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Synthesis and Steric Structure of [2-(3-Pyridyl)piperidino](2-vinyloxyethylamino)methanethione

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Abstract—Thioureas derivatives were synthesized on the basis of anabasine, piperidine, and morpholine, and 2-vinyloxyethyl isothiocyanate. X-Ray diffraction was used to determine the steric structure of [2-(3-pyridyl)piperidino](2-vinyloxyethylamino)methanethione.

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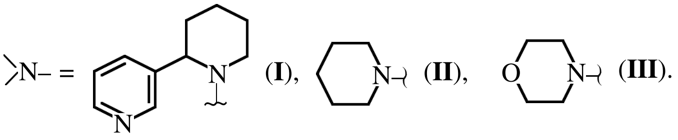
The interest in thiourea and its derivatives is explained by their diverse biologic activity. Specifically, these compounds have exhibited valuable pharmacologic properties [1], as well as insecticide [2], fungicide [3], and antitubercular activity [4].

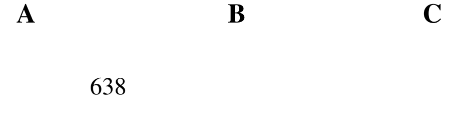
Previously we made use of the reaction of anabasine with dialkoxyphosphoryl isothiocyanates to synthesize a series of thioureas that exhibited high antimicrobial and insecticide activity and low toxicity in screening tests [5, 6]. To reveal structure–bioactivity interrelationship in this series of compounds, we set ourselves the task to synthesize new thiourea derivatives on the basis of mentioned compounds.

The condensation of 2-vinyloxyethyl isothiocyanate with heterocyclic amines was performed in alcohols or acetone at equimolar reactant ratios.

$$>NH + CH_2{=}CHOC_2H_4N{=}C{=}S \longrightarrow \underset{\textbf{I–III}}{CH_2{=}CHOC_2H_4NHC(S)N<}$$



The addition of amines to isothiocyanates classed with heterocumulenes presumably occurs by the following scheme: Nucleophile (amine with a lone electron pair) attacks the electron-deficient center in isothiocyanate, viz. the N=C=S carbon atom, to form dipolar intermediate **A**. Proton transfer from nitrogen to sulfur gives rise to isothiourea **B** that readily isomerizes into a more stable form, thiourea **C**.



$$RN{=}C{=}S + >NH \longrightarrow \underset{\textbf{A}}{RN{=}C\begin{smallmatrix} S^- \\ \overset{+}{N}H< \end{smallmatrix}} \rightleftarrows \underset{\textbf{B}}{RN{=}C\begin{smallmatrix} SH \\ N< \end{smallmatrix}} \longrightarrow \underset{\textbf{C}}{RNH{-}\underset{\underset{S}{\|}}{C}{-}N<}$$

The reaction products are colorless crystals (**I**, **III**) or a light yellow oil (**II**). Their composition, structure, and individuality were proved by elemental analysis, ^{1}H NMR and IR spectroscopy, and TLC. The IR spectra of compounds **I**–**III** contain C=S and C–O–C absorption bands at 1550–1525 and 1205–1190 cm^{-1}, and the C=C bond appears at 1635–1620 cm^{-1}.

To establish the steric structure of [2-(3-pyridyl)-piperidino](2-vinyloxyethylamino)methanethione (**I**), we made use of X-ray diffraction analysis. The general view of molecule **I** is given in the figure.

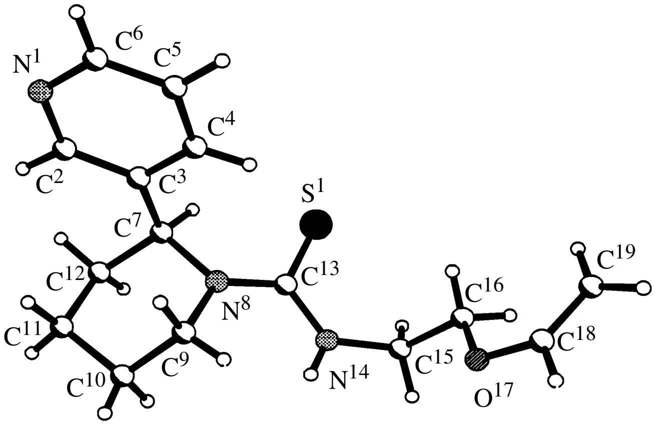
The bond lengths and angles are close to normal. The piperidine ring adopts a *chair* conformation (ΔC_s^8 2.2 Å), like in *O,O*-diethyl (3-pyridyl)piperidino thiophosphate (**IV**) and *O,O*-diisopropyl (3-pyridyl)-piperidino thiophosphate (**V**) [7]. The pyridine ring is planar within ±0.009 Å. The pyridine ring is arranged axially ($C^3C^7N^8C^9$ torsion angle 72.4°) with respect to the piperidine ring, which distinguishes compound **I** from **IV** and **V**, where this ring is equatorial. In our opinion, this is explained by the nonbonded repulsion between the bulky substituent on N^8 and the pyridine ring.

