1,2,4-Triazines. 7. Regioselective N2-Amination of 3-Methylthio-1,2,4-triazin-5(2*H*)-ones. A Novel Synthesis of [1,2,4]Triazolo[2,3-*b*][1,2,4]triazinones and -triazine [1]

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A regioselective synthesis of 2-aminotriazinones **6a-d** is reported, by reaction of 3-methylthio-1,2,4-triazinones **5a-d** with *O*-(2,4-dinitrophenyl)hydroxylamine (**2**) as an amino-transfer agent. A spectroscopic study and an unequivocal synthesis of 2-amino-4-methyl-6-phenyl-1,2,4-triazinedione (**11a**) has shown the site of amination to be N2 of the 1,2,4-triazinone ring. Subsequent reaction of 2-amino-1,2,4-triazinones **6a-b** with amines, followed by ring closure with aliphatic acids provided [1,2,4]triazolo[2,3-*b*][1,2,4]triazine-7(1*H*)-ones **13a-e**. Conversion of [1,2,4]triazolo[2,3-*b*][1,2,4]triazinone **13c** to unsubstituted [1,2,4]triazolo[2,3-*b*][1,2,4]triazine (**15**) was attained.

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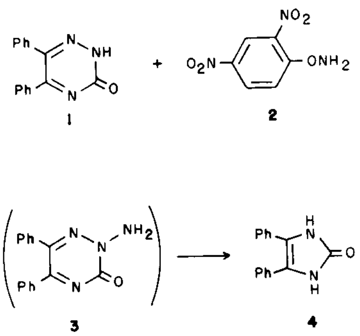
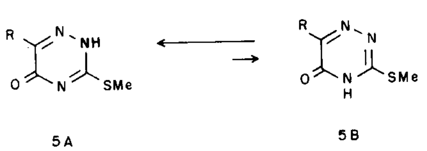
4-Amino-1,2,4-triazin-5(4*H*)-one derivatives have attracted considerable interest, because of their herbicidal activities [2] and important intermediates to the preparation of the fused 1,2,4-triazinone heterocycles [3]. However their regioisomers, 2-amino-1,2,4-triazin-5(2*H*)-ones have not been known until very recently [4]. Attempted N2-amination of 1,2,4-triazin-3(2*H*)-ones **1** with aminating agents such as hydroxyl-*O*-sulphonic acid and *O*-(2,4-dinitrophenyl)hydroxylamine (**2**) was reported to lead to the formation of imidazolin-2-ones **4** in a new ring contraction reaction [5]. 2-Aminotriazinone (**3**) was proposed as the intermediates but it was not isolated (Scheme I).

Scheme I



Since then, few reports have appeared on the synthesis of 2-amino analogues of the 1,2,4-triazine system. In this communication we wish to report a new synthesis of 2-amino-3-methylthio-1,2,4-triazin-5(2*H*)-ones, this being produced by regioselective N2-amination of 3-methylthio-1,2,4-triazin-5(2*H*)-ones **6a-d** with an aminating agent [6] such as *O*-(2,4-dinitrophenyl)hydroxylamine. Also, the transformation of 2-amino-3-methylthio-1,2,4-triazinones **6a-b** to the fused 1,2,4-triazines heterocycles, [1,2,4]triazolo[2,3-*b*][1,2,4]triazinones **13a-e** was accomplished by the reaction of **6a-b** with amines followed by ring closure with aliphatic acids. In addition, [1,2,4]triazolo[2,3-*b*][1,2,4]triazinone (**13c**) has converted into unsubstituted [1,2,4]triazolo[2,3-*b*][1,2,4]triazine by a multistep synthesis.

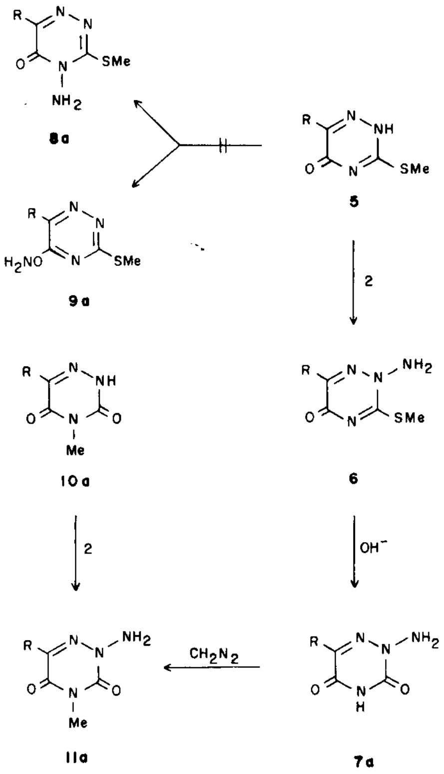
Scheme II



N2-Amination of 3-Methylthio-1,2,4-triazin-5(2*H*)-ones.

