after water-insoluble material was removed by filtration. The yield of triethylenemelamine was 86%. Yields were about 5% lower when technical grade cyanuric chloride was used.

The additional agitation following the addition was necessary to ensure high yields of triethylenemelamine. In an experiment that was worked up immediately upon completion of the addition, a 57.5% yield of triethylenemelamine and 47.5% of water-insoluble material was obtained. From these water insolubles, 2,4-bis-(1-aziridinyl)-6-chloro-*s*-triazine,[4] m.p. 139° dec., was isolated by recrystallization from carbon tetrachloride.

Anal. Calcd. for $C_7H_8N_5Cl$: Cl, 17.95. Found: Cl, 17.8.

Solubility of Triethylenemelamine.—The approximate solubilities in a variety of solvents, summarized in Table I, were determined by adding weighed increments of triethylenemelamine to 20-ml. portions of the solvents in stoppered flasks. Solution was facilitated by vigorous shaking, and was considered complete when solid particles remained undissolved.

After 5.00 g. of triethylenemelamine had been equilibrated with a mixture of 50 ml. of water and 50 ml. of chloroform, 3.56 g. of I was recovered from the chloroform layer leaving 1.44 g. in the water layer. It would appear that compound I was distributed between these solvents in inverse relation to its solubilities in them (Table I). However, when the distribution coefficient is calculated on a mole-fraction basis, the saturated system gives

$$K_{sat} = \frac{\text{mole fraction I in } CHCl_3}{\text{mole fraction I in } H_2O} = 3.35$$

and the data from the distribution experiment give

$$K_{dil} = 10.8$$

Although these coefficients differ by a factor of about three, both (being greater than unity) show that extraction of I into the chloroform is favored. This difference is undoubtedly attributable to the non-ideal behavior of these solutions at high concentration. It indicates that the activity coefficient of triethylenemelamine changes more rapidly in water than in chloroform solution with changing concentration. It implies that I "solubilizes" itself as the concentration increases. From a structural standpoint, the reason for the high solubility of I, compared with II, is unexplained.

Storage Stability of Triethylenemelamine.—Samples of triethylenemelamine recrystallized from chloroform were stored in partly filled screw-capped bottles. In concurrent tests, duplicate samples were stored under nitrogen. Periodically, 1.0-g. portions of the samples were removed and digested with 50–60 ml. of chloroform at room temperature. The insolubles were collected on a Gooch funnel and weighed after drying at 100°. No polymer was found in samples stored in air at 5 or 25° or under nitrogen at 5° for 48 days. A sample stored at 75° polymerized at a rate of about 0.25% per day. Samples placed in an oven at 110° decomposed violently within 15 minutes. There is some indication that polymer formation may be inhibited by atmospheric oxygen.

Hendry[17] has reported that "aqueous solutions (of triethylenemelamine) have been kept for some months at 4° without appreciable change in composition."

(17) J. A. Hendry, R. F. Homer, F. L. Rose and A. L. Walpole, *Brit. J. Pharmacol.*, **6**, 357 (1951).

STAMFORD, CONN.

[CONTRIBUTION FROM THE STAMFORD LABORATORIES, RESEARCH DIVISION, AMERICAN CYANAMID CO.]

Mono- and Bis-(1-aziridinyl)-*s*-triazines

BY FRED C. SCHAEFER, JOHN T. GEOGHEGAN AND DONALD W. KAISER

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Methods for the preparation of mono- and bis-(1-aziridinyl)-*s*-triazines have been investigated. A variety of such compounds has been prepared for testing in the chemotherapy of cancer.

Reports of tumor inhibition by triethylenemelamine (2,4,6-tris-1-aziridinyl-*s*-triazine) observed in several screening programs[1] and especially its successful clinical application[2] prompted us to prepare a variety of 1-aziridinyl-*s*-triazines for comparative testing. In view of the continuing interest in this class of compounds[3] it seems appropriate to report our work in some detail as a guide to the synthetic methods and to record the characteristics of our products. Portions of our results have been published in a United States Patent.[4] A British Patent[5] also describes the preparation of a variety of bis-(1-aziridinyl)-*s*-triazines, partially duplicating some of our work.

