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A SIMPLE AND EFFECTIVE SYNTHETIC APPROACH TO PYRIDO[2,1-*b*]THIAZINES

V. D. Dyachenko[1] and A. N. Chernega[2]

The reaction of partially hydrogenated 2-pyridinethiols with 1,3-dibromopropane gives substituted pyrido[2,1-b][1,3]thiazines. The structure of 7,9-dicyano-6-oxo-3,4,6,7-tetrahydro-2H-spirocyclohexane-1',8-pyrido[2,1-b][1,3]thiazine was solved by X-ray diffraction structural analysis.

Keywords: 1,3-dibromopropane, pyrido[2,1-*b*][1,3]thiazines, partially hydrogenated 2-pyridinethiols, alkylation, X-ray diffraction structural analysis.

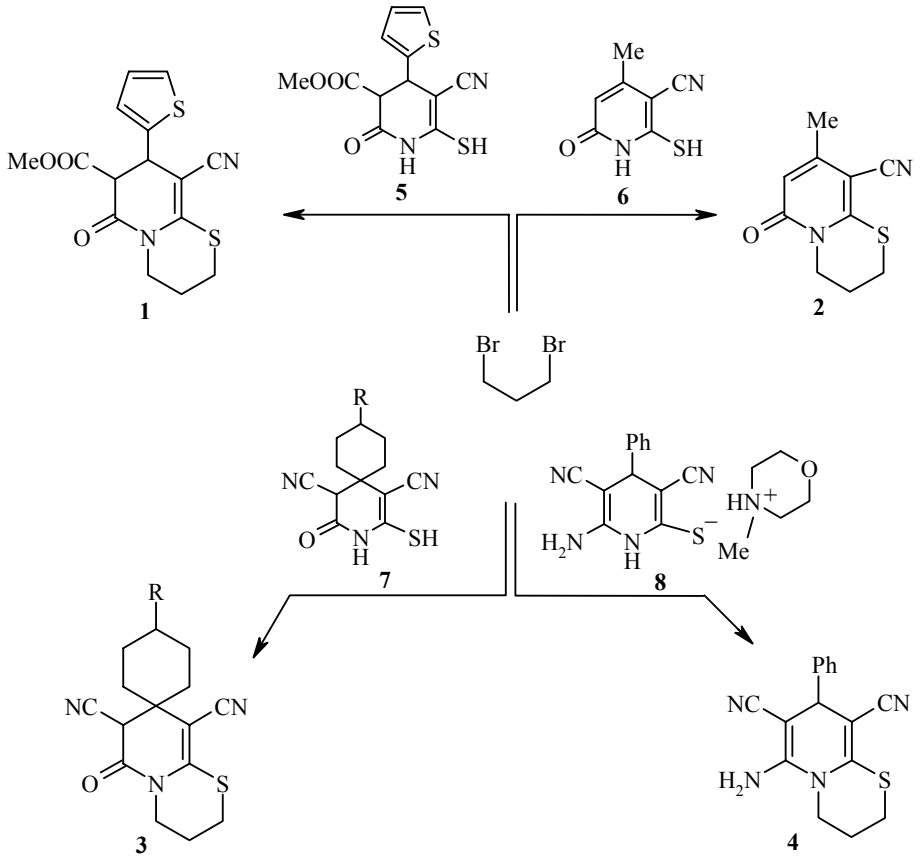
The reported methods for the synthesis of substituted pyrido[2,1-*b*][1,3]thiazines are based on the reaction of 2-pyridinethiol with β-bromopropionic acid [1], reaction of tetrahydro-2-pyridinethione with benzylidenemalononitrile [2], reaction of 3,4-dihydropyridine-2(1H)-thione with epichlorhydrin [3], and acylation of 3,4-dihydro-2(1H)-pyridinethione with cinnamyl chloride [4].

In the present work, we have found a simple and efficient method for preparing previously unreported substituted, partially hydrogenated pyrido[2,1-*b*][1,3]thiazines **1-4** consisting of the regioselective alkylation of 2-pyridinethiols **5-7** and 2-pyridinethiolate **8** by 1,3-dibromopropane in DMF in the presence of aqueous KOH.

