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Steric Structure of *N*-(2-Hydrazono-2-hydroxyethyl)-*d*-Pseudoephedrine and Its Intramolecular Heterocyclization Under the Action of Orthoformic Ester

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Abstract — An X-ray structural investigation of *N*-(2-hydrazono-2-hydroxyethyl)-*d*-pseudoephedrine is performed, and intramolecular heterocyclization of this compound with orthoformic ester is studied. The final reaction product is found to be a compound containing a morpholone ring rather than substituted 1,3,4-oxadiazole.

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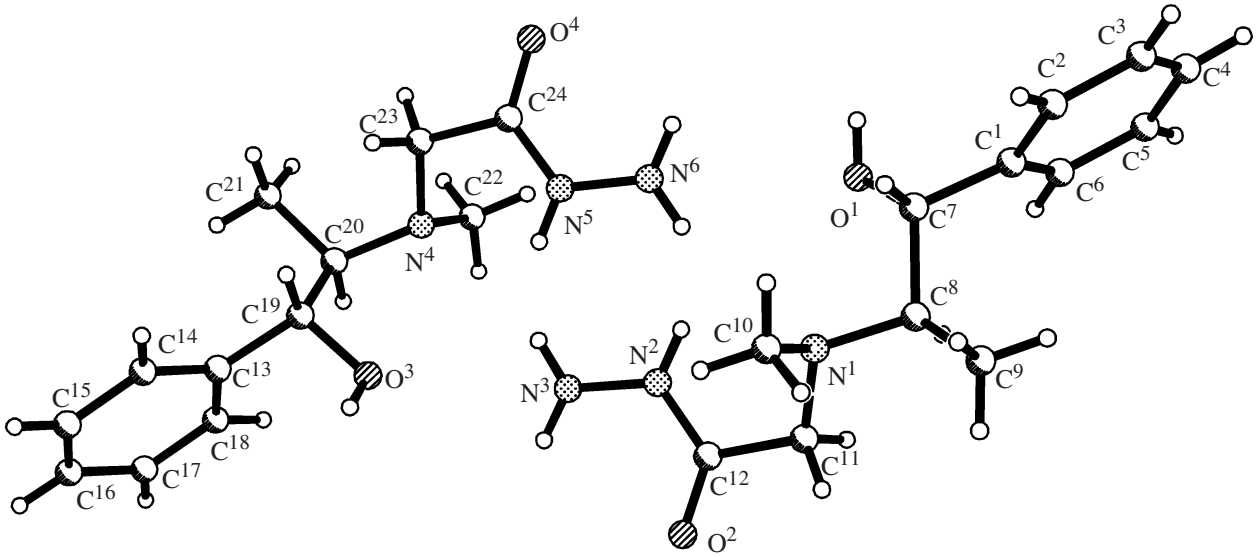
The interest in the chemistry of hydrazides owes to the fact that most hydrazide derivatives show a broad-spectrum physiological activity, including a pronounced antitubercular activity [1–5]. Earlier we synthesized hydrazides and acylhydrazides of N-substituted aminoacetic acids derived from physiologically active ephedrine alkaloids [6].

To assess the steric structure of hydrazide **I**, we performed an X-ray diffraction investigation. The general view of the molecule is shown in the figure. The crystal lattice of the molecule is found consisting of a dimer.

The crystals of hydrazide **I** consist of two crystallographically independent molecules whose bond lengths (Table 1) and bond angles (Table 2) are close to each other and to standard values [7]. An exception are torsion angles (Table 3) which characterize the molecular conformation of 1-ephedrine and its deriva-



Molecular structure of *N*-(2-hydrazono-2-hydroxyethyl)-*d*-pseudoephedrine (**I**).

