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# A NEW ROUTE TO PARTIALLY HYDROGENATED THIAZOLO[3,2-*a*]PYRIDINE

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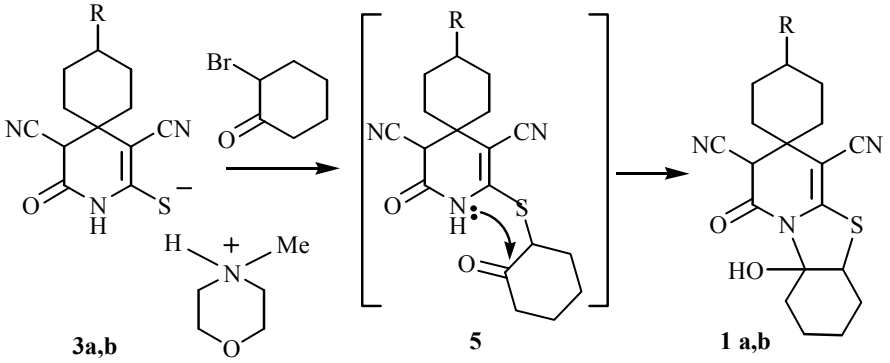
*Partially hydrogenated thiazolo[3,2-a]pyridines have been synthesized by the interaction of functionally substituted ammonium di- and tetrahydropyridine-2-thiolates with bromocyclohexanone. The structure of 6,8-dicyano-3-hydroxy-5-oxo-1,3-tetramethylene-2,3,4,5,6,7-hexahydrospiro[thiazolo-[3,2-a]pyridine-7,1'-(4'-methylcyclohexane)] has been determined by X-ray crystallography.*

**Keywords:** 2-bromocyclohexanone, ammonium pyridin-2-thiolates, thiazolo[3,2-*a*]pyridines, alkylation, dehydration, dehydrogenation, X-ray crystallography, cyclization.

Partially hydrogenated thiazolo[3,2-*a*]pyridines are a known class of biologically active compounds [1]. They are obtained by the condensation of acyclic 1,5-dicarbonyl compounds with α-amino-β-mercaptopropionic acid [2, 3] and by building on the thiazole ring to pyridin-2-thione. The latter is based on the following method: interaction of 1,4-dihydropyridine-2-thiolates with 1,2-dibromoethane [4] and also by the intramolecular condensation of 2-carbamoylmethylthio-1,4-dihydropyridines [5], 2-allylthiopyridines [6], and 2-cyclohex-2-enylthiopyridines [7].

We have proposed a method for the synthesis of 6,8-dicyano-3-hydroxy-5-oxo(amino)-2,3-tetramethylene-2,3,4,5,6,7-hexahydrospiro[thiazolo[3,2-*a*]pyridine-7,1'-(4'-R-cyclohexanones)] **1a, 1b** and **2** by alkylating the corresponding salts **3a, 3b,** and **4** with 2-bromocyclohexanone. The first step in the reaction is the alkylation of the anions of salts **3a, 3b,** and **4** at the sulfur atom with the formation of the sulfide **5.** Evidently stereospecific nucleophilic attack by the unshared pair of electrons of the nitrogen atom at the carbonyl carbon then occurs with formation of the partially hydrogenated thiazolopyridines **1a, 1b,** and **2**:




**1**, **3 a** R = Me; **b** R = H

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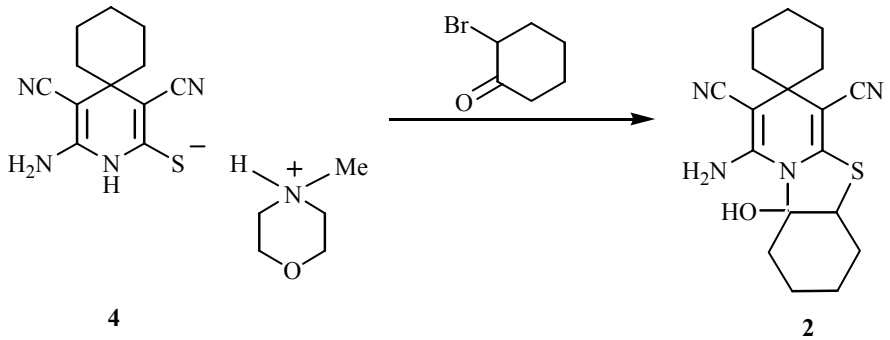
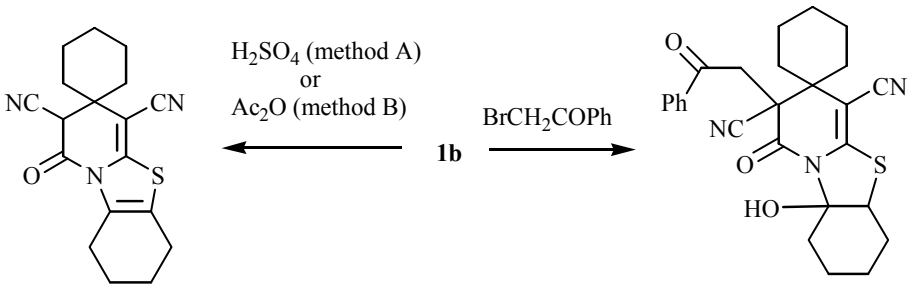


