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REGIOSELECTIVE SYNTHESIS AND PROPERTIES OF 6-AMINO-3-CARBAMOYL-5-CYANO-3,4-DIHYDROSPIROCYCLOHEXANE-4-PYRIDINE-2-THIOL AND 5-CYANO-3-THIOCARBAMOYL-4-SPIROCYCLOHEXANEPIPERIDINE-2,6-DIONE

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Treatment of monothiomalonodiamide with cyclohexylidenemalononitrile or cyclohexylidenecyanoacetic ester in the presence of sodium ethylate gave 6-amino-3-carbamoyl-5-cyano-3,4-dihydrospirocyclohexane-4-pyridine-2-thiol and 5-cyano-3-thiocarbamoyl-4-spirocyclohexane-piperidine-2,6-dione. Their alkylation and hydrolysis have been studied.

Keywords: 3,4-dihydrospirocyclohexane-4-pyridine-2-thiol, monothiomalonodiamide, spirocyclohexane-4-piperidine-2,6-dione, cyclohexylidenemalononitrile, cyclohexylidenecyanoacetic ester, alkylation, hydrolysis, Michael reaction, regioselective synthesis, cyclization, cyclocondensation.

By contrast with the quite well studied 4-aryl-substituted 3-cyanopyridine-2(1H)-thiones [1], there have been reported in the literature few of the carbamoyl-substituted analogs [2-6] and the spiro-substituted 3-carbamoylpyridine-2-thiones are unknown. At the same time, spiro-substituted heterocycles are of interest for pharmacological study [7]. In connection with the above we now report the development of regioselective methods of synthesis of 6-amino-3-carbamoyl-5-cyano-3,4-dihydrospirocyclohexane-4-pyridine-2-thiol (**1**) and 5-cyano-3-thiocarbamoyl-4-spirocyclohexanepiperidine-2,6-dione (**2**).

The thiol **1** was prepared in high yields (78-83%) by two methods. First from monothiomalonodiamide (**3**) and cyclohexylidenemalononitrile (**4**) *via* a Michael reaction and secondly by the cyclocondensation of the CH-acid **3** with cyclohexylidenecyanothioacetamide (**5**). Both reactions occur at 25°C in absolute ethanol with catalysis by EtONa and apparently include the formation of the corresponding intermediate Michael adducts **6** and **7** which, however, could not be separated.

The composition and structure of compound **1** was confirmed through elemental analysis, spectroscopic data (Tables 1-3), and some chemical reactions. Hence the treatment of the thiol **1** with an aqueous HCl solution occurred even at room temperature with hydrolysis of the enamine fragment to form 3-carbamoyl-5-cyano-6-oxo-4-spirocyclohexanepiperidine-2-thione (**8**), which is an isomer of compound **2**. The reaction of thiol **1** with the alkylating agents **9** in basic medium gave the organic sulfides **10a-f**.

