1,2,4-Triazines, 9. The Synthesis of Novel 4-Amino-1,6-dihydro-1,2,4-triazinones [1]

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3-Alkylthio-4-amino-1,6-dihydro-1,2,4-triazin-5(4*H*)-ones were synthesized by the reduction of 3-thio-4-amino-1,2,4-triazine-3,5(2*H*,4*H*)-diones and successive *S*-alkylation. The regiospecific alkylation on the N-1 position or the exo amino group leads to a variety of 1,6-dihydro-1,2,4-triazin-5(4*H*)-one derivatives. An alternative synthesis of 3-thio-4-amino-1,6-dihydro-1,2,4-triazine-3,5(2*H*,4*H*)-diones was accomplished through the cyclization of 1-thiocarbohydrazidoacetamide derivatives.

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1,2,4-Triazin-5-ones are one of the most interesting chemical branches for biological activities (for example, metribuzin is a potent herbicide [2]). The significant herbicidal activity observed for certain 1,6-dihydro-1,2,4-triazin-5-ones developed in our laboratory, *e.g.* 1,6-dihydro-1,2,4-triazine-3,5(2*H*,4*H*)-diones [3] and 3-thio-1,6-dihydro-1,2,4-triazine-3,5(2*H*,4*H*)-dione [4], prompts us to continue our research efforts in the dihydrotriazine area. Meanwhile, the reduction of some 1,2,4-triazinones leading to dihydro derivatives of them was actively examined by us [5] and the other groups [6], however, little attention has been devoted to the synthesis of 4-aminodihydrotriazines which could be considered to hold a very important position in triazine chemistry because of their biological activity. This paper describes the first synthesis of 3-methylthio-4-amino-1,6-dihydro-1,2,4-triazin-5(4*H*)-one (**6a**, dihydro-metribuzin) and its derivatives which may be expected to have high herbicidal activity. Also, an alternative synthesis of 3-thio-1,6-dihydro-1,2,4-triazine-3,5(2*H*,4*H*)-diones which involves the cyclization of 1-thiocarbohydrazidoacetamide derivatives is described.

Results and Discussion.

The convenient method for the preparation of 3-thio-4-amino-1,6-dihydro-1,2,4-triazine-3,5(2*H*,4*H*)-diones **3** seems to be the direct reduction of the readily available 3-thio-4-amino-1,2,4-triazine-3,5(2*H*,4*H*)-diones **1** [7]. A brief look in the literature indicated that a few 3-thio-4-alkyl-1,2,4-triazine-3,5(2*H*,4*H*)-diones were reduced by use of sodium-amalgam in water [8]. A careful modification of this reduction method to 3-thio-4-amino-1,2,4-triazine-3,5(2*H*,4*H*)-diones led to the formation of the requisite 3-thio-4-amino-1,6-dihydro-1,2,4-triazine-3,5(2*H*,4*H*)-diones **3**. The successful reduction must be conducted below 5°. Higher temperature (above 5°) resulted in the ring opening to afford thiocarbohydrazidoacetic acids **5**, and hence **3** was obtained in low yield. The reaction yield is dependent upon the substitution pattern at the 6-position of the triazinediones (Table I). The more bulky the group, the higher the yield that was obtained. On the other hand, either the limitation of temperature or structural requirements cannot be observed in the case of the 3-thio-4-methyl-1,2,4-triazine-3,5(2*H*,4*H*)-diones. No other reducing agents such as sodium borohydride, lithium aluminum hydride, or Zn-acetic acid afforded the corresponding 1,6-dihydrotriazines **3** and **4**.

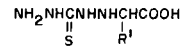

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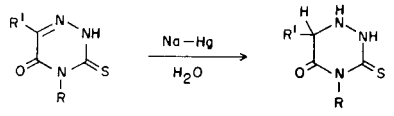
Table I

Sodium-amalgam Reduction of Various 3-Thio-1,2,4-triazine-3,5(2*H*,4*H*)-diones



1, R = NH_2
2, R = CH_3

3, R = NH_2
4, R = CH_3

3	R¹	Yield (%) [a]	**4**	R¹	Yield (%) [a]
a	2,2-dimethylpropyl	25 [b]	**a**	methyl	31 [b,c]
b	*iso*-propyl	29 [b]	**b**	*iso*-propyl	63 [b]
c	*sec*-butyl	50 [b]	**c**	*sec*-butyl	67 [d]
d	1-ethylpropyl	62 [b]	**d**	*t*-butyl	71 [d]
e	cyclohexyl	80 [b]			
f	*t*-butyl	80 [b]			

[a] Yields refer to the isolated ones. [b] Reaction temperature is at 0°. [c] See reference [1]. [d] Reaction temperature is at 25°.

The structure of **3** was determined on the basis of the following physical data. In mass spectrum of **3**, the parent peak was greater by two than that of the starting material. In the ^{1}H-nmr spectrum, the C*H* proton at the 6-position coupled with the N*H* proton at the N-1 position and appeared at δ 3.1-3.8.