**4** **2**

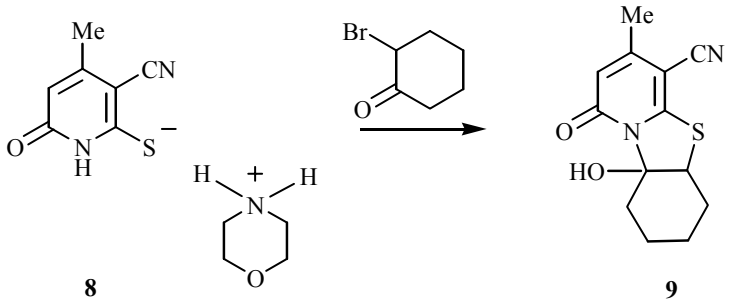
When compound **1b** is boiled in ethanol in the presence of conc. $H_2SO_4$ water is eliminated to give 6,8-dicyano-5-oxo-2,3-tetramethylene-4,5,6,7-tetrahydrospiro[thiazolo[3,2-*a*]pyridine-7-cyclohexane] (**6**) (method A). The same product was obtained when acetic anhydride was used as the dehydrating agent (method B).

Using as an example the reaction of compound **1b** with α-bromoacetophenone in DMF in the presence of KOH it was shown that regioselective alkylation of the partially thiazolopyridines at $C_{(6)}$ was possible to give compound **7**, with a structure corresponding to that of the initial heterocycle.



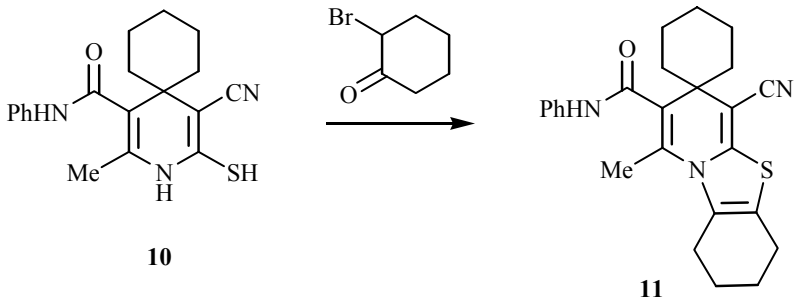
**6** **1b** **7**

Alkylation of morpholinium 4-methyl-6-oxo-1,6-dihydropyridine-2-thiolate (**8**) with 2-bromocyclohexanone also gave a compound containing an OH group, 8-cyano-3-hydroxy-7-methyl-5-oxo-2,3-tetramethylene-2,3,4,5-tetrahydrothiazolo[3,2-*a*]pyridine (**9**).

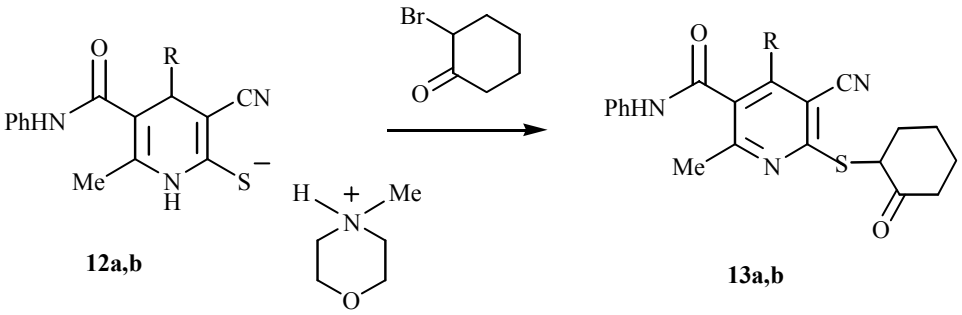


**8** **9**

At the same time alkylation under the same conditions of 3-cyano-6-methyl-5-phenylcarbamoyl-4-spirocyclohexane-1,4-dihydropyridin-2-thiol (**10**) with 2-bromocyclohexanone gave the dehydration product of the initial cyclization **11**.

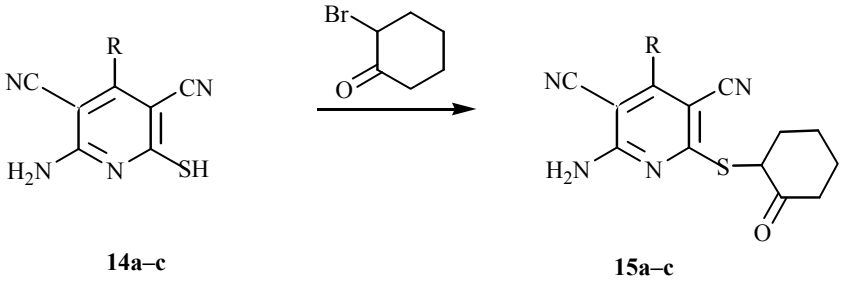



It should also be noted that alkylation of the aryl-substituted 1,4-dihydropyridinethiolates **12** with 2-bromocyclohexanone led to aromatization, probably caused by aerial oxygen, to give 4-aryl-substituted 2-(2-oxocyclohexylthio)pyridines **13**.