Table 1. Bond angles (ω, deg) in structure **I**

Angle	ω	Angle	ω
$C^{24}N^5N^6$	122.7(3)	$C^6C^1C^2$	118.6(4)
$C^{23}N^4C^{22}$	110.8(3)	$C^6C^1C^7$	121.5(3)
$C^{23}N^4C^{20}$	114.3(3)	$C^2C^1C^7$	119.9(3)
$C^{22}N^4C^{20}$	111.4(3)	$C^{17}C^{18}C^{13}$	121.4(4)
$C^{12}N^2N^3$	122.5(3)	$C^{14}C^{13}C^{18}$	117.5(4)
$C^{11}N^1C^{10}$	110.9(3)	$C^{14}C^{13}C^{19}$	120.6(4)
$C^{11}N^1C^8$	112.5(2)	$C^{18}C^{13}C^{19}$	121.7(3)
$C^{10}N^1C^8$	113.4(3)	$C^{16}C^{15}C^{14}$	119.9(4)
$O^2C^{12}N^2$	123.4(3)	$C^{13}C^{14}C^{15}$	121.9(4)
$O^2C^{12}C^{11}$	120.9(3)	$O^1C^7C^1$	107.9(3)
$N^2C^{12}C^{11}$	115.7(3)	$O^1C^7C^8$	109.0(3)
$N^4C^{20}C^{21}$	115.2(3)	$C^1C^7C^8$	113.8(3)
$N^4C^{20}C^{19}$	108.6(3)	$C^1C^2C^3$	120.7(4)
$C^{21}C^{20}C^{19}$	112.3(3)	$O^3C^{19}C^{13}$	107.9(3)
$O^4C^{24}N^5$	123.0(3)	$O^3C^{19}C^{20}$	109.4(3)
$O^4C^{24}C^{23}$	121.3(3)	$C^{13}C^{19}C^{20}$	113.6(3)
$N^5C^{24}C^{23}$	115.7(3)	$C^1C^6C^5$	120.1(4)
$N^4C^{23}C^{24}$	113.4(3)	$C^5C^4C^3$	119.5(4)
$N^1C^8C^9$	115.5(3)	$C^{15}C^{16}C^{17}$	118.9(4)
$N^1C^8C^7$	106.9(3)	$C^4C^3C^2$	120.3(4)
$C^9C^8C^7$	112.6(3)	$C^{18}C^{17}C^{16}$	120.3(4)
$N^1C^{11}C^{12}$	114.2(3)	$C^4C^5C^6$	120.7(4)

Table 2. Bond lengths (*d*, Å) in structure **I**

Bond	*d*	Bond	*d*
N^5C^{24}	1.332(4)	O^3C^{19}	1.404(5)
N^5N^6	1.408(4)	C^8C^9	1.525(5)
O^4C^{24}	1.232(4)	C^8C^7	1.537(4)
N^3N^2	1.413(4)	C^1C^6	1.384(6)
N^4C^{23}	1.455(4)	C^1C^2	1.384(5)
N^4C^{22}	1.462(4)	C^1C^7	1.510(5)
N^4C^{20}	1.486(4)	$C^{18}C^{17}$	1.373(6)
N^2C^{12}	1.327(4)	$C^{18}C^{13}$	1.376(6)
O^2C^{12}	1.229(4)	$C^{13}C^{14}$	1.365(5)
N^1C^{11}	1.456(4)	$C^{13}C^{19}$	1.516(5)
N^1C^{10}	1.461(4)	$C^{15}C^{16}$	1.360(7)
N^1C^8	1.490(4)	$C^{15}C^{14}$	1.388(6)
$C^{12}C^{11}$	1.518(4)	C^2C^3	1.385(6)
$C^{20}C^{21}$	1.526(5)	C^6C^5	1.394(6)
$C^{20}C^{19}$	1.532(5)	C^4C^5	1.366(8)
$C^{24}C^{23}$	1.522(5)	C^4C^3	1.374(8)
O^1C^7	1.422(5)	$C^{16}C^{17}$	1.384(7)

