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Synthesis and structural and conformational study of some amines derived from the norgranatane system

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Abstract

A series of *N*-substituted-9-phenethyl-3-amino norgranatane derivatives have been synthesized and studied by ^{1}H and ^{13}C NMR spectroscopy. The compounds studied display in deuterochloroform the same preferred flattened chair-boat conformation with the disubstituted ring in a slightly distorted boat form. The arylamino groups, in the C-3α position lie in the symmetry plane with respect to the bicyclic system.

INTRODUCTION

As part of a research program related to the synthesis and structural study of potential analgesic compounds and in connection with our interest in the preparation and the structural study of norgranatane derivatives [1–5], 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 *N*-phenethylnorgranatane-3-amines *N*-arylsubstituted **III a–d** (Scheme 1).

SYNTHETIC METHODS

The synthesis of compounds **III a–d** is shown in Scheme 1. Reaction of *N*-phenethylnorgranatanone **I** [6,7] with the corresponding aromatic amine at an approximate pH value of 6.6 in the presence of $NaBH_3CN$ led to the amines **III** via reductive amination [8].

The more stable conformation of **I** in $CDCl_3$ solution is as represented in Scheme 1 [3]. By supposing the same favoured conformation for the ketimines **II a–d** in CH_3OH, and on kinetic grounds, the attack by the hydride anion could be expected to be favoured in the β-direction (in the α-direction the C-7 methylene group would hinder the hydride attack), and according to this

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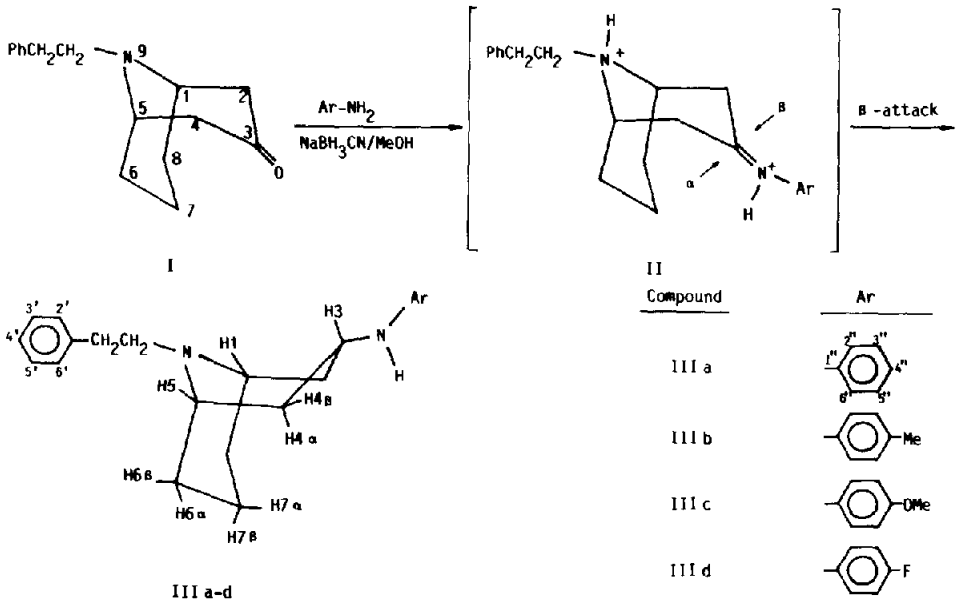

Scheme 1.

assumption, in this case, compounds **III a–d** are the only ones isolated in complete agreement to that observed by us in the case of 9-(2′-hydroxyethyl)-9-azabicyclo[3.3.1]nonan-3α-ol **IV** [1]. From the results obtained by reduction of compounds **II a–d** and *N*-β-hydroxylethylnorgranatanone [1], it seems to be clear that the main factor determining the stereochemistry of hydride attack of these ketones and ketimines is the conformation of the bicyclic system.

EXPERIMENTAL

All melting points were taken in open capillary tubes in an Electrothermal IA6304 apparatus, and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 883 spectrophotometer in the solid state (KBr). NMR spectra were recorded on a Varian UNITY-300 spectrometer, in $CDCl_3$ with TMS as internal standard. The ^1H NMR spectra were obtained at 300 MHz using spectral widths of 4000 Hz and acquisition times of 3.0 s over 64 transients. Conventional irradiation was used for the double resonance experiments.

The ^{13}C spectra were recorded at 75 MHz using spectral width of 16.500 Hz, acquisition time of 1.0 s and pulse width of 4 μs. APT experiments were performed by using standard Varian pulse sequences.

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

The elemental analyses were made in a Perkin-Elmer Elemental Analyzer model 240 B.