EXPERIMENTAL

The IR spectra were measured on an Avatar-320 instrument in KBr pellets and thin films. The ^{1}H NMR spectra of C_6D_6 solutions were recorded on a Varian Mercury-300 instrument at 300 MHz. The melting points were measured on a Boetius hot stage.

X-ray diffraction experiment. The unit cell parameters and the intensities of 1721 unique reflections were measured on a Syntex-P21 diffractometer (CuK_α radiation, graphite monochromator, $\theta/2\alpha$ scanning, $2\theta \le 138.8°$). Rhombic crystals, *a* 7.509(2), *b* 13.461(3), *c* 15.667(3) Å; *V* 1583.6(6) Å^3, d_{calc} 1.222 g cm^{-3}, *Z* 4. $C_{15}H_{21}N_3OS$. Space group $P2_12_12_1$. The structure was solved by the direct method and refined by full-matrix least squares in the anisotropic approximation for nonhydrogen atoms. Hydrogen atoms were revealed by difference synthesis in the anisotropic approximation. The calculations involved 1641 reflections with $I > 2\sigma(I)$. Final divergence factors: *R* 0.037 and wR_2 0.098. The structure was solved and refined using the SHELXS-97 and SHELXL-97 programs. The atomic coordinates are available from the authors.

[2-(3-Pyridyl)piperidino](2-vinyloxyethylamino)-methanethione (I). To a solution of 16.7 g of anabasine in 20 ml of benzene, a solution of 12.9 g of 2-vinyloxyethyl isothiocyanate in 25 ml of absolute benzene was added dropwise with stirring at room temperature. The reaction mixture was then stirred at room temperature for 1 h and at 35–40°C for 2 h, and the solvent was distilled off. Yield 75–83%. ^{1}H NMR spectrum, δ, ppm: 8.40 d (1H, CH?, 3J 4.8 Hz), 7.09 d.d (1H, CH$^\beta$, ^3J 7.4 Hz), 7.52 d (1H, CH$^\gamma$), 1.32–1.58 m (6H, ring CH$_2$), 3.16 t (2H, NCH$_2$), 3.42 t (2H, CH$_2$O), 6.35 q (1H, CHO), 3.86 d.d (2H, CH=C*H*$_2$, *J* 5.7 Hz). Found, %: C 61.87; H 7.19; N 14.49. $C_{15}H_{21}N_3OS$. Calculated, %: C 61.82; H 7.26; N 14.42.



Molecular structure of [2-(3-pyridyl)piperidino](2-vinyloxyethylamino)methanethione (**I**).

Piperidino(2-vinyloxyethylamino)methanethione (II) was prepared in a similar way as a light yellow oily material. Yield 87–90%. ^{1}H NMR spectrum, δ, ppm: 1.57–2.12 m (10H, ring CH$_2$), 3.21 t (2H, NCH$_2$), 3.44 t (2H, CH$_2$O), 6.37 q (1H, CHO), 3.89 d.d (2H, CH=C*H*$_2$, *J* 5.6 Hz). Found, %: C 56.11; H 8.41; N 13.15. $C_{10}H_{18}N_2OS$. Calculated, %: C 56.04; H 8.47; N 13.07.

Morpholino(2-vinyloxyethylamino)methanethione (III) was prepared in a similar way as colorless crystals. Yield 79–83%, mp 56-58°C. ^{1}H NMR spectrum, δ, ppm: 2.98 m (4H, NCH$_2$), 3.15 m (4H, OCH$_2$), 3.19 t (2H, NCH$_2$), 3.40 t (2H, CH$_2$O), 6.38 q (1H, CHO), 3.87 d.d (2H, CH=C*H*$_2$, *J* 5.6 Hz). Found, %: C 50.04; H 7.38; N 12.99. $C_9H_{16}N_2O_2S$. Calculated, %: C 49.98; H 7.46; N 12.95.

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