**12, 13 a** R = 2-thienyl; **b** R = 4-pyridyl

2-Mercaptopyridines **14a-c** react with 2-bromocyclohexanone in basic media to give the sulfides **15a-c** only.




**14, 15 a** R = 4-$HOC_6H_4$; **b** R = 2-furyl; **c** R = $Me_2CHC_6H_4$

The physicochemical and spectroscopic characteristics confirmed the structures of the synthesized compounds. A peculiarity of the $^1$H NMR spectra (DMSO-$d_6$) of the partially hydrogenated thiazolopyridines **1a** and **1b** is the presence of paired equally intense signals for the SCH-, HO- and $C_{(6)}H$ protons which is evidently explained by the presence of equal amounts of two diastereomers in solution (Table 2). However in the $^1$H NMR spectrum of compound **1b** in $CDCl_3$ the doubled signals are not observed. This fact requires additional study which will be forthcoming shortly.

The molecular and crystal structures of 6,8-dicyano-3-hydroxy-5-oxo-2,3-tetramethylene-2,3,4,5,6,7-hexahydrospiro[thiazolo[3,2-*a*]pyridin-7,1'-(4'-methylcyclohexane)] **1a** were determined by X-ray crystallography (Fig. 1 and Table 3). Both the six-membered heterocycle $N_{(1)}C_{(1-5)}$ and the five-membered heterocycle $S_{(1)}C_{(1)}N_{(1)}C_{(14)}C_{(15)}$ are considerably non-planar, the displacement of atoms from the least squared plane reached

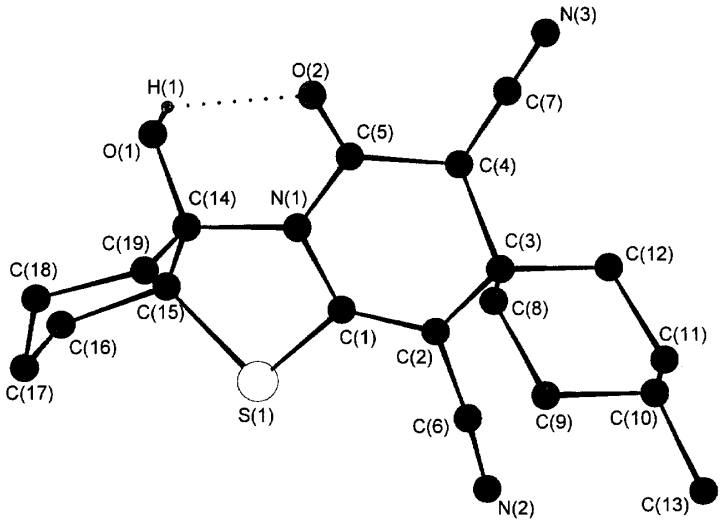



Fig. 1. General view of the molecule (**1a**) with numbering of the atoms (the only hydrogen atom numbered is $H_{(1)}$.

0.33 and 0.24 Å respectively. The interfacial angle between the rings is 13.4°. The five-membered heterocycle has an *envelope* conformation: atoms $S_{(1)}$, $C_{(1)}$, $N_{(1)}$, and $C_{(14)}$ are coplanar within limits of 0.05 Å, while atom $C_{(15)}$ is 0.06 Å out of the plane. The interfacial angle between the planes $S_{(1)}C_{(1)}N_{(1)}C_{(14)}$ and $S_{(1)}C_{(14)}C_{(15)}$ is 36.6°.

TABLE 1. Characteristics of the Compounds Synthesized

| Compound | Empirical formula | Found, % / Calculated, % | | | mp, °C* | Yield, % |
|---|---|---|---|---|---|---|
| | | C | H | N | | |
| **1a** | $C_{19}H_{23}N_3O_2S$ | 63.89 / 63.84 | 6.30 / 6.48 | 11.93 / 11.76 | 223-225 | 59 |
| **1b** | $C_{18}H_{21}N_3O_2S$ | 63.11 / 62.95 | 5.92 / 6.16 | 12.41 / 12.23 | 174-176 | 64 |
| **2** | $C_{18}H_{22}N_4OS$ | 62.98 / 63.13 | 6.35 / 6.48 | 16.41 / 16.36 | 197-199 | 73 |
| **6** | $C_{18}H_{19}N_3OS$ | 66.39 / 66.43 | 5.72 / 5.88 | 13.04 / 12.91 | 150-152 | 55 |
| **7** | $C_{26}H_{27}N_3O_3S$ | 67.50 / 67.65 | 5.81 / 5.90 | 8.96 / 9.10 | 230-232 | 58 |
| **9** | $C_{13}H_{14}N_2O_2S$ | 59.65 / 59.52 | 5.17 / 5.38 | 10.59 / 10.68 | 193-195 | 81 |
| **11** | $C_{25}H_{27}N_3OS$ | 72.02 / 71.91 | 6.47 / 6.52 | 9.89 / 10.06 | 137-139 | 76 |
| **13a** | $C_{24}H_{21}N_3O_2S_2$ | 64.25 / 64.40 | 4.57 / 4.73 | 9.43 / 9.39 | 207-209 | 53 |
| **13b** | $C_{25}H_{22}N_4O_2S$ | 67.71 / 67.85 | 4.86 / 5.01 | 12.73 / 12.66 | 209-211 | 51 |
| **15a** | $C_{19}H_{16}N_4O_2S$ | 62.79 / 62.62 | 4.51 / 4.43 | 15.44 / 15.38 | 230-231 | 53 |
| **15b** | $C_{17}H_{14}N_4O_2S$ | 60.47 / 60.34 | 3.98 / 4.17 | 16.69 / 16.56 | 222-224 | 60 |
| **15c** | $C_{22}H_{22}N_4OS$ | 67.81 / 67.66 | 5.51 / 5.68 | 14.48 / 14.35 | 267-268 | 57 |

* Compounds **1a,b, 2, 6, 11, 13a, b** were crystallized from ethanol, compounds **7, 9, 15a-c** from acetic acid.

