PAPER

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Synthesis, spectroscopic and crystallographic study of some carbamates from an azabicyclic chloroformate and primary heterocyclic amines

Isabel Iriepa,*[a] F. Javier Villasante,[a] Enrique Gálvez,[a] Juana Bellanato,[b] Avelino Martín[c] and Pilar Gómez-Sal[c]

[a] *Dpto. Química Orgánica, Universidad de Alcalá, Ctra. Madrid-Barcelona Km 33,600, Alcalá de Henares, 28871, Madrid, Spain. E-mail: isabel.iriepa@uah.es; Fax: +34 91 885 4686; Tel: +34 91 885 4651.*

[b] *Instituto de Estructura de la Materia (CSIC), Serrano 121, 28006, Madrid, Spain. E-mail: imtb429@iem.cfmac.csic.es; Fax: +34 91 564 5557; Tel: +34 91 561 6800*

[c] *Dpto. Química Inorgánica, Universidad de Alcalá, Ctra. Madrid-Barcelona Km 33,600, Alcalá de Henares, 28871, Madrid, Spain. E-mail: avelino.martin@uah.es; Fax: +34 91 885 4683; Tel: +34 91 885 4684*

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A series of benzimidazole, thiazole and benzothiazole carbamates derived from 9-methyl-9-azabicyclo[3.3.1]nonan-3β-ol was synthesized and studied by ^{1}H, ^{13}C, 2D NMR and IR spectroscopy. The crystal structure of *N*-(benzimidazol-2-yl)-9-methyl-9-azabicyclo[3.3.1]nonan-3β-yl-carbamate (**8**) was determined by X-ray diffraction. It has been found that two different carbamates can be obtained in the case of the benzimidazole derivatives. The structure of the studied compounds corresponds to the amino form of the molecules and show different types of hydrogen bonds. In $CDCl_3$ solution all the carbamates displayed a preferred flattened chair-chair conformation similar to that observed for compound **8** in the solid state.

Introduction

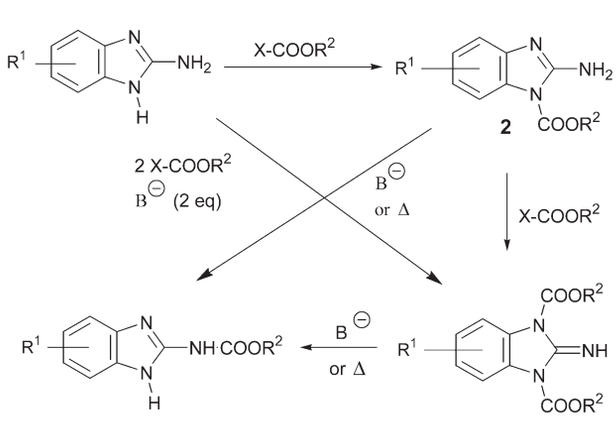
Piperazinyl benzimidazoles[1] and piperazinyl thiazoles[2] are compounds endowed with 5-HT_3 antagonist properties. 5-HT_3 antagonists are a class of therapeutic agents that are highly effective in the control of cancer chemotherapy-induced emesis.[3,4] As a result of our interest in the area of 5-HT_3 research,[5–7] we have designed and prepared a series of benzimidazole, thiazole and benzothiazole carbamates.

Several methods have been reported to prepare carbamates from aromatic nitro compounds,[8] amides,[9] cyanates,[10] but one of the most utilized methods is the condensation of isocyanates[11] with alcohols. Usually, the isocyanate is prepared *in situ* from the corresponding amine and phosgene. However, the toxicity of the latter discouraged us from carrying out this procedure. Several procedures have also been described for the preparation of alkyl benzimidazole carbamates. Condensation of *o*-phenylenediamine with the reaction product of *S*-methylthiourea and an alkyl chloroformate yields the alkyl benzimidazole-2-carbamate. This reaction is not easy to execute and the evolution of odiferous and toxic mercaptans have motivated the search for an effective, nontoxic and inexpensive procedure, giving a readily obtainable product. An alternative synthetic route was published by Ridi and Checci[12] but it only permits to obtain derivatives at the 1-position. Acylation of 2-aminobenzimidazoles with a large variety of alkyl haloformates[13] gives alkyl benzimidazole-2-carbamates in good yields although better yields can be obtained using alkyl chloroformates.[13–15]

According to the literature,[13–15] the formation of 2-carbamates (**1**) may proceed *via* the 1-carbamate (**2**) (formed in the first step under cold conditions), which, after treatment with a base[14] or by heating in the presence of a nonhydroxylic solvent (preferably pyridine),[13,15] gives rise to **1**. Another possibility is the formation of the disubstituted benzimidazole (**3**; acylation at both endocyclic nitrogens) followed by treatment with a base or by heating (Scheme 1).

2-Aminobenzothiazoles and 2-aminothiazoles react with alkyl halides to give mainly the product of alkylation at the endocyclic nitrogen, when the reaction is conducted in the absence of strong bases;[16] with acyl halides,[17] the exocyclic nitrogen becomes the main nucleophilic site. The reaction study with isocyanates and isothiocyanates showed that initial attack occurs at the endocyclic nitrogen (kinetic control). This adduct may then undergo intramolecular N–N rearrangement and/or dissociate to reactants that recombine by reaction at the exocyclic nitrogen (thermodynamic control).[18]

The reaction of 2-aminobenzothiazole with choroformates to prepare carbamates has been studied by Yadav and



Scheme 1

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collaborators.[19] Among the compounds synthesized two benzothiazole-2-carbamates were obtained in high yields as a result of the attack on the exocyclic nitrogen.