Subsequent *S*-methylation of **3** gave rise to 3-methylthio-4-amino-1,6-dihydro-1,2,4-triazin-5(4*H*)-ones **6** in 82-93% yields. 1,6-Dihydrotriazinones **6** thus obtained are chemically attractive structures which possess two types of

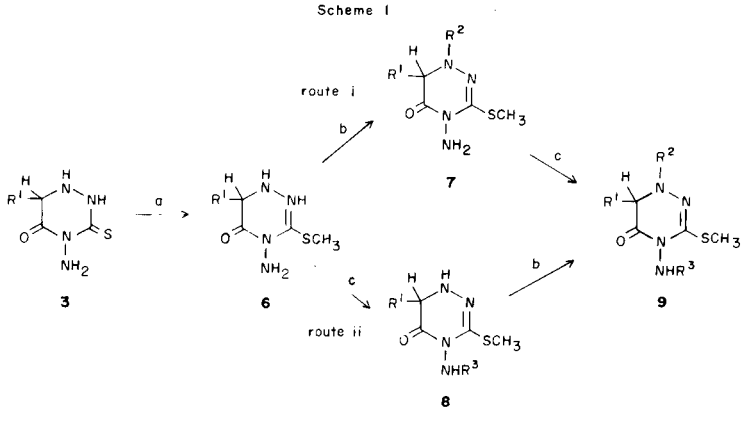
Table II

The Synthesis of 4-Amino-1,6-dihydro-1,2,4-triazin-5(4*H*)-ones

	Substrate				Reaction conditions	Product [a]				Yield (%) [b]
		R^1	R^2	R^3			R^1	R^2	R^3	
1	**6a**	*t*-Bu	—	—	Ac_2O/Py	**7a**	*t*-Bu	Ac	—	100
2	**6a**	*t*-Bu	—	—	CH_3I/NaH	**7b**	*t*-Bu	CH_3	—	95
3	**6a**	*t*-Bu	—	—	CH_3I/MeMgI	**7b**	*t*-Bu	CH_3	—	46
4	**6a**	*t*-Bu	—	—	CH_3I/NaOH	**7b**	*t*-Bu	CH_3	—	42
5	**6b**	*sec*-Bu	—	—	CH_3I/NaH	**7c**	*sec*-Bu	CH_3	—	66
6	**6a**	*t*-Bu	—	—	$PhCH_2Br$/NaH	**7d**	*t*-Bu	$PhCH_2$	—	88
7	**6a**	*t*-Bu	—	—	CH_3I/*n*-BuLi	**8a**	*t*-Bu	—	CH_3	65
8	**6a**	*t*-Bu	—	—	CH_2=$CHCH_2Br$/BuLi	**8b**	*t*-Bu	—	allyl	57
9	**6c**	1-ethyl-propyl	—	—	CH_3I/*n*-BuLi	**8c**	1-ethyl propyl	—	CH_3	50
10	**7d**	*t*-Bu	$PHCH_2$	—	CH_3I/*n*-BuLi	**9a**	*t*-Bu	$PhCH_2$	CH_3	56
11	**8a**	*t*-Bu	—	CH_3	$PhCH_2Br$/NaH	**9a**	*t*-Bu	$PhCH_2$	CH_3	68

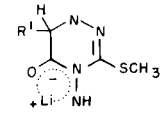
[a] The structure of all new compounds is satisfied by spectral and analytical data. [b] Yields refer to the isolated ones.

Scheme I



a, CH_3I/NaOH – H_2O, below 5°C b, R^2X/base c, R^3X/n-BuLi, –20°C

active hydrogen (the N-1 position and an exo amino group). Regiospecific acetylation and alkylation were examined. Acetylation of **6** with acetic anhydride provided predominantly the N-1 acetylated derivative **7a** (entry 1 in Table II), suggesting that the hydrogen atom at the N-1 position is more acidic than that of the exo amino group. Meanwhile, alkylation of **6** with a variety of bases gave interesting results. The N-1 anion was prepared with sodium hydride at 25°, methylmagnesium iodide at 25° or sodium hydroxide at 70° followed by treatment with methyl iodide, specifically providing an N-1 methylated compound **7** (route i in Scheme I, entries 2- and 6 in Table II). In contrast, the anion produced by *n*-butyllithium at −20° was directed to the methylation of the exo amino group to give **8** with no traces of **7** (route ii in Scheme I, entries 7, 8 and 9 in Table II). This latter result indicated that the chemospecificity can be rationalized on the basis of the formation of a 5-membered conjugated anion **10**.



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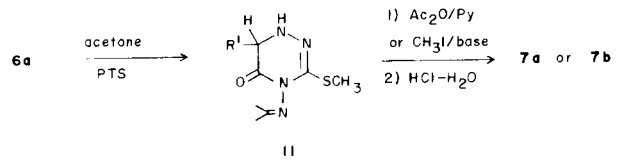
The structures of isomers **7** and **8** were unequivocally determined by spectroscopic analysis and chemical conversions. For example, in the ^1H nmr spectrum of **8a**, the doublet signal for the methyl protons due to the methylamino group appeared at δ 2.65 (J = 5.7 Hz) and the quartet signal for N*H*CH_3 was observed at δ 5.00 with the same coupling constant. In **7b**, the methyl protons at the N-1 position showed a singlet (δ 3.10). On the other hand, it is difficult spectroscopically to assign the acetylation product **7a**. This problem was solved by using a protective group. As shown in Scheme II, acetylation of **11**, easily prepared from **6a**, followed by acid hydrolysis, yielded **7a**, which

was identical in all respects with the direct acetylation product of **6a**. Similarly, this method was applied to the structure determination of the N-1 methylation product **7b**. The bifunctional derivatives **9** of **6** were synthesized from both **7** and **8** (entries **10** and **11** in Table II).

