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SYNTHESIS, STRUCTURE, AND SOME PROPERTIES OF SUBSTITUTED 3-CARBETHOXY-(METHOXY)-5-CYANO-1,2,3,4-TETRAHYDROSPIRO-CYCLOHEXANE-4-PYRIDINE-2-THIONES

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The condensation of cyclohexylidenemalononitrile or cyclohexylidenecyanoacetic ester with thioamidoethyl(methyl)malonate in the presence of sodium ethylate gave 6-amino-3-carbethoxy-5-cyano-4-spirocyclohexane-1,2,3,4-tetrahydropyridine-2-thione and 3-carbethoxy(methoxy)-5-cyano-6-oxo-4-spirocyclohexanepiperidine-2-thiones which were used in the synthesis of the corresponding substituted 2-alkylthiotetrahydropyridines. 5-Carbethoxy-3-cyano-3-methyl-6-methylthio-4-spiro-cyclohexane-3,4-dihydropyridine-2(1H)-one was studied by X-ray crystallography.

Keywords: thioamidoethyl(methyl)malonate, 4-cycloalkanespiro-substituted pyridine-2-thiones, cyclohexylidenemalononitrile, cyclohexylidenecyanoacetic ester, alkylation, intramolecular Claisen condensation, Michael reaction, X-ray crystallography.

We have previously prepared 3-cyano-4-cycloalkanespiro-substituted, partially hydrogenated pyridine-2-thiones [1-3], which are promising intermediates in the search for preparations with medicinal value [4, 5]. In extending our investigation in this direction we have discovered a route for the synthesis of 3-carbethoxy(methoxy)-substituted analogs of the class of compound mentioned above which involves the reaction of the cyclohexylidenemalononitrile (**1**) with thioamidoethylmalonate (**2**) in ethanol in the presence of sodium ethylate. During the reaction the formation of the 6-amino-3-carbethoxy-5-cyano-4-spirocyclohexane-1,2,3,4-tetrahydropyridine-2-thione (**3**) is apparently preceded by the generation of the corresponding Michael adduct **4** (Scheme 1).

In order to prove the structure of compound **3** (Table 1) we have used the alkylation by the halides **5** in basic medium together with spectroscopic methods (see Experimental section and Table 2). The organic sulfides **6** obtained in this way are in accord with the general trends in the chemistry of pyridinethiones [6].

The use of the cyclohexylidenecyanoacetate ester **7** as Michael acceptor in the reaction with the CH-acids **2** led to the preparation of 3-carbethoxy(methoxy)-5-cyano-6-oxo-4-spirocyclohexanepiperidine-2-thiones **8**. In this case, the hypothetical Michael adduct **9** could not be isolated. The use of alkylation as a "characteristic reaction" of thiones [6] together with a series of spectroscopic methods (see Experimental section and Table 2) readily prove the structure of compound **8** (Scheme 2).