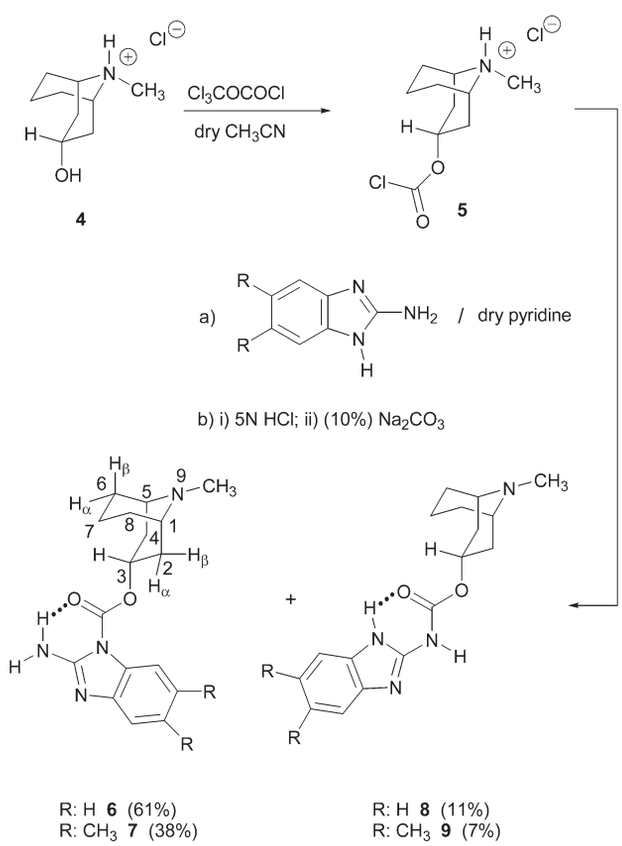
In this paper, we report the synthesis of a series of carbamates through condensation of 9-methyl-9-azabicyclo[3.3.1]nonan-3β-chloroformate with 2-aminothiazole, 2-aminobenzimidazole, 2-aminobenzothiazole and substituted derivatives. Due to the ambident nucleophilic nature of these heterocyclic amines a comparison of the behaviour towards acylation under the same conditions has been made. The structures and preferred conformations of the compounds have been determined with the aid of ^{1}H, ^{13}C, 2D NMR (^{1}H–^{1}H COSY,^{1}H–^{13}C correlation spectra), DEPT, double resonance experiments, IR spectroscopy and also X-ray data for compound **8**.

Results and discussion

Aminobenzimidazole derivatives

For the synthesis of alkyl benzimidazole carbamates, we started with the alkyl chloroformate hydrochloride **5** obtained from the previously prepared[20] 9-methyl-9-azabicyclo[3.3.1]-nonan-9β-ol hydrochloride (**4**) and commercially available trichloromethyl chloroformate[21,22] (Scheme 2). Reaction of **5** with 2-aminobenzimidazole in dry pyridine as solvent, at room temperature, yielded mainly two compounds. The isolation and purification of these compounds was based upon their different solubility. One of them (**6**) precipitated out from pyridine solution as the hydrochloride, while the other one (**8**) remained in solution and further work-up allowed its isolation.

The structures of these compounds were assigned on the basis of their characteristic ^{1}H NMR (Table 1), ^{13}C NMR (Table 2) and IR (Table 3) spectra. The ^{1}H and ^{13}C NMR spectra for these two compounds show a great similarity in the aliphatic region, with the aromatic region being that where



Scheme 2

the differences are more pronounced. The most characteristic signals that permitted us to assign the structure of these compounds are, on the one hand, a broad singlet ($\delta = 6.20$) corresponding to the two protons of the NH_2 group for the more insoluble compound (**6**), and, on the other hand, two broad singlets ($\delta = 10.80$ and 13.60) observed in compound (**8**), each one corresponding to an NH proton. For the first compound the structure corresponds to a carbamate where the acylation takes place on the endocyclic nitrogen atom of the 2-aminobenzimidazole, whereas the second one is the carbamate where the acylation occurs on the exocyclic nitrogen atom. X-Ray data for compound **8** confirmed the structure.

As it was said above, under our reaction conditions a mixture of benzimidazole-1-carbamate (**6**) and benzimidazole-2-carbamate (**8**) was formed from which the 1-carbamate was obtained as the major product (61%), along with the 2-carbamate in 11% yield. These results correlate with those published by Cativela *et al.*[14] They reported the production of a mixture of methyl benzimidazole-1-carbamate and methyl benzimidazole-2-carbamate from the reaction of 2-aminobenzimidazole and methyl chloroformate using NaOH (10%) as base and chloroform as solvent. However, they did not mention the ratio of the two carbamates and only the final yield after the conversion of the 1-carbamate into the 2-carbamate was given. It should be pointed out that other authors isolated only the 1-carbamate when they used reaction conditions similar to those of the current work except for the temperature.[13,15]

As indicated in the Introduction, benzimidazole-2-carbamates can be obtained from benzimidazole-1-carbamates.[13,15] Nevertheless, all our attempts to convert the alkyl benzimidazole-1-carbamate (**6**) into the alkyl benzimidazole-2-carbamate (**8**) by heating in pyridine solution were unsuccessful and only decomposition products of the starting material were obtained.

Furthermore, reaction of **5** with 5,6-dimethyl-2-aminobenzimidazol in dry pyridine yielded the alkyl benzimidazole-1-carbamate **7** and the alkyl benzimidazole-2-carbamate **9** (Scheme 2). These compounds were isolated and purified using similar procedures to those for compounds **6** and **8** and again, the yield obtained for the 1-carbamate (**7**) was higher (38%) than that of the 2-carbamate (**9**; 7%). The structures of compounds **7** and **9** have been deduced on the basis of their characteristic ^{1}H NMR (Table 1), ^{13}C NMR (Table 2) and IR (Table 3) spectra and by comparison with carbamates **6** and **8**.