Scheme II



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From the standpoint of the industrial production of 3-thio-4-amino-1,6-dihydro-1,2,4-triazine-3,5(2*H*,4*H*)-diones, an alternative synthesis of **3** was attempted. Starting with 2-bromoacetamides **12**, 2-hydrazinoacetoamides **13** were obtained upon treatment with hydrazines. When **13** was reacted with carbon disulfide in the presence of sodium hydride followed by *S*-methylation with methyl iodide, **14** was obtained. When R^2 = H in **13**, it is noteworthy that thiocarbonylation occurred at the N-2 position due to the bulkiness of the R^1 substituent (*t*-Bu). Hydrazinolysis of **14** effected the removal of the methylthio group to give **15**. Acid cyclization of **15** in hydrochloric acid under reflux re-

Table III

Physical Data of 3-Thio-1,6-dihydro-1,2,4-triazin-3,5(2*H*,4*H*)-diones **3** and **4**

Compound	Mp (°C) [a]	Formula	Analysis, % Calcd./Found C	H	N	S
3a	156.8 [A]	$C_8H_{16}N_4OS$	44.42	7.46	25.90	—
			44.17	8.00	25.61	—
3b	135.2 [A]	$C_6H_{12}N_4OS$	38.27	6.43	29.76	17.03
			38.32	6.51	29.88	17.01
3c	95.9 [B]	$C_7H_{14}N_4OS$	41.56	6.97	27.70	15.85
			41.70	7.00	27.65	15.60
3d	128.9 [A]	$C_8H_{16}N_4OS$	44.42	7.46	25.90	14.82
			44.31	7.54	25.85	14.84
3e	175.5 [A]	$C_9H_{16}N_4OS$	47.35	7.07	24.54	14.05
			47.23	7.31	24.33	14.12
3f	185.6 [A]	$C_7H_{14}N_4OS$	41.56	6.97	27.70	15.85
			41.64	7.30	27.47	15.62
4a	184.7 [B]	$C_5H_9N_3OS$	37.72	5.70	26.39	—
			37.78	5.86	26.45	—
4b	147.5 [A]	$C_7H_{13}N_3OS$	44.89	6.99	22.43	17.12
			45.18	6.98	22.43	16.93
4c	108.3 [B]	$C_8H_{15}N_3OS$	47.73	7.51	20.87	15.93
			47.67	7.78	20.97	15.64
4d	154.1 [A]	$C_8H_{15}N_3OS$	47.73	7.51	20.87	15.93
			47.73	7.60	20.78	15.95

[a] Recrystallization solvents: [A] = ethanol, [B] = *n*-hexane-ethanol.

Table IV

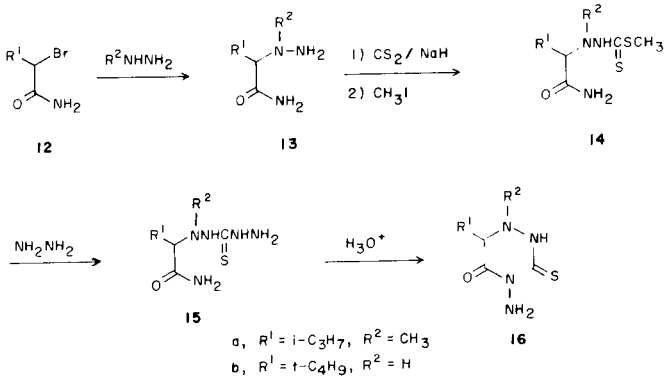
Spectral Data of 3-Thio-1,6-dihydro-1,2,4-triazine-3,5(2*H*,4*H*)-diones **3** and **4**