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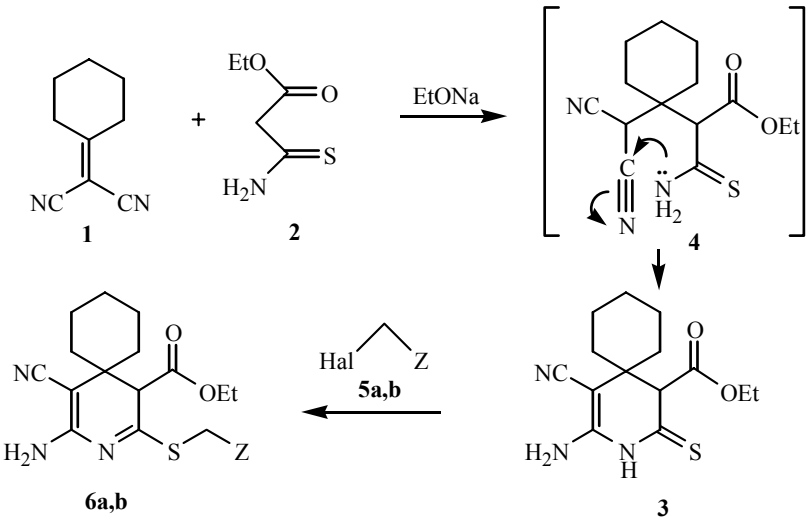
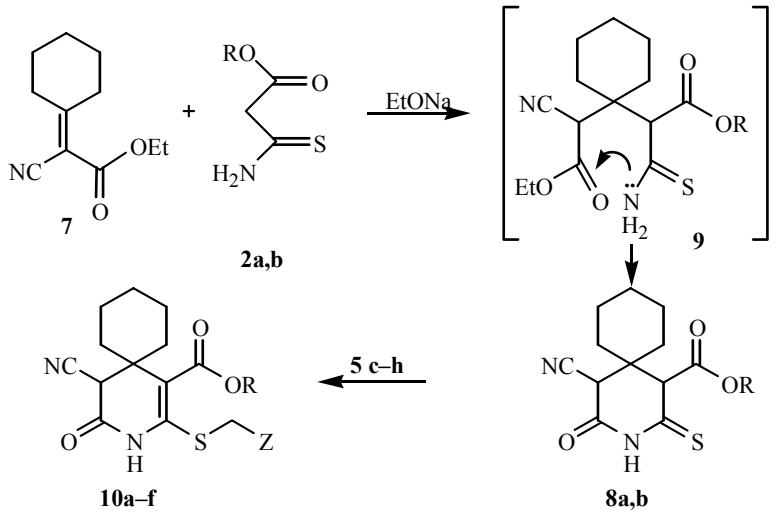
Scheme 1



5 a Hal = Br, **b** Hal = Cl; **5, 6 a** Z = 4-$O_2NC_6H_4CO$; **b** Z = thiazol-2-ylcarbamoyl

Scheme 2

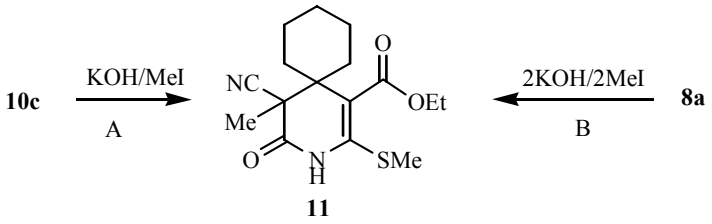


2, **8 a** R = Et, **b** R = Me; **5 c** Hal = Cl, Z = PhNHCO, **d** Hal = Cl, Z = Ph, **e** Hal = I, Z = H, **f** Hal = Cl, Z = 4-BrC_6H_4NHCO, **g** Hal = I, Z = Me, **h** Hal = Br, Z = PhCO; **10 a** R = Et, Z = PhNHCO, **b** R = Et, Z = Ph, **c** R = Et, Z = H, **d** R = Et, Z = 4-BrC_6H_4NHCO, **e** R = Me, Z = Me, **f** R = Me, Z = PhCO

The sulfides **10** obtained by this means can undergo further reactions. Hence the reaction of compound **10c** with MeI in basic medium occurs regioselectively *via* C-methylation to give 5-carbethoxy-3-cyano-3-methyl-6-methylthio-4-spirocyclohexane-3,4-dihydropyridine-2(1H)-one (**11**) (method A), which can also be synthesized in a single stage from the thione **8a** and MeI (method B).

