

SYNTHESIS AND CRYSTALLINE AND MOLECULAR STRUCTURES OF THE MORPHOLINYLAMIDE OF N(R)-*l*-EPHEDRINYLACETIC ACID

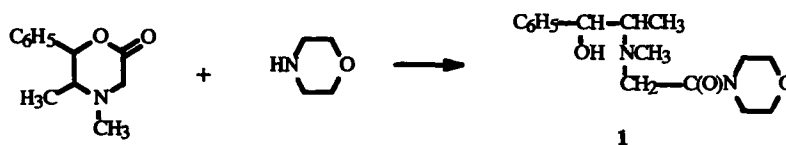
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The synthesis of the morpholinylamide of N(R)-l-ephedrinylacetic acid has been achieved by the interaction of (5S,6R)-4,5-dimethyl-6-phenylmorpholin-2-one with morpholine, and its structure has been shown by IR and PMR spectroscopies and x-ray structural analysis.

It is known that morpholine derivatives possess a broad spectrum of pharmacological activity and are of definite interest in the construction of biologically active compounds, including those simultaneously containing fragments of natural compounds in the molecule [1, 2].

In view of this, we have synthesized the morpholinylamide of N(R)-*l*-ephedrinylacetic acid (1), containing the main fragment of the natural alkaloid *l*-ephedrine, by the interaction of (5S,6R)-4,5-dimethyl-6-phenylmorpholin-2-one with morpholine in isopropyl alcohol. The yield of the desired product amounted to 74.2%.



The IR spectrum of compound (1) contained absorption bands in the regions of 1682 and 3410 cm^{-1} , confirming the presence of amide and hydroxy groups. In the PMR spectrum of the amide (1), in addition to the signals of the protons of the alkaloid moiety, there was a singlet with a chemical shift of 2.89 ppm for the protons of the NCH_2C fragment, while the methylene protons of the NCH_2 and CH_2O groups of the morpholine fragment appeared in the form of two triplets in the 2.89 and 3.15 ppm regions, respectively.

In order to establish the spatial structure of compound (1), we have carried out an x-ray structural examination of it. The unit cell of the crystal of (1) contains two crystallographically independent molecules (1a) and (1b). The structure of the molecule of (1) is shown in Fig. 1. The bond lengths (Table 1) and valence angles (Table 2) have values close to the usual ones [3], with the exception of the bonds $\text{N2}-\text{C12}$ and $\text{O2}=\text{C12}$ (in (1a) and (1b), $\text{N2}-\text{C12}$ and $\text{O2}=\text{C12}$ are, respectively, 1.333 and 1.331 Å, and 1.243 and 1.229 Å) and the valence angles at the N2 atom (the sum of the valence angles amounts to 359.96° and 359.93° in (1a) and (1b)). The deviation of these bond lengths from the standard values and the plane trigonal coordination of the N2 nitrogen are due to the double-bond nature of the $\text{N2}-\text{C12}$ bond as a result of the delocalization of the unshared electron pair of the nitrogen on the electrons of the CO group (mesomeric effect).

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TABLE 1. Bond Lengths (Å) in the (1a) and (1b) Molecules

Bond	d	d	Bond	d	d
	1a	1b		1a	1b
O1-C7	1.425(3)	1.428(3)	C1-C6	1.400(3)	1.397(3)
O2-C12	1.243(2)	1.229(3)	C1-C7	1.497(3)	1.494(3)
O3-C14	1.426(3)	1.423(3)	C2-C3	1.382(3)	1.377(3)
O3-C15	1.430(3)	1.426(3)	C3-C4	1.388(3)	1.387(3)
N1-C8	1.471(3)	1.468(3)	C4-C5	1.357(4)	1.370(4)
N1-C10	1.468(3)	1.453(3)	C5-C6	1.379(3)	1.372(3)
N1-C11	1.452(3)	1.472(3)	C7-C8	1.535(3)	1.537(3)
N2-C12	1.333(3)	1.331(3)	C8-C9	1.525(3)	1.520(3)
N2-C13	1.472(3)	1.460(3)	C11-C12	1.509(3)	1.521(3)
N2-C16	1.456(3)	1.463(3)	C13-C14	1.491(4)	1.488(4)
C1-C2	1.372(3)	1.381(3)	C15-C16	1.476(3)	1.490(4)