Compound	^{1}H NMR δ ppm [a]	Mass Spectra (relative intensity)	IR (nujol), cm^{-1}
3a	1.18 (s, 9H), 1.49-1.93 (m, 2H), 3.55-3.97 (m, 1H), 4.86-5.34 (m, 1H), 5.50 (br s, 2H) [A]	216 (M^+, 23), 117 (52), 60 (29), 57 (100)	3220 s, 3180 s, 1695 s, 1555 m, 1190 m
3b	0.94 (d, J = 6.0 Hz, 6H), 1.64-2.25 (m, 1H), 3.28 (dd, J = 5.4, 7.2 Hz, 1H), 6.05 (d, J = 7.2 Hz, 1H) [B]	189 (M+1, 18), 188 (M^+, 80), 145 (55), 117 (100), 60 (29)	3250 s, 3200 m, 1685 s, 1505 m, 1195 s
3c	0.68-1.00 (m, 6H), 1.00-1.96 (m, 3H), 3.19-4.12 (m, 1H), 5.25-5.85 (m, 1H), 6.03 (br s, 2H) [B]	202 (M^+, 14), 145 (27), 117 (100), 60 (42), 57 (40)	3200 s, 3160 s, 1720 s, 1520 m, 1230 s, 1170 m
3d	0.68-0.97 (m, 6H), 1.15-1.87 (m, 5H), 3.40 (t, J = 6.6 Hz, 1H), 5.55 (br s, 2H), 5.92 (d, J = 6.6 Hz, 1H) [B]	216 (M^+, 40), 145 (48), 117 (100)	3280 m, 3160 m, 1700 s, 1585 m, 1200 m
3e	0.74-2.00 (m, 11H), 3.24 (dd, J = 4.8, 6.6 Hz, 1H), 5.92 (d, J = 6.6 Hz, 1H) [B]	228 (M^+, 11), 145 (18), 117 (100), 60 (32), 57 (60)	3280 m, 3240 m, 1685 s, 1505 m, 1180 m
3f	0.99 (s, 9H), 3.24 (d, J = 6.0 Hz, 1H), 5.55 (br s, 2H), 5.08 (d, J = 6.0 Hz, 1H) [B]	202 (M^+ 34), 174 (14), 145 (32), 117 (100), 57 (45)	3240 s, 3180 m, 1685 s, 1545 m, 1180 m
4a	1.18 (d, J = 6.6 Hz, 3H), 3.05-3.35 (m, 1H), 3.30 (m, 3H), 5.65-6.05 (m, 1H) [B]	160 (M+1, 17), 159 (M^+, 100), 144 (51), 58 (29)	3150 m, 1690 s, 1530 m, 1285 m, 1190 m
4b	1.00 (d, J = 6.0 Hz, 6H), 1.63-2.24 (m, 1H), 3.20 (dd, J = 6.0, 7.8 Hz, 1H), 3.36 (s, 3H) 5.97 (d, J = 6.0 Hz, 1H) [B]	187 (M^+, 41), 144 (100), 89 (16), 87 (16)	3260 m, 3160 w, 1695 s, 1505 m, 1280 m, 1280 m, 1085 m
4c	0.75-1.11 (m, 6H), 1.17-2.22 (m, 3H), 3.25-3.50 (m, 1H), 3.48 (s, 3H), 4.39-4.66 (m, 1H), 8.62 (br s, 1H) [C]	201 (M^+, 36), 145 (17), 144 (100), 87 (9), 57 (8)	3160 m, 1700 s, 1280 s, 1090 m
4d	0.96 (s, 9H), 3.07 (d, J = 6.0 Hz, 1H), 3.28 (s, 3H), 4.90 (d, J = 6.0 Hz, 1H) [B]	210 (M^+, 31), 145 (36), 144 (63), 84 (62), 57 (100)	3250 s, 3200 w, 1690 s, 1510 m, 1295 m, 1100 s

[a] Measured solvents: [A] = deuteriochloroform-DMSO-d_6, [B] = DMSO-d_6, [C] = deuteriochloroform.

sulted in the formation of 3-thio-4-amino-1,6-dihydro-1,2,4-triazine-3,5(2*H*,4*H*)-diones **16**. Compound **16b** was identical in all respects with **3f** described above.

Scheme III



In conclusion, we have synthesized the novel 4-amino-1,6-dihydro-1,2,4-triazin-5(4*H*)-ones and their various derivatives by regiospecific *N*-alkylation. Likewise 3-thio-4-amino-1,6-dihydro-1,2,4-triazine-3,5(2*H*,4*H*)-diones were prepared by two methods, reduction and cyclization.

Some of these 1,6-dihydro-1,2,4-triazin-5(4*H*)-ones have potentially high herbicidal activity which will later be described elsewhere in detail.

Table V

Physical Data of 3-Methylthio-4-amino-1,6-dihydro-1,2,4-triazin-5(4*H*)-ones **6**, **7**, **8** and **9**

Compound	Mp (°C) [a]	Formula	Analysis, % Calcd./Found C	H	N	S
6a	162.4 [A]	$C_8H_{16}N_4OS$	44.42	7.46	25.90	14.82
			44.50	7.49	25.70	14.69
6b	138.4 [A]	$C_8H_{16}N_4OS$	44.42	7.46	25.90	14.82
			44.57	7.42	25.76	14.69
6c	116.0 [A]	$C_9H_{18}N_4OS$	46.93	7.88	24.33	13.92
			46.89	8.05	24.36	14.05
7a	169.6 [B]	$C_{10}H_{18}N_4O_2S$	46.50	7.02	21.69	12.41
			46.32	6.99	21.48	12.46
7b	81.9 [B]	$C_9H_{18}N_4OS$	46.93	7.88	24.33	13.92
			46.76	8.00	24.08	13.67
7c	72.9 [B]	$C_9H_{18}N_4OS$	46.93	7.88	24.33	13.92
			46.83	7.84	14.48	13.85
7d	86.3 [B]	$C_{15}H_{22}N_4OS$	—	—	—	—
8a	176.3 [B]	$C_9H_{18}N_4OS$	46.93	7.88	24.33	13.92
			46.78	8.13	24.17	13.96
8b	114.4 [B]	$C_{11}H_{20}N_4OS$	51.52	7.86	21.85	12.51
			51.50	7.89	21.81	12.71
8c	90.7 [B]	$C_{10}H_{20}N_4OS$	49.14	8.25	22.93	13.12
			49.11	8.28	22.74	13.31
9a	83.1 [B]	$C_{16}H_{24}N_4OS$	59.96	7.55	17.48	10.00
			59.80	7.73	17.36	9.90

[a] Recrystallization solvents: [A] = ethanol, [B] = *n*-hexane-ethanol.