TABLE 1. Parameters for Compounds **3, 6a,b, 8a,b, 10a-f, 11, 12**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C (crystallization solvent)	Yield, %
		C	H	N		
3	$C_{14}H_{19}N_3O_2S$	57.12 / 57.31	6.46 / 6.53	14.54 / 14.32	192-194 (EtOH)	83
6a	$C_{22}H_{24}N_4O_5S$	57.96 / 57.88	5.19 / 5.30	12.20 / 12.27	180-182 (EtOH–DMF, 1:1)	66
6b	$C_{19}H_{23}N_5O_3S_2$	52.51 / 52.64	5.41 / 5.35	16.00 / 16.15	164-166 (EtOH)	76
8a	$C_{14}H_{18}N_2O_3S$	56.95 / 57.12	5.98 / 6.16	9.31 / 9.52	154-156 (EtOH)	75
8b	$C_{13}H_{16}N_2O_3S$	55.73 / 55.69	5.69 / 5.75	9.84 / 10.00	139-141 (MeOH)	61
10a	$C_{22}H_{25}N_3O_4S$	61.90 / 61.81	5.73 / 5.89	9.92 / 9.83	153-155 (AcOH)	79
10b	$C_{21}H_{24}N_2O_3S$	65.73 / 65.60	6.31 / 6.29	7.12 / 7.29	179-181 (EtOH)	71
10c	$C_{15}H_{20}N_2O_3S$	58.35 / 58.42	6.39 / 6.54	8.97 / 9.09	135-137 (EtOH)	62
10d	$C_{22}H_{24}BrN_3O_4S$	52.02 / 52.18	4.91 / 4.78	8.13 / 8.30	173-175 (AcOH)	57
10e	$C_{15}H_{20}N_2O_3S$	58.31 / 58.42	6.59 / 6.54	8.97 / 9.09	156-158 (MeOH)	53
10f	$C_{21}H_{22}N_2O_4S$	63.35 / 63.29	5.50 / 5.57	6.99 / 7.03	178-180 (MeOH–DMF, 1:1)	55
11	$C_{16}H_{22}N_2O_3S$	59.67 / 59.60	6.73 / 6.88	8.79 / 8.69	191-193 (EtOH)	58
12	$C_{20}H_{18}N_2O_3S$	65.61 / 65.55	5.05 / 4.95	7.41 / 7.65	268-269 (DMF)	68



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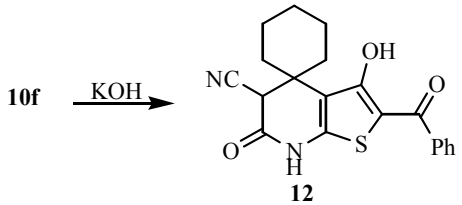
Treatment of compound **10f** with an aqueous solution of KOH in refluxing ethanol gives 2-benzoyl-5-cyano-3-hydroxy-6-oxo-4,5,6,7-tetrahydrospiro(cyclohexane-4-thieno[2,3-*b*]pyridine) (**12**) as a result of an intramolecular Claisen condensation.



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To establish the regioselectivity of the alkylation of functionally substituted tetrahydropyridines which contain several nucleophilic centers unambiguously, we have studied compound **11** using an X-ray structural method (Fig. 1 and Table 3).