The starting material chosen was the readily accessible

Scheme III



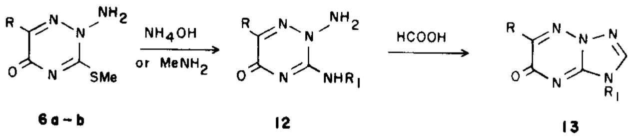
a, R = Ph : b, R = H : c, R = t-Bu : d, R = CH_2Ph

3-methylthio-1,2,4-triazinones **5a-d** [7] which are known to exist as a mixture of tautomers **5A**(2H) and **5B**(4H) (Scheme II). Spectroscopic analysis [8] concludes that **5A**(2H) is a main tautomer and this is supported by the selective alkylation and arylation of **5** at the N2 nitrogen atom [9]. Based on these precedents, our initial investigations were directed towards the direct amination of **5** in the expectation of the selective N2 amination.

The reaction of 3-methylthio-6-phenyl-1,2,4-triazinone (**5a**) with **2** in the presence of *n*-butyllithium in tetrahydrofuran at room temperature afforded only one product after chromatography on silicic acid. The compound **6a** has the expected molecular formular, $C_{10}H_{10}N_4OS$. The ^{1}H nmr spectrum exhibits a broad signal at δ 6.67 due to an amino group which is extinguished by addition of deuterium oxide, indicating the introduction of an amino group into **6a**.

A priori, one might expect to get either N2-, N4- or O5-aminated product (**6a**, **8a** and **9a**). The structure of **6a** was elucidated on the basis of spectroscopic and chemical evidences. The fact that **6a** is different from the known 4-amino-3-methylthio-6-phenyl-1,2,4-triazin-5(4*H*)-one [10] in every respect (melting point, mixture melting point and infrared spectrum), clearly established that no N4 amination has taken place. The possibility of O5 amination to give 6-phenyl-1,2,4-triazine (**9a**) was ruled out due to the presence of the carbonyl group at 1620 cm^{-1} in its infrared spectrum. Accordingly, the compound must have structure **6a**. More solid evidence must be amassed before this conclusion can stand.

Scheme IV



6a-b 12 13

a, R = Ph, R₁ = H
b, R = Ph, R₁ = Me
c, R = R₁ = H
d, R = H, R₁ = Me

When **6a** was heated with 1.1 equivalents of sodium hydroxide under reflux for 1 hour, **7a** was obtained in 63% yield after neutralization with glacial acetic acid. Use of excess basic media (more than 1.3 equivalents) and prolonged reaction time (longer than 2 hours) resulted in decomposition. Attempts to hydrolyze **6a** with 18% hydro-

Table I

Analytical and Spectral Data of 2-Amino-1,2,4-triazinones and 2-Amino-1,2,4-triazinediones