EXPERIMENTAL

Melting points were determined in capillary tubes with a Mettler FP 61 instrument and were uncorrected. Short-path (bulb-to-bulb) distillation was carried out in a Kugelrohr apparatus. Microanalyses were obtained with a Perkin-Elmer 240 or 240B instrument. Measurement of the infrared spectra was made on a Hitachi 260-10 spectrometer. Proton magnetic resonances (^{1}H nmr) spectra were measured at 60 MHz on a Hitachi R-24B NMR spectrometer with tetramethylsilane as an internal standard. Mass spectra were run on a Shimadzu LKB-9000B instrument.

3-Thio-1,6-dihydro-1,2,4-triazine-3,5(2*H*,4*H*)-diones **3** or **4**.

General Procedure.

To a solution of substrate **1** or **2** (50 mmoles) and sodium hydroxide (50 mmoles) in water (50 ml) was gradually added 5% sodium-amalgam (75 g) divided into four portions during 1 hour at the indicated temperature. After stirring for an additional hour, the resultant mixture was subjected to filtration to remove insoluble materials. The filtrate was cooled with ice and neutralized with acetic acid. The precipitated white solid was collected by filtration, washed with water (50 ml) and recrystallized to give **3** or **4**. Physical properties are shown in Table III and Table IV.

3-Methylthio-4-amino-1,6-dihydro-1,2,4-triazin-5(4*H*)-ones **6**.

General Procedure.

To a solution of sodium hydroxide (22 mmoles) in water (50 ml) was added **3** (20 mmoles) with ice-cooling and then methyl iodide (30 mmoles) was added thereto followed by stirring for 4 hours. The precipitated white crystals were collected by filtration, washed with water and recrystallized to give **6**. The yield of **6a** was 93%; **6b** was 82%; **6c** was 83%. Physical properties are shown in Table V and Table VI.

1-Acetyl-3-methylthio-4-amino-6-*t*-butyl-1,6-dihydro-1,2,4-triazin-5(4*H*)-one (**7a**). From **6a**.

To a solution of **6a** (220 mg, 1 mmole) and pyridine (2 ml) was added acetic anhydride (120 mg, 1.2 mmoles) at 0°. The reaction mixture was stirred at room temperature for 6 hours. After evaporation of the solvent, the residue was directly subjected to a column purification (silica gel, *n*-hexane-ethyl acetate) to give **7a** (260 mg, 100% yield). An analytically pure sample was obtained by recrystallization from *n*-hexane-ethanol. Physical properties are shown in Table V and Table VI.

From **11**.

To a solution of **11** (180 mg, 0.7 mmole) and pyridine (83 mg, 1.05 mmoles) in ethyl acetate (20 ml) was added acetyl chloride (66 mg, 0.84 mmole) at 0°. After being stirred for 30 minutes, the reaction mixture was washed with aqueous sodium bicarbonate and dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The residue was heated at 70° for 1 hour with *p*-toluenesulfonic acid (3 mg) in 80% aqueous ethanol. The usual extractive workup with chloroform gave **7a** (180 mg, 100% yield).

1-Methyl-3-methylthio-4-amino-6-*t*-butyl-1,6-dihydro-1,2,4-triazin-5(4*H*)-one (**7b**). From **6a**.

Method A.

To a solution of 60% sodium hydroxide (44 mg, 1.1 mmoles) in DMF (3 ml) was added **6a** (216 mg, 1 mmole) in THF (6 ml) at room temperature. After the reaction mixture was stirred at the same temperature for 30 minutes, methyl iodide (94 $\mu\ell$, 1.5 mmoles) was added. The reaction mixture was refluxed for 3 hours. The usual extractive workup with ethyl acetate and removal of the solvent gave crude **7b**, which was purified by column chromatography (silica gel, *n*-hexane-ethyl acetate) to afford pure **7b** (219 mg, 95% yield). Analytically pure material was obtained by recrystallization from *n*-hexane-ethanol. Physical properties are shown in Table V and Table VI.

Method B.

To a solution of methylmagnesium iodide (1*M* in ether, 1.1 ml) in THF (15 ml) was added a solution of **6a** (216 mg, 1 mmole) in THF (5 ml) at room temperature. The following procedure was similar to that of Method A.

Method C.

To a solution of sodium hydroxide (1*M* in water, 1.1 ml) in water (5 ml) and methanol (10 ml) was added **6a** (216 mg, 1 mmole) and methyl iodide (190 μl). After the reaction mixture was heated under reflux for 4 hours, methyl iodide (150 μl) was added. The reaction mixture was refluxed for an additional 2 hours. The following procedure was similar to that of Method A.

