1,2,4-Triazines. III. A Convenient Synthesis of 1,2,4-Triazines and their Covalent Hydration.

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A general synthesis of 1,2,4-triazines, from 3-methylthiotriazines is described. It has been shown that 1,2,4-triazines undergo covalent hydration across the N_4-C_5 bond.

We recently reported the synthesis of 1,2,4-triazine, the analysis of its NMR and mass spectra, along with some of its pertinent physical constants (1,2). Since these publications have appeared, a similar synthesis of this compound has been reported and the various physical properties described by us have been confirmed (3,4).

Both of these preparations involve multistep sequences with rather low overall yields. Consequently, in order to enable us to study the chemistry of 1,2,4-triazine extensively, it became necessary to investigate alternate and more facile syntheses of this compound.

We now wish to report the results of this synthetic study and the behavior of 1,2,4-triazine when subjected to treatment with aqueous acid.

The condensation of *S*-methylthiosemicarbazide (**2**) with glyoxal (**3a**) or other α,β-dicarbonyl compounds (**3b-e**) readily affords the 3-methylthio derivatives of 1,2,4-triazines (**4**). These substances are easily converted to their 3-hydrazino derivatives (**5**) by means of hydrazine, and are then conveniently oxidized with active manganese dioxide to the appropriate 1,2,4-triazine (**1**).

Unfortunately, the formation of the 3-hydrazino-1,2,4-triazine (**5a**) from the 3-methylthio-1,2,4-triazine is a rather low yield transformation.

It was, however, found that this shortcoming could be overcome by first converting the 3-methylthio-1,2,4-triazine (**4a**) to its 3-methoxy derivative (**6a**), which is then converted, in high yield, to the 3-hydrazino-1,2,4-triazine (**5a**). The latter compound is readily oxidized to the parent compound (**1a**) by means of activated manganese dioxide. These transformations are delineated in Scheme I.

SCHEME I

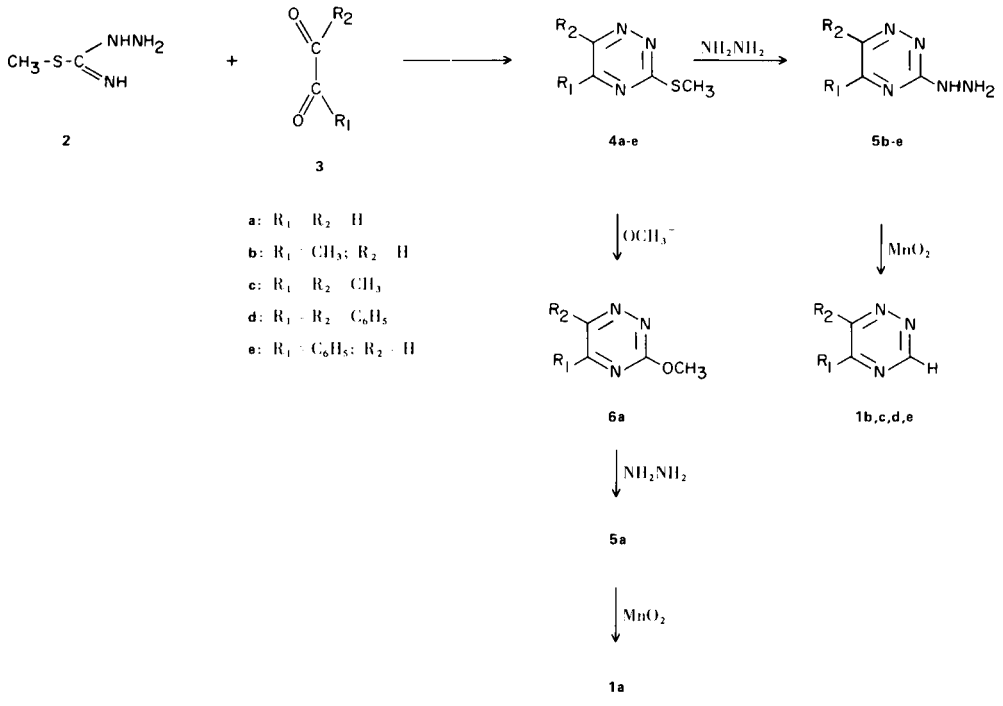
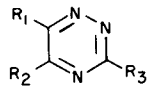
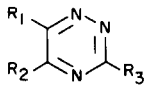


