Journal of Molecular Structure, 220 (1990) 55–61
Elsevier Science Publishers B.V., Amsterdam — Printed in The Netherlands

SYNTHESIS AND STRUCTURAL STUDY OF TROPANE BENZAMIDES
Part IV. *N*-(8-Alkyl (or aralkyl) nortropan-3-*β*-yl)-3,4,5-trimethoxybenzamides

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(Received 3 July 1989)

ABSTRACT

A series of *N*-(8-alkyl (or aralkyl) nortropan-3-*β*-yl)-3,4,5-trimethoxybenzamides have been synthesized and their molecular structures determined by ^{1}H-NMR and ^{13}C-NMR methods. The pyrrolidine and piperidine rings adopt a flattened N8 envelope and a slightly distorted chair conformation puckered at N8, with the *N*-substituent and the amido group at C3 position in the axial and equatorial positions, respectively, with respect to the piperidine ring.

INTRODUCTION

The synthesis, ^{1}H-NMR, ^{13}C-NMR and infrared (IR) studies and the crystal structure of a pharmacologically interesting series of tropane benzamides has been reported [1–3]. In anticipation of a subsequent structure–activity relationship study, we report here the structural study, by several methods, of *N*-(8-alkyl (or aralkyl) nortropan-3-*β*-yl)-3,4,5-trimethoxybenzamides (compounds **I–III**, Scheme 1) in order to determine the preferred conformation in solution, and to carry out a comparative study with the *N*-(8-isopropylnortropan-3-*β*-yl)-2-methoxy-4-amino-5-chloro-benzamide (**V**) [3].

EXPERIMENTAL

All melting points were taken in open capillary tubes and are uncorrected.

The IR spectra were recorded in the solid state (KBr disc) on a Perkin-Elmer 883 spectrometer.

The ^{1}H-NMR spectra were recorded at 360 MHz (spectral width 3300 Hz)

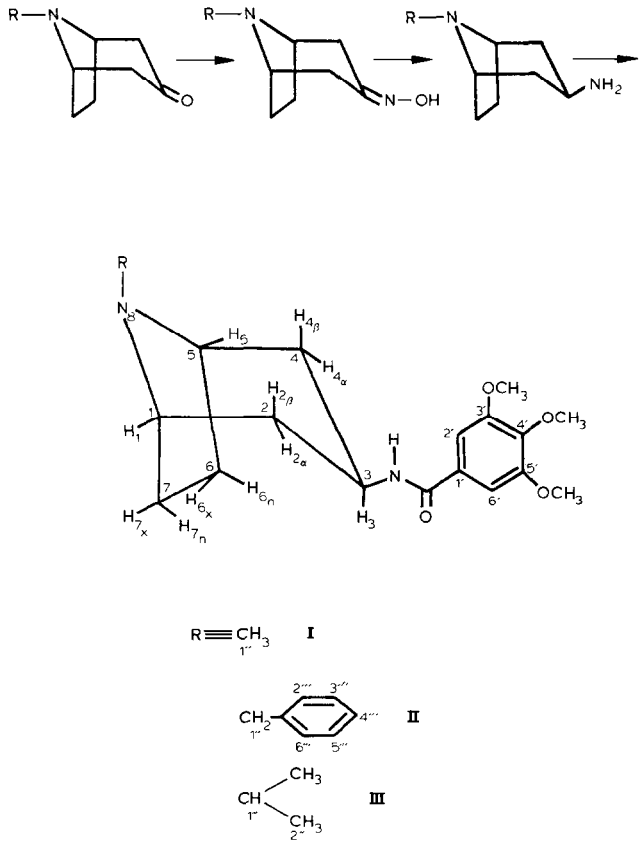
0022-2860/90/$03.50

with a Bruker WM 360 spectrometer. The ^{13}C-NMR spectra were obtained at 50.32 MHz on a Bruker WM-200-SY spectrometer at a spectral width of 11363 Hz and a pulse width of 2.3 s (35°). Two types of spectra were recorded: proton noise-decoupled spectra to determine the chemical shifts (acquisition time 0.36 s) and proton-coupled spectra in order to help in assigning the signals and to estimate the coupling constants (acquisition time 0.7 s; delay time 4.0 s; gated decoupling with decoupler on during delay). Solutions in $CDCl_3$ at 303 K with TMS as internal reference were used.

