Journal of Molecular Structure, 172 (1988) 381—394
Elsevier Science Publishers B.V., Amsterdam — Printed in The Netherlands

SYNTHESIS AND STRUCTURAL STUDY OF *N*-(8-ISOPROPYL-NORTROPAN-3-α-YL)-2-METHOXY-4-AMINO-5-CHLOROBENZAMIDE

N. CABEZAS and M. MARTINEZ

Departamento de Química Orgánica y Farmaceutica, Facultad de Farmacia, Universidad Complutense, 28040-Madrid (Spain)

E. GALVEZ* and M. S. ARIAS

Departamento de Química Orgánica, Universidad de Alcalá de Henares (Spain)

F. FLORENCIO and S. GARCIA-BLANCO

Instituto "Rocasolano", Departamento de Rayos-X, C.S.I.C., Serrano 121, Madrid (Spain)

(Received 27 July 1987)

ABSTRACT

N-(8-Isopropyl-nortropan-3-α-yl)-2-methoxy-4-amino-5-chlorobenzamide has been synthesized and its crystal and molecular structures determined by X-ray diffraction, IR, ^{1}H-NMR and ^{13}C-NMR methods. The pyrrolidine and piperidine rings adopt a flattened N-8 envelope and distorted chair conformation puckered at N-8 and flattened at C-3 respectively, with the *N*-isopropyl substituent and the amido group in axial position with respect to the piperidine ring. A great predominance in solution of the conformer observed in the solid state is proposed.

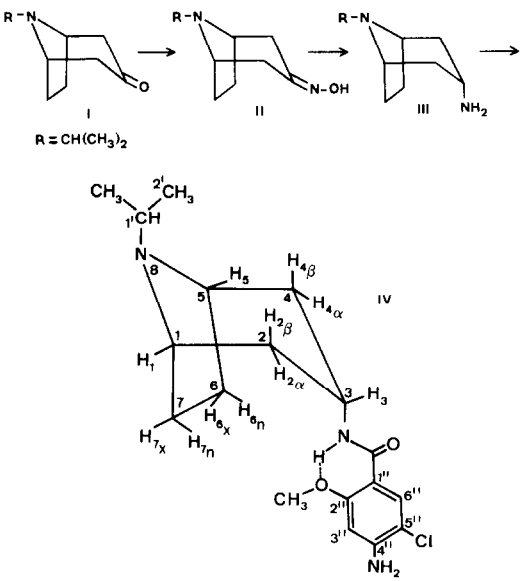
INTRODUCTION

As a part of a research program related to the synthesis and structural study of benzamide neuroleptics, this paper reports the synthesis and structural analysis with the aid of X-ray diffraction data and ^{1}H NMR, ^{13}C NMR and IR spectroscopy of *N*-(8-isopropyl-nortropan-3-α-yl)-2-methoxy-4-amino-5-chlorobenzamide in order to determine the preferred conformations both in solution and in the solid state.

SYNTHESIS

The synthesis of the title compound is shown in Scheme 1. *N*-Isopropyl-nortropinone (I) was transformed to the oxime (II). From reduction of II with lithium aluminium hydride, the amine (III) was obtained. Compound IV was prepared by treatment of III with 2-methoxy-4-amino-5-chlorobenzoic acid and ethylchloro carbonate.

0022-2860/88/$03.50



Scheme 1

EXPERIMENTAL

Experimental and X-ray structural data are collected in Table 1 [1–5]. An absorption correction is made on F_0 [6].

The IR spectra were recorded in the solid state (KBr) on a Perkin-Elmer 577 spectrometer.

The ^{1}H-NMR spectra were recorded at 500 MHz (spectral width 5000 Hz) in $CDCl_3$ solution and 360 MHz (spectral width 3300 Hz) in C_6D_6 solution using Bruker AM-500 FT-NMR and Bruker WM 360 spectrometers, respectively. Conventional irradiation was used for the double resonance experiments in C_6D_6 solution at 360 MHz.

The ^{13}C-NMR spectra were obtained at 50.32 MHz on a Bruker WM-200-SY pulse Fourier transformation (PFT) spectrometer in $(CD_3)_2SO$ solution. Two types of spectra were recorded: a proton noise decoupled spectrum to determine the chemical shifts and an attached proton test (APT) spectrum to help assign the signals. All measurements were carried out at 303 K with TMS as the internal standard.

The agreement between the observed spectrum and the parameters deduced from the analysis with the LAOCOON III program was verified by simulation of the calculated spectrum using the SIMEQ program of the standard Varian software.

The elemental analysis were made in a Carlo Erba elemental analyzer model 1104 equipped with a C.S.I. digital integrator model C SI 38.