TABLE 2. IR and ^{1}H NMR Spectra for Compounds **3, 6a,b, 8a,b, 10a-f, 11, 12**

Compound	IR spectrum, ν, cm^{-1}		^{1}H NMR spectrum, δ, ppm (*J*, Hz)
	NH	C≡N, C=O	
3	3430, 3330	2170, 1715	11.73 (1H, s, NH); 6.02 (2H, br. s, NH_2); 4.08 (3H, m, OCH_2 and H-3); 1.35-1.68 (10H, m, $(CH_2)_5$); 1.23 (3H, t, *J* = 7.0, CH_3)
6a	3510, 3390	2170, 1720, 1700	8.27 (4H, two d, *J* = 9.0, Ar); 5.97 (2H, br. s, NH_2); 4.78 (2H, q, SCH_2); 4.11 (2H, q, OCH_2); 3.54 (1H, s, H-3); 1.33-1.76 (10H, m, $(CH_2)_5$); 1.22 (3H, t, CH_3)
6b	3420, 3300, 3150	2165, 1740, 1680	12.14 (1H, br. s, NH); 7.38 and 7.02 (2H, both d, *J* = 3.3, Het); 6.12 (2H, br. s, NH_2); 4.07 (4H, m, SCH_2 and OCH_2); 3.50 (1H, s,H-3); 1.27-1.79 (10H, m, $(CH_2)_5$); 1.18 (3H, t, CH_3)
8a	3180	2255, 1710	13.42 (1H, br. s, NH); 4.75 and 4.51 (2H, both s, H-3 and H-5); 4.21 (2H, q, OCH_2); 1.39-1.73 (10H, m, $(CH_2)_5$); 1.22 (3H, t, CH_3)
8b	3210	2245, 1710	13.39 (1H, br. s, NH); 4.77 and 4.52 (2H, both s, H-3 and H-5); 3.80 (3H, s, OCH_3); 1.42-1.72 (10H, m, $(CH_2)_5$)
10a	3320	2265, 1720, 1700, 1660	10.60 (1H, s, NH); 10.12 (1H, s, C_6H_5NHCO); 7.54 (2H, d, *J* = 7.6, C_6H_5); 7.26 (2H, dd, C_6H_5); 7.03 (1H, dd, *J* = 7.3, C_6H_5); 4.09 (3H, m, OCH_2 and H-3); 3.67 (2H, q, SCH_2); 1.38-1.93 (10H, m, $(CH_2)_5$); 1.22 (3H, t, CH_3)
10b	3270, 3180	2250, 1735, 1710	10.48 (1H, s, NH); 7.25 (5H, m, C_6H_5); 4.09 (5H, m, SCH, OCH_2 and H-3); 1.35-1.72 (10H, m, $(CH_2)_5$); 1.21 (3H, t, CH_3)
10c	3240	2250, 1710, 1680	10.37 (1H, s, NH); 4.18 (2H, q, OCH_2); 4.04 (1H, s, H-3); 2.31 (3H, s, SCH_3); 1.39-1.84 (10H, m, $(CH_2)_5$); 1.18 (3H, t, CH_3)
10d	3350	2255, 1700, 1685, 1665	10.42 (1H, s, NH); 10.17 (1H, s,4-BrC_6H_4N<u>H</u>CO); 7.53 and 7.46 (2H, both d, *J* = 9.0, Ar); 4.18 (3H, m, OCH_2 and H-3); 3.69 (2H, q, SCH_2); 1.38-1.84 (10H, m, $(CH_2)_5$); 1.21 (3H, t, CH_3)
10e	3300	2250, 1720, 1700	10.36 (1H, s,NH); 4.02 (1H, s,H-3); 3.74 (3H, s,OCH_3); 2.86 (2H, q, SCH_2); 1.43-1.76 (10H, m, $(CH_2)_5$); 1.23 (3H, t, *J* = 7.2, CH_3)
10f	3420	2270, 1710, 1670	10.41 (1H, s,NH); 7.32-7.47 (5H, m, C_6H_5); 4.29 (1H, s,H-3); 3.78 (3H, s,OCH_3); 3.42 (2H, q, SCH_2); 1.25-1.80 (10H, m, $(CH_2)_5$)
11	3270-3210	2250, 1710, 1680	10.37 (1H, s,NH); 4.19 (2H, q, OCH_2); 2.28 (3H, s,SCH_3); 1.12-2.19 (10H, m, $(CH_2)_5$); 1.47 (3H, s,CH_3); 1.30 (3H, t, OCH_2<u>CH_3</u>)
12	3430	2255, 1710, 1690	14.20 (1H, br. s, OH); 12.01 (1H, s, NH); 7.51-7.87 (5H, m, C_6H_5); 4.61 (1H, s,H-5); 2.65 (1H, m, CH); 1.93 (1H, m, CH); 1.29-1.67 (8H, m, $(CH_2)_4$)

TABLE 3. Basic Bond Lengths (*d*) and Valence Angles (ω) in the Compound **11** Molecule