An X-ray diffraction structural analysis of **3a** was carried out to establish the regioselectivity of the alkylation of 2-pyridinethiols **5-8** by 1,3-dibromopropane. We found that there are two symmetrically independent molecules **A** and **B** in the crystal of this compound. The major geometrical parameters of these molecules are given in Table 1, while a general view of these molecules is given in Figs. 1 and 2. The bond lengths and bond angles in **3a(A)** and **3a(B)** are virtually identical. In particular, $N_{(1)}$ in both molecules has planar trigonal configuration: the sum of the bond angles at this atom is 359.0(6)° in **3a(A)** and 359.9(6)° in **3a(B)**. In both molecules, the $N_{(1)}$–$C_{(4)}$ and $N_{(1)}$–$C_{(8)}$ bonds are markedly shortened relative to the standard value for the pure N(sp^2)–C(sp^2) single bond (1.45 Å) [5] due to $n(N_{(1)})$–$\pi(C_{(4)}=C_{(5)})$ and $n(N_{(1)})$–$\pi(C_{(8)}=O_{(1)})$ conjugation. On the other hand, the conformations of these molecules differ considerably, as indicated both by the endocyclic torsion angles (Table 2) and the modified Kramer-Pople parameters, *S*, θ, and Ψ [6]. Thus, while the $S_{(1)}N_{(1)}C_{(1)}C_{(2)}C_{(3)}C_{(4)}$ heterocycle in molecule **A** has *chair* conformation ($S = 0.99$, $\theta = 12.2°$, $\psi = 8.8°$), this heterocycle in molecule **B** has *twist-boat* conformation ($S = 0.82$, $\theta = 65.0°$, $\Psi = 10.0°$). The central $N_{(1)}C_{(4)}C_{(5)}C_{(6)}C_{(7)}C_{(8)}$ ring in molecule **A** has close to *half-boat* conformation ($S = 0.71$, $\theta = 53.2°$, $\Psi = 24.2°$), while this ring in molecule **B** has a conformation intermediate between *half-boat* and *half-chair* ($S = 0.77$, $\theta = 64.8°$, $\Psi = 15.7°$). Furthermore, the arrangement of the endocyclic substituents differs significantly. Thus,

[1]Taras Shevchenko Lugansk National Pedagogical University, Lugansk 91001, Ukraine; e-mail: dvd_lug@online.lg.ua. [2]Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Kiev 02094, Ukraine. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1428-1433, September, 2007. Original article submitted December 5, 2006.

while the $C_{(8)}=O_{(1)}$ and $C_{(7)}–C_{(14)}≡N_{(2)}$ groups in molecule **B** have *cis* orientation relative to the $C_{(7)}–C_{(8)}$ bond (the $O_{(1)}–C_{(8)}–C_{(7)}–C_{(14)}$ torsion angle is 9.1°), this torsion angle in molecule **A** is –104.6°. Only the cyclohexane ring in both independent molecules has identical *chair* conformation though the orientation of this ring relative to the bicyclic $S_{(1)}N_{(1)}C_{(1)}C_{(2)}C_{(3)}C_{(4)}C_{(5)}C_{(6)}C_{(7)}C_{(8)}$ system in molecules **A** and **B** differs significantly: the $C_{(10)}C_{(11)}C_{(12)}$ cyclohexane "corner" is twisted toward the $C_{(5)}–C_{(15)}≡N_{(3)}$ substituent, while it is twisted in the opposite direction in molecule **B**.



3, **7** **a** R = H, **b** R = Me

Thus, our X-ray diffraction structural analysis showed that two conformers exist in the crystal of **3a**. This phenomenon is not uncommon in modern crystallography.