TABLE 1

Experimental data and structure refinement procedures

Crystal data	
Formula	C16 H21 N3 O2 Cl
Crystal habit	Prismatic
Crystal size (mm)	0.2 × 0.2 × 0.3
Symmetry	Monoclinic, $P2_1/n$
Unit cell determination	Least-squares fit from reflections ($\theta < 65°$)
Unit cell dimensions	15.238(1), 12.756(1), 9.270(1) Å 90.0, 94.59(1), 90.0°
Packing: V (Å^3), Z	1796.1(1), 4
D_c (g cm^{-1}), M, $F(000)$	1.1938, 322.814, 684
Experimental data	
Technique	Four circle diffractometer: PW 1100 Philips Bisecting geometry Graphite oriented monochromator: Cu K_α $w/2\theta$ scans Detector apertures 1 × 1°, up θ max. 65°
Number of reflections	
Measured	6077
Independent	3036
Observed	2478, (2 $\sigma(I)$ criterion)
Range of hkl	−18 18, 0 15, 0 11, (sin θ/λ) max. 0.60
Standard reflections	2 reflections every 90 min Variation: no
Solution and refinement	
Solution	Direct and Fourier methods
Refinement	L.S. on F_{obs} with 1 blocks
Parameters	
Number of variables	283
Degrees of freedom	2753
Ratio of freedom	10.7
H atoms	Difference synthesis
Final shift/error	0.002
w-scheme	Empirical so as to give no trends in $\langle w\Delta^2 F\rangle$ vs. $\langle\|F_{obs}\|\rangle$ and $\langle\sin\theta/\lambda\rangle$ [1]
Final ΔF peaks	0.15 e Å^{-3}
Final R and Rw	0.037, 0.047
Computer and programs	Vax 11/750, Multan 80 [2], X-ray 76 [3], Parst [4]
Scattering factors	Int. Tables for X-Ray Crystallography [5]
Anomalous dispersion	Int. Tables for X-Ray Crystallography [5]

Compounds

Compounds I–III

The synthesis and purification of compounds I, II and III have previously been described [7–9].

2-Methoxy-4-amino-5-chlorobenzoic acid

To a solution of 2-methoxy-4-amino-5-chloromethylbenzoate (3 g) (ref. 10) in toluene (250 ml) was added ethanolic potassium hydroxide at 3.4% (100 ml). The resulting mixture was maintained in an ultrasound bath for 30 h. The precipitated solid was filtered under reduced pressure, and dissolved in water. The mixture was acidified with hydrochloric acid at pH 4.5. The aqueous layer was extracted three times with chloroform (100 ml). The solution was dried (anhydrous sodium sulfate) and concentrated under reduced pressure, and the solid precipitate was recrystallized from toluene; 1.9 g (81%) of the product (m.p. 209–210°C) was obtained.

Elemental analysis. Calculated for $C_8H_8NO_3Cl$: C, 47.64; H, 3.99; N, 6.94 (%). Found: C, 47.50 H, 3.87; N, 6.96 (%).

IR (potassium bromide): 3340, 3230 (N—H), 1705 (C=O) cm^{-1}.

^1H NMR (hexadeuterio-dimethylsulfoxide): δ = 10.00 (brs, 1H, OH), 6.50 (s, 1H, ArH), 6.10 (s, 2H, NH_2), 3.75 (s, 3H, OCH_3).

N-*(8-Isopropyl-nortropan-3-α-yl)-2-methoxy-4-amino-5-chlorobenzamide (IV)*

To a solution of 2-methoxy-4-amino-5-chlorobenzoic acid (1.85 g) and triethylamine (0.94 ml) in anhydrous DMF (26 ml) externally cooled was added ethylchloroformate (0.65 ml) under nitrogen atmosphere. The mixture was maintained at 0°C for 1 h. To the resulting mixture was added a solution of III (1.13 g) in anhydrous DMF (7 ml) under nitrogen atmosphere, and the solution was maintained at room temperature for 24 h. The white solid precipitate was filtered and dissolved in chloroform, the solution washed with aqueous 2 N NaOH and water, dried (anhydrous sodium sulfate) and concentrated. The residue that separated was crystallized from ethylacetate, 0.9 g (38%) of the product (m.p. 208°C) being obtained.

Elemental analysis. Calculated for $C_{16}H_{22}N_3O_2Cl$: C, 61.41; H, 7.45; N, 11.94 (%). Found: C, 61.80; H, 7.29; N, 11.55 (%).

RESULTS AND DISCUSSION

Description of the structure

Figure 1 displays the structural formula of compound IV with the atomic labelling. Atomic parameters are given in Tables 2 and 3. Bond length, valence and torsion angles are given in Tables 4 and 5. The molecule consists of a piperidine and a pyrrolidine ring formed by a common C—N—C bridge, with an isopropyl group attached to the N8 atom and a substituted benzamido group attached at the C3 atom; both groups occupy an axial position with respect to the piperidine ring. This ring adopts a distorted chair conformation flattened at C3. The pyrrolidine ring adopts a puckering N8 envelope conformation; the deviation of N8 atom from the plane through C1, C5, C6 and C7 is 0.73(2) Å.

The nortropane bicycle has a chair—envelope conformation. Asymmetric

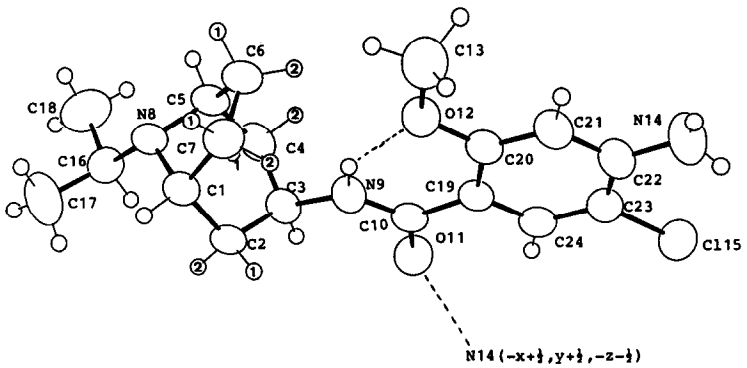


Fig. 1. Perspective view and atomic labelling of molecule IV for the crystallographic study.