The alkyl benzimidazole-1-carbamates (**6** and **7**) and alkyl benzimidazole-2-carbamates (**8** and **9**) may exist in two tautomeric forms (amino (NH_2), imino (=NH) for compounds **6** and **7** and amido, imido for compounds **8** and **9** (Scheme 3). Infrared spectroscopy has been used to study the amino-imine tautomerism of heteroaromatic compounds.[23] Concerning the tautomeric structure of amino compounds, in the case of mono- and dicyclic N-heteroaromatic amines it has been shown by various physical methods, including infrared, that these compounds exist predominantly in the amino and not in the tautomeric imino form. In dilute chloroform or carbon tetrachloride solution such amines give two infrared bands in the 3550–3350 cm^{-1} region (as a result of coupling) and another in the 1650–1600 cm^{-1} region; these are assigned to the asymmetric and symmetric stretching vibrations and the deformation mode of the amino group, respectively. A marked distinction is observed between the spectral characteristics of the absorption bands due to the imine and the amino N–H stretching vibrations. The imines absorb relatively weakly near 3300 cm^{-1}, whilst the amines give bands five to ten times as intense at frequencies higher by 100–200 cm^{-1}.[24] The tautomeric amino-imino equilibrium of monoamino derivatives of 4*H*-imidazoles has been studied by spectroscopic methods in different working conditions; the corresponding ν(N–H) of both forms and the exocyclic imino ν(C=N) frequencies could be determined.[25,26]

Table 1 ^{1}H NMR chemical shifts (δ) for compounds **6**–**12** in $CDCl_3$ (~0.05 M)[a]

	6	7	8	9	10	11	12
H1(5)	3.10 (at)	3.09 (br s)	3.08 (at)	3.06 (at)	3.03 (at)	3.03 (at)	3.03 (at)
H2(4)β	2.28 (tdd)	2.24 (td)	2.23 (td)	2.21 (td)	2.10 (tdd)	2.07 (tdd)	2.10 (td)
H2(4)α	2.10 (dd)	2.11 (dd)	1.94 (dd)	1.96 (ddd)	1.94 (ddd)	1.97 (ddd)	1.94 (dd)
H6(8)β	2.09 (tt)	2.06 (tt)	2.04 (m)	2.03 (m)	2.00 (m)	2.00 (m)	2.00 (tt)
H6(8)α	1.58 (dd)	1.55 (dd)	1.64 (dd)	1.63 (dd)	1.58 (d)	1.52 (d)	1.60 (dd)
H7β	1.78 (dt)	1.76 (dt)	1.76 (m)	1.74 (m)	1.70 (m)	1.70 (m)	1.70 (m)
H7α	1.71 (qt)	1.70 (qt)	1.76 (m)	1.74 (m)	1.70 (m)	1.70 (m)	1.70 (m)
N–CH_3	2.59 (s)	2.59 (s)	2.61 (s)	2.50 (s)	2.54 (s)	2.54 (s)	2.58 (s)
H3	5.88 (tt)	5.85 (tt)	5.73 (tt)	5.68 (tt)	5.71 (tt)	5.64 (tt)	5.70 (tt)
H4′	7.66 (dd)	7.44 (s)	7.20 (d)[b]	7.30 (br s)	7.92 (d)	7.39 (d)	7.84 (d)
H5′	7.06 (td)	–	7.40 (br s)	–	7.41 (td)[b]	6.91 (d)	7.05 (dd)
H6′	7.21 (td)	–	7.74 (br s)	–	7.29 (td)[b]	–	–
H7′	7.34 (d)	7.10 (s)	7.19 (d)[b]	7.30 (br s)	7.80 (d)	–	7.27 (d)
NH carbamate	–	–	10.80 (br s)	10.70 (br s)	11.00 (br s)	11.50 (br s)	10.80 (br s)
NH imidazole	–	–	13.60 (br s)	ND[c]	–	–	–
NH_2	6.20 (br s)	6.20 (br s)	–	–	–	–	–
OCH_3	–	–	–	–	–	–	3.83 (s)
CH_3	–	2.29 (s) 2.31 (s)	–	2.34 (s)	–	–	–

[a] Abbreviations: at, apparent triplet; br s, broad singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; dt, doublet of triplets; m, multiplet; qt, quartet of triplets; s, singlet; td, triplet of doublets; tdd, triplet of doublet of doublets; tt, triplet of triplets. [b] These values may be interchanged. [c] Not determined.

Finally, the infrared partial deuteration criterion has been used by several authors to confirm the predominance of the amino form for certain compounds. In the NHD group, coupling between N–H and N–D is weak and the N–H stretch shows up at a frequency between those of the symmetric and asymmetric NH_2 stretching modes.[27] On the other hand, two bands corresponding to the cis and trans isomers will appear if intramolecular hydrogen bonding occurs to one proton or other factors cause the two N–H bonds in the primary amino group to be non-equivalent.[28,29]

