

Ethylenimine Derivatives of some 1,2,4-Triazines

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The first 3-ethylenimino-1,2,4-triazines (**9**) have been synthesized from the corresponding 3-(β -chloroethyl)amino-1,2,4-triazines (**8**). In addition some 2,3-dihydroimidazo[1,2-*b*]-1,2,4-triazines and imidazo[1,2-*b*]-1,2,4-triazines were obtained. The stability, properties and potential therapeutic value of these compounds are discussed.

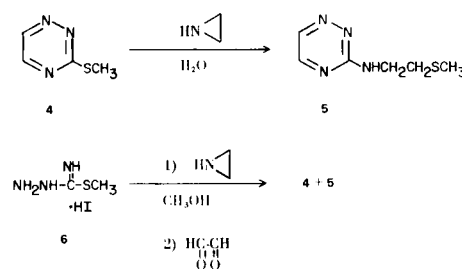
J. Heterocyclic Chem., 13, 807 (1976).

As an extension of our studies on 1,2,4-triazines and because of the known anticancer activities of 6-azauracil (**1**), its derivatives (**2-4**), and of 2,4,6-triethylenimino-1,3,5-triazine (**5**), we became interested in the syntheses of some 3-ethylenimino-1,2,4-triazines. We now wish to report the results of this study.

The reaction of 3-methoxy-1,2,4-triazine (**1**) with ethylenimine, in the absence of a solvent, afforded a compound $C_7H_{11}N_5$ (**2**). This molecular formula clearly indicates the incorporation of two ethylenimine fragments into the 1,2,4-triazine ring. The 1H nmr spectrum of this compound shows the presence of two aromatic protons (*cf.* Table I) as an AB system. In addition to this an A_2B_2 as well as an A_2B_2X pattern is present in the spectrum. The addition of deuterium oxide to a solution of the compound in deuteriochloroform, causes the A_2B_2X pattern to collapse to an A_2B_2 system. Consequently, we are dealing with structure **2** (*cf.* Scheme I). Since one might surmise that the desired 3-ethylenimino-1,2,4-triazine was formed as an intermediate in this reaction, several modifications of the reaction, such as controlling the relative proportions of ethylenimine and 3-methoxy-1,2,4-triazine were attempted. Yet, in no instance was any of the desired ethylenimino derivative obtained. Thus, if 3-ethylenimino-1,2,4-triazine is formed as an intermediate, it reacts more readily with ethylenimine than does the 3-methoxy-1,2,4-triazine.

When compound **2** is heated with dilute hydrochloric acid, it is readily transformed to an isomeric material whose 1H nmr spectrum (*cf.* Table I), clearly identifies it as the 3-(*N*-piperazino)-1,2,4-triazine (**3**).

These results prompted us to investigate the potential formation of 3-ethylenimino-1,2,4-triazines by the routes and with the results indicated below:

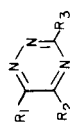


The formation of compound **5** from both of these reactions again suggests the possible intermediate formation of the desired 3-ethylenimino-1,2,4-triazine and demonstrates its expected reactivity.

The formation of the desired compound was finally accomplished in the stepwise fashion as indicated in Scheme I. The formation of the 3-(2-hydroxyethylamino)-1,2,4-triazines from the corresponding 3-methoxy derivatives proceeds in 70-85 percent yields while their transformation to the 3-(2-chloroethyl)-1,2,4-triazines takes place in 30-80 percent yields.