EXPERIMENTAL

A monocrystal of **3a** was rolled to give spherical form with diameter 0.38 mm. The X-ray diffraction structural analysis was carried out at room temperature on an Enraf-Nonius CAD-4 automatic four-circle diffractometer using MoKα radiation, $\lambda = 0.71069$ Å, relative scanning rate $2\theta/\omega = 1.2$, $\theta_{max} = 25°$, sphere segment $0 \le h \le 19$, $-13 \le k \le 13$, $-16 \le k$ 16. A total of 5152 reflections were measured, of which 4811 were symmetrically independent ($R_{int} = 0.020$). The unit cell parameters of triclinic crystals of **3a** are as follows: $a = 9.372(3)$, $b = 11.758(3)$, $c = 13.892(4)$ Å, $\alpha = 76.78(2)$, $\beta = 86.06(2)$, $\gamma = 74.26(2)°$, $V = 1434.5(7)$ Å^3, $M = 287.38$, $Z = 4$ (two independent molecules), $d_{calc} = 1.33$ g/cm^3, $\mu = 2.14$ cm^{-1}, $F(000) = 320.3$, space group $P\bar{1}$ (N 2). The structure was solved by the direct method and refined by the method of least squares in the

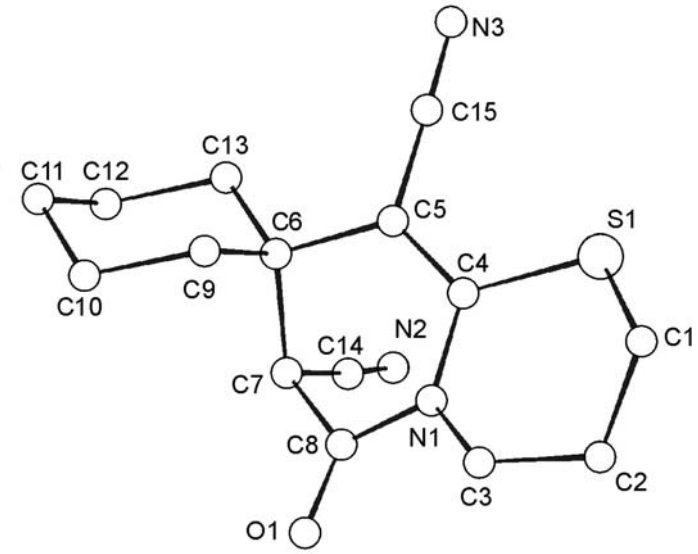


Fig. 1. General view of molecule **3a(A)** with numbering of the atoms
(the hydrogen atoms are not shown).

full-matrix anisotropic approximation using the CRYSTALS program package [7]. A total of 3142 reflections with $I > 3(I)$ were used in the refinement (361 refined parameters, reflections per parameter 8.7). All the hydrogen atoms were found in the electron density map and included in the refinement with fixed positional and temperature parameters. Absorption was taken into account using the azimuthal scanning method [8]. The Chebisov weighting scheme [9] was used in the refinement with five parameters: 1.35, 1.53, 1.34, 0.48, and 0.28. The final $R = 0.047$ and $R_w = 0.049$, GOOF = 1.155. The coordinates of the non-hydrogen atoms may be obtained from the authors.

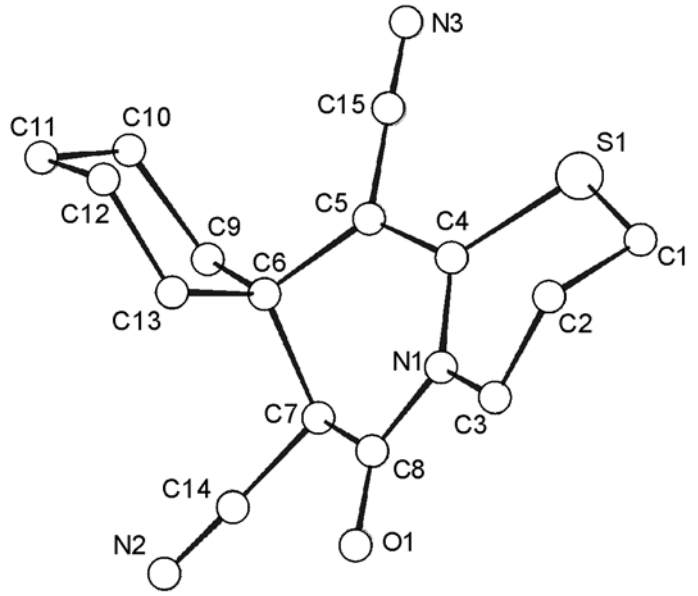


Fig. 2. General view of molecule **3a(B)** with numbering of the atoms
(the hydrogen atoms are not shown).