In the case of compounds **6** and **7**, the infrared results reveal that they exist in the amino form: they present in CCl_4 and $CDCl_3$ solution two characteristic bands in the 3520–3390 cm^{-1} region, assigned to the asymmetric and symmetric $\nu(NH_2)$ vibrations, respectively. On N-deuteration of **6** in $CDCl_3$ both bands disappear and two new bands appear at 2633 and 2476 cm^{-1}, assigned to the corresponding vibrations of the ND_2 group, respectively. Moreover, a great decrease in the intensity and a shift towards 1629 cm^{-1} of the 1640 cm^{-1} strong band were observed, indicating a contribution of the $\delta(NH_2)$ mode to this absorption. On the other hand, the N-deuteration of **6** in dilute CCl_4 solution was a stepwise process much slower than that in $CDCl_3$. In the early stages, the infrared spectra showed a gradual decrease of the original ν(N–H) bands and the appearance of two new ν(N–H) bands at 3480 and 3433 cm^{-1} and two ν(N–D) bands of the monodeuterated species at 2564 and 2539 cm^{-1}. Two other bands at 2636 and 2477 cm^{-1}, whose intensity increased gradually, also appeared and were assigned to the N-dideuterated compound. These results confirm the predominance of the tautomeric amino form. The broad singlet at 6.20 ppm (Table 1) in the ^{1}H NMR spectrum also suggests the presence of the NH_2 group. For the imino structure two signals corresponding to the NH groups would be expected in the ^{1}H NMR spectrum.

Compounds **8** and **9** can also be described as the amido tautomers (Scheme 3). ^{1}H NMR spectrum at −70 °C of compound **8** showed the presence of only one tautomer, the amido form, and no equilibrium between amido and imido tautomers was observed. X-ray data for **8** are in agreement with this conclusion (see Fig. 1). On the other hand, the IR spectrum showed a similar amido structure for compound **9.**

Table 2 ^{13}C NMR chemical shifts (δ) for compounds **6**–**12** in $CDCl_3$ (~0.1 M)

	6	7	8	9	10	11	12
C1(5)	53.95	53.78	54.02	54.10	54.02	53.83	54.03
C3	73.55	73.60	71.08	71.09	72.07	70.98	71.95
C2(4)	31.71	32.29	30.17	30.55	30.64	31.97	30.59
C6(8)	26.71	26.27	28.70	28.65	28.16	26.90	28.24
C7	20.20	20.03	20.19	20.31	20.22	20.23	20.22
N–CH_3	40.62	40.67	40.69	40.98	40.74	40.67	40.79
C=O	153.51	153.05	155.34	156.04	161.06	161.62	159.09
O–CH_3							55.84
CH_3		20.37		20.11			
C2′	151.82	151.64	155.34	156.04	153.46	153.66	153.51
C3a′	142.25	140.33	148.83	148.72	148.75		142.92
C4′	114.13	114.93	115.00	115.00	120.78	136.90	121.36
C5′	124.62	132.87	121.62	130.34	125.83	112.42	104.07
C6′	120.90	129.18	121.62	130.34	123.54		156.52
C7′	116.48	117.21	115.00	115.00	121.17		114.78
C7a′	130.15	128.38	148.83	148.72	131.63		132.85

X-Ray crystal structure determination of compound 8

White crystals were obtained by vapour diffusion of hexane into a chloroform solution of compound **8**. All data were collected on an ENRAF NONIUS CAD4 diffractometer at room temperature.

The asymmetric unit of compound **8** contains two crystallographically independent molecules, both having similar geometries with only very slight differences (Fig. 1). These two molecules are bonded together by two fairly strong N–H···N hydrogen bonds, forming dimeric pairs. Within each molecule there is an intramolecular hydrogen bond (between O3 and H23 in one molecule and between O1 and H1 in the other) Metric parameters for the hydrogen bonds are given in Table 4.

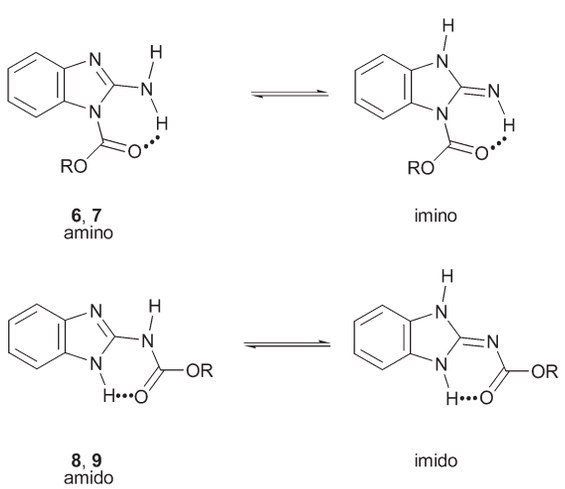
The bicyclic system shows a chair-chair conformation, both chairs being flattened. This flattening is caused by the increase of the angles C26–C33–C32 [113.1(5)°], C26–C27–C28 [112.6(5)°], C28–C29–C30 [115.1(6)°], C30–C31–C32 [114.3(6)°]