Table 3. Torsion angles (φ, deg) in structure **I**

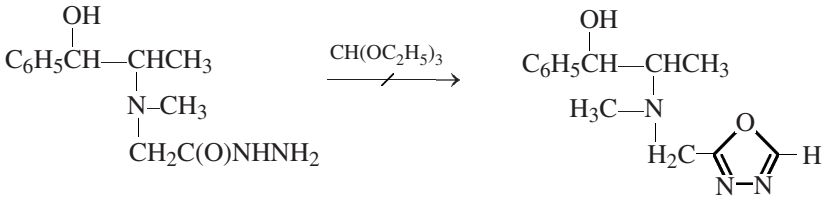
Angle	φ	Angle	φ
$N^3N^2C^{12}O^2$	6.4(5)	$C^2C^1C^7O^1$	123.1(4)
$N^3N^2C^{12}C^{11}$	–176.2(3)	$C^6C^1C^7C^8$	66.9(4)
$C^{23}N^4C^{20}C^{21}$	42.6(4)	$C^2C^1C^7C^8$	–115.9(4)
$C^{22}N^4C^{20}C^{21}$	–83.8(4)	$N^1C^8C^7O^1$	–54.3(3)
$C^{23}N^4C^{20}C^{19}$	–84.4(3)	$C^9C^8C^7O^1$	177.9(3)
$C^{22}N^4C^{20}C^{19}$	149.1(3)	$N^1C^8C^7C^1$	–174.7(3)
$N^6N^5C^{24}O^4$	–3.8(5)	$C^9C^8C^7C^1$	57.5(4)
$N^6N^5C^{24}C^{23}$	177.2(3)	$C^6C^1C^2C^3$	1.6(6)
$C^{22}N^4C^{23}C^{24}$	–72.1(4)	$C^7C^1C^2C^3$	–175.7(4)
$C^{20}N^4C^{23}C^{24}$	161.2(3)	$C^{14}C^{13}C^{19}O^3$	104.6(5)
$O^4C^{24}C^{23}N^4$	153.5(3)	$C^{18}C^{13}C^{19}O^3$	–70.5(5)
$N^5C^{24}C^{23}N^4$	–27.4(4)	$C^{14}C^{13}C^{19}C^{20}$	–133.9(4)
$C^{11}N^1C^8C^9$	–80.4(4)	$C^{18}C^{13}C^{19}C^{20}$	51.0(5)
$C^{10}N^1C^8C^9$	46.5(4)	$N^4C^{20}C^{19}O^3$	–49.8(4)
$C^{11}N^1C^8C^7$	153.5(3)	$C^{21}C^{20}C^{19}O^3$	–178.5(4)
$C^{10}N^1C^8C^7$	–79.6(3)	$N^4C^{20}C^{19}C^{13}$	–170.5(3)
$C^{10}N^1C^{11}C^{12}$	72.0(4)	$C^{21}C^{20}C^{19}C^{13}$	60.8(4)
$C^8N^1C^{11}C^{12}$	–159.7(3)	$C^2C^1C^6C^5$	–0.8(6)
$O^2C^{12}C^{11}N^1$	–158.5(3)	$C^7C^1C^6C^5$	176.4(4)
$N^2C^{12}C^{11}N^1$	23.9(4)	$C^{14}C^{15}C^{16}C^{17}$	1.9(7)
$C^{17}C^{18}C^{13}C^{14}$	1.9(7)	$C^5C^4C^3C^2$	–1.5(7)
$C^{17}C^{18}C^{13}C^{19}$	177.1(4)	$C^1C^2C^3C^4$	–0.5(7)
$C^{18}C^{13}C^{14}C^{15}$	–0.9(6)	$C^{13}C^{18}C^{17}C^{16}$	–1.0(8)
$C^{19}C^{13}C^{14}C^{15}$	–176.2(4)	$C^{15}C^{16}C^{17}C^{18}$	–0.9(8)
$C^{16}C^{15}C^{14}C^{13}$	–0.9(7)	$C^3C^4C^5C^6$	2.2(7)
$C^6C^1C^7O^1$	–54.1(4)	$C^1C^6C^5C^4$	–1.1(7)