TABLE 2. Valence Angles (degrees) in the (1a) and (1b) Molecules

Angle	α	α	Angle	α	α
	1a	1b		1a	1b
C14O3C15	11.0(2)	110.2(2)	O1C7C1	111.4(2)	112.0(2)
C8N1C11	114.2(2)	113.8(2)	O1C7C8	105.5(2)	106.0(2)
C8N1C11	110.7(2)	111.6(2)	C1C7C8	113.3(2)	112.1(2)
C10N1C11	110.9(2)	111.5(2)	N1C8C7	111.0(2)	111.0(2)
C12N2C13	126.9(2)	125.5(2)	N1C8C9	114.4(2)	115.3(2)
C12N2C16	120.2(2)	121.4(2)	C1C8C9	110.9(2)	110.4(2)
C13N2C16	112.9(2)	113.0(2)	N1C11C12	114.3(2)	117.1(2)
C2C1C6	118.4(2)	118.1(2)	O2C12N2	122.4(2)	121.6(2)
C2C1C7	119.8(2)	119.7(2)	O2C12C11	118.9(2)	118.0(2)
C6C1C7	121.9(2)	122.2(2)	N2C12C11	118.7(2)	120.2(2)
C1C2C3	120.8(2)	120.5(2)	N2C13C14	109.4(2)	108.3(2)
C2C3C4	119.6(2)	120.3(2)	O3C14C13	111.7(2)	111.4(2)
C3C4C5	120.5(2)	120.0(2)	O3C15C16	111.4(2)	111.8(2)
C4C5C6	119.8(2)	119.5(2)	N2C16C15	109.4(2)	109.8(2)
C1C6C5	120.9(2)	121.2(2)			

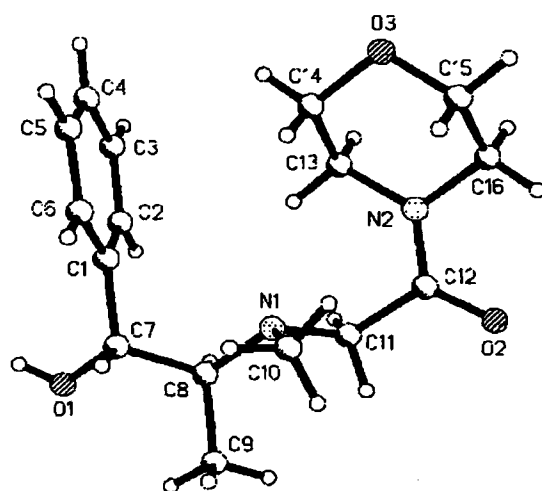


Fig. 1. Structure of the molecule (1).

TABLE 3. Coordinates of the Atoms ($\times 10^4$; for H Atoms, $\times 10^3$) in the (1a) and (1b) Molecules

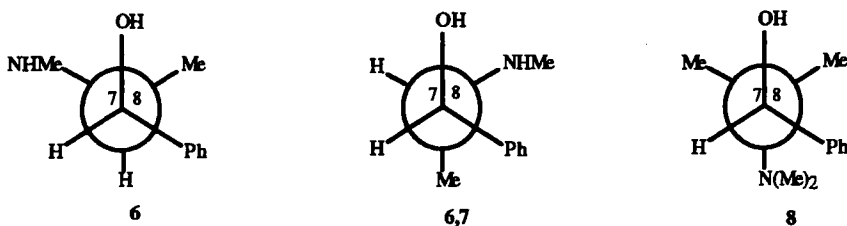
Atom	x	y	z	x	y	z
	1a			1b		
O1	4993(2)	7025(2)	4315(1)	5693(1)	3178(2)	681(2)
O2	-2436(2)	5896(2)	4017(1)	-1466(1)	4444(2)	1027(1)
O3	-1227(1)	318(2)	3089(1)	642(1)	10151(2)	1852(0)
N1	1228(2)	5628(2)	4179(1)	2051(2)	4692(2)	769(1)
N2	-1474(2)	4011(3)	3420(1)	134(2)	6435(2)	1541(1)
C1	3820(2)	4243(3)	3876(1)	4678(2)	5937(3)	1142(1)
C2	4033(2)	2432(3)	4049(1)	4978(2)	7785(3)	993(1)
C3	4007(2)	1051(3)	3629(1)	5364(2)	9106(3)	1432(1)
C4	3726(2)	1495(4)	3024(1)	5749(2)	8595(3)	2030(1)
C5	3503(2)	3277(4)	2843(1)	5748(2)	6769(4)	2186(1)
C6	3569(2)	4657(4)	3264(1)	5381(2)	5455(3)	1747(1)
C7	3889(2)	5716(3)	4341(1)	4583(2)	4523(3)	658(2)
C8	2495(2)	6844(3)	4265(1)	3224(2)	3438(3)	708(1)
C9	2595(2)	8243(3)	4771(1)	2849(2)	2034(3)	204(1)
C10	1055(2)	4666(3)	4725(1)	1389(2)	5636(3)	217(1)
C11	-73(2)	6633(3)	3909(1)	968(2)	3753(3)	1036(2)
C12	-1420(2)	5466(3)	3782(1)	-209(2)	4946(3)	1198(1)
C13	-387(2)	3464(3)	3082(1)	1593(2)	7102(3)	1781(1)
C14	7(2)	1488(3)	3208(1)	1659(2)	9087(3)	1622(1)
C15	-2211(2)	861(3)	3451(1)	-785(2)	9523(3)	1606(1)
C16	-2711(2)	2777(3)	3322(1)	-970(2)	7533(3)	1738(2)
HO1	5690(3)	6530(3)	4250(1)	6510(3)	3780(4)	777(2)