Bond	*d*, Å	Angle	ω, deg.
$S_{(1)}$–$C_{(5)}$	1.747(5)	$C_{(5)}$–$S_{(1)}$–$C_{(16)}$	100.3(3)
$S_{(1)}$–$C_{(16)}$	1.806(7)	$C_{(1)}$–$N_{(1)}$–$C_{(5)}$	123.2(5)
$O_{(1)}$–$C_{(1)}$	1.220(6)	$N_{(1)}$–$C_{(1)}$–$C_{(2)}$	114.5(4)
$N_{(1)}$–$C_{(1)}$	1.368(7)	$C_{(1)}$–$C_{(2)}$–$C_{(3)}$	110.8(4)
$N_{(1)}$–$C_{(5)}$	1.409(6)	$C_{(2)}$–$C_{(3)}$–$C_{(4)}$	105.4(4)
$N_{(2)}$–$C_{(7)}$	1.146(8)	$C_{(3)}$–$C_{(4)}$–$C_{(5)}$	120.6(4)
$C_{(1)}$–$C_{(2)}$	1.519(8)	$S_{(1)}$–$C_{(5)}$–$N_{(1)}$	115.5(4)
$C_{(2)}$–$C_{(3)}$	1.560(7)	$S_{(1)}$–$C_{(5)}$–$C_{(4)}$	124.2(4)
$C_{(3)}$–$C_{(4)}$	1.528(7)	$N_{(1)}$–$C_{(5)}$–$C_{(4)}$	120.3(5)
$C_{(4)}$–$C_{(5)}$	1.339(7)		

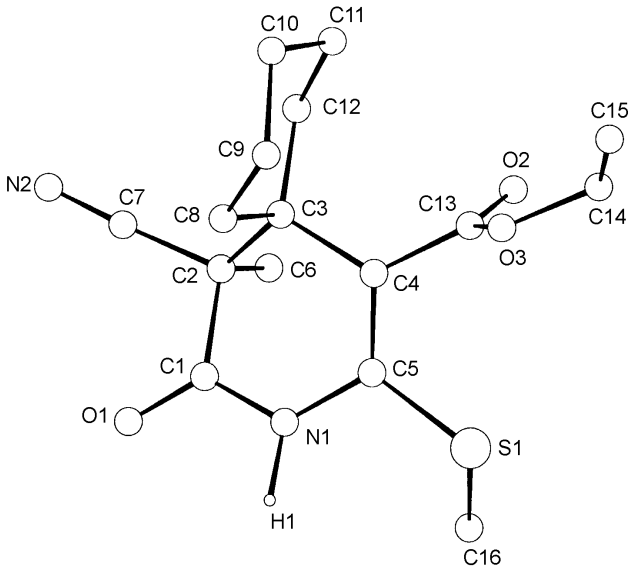

Fig. 1. Overall view of the compound **11** molecule with atomic numbering.

TABLE 4. Atomic Coordinates and Equivalent Isotropic Thermal Parameters (U_{eq}) in the Structure **11**

Atom	*x*	*y*	*z*	U_{eq}, Å^2
$S_{(1)}$	0.8651(3)	0.54250(13)	0.36655(18)	0.0635
$O_{(1)}$	0.3574(7)	0.4335(4)	-0.0136(4)	0.0696
$O_{(2)}$	0.6745(8)	0.3079(4)	0.5418(4)	0.0713
$O_{(3)}$	0.9580(7)	0.2828(5)	0.4852(4)	0.0807
$N_{(1)}$	0.5942(7)	0.4689(4)	0.1632(4)	0.0503
$N_{(2)}$	0.140(1)	0.1648(7)	-0.0015(7)	0.0972
$C_{(1)}$	0.4353(8)	0.4061(5)	0.0940(5)	0.0491
$C_{(2)}$	0.3622(8)	0.3073(5)	0.1643(5)	0.0468
$C_{(3)}$	0.5416(8)	0.2362(4)	0.2459(5)	0.0421
$C_{(4)}$	0.6728(8)	0.3285(5)	0.3291(4)	0.0433
$C_{(5)}$	0.6983(8)	0.4364(5)	0.2849(5)	0.0476
$C_{(6)}$	0.2250(9)	0.3642(6)	0.2382(6)	0.0662
$C_{(7)}$	0.2383(9)	0.2284(6)	0.0687(6)	0.0633
$C_{(8)}$	0.6636(8)	0.1812(5)	0.1595(5)	0.0479
$C_{(9)}$	0.8232(9)	0.0946(5)	0.2258(6)	0.0626
$C_{(10)}$	0.7324(12)	-0.0038(6)	0.2834(7)	0.0741
$C_{(11)}$	0.6236(12)	0.0433(6)	0.3745(7)	0.0742
$C_{(12)}$	0.466(1)	0.1380(5)	0.3162(5)	0.0596
$C_{(13)}$	0.7682(9)	0.3052(5)	0.4632(5)	0.0555
$C_{(14)}$	1.0631(17)	0.2650(12)	0.6163(8)	0.1438
$C_{(15)}$	1.205(2)	0.1833(13)	0.636(1)	0.1535
$C_{(16)}$	0.7037(11)	0.6707(6)	0.3478(6)	0.0658
$H_{(1)}$	0.644(14)	0.542(8)	0.102(9)	0.12(3)