tives. In the first molecule of the crystal they are as follows: $\tau(C^6C^1C^7O^1)$ –54.2°, $\omega(O^1C^7C^8N^1)$ –54.3°, and $\chi(C^7C^8N^1C^{10})$ –79.6°. The torsion angles in the second molecule are as follows: $\tau(C^{18}C^{13}C^{19}O^3)$ –70.4°, $\omega(O^3C^{19}C^{20}N^4)$ –49.8°, and $\chi(C^{19}C^{20}N^4C^{22})$ 149.2°. The difference in the χ angles is explained by the formation of the following intramolecular hydrogen bonds: N^2–H···H–N^6 (*x, y, z*) [$r(N^2\cdots N^6)$ 2.99 Å), N^3–H···H– (*x, y, z*) [$r(N^3\cdots N^5)$ 2.97 Å)], N^3–H···O^3 (*x, y, z*) [$r(N^3\cdots O^3)$ 2.99 Å, $r(HN^3A\cdots O^3)$ 2.8 Å), and N^6–H···O^1 (*x, y, z*) [$r(N^6\cdots O^1)$ 3.04 Å, $r(HN^6A\cdots O^1)$ 2.8 Å). Hydrogen bonding stabilizes the molecular conformation and forms infinite tapes along the 2_1 [0, 0, *y*] axis.

Modification of hydrazides under the action of appropriate reagents is known to be a useful method for attenuating their toxicity and synthesizing new dinitrogenous heterocycles. To correlate the biologic activity of hydrazide **I** with its structure and synthesize 1,3,4-oxadiazoles on the basis of this compound, we performed its condensation with orthoformic ester.

Orthoformic ester is often used in heterocyclic synthesis [8]. The use of orthoformic ester in the synthesis of 1,3,4-oxadiazoles from carboxylic acid hydrazides has been described [9]. The condensation reaction was carried out by refluxing hydrazide **I** with

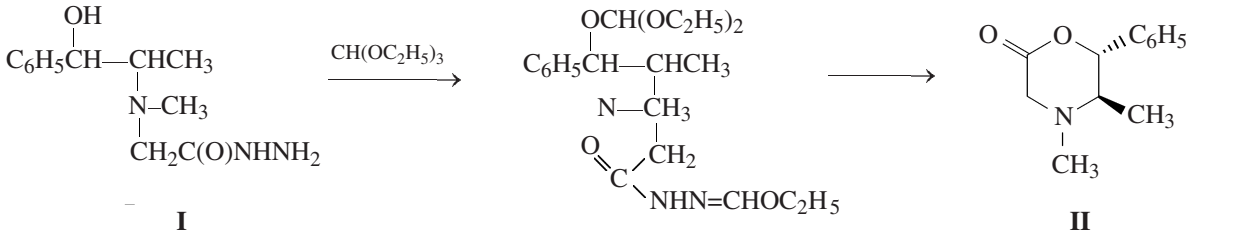
a 3-fold molar excess of orthoformic acid for 8–10 h. Were the hydroxy group in the hydrazide molecule inert, the reaction would afford a substituted 1,3,4-oxadiazole by the following scheme:



However, we isolated from the reaction mixture (5*S*,6*S*)-4,5-dimethyl-6-phenylmorpholin-2-one (**II**) which we used as the parent compound in the synthesis of hydrazide **I**.

The formation of morpholone **II** was proved by comparing its physicochemical constants, chemical transformations, and ^{1}H NMR spectrum with those of the same compound synthesized earlier. The steric configuration of the resulting morpholone is the same as that of the parent alkaloid.

Morpholone **II** is formed through intermediate formation of hydrazones and transesterified substituted esters, followed by intramolecular nucleophilic attack of the alkoxyl oxygen on the electron-deficient carbonyl carbon, resulting in ring closure.



I **II**

The ^{1}H NMR spectrum of compound **II** contains a doublet signal of CH–CH_3 methyl protons at 0.23 ppm (*J* 5.0 Hz). The singlet at δ 1.65 ppm belongs to the *N*-methyl group. The C*H*–CH_3 methine proton appears as a multiplet in the region of 2.32–2.50 ppm, and the C*H*–O proton, as a doublet at δ 5.17 ppm. Aromatic protons resonate in the region of 7.03 ppm. Note that the NCH_2C(O) methylene protons are nonequivalent (δ_{H^a} 2.72 and δ_{H^c} 3.37 ppm) and appear as two doublets with a coupling constant of 14.2 Hz.

