 125 (9), 109 (31), 83 (49), 82 (70), 58 (100).

The dihydrochloride salt had mp 248-249° dec; ir (potassium bromide): C=O; 1691 cm^{-1}.

3,7-Dimethyl-9-benzylamino-3,7-diazabicyclo[3.3.1]nonane-9-carboxamide (**IVb**).

This compound was obtained in 47% yield, mp 172-173° dec; ir (potassium bromide): C=O, 1659 cm^{-1}; ^{1}H nmr (see Tables 12 and 13); ^{13}C nmr: (see Table 14); ms: m/z 302 (M^{+}, 2%), 258 (6), 215 (2), 199 (9), 197 (25), 137 (11), 91 (64), 83 (12), 82 (16), 58 (100).

The dihydrochloride salt had mp 220-221° dec; ir (potassium bromide): C=O, 1672 cm^{-1}.

3,7-Dimethyl-9-p-fluorobenzylamino-3,7-diazabicyclo[3.3.1]nonane-9-carboxamide (**IVc**).

This compound was obtained in 59% yield, mp 164-166° dec; ir (potassium bromide): C=O, 1681 cm^{-1}; ^{1}H nmr: (see Tables 12 and 13); ^{13}C nmr: (see Table 14); ms: m/z 320 (M^{+}, 2%), 276 (7), 233 (2), 217 (7), 197 (29), 137 (15), 109 (79), 83 (22), 82 (18), 58 (100).

The dihydrochloride salt had mp 222-223° dec; ir (potassium bromide): C=O, 1693 cm^{-1}.

3,7-Dimethyl-9-phenethylamino-3,7-diazabicyclo[3.3.1]nonane-9-carboxamide (**IVd**).

This compound was obtained in 40% yield, mp 164-166° dec; ir (potassium bromide): C=O, 1660 cm^{-1}; ^{1}H nmr: (see Tables 12 and 13); ^{13}C nmr: (see Table 14); ms: m/z 316 (M^{+}, 3%), 272 (6), 229 (2), 213 (5), 197 (7), 137 (7), 83 (7), 83 (10), 58 (100).

The dihydrochloride salt had mp 181-182° dec; ir (potassium bromide): C=O, 1678 cm^{-1}.

Results obtained in the elemental analysis (C,H,N) of compounds **IIa-d** and **IVa-d** were within ± 0.4% of theoretical values.

Acknowledgement.

We thank the Commission Interministerial de Ciencia y Energía (Grant FAR-0440) for support of this research.

REFERENCES AND NOTES

[1] E. Gálvez, M. S. Arias, J. Bellanato, J. V. García-Ramos, F. Florencio, P. Smith-Verdier and S. García-Blanco, *J. Mol. Struct.*, **127**, 185 (1985) and references therein.

[2] M. L. Izquierdo, B. Rico, E. Gálvez and J. J. Vaquero, *J. Mol. Struct.*, **213**, 175 (1989).

[3] J. E. Douglass and T. B. Ratliff, *J. Org. Chem.*, **33**, 355 (1968).

[4] P. T. Beursken, W. P. Bosman, H. M. Doesburg, R. O. Gould, T. E. M. Van der Hark, P. A. J. Prick, J. H. Noordik, G. Breurken and V. Parthasarathi, DIRDIF, Crystallography Laboratory, Tournooiveld, 6525 ED, Nijmegen, The Netherlands, 1982.

[5] J. P. Stewart, P. A. Machin, C. W. Dickinsin, H. L. Ammon, H. Heck and H. Flack, The X-ray 76 System, Computer Science Center, University of Maryland, College Park, MD, 1976.

[6] M. Martinez-Ripoll and F. H. Cano, PESOS: A Computer Program for the Automatic Treatment of Weighting Schemes, Institute Rocasolano, CSIC, Madrid, 1975.

[7] M. Nardelli, *Comput. Chem.*, **7**, 95 (1983).

[8] International Tables for X-Ray Crystallography, Vol **4**, Kynoch Press, Birmingham, England, 1974, p 72-98.

[9] S. C. Abrahams, and Keve, E. T. Keve, *Acta Crystallogr., Sect. A*, **27**, 157 (1971).

[10] D. Cremer and J. A. Pople, *J. Am. Chem. Soc.*, **97**, 1354 (1975).

[11] G. G. Trigo, E. Gálvez and C. Avendaño, *J. Heterocyclic Chem.*, **15**, 907 (1978).

[12] A. Bax and R. Freeman, *J. Magn. Reson.*, **44**, 542 (1981).

[13] A. E. Derome Modern NMR Techniques for Chemistry Research, Pergamon Press, Oxford, 1987.

[14] M. Perpick-Dumont, W. F. Reynolds and R. Enriquez, *Magn. Reson. Chem.*, **26**, 358 (1988).

[15] W. F. Reynolds, S. McLean, M. Perpick-Dumont and R. Enriquez, *Magn. Reson. Chem.*, **26**, 1068 (1988).

[16] M. S. Arias, E. Galvez, J. C. del Castillo, J. J. Vaquero, J. Chicharro, *J. Mol. Struct.*, **156**, 239 (1987).

[17] P. C. Ruenitz, E. E. Smissman and D. S. Wright, *J. Heterocyclic Chem.*, **14**, 423 (1977).

[18] E. Galvez, C. Avendaño and M. Martínez, *J. Heterocyclic Chem.*, **17**, 1417 (1980).