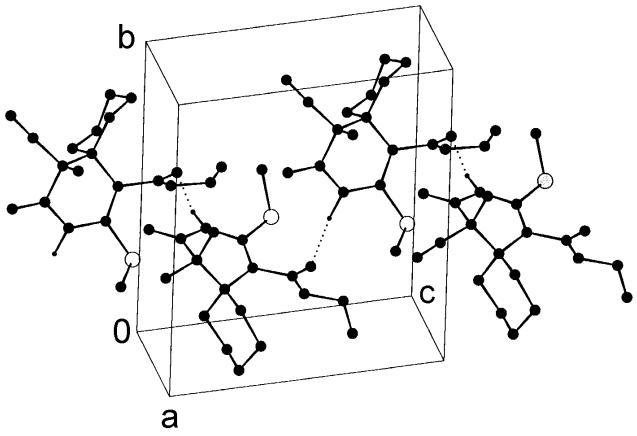

Fig. 2. Crystal packing for compound **11**
(the dotted lines show the intermolecular hydrogen bonds).

The central six-membered $N_{(1)}C_{(1-5)}$ heterocycle is markedly non-planar and exists in a *half-boat* conformation (the modified Kremer-Pople [7] S, θ, and ψ parameters being 0.69, 47.8°, and 25.8° respectively). The ring torsional angles are: $N_{(1)}C_{(1)}C_{(2)}C_{(3)}$ -43.6, $C_{(1)}C_{(2)}C_{(3)}C_{(4)}$ 55.9, $C_{(2)}C_{(3)}C_{(4)}C_{(5)}$ -38.0, $C_{(3)}C_{(4)}C_{(5)}N_{(1)}$ 4.0, $C_{(4)}C_{(5)}N_{(1)}C_{(1)}$ 14.1, and $C_{(5)}N_{(1)}C_{(1)}C_{(2)}$ 7.5°. The $N_{(1)}$ atom has a planar trigonal bond configuration with overall valence angles at this atom of 369.3°. As a consequence of the conjugation of the unshared electron pair of the $N_{(1)}$ atom with the $O_{(1)}=C_{(1)}$ and $C_{(4)}=C_{(5)}$ double bond π-systems, the interatomic distances for $N_{(1)}–C_{(1)}$ of 1.368(7) and $N_{(1)}–C_{(5)}$ 1.409(6) Å are markedly shortened when compared with the standard value of 1.45 Å for a typical $N(sp^2)–C(sp^2)$ bond [8]. The basic geometrical parameters for molecule 11 are typical [9]. In particular, the bond lengths for $S_{(1)}–C_{(5)}$ of 1.747(5) and $S_{(1)}–C_{(16)}$ 1.806(7) Å are almost identical to the corresponding parameters in the Ph–S–Me molecule ($S–C(sp^2)$ 1.749(4) and $S–C(sp^3)$ 1.803(4) Å) [10].

In the crystal of compound **11** the molecules are combined in infinite chains *via* $O_{(2)}\cdots H_{(1)}–N_{(1)}$ hydrogen bonding (Fig. 2) ($O_{(2)}\cdots N_{(1)}$ 2.973(7), $O_{(2)}\cdots H_{(1)}$ 1.90(10) Å, $O_{(2)}H_{(1)}N_{(1)}$ 164(5)°).