The cyclization of the chloroethyl compounds (**8a-d**) was accomplished after considerable experimentation with different bases, and in adequate yields, with potassium *t*-butoxide. The resulting material, after chromatography, was separated into two isomeric compounds. The 1H nmr spectra of the lower melting isomers in each of the instances showed, in addition to the expected 1,2,4-triazine protons and their substituents, a 4-proton singlet (τ 7.4, *cf.* Table I). This chemical shift is typical for that of ethylenimines with an aromatic substituent on nitrogen (**6**). Therefore, the lower melting isomers are the desired 3-ethylenimino-1,2,4-triazines (**9a-d**). The higher melting isomers no longer contain the "typical" 1,2,4-triazine absorptions. In fact, the chemical shifts of the deshielded protons in these compounds are in the region previously observed for

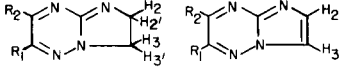
Table I
¹H Nmr and Analytical Data for Some 1,2,4-Triazines



Compound No.	Molecular Formula	R ₁	R ₂	R ₃ (a)	Chemical Shifts (τ) (b)								
					R ₁	R ₂	R ₃	%C	%H	%N			
7a	C ₅ H ₈ N ₄ O	H	H	NHCH ₂ CH ₂ OH	1.57	1.97	6.18 6.38	42.8	5.8	40.0	42.8	5.7	39.6
8a	C ₅ H ₇ ClN ₄	H	H	NHCH ₂ CH ₂ Cl	1.44	1.88	6.20	37.9	4.5	35.3	37.8	4.5	39.6
9a	C ₅ H ₆ N ₄	H	H	N(CH ₂) ₂	1.11	1.64	7.44	49.2	4.9	45.9	49.0	5.0	45.9
7b	C ₆ H ₁₀ N ₄ O	H	CH ₃	NHCH ₂ CH ₂ OH	1.67	7.67	6.13 6.36	46.7	6.5	36.3	46.5	6.7	36.1
8b	C ₆ H ₉ ClN ₄	H	CH ₃	NHCH ₂ CH ₂ Cl	1.49	7.62	6.16	41.7	5.3	32.5	41.8	5.3	32.4
9b	C ₆ H ₈ N ₄	H	CH ₃	N(CH ₂) ₂	1.22	7.52	7.47	52.9	5.9	25.9	52.7	6.0	25.9
7c	C ₁₁ H ₁₂ N ₄ O	H	Ph	NHCH ₂ CH ₂ CH	0.96	1.87 2.43	6.02 6.18	61.1	5.6	25.9	61.2	5.6	25.9
8c	C ₁₁ H ₁₁ ClN ₄	H	Ph	NHCH ₂ OH ₂ Cl	0.91	1.90 2.48	6.12	56.3	4.7	23.9	56.2	4.8	23.9
9c	C ₁₁ H ₁₀ N ₄ O	H	Ph	N(CH ₂) ₂	0.67	1.84 2.47	7.42	66.7	5.1	19.2	66.6	5.1	19.0
7d	C ₁₇ H ₁₆ N ₄ O	Ph	Ph	NHCH ₂ CH ₂ OH	2.64	2.64	6.08 6.27	69.8	5.5	19.2	69.9	5.6	19.0
8d	C ₁₇ H ₁₅ ClN ₄	Ph	Ph	NHCH ₂ CH ₂ Cl	2.61	2.61	6.14	65.7	4.9	18.0	65.8	4.9	18.0
9d	C ₁₇ H ₁₄ N ₄	Ph	Ph	N(CH ₂) ₂	2.61	2.61	7.40	74.4	5.1	20.4	73.6	5.3	19.9
2a	C ₇ H ₁₁ N ₅	H	H	NHCH ₂ CH ₂ X (c)	1.51	1.89	6.30 7.50	50.9	7.0	42.4	50.8	6.8	42.5
5a	C ₇ H ₁₀ N ₄ S	H	H	NHCH ₂ CH ₂ Y (d)	1.46	1.85	6.27	42.3	5.9	32.9	42.6	5.9	32.6

(a) The chemical shifts of the N-H proton is 3.0 ± 0.5. (b) The coupling constants of the triazine ring protons are 2.0 ± 0.3. (c) X = N(CH₂)₂, chemical shifts τ 8.22, 8.80. (d) Y = SCH₃, chemical shift τ 7.87.