TABLE 2. $^1$H NMR, IR, and Mass Spectra of Compounds **1a, b, 2, 6, 7, 9, 11, 13a, b, 15a-c**

| Compound | Mass spectrum, *m/z* ($I_{rel}$,%) | | IR spectrum, ν, cm$^{-1}$ | | | | $^1$H NMR spectrum, δ, ppm (*J*, Hz) |
|---|---|---|---|---|---|---|---|
| | $M^+$ | Other fragments | OH | NH ($NH_2$) | C≡N | C=O | |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| **1a** | —* | —* | 3330 | — | 2197, 2252 | 1710 | 7.23 and 7.13 (1H, two s, OH); 4.82 and 4.48 (1H, two s, $C_{(6)}H$); 3.67-3.39 (1H, m, SCH); 2.12-1.17 (17H, m, CH and $(CH_2)_8$); 0.93 (3H, d, *J* = 5.8, $CH_3$) |
| **1b** | 343 (59) | 310 (23), 300 (27), 246 (47), 216 (23), 128 (25), 97 (100), 69 (47) | 3450 | — | 2195, 2250 | 1690 | 7.10 and 7.01 (1H, two s, OH); 4.49 and 4.36 (1H, two s, $C_{(6)}H$); 3.50 and 3.60 (1H, two t, *J* = 4.4, SCH); 2.17-1.23 (18H, m, $(CH_2)_9$) |
| **2** | 342 (62) | 324 (10), 299 (41), 245 (83), 203 (25), 147 (10), 41 (100) | 3420 | 3330 | 2160, 2188 | — | 7.92 (1H, s, OH); 6.13 (2H, br. s, $NH_2$); 3.89 (1H, m, SCH); 2.21-1.43 (18H, m, $(CH_2)_9$) |
| **6** | 325 (20) | 300 (38), 246 (33), 179 (15), 97 (35) | — | — | 2200, 2249 | 1700 | 4.82 (1H, s, $C_{(6)}H$); 2.73 (2H, m, $CH_2$); 2.38 (2H, m, $CH_2$); 1.85-1.15 (14H, m, $(CH_2)_7$) |
| **7** | 461 (32) | 356 (43), 260 (58), 179 (29), 105 (100), 77 (91) | 3430 | — | 2190, 2268 | 1710, 1740 | 8.05-8.01 (2H, m, $C_{(2)}H$ and $C_{(6)}H$, $C_6H_5$); 7.63-7.47 (3H, m, $C_6H_5$); 7.03 (1H, s, OH); 3.98-3.59 (3H, m, SCH and $CH_2CO$); 2.07-1.23 (18H, m, $(CH_2)_9$) |
| **9** | 262 (66) | 244 (29), 219 (55), 97 (54), 96 (52), 55 (54), 41 (100), 39 (45) | 3380 | — | 2205 | 1680 | 7.10 (1H, s, OH); 6.02 (1H, s, CH); 3.88 (1H, t, *J* = 4.4, SCH); 2.33 (2H, m, $CH_2$); 2.23 (3H, s, $CH_3$); 2.14-1.79 (2H, m, $CH_2$); 1.59-1.47 (4H, m, $(CH_2)_2$) |

TABLE 2 (continued)