EXPERIMENTAL

X-ray Structural Investigation of the Monocrystal of Compound 11 with the linear parameters 0.16 × 0.19 × 0.68 mm was carried out at room temperature on an Enraf-Nonius CAD-4, automatic, four circle diffractometer (CuKα irradiation, relative scanning rate $2\theta/\omega = 1.2$, $\theta_{max} = 70°$, spherical segment $0 \le h \le 8$, $0 \le k \le 13$, $-13 \le l \le 13$). In all, 1826 reflections were gathered of which 1598 are symmetrically independent ($R_{int} = 0.028$). Crystals of compound **11** are monoclinic with $a = 6.923(1)$, $b = 11.265(3)$, $c = 11.117(3)$ Å; $\beta = 104.75(2)°$; $V = 838.4$ Å^3; M = 332.4; $Z = 2$; $d_{calc} = 1.28$ g/cm^3; $\mu = 17.9$ cm^{-1}; $F(000) = 345.5$, and space group *Pc*. The structure was solved using a direct method and refined using least squares analysis in a full matrix, anisotropic approximation with the CRYSTALS program package [11]. 1365 Reflections with $I > 3(I)$ were used in the refinement (203 refinement parameters, number of reflections per parameter 6.7). All of the hydrogen atoms were revealed in electron density difference synthesis and included in the calculation with fixed positions and thermal parameters (only atom $H_{(1)}$ was refined isotropically). Calculation of the absorbance in the crystal was carried out using the azimuthal scanning method [12]. The Chebyshev weighting scheme [13] was used in the refinement with the parameters 0.96, 0.95, and -0.20. The final values of the difference factors were $R = 0.058$ and $R_w = 0.062$, $GOF = 1.103$. The absolute configuration was established using the Flack method

[14] (enantiopolar parameter refinement to 0.07(1) for 1486 reflections with non averaged Friedel equivalents). The complete set of X-ray structural information has been deposited in the Cambridge structural data bank (reg. No. CCDC176372).

IR Spectra were taken on an IRS-29 spectrometer using vaseline oil. ^{1}H NMR spectra were recorded on Gemini-200 (199 MHz) (compounds **6a,b, 10a,c,e, 12**), Bruker AM-300 (300 MHz) (compounds **3, 8a,b**), and Bruker DRX500 (500 MHz) (compounds **10b,d,f, 11**) equipment using DMSO-d_6 solvent and TMS internal standard. Mass spectra were recorded on a Kratos MS-890 (70 eV) spectrometer. Melting points were determined on a Koffler block. Monitoring of the reaction course and the purity of the compounds obtained was carried out using TLC (Silufol UV-254, acetone-hexane, 3: 5) and revealed using iodine vapor. The physicochemical and spectroscopic parameters for compounds **3, 6, 8, 10, 11, 12** are given in Tables 1 and 2.

6-Amino-3-carbethoxy-5-cyano-4-spirocyclohexane-1,2,3,4-tetrahydropyridine-2-thione (3). A solution obtained from sodium (0.23 g, 10 mmol) in ethanol (5 ml) was added to a solution of thioamidoethylmalonate (1.47 g, 10 mmol) in ethanol (20 ml). Cyclohexylidenemalononitrile (1.46 g, 10 mmol) was then added with stirring. The reaction mixture was stirred for 2 h and left for 1 day after which it was acidified with 10% aqueous HCl solution to pH 5. The precipitate formed was filtered off and washed with 40% aqueous ethanol to give compound **3**. The mass spectrum of compound **3** (EI, 70 eV), *m/z* (I_{rel}, %) showed: 293 [M^+] (73), 247 (29), 220 (70), 178 (100), 155 (58).