Table 3 Infrared frequencies (cm^{-1}) of compounds **6–12**

Compound	Medium	$\nu(NH_2)$ [b]	$\nu(NH_2)$ [d]	$\nu(NH_2)$ [e]	$\nu(NH)$ [a b]	$\nu(NH)$ [c]	$\nu(C=O)$	Heterocyclic ring		
6	KBr	3437 m[f]		~3040 w, br[g]			1732 vs	1663 s	1605 m[h]	1548 w
								1643 sh	1594 w	1534 sh
	$CDCl_3$	3510 w	3390 w				1728 vs	1655 sh	1604 m[h]	1544 w
								1640 s	1591 s	1533 w
	CCl_4	3516 m	3396 m				NM[i]	NM[i]	NM[i]	NM[i]
7	KBr	3443 m		~3060 m, br[g]			1727 vs	1660 s	1618 m	1558 w
	$CDCl_3$	3508 w–m	3390 w–m				1726 vs	1656 sh	1611 s[h]	1546 vw
								1642 s	1585 w–m	1527 vw
	CCl_4	3514 m	3395 m				NM[i]	NM[i]	NM[i]	NM[i]
8	KBr				3402 m	~2800 m, br[e]	1715 s	1639 vs	1597 vs[h]	1621 w
									1589 sh	
	$CDCl_3$				3411 m	3450 sh[j]	1707 s	1641 vs	1598 vs[h]	1519 w
						~2800 m, br[e]				
	CCl_4				3407 m	3457 w[j]	NM[i]	NM[i]	NM[i]	NM[i]
9	KBr				3375 s	~2800 m, br[e]	1707 s	1644 vs	1602 vs[h]	1518 w–m
								1629 m		
	$CDCl_3$				3417 m	3470 sh[j]	1703 s	1648 s	1599 vs[h]	1520 w
						~2800 m, br[e]				
	CCl_4				3409 m	3475 vw[j]	NM[i]	NM[i]	NM[i]	NM[i]
						~2800 m, br[e]				
10	KBr					NM[i]	1715 vs		1604 s	1559 vs
	$CDCl_3$					3411 m[j]	1723 s		1604 s	1560 s–vs
										1546 vs
	CCl_4					3423 s[j]	NM[i]		NM[i]	NM[i]
11	KBr					~2110[k]	1719 s		1582 s	1551 sh
							1704 sh			
	$CDCl_3$					3415 w[j]	1710 vs		1575 vs	1541 s
	CCl_4					3425 m[j]	NM[i]		NM[i]	NM[i]
12	KBr					~2050[k]	1725 s		1610 s	1578 s
										1559 s
	$CDCl_3$					3412 w[j]	1723 s		1608 s	1573 sh
										1552 s
	CCl_4					3425 m[j]	NM[i]		NM[i]	NM[i]

[a] Heterocycle. [b] Intramolecularly bonded NH. [c] Carbamate group. [d] Symmetric mode of the NH_2 group. [e] Intermolecularly bonded NH. [f] Abbreviations: br, broad; m, medium; s, strong; sh, shoulder; v, very; w, weak. [g] Tentative assignment. [h] Probable contribution of phenyl ring band. [i] Not measured. [j] Free N–H group. [k] Transmission maximum of the double band system.

in one molecule and C9–C16–C15 [113.6(6)°], C9–C10–C11 [114.5(6)°], C11–C12–C13 [115.1(6)°], C13–C14–C15 [112.8(7)°] in the other. They are all greater than the ideal value of 109.5°. Such a distortion forces the C9···C13 and C26···C30 distances [3.057(12) and 3.062(12) Å, respectively] to become greater than the 2.52 Å expected for an idealized bicyclo[3.3.1]nonane.[30] The N-methyl and carbamate groups are in axial and equatorial positions, respectively, relative to the disubstituted ring.



Scheme 3

Thiazole and benzothiazole derivatives

The synthesis of the thiazole and benzotiazole carbamates studied (**10–12**) was carried out in a similar manner to that described above for the benzimidazole derivatives

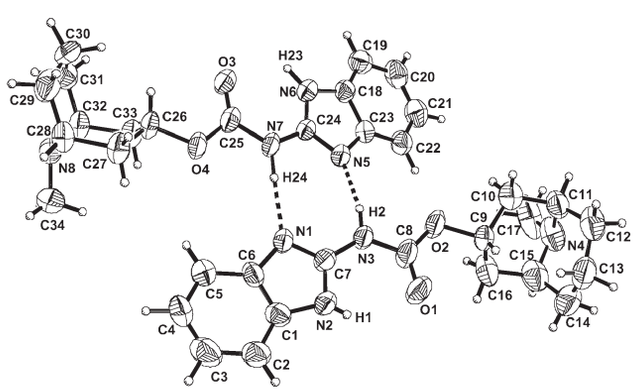


Fig. 1 ORTEP view of compound **8** showing the intermolecular hydrogen bonding interactions with the numbering used in the crystallographic study.

Table 4 Hydrogen bonding interactions (Å, deg) in compound **8** with esd values in parentheses.

D–H···A	D···A	H···A	∠D–H···A
(a) Intramolecular			
N2–H1···O1	2.712(8)	2.228(6)	129.7(5)
N6–H23···O3	2.694(8)	2.164(5)	116.9(4)
(b) Intermolecular			
N7–H24···N1	2.873(7)	1.871(5)	174.6(3)
N3–H2···N5	2.801(7)	1.845(5)	167.2(3)

(Scheme 4). As expected, in this case only one carbamate was obtained as a result of the reaction between the NH_2 group in the 2-position of the thiazole ring and the carbonyl group of the chloroformate hydrochloride **5**. The structure of these compounds was determined by NMR (Tables 1 and 2) and IR (Table 3) studies.

Due to the great similarity observed among the ^1H NMR spectra of alkyl benzimidazole-2-carbamates (**8** and **9**) and the alkyl benzothiazole and thiazole carbamates (**10**–**12**) a similar structure can be deduced. The broad signal at ~11 ppm corresponding to one proton confirms the absence of an NH_2 group and therefore the carbamate group is at the 2-position of the benzothiazole or thiazole ring. With respect to the ^{13}C NMR spectra the most pronounced difference among **8**–**9** and **10**–**12** corresponds to the chemical shift of the carbonyl group ($\Delta\delta \approx 5$–6 ppm) indicating that in compounds **10**–**12**, this group is not involved in an intramolecular hydrogen bond. These conclusions agree with IR results.

Molecular interactions study

The compounds reported in this paper possess both acidic hydrogens and electron-rich nitrogen atoms and can associate through intra- and/or intermolecular hydrogen bonds. IR (solid and solution) studies were carried out to determine the nature of these interactions. In addition, X-ray data for compound **8** and ^{13}C NMR data were taken into consideration.