TABLE 2

Atomic parameters for non H-atoms[a]

Atom	*X/A*	*Y/B*	*Z/C*	U_{eq}
C1	0.05519(13)	0.29695(17)	−0.86257(23)	506(7)
C2	0.05700(14)	0.22940(16)	−0.72584(25)	538(7)
C3	0.01968(12)	0.28569(15)	−0.59751(22)	464(6)
C4	−0.05933(12)	0.35446(17)	−0.64772(22)	464(6)
C5	−0.05043(13)	0.40873(15)	−0.79351(22)	456(6)
C6	0.03205(14)	0.47739(16)	−0.79277(25)	526(7)
C7	0.10305(14)	0.40209(18)	−0.84069(26)	556(7)
N8	−0.03446(10)	0.33336(13)	−0.90875(17)	453(5)
N9	0.08870(11)	0.34549(13)	−0.51374(19)	482(5)
C10	0.12070(11)	0.32130(13)	−0.38021(20)	403(6)
O11	0.08944(10)	0.25002(12)	−0.31051(16)	595(5)
O12	0.21537(9)	0.49058(11)	−0.51794(15)	523(5)
C13	0.25842(20)	0.57353(21)	−0.58790(32)	708(10)
N14	0.41308(14)	0.53574(18)	−0.09251(28)	685(8)
Cl15	0.33288(4)	0.36479(5)	0.07505(6)	636(2)
C16	−0.10213(14)	0.25451(18)	−0.94716(23)	549(7)
C17	−0.07030(28)	0.17982(32)	−1.05982(39)	952(14)
C18	−0.18653(20)	0.31042(30)	−1.00233(45)	893(12)
C19	0.19702(12)	0.38289(13)	−0.31393(20)	392(5)
C20	0.24281(12)	0.46491(14)	−0.37797(21)	421(6)
C21	0.31213(13)	0.51554(16)	−0.30308(24)	493(6)
C22	0.34169(13)	0.48646(15)	−0.16231(23)	495(6)
C23	0.29748(13)	0.40398(15)	−0.09966(21)	469(6)
C24	0.22738(13)	0.35506(15)	−0.17380(21)	433(6)

[a]Coordinates and thermal parameters as U_{eq} = (1/3) sum (U_{ij} A_i × A_j × A_i A_j cos (A_i, A_j)) 10^4.

parameters are ΔC_s^3 = 0.007(1), ΔC_2^{1-8} = 0.061(1), ΔC_2^{1-2} = 0.131(1)° for the six membered ring and ΔC_s^8 = 0.113(2) for the five membered ring [11].

TABLE 3

Atomic parameters for H-atoms[a]

Atom	*X/A*	*Y/B*	*Z/C*	*U*
H1	0.077(1)	0.258(2)	−0.945(2)	41(6)
H21	0.119(2)	0.209(2)	−0.699(3)	42(7)
H22	0.023(2)	0.163(2)	−0.750(2)	30(6)
H3	0.001(2)	0.230(2)	−0.529(3)	35(6)
H41	−0.114(1)	0.309(2)	−0.658(2)	23(6)
H42	−0.064(2)	0.407(2)	−0.571(3)	36(6)
H5	−0.105(2)	0.448(2)	−0.818(2)	30(6)
H61	0.022(2)	0.533(2)	−0.865(3)	42(7)
H62	0.049(1)	0.509(2)	−0.693(2)	24(5)
H71	0.122(2)	0.428(2)	−0.936(3)	49(7)
H72	0.155(2)	0.394(2)	−0.769(3)	34(6)
H9	0.113(2)	0.395(2)	−0.555(3)	40(7)
H131	0.230(2)	0.577(2)	−0.687(4)	59(9)
H132	0.251(2)	0.640(3)	−0.536(4)	67(10)
H133	0.326(2)	0.560(2)	−0.588(3)	59(9)
H141	0.423(2)	0.607(3)	−0.124(3)	61(9)
H142	0.419(2)	0.522(2)	−0.003(3)	49(9)
H16	−0.115(1)	0.213(2)	−0.858(3)	33(6)
H171	−0.115(2)	0.135(3)	−1.095(3)	64(9)
H172	−0.054(2)	0.221(3)	−1.140(4)	89(12)
H173	−0.013(3)	0.140(4)	−1.021(5)	128(19)
H181	−0.229(2)	0.259(3)	−1.040(3)	61(9)
H182	−0.173(2)	0.358(3)	−1.078(6)	83(11)
H183	−0.212(4)	0.353(4)	−0.917(4)	147(22)
H21	0.342(2)	0.572(2)	−0.342(3)	41(7)
H24	0.199(1)	0.301(2)	−0.132(2)	23(5)

[a]Coordinates and thermal parameters as $\exp(-8\pi^2 U(\sin\theta/\lambda)^2 \times 10^3)$.