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|
| **11** | 417 (38) | 374 (100), 297 (21), 259 (10), 198 (5), 77 (15) | — | 3360 | 2170 | 1670 | 10.03 (1H, br. s, NH); 7.61 (2H, d, $C_{(2)}H$ and $C_{(6)}H$, $C_6H_5$); 7.37 (2H, dd, $J$ = 7.7 and $J$ = 8.4, $C_{(3)}H$ and $C_{(5)}H$, $C_6H_5$); 7.02 (1H, dd, $C_{(4)}H$, $C_6H_5$); 2.65 (2H, m, $CH_2$); 2.12 (3H, s, $CH_3$); 1.29-1.92 (16H, m, $(CH_2)_8$) |
| **13a** | —* | —* | — | 3320 | 2215 | 1680, 1710 | 10.36 (1H, br. s, NH); 7.69-7.06 (8H, m, 3H, $C_4H_3S$ +5H, $C_6H_5$); 4.86 (1H, m, SCH); 2.59 (3H, s, $CH_3$); 2.13-1.81 (8H, m, $(CH_2)_4$) |
| **13b** | 442 (100) | 413 (42), 350 (61), 315 (84), 254 (69), 238 (46), 194 (21), 93 (20) | — | 3330 | 2220 | 1670, 1710 | 10.28 (1H, br. s, NH); 9.23 (2H, d, $J$ = 6.0, $C_{(3)}H$ and $C_{(5)}H$, $C_5H_4N$); 7.43 (2H, d, $C_{(2)}H$ and $C_{(6)}H$, $C_5H_4N$); 7.35 (2H, d, $C_6H_5$); 7.21 (2H, dd, $J$ = 7.6 and $J$ = 8.2, $C_{(3)}H$ and $C_{(5)}H$, $C_6H_5$); 7.03 (1H, dd, $C_{(4)}H$, $C_6H_5$); 4.87 (1H, m, SCH); 2.62 (3H, s, $CH_3$); 2.15-1.82 (8H, m, $(CH_2)_4$) |
| **15a** | —* | —* | 3450 | 3330, 3250 | 2215 | 1710 | 9.82 (1H, br. s, OH); 7.68 (2H, br. s, $NH_2$); 7.30 (2H, d, $J$ = 10.8, $C_{(3)}H$ and $C_{(5)}H$, $C_6H_4OH$); 6.91 (2H, d, $C_{(2)}H$ and $C_{(6)}H$, $C_6H_4OH$); 4.81 (1H, dd, $J$ = 5.1 and $J$ = 8.5, SCH); 2.63 (2H, m, $CH_2$); 2.12-1.76 (6H, m, $(CH_2)_3$) |
| **15b** | —* | —* | — | 3330 | 2205 | 1690 | 7.96 (1H, d, $J$ = 2.2, $C_{(5)}H$, $C_4H_3O$); 7.72 (2H, br. s, $NH_2$); 7.39 (1H, dd, $C_{(4)}H$, $C_4H_3O$); 6.75 (1H, d, $J$ = 3.0, $C_{(3)}H$, $C_4H_3O$); 4.79 (1H, dd, $J$ = 4.8 and $J$ = 8.3, SCH); 2.65 (2H, m, $CH_2$); 2.23-1.78 (6H, m, $(CH_2)_3$) |
| **15c** | 390 (65) | 347 (100), 319 (36), 279 (31), 263 (81) | — | 3314, 3330, 3472 | 2196 | 1711 | 7.78 (2H, br. s, $NH_2$); 7.43 (4H, s, Ar); 5.01 (1H, dd, $J$ = 5.9 and $J$ = 8.9, SCH); 3.02 (1H, m, CH); 2.67 (2H, m, $CH_2$); 2.23-1.92 (6H, m, $(CH_2)_3$); 1.31 (6H, d, $J$ = 8.1, $(CH_3)_2$) |

* Mass spectrum not taken.

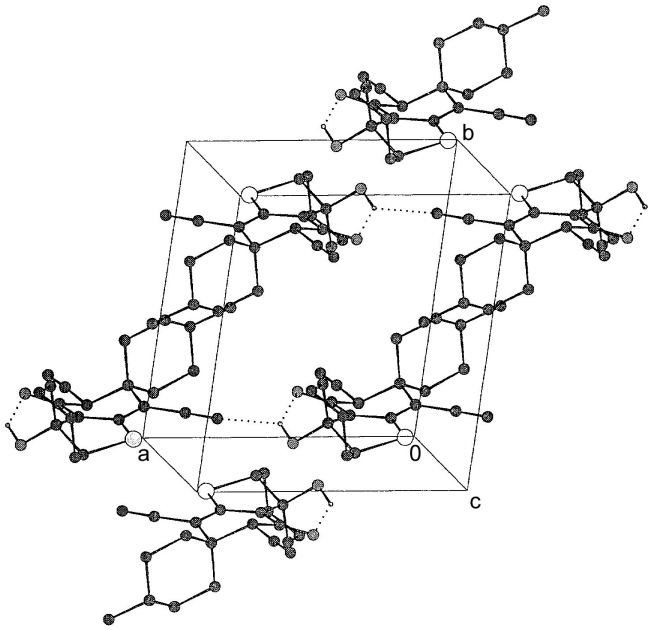



Fig. 2. Crystal packing of compound **1a**.

TABLE 3. Basic Bond Lengths (*d*) and Bond Angles (ω) in the Molecule of Compound **1a**