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

SYNTHESES

The synthesis of compounds **I–III** is shown in Scheme 1. The *N*-substituted nortropinone was transformed to the oxime. From reduction of the oxime with



Scheme 1.

sodium in isoamyl alcohol, the corresponding amine was obtained. The amides were prepared by treatment of the corresponding amine with 3,4,5-trimethoxy benzoic acid. The synthesis and purification of the ketones, oximes and amines have been described in detail previously [3,4].

*Synthesis of the amides **I–III***

General procedure

To a solution of the corresponding amine (6.0 mM) in anhydrous benzene (18 ml) was added anhydrous sodium carbonate (0.8 g) and the resulting mixture was heated under reflux. To the refluxing solution was added dropwise a solution of 3,4,5-trimethoxy benzoic acid (1.17 g) dissolved in anhydrous benzene (50 ml). The reflux was maintained for 4 h. The mixture was cooled to room temperature, filtered, treated with aqueous 5-N NaOH and water, dried (anhydrous sodium sulphate) and concentrated. The residue that separated was crystallized from ethyl acetate.

N-*(8-Methylnortropan-3-β-yl)-3,4,5-trimethoxybenzamide (**I**)*

This compound was obtained in 70% yield, m.p. 165–166 K. IR (potassium bromide): νCO 1630 cm^{-1}. ^{1}H-NMR: see Tables 1 and 2. ^{13}C-NMR: see Table 3.

TABLE 1

^{1}H-NMR chemical shifts of compounds **I–III** ($CDCl_3$; 360 MHz)

Chemical shift[a]	δ (ppm)		
	I	**II**	**III**
H1(5) (brs)	3.16 ($W_{\frac{1}{2}}$ = 11 Hz)	3.21 ($W_{\frac{1}{2}}$ = 10 Hz)	3.52 ($W_{\frac{1}{2}}$ = 11 Hz)
H2(4)β (m)	1.57	1.57	1.61
H2(4)α (m)	1.89	1.87	1.80
H3 (m)	4.25	4.29	4.32
H6(7)n (m)	1.70	1.72	1.70
H6(7)x (m)	2.02	2.03	1.91
H1″	2.24 (s)	3.48 (s)	2.67 (m)
H2″	—	—	1.04 (d)
OCH_3-3′(5′) (s)	3.83	3.83	3.83
OCH_3-4′ (s)	3.80	3.80	3.80
NH (d)	5.76	5.83	5.84
H-2′(6′) (s)	6.86	6.87	6.87
C_6H_5 (m)	—	7.19-7.32	—

[a]br, Broad; d, doublet; m, multiplet; s, singlet. Values deduced by first-order analysis of the spectra; error ±0.05 ppm.

TABLE 2

Coupling constants deduced from the first-order analysis of the ^{1}H-NMR spectra of compounds **I–III** ($CDCl_3$; 360 MHz)

Coupling constant[a]	J (Hz)		
	I	**II**	**III**
H2(4)α-H2(4)β	−13.0	−13.3	−13.2
H2(4)α-H1(5)	3.0	3.0	2.9
H2(4)α-H3	5.9	6.1	6.1
H2(4)β-H3	11.1	11.1	11.4
H3-NH	8.2	8.3	8.1
H1″-H2″	—	—	6.2

[a]Error ±0.3 Hz. ^3JH2(4)β-H1(5) could not be established as well as the couplings of H6(7)n and H6(7)x protons due to the poor resolution of the respective signals.

TABLE 3

^{13}C-NMR chemical shifts of compounds **I–III** ($CDCl_3$; 50.32 MHz)

Chemical shift[a]	δ (ppm)		
	I	**II**[b]	**III**
C-1(5)	60.56	58.58	54.53
C-2(4)	37.47	37.99	33.88
C-3	41.31	41.97	41.53
C-6(7)	25.85	26.33	27.02
C-1″	39.40	55.99	45.13
C-2″	—	—	21.37
OCH_3-3′(5′)	55.93	55.99	55.78
OCH_3-4′	60.56	60.62	60.46
C-1′	129.92	129.99	129.65
C-2′(6′)	104.22	104.31	104.10
C-3′(5′)	152.80	152.88	152.68
C-4′	140.51	140.59	140.33
CO	166.22	166.22	165.93

[a]Directly measured on the spectra; error ±0.03 ppm. [b]Aromatic carbons: C1‴, 139.69; C2‴ (6‴), 128.31; C3‴ (5‴), 127.96; C4‴, 126.60.