TABLE 1. Major Bond Lengths (*d*) and Valence Angles (ω) in the Two Symmetrically Independent Molecules **A** and **B** in **3a**

Bond	*d*, Å		Angle	ω, deg	
	A	**B**		**A**	**B**
$S_{(1)}$–$C_{(1)}$	1.809(4)	1.815(4)	$C_{(1)}$–$S_{(1)}$–$C_{(4)}$	102.6(2)	102.9(2)
$S_{(1)}$–$C_{(4)}$	1.759(3)	1.761(3)	$C_{(3)}$–$N_{(1)}$–$C_{(4)}$	121.2(2)	123.4(2)
$C_{(1)}$–$C_{(2)}$	1.506(5)	1.507(6)	$S_{(1)}$–$C_{(1)}$–$C_{(2)}$	112.0(2)	112.0(3)
$C_{(2)}$–$C_{(3)}$	1.490(5)	1.493(5)	$C_{(1)}$–$C_{(2)}$–$C_{(3)}$	112.6(3)	111.6(4)
$N_{(1)}$–$C_{(3)}$	1.481(4)	1.485(4)	$N_{(1)}$–$C_{(3)}$–$C_{(2)}$	113.8(3)	113.7(3)
$N_{(1)}$–$C_{(4)}$	1.406(3)	1.405(4)	$S_{(1)}$–$C_{(4)}$–$N_{(1)}$	119.0(2)	119.8(2)
$N_{(1)}$–$C_{(8)}$	1.379(4)	1.371(4)	$C_{(4)}$–$N_{(1)}$–$C_{(8)}$	120.3(2)	120.2(2)
$C_{(4)}$–$C_{(5)}$	1.348(4)	1.344(4)	$N_{(1)}$–$C_{(4)}$–$C_{(5)}$	121.1(2)	120.4(2)
$C_{(5)}$–$C_{(6)}$	1.529(4)	1.534(4)	$C_{(4)}$–$C_{(5)}$–$C_{(6)}$	121.0(2)	121.2(2)
$C_{(6)}$–$C_{(7)}$	1.556(4)	1.562(4)	$C_{(5)}$–$C_{(6)}$–$C_{(7)}$	104.5(2)	102.6(2)
$C_{(7)}$–$C_{(8)}$	1.539(4)	1.526(4)	$C_{(6)}$–$C_{(7)}$–$C_{(8)}$	109.6(2)	109.7(2)
			$N_{(1)}$–$C_{(8)}$–$C_{(7)}$	115.9(2)	115.2(2)

TABLE 2. Major Endocyclic Torsion Angles (τ) in the Two Symmetrically Independent Molecules **A** and **B** in **3a**

Angle	τ, deg		Angle	τ, deg	
	A	**B**		**A**	**B**
$S_{(1)}$–$C_{(1)}$–$C_{(2)}$–$C_{(3)}$	-60.1	64.4	$N_{(1)}$–$C_{(4)}$–$C_{(5)}$–$C_{(6)}$	-0.9	-28.1
$C_{(1)}$–$C_{(2)}$–$C_{(3)}$–$N_{(1)}$	59.9	-57.7	$C_{(4)}$–$C_{(5)}$–$C_{(6)}$–$C_{(7)}$	-37.2	-37.7
$C_{(2)}$–$C_{(3)}$–$N_{(1)}$–$C_{(4)}$	-47.8	7.5	$C_{(5)}$–$C_{(6)}$–$C_{(7)}$–$C_{(8)}$	57.1	59.5
$C_{(3)}$–$N_{(1)}$–$C_{(4)}$–$S_{(1)}$	36.6	31.5	$C_{(6)}$–$C_{(7)}$–$C_{(8)}$–$N_{(1)}$	-44.8	-46.4
$N_{(1)}$–$C_{(4)}$–$S_{(1)}$–$C_{(1)}$	-32.0	-20.2	$C_{(7)}$–$C_{(8)}$–$N_{(1)}$–$C_{(4)}$	5.1	3.3
$C_{(4)}$–$S_{(1)}$–$C_{(1)}$–$C_{(2)}$	43.3	-24.9	$C_{(8)}$–$N_{(1)}$–$C_{(4)}$–$C_{(5)}$	19.7	23.2

