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Synthesis and Structure of Dithiocarbamates Derived from Ephedrine Alkaloids

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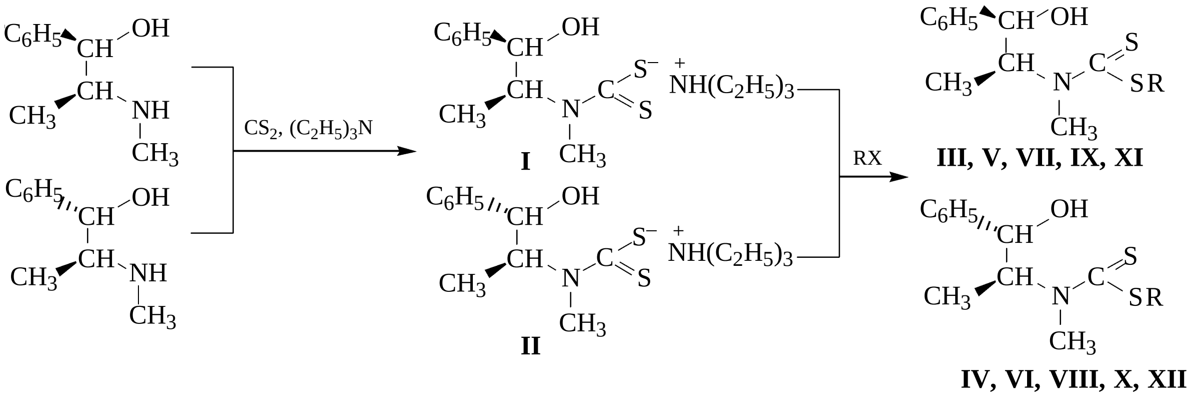
Abstract—Products of the reactions of *l*-ephedrine and *d*-pseudoephedrine with saturated and unsaturated alkyl halides and carbon disulfide in the presence of triethylamine were obtained. Methyl *N*-*l*-ephedrinodithiocarbamate was studied by X-ray diffraction.

Derivatives of dithiocarbamic acids exhibit a broad-spectrum physiologic activity [1]. They were found to act as fungicides, herbicides, insecticides, acaricides, zoocides, nematocides, growth regulators, bactericides, etc. Such dithiocarbamic acid derivatives as Carbathion, Cineb, Vegadex and Cyram, have found practical application in agriculture as pesticides.

Proceeding with search for biologically active compounds among alkaloids, we have synthesized *N*-*l*-ephedrino(*d*-pseudoephedrino)dithiocarbamates **III**–**XII**. The synthesis involved one stage, namely, reaction of *l*-ephedin or *d*-pseudoephedrine with carbon disulfide and organic halide in chloroform in the presence of triethylamine. The reaction involves intermediate formation of triethylammonium *N*-*l*-ephedrino(*d*-pseudoephedrino)dithiocarbamate (**I** or **II**, respectively) whose alkylation with alkyl halides provides final products **III**–**XII**.



R = CH$_3$ (**III, IV**), C$_2$H$_5$ (**V, VI**), C$_3$H$_7$ (**VII, VIII**), CH$_2$=CHCH$_2$ (**IX, X**), CH≡CCH$_2$ (**XI, XII**).

The IR spectra of compounds **III**–**XII** have an absorption band at 1240–1205 cm^{-1}, characteristic of the C=S group, as well as absorption bands at 1635–1625 (**VI**, **XI**) and 2120–2100 cm^{-1} (**VII, XII**), assignable to C=C and C≡C vibrations.

Bond lengths and angles in molecule **III** are close to normal [2]. The $\tau(C^6C^1C^7O^1)$, $\omega(O^1C^7C^8N^1)$, $\chi(C^{10}N^1C^8C^7)$, and $\Psi(HO^1C^7C^8)$ torsion angles (Table 2) that characterize the molecular conformation of ephedrine and its derivatives are –19.7°, –68.2°, 86.2°, and 164.5°, respectively. All torsion angles, except for χ, are close to the corresponding angles in ephedine hydrochloride (**XIII**) [3] (τ –21.4°, ω –70.5°, χ –170.0°, and Ψ 175.0°) and ephedine thiocyanate (**XIV**) [4] (τ –23.6°, ω –62.2°, χ –161.9°, and Ψ

Table 1. Yields, physicochemical constants, and elemental analyses of dithiocarbamates **III**–**XII**

Comp. no.	Yield, %	mp, °C	n_D^{20}	R_f [a]	Found, %		Formula	Calculated, %	
					C	N		C	N
III	75	96–97	–	0.63	56.16	5.05	$C_{12}H_{17}NOS_2$	56.47	5.49
IV	68	94–95	–	0.81	56.29	5.35	$C_{12}H_{17}NOS_2$	56.47	5.49
V	66	–	1.6041	0.84	57.46	5.10	$C_{13}H_{19}NOS_2$	57.99	5.20
VI	71	–	1.6090	0.85	57.39	5.15	$C_{13}H_{19}NOS_2$	57.99	5.20
VII	68	172–173	–	0.83	59.28	4.90	$C_{14}H_{21}NOS_2$	59.36	4.95
VIII	67	169–170	–	0.82	59.32	4.93	$C_{14}H_{21}NOS_2$	59.36	4.95
IX	82	–	1.6061	0.83	59.25	4.55	$C_{14}H_{19}NOS_2$	59.79	4.98
X	65	–	1.6010	0.75	59.78	4.83	$C_{14}H_{19}NOS_2$	59.79	4.98
XI	80	–	1.6012	0.78	60.11	5.00	$C_{14}H_{17}NOS_2$	60.21	5.02
XII	67	–	1.6023	0.80	60.05	5.04	$C_{14}H_{17}NOS_2$	60.21	5.02

[a] Eluent benzene–acetone, 1:1.