Table II

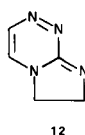
¹H Nmr and m.p. Data (a) for Some 2,3-Dihydroimidazo and Imidazo[1,2-*b*]-1,2,4-triazines


Compound No.	Molecular Formula	R ₁	R ₂	Chemical Shifts (τ)		H ₂ , H ₃	M.p.
				R ₁	R ₂		
10b	C ₆ H ₈ N ₄	H	CH ₃	2.91	8.47	6.18	193-195°
10c	C ₁₁ H ₁₀ N ₄	H	Ph	2.33	1.96 2.50	5.96	140-143°
10d	C ₁₇ H ₁₄ N ₄	Ph	Ph	2.73	2.73	5.88	80-90° dec.
11a (b)	C ₅ H ₄ N ₄	H	H	1.55	1.65	2.01	111-112°
11c (c)	C ₁₁ H ₈ N ₄	H	Ph	1.13	1.80 2.46	2.04	162-164°
11d (d)	C ₁₇ H ₁₂ N ₄	Ph	Ph	2.60	2.60	2.02	130-132°

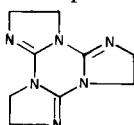
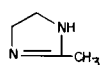
(a) Dilute solutions in deuteriochloroform. (b) Identical in all respects with an authentic sample. (c) *Anal.* Calcd. for C₁₁H₈N₄: C, 67.33; H, 4.11. Found: C, 67.34; H, 4.14. (d) *Anal.* Calcd. for C₁₇H₁₂N₄: C, 74.98; H, 4.44. Found: C, 74.85; H, 4.48.

the triazine protons in 2,3-dihydro-3-oxo-1,2,4-triazine (7).

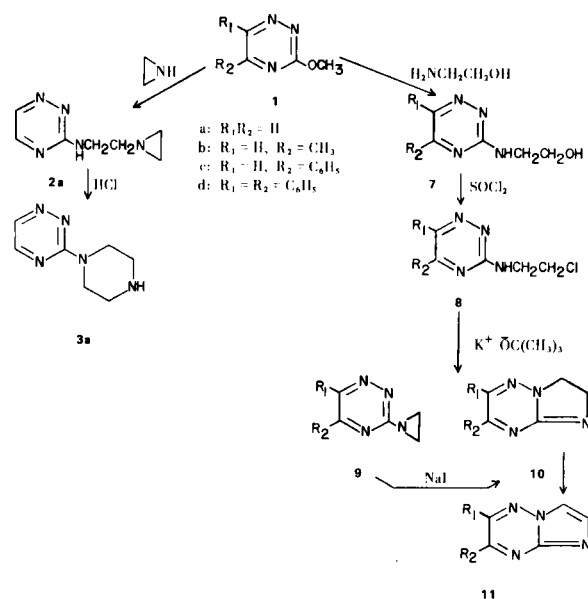
These compounds must, consequently, have either structure **10** (Scheme I) or structure **12**.



Since we have already described the syntheses and structure proofs of the imidazo-1,2,4-triazines (**11**) (**8**), we converted the dihydroaromatics (**10** or **12**) to the aromatic analogs by dehydrogenation. In all of the instances, the imidazo[1,2,4]triazines of general structure **11** were obtained. In fact, when the 5-phenyl or the 5,6-diphenyl-3-(2-chloroethylamino)-1,2,4-triazines were treated with potassium *t*-butoxide, some of the aromatic bicyclic system (**11c,d**) was isolated from the reaction itself. Since it is well known that *N*-acetylenimine (9) as well as 2,4,6-triethylenimino-1,3,5-triazine (**10**) rearrange, in the presence of sodium iodide, to compounds **13** and **14**, respectively, we reacted the ethylenimino compounds (**9a-d**) with the same reagent. As expected, they are readily isomerized to the dihydro compounds (**10a-d**).



Scheme I



EXPERIMENTAL

The 3-methylthio- and the 3-methoxy-1,2,4-triazine (**1**) were prepared by the method of Paudler and Chen (11). Tetrahydrofuran was purified by distillation from sodium hydride. The chloroform (for thionyl chloride reactions) was purified by washing it with concentrated sulphuric acid, followed by water, drying

over calcium chloride and distillation.