The IR spectra of the products were taken on an IKS-29 spectrometer in vaseline mull. The ^{1}H NMR spectra were taken on a Bruker WM-250 spectrometer at 250 MHz (for **3a**), Gemini-200 spectrometer at 200 MHz (for **2** and **4**), Bruker DR-500 spectrometer at 500 MHz (for **1** and **5**), and Bruker WP-100 SY spectrometer at 100 MHz (for **3b**) in DMSO-d_6 with TMS as the internal standard. The mass spectra were taken on a Kratos MS-890 mass spectrometer at 70 eV. The melting points were determined on a Koefler block. The course of the reactions was followed by thin-layer chromatography on Silufol UV-254 plates with 3:5 acetone-hexane as the eluent and development by iodine vapor or UV light.

Preparation of 1-4 (General Method). 10% Aqueous KOH (5.6 ml, 10 mmol) and 1,3-dibromopropane (1.02 ml, 10 mmol) were added to a stirred solution of corresponding pyridinethiol **5-8** (10 mmol) in DMF (10 ml) at 20°C and left for 24 h. Then, an additional 10% aqueous KOH (5.6 ml, 10 mmol) was added and stirred for 2 h. Then, water (10 ml) was added. The precipitate formed was filtered off and washed with 40% aqueous ethanol to give **1-4**, which were recrystallized from glacial acetic acid.

9-Cyano-7-methoxycarbonyl-6-oxo-8-(2-thienyl)- 3,4,6,7-tetrahydro-2H,8H-pyrido[2,1-*b*][1,3]thiazine (1). Yield 2.4 g (72%); mp 159-160°C. IR spectrum, ν, cm^{-1}: 1718 (C=O), 2203 (C≡N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.34 (1H, dd, *J* = 1.4 and *J* = 4.3, H-5 thienyl); 6.96 (2H, m, H-4 and H-3 thienyl); 4.43 (1H, d, *J* = 6.2, H-7); 3.98 (1H, d, *J* = 6.2, H-8); 3.93 (2H, t, *J* = 6.2, NCH_2); 3.71 (3H, s, CH_3); 3.19 (2H, m, SCH_2); 2.14 (2H, m, CH_2). Mass spectrum, *m/z* (I_{rel}, %): 334 $[M]^+$ (9), 277 (11), 276 (18), 275 (100). Found, %: C 53.70; H 4.01; N, 8.47. $C_{15}H_{14}N_2O_3S_2$. Calculated, %: C, 53.87; H, 4.22; N, 8.38.

9-Cyano-8-methyl-6-oxo-2,3,4,6-tetrahydropyrido[2,1-*b*][1,3]thiazine (2). Yield 1.73 g (84%); mp 224-225°C. IR spectrum, ν, cm^{-1}: 2214 (C≡N), 1675 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.03 (1H, s, H-7); 3.98 (2H, t, *J* = 5.5, NCH_2); 3.25 (2H, t, *J* = 6.3, SCH_2); 2.20 (5H, m, CH_3 and CH_2). Mass spectrum, *m/z* (I_{rel}, %): 206 $[M]^+$ (100); 205 (17), 191 (48), 178 (224), 173 (20), 150 (23). Found, %: C 58.03; H 5.12; N 13.40. $C_{10}H_{10}N_2OS$. Calculated, %: C 58.23; H 4.89; N 13.58.