161°). The specified value of the χ angle in structure **III** relates to such conformation along the C^8–N^1 bond, that favors strong nonbonded repulsion of the methyl groups at C^8 and N^1 (C^9–C^{10} distance 2.887 Å).

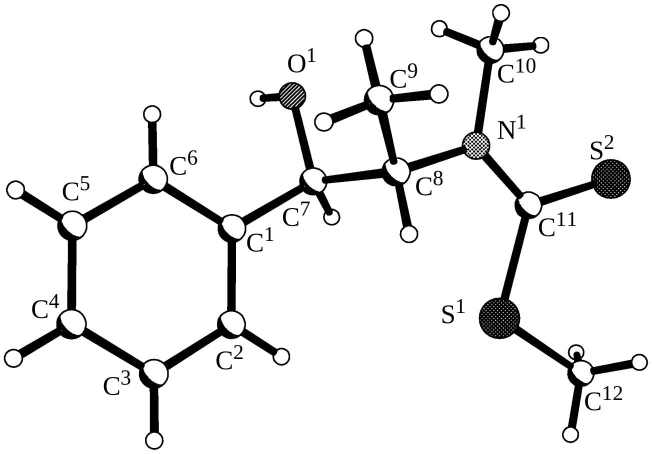


Fig. 1. Molecular structure of methyl *N*-*l*-ephedrinodithiocarbamate (**III**).

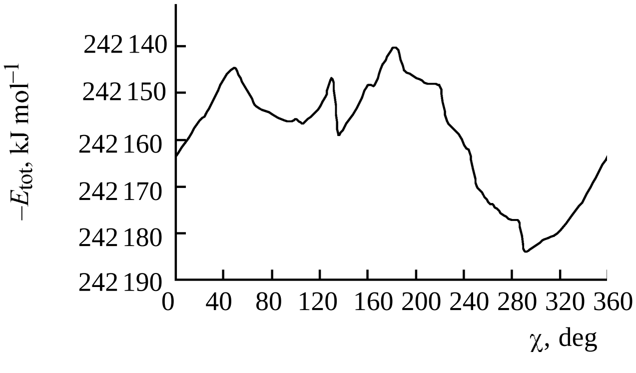


Fig. 2. Dependence of the total energy of molecule **III** on coordinate along the C^8–N^1 bond.

Table 2. Torsion angles in structure **III**

Angle	ω, deg	Angle	ω, deg
$C^6C^1C^2C^3$	–0.8(5)	$C^{10}N^1C^8C^9$	–39.6(3)
$C^7C^1C^2C^3$	179.1(3)	$C^{11}N^1C^8C^7$	–90.4(3)
$C^1C^2C^3C^4$	1.1(5)	$C^{10}N^1C^8C^7$	86.2(3)
$C^2C^3C^4C^5$	–1.1(6)	$O^1C^7C^8N^1$	–68.2(2)
$C^3C^4C^5C^6$	0.9(6)	$C^1C^7C^8N^1$	167.8(2)
$C^4C^5C^6C^1$	–0.6(5)	$O^1C^7C^8C^9$	56.9(3)
$C^2C^1C^6C^5$	0.6(5)	$C^1C^7C^8C^9$	–67.2(3)
$C^7C^1C^6C^5$	–179.4(3)	$C^{10}N^1C^{11}S^2$	4.3(4)
$C^6C^1C^7O^1$	–19.7(4)	$C^8N^1C^{11}S^2$	–179.12(2)
$C^2C^1C^7O^1$	160.4(3)	$C^{10}N^1C^{11}S^1$	–174.9(2)
$C^6C^1C^7C^8$	101.5(3)	$C^8N^1C^{11}S^1$	1.6(3)
$C^2C^1C^7C^8$	–78.4(3)	$C^{12}S^1C^{11}N^1$	–178.1(3)
$C^{11}N^1C^8C^9$	143.8(3)	$C^{12}S^1C^{11}S^2$	2.6(3)

Actually, according to quantum-chemical calculations, three conformations along the C^8–N^1 bond are possible (χ 90°, 135°, and 295°, Fig. 2). The last minimum is global and corresponds to *anti* orientation of the C^9H_3 and $C^{10}H_3$ groups. The stabilization of the energetically less favored conformer of molecule **III** in crystal is explained by the formation of an intermolecular H bond O^1–S (*x*, *y*, *z*) [$O^1 \cdots S^2$ (–*x*, 1.5 + *y*, –*z*)] (O···S 3.243 Å, H···S 2.34 Å, ∠OHS 161.5°). The hydrogen bond stabilizes this conformation and form endless tapes along the 2_1 axis [0, 0, *y*] (Fig. 3).