Analysis. Calc. for $C_{18}H_{26}N_2O_4$: C, 64.64; H, 7.83; N, 8.37. Found: C, 64.42; H, 7.59; N, 8.26.

N-*(8-Benzylnortropan-3-β-yl)-3,4,5-trimethoxybenzamide (**II**)*

This compound was obtained in 65% yield, m.p. 190–192 K. IR (potassium bromide): νCO 1630 cm^{-1}. ^{1}H-NMR: see Tables 1 and 2. ^{13}C-NMR: see Table 3.

Analysis. Calc. for $C_{24}H_{30}N_2O_4$: C, 70.21; H, 7.36; N, 6.82. Found: C, 70.32; H, 7.23; N, 6.95.

N-*(8-Isopropylnortropan-3-β-yl)-3,4,5-trimethoxybenzamide (III)*

This compound was obtained in 60% yield, m.p. 185–187 K. IR (potassium bromide): νCO 1630 cm^{-1}. ^{1}H-NMR: see Tables 1 and 2. ^{13}C-NMR: see Table 3.

Analysis. Calc. for $C_{20}H_{30}N_2O_4$: C, 66.27; H, 8.34; N, 7.72. Found: C, 66.20; H, 8.30; N, 7.63.

RESULTS AND DISCUSSION

NMR spectra

^{1}H- (360 MHz) and ^{13}C-NMR (50.32 MHz) spectroscopy were used to provide the required information. Assignments of proton and carbon resonances were made taking into account our previous studies of some 8-substituted 8-azabicyclo-(3,2,1)-octan-3-ones [5], *N*-(8-isopropylnortropan-3-α-yl)-2-methoxy-4-amino-5-chlorobenzamide (**IV**) [2], the corresponding β-epimer (**V**) [3], and literature data for several tropane and related systems [2,3].

In $CDCl_3$, all the proton signals were well differentiated and all the tropane proton resonances could be assigned. The long-range (*W*) couplings ^4JH2β–H7x or ^4JH4β–H6x were not observed. The H1(5) signal appeared as a non-resolvable wide singlet ($W_{\frac{1}{2}} = 10$ or 11 Hz). The H2(4)β signal appeared as an apparent triplet of low resolution, due to the geminal coupling with H2(4)α and the vicinal coupling with H3. ^2JH2(4)α–H2(4)β and ^3JH2(4)β–H3 exhibited similar values and ^3JH2(4)β–H1(5) was only suggested; a maximum value of 2 Hz has been estimated for this coupling constant on the basis of the $W_{\frac{1}{2}}$ values of the external lines of the signals. The H3 signal is a complex multiplet that could not be analysed and the NH signal appeared as a doublet because of the vicinal coupling with H3.

The multiplets corresponding to H2(4)α and H2(4)β have been considered as parts of the four spin system formed by the H1, H2α, H2β and H3 (or H5, H4α, H4β and H3) protons. The first-order analysis of which allowed the following parameters to be established: δH2(4)α, δH2(4)β, ^2JH2(4)α–H2(4)β, ^3JH2(4)α–H1(5), ^3JH2(4)α–H3 and ^3JH2(4)β–H3 (Tables 1 and 2).

The assignment of the H6(7)n and H6(7)x signals was made bearing in mind the previous studies on some 8-substituted 8-azabicyclo[3,2,1]octan-3-ones [5], compounds **IV** [2] and **V** [3] and the similarity of the ^{1}H-NMR spectra of compounds **I**–**III** and **V** [3]. The chemical shifts of H6(7)n and H6(7)x protons are given in Table 1 together with the chemical shifts and the coupling constants (Table 2) of the remaining groups measured directly from the spectra.