Mass spectra were recorded with a Hitachi Perkin-Elmer RMU-6M instrument on all new compounds. Their molecular ions and fragmentation patterns are consistent with the indicated structure. A Varian HA-100 instrument was used to record the ^1H nmr spectra. Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are corrected. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, Georgia and the Analytical Services Laboratory, Department of Chemistry, The University of Alabama.

Reaction of 3-Methoxy-1,2,4-triazine (**1a**) with ethylenimine.

To a 10 ml. flask fitted with a reflux condenser was added 2.22 g. (0.02 mole) of 3-methoxy-1,2,4-triazine and 5 ml. (excess) of ethylenimine. The solution was refluxed in an oil bath at 75° for 10 hours during which time its color changed from yellow to dark maroon. The excess ethylenimine was removed *in vacuo*, leaving a viscous yellow oil which, by tlc, (alumina/chloroform) showed one major component. Sublimation of this oil at $56^\circ/0.005$ torr afforded 2.11 g. of a pale yellow crystalline air-sensitive solid, (**2a**) (m.p. $58-59.5^\circ$, 64.2%).

Anal. Calcd. for $\text{C}_7\text{H}_{11}\text{N}_5$: C, 50.91; H, 6.99; N, 42.42. Found: C, 50.79; H, 6.82; N, 42.51.

Reaction of 3-[2-(1-Ethylenimino)ethylamino]-1,2,4-triazine with Hydrochloric Acid.

To 40 ml. of a 6 N hydrochloric acid solution was added 3.30 g. (0.02 mole) of 3-[2-(ethylenimino)ethylamino]-1,2,4-triazine (**2a**) and the solution was heated at $85-90^\circ$ for 24 hours. The reaction mixture was cooled and neutralized with 20% aqueous potassium hydroxide and carefully made basic to pH 8-9. This solution was extracted with chloroform (3 x 50 ml.) and the combined organic extracts were dried over anhydrous sodium carbonate. Upon removal of the solvent *in vacuo*, 2.34 g. of a yellow air-sensitive oil **3a** (71%) was obtained. Compound **3a**, ^1H nmr (deuteriochloroform): τ 1.48 (d, 1H), τ 1.86 (d, 1H), τ 3.18 (broad, 1H), τ 6.38 (t, 4H), τ 7.05 (t, 4H); mass spectrum: mw 165. Elemental analytical data could not be obtained because of the compound's air sensitivity.

Reaction of 3-Methylthio-1,2,4-triazine (**4**) with Ethylenimine.

To a solution of 2.54 g. (0.02 mole) of **4** in 10 ml. of water was added 4 ml. (0.07 mole) ethylenimine and the reaction mixture was heated in a hood at $75-80^\circ$ in an oil bath for 24 hours. The reaction mixture was extracted with chloroform (5 x 30 ml.). The chloroform was dried, filtered and evaporated *in vacuo*. The resulting residue was chromatographed on alumina (grade III) with dichloromethane-chloroform (1:1) followed by chloroform to give compound **4** and 340 mg. of compound **5** (10%). Compound **9** was further purified by sublimation at 70° (0.2 torr).

Reaction of the Hydrogen Iodide Salt of 4-Methylthio Semicarbazide (**6**) with Ethylenimine and Glyoxal.

To 12.30 g. (0.05 mole) of compound **6** dissolved in 120 ml. of absolute methanol was added dropwise 3 ml. (0.059 mole) of ethylenimine dissolved in 10 ml. of methanol. The solution was stirred at room temperature for 40 hours and the volume was reduced to 80-90 ml. *in vacuo*. The reaction mixture was stirred with 100 g. of ice and a solution of 7.70 g. (0.052 mole) of 40% glyoxal and 4.40 g. (0.51 mole) of sodium bicarbonate in 200 ml. of ice was added. The reaction mixture was stirred until the ice melted and was then refrigerated overnight. The methanol was evaporated *in vacuo* and sodium chloride (60 g.) was added. The resulting slurry was extracted with chloroform (5 x 60 ml.). The

chloroform extract was dried, filtered, and evaporated *in vacuo*. The resulting residue was chromatographed on alumina (grade III) with benzene-chloroform (1:1) followed by chloroform to give compound **8** and 1.70 g. of compound **5** (20%). This material was identical in all respects with an authentic sample.