Compound	Mp, °C [a]	Yield % [b]	Formula	Analysis, % Calcd./Found C	H	N	MS M$^+$	IR, cm^{-1} (C=O) [d]	PMR (DMSO-d$_6$) δ ppm
6a	221-222	62 [c]	$C_{10}H_{10}N_4OS$	51.28	4.30	23.92	234	1620	2.47 (s, 3H, SCH$_3$), 6.67 (s, 2H, NH$_2$), 7.30-8.30 (m, 5H, aromatic)
	(A)			51.20	3.98	24.00			
6b	215-216	35 [c,e]	$C_4H_6N_4OS$	30.38	3.82	35.44	158	1620	2.30 (s, 3H, SCH$_3$), 6.51 (s, 2H, NH$_2$), 7.48 (s, 1H, H6)
	(A)			30.34	3.70	35.17			
6c	165-166	75 [c]	$C_8H_{14}N_4OS$	44.85	6.59	26.16	214	1625	1.30 (s, 9H, *t*-butyl), 6.55 (s, 2H, NH$_2$)
	(A)			44.80	6.63	26.08			
6d	160-161	68 [c]	$C_{11}H_{12}N_4OS$	53.22	4.87	22.57	248	1620	2.29 (s, 3H, SCH$_3$), 3.81 (s, 2H, CH$_2$), 6.48 (s, 2H, NH$_2$), 7.23 (s, 5H, aromatic)
	(A)			53.20	4.85	22.46			
7a	169-170	63	$C_9H_8N_4O_2$	52.94	3.95	27.44	204	1680	5.75-5.95 (br s, 2H, NH$_2$), 7.30-8.10 (m, 5H, aromatic)
	(A)			53.05	3.85	27.41		1720	
11a	118-119	89 [f]	$C_{10}H_{10}N_4O_2$	55.04	4.62	25.68	218	1640	3.35 (s, 3H, CH$_3$), 4.90-5.50 (br s, 2H, NH$_2$), 7.20-8.20 (m, 5H, aromatic)
	(A)	47 [c,g]		54.88	4.57	25.74		1700	
12a	273-274	77	$C_9H_9N_5O$	53.19	4.46	34.47	203	1680	6.17 (s, 2H, N-NH$_2$), 7.00-7.30 (br s, 2H, NH$_2$), 7.20-8.20 (m, 5H, aromatic)
	(B)			53.25	4.49	34.44			
12b	202-203	70	$C_{10}H_{11}N_5O$	55.29	5.10	32.24	217	1650	2.90 (d, 3H, CH$_3$), 5.62 (s, 2H, N-NH$_2$), 6.50-6.90 (m, 1H, NH), 7.22-8.15 (m, 5H, aromatic)
	(B)			55.60	5.14	32.43			
12c	279-280	83	$C_3H_5N_5O$	28.35	3.97	55.10	127	1660	6.00 (s, 2H, N-NH$_2$), 6.85-7.25 (br s, 2H, NH$_2$), 7.05 (s, 1H, H6)
	(B)			28.40	3.78	54.98			
12d	204-205	79	$C_4H_7N_5O$	34.04	5.00	49.63	141	1660	2.78 (s, 3H, CH$_3$), 6.06 (s, 2H, NH$_2$), 7.10 (s, 1H, H6), 7.22-7.65 (br s, 2H, NH$_2$)
	(B)			34.30	5.29	49.54			

[a] Recrystallization solvents: A = methanol; B = isopropyl alcohol. [b] Isolation yields after recrystallization, unless otherwise noted. [c] Isolation yields after silica gel chromatography. [d] Potassium bromide disc spectra. [e] Recovery of the starting material was 35%. [f] Yield from **7a**. [g] Yield from **10a**.

chloric acid were unsuccessful. Structure assignment of **7a** was based on elemental analysis and on the spectral data. Infrared spectrum showed strong absorption at 1640 cm^{-1} and 1700 cm^{-1} (two C=O). The ^{1}H nmr spectrum showed broad signal at δ 12.15-12.65 for H2 and no peak for the methylthio group of **6a**.

Further treatment of **7a** with ethereal diazomethane in methanol at 0° for 2 hours gave rise to a monomethylated triazinedione **11a** in 89% yield. That methylation had occurred on a ring nitrogen rather than the exocyclic amino group was established by the appearance of a sharp singlet at δ 3.35 for the methyl group in ^{1}H nmr spectrum. On the other hand, amination of 4-methyl-6-phenyl-1,2,4-triazine-3,5(2*H*,4*H*)-dione (**10a**) [11] was accomplished, upon treatment with **2**, to afford 2-amino-1,2,4-triazinedione which was identical in all respects (melting point, mixture melting point, and infrared spectrum) with 2-amino-4-methyl-6-phenyl-1,2,4-triazinedione (**11a**) prepared by the methylation of **7a** (Scheme III).

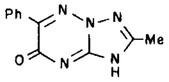
Therefore, on the basis of the above, we can unequivocally state that amination of **5a** with **2** under basic conditions proceeds regioselectively to give the N2-aminated 1,2,4-triazinone **6a**. Likewise, 2-amino-3-methylthio-1,2,4-triazin-5(2*H*)-ones were also prepared under similar condition as described above (Table I).

Conversion of 2-Amino-3-methylthio-1,2,4-triazinones to [1,2,4]Triazolo[2,3-*b*][1,2,4]triazin-7(1*H*)-ones.

2-Amino-3-methylthio-1,2,4-triazin-5(2*H*)-ones now readily available are highly promising as synthetic intermediates for the preparation of fused [1,2,4]triazine heterocycles. Conversion of **6a-b** to [1,2,4]triazolo[2,3-*b*][1,2,4]triazin-7(1*H*)-ones was attempted.