From **11**.

To a solution of 60% sodium hydride (13 mg, 0.6 mmole) in DMF (3 ml) was added a solution of **11** (128 mg, 0.5 mmole) in DMF (2 ml) at 0°. After the reaction mixture was stirred for 10 minutes methyl iodide (155 μl) was added. The reaction mixture was heated at 70° for 1 hour. After being cooled to room temperature, *p*-toluenesulfonic acid (15 mg) and water (5 ml) was added and the resultant mixture was heated at 70° for 1 hour. The usual extractive workup with ethyl acetate and removal of the solvent gave crude **7b**, which was purified by column chromatography (silica gel, *n*-hexane-ethyl acetate) to provide pure **7b** (70 mg, 61% yield).

Alkylation on the exo Amino Group of Compounds **6** or **7**.

General Procedure.

A solution of **6** or **7** (1 mmole) in THF (10 ml) was cooled to −20°. To the solution, *n*-butyllithium (1.6 *M* in *n*-hexane, 0.69 ml) was added. The resultant mixture was stirred at −20° for 10 minutes, followed by addition of the alkylating agent (1.5 mmoles). The reaction mixture was gradually raised to room temperature and stirred for 10 hours. The usual extractive workup with ethyl acetate and removal of the solvent afforded crude **8** or **9**, which was purified by column chromatography (silica gel, *n*-hexane-ethyl acetate) to give pure **8** or **9**. An analytically pure sample was obtained by recrystallization from *n*-hexane-ethanol. The physical properties are recorded in Table V and Table VI.

3-Methylthio-4-isopropylideneamino-6-*t*-butyl-1,6-dihydro-1,2,4-triazin-5(4*H*)-one (**11**).

A mixture of **6a** (890 mg, 4.1 mmoles) and *p*-toluenesulfonic acid (10 mg) in acetone (30 ml) was heated under reflux for 5 hours. After being cooled to room temperature an excess of acetone was evaporated under reduced pressure. Recrystallization of the residue from ethanol gave pure **11** (470 mg, 45%), mp 144.7°; ir (nujol): 3280 m, 1700 s, 1510 m, 1265 m, 1225 m cm^{-1}; nmr (deuteriochloroform): δ 1.13 (s, 9 H), 1.90 (s, 3 H), 2.20 (s, 3 H), 2.29 (s, 3 H), 3.38 (s, 1 H), 5.25 br s, 1 H); ms: m/e (relative intensity) 256 (M^+, 9), 199 (69), 144 (18), 56 (100).

Anal. Calcd. for $C_{11}H_{20}N_4OS$: C, 51.52; H, 7.86; N, 21.85; S, 12.50. Found: C, 51.53; H, 7.99; N, 21.70; S, 12.30.

2-(1-Methylhydrazino)-3-methylbutanamide (**13a**).

A mixture of **12a** (5.40 g, 30 mmoles) and hydrazine hydrate (10 ml) was heated under reflux for 3 hours. After being cooled to room temperature, excess hydrazine and water were removed under reduced pressure. To the concentrated residue was added chloroform (50 ml) and water (5 ml) and the resultant mixture was stirred well and separated. Removal of the chloroform gave crude **13a**, which was purified by column chromatography (silica gel, chloroform-methanol) to provide pure **13a** (2.72 g, 62% yield). An analytically pure sample was obtained by recrystallization from *n*-hexane-ethanol, mp 120.5°; ir (nujol): 3050-3430 br m, 1660 s, 1570 m cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.96 (d, J = 6.6 Hz, 3 H), 1.01 (d, J = 6.6 Hz, 3 H), 1.75-2.32 (m, 1H), 2.51 (s, 3H), 2.59 (d, J = 8.4 Hz, 1H), 3.12 (br s, 2 H), 6.04 (br s, 2 H); ms: m/e (relative intensity) 145 (M^+, 5), 101 (100), 85 (21), 45 (66)..

Anal. Calcd. for $C_6H_{15}N_3O$: C, 49.63; H, 10.41; N, 28.94. Found: C, 49.66; H, 10.36; N, 29.05.

Table VI

Spectral Data of 3-Methylthio-4-amino-1,6-dihydro-1,2,4-triazin-5(4*H*)-ones **6**, **7**, **8** and **9**