The torsional angles characterizing the conformation of the molecules of ephedrine and its derivatives have the following values: $\tau(\text{C6C1C7O1}) = -59.0^\circ$ and -55.1° , $\omega(\text{O1C7C8N1}) = 170.3^\circ$ and 172.5° , $\chi(\text{C10N1C8C7}) = 73.4^\circ$ and 72.0° , $\psi(\text{HO1C7C8}) = -162.3^\circ$ and -161.3° for the (1a) and (1b) molecules, respectively. The first three torsional angles are close to the corresponding ones in the structures of N(R)-(4-methylcyclohexylidene)fluoroacetyl-*l*-ephedrine (2) ($\tau = -62.3^\circ$, $\omega = 172.0^\circ$, $\chi = 61.3^\circ$ [4] and N(R)-methylphenylphosphineborane-*l*-ephedrine (3) ($\tau = -55.9^\circ$, $\omega = -177.3^\circ$, $\chi = 60.4^\circ$) [5] but differ from the values of these angles in the molecules of ephedrine hydrochloride (4) ($\tau = -21.4^\circ$, $\omega = -70.5^\circ$, $\chi = -170.1^\circ$) [6] and ephedrine thiocyanate (5) ($\tau = -23.6^\circ$, $\omega = -62.2^\circ$, $\chi = -161.9^\circ$) [7].

The values of the torsional angle ψ in the (1–5) molecules differ considerably, which is connected with the formation of intermolecular hydrogen bonds and the effect of crystal packing. The morpholine fragment in the molecule of (1a) {(1b)} has the form of a distorted chair ($\Delta C_s^{14} = 5.7^\circ$; $\Delta C_s^{13} = 5.6^\circ$) with a departure of the C14(C13) and C(16)(C15) atoms by 0.64 {0.67} and 0.65 {0.64} Å in different directions from the mean plane of the other atoms of the ring.

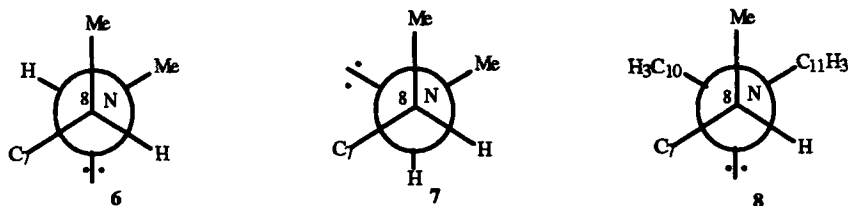
The observed different conformational states with respect to the C7—C8 and C8—N1 bonds realized in the (1)–(3) molecules, on the one hand, and the (4) and (5) molecules, on the other hand, may be a consequence of the replacement of hydrogen on the N1 nitrogen atom by a more voluminous substituent. To check this, we performed by the method of molecular mechanics a conformational analysis of the ephedrine molecule with different configurations of the nitrogen atom (the S- (6) and R- (7) configurations) and of N(R)-methylephedrine (8).

It was found that for the (6) molecule the most favorable are the -(synclinal) ($\varphi_{7,8}^1$) and (+)synclinal ($\varphi_{7,8}^1$) conformation of the C7—C8 bond, for the (7) molecule the (+)synclinal ($\varphi_{7,8}^1$), and for the (8) molecule the antiperiplanar ($\varphi_{7,8}^3$) conformation.