When **6a-b** was heated in a sealed tube at 100° with 18% ammonium hydroxide or 40% methylamine in pyridine, nucleophilic displacement occurred to afford the corresponding 2,3-diamino-1,2,4-triazinones **12a**, **12c** and 2-amino-3-methylamino-1,2,4-triazinones **12b**, **12d** in good yields, respectively (Scheme IV).

Ring closure of **12a-d** was accomplished using excess formic acid under reflux for 8 hours to furnish the desired [1,2,4]triazolo[2,3-*b*][1,2,4]triazinones **13a-d**. Ring cyclization was established on the basis of ^{1}H nmr spectra which showed a sharp singlet for H2 at δ 8.05-8.78. Treatment of **9a** with excess hot acetic acid produced compound **13e** which precipitated from the reaction mixture on cooling. Compound **13e** could be also prepared by refluxing **9a** in acetic anhydride. Its ^{1}H nmr spectrum contained a sharp singlet for the methyl group at δ 2.40, indicating that ring closure had been effected with acetic acid or acetic anhydride to provide 2-methyl[1,2,4]triazolo[2,3-*b*][1,2,4]triazinone (**13e**).



13e

Conversion of [1,2,4]Triazolo[2,3-*b*][1,2,4]triazin-7(1*H*)-one to Unsubstituted [1,2,4]Triazolo[2,3-*b*][1,2,4]triazine.

Table II

Analytical and Spectral Data of Triazolotriazinones and Triazolotriazines

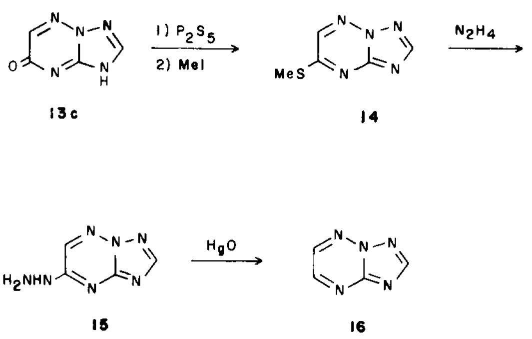
Compound	Mp, °C [a]	Yield % [b]	Formula	Analysis, % Calcd./Found C	H	N	MS M$^+$	IR, cm^{-1} (C=O) [c]	PMR (δ ppm) [d]
10a	252	78	$C_{10}H_7N_5O$	56.33	3.31	32.85	213	1620	7.35-8.20 (m, 5H, aromatic), 8.10 (s, 1H, H2) (D)
	(A)			56.60	3.15	32.83			
10b	161	93	$C_{11}H_9N_5O$	58.14	3.99	30.82	227	1600	3.58 (s, 3H, CH_3), 7.40-8.15 (m, 5H, aromatic), 8.78 (s, 1H, H2) (D)
	(A)			58.22	3.95	30.88			
10c	213	95	$C_4H_3N_5O$	35.04	2.21	51.09	137	1620	7.60-8.20 (br s, 1H, NH), 7.85 (s, 1H, H6), 8.05 (s, 1H, H2) (D)
	(A)			35.30	2.39	51.32			
10d	228	66	$C_5H_5N_5O$	39.73	3.33	46.34	151	1640	3.50 (s, 3H, CH_3), 7.68 (s, 1H, H6), 8.68 (s, 1H, H2) (D)
	(A)			40.00	3.32	46.53			
10e	252	78 [e]	$C_{11}H_9N_5O$	58.14	3.99	30.82	227	1610	2.40 (s, 3H, CH_3), 7.30-8.00 (m, 5H, aromatic) (D)
	(A)	85 [f]		58.20	3.95	30.59			
14	162	82	$C_5H_5N_5S$	35.93	3.02	41.91	167		2.70 (s, 3H, SCH_3), 8.20 (s, 1H, H2), 8.35 (s, 1H, H6) (E)
	(B)			35.93	2.92	41.62			
15	267	97	$C_4H_5N_7$	31.79	3.33	64.88	151		3.00-4.00 (m, 3H, $NHNH_2$), 7.92 (s, 2H, H2 and H6)
	(A)			31.65	3.10	64.65			
16	165	84	$C_4H_3N_5$	39.67	2.50	57.83	121		8.67 (d, 1H, $J_{6,7}$ = 2.5 Hz, H6), 8.72 (s, 1H, H2), 8.87 (d, 1H, H7), (E)
	(C)			39.54	2.20	57.59			

[a] Recrystallization solvents: A = methanol; B = ethanol; C = acetone. [b] Isolation yields after recrystallization. [c] Potassium bromide disc spectra. [d] Measured solvents: D = DMSO-d$_6$; E = deuteriochloroform. [e] Yield from acetic acid. [f] Yield from acetic anhydride.