The average bond length within the benzene ring is 1.392(3) Å. The chlorine atom is almost coplanar with the benzene ring with a deviation of 0.0243(7) Å; also, the O11, C10, N9, O12, C13 and N14 atoms are in the plane of the benzene ring with deviations of 0.019(2), −0.000(2), −0.015(2), 0.053(1), 0.055(3) and 0.045(3) Å respectively. There is an intramolecular hydrogen bond: N9—H9 · · · O12 (N9—H9 = 0.84(3), H9 · · · O12 = 1.99(3), N9 · · · O12 = 2.677(2) Å and N9—$\hat{\text{H}}$9 · · · O12 = 139(2)°). Consequently, the benzamido group is nearly planar, and there is an electronic interaction (conjugative effect) through this group.

The molecules are held together by van der Waals forces and an intermolecular H bond: N14 · · · O11 ($-x + 1/2, y + 1/2, -z - 1/2$) = 2.877(3), N14–H141 = 0.97(3), H141 · · · O11 = 1.93(3) Å, N14—$\hat{\text{H}}$141 · · · O11 = 165(3)°.

TABLE 4

Bond distances, angles and selected torsion angles for compound IV

Parameter	Value	Parameter	Value
Bond distances (Å)			
C1–C2	1.531(3)	C1–C7	1.532(3)
C1–N8	1.474(3)	C2–C3	1.537(3)
C3–C4	1.532(3)	C3–N9	1.470(3)
C4–C5	1.534(3)	C5–C6	1.532(3)
C5–N8	1.472(3)	C6–C7	1.539(3)
N8–C16	1.464(3)	N9–C10	1.330(3)
C10–O11	1.233(2)	C10–C19	1.494(2)
O12–C13	1.428(3)	O12–C20	1.371(2)
N14–C22	1.373(3)	Cl15–C23	1.739(2)
C16–C17	1.521(5)	C16–C18	1.523(4)
C19–C20	1.414(3)	C19–C24	1.390(3)
C20–C21	1.378(3)	C21–C22	1.396(3)
C22–C23	1.400(3)	C23–C24	1.373(3)
Bond angles (°)			
C7–C1–N8	100.5(2)	C2–C1–N8	111.9(2)
C2–C1–C7	114.0(2)	C1–C2–C3	113.2(2)
C2–C3–N9	111.0(2)	C2–C3–C4	111.3(2)
C4–C3–N9	112.0(2)	C3–C4–C5	113.8(2)
C4–C5–N8	112.1(2)	C4–C5–C6	112.6(2)
C6–C5–N8	101.2(2)	C5–C6–C7	103.7(2)
C1–C7–C6	104.3(2)	C1–N8–C5	101.4(2)
C5–N8–C16	118.1(2)	C1–N8–C16	118.2(2)
C3–N9–C10	124.4(2)	N9–C10–C19	118.4(2)
N9–C10–O11	122.0(2)	O11–C10–C19	119.5(2)
C13–O12–C20	119.4(2)	N8–C16–C18	108.6(2)
N8–C16–C17	109.9(2)	C17–C16–C18	111.7(2)
C10–C19–C24	116.1(2)	C10–C19–C20	127.6(2)
C20–C19–C24	116.3(2)	O12–C20–C19	116.8(2)
C19–C20–C21	121.3(2)	O12–C20–C21	121.9(2)
C20–C21–C22	121.6(2)	N14–C22–C21	120.2(2)
C21–C22–C23	117.2(2)	N14–C22–C23	122.6(2)
C115–C23–C22	118.6(2)	C22–C23–C24	121.0(2)
C115–C23–C24	120.4(2)	C19–C24–C23	122.6(2)
Some torsion angles (°)			
C2–C3–N9–C10		−111.2(2)	
C4–C3–N9–C10		123.7(2)	
C5–N8–C16–C17		−175.9(2)	
C1–N8–C16–C18		−175.6(2)	
C3–N9–C10–O11		−5.9(3)	
C3–N9–C10–C19		174.0(2)	
N9–C10–C19–C20		−1.7(3)	
O11–C10–C19–C20		178.2(2)	
C13–O12–C20–C19		179.3(2)	

TABLE 5

Torsional angles (°) for compound IV[a]

Angle	Value
H1—C1—C2—H21	61(2)
H1—C1—C2—H22	−55(2)
H21—C2—C3—H3	−82(2)
H22—C2—C3—H3	36(2)
H41—C4—C5—H5	57(2)
H42—C4—C5—H5	−64(2)
H3—C3—C4—H41	−36(2)
H3—C3—C4—H42	82(2)
H3—C3—N9—H9	178(3)
H1—C1—C7—H71	30(2)
H1—C1—C7—H72	−92(2)
H5—C5—C6—H61	−32(2)
H5—C5—C6—H62	91(2)
H61—C6—C7—H71	0(2)
H62—C6—C7—H72	0(2)
H61—C6—C7—H72	123(2)
H62—C6—C7—H71	−123(2)

[a]Error standard deviations (e.s.d.) are given in parentheses. H21 ≡ $H2_{\alpha}$; H22 ≡ $H2_{\beta}$; H41 ≡ $H4_{\beta}$; H42 ≡ $H4_{\alpha}$; H61 ≡ $H6_{x}$; H62 ≡ $H6_{n}$; H71 ≡ $H7_{x}$; H72 ≡ $H7_{n}$; H9 ≡ H of amido group.