The infrared spectra of **6** and **7** in the solid state show a sharp, medium intensity band at 3437–3443 cm^{-1} and a poorly defined absorption at about 3040–3060 cm^{-1}; upon dilution in CCl_4 (0.0005 M) these bands are replaced by two medium ones at 3516–3514 and 3396–3395 cm^{-1}. In $CDCl_3$ (0.05 M) the bands appear at 3510–3508 and 3390 cm^{-1}. Taking into consideration results in the solid state at liquid air temperature,[7] the higher frequency band is assigned to the stretching vibration of an intramolecularly bonded NH (NH···O=C) of the primary amino group (Scheme 2). The lower frequency band is assigned to an intermolecularly bonded NH (NH···N) of the primary amino group in a cyclic dimer. As it was mentioned before, in solution, the two observed bands correspond to the asymmetric and symmetric modes of the NH_2 group, respectively. It should be remarked that in $CDCl_3$ solution (0.05 M) some of the molecules remain bonded and are in equilibrium with free species.

In the double bond region a strong band appears at 1732–1728 cm^{-1} in **6** and at 1727–1726 cm^{-1} in **7**; this band is assigned to the ν(C=O) of the carbamate system. Bands characteristic of the heterocyclic ring show up in the 1670–1500 cm^{-1} region. The differences observed between solid and solution states in the double bond region are mainly due to the breaking of intermolecular hydrogen bonds, which implies changes in the coupling of the $\delta(NH_2)$ with heterocyclic ν(C=N) vibrations as it has been confirmed by N-deuteration of compound **6**.

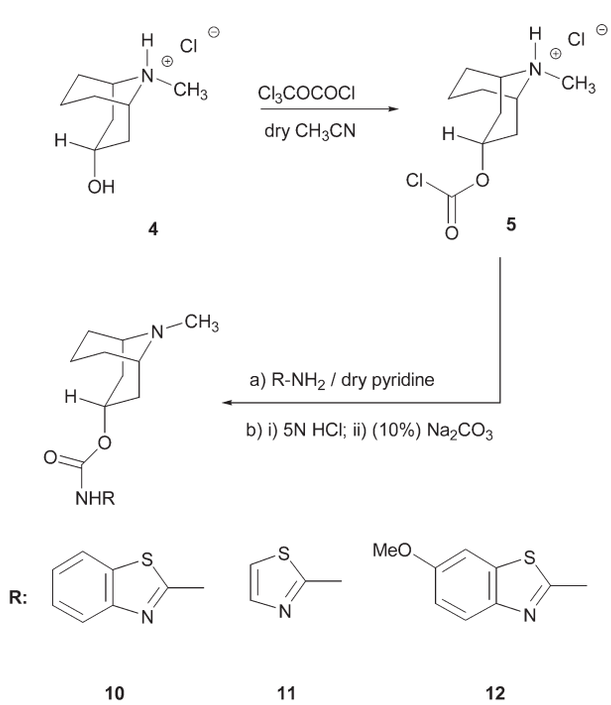
In the case of compound **8** the infrared spectrum in the solid state shows a medium band at 3402 cm^{-1}, which shifted to 3407 cm^{-1} in CCl_4 (3411 cm^{-1} in $CDCl_3$). These results suggest the presence of intramolecular bonding between the C=O carbamate and the NH of the benzimidazole ring, as it is confirmed by the X-ray data for this compound (Table 4). A broad absorption at lower frequency (~2800 cm^{-1}) is assigned to strong NH···N bonding, also in accordance with the X-ray data (Table 4, Fig. 1). As expected, this band shifted to higher frequencies in 0.0005 M CCl_4 solution (3457 cm^{-1}) or in 0.05 M $CDCl_3$ solution (3450 cm^{-1}). A greater proportion (than in CCl_4) of bonded molecules are present in $CDCl_3$ due to the strong hydrogen bond interaction.

Infrared results for compound **9** are similar to those obtained for **8**, although small differences in the ν(N–H) and ν(C=O) frequencies are observed.

The infrared spectra of compounds **10**–**12** in the solid state show broad absorptions below 3000 cm^{-1}, and upon dilution in CCl_4 (0.0005 M), one band at 3425–3423 cm^{-1} (3415–3411 cm^{-1} in 0.05 M $CDCl_3$). In both solvents bonded molecules exist in equilibrium with free molecules. These results indicate the presence of a strong intermolecular hydrogen bond, which is formed either between the carbamate NH group and the basic piperidine nitrogen atom or between the carbamate NH group and the nitrogen atom of the benzothiazole (or thiazole) ring.

In the double bond region a strong band appears at 1719–1725 cm^{-1} (Table 3), which is assigned to the carbamate ν(C=O). Characteristic bands of the benzothiazole or thiazole ring are present in the 1610–1540 cm^{-1} region. Differences between the solid and solution spectra can be explained by coupling between ν(NH) and ν(C=N) modes.

For compounds **8** and **9**, ^{13}C NMR data also suggest intramolecular hydrogen bonding under our working conditions: The $\Delta[\delta C{=}O$ (**10**–**12**) $- \delta C{=}O$ (**8**)] difference of ~6 ppm may due to the fact that in compound **8** the C=O group is hydrogen-bonded (Scheme 2). The $\Delta[\delta C{=}O$ (**10**–**12**) $- \delta C{=}O$ (**9**)] difference of ~5 ppm can also be explained in the same way (Scheme 2).