Compound	^1H NMR (Deuteriochloroform) δ ppm	Mass Spectra (relative intensity)	IR (nujol), cm^{-1}
6a	1.08 (s, 9H), 2.22 (s, 3H), 3.33 (s, 1H), 4.24 (s, 2H), 5.49 (br s, 1H)	216 (M^+, 17), 159 (100) 144 (12), 115 (8)	3320 m, 3290 m, 3170 w, 1685 s, 1615 s, 1160 m
6b	0.77-1.10 (m, 6H), 1.17-2.04 (m, 3H), 2.26 (s, 3H), 3.48 (d, J = 4.2 Hz, 1H), 4.30 (s, 2H), 5.39 (br s, 1H)	216 (M^+, 15), 159 (100), 115 (6)	3310 m, 3020 w, 1695 s, 1610 s, 1160 m
6c	0.79-1.09 (m, 6H), 1.21-2.06 (m, 5H), 2.27 (s, 3H), 3.68 (t, J = 3.6 Hz, 1H), 4.35 (s, 2H), 5.35 (br s, 1H)	230 (M^+, 11), 159 (100), 115 (8)	3310 m, 3150 w, 1670 s, 1495 m, 1250 m, 1150 m
7a	1.00 (s, 9H), 2.31 (s, 3H), 2.39 (s, 3H), 4.35 (s, 2H), 5.30 (s, 1H)	258 (M^+, 13), 202 (24), 159 (100), 144 (51), 57 (21)	3310 m, 3190 m, 1710 s, 1650 s, 1605 m, 1150 m
7b	1.00 (s, 9H), 2.32 (s, 3H), 3.09 (s, 3H), 3.59 (s, 1H), 4.31 (s, 2H)	230 (M^+, 9), 173 (100)	3310 m, 3210 w, 1685 s, 1630 m, 1290 m, 1195 m
7c	0.79-1.12 (m, 6H), 1.26-2.08 (m, 3H), 2.24 (s, 3H), 2.83 (s, 3H), 3.43 (d, J = 3.6 Hz, 1H), 4.20 (s, 2H)	230 (M^+, 10), 173 (100), 144 (3)	3320 m, 3240 w, 1695 s, 1605 m, 1590 m, 1185 m
7d	1.04 (s, 9H), 2.32 (s, 3H), 3.68 (s, 1H), 4.17 (s, 2H), 4.18 (d, J = 13.8 Hz, 1H), 4.63 (d, J = 13.8 Hz, 1H), 7.24 (s, 5H)	306 (M^+, 6), 249 (59), 91 (100)	3320 w, 1685 s, 1615 m, 1320 m, 1290 m
8a	1.07 (s, 9H), 2.21 (s, 3H), 2.65 (d, J = 5.7 Hz, 3H), 3.36 (s, 1H), 5.00 (q, J = 5.7 Hz, 1H), 5.58 (br s, 1H)	230 (M^+, 19), 173 (100), 144 (10)	3320 m, 3240 m, 1675 s, 1320 m, 1285 m
8b	1.06 (s, 9H), 2.21 (s, 3H), 3.38-3.66 (m, 3H), 4.98-5.40 (m, 3H), 5.62-6.18 (m, 2H)	256 (M^+, 16), 199 (100), 144 (24), 57 (17)	3340 m, 3230 m, 1700 s, 1620 m, 1330 m, 1285 m
8c	0.74-1.07 (m, 6H), 1.23-2.08 (m, 5H), 2.26 (s, 3H), 2.66 (d, J = 5.7 Hz, 3H), 3.61 (d, J = 3.6 Hz, 1H), 5.09 (q, J = 5.7 Hz, 1H), 5.45 (br s, 1H)	244 (M^+, 20), 173 (100), 145 (7), 70 (7)	3320 m, 1680 s, 1605 m, 1260 m
9a	0.99 (s, 9H), 2.25 (s, 3H), 2.42 (d, J = 5.7 Hz, 3H), 3.54 (s, 1H), 4.03 (d, J = 13.8 Hz, 1H), 4.51 (d, J = 13.8 Hz, 1H), 4.74 (q, J = 5.7 Hz, 1H), 7.15 (s, 5H)	320 (M^+, 3), 263 (39), 91 (100)	3290 m, 1675 s, 1570 m, 1335 m

2-Hydrazino-3,3-dimethylbutanamide (**13b**).

A mixture of **12b** (970 mg, 5 mmoles) and hydrazine hydrate (5 ml) was heated under reflux for 8 hours. A similar procedure to that used to make **13a** gave crude **13b** which was distilled at 140-146°/0.7 mm Hg to afford **13b** (520 mg, 71% yield). Pure **13b** was obtained by recrystallization from THF, mp 153.4°; ir (nujol): 3480 m, 3240 s, 3130 w, 3040 w, 1630 s, 1505 m cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.00 (s, 9 H), 2.86 (s, 1 H), 2.87-3.77 (m, 4 H); ms: m/e (relative intensity) 145 (M^+, 2), 101 (100), 88 (94), 71 (70), 57 (23).

2-(1-Methyl-2-methylthiothiocarbonylhydrazino)-3-methylbutanamide (**14a**).

To a solution of 62.7% sodium hydride (284 mg, 7.43 mmoles) in THF (5 ml) was added a solution of **13a** (980 mg, 6.75 mmoles) in THF (15 ml) at room temperature and the resultant mixture was stirred for 20 minutes. Carbon disulfide was added to the mixture, which was stirred for an additional 1 hour. To the mixture were added water (5 ml) and, 5 minutes later, methyl iodide (506 μl). After the reaction mixture was stirred for 1 hour, the usual extractive workup with ethyl acetate provided crude **14a** which was purified by column chromatography (silica gel, *n*-hexane-ether) to give pure **14a** (979 mg, 62% yield). An analytically pure sample was obtained by recrystallization from *n*-hexane-ethanol, mp 147.2°; ir (nujol): 3370 m, 3220 w, 3130 m, 1670 s, 1035 m cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.00 (d, J = 6.6 Hz, 3 H), 1.13 (d, J = 6.6 Hz, 3 H), 1.76-2.32 (m, 1 H), 2.54 (s, 3 H), 2.70 (s, 3 H), 2.92 (d, J = 8.4 Hz, 1 H), 6.44 (br s, 1 H), 6.82 (br s, 1 H), 10.00 (br s, 1 H); ms: m/e (relative intensity) 235 (M^+, 5), 191 (17), 143 (79), 129 (30), 86 (54), 85 (46), 84 (100), 70 (71).