Infrared spectra

The IR spectrum of IV in the solid state shows two sharp medium-strong bands at 3440 and 3420 cm^{-1} and two broad medium-strong bands at 3295 and 3190 cm^{-1} with a shoulder at 3340 cm^{-1}. The bands at 3440 and 3420 cm^{-1} are assigned to the stretching of the free N—H bond. The bands at 3295 and 3190 cm^{-1} are explained by the existence of two strong inter- and intramolecular hydrogen bonds respectively. These assignments are in good agreement with the results obtained by X-ray diffraction and previous literature data [11].

In the carbonyl region there are four strong bands at 1642, 1630, 1608 and 1592 cm^{-1}.

NMR spectra

^{1}H (360 MHz and 500 MHz) and ^{13}C NMR (50.32 MHz) spectroscopy and double resonance (DR) experiments were used to provide the information required. Assignments of proton and carbon resonances were made taking into account literature data for several tropane systems [12–19], norbornanes [20—23], norbornenes [20, 22], bicyclo[2,2,2]octane derivatives [20] and related systems [24—26].

In $CDCl_3$ (500 MHz) and C_6D_6 (360 MHz) all the tropane proton signals appear well differentiated and only in the former case is the multiplet at 1.844 ppm partially obscured by the slight broad single peak due to NH_2 protons. The long-range (W) couplings: ^4JH2$_\beta$—H7$_x$ or ^4JH4$_\beta$—H6$_x$ were not observed. The H1(5) signal appears as a non-resolvable wide singlet ($W_{\frac{1}{2}}$ = 9 Hz). The H2(4)$_\alpha$ signal appears as a doublet due to the geminal coupling with H2(4)$_\beta$ and H3 as an apparent quartet because of the vicinal couplings with H2(4)$_\beta$ and NH. The vicinal coupling constants ^3JH2(4)$_\alpha$– H1(5) and ^3JH2(4)$_\alpha$—H3 were not observed and a maximum value of 2 Hz has been estimated on the basis of $W_{\frac{1}{2}}$ values of the doublet signals corresponding to H2(4)$_\alpha$. ^3JH2(4)$_\beta$—H3 and ^3JH3—NH would present similar values.

The multiplet corresponding to H2(4)$_\beta$ has been considered as a part of the four spin system formed by H1, H2$_\alpha$ H2$_\beta$ and H3 (or H5, H4$_\alpha$, H4$_\beta$ and H3) protons, whose first order analysis allowed the establishment of the following parameters: δH2(4)$_\beta$, ^2JH2(4)$_\alpha$—H2(4)$_\beta$, ^3JH2(4)$_\beta$—H1(5) and ^3JH2(4)$_\beta$—H3 (Tables 6 and 7).

The assignment and analysis of the H6(7)$_x$ and H6(7)$_n$ signals has been carried out by means of double resonance (DR) experiments in C_6D_6 solution at 360 MHz and literature data for related systems [19– 23, 26]. Furthermore, these experiments lead to more accurate data for the remaining tropane system

TABLE 6

^{1}H and ^{13}C chemical shifts of compound IV

^{1}H chemical shifts[a]	δ (ppm)		^{13}C chemical shifts[b]	δ (ppm)
	$CDCl_3$	C_6D_6		
H1(5) (brs. $W_{\frac{1}{2}}$ = 9 Hz)	3.464	3.31	C1(5)	53.79
H2(4)$_\alpha$ (d)	1.495	1.52	C2(4)	33.30
H2(4)$_\beta$ (m)	2.235	2.15	C3	45.43
H3 (q, apparent)	4.310	4.61	C6(7)	26.27
H6(7)$_x$ (m)	2.034	1.893(0.005)	C1′	40.49
H6(7)$_n$ (m)	1.844	1.779(0.005)	C2′	21.09
H1′ (m)	2.723	2.49	C1″	109.16[c]
H2′ (d)	1.068	0.97	C2″	157.20
H3″ (s)	6.283	5.48	C3″	97.59
H6″ (s)	8.076	8.75	C4″	148.43
CH_3O (s)	3.895	3.15	C5″	110.26[c]
NH_2 (s)	1.827	3.44	C6″	131.52
NH(d)	8.321	8.20	CH_3O	56.09
			CO	162.14

[a]The abbreviations: br, broad; d, doublet; m, multiplet; q, quartet; s, singlet are used. Directly measured on the spectra with an error of ±0.001 ppm for $CDCl_3$ (500 MHz) and ±0.01 ppm for C_6D_6 (360 MHz) except for indicated cases (in parentheses) where they have been calculated by means of the LAOCOON III program. [b]Directly measured on the spectrum ($(CD_3)_2SO$, 50.32 MHz); error ± 0.05 ppm; signal multiplicity obtained from APT spectrum. [c]Values may be interchanged.