Scheme 4

Conformational study

Conformationally, the 9-azabicyclo[3.3.1]nonane derivatives are highly interesting due to the great influence exerted by the substituents. Disregarding the less favorable boat-boat

form, the granatane system can adopt four conformations, two chair-chair forms, by nitrogen inversion, and two chair-boat forms. ^{1}H and ^{13}C NMR spectroscopic parameters are very useful for the conformational analysis of this bicyclic system; nevertheless, owing to the complexity of their ^{1}H NMR spectra, additional experiments were required in order to determine the proton magnetic parameters. With respect to the bicyclic ring the more relevant information deduced from the ^{1}H NMR spectra is as follows: the value of *ca.* 11.75 Hz observed for $W_{1/2}$ of H1(5) is in good agreement with previously reported values for a flattened chair-chair conformation in related bicyclic systems.[31,32] ^{3}JH2(4)$_{\beta}$–H1(5) (~5.5 Hz) is greater than ^{3}JH2(4)$_{\alpha}$–H1(5) (estimated values <2 Hz) and, consequently, the dihedral angle H2(4)$_{\beta}$–C–C–H1(5) is less than the angle H2(4)$_{\alpha}$–C–C–H1(5). This fact is more consistent with a flattened chair-chair conformation for the disubstituted ring than with an equilibrium between chair and boat forms. Moreover, the values of the corresponding constants ^{3}JH2(4)$_{\beta}$–H3 (~11 Hz) and ^{3}JH2(4)$_{\alpha}$–H3 (~7 Hz) also support a slight flattened chair conformation with the carbamate group in an equatorial disposition. The preferred conformation deduced in solution is in good agreement with that observed in the solid state for compound **8**.

Finally, taking into account the ^{13}C NMR data and bearing in mind the similarity of the chemical shift of C7 for compounds **6**–**12** (~20 ppm) and the reported value for β-granatanol (~19.8 ppm),[33] it is clear that compounds **6**–**12** and β-granatanol should adopt the same preferred conformation in solution, a flattened chair-chair conformation.

Conclusions

The reaction of heterocyclic primary amines with azabicyclic chloroformates provides a simple and convenient process to obtain carbamates from readily available starting materials. These compounds were expected to be biologically active as 5-HT$_3$ antagonists; however, the results of the pharmacological evaluation showed that the reference compounds were more active than the tested substances.

Acylation of 2-aminobenzimidazole and derivatives took place at the exocyclic and endocyclic nitrogens with production of the 2-carbamate and the 1-carbamate, respectively. Both carbamates are obtained in an approximately 6:1 ratio (for compounds **6** and **8**) and in a 5:1 ratio (for compounds **7** and **9**) in favour of the 1-carbamate. In this work, a multi-technique approach to the structural studies of the synthesized compounds has been used. Each technique provides evidence to confirm the conformation and the presence of intra- and/or intermolecular interactions in the systems under investigation.

Experimental

General

Trichoromethyl chloroformate was purchased from Fluka and heterocyclic amines were purchased from Aldrich; they were used without further purification. 9-Methyl-9-azabicyclo[3.3.1]-nonan-3α-ol was synthesized according to the reported method.[20] Acetonitrile was dried over calcium hydride, pyridine was distilled over sodium hydroxide pellets, and ethyl ether was dried over sodium and benzophenone.

Melting points were determined in open capillaries on a Gallenkamp MFB-595-010M apparatus and are uncorrected.

The IR spectra for compounds **6**–**12** were recorded on a Perkin–Elmer FTIR 1725X spectrophotometer, assisted by a computer, in the solid state (KBr) in the 4000–400 cm^{-1} range and in $CDCl_3$ solution (0.05 M) in the 4000–900 cm^{-1} region using 0.2 mm NaCl cells. Spectra for very dilute CCl_4 solutions were taken in the 4000–2500 cm^{-1} region with 4 cm quartz cells. The reported wavenumbers are estimated to be accurate to within ±3 cm^{-1}.

^{1}H NMR spectra were recorded on a Varian Unity-300 spectrometer (299.949 MHz). Spectral parameters included sweep width of 4000 Hz in 24 K memory and acquisition times of 3 s over 64 transients. Resolution enhancement using lb = −0.80; gf = 0.50; gfs = 0.20 was followed by zero-filling into 32 K memory prior to Fourier transformations.

The double resonance experiments involved the use of conventional irradiation. The 2D experiments were performed on a Varian Unity-500 spectrometer, using standard pulse sequences and a sine bell window function was applied in both domains.

The ^{13}C NMR spectra were obtained at 75 MHz on a Varian Unity-300 spectrometer. The information about the number of C-attached protons was obtained from DEPT experiments.

X-Ray crystallography

Intensity measurements were performed by $\omega-\theta$ scans in the range $6° < 2\theta < 50°$. Of the 6212 measured reflections for **8**, 5948 [R(int) = 0.0925] were independent; $R_1 = 0.085$ and $wR_2 = 0.229$ [for 2376 reflections with $F > 4\sigma(F)$]. The structure was solved using the WINGX package,[34] by direct methods (SHELXS-97) and refined by least-squares against F^2 (SHELXL-97).[35] Compound **8** crystallized with hexane (solvent) but only one of the carbon atoms could be located and refined (C100). All non-hydrogen atoms were anisotropically refined. The hydrogen atoms were positioned geometrically and refined by using a riding model in the last cycles of refinement, except those H atoms linked to N3 and N7, which were located and refined.†

Crystal data for compound **8**. $C_{17}H_{22}N_4O_2 \cdot 1/2C_6H_{14}$, $M = 357.47$, monoclinic, space group $P2_1/c$ (n. 14), $Z = 8$, $a = 13.644(3)$, $b = 14.574(5)$, $c = 17.816(4)$ Å, $\beta = 106.64(1)°$, $U = 3394.3(16)$ Å^3, $T = 298$ K, μ(Mo–Kα) = 0.09 mm^{-1}.