Anal. Calcd. for $C_8H_{17}N_3OS_2$: C, 40.82; H, 7.28; N, 17.85; S, 27.24. Found: C, 40.64; H, 7.63; N, 17.74; S, 27.20.

2-(2-Methylthiothiocarbonylhydrazino)-3,3-dimethylbutanamide (**14b**).

The procedure used to make **14a** was applied, yield 45%, mp 133.5° (from *n*-hexane-ethanol); ir (nujol): 3340 m, 3240 w, 3150 m, 1675 s, 1650 s, 1025 m cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.07 (s, 9 H), 2.51 (s, 3 H), 3.14 (d, J = 10.5 Hz, 1 H), 4.83 (d, J = 10.5 Hz, 1 H), 6.12 (br s, 1 H), 7.86 (br s, 1 H), 9.52 (br s, 1 H); ms: m/e (relative intensity) 235 (M^+, 12), 178 (44), 143 (75), 130 (59), 73 (43), 57 (100).

2-(1-Methyl-1-thiocarbohydrazido)-3-methylbutanamide (**15a**).

A mixture of **14a** (706 mg, 3 mmoles) and hydrazine hydrate (0.75 g) in ethanol (10 ml) was heated under reflux for 1 hour. Removal of the solvent and excess of hydrazine provided crude **15a**, which was purified by recrystallization from ethanol to give pure **15a** (440 mg, 67% yield), mp 188.6°; ir (nujol): 3300 w, 3180 m, 1660 s, 1505 s, 1245 m cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.84-1.11 (m, 6 H), 1.80-2.31 (m, 1 H), 2.95 (d, J = 6.6 Hz, 1 H), 4.67 (br s, 2 H), 7.77 (br s, 1 H); ms: m/e (relative intensity) 219 (M^+, 8), 129 (18), 86 (100), 84 (33), 42 (73).

2-(1-Thiocarbohydrazido)-3,3-dimethylbutanamide (**15b**).

A mixture of **14b** (412 mg, 1.75 mmoles) and hydrazine hydrate (0.88 g) in methanol (10 ml) was heated under reflux for 1 hour. After removal of the solvent and excess hydrazine, the residue was purified by column chromatography (silica gel, chloroform-methanol) to provide **15a** (209 mg, 54% yield). An analytically pure material was obtained by recrystallization from ethanol, mp 174.2°; ir (nujol): 3400 w, 3290 m, 3190 w, 3130 w, 1650 s, 1510 m, 1015 m cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.97 (s, 9 H), 3.08 (d, J = 3.6 Hz, 1 H), 5.12 (d, J = 3.6 Hz, 1 H), 7.07 (br s, 1 H), 7.36 (br s, 1 H), 8.94 (br s, 1 H); ms: m/e (relative intensity) 219 (M^+, 24), 162 (100), 117 (33), 90 (38), 86 (71), 60 (39), 57 (79).

Anal. Calcd. for $C_7H_{17}N_5OS$: C, 38.34; H, 7.82; N, 31.94; S, 14.62; Found; C, 38.36; H, 7.84; N, 32.14; S, 14.61.

1-Methyl-3-thio-4-amino-6-isopropyl-1,6-dihydro-1,2,4-triazine-3,5-(2*H*,4*H*)-dione (**16a**).

A mixture of **15a** (300 mg, 1.37 mmoles) and 1*N* hydrochloric acid (3 ml) in water (3 ml) was heated under reflux for 1 hour. The usual extractive workup with chloroform and removal of the solvent gave **16a** (126 mg, 45% yield). Analytically pure sample was obtained by recrystallization from *n*-hexane-ethanol, mp 126.9° dec; ir (nujol): 3300 w, 3180 m, 1690 s, 1500 m, 1190 s cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.00 (d, J = 6.6 Hz, 3 H), 1.07 (d, J = 6.6 Hz, 3 H), 1.58-2.21 (m, 1 H), 2.72 (s, 3 H), 3.05 (d, J = 9.6 Hz, 1 H), 4.99 (br s, 2 H), 8.66 (br s, 1 H); ms: m/e (relative intensity) 202 (M^+, 19), 159 (100), 131 (19), 71 (21).

Anal. Calcd. for $C_7H_{14}N_4OS$: C, 41.56; H, 6.97; N, 27.70; S, 15.55. Found; C, 41.61; H, 6.93; N, 27.75; S, 15.55.

3-Thio-4-amino-6-*t*-butyl-1,6-dihydro-1,2,4-triazine-3,5(2*H*,4*H*)-dione (**16b** = **3f**).

The procedure used to prepare **16a** was applied. The yield was 53%.

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