TABLE 7

Coupling constants deduced from the analysis of the ^1H NMR spectra of IV

Coupling constants[a]	J(Hz)	
	$CDCl_3$	C_6D_6
$H2(4)_\alpha$–$H2(4)_\beta$	−14.90(0.05)	−14.73(0.05)
$H2(4)_\beta$–H1(5)	3.50(0.05)	3.55(0.05)
$H2(4)_\beta$–H3	6.90(0.05)	6.81(0.05)
H3–NH	7.50(0.05)	7.85(0.05)
$H6_x$–$H6_n$	–	−13.07(0.08)
$H6_x$–$H7_x$	–	8.27(0.06)
$H6_x$–$H7_n$	–	4.99(0.08)
$H6_n$–$H7_n$	–	7.60(0.06)
H1′–H2′	6.20(0.05)	6.07(0.05)

[a] ^3JH2(4)$_\alpha$–H1(5), ^3JH2(4)$_\alpha$–H3 and ^3JH6(7)$_n$–H1(5) are very small and only a slight broadening of the respective signals has been observed; ^2JH6$_x$–H6$_n$ = ^2JH7$_x$–H7$_n$; ^3JH6$_x$–H7$_n$ = ^3JH6$_n$–H7$_x$; ^3JH6(7)$_x$–H1(5) could not be established.

protons. The saturation of the signal at 1.52 ppm only simplifies the multiplet due to $H2(4)_\beta$ at 2.15 ppm that collapses to a wide singlet ($W_{\frac{1}{2}}$ = 11 Hz). On the other hand, on saturating the $H2(4)_\beta$ signal at 2.15 ppm, the signals at 1.52 ppm and 4.61 ppm (H3) collapse to a wide singlet and a doublet, respectively, the other signals remaining practically unchanged. The signal at 4.61 ppm presents a splitting of 7.85 Hz due to the vicinal coupling ^3JH3–NH. There is no doubt, therefore, that: (a) the signal at 1.52 ppm corresponds to $H2(4)_\alpha$; (b) the value of the vicinal coupling ^3JH2(4)$_\alpha$–H3 is very low; (c) the multiplets at 1.80 and 1.90 ppm correspond to $H6(7)_x$ and $H6(7)_n$ protons.

On saturating the H1(5) signal at 3.31 ppm the signals at 1.52 ppm ($H2(4)_\alpha$), 1.80 ppm and 4.61 ppm (H3) did not change appreciably. The $H2(4)_\beta$ signal at 2.15 ppm simplifies into a doublet of doublets due to the geminal coupling ^2JH2(4)$_\alpha$–H2(4)$_\beta$ (−14.73 Hz) and the vicinal coupling ^3JH2(4)$_\beta$–H3 (6.81 Hz). These facts confirm the above considerations about $H2(4)_\alpha$, $H2(4)_\beta$; H1(5), H3 and NH in $CDCl_3$ and C_6D_6 solutions.

By saturation of the H1(5) signal, the multiplet at 1.90 ppm becomes simpler and symmetrical with respect to the signal at 1.80 ppm, so this latter signal has been assigned to $H6(7)_n$ protons which show a very small coupling with H1(5) whereas the signal at 1.90 ppm has been attributed to $H6(7)_x$. According to data from related systems [19–23] a limit value of 0.5 Hz has been admitted for ^3JH6(7)$_n$–H1(5); this small value explains why the $H6(7)_n$ signal remains practically unchanged by saturation of H1(5).

The $H6(7)_x$ and $H6(7)_n$ protons with the H1(5) protons decoupled appear as a four spin $AA'BB'$ system. This system was analyzed by means of the LAOCOON III program [27] and the following magnetic parameters could be optimized: $\delta H6(7)_x$; $\delta H6(7)_n$; ^2JH6$_x$–H6$_n$ = ^2JH7$_x$–H7$_n$; ^3JH6$_x$–H7$_x$;

^3JH6$_x$—H7$_n$ = ^3JH6$_n$—H7$_x$ and ^3JH6$_n$—H7$_n$. Their values, together with the most probable errors deduced from this analysis, and the chemical shifts and coupling constants of the remaining groups measured directly from the spectra are given in Tables 6 and 7. The ^3JH6(7)$_x$—H1(5) coupling constant could not be established because of the poor resolution of the H6(7)$_x$ signal on the normal spectra ($CDCl_3$ and C_6D_6 solutions).

^{13}C-NMR spectra

^{13}C-NMR chemical shifts of **IV** are tabulated with signal assignments in Table 6. Substituent steric and electronic effects on ^{13}C chemical shifts [28—30], signal multiplicity obtained from double spin-echo experiment (APT spectrum) and our previous studies of related compounds [18, 19, 24–26] were taken into consideration.

Conformational study

The $W_{\frac{1}{2}}$ of the H1(5) signal in the ^{1}H-NMR spectra of ca. 9Hz is in good agreement with previously reported values for a tropane system with the piperidine ring in a flattened chair conformation [12, 18, 19]. In both solvents the values deduced for the coupling constants are practically the same. ^3JH2(4)$_\beta$—H1(5) (3.5 Hz) is greater than ^3JH2(4)$_\alpha$—H1(5) (estimated value < 2Hz) and consequently, the dihedral angle H2(4)$_\beta$—C—C—H1(5) is smaller than H2(4)$_\alpha$—C—C—H1(5) according to the Karplus relationship [31]. This fact is also more consistent with a chair flattened conformation than with a boat conformation for the piperidine ring since the latter form should not only give a value of ca. 10 Hz for ^3JH2(4)$_\beta$—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 boat conformation [24].