*Synthesis of the amines (**III a–d**)*

General procedure

To a solution of the corresponding amine (60 mmol) in absolute methanol (25 ml) was added methanolic hydrogen chloride (5 N, 4 ml), *N*-phenethylnorgranatanone (2.43 g, 10 mmol) [6,7] and sodium cyanoborohydride (0.4 g, 6.25 mmol). The mixture was stirred at room temperature for 72 h, acidified with concentrated hydrochloric acid (12 N) at pH <2, and concentrated under reduced pressure. The residue was extracted with water (50 ml) and ether (4×25 ml). The aqueous layer was neutralized with potassium hydroxide at pH >10, saturated with sodium chloride and extracted with ether (5×25 ml), dried (anhydrous sodium sulfate) and concentrated under reduced pressure to give an oil. The primary amine in excess was distilled off. Then, the residual oil was purified on a silica gel column. Elution with ethylacetate/hexane (8:2) gave a solid which was crystallized in hexane.

TABLE 1

^{1}H NMR chemical shifts[a] δ (ppm) for compounds **III a–d**

	III a	**III b**	**III c**	**III d**
H1(5) (d)	3.15	3.14	3.15	3.15
H2(4)β (td)	2.46	2.46	2.46	2.44
H2(4)α (ddd)	1.11	1.09	1.09	1.09
H3 (tt)	3.79	3.76	3.71	3.71
H6(8)β (tt)	1.85	1.85	1.85	1.85
H6(8)α (d)	0.99	0.99	0.99	0.99
H7α (qt)	1.96	1.96	1.96	1.96
H7β (m)	1.47	1.47	1.47	1.48
CH_2-N (m)	2.87	2.86	2.87	2.87
CH_2-Ph (m)	2.71	2.70	2.70	2.71
Ph (m)	7.25	7.24	7.25	7.24
H2″(6″)	6.60(m)	6.54(d)	6.60(d)	6.53(m)
H3″(5″)	7.15(m)	6.96(d)	6.77(d)	6.86(m)
H4″	6.65(m)			
CH_3 (s)		2.22		
OCH_3 (s)			3.74	
NH	3.30(br)			3.15

[a]Abbreviations br, broad; d, doublet; ddd, doublet of doublets of doublets; m, multiplet; qt, quadruplet of triplets; s, singlet; td, triplet of doublets; tt, triplet of triplets. δ values were deduced from the first order analysis of the corresponding system protons with an error of ±0.05 ppm.

TABLE 2

Coupling constants [a] J (Hz) deduced from the analysis of the ^{1}H NMR spectra of compounds **III a–d**

	III a	**III b**	**III c**	**III d**
H2(4)α-H2(4)β	11.7	11.7	12.0	11.5
H2(4)α-H1(5)	3.2	3.2	3.2	3.3
H2(4)α-H3	11.4	11.5	11.4	11.4
H2(4)β-H1(5)	11.7	11.7	12.0	11.5
H2(4)β-H3	5.7	5.8	5.8	5.8
H6(8)β-H6(8)α	13.5	12.9	13.1	13.1
H6(8)β-H1(5)	3.9	3.9	3.9	3.9
H6(8)β-H7α	13.5	12.9	13.1	13.1
H6(8)β-H7β	3.9	3.9	3.9	3.9
H6(8)α-H7α	4.1	4.0	4.0	3.9
H7α-H7β	13.5	12.9	13.1	13.1
H2″(6″)-H3″(5″)		8.0	8.8	8.8
H3″(5″)-F				8.7
H2″(6″)-F				4.4

[a]Values deduced from the first order analysis of the corresponding system protons; error ± 0.05 Hz.

TABLE 3

^{13}C NMR chemical shifts[a] δ (ppm) for compounds **III a–d**

	III a	**III b**	**III c**	**III d**[c]
C1(5)	49.84	49.87	49.96	49.72
C2(4)	33.88	33.94	33.97	33.80
C3	44.44	44.77	45.41	45.15
C6(8)	24.90	24.94	25.04	24.67
C7	14.28	14.28	14.19	14.19
CH_2-N	53.63	53.66	53.62	53.45
CH_2-Ph	35.60	35.59	35.49	35.46
C1′	141.05	141.06	140.92	140.94
C2′(6′)	128.14[b]	128.13[b]	128.05[b]	128.10[b]
C3′(5′)	128.86[b]	128.86[b]	128.78[b]	128.82[b]
C4′	125.76	125.75	125.70	125.75
C1″	147.65	145.35	141.87	143.91
C2″(6″)	113.25	113.58	114.88	114.11
C3″(5″)	129.19	129.67	114.88	115.51
C4″	116.84	126.11	151.91	155.42
CH_3		20.34		
OCH_3			55.73	

[a]Directly measured on the spectra; error ± 0.05 ppm. [b]These values may be interchanged. [c]Coupling constants observed: J C2″(6″)-F 7.2 Hz; J C3″(5″)-F 22.5 Hz and J C4″-F 232.75 Hz.