7,9-Dicyano-6-oxo-3,4,6,7-tetrahydro-2H-spirocyclohexane-1',8-pyrido[2,1-*b*][1,3]thiazine (3a). Yield 1.98 g (69%); mp 144-146°C. IR spectrum, ν, cm^{-1}: 2247 ($C_{(7)}$–C≡N), 2200 (C≡N), 1680 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.58 (1H, s, H-7); 3.71-3.96 (2H, m, NCH_2); 2.14 (2H, t, *J* = 5.1, SCH_2); 1.28-1.90 (12H, m, $(CH_2)_6$). Mass spectrum, *m/z* (I_{rel}, %): 287 $[M]^+$ (79), 272 (8), 258 (26), 244 (98), 231 (100), 206 (27), 179 (38), 56 (48). Found, %: C 62.50; H 6.16; N 14.52. $C_{15}H_{17}N_3OS$. Calculated, %: C 62.69; H 5.96; N 14.62

7,9-Dicyano-6-oxo-3,4,6,7-tetrahydro-2H-spiro(4'-methylcyclohexane)-1',8-pyrido[2,1-*b*][1,3]thiazine (3b). Yield 2.08 g (69%); mp 152-164°C. IR spectrum, ν, cm^{-1}: 2246 ($C_{(7)}$–C≡N), 2208 (C≡N), 1678 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.71 (1H, s, H-7); 3.94 and 3.68 (both 1H, both t, *J* = 6.3, NCH_2); 3.13 and 3.07 (both 1H, both t, *J* = 6.5, SCH_2); 2.11 (2H, t, *J* = 5.8, CH_2); 1.88-1.15 (9H, m, CH and $(CH_2)_4$); 0.91 (3H, d, *J* = 4.7, CH_3). Found,%: C 63.60; H 6.28; N 14.07. $C_{16}H_{19}N_3OS$. Calculated, %: C 63.76; H 6.35; N 13.94.

6-Amino-7,9-dicyano-8-phenyl-3,4-dihydro-2H,8H-pyrido[2,1-*b*][1,3]thiazine (4). Yield 2.21 g (75%); mp 216-218°C. IR spectrum, ν, cm^{-1}: 3182, 3308, 3455 (NH_2), 2202 (C≡N), 1647 (δ NH_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.02-7.40 (5H, m, C_6H_5); 6.05 (2H, br. s, NH_2); 4.04 (1H, s, H-8); 3.93 and 3.49 (both 1H, both m, NCH_2); 2.98 (2H, t, *J* = 5.0, SCH_2); 2.29 and 2.10 (both 1H, both m, CH_2). Found, %: C 64.99; H 5.02; N 18.87. $C_{16}H_{14}N_4S$. Calculated, %: C 65.28; H 4.79; N 19.03.

5-Cyano-6-mercapto-3-methoxycarbonyl-4-(2-thienyl)-3,4-dihydropyridin-2(1H)-one (5) was obtained according to our procedure [10]. Yield 2.35 g (80%); mp 158-160°C (ethanol). IR spectrum, ν, cm^{-1}: 3345 (N-H), 2202 (C≡N), 1742 (C=O), 1685 (CONH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.70 (1H, br. s, NH); 7.34 (2H, dd, *J* = 1.4 and *J* = 4.3, H-5 thienyl); 6.93 (1H, m, H-4 thienyl); 6.87 (1H, m, H-3 thienyl); 4.20 (1H, d, *J* = 6.15, H-3); 3.62 (3H, s, CH_3); 3.58 (1H, br. s, SH); 3.52 (1H, d, *J* = 6.15, H-4). Mass spectrum, *m/z* (I_{rel}, %): 296 $[M+2]^+$ (5), 295 $[M+1]^+$ (9), 294 $[M]^+$ (35), 267 (48), 235 (100), 195 (63), 137 (47), 100 (72), 58 (60). Found, %: C 49.12; H 3.15; N 9.64. $C_{12}H_{10}N_2O_3S_2$. Calculated, %: C 48.97; H 3.42; N 9.52.

5-Cyano-6-mercapto-4-methyl-2(1H)-pyridinone (6) was characterized in our previous work [11]. **3,5-Dicyano-6-mercapto-3,4-dihydrospiro(cyclohexane-1',4-pyridin)-2(1H)-one (7a)** and **3,5-dicyano-6-mercapto-3,4-dihydrospiro(4'-methylcyclohexane-1',4-pyridin)-2(1H)-one (7b)** were characterized in our previous work [12]. **N-Methylmorpholinium 6-amino-3,5-dicyano-4-phenyl-1,4-dihydro-2-pyridinethiolate (8)** was characterized in our previous work [13].

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