Preparation of 3-(2-Hydroxyethylamino)-1,2,4-triazines (**7a-d**).

In a typical experiment, 12 ml. (0.18 mmole) of 95% ethanolamine was added to 11.10 g. (0.10 mole) of compound **1a** in 70 ml. of 2-propanol. The resulting solution was refluxed for 72 hours and allowed to come to room temperature. The 2-propanol was evaporated *in vacuo* and the excess ethanolamine was removed ($40^\circ/0.1$ torr). The residue was chromatographed on neutral alumina (grade III). Elution first with chloroform followed by ethanol-chloroform (1:14) afforded 11.3 g. of compound **7a** (81%). Compounds **7b-d** were isolated (80-85%) by similar procedures. Compounds **7c** and **7d** crystallized when the reaction mixtures were cooled to room temperature.

Preparation of 3-(2-Chloroethylamino)-1,2,4-triazines (**8a-d**).

In a typical experiment, 1.50 ml. (0.02 mole) of purified thionyl chloride in 50 ml. of ethanol-free chloroform was added dropwise to an ice-cooled solution of 2.65 g. (11.0 mmoles) of **7a** in 100 ml. of ethanol-free chloroform. The resulting suspension was allowed to warm to room temperature and refluxed for 0.5-0.75 hours. The reaction was allowed to come to room temperature and 30 ml. of water was slowly added. After stirring (5-10 minutes), a solution of 2.80 g. (0.02 mole) of potassium carbonate in 50 ml. of water was added. After vigorous mixing, the chloroform layer was separated and the water layer extracted with chloroform (2 x 50 ml.). The combined chloroform extracts were dried over anhydrous sodium sulfate and evaporated *in vacuo* at room temperature. The resulting oil was recrystallized from boiling hexane (oil transferred with dichloromethane) to give 860 mg. of compound **8a** (50%). Compounds **8a** (35%), **8c** (80%) and **8d** (85%) were prepared in a similar manner. Compounds **8c** and **8d** were recrystallized from hexane-dichloromethane (1:1).

Reaction of 3-(2-Chloroethylamino)-1,2,4-triazine (**8a**) with Potassium *t*-Butoxide.

To 0.2-0.3 ml. of *t*-butyl alcohol in 60 ml. of dry tetrahydrofuran was added 1.23 g. (0.011 mole) of potassium *t*-butoxide. To the resulting solution kept under a positive dry nitrogen pressure and cooled in an ice bath, was added, dropwise, a solution of 1.75 g. (0.011 mole) of compound **8a** dissolved in 30 ml. of dry tetrahydrofuran. The reaction mixture was allowed to come to room temperature and stirred for four hours. The resulting suspension was filtered through celite and evaporated *in vacuo* at room temperature. The remaining oil was chromatographed on neutral alumina (grade III) with chloroform-dichloromethane (1:5) to give 210 mg. (17%) of compound **9a**. Compound **9a** could be further purified by sublimation at $20-40^\circ/0.01$ torr into a dry-ice 2-propanol cooled cold-finger. Further elution of the alumina with ethanol-chloroform (1:50) gave a multi-component residue. This mixture was dissolved in 50 ml. of toluene and refluxed for 24 hours in the presence of 10% palladium/carbon. The suspension was filtered and the filtrate evaporated *in vacuo*. The residue was chromatographed on neutral alumina (grade III) to give compound **11a**. The highly fluorescent material (**11a**) was identical in all respects with an authentic sample of imidazo[1,2-*b*]-1,2,4-triazine.

Reaction of the 3-(2-Chloroethylamino)-5-methyl-1,2,4-triazine (**8b**) with Potassium *t*-Butoxide.