The flattening at C3 is also supported by the values of the coupling constants between H3 and H2(4) protons. ^3JH2(4)$_\alpha$—H3 is smaller than ^3JH2(4)$_\beta$—H3 and its value may be close to zero as deduced from the $W_{\frac{1}{2}}$ of the doublet peaks corresponding to H2(4)$_\alpha$ in the spectrum with H1(5) protons decoupled, so that the value of the dihedral angle H2(4)$_\alpha$—C—C—H3 has to be about 90° [31] and an axial disposition for the amido substituent of C3 may be assumed.

As is observed in several substituted norbornanes, norbornenes, bicyclo[2,2,2]octane derivatives [20—23] and 8-substituted-8-azabicyclo(3,2,1)-octan-3-ones [19], ^3JH6(7)$_n$—H1(5) is smaller than ^3JH6(7)$_x$—H1(5), its value being close to zero; so the value of the dihedral angle H6(7)$_n$—C—C—H1(5) has to be about 90°. ^3JH6$_x$—H7$_x$ is only slightly greater than ^3JH6$_n$—H7$_n$ as for norbornenes and asymmetrically substituted norbornanes [20—23] while for 8-substituted-8-azabicyclo(3,2,1)octan-3-ones [19] ^3JH6$_x$—H7$_x$ is markedly greater than ^3JH6$_n$—H7$_n$. The different functionalities at C3 with different hybridizations seem to be responsible for this different behaviour.

The high value of ^3JH3—NH accounts for a dihedral angle H3–C3–N–H close to 180° [32]. This fixed arrangement is favoured by an intramolecular hydrogen bonding between the hydrogen atom of the amido group and the oxygen atom of the methoxy moiety as is observed in the solid state.

The above preliminary statements about the observed coupling constants of tropane system protons and the respective dihedral angles are in surprisingly good agreement with the torsional angles of the structure observed by X-ray diffraction.

Two remarkable differences in chemical shifts with respect to the related system of 8-isopropyl-8-azabicyclo(3,2,1)octan-3-one, I [19], have been observed. In $CDCl_3$ solution $\Delta\delta$ H2(4)$_\beta$—H2(4)$_\alpha$ = 0.74 ppm for IV and 0.53 ppm for I; this fact has been attributed to an anisotropic effect exerted by the π bond of the amido group on H2(4)$_\alpha$. On the other hand, the fact that $\Delta\delta$ H6(7)$_x$—H6(7)$_n$ = 0.19 ppm for IV and 0.41 for I, is due to the change of the functionality of C3 and the deshielding effect exerted by the amido group on H6(7)$_n$ protons.

Bearing in mind a previous study on 8-substituted-8-azabicyclo[3,2,1]-octan-3-ones [19] and owing to the flattening of the piperidine chair that diminishes the steric hindrance by the H2(4)$_\beta$ hydrogen atoms [15], an axial arrangement of the isopropyl substituent of N8 with respect to the 6-membered ring is assumed.

^{13}C chemical shifts are in agreement with these observations [19].

Thus, a great predominance in solution of the conformer observed in the solid state can be proposed. The pyrrolidine and piperidine rings adopt a flattened N8 envelope and distorted chair conformation puckered at N8 and flattened at C3, respectively, with the *N*-isopropyl substituent and the amido group at C3 in axial positions with respect to the piperidine ring.

Compared to tropapride [33], a very potent benzamide with an *N*-benzyl group, different dispositions of the lone pair of the endocyclic nitrogen and the benzamido groups are observed. On the contrary, the quasi parallel orientation between the phenyl group and the lone pair, and the antiparallel position of the carbonyl group with respect to the lone pair are concordant with the results observed in tropapride [33].

By contrast, it is noteworthy to remark, that, as expected, in several tropane ortopramides [34–36], due to the steric hindrance between the carbonyl group and the *ortho* substituents, there is no coplanarity between the carbonyl and the phenyl groups. This non-coplanarity prevents the formation of an intramolecular hydrogen bond. As these compounds retain antidopaminergic activity, it seems that the neuroleptic power of such molecules is not directly related to the coplanarity of the benzamide moiety and the formation of the intramolecular hydrogen bond. This hypothesis is inconsistent with the structure–activity relationships reported for the benzamide neuroleptics [37]. In order to shed some light on this question, we are actually occupied in the synthesis and structural study of *N*-(8-isopropyl-nortropan-3-β-yl)-2-methoxy-4-amino-5-chlorobenzamide, and the pharmacological testing of the α and β epimers.

ACKNOWLEDGEMENT

We thank A. Gómez Morilla, Instituto de Estructura de la Materia, C.S.I.C., Madrid for recording 360 MHz ^{1}H NMR spectra and A. Torossian, Bruker Analytische Messtechnik, GMBH, for the spectra registered at 500 MHz.