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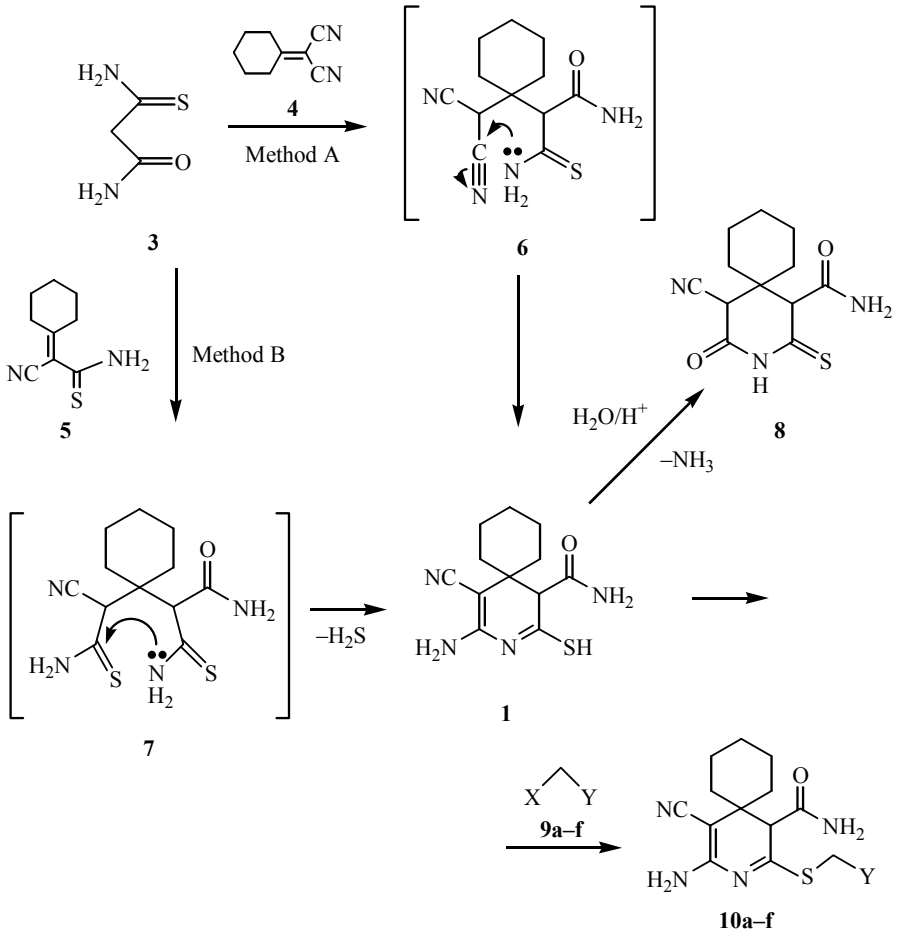
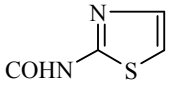
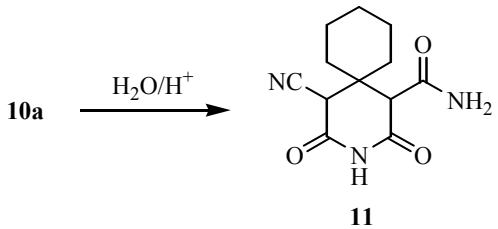


9 a X = I, **b**, **d**, **f** X = Cl, **c**, **e** X = Br; **9**, **10 a**, Y = H, **b** Y = CONHPh, **c** Y = COC_6H_4Me-4,

d Y = COOEt, **e** Y = $CH{=}CH_2$, **f** Y = 

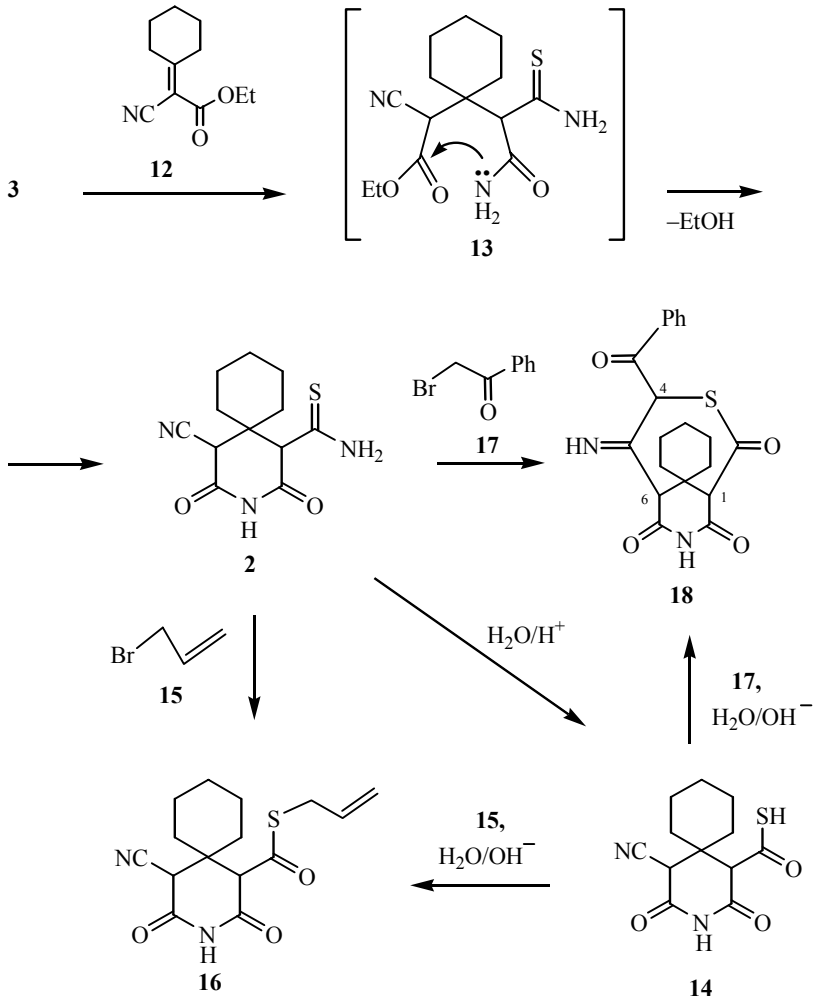
It should be noted that compound **10** also undergoes acid hydrolysis but it does not stop at the stage of the formation of the corresponding oxo compound of type **8**. Hence the treatment of the substituted dihydropiperidine **10a** with a 10% aqueous solution of HCl gave 3-carbamoyl-5-cyano-4-spirocyclohexanepiperidine-2,6-dione (**11**).