Recently, the synthesis of [1,2,4]triazolo[1,2,4]triazine heterocycles, in particular [1,2,4]triazolo[2,3-*b*][1,2,4]triazines was reported by Daunis *et al.* [12]. But attempts to prepare unsubstituted [1,2,4]triazolo[2,3-*b*][1,2,4]triazine (**15**) were unsuccessful. Starting with unsubstituted [1,2,4]-triazolo[2,3-*b*][1,2,4]triazin-7(1*H*)-one (**10a**), successful synthesis of **15** was achieved.

Treatment of [1,2,4]triazolo]2,3-*b*][1,2,4]triazinone (**13c**) with phosphorus pentasulfide in pyridine at 100° followed by S-methylation with methyl iodide led to 7-methylthio-[1,2,4]triazolo[2,3-*b*][1,2,4]triazine (**14**) in 82% overall yield. Nucleophilic displacement of the methylthio group with hydrazine and successively oxidation of the 7-hydrazino[1,2,4]triazolo[2,3-*b*][1,2,4]triazine with mercury oxide afforded unsubstituted [1,2,4]triazolo[2,3-*b*][1,2,4]triazine (**15**) in 81% overall yield. The structure of the compound **15** was confirmed by its ^{1}H nmr spectrum. It gave a sharp singlet at δ 8.72 due to H2 and a doublet at lower field (δ 8.87) for H7 with a fairly small coupling constant ($J_{6,7}$ = 2.5 Hz) (Scheme V).

Scheme V



In summary, this study represents the first example of the synthesis of 2-amino-3-methylthio-1,2,4-triazin-5(2*H*)-ones and a synthetic route for the [1,2,4]triazolo[2,3-*b*]-[1,2,4]triazinones and -triazine. Some of 2-amino-3-methylthio-1,2,4-triazin-5(2*H*)-one derivatives have the high potential herbicidal activities [13] which will be later described elsewhere in detail.

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover capillary melting apparatus and are uncorrected. The ^{1}H nmr spectra were recorded on a Hitachi R-900 spectrometer operating at 90 MHz as an internal standard. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6M instrument equipped with a solid sample injector; the ionizing voltage was 70 eV. The ir spectra were recorded on a Hitahi 260-10 spectrometer.

General Procedure for Preparation of 2-Amino-3-methylthio-1,2,4-triazin-5(2*H*)-ones **6a-d**.

A solution of 5.0 mmoles of 1,2,4-triazinones **5a-d** in 50 ml of dry tetrahydrofuran was cooled in a dry ice-acetone bath under a nitrogen atmosphere, and then 2.6 ml (6.0 mmoles) of 2.3 *M* *n*-butyllithium in hexane was added over 10 minutes at temperature below −35°. Thereafter a solution of 1.3 g (6.5 mmoles) of *O*-(2,4-dinitrophenyl)hydroxylamine in 20 ml of dry tetrahydrofuran was added over 15 minutes at temperature below −10°; the cooling bath was removed and stirring continued for 24 hours at room temperature. Addition of 10 ml of methanol was followed by removal of tetrahydrofuran under reduced pressure. The crude product was chromatographed over silicic acid; methanol-chloroform (1:80) eluted 2-amino-1,2,4-triazinones **6a-d**, which on recrystallization from methanol yielded an analytical sample. Yields and physical constants are shown in Table I.

2-Amino-6-phenyl-1,2,4-triazine-3,5(2*H*,4*H*)-dione (**7a**).

A mixture of 2.3 g (9.8 mmoles) of 2-amino-3-methylthio-6-phenyl-1,2,4-triazinone (**6a**) and 0.4 g (10.0 mmoles) of sodium hydroxide in 50 ml of water was heated under reflux. After 1 hour, the mixture was carefully neutralized with glacial acetic acid to give 2-amino-6-phenyl-1,2,4-triazinedione (**7a**) which on recrystallization from methanol yielded an analytical sample. Yield and physical properties are shown in Table I.

2-Amino-4-methyl-6-phenyl-1,2,4-triazine-3,5(2*H*,4*H*)-*dione* (**11a**).