REFERENCES

1 M. Martínez-Ripoll and F. H. Cano, PESOS: a computer program, Instituto Rocasolano, C.S.I.C., Madrid, Spain, 1975.
2 P. Main, S. J. Fiske, S. E. Hull, L. Lessinger, G. Germain, J. P. Declerq and M. M. Woolfson, MULTAN 80 programs, Universities of York, Great Britain and Louvain, Belgium, 1980.
3 J. M. Stewart, P. A. Machin, C. W. Dickinson, H. L. Ammon, H. Heck and H. Flack, The X-Ray 76 System, Computer Science Center, University of Maryland, College Park, MD, 1976.
4 M. Nardelli, Comput. Chem., 7 (1983) 95.
5 International Tables for X-ray Crystallography, Vol. IV, Kynoch Press, Birmingham (U.K.), 1974.
6 N. Walker and D. Stuart, Acta Crystallogr., Sect. A, 39 (1983) 158.
7 S. P. Findlay, J. Org. Chem., 22 (1957) 1385.
8 S. Dokic and M. Cakara, Kem. Ind., 13 (1964) 261; Chem. Abstr., 61 (1964) 10545.
9 R. E. Lyke and H. J. Troscianec, J. Org. Chem., 20 (1955) 1757.
10 N. Cabezas, Thesis, Universidad Complutense, Madrid, 1986.
11 N. Cabezas, G. G. Trigo, M. Martinez and E. Galvez, J. Mol. Struct., 142 (1986) 417.
12 (a) A. F. Casy, Proton Magnetic Resonance Spectroscopy in Medicinal and Biological Chemistry, Academic Press, New York, 1971.
(b) A. F. Casy and J. E. Coates, Org. Magn. Reson., 6 (1974) 441.
13 J. H. Supple and E. Eklum, J.. Am. Chem. Soc., 93 (1971) 6684.
14 N. Dennis, A. R. Katritzky, S. K. Parton, Y. Nomura, Y. Takahashi and Y. Takeuchi, J. Chem. Soc., Perkin Trans 1, (1976) 2289.
15 H. J. Schneider and L. Sturm, Angew. Chem., Int. Ed. Engl., 15 (1976) 545.
16 P. Hanisch, A. J. Jones, A. F. Casey and J. E. Coates, J. Chem. Soc., Perkin Trans. 2, (1977) 1202.
17 A. R. Katritzky, N. Dennis and G. J. Sabongi, Org. Magn. Reson., 12 (1979) 357.
18 (a) G. G. Trigo, M. Martinez and E. Galvez, J. Pharm. Sci., 70 (1981) 87.
(b) E. Galvez, M. Martinez, J. Gonzalez, G. G. Trigo, P. Smith-Verdier, F. Florencio and S. Garcia Blanco, J. Pharm. Sci., 72 (1983) 881.
19 M. S. Arias, E. Galvez, M. L. Izquierdo and C. Burgos, J. Mol. Struct., 147 (1986) 381.
20 A. P. Marchand, Stereochemical Applications of NMR Studies in Rigid Bicyclic Systems, Verlag Chemie, Weinheim, 1982.
21 J. L. Marshall, S. R. Walter, M. Barfield, A. P. Marchand, N. W. Marchand and A. L. Segre, Tetrahedron, 32 (1976) 537.
22 (a) R. J. Abraham and J. Fisher, Magn. Reson. Chem., 23 (1985) 856.
(b) R. J. Abraham and J. Fisher, Magn. Reson. Chem., 24 (1986) 451.
23 R. J. Abraham and J. Fisher, Magn. Reson. Chem., 23 (1985) 862.
24 E. Galvez, M. S. Arias, J. Bellanato, J. V. Garcia-Ramos, F. Florencio, P. Smith-Verdier and S. Garcia Blanco, J. Mol. Struct., 127 (1985) 185.
25 M. S. Arias, E. Galvez, J. del Castillo, J. J. Vaquero and J. Chicharro, J. Mol. Struct., 156 (1987) 239.
26 M. S. Arias, E. Galvez, I. Ardid, J. Bellanato, J. V. Garcia-Ramos, F. Florencio and S. Garcia-Blanco, J. Mol. Struct., 161 (1987) 151.

27 S. Castellano and A. A. Bothner-By, J. Chem. Phys., 41 (1963) 3863.
28 F. W. Werhli and T. Wirthlin, Interpretation of Carbon-13 NMR Spectra, Heyden, London, 1980.
29 E. Breitmaier and W. Voelter, ^{13}C NMR Spectroscopy Methods and Applications in Organic Chemistry, 2nd edn., Verlag Chemie, Weinheim, 1978.
30 E. Pretsch, T. Clerc, J. Seibl and W. Simon, Tabellen zur Strukturaufklärung Organisher Verbindungen mit Spektroskopischen Metoden, Springer Verlag, Berlin, 1976.
31 C. A. G. Haasnoot, F. A. A. M. de Leeuw and C. Altona, Tetrahedron, 36 (1980) 2783.
32 V. F. Bystrov, V. T. Ivanov, S. L. Portnova, T. A. Balashova and Y. A. Ovchinnikov, Tetrahedron, 29 (1973) 873.
33 M. Jalfre, B. Bucher, N. Dorme, G. Mouet and R. D. Porsolt, Arch. Int. Pharmacodyn. Ther., 264 (1983) 232.
34 F. Durant, P. Renard, G. Evrard and A. Michel, Acta Crystallogr., Sect. C, 41 (1985) 1361.
35 F. Durant, P. Renard and G. Evrard, Bull. Soc. Chim. Belg., 93(5) (1984) 419.
36 G. Evrard, P. Renard, V. De Beys and F. Durant, Bull. Soc. Chim. Belg., 93(5) (1984) 417.
37 H. Van de Waterbeemd and B. Testa, J. Med. Chem., 26(2) (1983) 203.