The second target product (dione **2b**) was synthesized in 93% yield by the condensation of the monothiomalonodiamide (**3**) with cyclohexylidenecyanoacetic ester (**12**) under Michael reaction conditions and probably occurs *via* the hypothetical adduct **13**.

Hydrolysis of compound **2** in acidic medium leads to the thiocarboxylic acid **14** and alkylation with allyl bromide **15** in basic medium to the thioester **16**. Compound **16** could also be prepared by an independent route from the substituted glutarimide **14** and allyl bromide **15** in the presence of aqueous KOH solution. The data presented above infers that the formation of **16** involves the basic hydrolysis of the thioamide fragment of compound **2**, leading to the thiocarboxylic acid anion which subsequently undergoes alkylation.

The alkylation of the thioamide **2** by phenacyl bromide **17** allows the synthesis of the novel heterocyclic system 4-benzoyl-5-imino-10-spirocyclohexane-8-aza-3-thiabicyclo[1,3,4]decane-2,7,9-trione (**18**).



The production of **18** indicates that the reaction may not stop at the stage of formation of the type **16** thioester but can proceed further *via* a Thorpe-Ziegler cyclization [8] to the imino derivative **18**. The latter compound can also be obtained by the alkylation of the thiocarboxylic acid **14** with compound **17**.

The structure and composition of compound **18** were confirmed by the results of elemental analysis and from spectroscopic data. Hence the IR spectrum of compound **18** showed characteristic absorption bands for the stretching vibrations of the imide, imine, and carbonyl groups (Table 2). At the same time, the absorption band for the stretching vibrations of the nitrile group are absent in this spectrum. The appearance of the signal for the H-4 proton at quite low field (δ 6.71 ppm) is a feature of the ^{1}H NMR spectrum and is explained in terms of the deshielding by three, neighboring C=O, C=NH, and S–C=O electron acceptor groups.

TABLE 1. Characteristics of Compounds **1, 2, 8, 10a-f, 11, 14, 16, 18**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
1	$C_{12}H_{16}N_4OS$	54.40 / 54.52	5.97 / 6.10	21.26 / 21.19	309-311	78
2	$C_{12}H_{15}N_3O_2S$	54.23 / 54.32	5.77 / 5.70	15.91 / 15.84	253-255	93
8	$C_{12}H_{15}N_3O_2S$	54.20 / 54.32	5.79 / 5.70	15.97 / 15.84	230-232	85
10a	$C_{13}H_{18}N_4OS$	55.96 / 56.09	6.62 / 6.52	20.01 / 20.13	216-218	57
10b	$C_{20}H_{23}N_5O_2S$	60.63 / 60.43	5.76 / 5.83	17.79 / 17.62	221-223	71
10c	$C_{21}H_{24}N_4O_2S$	63.56 / 63.61	6.14 / 6.10	14.25 / 14.13	192-194	64
10d	$C_{16}H_{22}N_4O_3S$	54.96 / 54.84	6.45 / 6.33	16.12 / 15.99	174-176	76
10e	$C_{15}H_{20}N_4OS$	59.33 / 59.18	6.53 / 6.62	18.22 / 18.40	166-168	52
10f	$C_{17}H_{20}N_6O_2S_2$	50.56 / 50.48	5.11 / 4.98	20.71 / 20.76	213-215	81
11	$C_{12}H_{15}N_3O_3$	58.00 / 57.82	5.91 / 6.07	16.75 / 16.86	258-260	41
14	$C_{12}H_{14}N_2O_3S$	54.39 / 54.12	5.19 / 5.30	10.49 / 10.52	277-278	80
16	$C_{15}H_{18}N_2O_3S$	58.94 / 58.80	6.05 / 5.92	9.01 / 9.14	199-200	54
18	$C_{20}H_{20}N_2O_4S$	62.64 / 62.48	5.10 / 5.24	7.33 / 7.29	255-257	59