TABLE I
ANALYTICAL DATA FOR SOME 1,2,4-TRIAZINES



Compound No.	Molecular Formula	NMR DATA								Anal:					
					Chemical Shifts (τ)			Coupling Constants (cps)		Calcd:			Found:		
		R_1	R_2	R_3	R_1	R_2	R_3	$J_{R_1R_2}$	Solvent	%C	%H	%N	%C	%H	%N
4a	$C_4H_5N_3S$	H	H	SCH_3	1.00	1.54	7.36	2.3	$CDCl_3$	37.80	3.94	33.07	38.07	3.80	33.00
6a	$C_4H_5N_3O$	H	H	OCH_3	0.84	1.44	4.85	2.3	$CDCl_3$	43.24	4.50	37.84	43.34	4.33	37.93
5a	$C_3H_5N_5$	H	H	$NHNH_2$	1.41	1.63	------	2.4	D_2O	32.43	4.50	63.06	32.43	4.52	63.55
4c	$C_5H_7N_3S$	H	CH_3	SCH_3	1.18	7.48	7.34		$CDCl_3$	42.54	5.00	29.76	42.60	4.98	29.61
6c	$C_5H_7N_3O$	H	CH_3	OCH_3	1.14	7.46	5.84		$CDCl_3$	48.00	5.60	33.60	47.88	5.60	33.79
5c	$C_4H_7N_5$	H	CH_3	$NHNH_2$	1.42	5.22	------		D_2O	38.40	5.60	56.00	38.42	5.87	56.43
4e	$C_9H_9N_3S$	H	C_6H_5	SCH_3	0.68	1.90 (M) 2.49 (M)	7.31		$CDCl_3$	59.11	4.43	20.69	59.02	4.38	20.86
6e	$C_9H_9N_3O$	H	C_6H_5	OCH_3	0.60	1.86 (M) 2.48 (M)	5.78		$CDCl_3$	64.17	4.81	22.46	64.06	5.09	22.45
5e	$C_9H_9N_5$	H	C_6H_5	$NHNH_2$	0.70	2.38 (M) 1.73 (M)	6.1 (ca)		DMSO-d_6	57.75	4.81	37.43	57.70	4.90	37.20
4b	$C_6H_9N_3S$	CH_3	CH_3	SCH_3	7.46	7.58	7.43		$CDCl_3$	46.42	5.81	27.10	46.50	5.82	26.90
6b	$C_6H_9N_3O$	CH_3	CH_3	OCH_3	7.37	7.48	5.87		$CDCl_3$	51.80	6.47	30.22	51.75	6.61	30.25
5b	$C_5H_9N_5$	CH_3	CH_3	$NHNH_2$	7.49	7.60	7.89 2.78		$CDCl_3$	43.17	6.47	50.36	42.95	6.64	50.62
4d	$C_{16}H_{13}N_3S$	C_6H_5	C_6H_5	SCH_3	2.49 (M)	2.66 (M)	7.25		$CDCl_3$	68.82	4.66	15.05	68.53	4.66	15.11
6d	$C_{16}H_{13}N_3O$	C_6H_5	C_6H_5	OCH_3	2.60 (M)	2.60 (M)	5.76		$CDCl_3$	73.00	4.92	15.97	72.88	5.00	16.00
5d	$C_{15}H_{13}N_5$	C_6H_5	C_6H_5	$NHNH_2$	2.70 (M)	2.70 (M)	6.06		$CDCl_3$	68.44	4.94	26.62	68.82	5.18	26.90

TABLE II
Experimental Variables For the Syntheses of Various Triazines

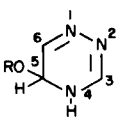


No:	Compound			Reactants	Procedure	Reaction Time (hr.)	Reaction Temp. (°C)	% Yield	m.p.	b.p. (mmHg)
	R_1	R_2	R_3							
4b	CH_3	CH_3	SCH_3	**2**, diacetyl	A	5	5	86	-----	105-106 (0.3)
6b	CH_3	CH_3	OCH_3	CH_3ONa, **4b**	B	12	28	65	-----	67-68 (0.15)
5b	CH_3	CH_3	$NHNH_2$	NH_2NH_2, **4b**	C	36	reflux	72	125.5-128.8	-------
1b	CH_3	CH_3	H	MnO_2, **5b**	D	1 ½	28	50	-----	83-85 (13) (a,d)
4c	H	CH_3	SCH_3	**2**, methylglyoxal	A	5	5	64	74-69	60-63 (0.3)
6c	H	CH_3	OCH_3	CH_3ONa, **4c**	B	24	28	75	89-90.5	-------
5c	H	CH_3	$NHNH_2$	NH_2NH_2, **4c**	C	8	reflux	72	163-165	-------
1c	H	CH_3	H	MnO_2, **5c**	D	2 ½	28	55	-----	88-90 (13) (e)
4e	H	C_6H_5	SCH_3	**2**, phenylglyoxal	A	5	5	81	99-100.5	-------
6e	H	C_6H_5	OCH_3	CH_3ONa, **4e**	B	36	28	45	76.5-78	-------
5e	H	C_6H_5	$NHNH_2$	$NHNH_2$, **4e**	C	9	reflux	64	149-151	-------
1e	H	C_6H_5	H	MnO_2, **5e**	D	3 ½	28	35	99.5-102 (f)	
4d	C_6H_5	C_6H_5	SCH_3	**2**, diphenylgloxal	A	20	5	88	121-122.5	-------
6d	C_6H_5	C_6H_5	OCH_3	CH_3ONa, **4f**	B	24	28	62	77-79 (b)	-------
5d	C_6H_5	C_6H_5	$NHNH_2$	NH_2NH_2, **4f**	C	24	reflux	64	170-172 (c)	-------
1d	C_6H_5	C_6H_5	H	MnO_2, **5f**	D	5	28	40	116-118 (g)	-------