The ^{13}C-NMR chemical shifts of compounds **I–III** are tabulated together with the signal assignments in Table 3. The substituent steric and electronic effects on the ^{13}C chemical shifts [6,7] and signal multiplicities obtained from proton-coupled spectra were taken into consideration. Previous ^{13}C-NMR assignments of 8-substituted 8-azabicyclo[3,2,1]octan-3-ones [5], compounds **IV** [2] and **V** [3] and related systems [2,3] were used as references. The assignment of the OCH_3–3′ (5′) and OCH_3–4′ carbons of the benzamide group was made on the basis of the intensity of the respective signals in the proton-coupled spectra recorded with gated decoupling. Intervals between pulses of 4.0 s allow a relaxation of the carbon nuclei and the observed intensity of the signals could be considered quantitatively as a measure of the number of carbon atoms [6,7].

The proton-coupled spectra of compounds **I–III** show complex signals except for OCH_3 groups. The ^1JC–H values for the carbon atoms of the tropane system are almost the same as each other and close to those reported for the 8-substituted 8-azabicyclo[3,2,1]octan-3-ones [5]. The mean values are: ^1JC1–H1 = 144 Hz; ^1JC2–H2 = 129 Hz; ^1JC3–H3 = 137 Hz; ^1JC6–H6 = 132 Hz; ^1JC–H(OCH_3) = 144.5 Hz; ^2JC3′–H2′ = 12.01 Hz; ^3JC3′–H(OCH_3) = 2.0 Hz.

Conformational study

The proton magnetic parameters of compounds **I–III** are virtually the same and very similar to those described for the *N*-(8-isopropylnortropan-3-β-yl)-2-methoxy-4-amino-5-chlorobenzamide (**V**) [3]. The $W_{\frac{1}{2}}$ of the H1(5) signal of 10–11 Hz and the values deduced for the ^3JH2(4)α–H1(5) (3.0 Hz) and ^3JH2(4)β–H1(5) ($\leqslant$2.0 Hz) coupling constants are in agreement with an almost perfect chair conformation for the piperidine ring. This fact and the equatorial disposition of the benzamide group are confirmed by the values of the coupling constants between H3 and H2(4) protons: ^3JH2(4)α–H3 ca. 6.0 Hz and ^3JH2(4)β–H3 ca. 11.2 Hz. Therefore, the values of the dihedral angles H2(4)α–C–C–H3 and H2(4)β–C–C–H3 must be in the ranges 45–60° and 180°, respectively, according to the Karplus relationship [8]. The high value of ^3JH3–NH accounts for the dihedral angle H3–C3–N–H being close to 180° [9]. Nevertheless, this arrangement in compounds **I–III** could not be ascribed to intramolecular hydrogen bonding between the hydrogen atom of the amido group and the oxygen atom of the methoxy moieties, as in the case of compound **V**.

The N–H signal in compounds **I–III** is shifted to higher field (ca. 1.6 ppm) with respect to its chemical shift in compound **V**. The difference between the values observed for ^3JH2(4)β–H1(5) ($\leqslant$2.0 Hz) in compounds **I–III** and those described for the 8-substituted 8-azabicyclo[3,2,1]octan-3-ones [5] (mean value 4.12 Hz) could be ascribed to less flattening of the six-membered ring in

the former case due to a change in the C3 hybridization (in order to accommodate the sp^2 hybridized carbonyl carbon, flattening takes place more easily).

In the ^{13}C-NMR spectra the trend in the C1(5) chemical shifts from **I** to **III** is in agreement with the increase of the γ-shielding effect exerted by the *N*-substituent from Me to Pr^i. The C2(4) chemical shifts confirm the chair conformation of the piperidine ring and an axial disposition of the *N*-substituent with respect to this ring [2,3,5]. Therefore, the influence of the shape and size of the group attached to the piperidine nitrogen atom on the δC6(7) values and the shielding of ca. 3.8 ppm for the chemical shift of C2(4) in **III** can be justified. The similarity of the protonic magnetic parameters for the tropanic system is in agreement with the above facts because they are less sensitive to these effects. The large shielding effect (ca. 3.8 ppm) observed for the δC2(4) with respect to that described (2.37 ppm) in the series of 8-azabicyclo[3,2,1]octan-3-ones [5] supports the less flattening of the piperidine ring in compounds **I–III**.

Hence, the preferred conformation for compounds **I–III** is the same in all cases and similar to that of benzamide **V**. The pyrrolidine and piperidine rings adopt a flattened N8 envelope and a slight distorted chair conformation puckered at N8, with the *N*-substituent and the amido group in axial and equatorial positions, respectively, with respect to the piperidine ring.

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.

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