From **7a**; to a solution 2.0 g (9.8 mmoles) of **7a** in 10 ml of methanol was added an ethereal solution of diazomethane prepared from, 6.3 g (29.4 mmoles) of *p*-toluenesulfonyl methyl nitroamide according to the procedure described by de Boer *et al.* [14], and the mixture was allowed to stand for 10 hours at room temperature. After removal of methanol, the residue was recrystallized from methanol yielding 1.9 g (89%) of **11a** (Table I).

From **10a**; according to the general method for the preparation of **6a-d** described above, 2.0 g (9.8 mmoles) of 4-methyl-6-phenyl-1,2,4-triazinone (**10a**) was allowed to react with 2.5 g (12.7 mmoles) of 2 in 100 ml of dry tetrahydrofuran in the presence of 5.1 ml of 2.3 *M* *n*-butyllithium. The reaction mixture was stirred for 24 hours at room temperature and then neutralized cautiously with glacial acetic acid. After removal of tetrahydrofuran under reduced pressure, the residue was partitioned between chloroform (50 ml) and water (20 ml). The obtained chloroform-soluble material was recrystallized from methanol to give 1.0 g (47%) of colorless crystals; ^{1}H nmr, ir and mixture melting point indicated that this heterocycle was identical with **11a** obtained above.

General Procedure for Preparation of 2,3-Diamino-1,2,4-triazin-5(2*H*)-ones **12a**, **12c** and 2-Amino-3-methylamino-1,2,4-triazin-5(2*H*)-ones **12b**, **12d**.

A mixture of 5.0 mmoles of 2-amino-3-methyl-1,2,4-triazin-5(2*H*)-ones **6a-b** and 50 mmoles of 18% ammonium hydroxide or 40% methylamine in pyridine (10 ml) was heated in a sealed tube at 100° for 3 hours. After removal of the solvent *in vacuo* the residue was recrystallized from isopropyl alcohol to give an analytical sample. Yields and physical properties are shown in Table I.

General Procedure for Preparation of [1,2,4]Triazolo[2,3-*b*][1,2,4]triazin-7(1*H*)-ones **13a-e**.

A mixture of 5.0 mmoles of 2,3-diamino- and 2-amino-3-methylamino-triazin-5(2*H*)-ones **12a-d** and 50 mmoles of aliphatic acids or acetic anhydride was heated under reflux for 4 hours. After removal of the solvent *in vacuo* the residue was recrystallized from methanol to give an analytical sample. Yield and physical properties were exhibited in Table II.

7-Methylthio[1,2,4]triazolo[2,3-*b*][1,2,4]triazine (**14**).

A mixture of 0.5 g (3.6 mmoles) of [1,2,4]triazolo[2,3-*b*][1,2,4]triazin-7(1*H*)-one (**10a**) and 0.6 g of phosphorus pentasulfide was heated for 2 hours. After evaporation to dryness the residue was poured into 15 ml of hot water and the precipitate (0.7 g) was removed by filtration. A stirred solution of the crude product (0.7 g) in 5.0 ml of 4% aqueous sodium hydroxide and 0.4 ml of methyl iodide was allowed to stand at room temperature for 1 hour, the organic product was extracted with chloroform and the extract evaporated to dryness giving 7-methylthio[1,2,4]triazolo-[2,3-*b*][1,2,4]triazinone (**14**) which was recrystallized from ethanol to furnish an analytical sample. Yield and physical properties are indicated in Table II.

7-Hydrazino[1,2,4]triazino[2,3-*b*][1,2,4]triazine (**15**).

A mixture of 0.4 g (2.4 mmoles) of 7-methylthio[1,2,4]triazolo[2,3-*b*]-[1,2,4]triazine (**14**) and 0.24 g (4.8 mmoles) of hydrazine hydrate in 10 ml of ethanol was refluxed for 1 hour. After cooling, the precipitate was collected by means of suction filtration. Recrystallization from methanol gave an analytical sample. Yield and physical properties are shown in Table II.

[1,2,4]Triazolo[2,3-*b*][1,2,4]triazine (**16**).

A mixture of 0.3 g (2.0 mmoles) of 7-hydrazino[1,2,4]triazolo[2,3-*b*]-[1,2,4]triazine (**15**) and 2.0 g of mercuric oxide in 30 ml of ethanol was refluxed for 3 hours. The solid was filtered and the filtrate concentrated to dryness, affording the unsubstituted [1,2,4]triazolo[2,3-*b*][1,2,4]triazine (**16**). It was recrystallized from acetone leaving an analytical sample. Yield and physical properties are shown in Table II.

REFERENCES AND NOTES

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