General procedure for preparing carbamates 6–12

9-Methyl-9-azabicyclo[3.3.1]nonan-3α-ol hydrochloride (**4**; 1.66 g, 8.67 mmol) was suspended in 15 ml of dry acetonitrile and 2.14 g (10.8 mmol) of trichloromethyl chloroformate was added dropwise at 0 °C. The reaction mixture was stirred at this temperature for 30 min and then at room temperature for 24 h until a clear solution was obtained. The solvent was removed under vacuum and the residue triturated with ethyl ether to afford **5** (95%) pure enough to be used in the following step.

The corresponding amine (1.18 mmol) was dissolved in dry pyridine (2 ml) at room temperature and **5** (1.18 mmol) was then added in portions with stirring. The mixture was stirred for 2 h. After this time the carbamate hydrochloride crystallized; then it was recovered by filtration and washed with ethyl ether. The carbamate hydrochloride obtained was then dissolved in 5 N HCl and 10% aqueous potassium carbonate was added until no further precipitation was observed. This precipitate was filtered, washed with water and then dried under vacuum. Further purification was carried out by recrystallization from $CHCl_3$–hexane. In this way, carbamates **6**, **7** and **10**–**12** could be obtained.

For carbamates **8** and **9**, the filtrate (pyridine) and washings (ether) were combined and concentrated under vacuum. The residue was taken up with 5 N HCl and 10% aqueous potassium carbonate was added until no further precipitation was observed. This precipitate was filtered, washed with water and then dried under vacuum. Finally, it was purified by

† CCDC reference numbers 207611. See http://www.rsc.org/suppdata/nj/b3/b309065e/ for crystallographic data in .cif or other electronic format.

chromatography column on silica gel with 5:95 MeOH (saturated with ammonia gas)–$CHCl_3$ and then recrystallized from $CHCl_3$–hexane to give the corresponding carbamate.

9-Methyl-9-azabicyclo[3.3.1]nonan-3β-yl 2-amino-1*H*-benzimidazole-1-carboxylate (6) and N-(benzimidazol-2-yl)-9-methyl-9-azabicyclo[3.3.1]nonan-3β-ylcarbamate (8). Following the general procedure, chloroformate 5 (0.3 g, 1.18 mmol) and 2-aminobenzimidazole (0.16 g, 1.18 mmol) in 2 ml of dry pyridine, after stirring for 2 h at room temperature, gave 227 mg (61%) of **6**: m.p. 126–127 °C (decomp.); anal. calcd for $C_{17}H_{22}N_4O_2$: C, 64.95; H, 7.05; N, 17.82; found: C, 64.83; H, 6.98; N 17.94. Following the general procedure for carbamates **8** and **9**, 39 mg (11%) of carbamate **8** were obtained: mp. 145 °C (decomp.); anal. calcd for $C_{17}H_{22}N_4O_2$: C, 64.95; H, 7.05; N, 17.82; found: C, 65.12; H, 7.22; N, 17.88.

9-Methyl-9-azabicyclo[3.3.1]nonan-3β-yl 2-amino-5,6-dimethyl-1*H*-benzimidazole-1-carboxylate (7) and *N*-(5,6-dimethylbenzimidazol-2-yl)-9-methyl-9-azabicyclo[3.3.1] nonan-3β-ylcarbamate (9). Following the general procedure, chloroformate 5 (0.3 g, 1.18 mmol) and 2-amino-5,6-dimetilbenzimidazole (0.19 g, 1.18 mmol) in 2 ml of dry pyridine, after stirring for 24 h at room temperature, gave 153 mg of **7** (38%): m.p. 155-156 °C (decomp); anal. calcd for $C_{19}H_{26}N_4O_2$: C, 66.64; H, 7.65; N, 16.36; found: C, 66.38; H, 7.69; N, 16.29. Following the described procedure, 26 mg (7%) of carbamate **9** were obtained: m.p. 153 °C (decomp.); anal. calcd for $C_{19}H_{26}N_4O_2$: C, 66.64; H, 7.65; N, 16.36; found: C, 66.72; H, 7.82; N, 16.48.

***N*-(Benzothiazol-2-yl)-9-methyl-9-azabicyclo[3.3.1]nonan-3-yl-carbamate (10).** Using the general procedure, chloroformate **5** (0.1 g, 0.39 mmol) and 2-aminobenzothiazole (59.2 mg, 0.39 mmol) in 0.4 ml of anhydrous pyridine gave 47 mg of **10** (36%): m.p. 190–191 °C (decomp.); anal. calcd for $C_{17}H_{21}N_3O_2S$: C, 61.61; H, 6.39; N, 12.68; found: C, 61.54; H, 6.04; N, 12.82.

***N*-(Thiazol-2-yl)-9-methyl-9-azabicyclo[3.3.1]nonan-3β-ylcarbamate (11).** Following the general procedure, chloroformate 5 (0.1 g, 0.39 mmol) and 2-aminothiazole (39.4 mg, 0.39 mmol) in 0.3 ml of anhydrous pyridine gave 68 mg of **11** (61%): m.p. 201 °C (decomp.); anal. calcd for $C_{13}H_{19}N_3O_2S$: C, 55.49; H, 6.81; N, 14.09; found: C, 55.62; H, 6.90; N, 13.88.

***N*-(6-Methoxybenzothiazol-2-yl)-9-methyl-9-azabicyclo-[3.3.1]-nonan-3β-ylcarbamate (12).** Using the general procedure, chloroformate **5** (0.1 g, 0.39 mmol) and 2-amino-6-methoxybenzimidazole (0.1 g, 0.39 mmol) in 0.3 ml of dry pyridine gave 77 mg of **12** (54%): m.p. 182 °C (decomp.); anal. calcd for $C_{18}H_{23}N_3O_3S$: C, 59.81; H, 6.41; N, 11.63; found: C, 59.63; H, 6.62; N, 11.48.

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