EXPERIMENTAL

The ^{1}H NMR spectra are recorded on a Tesla BS-597 instrument at 80 MHz, solvent C_6D_6, internal reference HMDS. The melting point was measured on a Boetius hot stage.

X-Ray diffraction experiment. The unit cell parameters and intensities of 2783 unique reflections of compound **I** were measured at 20oC on a Bruker-P4 automatic four-circle difractometer (MoK_α radiation, graphite monochromator, θ/2θ scanning, 2θ < 52°). The crystals are monoclinic, *a* 5.6892(5), *b* 35.363(2), *c* 6.8257(5) Å, β 112.426(5)°, *V* 1269.37(17) Å^3, d_{calc} 1.289 g cm^{-3}, *Z* 4 ($C_{24}H_{38}N_6O_4$). Space group $P2_1$.

The calculations involved 2535 reflections with $I > 2\sigma(I)$. The structure was decoded by the direct method using the SHELXS-97 program and refined by full-matrix least squares anisotropically for nonhydrogen atoms. Hydrogen atoms were located geometrically and fixed by the rider model. Final divergence factors: *R* 0.0477 and WR_2 0.1356. Geometry refinement was performed using the SHELXL-97 program. The coordinates of nonhydrogen atoms are listed in Table 4.

(5*S*,6*S*)-4,5-Dimethyl-6-phenylmorpholin-2-one (II). Orthoformic ester, 2.22 g (0.015 mol), was added to 1.18 g (0.005 mol) of hydrazide **I**. The mixture was

Table 4. Atomic coordinates ($\times 10^4$, for $H \times 10^3$) in structure **I** in cell fractions

Atom	*x*	*y*	*z*
N^5	5495(5)	2436(1)	5532(4)
O^4	3668(5)	2566(1)	2042(4)
N^3	7648(6)	2394(1)	10246(4)
N^4	3265(5)	3058(1)	6508(4)
N^2	8332(5)	2018(1)	10015(4)
O^2	10307(5)	1905(1)	13511(4)
N^1	10432(5)	1387(1)	8995(4)
N^6	6170(6)	2062(1)	5270(4)
C^{12}	9703(6)	1805(1)	11656(5)
C^{20}	3434(6)	3443(1)	7433(5)
C^{24}	4231(5)	2661(1)	3902(5)
O^1	6686(6)	1206(1)	5169(5)
O^3	7443(7)	3241(1)	10011(6)
C^{23}	3547(6)	3050(1)	4477(5)
C^8	10221(6)	989(1)	8236(5)
C^{11}	10413(6)	1416(1)	11117(5)
C^1	8436(6)	616(1)	4776(5)
C^{18}	5471(9)	3954(1)	11358(7)
C^{13}	6656(7)	3897(1)	9961(6)
C^{15}	8898(10)	4482(1)	11191(8)
C^{14}	8374(8)	4163(1)	9913(7)
C^{22}	932(8)	2866(1)	6367(8)
C^{10}	12605(7)	1589(1)	8858(6)
C^7	9010(7)	1002(1)	5803(5)
C^2	9679(8)	496(1)	3495(6)
C^{19}	6244(7)	3540(1)	8644(6)
C^9	12684(8)	761(1)	9060(7)
C^6	6605(8)	383(1)	5011(7)
C^4	7206(10)	–72(1)	2639(7)
C^{21}	2020(9)	3752(1)	5868(7)
C^{16}	7657(9)	4540(1)	12519(7)
C^3	9058(11)	154(1)	2428(8)
C^{17}	5938(10)	4271(1)	12612(7)
C^5	6019(9)	38(1)	3948(8)

refluxed for 8 h, after which it was diluted with chloroform, filtered to remove a little precipitate, and evaporated in a vacuum. The residue was subjected to column chromatography on SiO_2, eluent benzene, and recrystallized from petroleum ether to isolate compound **II**, mp 55–56°C.

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