TABLE 2. Spectroscopic Characteristics of Compounds **1, 2, 8, 10a-f, 11, 14, 16, 18**

Compound	IR spectrum, ν, cm^{-1}		^{1}H NMR spectrum, δ, ppm (*J*, Hz)
	NH, NH_2	C≡N, NHCO	
1	2	3	4
1	3210, 3270, 3330, 3410, 3485	2160, 1680	6.67 and 6.56 (1H and 1H, two br. s, $CONH_2$); 5.38 (2H, br. s, NH_2); 3.72 (1H, s, H-3); 1.17-1.58 (10H, m, $5CH_2$)*
2	3330	2260, 1690	11.11 and 9.78 (1H and 1H, two br. s, $CSNH_2$); 9.22 (1H, br. s, NH); 4.00 (1H, s, H-5); 3.63 (1H, s, H-3), 1.33-1.59 (10H, m, $5CH_2$)
8	3310, 3470	2250, 1690, 1660	12.86 (1H, br. s, NH); 8.18 and 7.45 (1H and 1H, two br. s, $CONH_2$); 5.01 (1H, s, H-5); 4.55 (1H, s, H-3); 1.19-1.82 (10H, m, $5CH_2$)
10a	3360, 3530	2165, 1683	7.35 and 6.97 (1H and 1H, two br. s, $CONH_2$); 5.76 (2H, br. s, NH_2); 3.46 (1H, s, H-3); 2.42 (3H, s, SCH_3); 1.27-1.62 (10H, m, $5CH_2$)
10b	3210, 3315, 3375, 3425	2185, 1670	9.89 (1H, s, NH); 7.53 (2H, d, *J* = 7.6, C_6H_5); 7.47 (1H, br. s, $CONH_2$); 7.25 (2H, dd, *J* = 8.0, C_6H_5); 7.00 (2H, m, C_6H_5 and $CONH_2$); 5.97 (2H, br. s, NH_2); 3.91 and 3.88 (1H and 1H, two d, *J* = 3.9, SCH_2); 3.55 (1H, s, H-3); 1.24-1.63 (10H, m, $5CH_2$)

TABLE 2 (continued)

1	2	3	4
10c	3300, 3360, 3450	2175, 1695, 1680	7.91 and 7.34 (2H and 2H, two d, J = 8.2, Ar); 7.47 and 7.02 (1H and 1H, two br. s, $CONH_2$); 5.81 (2H, br. s, NH_2); 4.78 and 4.60 (1H and 1H, two d, J = 16.8, SCH_2); 3.56 (1H, s, H-3); 2.44 (3H, s, CH_3); 1.27-1.64 (10H, m, $5CH_2$)
10d	3210, 3390, 3510	2170, 1740, 1695	7.45 and 7.00 (1H and 1H, two s, $CONH_2$); 5.80 (2H, br. s, NH_2); 4.08 (2H, q, J = 7.2, OCH_2); 4.01 and 3.89 (1H and 1H, two d, J = 16.3, SCH_2); 3.49 (1H, s, H-3); 1.25-1.58 (10H, m, $5CH_2$); 1.21 (3H, t, J = 7.2, CH_3)
10e	3340, 3450, 3510	2163, 1680	7.37 and 6.96 (1H and 1H, two s, $CONH_2$); 5.82 (3H, m, NH_2 and CH=); 5.33 and 5.14 (1H and 1H, two d, J = 16.8, J = 9.9, CH_2); 3.70 (2H, t, J = 7.0, SCH_2); 3.43 (1H, s, H-3); 1.29-1.60 (10H, m, $5CH_2$)
10f	3350, 3420	2155, 1660, 1650	12.08 (1H, s, NH); 7.43 (2H, m, H-4 thiazole and $CONH_2$); 7.16 (1H, d, J = 4.0, H-5 thiazole); 6.94 (1H, br. s, $CONH_2$); 5.89 (2H, br. s, NH_2); 4.13 and 4.01 (1H and 1H, two d, J = 15.2, SCH_2); 3.52 (1H, s, H-3); 1.28-1.63 (10H, m, $5CH_2$)
11	3240, 3450	2250, 1710, 1680	11.50 (1H, br. s, NH); 8.12 and 7.52 (1H and 1H, two br. s, $CONH_2$); 5.06 (1H, s, H-5); 3.99 (1H, s, H-3); 1.23-1.71 (10H, m, $5CH_2$)
14	3240	2255, 1730	13.07 (1H, br. s, SH); 11.61 (1H, br. s, NH); 4.23 (1H, s, H-3); 3.76 (1H, s, H-5); 1.36-1.51 (10H, m, $5CH_2$)
16	3210	2265, 1760, 1720, 1710	11.32 (1H, s, NH); 5.87 (1H, m, CH=); 5.35 and 5.19 (1H and 1H, two d, J = 17.0, J = 10.1, CH_2); 3.82 (3H, m, SCH_2 and H-5); 3.63 (1H, s, H-3); 1.38-1.57 (10H, m, $5CH_2$)
18	3210, 3364	1745, 1710, 1640	11.78 (1H, s, =NH); 11.46 (1H, s, NH); 8.01 (2H, d, C_6H_5); 7.63 (1H, m, C_6H_5); 7.54 (2H, m, C_6H_5); 6.71 (1H, s, SCH); 3.92 (1H, s, H-1); 3.59 (1H, s, H-6); 1.37-1.60 (10H, m, $5CH_2$)