N-*Phenethyl-3-α-phenylaminonorgranatane (**III a**)*

This compound was obtained in 44% yield, m.p. 63–64°C; IR (KBr): νNH, 3401 cm^{-1}; ^1H NMR (see Tables 1 and 2); ^{13}C NMR (see Table 3); *m/z* 320 (M^+, 2%), 229 (16), 228 (4), 186 (2), 132 (2), 118 (6), 105 (12), 97 (7), 96 (100), 91 (12), 79 (6), 77 (11).

Analysis. Calculated for $C_{22}H_{28}N_2$: C, 82.45; H, 8.80; N, 8.74. Found: C, 82.06; H, 9.13; N, 8.59.

N-*Phenethyl-3-α-(4'-tolylamino)norgranatane (**III b**)*

This compound was obtained in 49% yield, m.p. 82–83°C; IR (KBr) νNH, 3338 cm^{-1}; ^1H NMR (see Tables 1 and 2); ^{13}C NMR (see Table 3); *m/z* 334 (M^+, 2%), 243 (11), 228 (4), 186 (3), 132 (3), 121 (5), 105 (18), 97 (13), 96 (100), 91 (13), 82 (5), 79 (8), 77 (7).

Analysis. Calculated for $C_{23}H_{30}N_2$: C, 82.58; H, 9.04; N, 8.37. Found: C, 82.38; H, 9.46; N, 8.11.

N-*Phenethyl-3-α-(4'-methoxyphenylamino)norgranatane (**III c**)*

This compound was obtained in 40% yield, m.p. 70–71°C; IR (KBr) νNH, 3346 cm^{-1}; ^1H NMR (see Tables 1 and 2); ^{13}C NMR (see Table 3); *m/z* 350 (M^+, 3%), 259 (7), 228 (5), 186 (2), 130 (6), 122 (5), 105 (16), 97 (11), 96 (100), 91 (6), 82 (5), 79 (7), 77 (6).

Analysis. Calculated for $C_{23}H_{30}N_2O$: C, 78.81; H, 8.62; N, 7.99. Found: C, 78.52; H, 8.93; N, 7.74.

N-*Phenethyl-3-α-(4'-fluorophenylamino)norgranatane (**III d**)*

This compound was obtained in 41% yield, m.p. 85–86°C; IR (KBr) νNH, 3334 cm^{-1}; ^1H NMR (see Tables 1 and 2); ^{13}C NMR (see Table 3); *m/z* 338 (M^+, 2%), 247 (14), 228 (4), 186 (2), 136 (5), 105 (12), 97 (7), 96 (100), 95 (5), 91 (8), 79 (5), 77 (5).

Analysis. Calculated for $C_{22}H_{27}N_2F$: C, 78.06; H, 8.04; N, 8.27. Found: C, 77.81; H, 8.32; N, 8.06.

RESULTS AND DISCUSSION

NMR spectra

The ^1H and ^{13}C NMR data of compounds **III a–d** are summarized in Tables 1–3. The ^1H and ^{13}C spectra show a great similarity. Assignments of proton and carbon resonances were made from our previous studies on related compounds [1–5] and literature data of α- and β-granatanols [9,10].

Spectral analysis

At 300 MHz in $CDCl_3$ solution the signals due to H3, H1(5), H(CH_2–N), H(CH_2–Ph), H2(4)β, H7β, H2(4)α and H6(8)α appear well differentiated in all cases. Overlapping resonances between H1(5) and NH in some cases, and H6(8)β and H7α signals only were observed. The signals corresponding to H1(5) and H6(8)α protons appear as apparent doublets.

The signals corresponding to H2(4)α, H2(4)β and H3 appear simplified as a not well resolved doublet of doublets, a triplet of doublets, and a triplet of triplets, respectively, and have been considered as a pattern of the four spin system ABCD formed by H1, H2α, H2β and H3 (or H5, H4α, H4β and H3) protons, whose first order analysis allowed the establishment of the respective proton magnetic parameters (chemical shift and geminal and vicinal coupling constants) which are collected in Tables 1 and 2.

The signals corresponding to H6(8)β and H7α appear simplified as a triplet of triplets and a quartet of triplets respectively and have been considered as patterns of the five spin system ABCDE formed by H1, H8β, H8α, H7β and H7α (or H5, H6β, H6α, H7β and H7α). Their first order analysis led to the determination of the respective proton magnetic parameters (collected in Tables 1 and 2).