6-Amino-3-carbethoxy-5-cyano-2-(4'-nitrobenzoylmethylthio)-4-spirocyclohexane-3,4-dihydropyridine (6a), 6-Amino-3-carbethoxy-5-cyano-4-spirocyclohexane-2-(thiazol-2'-ylcarbamoylmethylthio)-3,4-dihydropyridine (6b), 5-Carbethoxy-3-cyano-2-oxo-6-phenylcarbamoylmethylthio-4-spirocyclohexane-1,2,3,4-tetrahydropyridine (10a), 6-Benzylthio-5-carbethoxy-3-cyano-2-oxo-4-spirocyclohexane-1,2,3,4-tetrahydropyridine (10b), 5-Carbethoxy-3-cyano-6-methylthio-2-oxo-4-spirocyclohexane-1,2,3,4-tetrahydropyridine (10c), 2-(4'-Bromophenylcarbamoylmethylthio)-5-carbethoxy-3-cyano-2-oxo-4-spirocyclohexane-1,2,3,4-tetrahydropyridine (10d), 5-Carbomethoxy-3-cyano-6-ethylthio-2-oxo-4-spirocyclohexane-1,2,3,4-tetrahydropyridine (10e), 6-Benzoylmethylthio-5-carbomethoxy-3-cyano-2-oxo-4-spirocyclohexane-1,2,3,4-tetrahydropyridine (10f). A mixture of the corresponding thione (10 mmol), 10% aqueous KOH (5.6 ml, 10 mmol), and the corresponding alkyl halide (10 mmol) in DMF (20 ml) was stirred at 20°C for 4 h and left for one day. The precipitate was filtered off and washed with 40% aqueous ethanol solution and hexane to give compounds **6a,b, 10a-f**. Mass spectrum of compound **10e** (EI, 70 eV), *m/z* (I_{rel}, %): 308 [M^+] (55), 279 (30), 249 (100), 180 (35).

3-Carbethoxy-5-cyano-6-oxo-4-spirocyclohexanepiperidine-2-thione (8a) and 3-Carbomethoxy-5-cyano-6-oxo-4-spirocyclohexanepiperidine-2-thione (8b). A solution obtained from sodium (0.23 g, 10 mmol) in ethanol (5 ml) was added to a solution of the corresponding compound **2** (10 mmol) in ethanol (20 ml). Cyclohexylidenecyanoacetic ester (1.93 g, 10 mmol) was then added with stirring. The reaction mixture was stirred for 2 h and left for one day after which it was acidified with 10% aqueous HCl solution to pH 5. The precipitate formed was filtered off and washed with 40% aqueous ethanol solution to give compounds **8a,b**. Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %), compound **8a**: 294 [M^+] (90), 249 (20), 222 (100), 194 (56), 166 (30), 148 (30), 138 (52), 122 (25); compound **8b**: 280 [M^+] (100), 221 (45), 193 (45), 160 (42), 148 (78), 133 (27).

5-Carbethoxy-3-cyano-3-methyl-6-methylthio-4-spirocyclohexane-3,4-dihydropyridine-2(1H)-one (11). A. A 10% aqueous solution of KOH (5.6 ml, 10 mmol) and then MeI (0.62 ml, 10 mmol) were added with stirring to a solution of compound **10c** (3.08 g, 10 mmol) in DMF (10 ml) and stirred was continued for 2 h. After 1 day the precipitate formed was filtered off and washed with ethanol and hexane to give compound **11**.

B. A 10% aqueous solution of KOH (5.6 ml, 10 mmol) and then MeI (0.62 ml, 10 mmol) were added with stirring to a solution of compound **8a** (1.47 g, 5 mmol) in DMF (10 ml) and stirring was continued for 2 h. After 1 day the precipitate formed was filtered off and washed with ethanol and hexane to give compound **11** in 72% yield. The melting point and the chromatographic and spectroscopic date agreed with the analogous data for compound **11** prepared as in method A. Mass spectrum of compound **11** (EI, 70 eV), *m/z* (I_{rel}, %): 322 [M^+] (70), 307 (100), 277 (32), 261 (69), 226 (35), 180 (55), 148 (48).

2-Benzoyl-5-cyano-3-hydroxy-6-oxo-4,5,6,7-tetrahydrospiro(cyclohexane-4-thioeno[2,3-*b*]pyridine) (12). A 10% aqueous solution of KOH (2.8 ml, 5 mmol) was added to a solution of compound **10f** (1.99 g, 5 mmol) in ethanol (25 ml) and refluxed for 1 h. After 1 day the precipitate formed was filtered off and washed with ethanol and hexane to give compound **12**.

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