(a) see also Experimental section for isolation of the 6-methyl derivative. (b) literature m.p. 77° (ref. 8). (c) literature m.p. 171-173° (ref. 9). (d) literature b.p. 83-85° (13 mm) (ref. 4). (e) literature b.p. 89-91° (13 mm) (ref. 4). (f) literature m.p. 103° (ref. 4). (g) literature m.p. 116-117° (ref. 4).

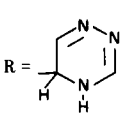
Covalent Hydration of 1,2,4-Triazine.

The addition of water to a solution of 1,2,4-triazine in trifluoracetic acid rapidly generates a new species as shown by the decrease in the signal intensity of the triazine protons and the appearance of a new ABX set of peaks at more shielded positions. The amount of this compound formed is directly proportional to the amount of water added to the acid solution, and finally becomes the sole component. The "new" NMR peaks appear at τ 1.45 (doublet), τ 2.40 (doublet of doublets) and τ 4.40 (doublet). This behavior strongly suggests that one of the following compounds is formed:



7

R = H or



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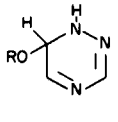
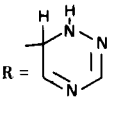
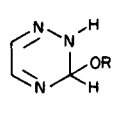


8

R = H or

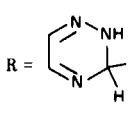


R =



9

R = H or



R =

If R is a hydrogen in these structures the compounds are simply covalently hydrated 1,2,4-triazines. If R is the indicated dihydro-1,2,4-triazinyl radical, the substances are ethers.

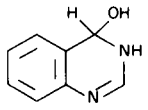
Since it is highly improbable that any long-range coupling between H_3 and H_6 exists in structure **9**, it appears reasonable to exclude it from consideration.

A differentiation between structures **7** and **8** is readily made, since a similar hydration product, obtained from the 5-methyl-1,2,4-triazine does not show the shielded (τ 4.40 doublet) signal in the NMR spectrum, while it still shows an AB system of resonance frequencies similar to that observed in the 1,2,4-triazine derivative (τ 1.52; τ 2.56). Thus, we can conclude that the correct structure for the "hydrated" compound is structure **7**.

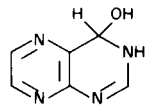
Addition of base to an aqueous solution of these compounds quantitatively regenerates the corresponding 1,2,4-triazines. Consequently, it appears that the ether structure (**7**, R ≠ H) can be excluded from consideration. This, however, does not mean that the ether may not be formed under more severe reaction conditions. Thus far, attempts at isolating the hydrated species from solution have invariably resulted in the recovery of the triazines themselves.

While covalent hydration of quinazolines, pteridines, and related ring systems (5) has been examined in some detail, there is no report in the literature describing this reaction as occuring on simple alkyl- or arylazines.

The propensity of the 1,2,4-triazines to undergo covalent hydration is clearly a consequence of the electron-withdrawing effect of *three* sp^2 nitrogen atoms in these compounds. The fact that the covalent hydration by addition across the N_4-C_5 bond is analogous to the sites of covalent hydration in quinazoline (**10**) and in pteridine (**11**) is noteworthy.



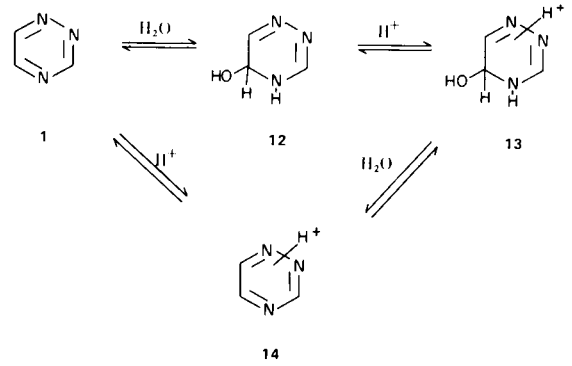
10



11

Since we have not observed any covalently hydrated species in neutral media, it appears that either the hydrated compound is stabilized by protonation (**12** → **13**) or that hydration occurs on the protonated 1,2,4-triazines (**14** → **13**).