* The SH signal was not found, evidently because of rapid deuterium exchange.

TABLE 3. Mass Spectra of Compounds **1, 2, 8, 10a,b, 11, 14, 16, 18**

Compound	m/z (I_{rel}, %)	
	M^+	Other fragments
1	264 (3)	221 (31), 178 (53), 165 (47), 121 (52), 81 (61), 68 (90), 55 (84), 41 (100)
2	265 (100)	232 (71), 210 (17), 179 (12), 123 (20), 102 (34), 79 (15)
8	265 (65)	248 (30), 221 (45), 179 (25), 145 (100), 118 (52), 102 (45), 44 (43)
10a	278 (23)	261 (8), 246 (2), 234 (19), 218 (13), 192 (100), 179 (26), 146 (8), 120 (8), 67 (12), 44 (39)
10b	397 (9)	293 (31), 263 (47), 218 (77), 190 (30), 177 (19), 135 (15), 120 (26), 93 (100), 65 (53), 39 (74)
14	266 (100)	233 (28), 206 (10), 195 (25), 141 (15), 122 (35), 79 (15)
16	306 (11)	291 (100), 265 (12), 194 (18), 180 (4), 138 (10), 123 (18), 86 (18), 41 (29)
18	—	352 (70), 355 (5), 324 (12), 307 (5), 296 (18), 275 (5), 238 (5), 214 (11), 186 (20), 146 (5), 123 (73), 105 (100), 77 (62)

EXPERIMENTAL

The ^{1}H NMR spectra of compounds **1, 2, 8, 10a-e, 11, 14** were recorded on a Gemini-200 instrument (199 MHz) and compounds **10f, 16, 18** on a Bruker DRX500 (500 MHz) using DMSO-d_6 solvent and TMS internal standard. Mass spectra were taken on a Kratos MS-890 spectrometer (70 eV). Melting points were determined on a Koffler block. IR spectra were recorded on an IRS-29 instrument using vaseline oil. Monitoring of the course of the reaction and the purity of the materials obtained was carried out using TLC on Silufol UV-254 plates in the system acetone-hexane, 3: 5 and revealed using iodine vapor.

6-Amino-3-carbamoyl-5-cyano-3,4-dihydrospirocyclohexane-4-pyridine-2-thiol (1). A. The monothiomalonodiamide **3** (1.18 g, 10 mmol) was added to a solution of sodium (0.23 g, 10 mmol) in absolute ethanol (20 ml) and the mixture was stirred to the formation of a solution, after which the cyclohexylidenemalononitrile **4** (1.46 g, 10 mmol) was added and the stirring was continued for 15 min. The formed yellow precipitate of **1** was filtered off and washed with ethanol and hexane.

B. Using the method described above with the cyclohexylidenecyanothioacetamide **5** (1.8 g, 10 mmol) in place of compound **4** to give the product **1**. The melting point, ^{1}H NMR spectrum, and R_f agreed with those for the sample prepared using method A.