| Bond | *d*, Å | Angle | ω, deg. |
|---|---|---|---|
| $S_{(1)}$–$C_{(1)}$ | 1.745(3) | $C_{(1)}$–$S_{(1)}$–$C_{(15)}$ | 91.90(14 |
| $S_{(1)}$–$C_{(15)}$ | 1.820(3) | $C_{(1)}$–$N_{(1)}$–$C_{(5)}$ | 121.4(3) |
| $O_{(1)}$–$C_{(14)}$ | 1.391(4) | $C_{(1)}$–$N_{(1)}$–$C_{(14)}$ | 115.4(2) |
| $O_{(2)}$–$C_{(5)}$ | 1.202(4) | $C_{(5)}$–$N_{(1)}$–$C_{(14)}$ | 122.8(2) |
| $N_{(1)}$–$C_{(1)}$ | 1.381(4) | $S_{(1)}$–$C_{(1)}$–$N_{(1)}$ | 110.6(2) |
| $N_{(1)}$–$C_{(5)}$ | 1.379(4) | $N_{(1)}$–$C_{(1)}$–$C_{(2)}$ | 123.8(3) |
| $N_{(1)}$–$C_{(14)}$ | 1.508(4) | $C_{(1)}$–$C_{(2)}$–$C_{(3)}$ | 121.3(3) |
| $C_{(1)}$–$C_{(2)}$ | 1.344(4) | $C_{(2)}$–$C_{(3)}$–$C_{(4)}$ | 103.9(2) |
| $C_{(2)}$–$C_{(3)}$ | 1.529(4) | $C_{(3)}$–$C_{(4)}$–$C_{(5)}$ | 113.8(3) |
| $C_{(3)}$–$C_{(4)}$ | 1.555(4) | $N_{(1)}$–$C_{(5)}$–$C_{(4)}$ | 112.6(3) |
| $C_{(4)}$–$C_{(5)}$ | 1.529(5) | $N_{(1)}$–$C_{(14)}$–$C_{(15)}$ | 102.8(2) |
| $C_{(14)}$–$C_{(15)}$ | 1.533(4) | $S_{(1)}$–$C_{(15)}$–$C_{(14)}$ | 105.1(2) |

Calculations on the six-membered ring $N_{(1)}C_{(1\text{-}5)}$ using modified Cremer–Pople parameters [8] ($S$ = 0.69, θ = 41.71°, ψ = 13.61°) showed that this ring has a conformation intermediate between *half-chair* and *half-boat*. Atom $N_{(1)}$ has a trigonal planar configuration of bonds (the sum of the bond angles is 359.6 (7)°). The $N_{(1)}$–$C_{(1)}$ (1.381(4) and $N_{(1)}$–$C_{(5)}$ (1.379(4) Å) bonds are notably shorter than the average range of 1.43-1.45 Å characteristic of N($sp^2$)-C($sp^3$) single bonds [9, 10] indicating effective $n(N_{(1)})$–$\pi^*(C_{(1)}{=}C_{(2)})$ and $n(N_{(1)})$–$\pi^*(O_{(2)}{=}C_{(5)})$ conjugation. Note that the conformation of the molecule **1a** is very suitable for such an interaction: the torsion angles $C_{(5)}$–$N_{(1)}$–$C_{(1)}$–$C_{(2)}$ and $C_{(14)}$–$N_{(1)}$–$C_{(1)}$–$C_{(2)}$ are 6.2 and -167.2°, while the torsion angles $C_{(1)}$–$N_{(1)}$–$C_{(5)}$–$O_{(2)}$ and $C_{(14)}$–$N_{(1)}$–$C_{(5)}$–$O_{(2)}$ are -164.3 and 8.6°. A characteristic of the structure of compound **1a** is the intramolecular hydrogen bond $O_{(1)}$–$H_{(1)}$···O(2) ($O_{(1)}$···$O_{(2)}$ 2.809(4), $H_{(1)}$···$O_{(2)}$ 2.18(6) A, $O_{(1)}H_{(1)}O_{(2)}$ 127(3)°).

TABLE 4. Atomic Coordinates and Equivalent Isotropic Thermal Parameters, $U_{eq}$, in the Structure of **1a**

| Atom | *x* | *y* | *z* | $U_{eq}$, Å$^2$ |
|---|---|---|---|---|
| $S_{(1)}$ | 0.09236(8) | 0.04485(9) | 0.25959(8) | 0.0484 |
| $O_{(1)}$ | 0.5206(3) | 0.0417(3) | 0.3392(3) | 0.0534 |
| $O_{(2)}$ | 0.5890(2) | 0.2610(3) | 0.5921(3) | 0.0675 |
| $N_{(1)}$ | 0.3502(3) | 0.1552(3) | 0.4490(2) | 0.0415 |
| $N_{(2)}$ | -0.1603(3) | 0.1474(4) | 0.4496(3) | 0.0711 |
| $N_{(3)}$ | 0.5899(4) | 0.3832(5) | 0.9229(4) | 0.1011 |
| $C_{(1)}$ | 0.1946(3) | 0.1422(3) | 0.4303(3) | 0.0382 |
| $C_{(2)}$ | 0.1332(3) | 0.2037(3) | 0.5297(3) | 0.0394 |
| $C_{(3)}$ | 0.2344(3) | 0.3008(3) | 0.6719(3) | 0.0384 |
| $C_{(4)}$ | 0.3806(3) | 0.2406(4) | 0.6938(3) | 0.0439 |
| $C_{(5)}$ | 0.4546(3) | 0.2230(3) | 0.5769(3) | 0.0460 |
| $C_{(6)}$ | -0.0302(4) | 0.1747(3) | 0.4902(3) | 0.0471 |
| $C_{(7)}$ | 0.4997(4) | 0.4997(4) | 0.8224(4) | 0.0662 |
| $C_{(8)}$ | 0.2717(4) | 0.4507(4) | 0.6757(4) | 0.0510 |
| $C_{(9)}$ | 0.1339(5) | 0.5174(4) | 0.6734(4) | 0.0662 |
| $C_{(10)}$ | 0.0667(5) | 0.5172(4) | 0.7924(4) | 0.0694 |
| $C_{(11)}$ | 0.0306(4) | 0.3705(4) | 0.7941(4) | 0.0597 |
| $C_{(12)}$ | 0.1640(4) | 0.2973(4) | 0.7894(3) | 0.0475 |
| $C_{(13)}$ | -0.0742(6) | 0.5790(6) | 0.7840(6) | 0.0997 |
| $C_{(14)}$ | 0.3973(3) | 0.1053(3) | 0.3190(3) | 0.0421 |
| $C_{(15)}$ | 0.2609(3) | -0.0139(3) | 0.2231(3) | 0.0454 |
| $C_{(16)}$ | 0.2544(4) | -0.0506(4) | 0.0716(4) | 0.0616 |
| $C_{(17)}$ | 0.2807(5) | 0.0741(5) | 0.0285(4) | 0.0716 |
| $C_{(18)}$ | 0.4300(5) | 0.1756(5) | 0.1196(4) | 0.0732 |
| $C_{(19)}$ | 0.4263(4) | 0.2251(4) | 0.2690(4) | 0.0554 |
| $H_{(1)}$ | 0.591(6) | 0.118(6) | 0.394(6) | 0.11(2) |