The vicinal coupling constants ^3J H6(8)α–H7β and ^3J H6(8)α–H1(5) could not be determined. A limit value of ca. 2 Hz has been estimated taking into account the value of ^3J H6(8)α–H7α (Table 2) deduced from the analysis of the H7α signal and the $W_{\frac{1}{2}}$ of each signal of the apparent doublet due to H6(8)α.

To strengthen these assumptions double resonance (DR) experiments were performed in $CDCl_3$ at 300 MHz with compound **III b**. By irradiation of the signal at 3.76 ppm, the triplet of doublets at 2.46 ppm collapses to a poorly resolved triplet, and the multiplet (ddd) at 1.09 ppm collapses to an unresolved doublet. On saturating the H1(5) signal at 3.14 ppm, the signal at 2.46 becomes an unresolved multiplet, and the signal at 1.09 ppm to a triplet. By saturation of the H2(4)β signal at 2.46 ppm, the triplet of triplets at 3.76 ppm collapses to a triplet, the H1(5) signal at 3.14 ppm collapses to a singlet, and the H2(4)α signal at 1.09 ppm, to an apparent triplet. By saturation of the signal at 1.96 ppm, the unresolved multiplet at 1.47 ppm collapses to an apparent triplet. On saturating the signal at 1.85 ppm, the H6(8)α signal, at 0.99 ppm becomes a wide singlet. By irradiation of the H2(4)α signal at 1.09 ppm, the signals corresponding to H2(4)β and H3 at 2.46 ppm and 3.76 ppm respectively become unresolved multiplets.

Conformational study

From the ^1H and ^{13}C NMR data of **III a–d** the following general features were deduced:

(a) The bicyclic system exists predominantly in a chair-boat conformation flattened at C6(8) (Scheme 1) in order to relieve the transannular steric interactions present in the chair–chair form between endo arylamino group and H7α hydrogens.

(b) There is a pseudo-mirror plane through the granatane skeleton defined by C3, C7 and N9 atoms; the arylamino conjugated group lies nearly in this plane with N–H and H3 atoms in trans disposition.

(c) The phenethyl group, as expected, occupies an axial position with respect to the chair piperidine ring.

These conclusions are supported by the following:

(a) The H1(5) signal and H2(4)β signal show a coupling constant (about 12 Hz) which is typical of eclipsed vicinal protons in piperidine systems [11].

The deduced coupling constant ^3J H2(4)α–H3 of about 11.4 Hz accounts for a trans-coplanar disposition of H2(4)α–C–C–H3.

The ^3J H6(8)β–H1(5) value of about 4 Hz correspond to a dihedral angle of about 60° according to the Karplus relationship [12]; this value is greater than ^3J H6(8)α–H1(5) (estimated value less than 2 Hz, dihedral angle about 90°). This fact is more consistent with a flattened chair conformation for a piperidine ring than with an equilibrium between chair and boat form [11].

The ^3J H6(8)β–H7α value of about 13 Hz accounts for a trans-coplanar disposition of H6(8)β–C–C–H7α.

The values $\Delta\delta$ H1(5) **III a–d** – H1(5) **IV** [1] $\approx$0.2 ppm, and $\Delta\delta$ H6(8)β **III a–d** – H6(8)β **IV** [1] $\approx$0.1 ppm can be attributed to an increasing charge transfer from H to C, due to increasing compression as a result of the greater 6(8) flattening in **III a–d** with respect to **IV**; this charge transfer also explains the shielding ($\delta \approx$ 1.8 ppm) of C6(8) in **III c,d** with respect to C6(8) in **IV** [1,11].

The observed chemical shifts for C7 of **III a–d** ($\approx$14.2 ppm) are similar to the reported values for α-granatanol (14.5 ppm) [10], and 9-(2′-hydroxyethyl)-9-azabicyclo[3.3.1]nonan-3α-ol (14.4 ppm) [1]; these two compounds show a preferred chair-boat conformation in $CDCl_3$ solution.

(b) The high field δH values for H2(4)α and H6(8)α, and the low field δH values for H7α and H2(4)β in **III a–d** can be due to the shielding and deshielding effect exerted by the arylamino group in the disposition proposed above.

The δH and δC values of the arylamino groups account for a conjugation between the N-lone pair and the π-system.

(c) The chemical shift values for C6(8) of **III a–d** are in close agreement with an axial disposition of the N-substituent in the chair granatane ring [1–4]. Moreover, the AA′BB′ appearance of the methylene protons signals, and the multiplet corresponding to the phenyl protons account for a distinct disposition of the phenethyl group.

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