Alternatively, a situation involving all of the indicated equilibria might be prevailing. It will require further studies to establish the positions and involvement of these various equilibria in the covalent hydration of 1,2,4-triazines.



1 12 13 14

EXPERIMENTAL (6)

3-Methylthio-1,2,4-triazine (**4a**) (General Procedure A).

A solution of 70 g. (0.48 mole) of 40% glyoxal and 37 g. (0.44 mole) of sodium bicarbonate in 1 liter of ice water was added to a solution of 93.2 g. (0.4 mole) of *S*-methylthiosemicarbazide hydrogen iodide dissolved in 600 ml. of ice-water. Within 10 minutes a vigorous gas evolution was observed. The resulting solution was kept in the refrigerator for 5 hours and was then extracted with chloroform (10 x 100 ml.). Evaporation of the solvent yielded 44 g. (88.6%) of 3-methylthio-1,2,4-triazine (m.p. 31-33°, b.p. 88-90° (0.4 mm)). Table I lists the analytical data for this compound.

3-Methoxy-1,2,4-triazine (**6a**) (General Procedure B).

A solution of 3-methylthio-1,2,4-triazine (25.4 g., 0.2 mole) and 5 g. of sodium metal reacted with 350 ml. of absolute methanol was stirred at room temperature for 12 hours. Dry ice was added to the solution and the precipitated inorganic material was removed by filtration. The filtrate was evaporated to dryness on a rotarory evaporator and the remaining residue was sublimed at 35°/0.3 mm to yield 17.6 g. (79%) of a yellow sublimate of 3-methoxy-1,2,4-triazine (m.p. 44-46°). The analytical data for this compound are listed in Table I.

3-Hydrazino-1,2,4-triazine (**5a**) (General Procedure C).

3-Methoxy-1,2,4-triazine (11.1 g., 0.1 mole) and 3.7 g. (0.105 mole) of 95% hydrazine dissolved in 50 ml. of tetrahydrofuran and 10 ml. of absolute methanol was refluxed on a steam bath for 3.5 hours. After cooling to room temperature, the reaction mixture was filtered and the residue was washed with tetrahydrofuran to yield 9.1 g. (82%) of 3-hydrazino-1,2,4-triazine (m.p. 140-142°). See Table I for the analytical data pertaining to this compound.

1,2,4-Triazine (**1a**) (General Procedure D).

A solution of 3-Hydrazino-1,2,4-triazine (3.8 g., 0.34 mole) was dissolved in 5.30 ml. of tetrahydrofuran (purified by passing it through a neutral alumina column before usage) and 40 g. of activated manganese dioxide (7) (pre-dried overnight at 110°) was added. Gas evolution started immediately and an exothermic reaction occured. The reaction mixture was stirred at room temperature for 8 hours, filtered and the residue was washed with tetrahydrofuran. The combined filtrate and washings were dried with anhydrous sodium carbonate, filtered and the filtrate was evaporated almost to dryness while keeping the temperature below 25°. The remaining solvent was then removed by distillation

below 70° and at atmospheric pressure. The liquid residue was then distilled at about 12 mm Hg to yield 0.78 g. (28.3%) of 1,2,4-triazine. This compound is identical in all of its properties (m.p., NMR, Mass spectrum) with those previously recorded for 1,2,4-triazine (1.4).

3-Methylthio-5-methyl- (**4c**) and 6-methyl-1,2,4-triazine.

The same procedure as described for the formation of 3-methylthio-1,2,4-triazine was employed. From 17.8 g. (0.08 mole) of *S*-methylthiosemicarbazide and 14.4 g. (0.08 mole) of 40% aqueous methylglyoxal there was obtained 9.2 g. of a mixture of 5-methyl and 6-methyl derivative. Based upon an NMR analysis, approximately 5% of this mixture is the 3-methylthio-6-methyl-1,2,4-triazine. The 3-methylthio-5-methyl-1,2,4-triazine (m.p. 74-76°) was obtained pure by crystallization from aqueous ethanol (6.7 g., 63.8%). Table I lists the analytical data.

Acknowledgment.

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(6) NMR spectra were obtained with a Varian HA-100 instrument as dilute solutions in the solvents indicated in Table I. The mass spectrometric molecular weights of all compounds were obtained with a Hitachi-Perkin Elmer RMU-6E instrument and were found to be in agreement with the theoretical values. Elemental analyses were done by Mrs. P. Jones of this department and are listed in Table I.

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