EXPERIEMNTAL

The IR spectra were obtained on a UR-20 instrument in KBr. The melting point was measured on a Boëtius hot stage.

Table 3. Atomic coordinates (Å × 10^4, for hydrogen atoms Å × 10^3) in structure **III** in cell fractions

Atom	x	y	z	Atom	x	y	z
S^1	1633(1)	9476(1)	3628(1)	C^6	2923(4)	2850(5)	1331(2)
S^2	5101(1)	11347(1)	4442(1)	C^7	3729(3)	5466(4)	2655(2)
O^1	5517(3)	4688(4)	2723(2)	C^8	3831(3)	7470(4)	2175(2)
N^1	4837(3)	8782(4)	2908(2)	C^9	4650(4)	7452(5)	1104(2)
C^1	2370(3)	4215(4)	2027(2)	C^{10}	6839(4)	8849(6)	2891(3)
C^2	511(4)	4427(5)	2142(2)	C^{11}	4017(4)	9823(4)	3610(2)
C^3	–743(4)	3319(6)	1565(3)	C^{12}	953(7)	11110(8)	4605(4)
C^4	–150(5)	1957(6)	877(3)	HO^1	565(8)	363(11)	316(5)
C^5	1659(5)	1744(6)	761(3)				

X-ray diffraction experiment. The unit cell parameters and the intensities of 1712 unique reflections were measured on a Bruker-P4 (MoK_α radiation, graphite monochromator, θ/2θ scanning 2θ ≤ 56°). Monoclinic crystals, *a* 3630(7), *b* 7.0084(7), *c* 12.8127(12) Å; β 93.620(8)°, *V* 659.85(11) Å^3, d_{calc} 1.285 g cm^{-3}, *Z* 2, $C_{12}H_{17}NOS_2$, space group $P2_1$. The structure was solved by the direct method and refined by full-matrix least squares in the anisotropic approximation for non-hydrogen atoms. Hydrogen atoms, except for the OH hydrogen, were located geometrically by the rider model. The calculations included 1659 reflections with $I > 2\sigma(I)$. Absorption correction was performed using the Ψ-curves. The final divergence factors were *R* 0.042 and R_W 0.117. The structure was solved and refined by the SHELXS-97 and SHELXL-97. The atomic coordinates are listed in Table 3. The conformational calculations for methyl *N*-*l*-ephedrinodithiocarbamate (**III**) were performed using the MOPAC-7 program with full geometry optimization.

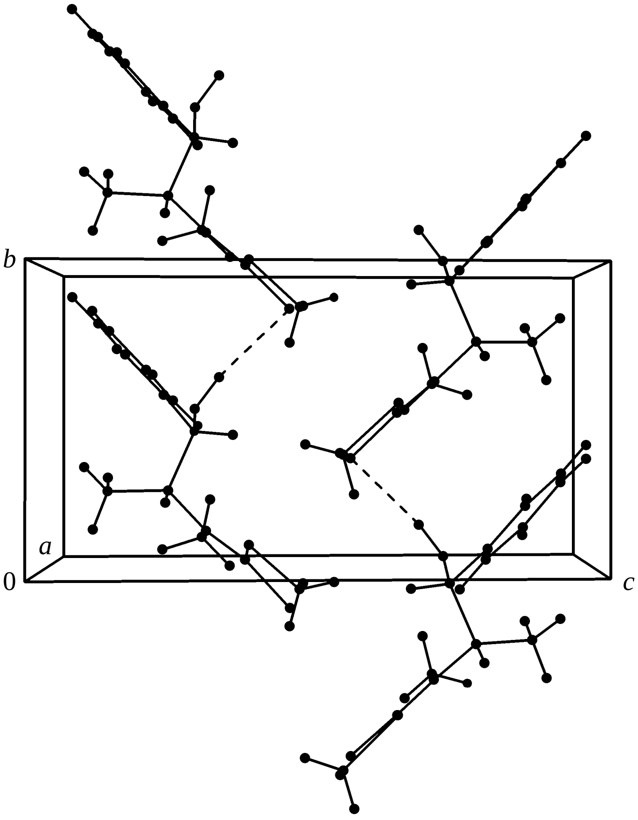


Fig. 3. Crystal packing of molecules **III**.

Methyl *N*-*l*-ephedrinodithiocarbamate (III). To a solution of 1 g of *l*-*l*-ephedrine and 0.61 g of triethylamine in 10 ml of chloroform, we added dropwise with stirring and cooling (0–5°C) to 0.45 g of carbon disulfide, after which 0.61 g of triethylamine and, with causion, 0.85 g of methyl iodide. The reaction mixture was stirred for 30 min at room temperature and then washed twice with water and dried with K2CO3. The solvent was removed, and the residue was passed through a column of silica gel, eluent benzene, to obtain 2.3 g (75%) of compound **III**, mp 96–97°C.

Thioesters **IV**–**XII** were prepared in a similar way.

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