The short intermolecular contacts $O_{(1)}\cdots N_{(2)}$ 2.818(4) ($H_{(1)}\cdots N_{(2)}$ 2.18(6) A, $O_{(1)}H_{(1)}N_{(2)}$ 129(3)°) shows the possibility of the formation $O_{(1)}$–$H_{(1)}\cdots N_{(2)}$ hydrogen bonds (Fig. 2).

## EXPERIMENTAL

IR spectra of nujol mulls were recorded on an IRS-29 spectrophotometer. $^1$H NMR spectra of DMSO-$d_6$ solutions with TMS as internal standard were recorded with Bruker WP-100 (100 MHz) (compound **1a**), Gemini-200 (199 MHz) (compounds **6** and **7**), Bruker WM-250 (250 MHz) (compound **15c**), and Bruker AM-300 (300 MHz) spectrometers (compounds **1b, 2, 9, 11, 13a,b, 15a,b**). Mass spectra were recorded with a Kratos MS-890 machine (70 eV). Melting points were recorded with a Kofler block. The course of reactions and the purity of synthesized compounds were monitored by TLC (Silufol UV-254, acetone–hexane 3:5, spots revealed with iodine vapor).

**The X-ray Diffraction Study of a Monocrystal of Compound 1a** with linear dimensions 0.16 × 0.22 × 0.34 mm was carried out at room temperature with an Enraf-Nonius CAD-4 automatic four-circle diffractometer (Cu$K_\alpha$ radiation, ratio of rates of scanning $\omega/2\theta = 1.2$, $\theta_{max} = 60°$, segment of the sphere $0 \le h \le 11$, $-12 \le k \le 12$, $-11 \le k \le 11$). A total of 2896 reflexions were collected of which 2700 were symmetrically independent *R* factor averaged 0.020). Crystals of compound **1a** are triclinic, $a$ = 9.199(2), $b$ = 10.286(2), $c$ = 10.651(2) Å; $\alpha$ = 107.62(2), $\beta$ = 103.37(2), $\gamma$ = 97.83(2)°; $V$ = 896.6 Å$^3$; M = 357.47; $Z$ = 2; $d_{calc}$ 1.32 g/cm$^3$; $\mu$ = 17.009 cm$^{-1}$; space group *P*(1)(*N2*). Calculation of absorption in the crystal was carried out

by azimuthal scanning [11]. The structure was solved by direct methods and refined by least squares analysis using the CRYSTALS suite of programs [12]. In the refinement 1977 reflexions with $I > 3\sigma(I)$ were used (230 parameters refined, reflexions per parameter 8.6). All hydrogen atoms were revealed from electron density difference synthesis and were included in the calculations with fixed positions and thermal parameters, only atom $H_{(1)}$ was refined isotropically. The Chebyshev weighting scheme [13] with parameters 1.56, -1.21, 0.80, and -0.74 was used in the refinement. The final residual factors were $R = 0.055$, $R_w = 0.054$, and GoF = 1.088. The residual electron densities in the difference Fourier series were 0.24 and -0.36 e/Å$^3$. Atom coordinates are given in Table 4.