To a solution of 0.2 ml. of *t*-butyl alcohol in 50 ml. of anhy-

drous tetrahydrofuran, kept under a positive dry nitrogen pressure, was added 400 mg. (0.35 mmole) of potassium *t*-butoxide. The resulting solution was cooled in an ice-bath and 600 mg. (0.34 mmole) of compound **8b** dissolved in 35 ml. of tetrahydrofuran was added dropwise. The reaction was allowed to come to room temperature after the addition was complete. The orange solution was stirred at room temperature for 3 hours and evaporated *in vacuo* at room temperature. Water (50 ml.) was added to the residue and the resulting slurry was extracted with chloroform (3 x 50 ml.). The combined chloroform extracts were dried over anhydrous sodium sulfate, filtered and evaporated *in vacuo*. The resulting oil was carefully chromatographed on alumina (grade III) with chloroform. A mixture of **9b** and **10b**, 230 mg. (22% and 28%, respectively) was thus obtained. Compound **9b** was obtained pure by subliming the mixture at 40-45°/0.01 torr, into a dry-ice 2-propanol cooled cold-finger. Compound **10b** could be obtained by preparative thin-layer chromatography on silica gel and development with ethanol-chloroform (1:14).

Reaction of 3-(2-Chloroethylamino)-5-phenyl-1,2,4-triazine (**8c**) with Potassium *t*-Butoxide.

To a solution of 0.2 ml. of *t*-butyl alcohol in 50 ml. of tetrahydrofuran, kept under a dry nitrogen atmosphere, was added 240 mg. (2.1 mmoles) of potassium *t*-butoxide. The resulting solution was cooled in an ice-bath and 500 mg. (2.1 mmoles) of **8c** dissolved in 30 ml. of tetrahydrofuran was added dropwise. The reaction was allowed to come to room temperature and stirred for 2 hours. The resulting solution was evaporated *in vacuo* at room temperature and water (50 ml.) was added. The slurry thus obtained was extracted with chloroform (3 x 50 ml.) dried over anhydrous sodium sulfate and evaporated *in vacuo*. The resulting residue was carefully chromatographed on alumina (grade III) using chloroform-dichloromethane (1:1) as the eluant to give 25 mg. of **11c** (6%), 75 mg. of **9c** (18%) and 205 mg. of **10c** (50%). Compound **11c** was further purified by sublimation or preparative thin-layer chromatography. Compound **11c** would also be obtained by oxidizing compound **10c**.

To a solution of **10c** in 50 ml. of toluene was added a catalytic amount of palladium/carbon (10%) and the resulting suspension was refluxed for 48 hours. Filtration, evaporation of the filtrate and chromatography of the residue gave the highly fluorescent compound **11c**.

Reaction of 3-(2-Chloroethylamino)-5,6-diphenyl-1,2,4-triazine (**8d**) with Potassium *t*-Butoxide.

To a solution of 0.2 ml. of *t*-butyl alcohol in 60 ml. of tetra-

hydrofuran, kept under a dry nitrogen atmosphere, was added 300 mg. (2.6 mmoles) of potassium *t*-butoxide. The resulting solution was cooled in an ice-bath and 800 mg. (2.6 mmoles) of **8d** dissolved in 35 ml. of tetrahydrofuran was added dropwise. The reaction was allowed to come to room temperature and stirred for 1.5 hours. The solution was evaporated *in vacuo* at room temperature and water (50 ml.) was added. The resulting slurry was extracted with chloroform (3 x 50 ml.) and the extracts were dried over anhydrous sodium sulfate, filtered and evaporated *in vacuo*. The residue was chromatographed on alumina (grade III) and eluted with chloroform to give 198 mg. of **9d** and **11d** (22% and 6%, respectively) and 210 mg. of **10d** (30%). Compounds **9d** and **11d** were separated by preparative thin-layer chromatography on silica gel with ethanol-chloroform (1:19). Compound **10d** could be oxidized to **11d** by refluxing in toluene in the presence of palladium/carbon (10%). Purification was accomplished by chromatography on neutral alumina (grade III) and elution with chloroform.

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