The (6) and (7) molecules in the φ^1_{7-8} and φ^5_{7-8} conformations have smaller energies than in the φ^3_{7-8} conformation (for the (6) and (7) molecules, $E_1 = 15.3$ and 14.8 , $E_3 = 15.5$ and 15.4 , and $E_5 = 15.25$ and 15.3 kcal/mole, respectively) because of the formation of a weak intramolecular hydrogen bond N—H...O (in the φ^1_{7-8} and φ^5_{7-8} conformers the N—H...O angles are, respectively, 59.2 and 99.6° in the molecule of (6), and 104 and 98° in (7); the O...N distances are 2.84 and 2.83 Å in (6) and 2.83 and 2.86 Å in (7); and O...H 3.22 and 2.48 Å in (6) and 2.42 and 2.53 Å (7)) [8]. The closeness of the O to the Me-group at N-atom increase strain energy (O—C10 distances are 3.52 and 4.15 Å in φ^5_{7-8} and φ^1_{7-8}), so φ^1_{7-8} conformational state is the most favorable.

In the (8) molecule, for the C7—C8 bond the φ^3_{7-8} state has the highest population probability with the minimum number of skew interactions (in the φ^1_{7-8} and φ^5_{7-8} states steric strain is also possible because of the closeness of the O to the Me group (C11) at the nitrogen atom, since the O—C11 distances are 2.93 and 2.95 Å in the conformers φ^1_{7-8} and φ^5_{7-8}).



For the C8—N bonds in the (6) and (7) molecules the most probable conformational states are φ^1_{8-N} and φ^3_{8-N} also with respect to the number of skew interactions, the preferential nature of these states most probably being determined by interaction of O with the Me group at the nitrogen (the O...C10 distances are 3.52 Å in the φ^3_{8-N} molecule of (6) and in the φ^5_{8-N} molecule of (7), while in the φ^1_{8-N} and φ^3_{8-N} states of these molecules the O...C10 distances amount to 4.12 and 4.15 Å, respectively). The (8) molecule has the minimum energy in the φ^1_{8-N} state, since in the φ^3_{8-N} and φ^5_{8-N} states the O atom and the Me group (C11) at N are closer (the O...C11 distances are 2.93 and 2.59 Å in φ^3_{8-N} and φ^5_{8-N} states).

The calculations performed also showed that the increase in the size of the torsional angle in the (1)—(3) and (8) molecules as compared with this angle in the (4)—(7) molecules took place as a consequence of a rotation of the plane of the Ph group by a large angle on the approach of this functional group to the N1 atom in the φ^3_{7-8} state. Thus, the stabilization of these conformational states in salts of ephedrine and of N-substituted ephedrine derivatives is determined by the formation of weak hydrogen bonds and the nonvalent repulsion of the substituents at the nitrogen atom with the other functional groups.

EXPERIMENTAL

IR spectra were taken on a UR-20 instrument (KBr), and ^1H NMR spectra were recorded on a Tesla BS-587A spectrometer with a working frequency of 80 MHz in C_6D_6 solution with HMDS as internal standard. Melting points were determined on a Boetius instrument.

The cell parameters and the intensities of 6392 independent reflections of a crystal of (1) were measured at 100°C on a Siemens SMART CCD three-circle diffractometer with monochromatized $\lambda(\text{MoK}\alpha)$ radiation ($\theta/2\theta$ scanning, $2\theta \leq 60^\circ$). The crystals were monoclinic, $a=9.508(9)$, $b=7.241(7)$, $c=22.85(2)$ Å, $\beta=102.46(2)^\circ$, $V=1536$ Å³, $d_{\text{calc}}=1.264$ g/cm³, $Z=4(\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_3)$. Space group $\text{P}2_1$.

In the calculations we used 4785 reflections with intensities $I \leq 2\theta(I)$. The structure was interpreted by the direct method and was refined by full-matrix MLS in the anisotropic approximation for the nonhydrogen atoms. The H atoms, with

the exception of those of hydroxy groups, revealed in a difference synthesis, are given geometrically and have not been refined. Weighting parameter 0.039. Final divergence factors $R = 0.043$, $R_w = 0.089$. The coordinates of the atoms are given in Table 3. All the calculations were conducted on a Silicon Graphics computer by means of the Siemens SHEXTL and SHELXL-95 program packets.

(5S,6R)-4,5-Dimethyl-6-phenylmorpholin-2-one was obtained previously as described in [9].

Morpholinylamide of N(R)-*l*-ephedrinylacetic Acid (1). A mixture of 2.05 g of morpholinone and 1.1 g of morpholine in 10 ml of propan-2-ol was boiled for 10 h. The solvent was distilled off in water-pump vacuum, and the residue was recrystallized from benzene—hexane. This gave 2.2 g (74.2%) of product (1) with mp 87°C.

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