**6,8-Dicyano-3-hydroxy-5-oxo-2,3-tetramethylene-2,3,4,5,6,7-hexahydrospiro[thiazolo[3,2-*a*]-pyridine-7,1'-(4'-methylcyclohexane)] (1a), 6,8-Dicyano-3-hydroxy-5-oxo-2,3-tetramethylene-2,3,4,5,6,7-hexahydrospiro[thiazolo[3,2-*a*]pyridine-7-cyclohexane] (1b), 5-Amino-6,8-dicyano-3-hydroxy-2,3-tetramethylene-2,3,4,7-tetrahydrospiro[thiazolo[3,2-*a*]pyridine-7-cyclohexane] (2), 8-Cyano-3-hydroxy-7-methyl-5-oxo-6-phenylcarbamoyl-2,3-tetramethylene-4,7-dihydrospiro[thiazolo[3,2-*a*]pyridine] (9), 8-Cyano-5-methyl-6-phenylcarbamoyl-2,3-tetramethylene-4,7-dihydrospiro[thiazolo[3,2-*a*]pyridine-7-cyclohexane] (11), 3-Cyano-6-methy-2-(2'-oxocyclohexylthio)-5-phenylcarbamoyl-4-(2'-thienyl)pyridine (13a), 3-Cyano-6-methyl-2-(2'-oxocyclohexylthio)-5-phenylcartbamoyl-4-(4'-pyridyl)pyridine (13b), 6-Amino-3,5-dicyano-4-(4'-hydroxyphenyl)-2-(2'oxocyclohexylthio)pyridine (15a), 6-Amino-3,5-dicyano-4-(2'-furyl)-2-(2'-oxocyclohexylthio)pyridine (15b), and 6-Amino-3,5-dicyano-4-(4'-isopropylphenyl)-2-(2'oxocyclohexylthio)pyridine (15c) (General Method).** A mixture of the corresponding thione or its salt (10 mmol) and 2-bromocyclohexanone (1.77 g, 10 mmol) in DMF (10 ml) was stirred at 20°C for 4 h and then kept for a day. The precipitate was filtered off, washed with 40% aqueous ethanol and hexane to give compounds **1a,b, 2, 9, 11, 13a,b, 15a-c** (Table 1). $^1$ NMR spectrum ($CDCl_3$) of compound **1a**, δ, ppm (*J*, Hz): 4.58 (1H, s, OH); 3.82 (1H, t, $J = 4.1$, $C_{(2)}H$); 3.66 (1H, s, $C_{(6)}H$); 2.27-1.22 (17H, m, $(CH_2)_4$ and $(CH_2)_2CH(CH_2)_2$); 0.96 (3H, d, $J = 5.7$, $CH_3$).

**6,8-Dicyano-5-oxo-2,3-tetramethylene-4,5,6,7-tetrahydrospiro[thiazolo[3,2-*a*]pyridine-7-cyclohexane] (6). A.** A mixture of compound **1b** (1.7 g, 5 mmol) and conc. $H_2SO_4$ (0.49 ml, 5 mmol) in ethanol (15 ml) was boiled for 2 h. The precipitate which formed over one day was filtered off and washed with ethanol and hexane to give compound **6** (Tables 1-2).

**B.** Compound **1b** (1.7 g, 5 mmol) was boiled in $Ac_2O$ (5 ml) for one hour. The precipitate which formed over one day was filtered off and washed with ethanol and hexane to give compound **6** (71% yield), identical by TLC and $^1$H NMR spectrum with the product from method A.

**6-Benzoylmethylene-6,8-dicyano-5-oxo-2,3-tetramethylene-2,3,4,5,6,7-hexahydrospiro[thiazolo[3,2-*a*]-pyridine-7-cyclohexane] (7).** 10% Aqueous KOH (2.8 ml, 5 mmol) was added with stirring to a suspension of compound **1b** (1.7 g, 5 mmol) in DMF (10 ml). α-Bromoacetophenone (1 g, 5 mmol) was then added with stirring over 5 minutes and the mixture was stirred for four hours. The precipitate which formed over one day was filtered off and washed with ethanol and hexane to give compound (Tables 1-2).

The methods of synthesis and the characteristics of the starting materials **3a,b, 4, 8, 10, 12a,b**, and **14a-c** are cited in [14].

## REFERENCES


1. V. P. Litvinov, L. A. Rodinovskaya, Y. A. Sharanin, A. M. Shestopalov, and A. Senning, *Sulfur Reports,* **13**, 1 (1992).
2. A. Roth and K. Goerlitzer, *Arch. Pharm.,* **326**, 642 (1993).
3. K. Goerlitzer and A. Roth, *Pharmazie*, **50**, 729 (1995).
4. A. D. Dyachenko, S. M. Desenko, V. D. Dyachenko, and V. P. Litvinov, *Khim. Geterotsikl. Soed.,* 554 (2000).

5. A Krauze and G. Duburs, *Khim. Geterotsikl. Soed.,* 1134 (1996).
6. A. M. Shestopalov, L. A. Rodinovskaya, Yu. A. Sharanin, and V. I. Litvinov, *Zhur. Org. Khim.,* **58**, 840 (1988).
7. V. I. Litvinov, A. M. Shestopalov, Yu . A Sharanin, V. Yu. Mortikov, and V. N. Nesterov, *Doklad. Akad. Nauk.,* **299**, 135 (1988).
8. N. S. Zefirov and V. A. Palyuyulin, *Doklad. Akad. Nauk,* **252,** 111 (1980).
9. M. Burke-Laing and M. Laing, *Acta Crystallogr.,* **B32**, 3216 (1976).
10. F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen, and R. Taylor, *J. Chem. Soc., Perkin Trans. 2*, P S1 (1987).
11. A. C. T. North, D. C. Phillips, F. Scott, and F. S. Mathews, *Acta Crystallogr.,* **A24**, 351 (1968).
12. D. J. Watkin, C. K. Prout, J. R. Carruthers, and P. W. Betteridge, *CRYSTALS Issue 10,* Chemical Crstallograhy Laboratory, Univ. of Oxford (1966).
13. J. R. Carruthers and D. J. Watkin, *Acta Crystallogr.,* **A35**, 698 (1979).
14. V. D. Dyachenko, Diss. Doctor Khim. Nauk, Moscow (1998).