5-Cyano-3-thiocarbamoyl-4-spirocyclohexanepiperidine-2,6-dione (2) was prepared similarly to compound **1** from equimolar amounts (both 10 mmol) of compounds **3** and **12**. The reaction mixture was held for 1 day at 20°C and compound **2** was filtered off.

3-Carbamoyl-5-cyano-6-oxo-4-spirocyclohexanepiperidine-2-thione (8). A solution of 10% aqueous HCl was added dropwise with stirring to a suspension of the thiol **1** (1.32 g, 5 mmol) in ethanol (10 ml) to pH 5. The mixture obtained was held for 1 day at room temperature and the light-yellow crystals of compound **8** were filtered off.

6-Amino-3-carbamoyl-5-cyano-2-methylthio-3,4-dihydrospirocyclohexane-4-piperidine (10a), 6-Amino-3-carbamoyl-5-cyano-2-phenylcarbamoylmethylthio-3,4-dihydrospirocyclohexane-4-pyridine (10b), 6-Amino-3-carbamoyl-5-cyano-2-(4-methylbenzoylmethylthio)-3,4-dihydrospirocyclohexane-4-pyridine (10c), 6-Amino-3-carbamoyl-2-carbethoxymethylthio-5-cyano-3,4-dihydrospirocyclohexane-4-pyridine (10d), 2-Allylthio-6-amino-3-carbamoyl-5-cyano-3,4-dihydrospirocyclohexane-4-pyridine (10e), and 6-Amino-3-carbamoyl-5-cyano-2-[(thiazol-2-ylcarbamoyl)methylthio]-3,4-dihydrospirocyclohexane-4-pyridine (10f). 10% Aqueous KOH (2.8 ml, 5 mmol) and then the halide **9** (5 mmol) were added with stirring to a solution of the thiol **1** (1.32 g, 5 mmol) in DMF (10 ml) at 20°C. The reaction mixture was stirred for 2 h. The precipitated product **10** was filtered off and washed with 40% aqueous ethanol and hexane.

3-Carbamoyl-5-cyano-4-spirocyclohexanepiperidine-2,6-dione (11). A mixture of compound **10a** (1.39 g, 5 mmol) and 10% aqueous HCl (2.74 ml, 7.5 mmol) was refluxed with a reflux condenser for 1 h and held at room temperature for 12 h. The precipitated product **11** was filtered off and washed with ethanol and hexane.

5-Cyano-3-thiocarboxy-4-spirocyclohexanepiperidine-2,6-dione (14) was prepared from the dione **2** (1.32 g, 5 mmol) similarly to the thione **8**. The product **14** was filtered off and washed with ethanol and hexane.

3-Allylthiocarbonyl-5-cyano-4-spirocyclohexanepiperidine-2,6-dione (16). A. A 10% aqueous solution of KOH (2.8 ml, 5 mmol) was added with stirring to a suspension of compound **2** (1.32 g, 5 mmol) in DMF (10 ml). After formation of a homogeneous mixture the allyl bromide **15** (0.42 ml, 5 mmol) was added and the reaction mixture was stirred for 4 h and then held for 1 day at room temperature. The precipitated product **16** was filtered, washed with ethanol and hexane, and recrystallized from ethanol.

B. As in method A replacing compound **2** with the thioacid **14** (1.33 g, 5 mmol) to give the product **16** whose chromatographic data, melting point, ^{1}H NMR spectrum, and R_f were identical to those for the sample prepared by method A.

4-Benzoyl-5-imino-10-spirocyclohexane-8-aza-3-thiabicyclo[1,3,4]decane-2,7,9-trione (18). A. A solution of 10% aqueous KOH (2.8 ml, 5 mmol) and then phenacyl bromide **17** (1.0 g, 5 mmol) were added with stirring to a suspension of compound **2** (1.32 g, 5 mmol) in DMF (10 ml). The reaction mixture was stirred for 4 h and held for 1 day at room temperature. The precipitated product **18** was filtered off, washed with ethanol and hexane, and recrystallized from glacial AcOH.

B. As in method A replacing compound **2** with the thioacid **14** (1.33 g, 5 mmol) to give the product **18**, identical to the sample prepared by method A (mp, ^{1}H NMR spectrum, R_f).

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