It has been found that the usual procedures for the conversion of chloro-*s*-triazines to amino-*s*-triazines[6] are generally applicable to ethylenimine. Two unusual considerations are of importance, however. Although ethylenimine is a relatively weakly basic aliphatic amine in water,[7] its steric requirements are such that it reacts unusually rapidly with chloro-*s*-triazines at lower than normal temperatures. A compensating adverse influence is the instability of the ethylenimino-*s*-triazine structure. Polymerization and other secondary reaction[8] frequently caused poor yields and recovery difficulties.

In principle, a mono- or bis-(1-aziridinyl)-*s*-triazine may be prepared from cyanuric chloride as outlined in the chart below by (1) condensing a suitable intermediate chloro-*s*-triazine with ethylenimine in the final step, or (2) condensing ethylenimine with cyanuric chloride to give 2-(1-aziridinyl)-4,6-dichloro-*s*-triazine (I) or 2,4-bis-(1-aziridinyl)-6-chloro-*s*-triazine (II) which then reacts further.

(1) (a) We were informed of this work by Dr. M. L. Crossley who had made samples of triethylenemelamine available for testing; (b) M. R. Lewis and M. L. Crossley, *Arch. Biochem.*, **26**, 319 (1950); (c) J. H. Burchenal, *et al.*, *ibid*, **26**, 321 (1950); (d) F. L. Rose, J. A. Hendry and A. L. Walpole, *Nature*, **165**, 993 (1950); (e) S. M. Buckley, *et al.*, *Cancer Res.*, **10**, 207 (1950); (f) J. H. Burchenal, *et al.*, *ibid.*, **10**, 208 (1950); (g) J. H. Burchenal, *et al.*, *Proc. Soc. Exptl. Biol. Med.*, **74**, 708 (1950).

(2) D. A. Karnofsky, *et al.*, *Arch. Internal. Med.*, **87**, 477 (1951).

(3) W. H. Bond, *et al.*, *ibid.*, **91**, 602 (1953); references to clinical use of triethylenemelamine are cited.

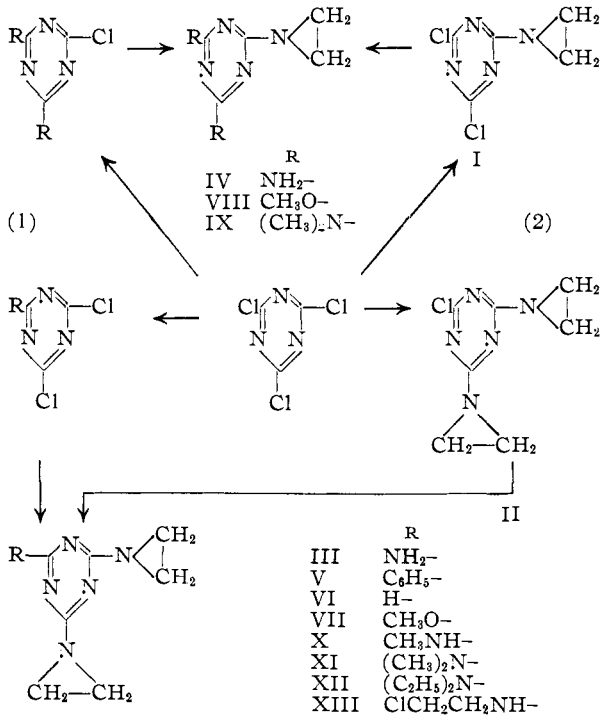
(4) D. W. Kaiser and F. C. Schaefer, U. S. Patent 2,653,934 (1953).

(5) J. A. Hendry and F. L. Rose, British Patent 680,652 (1952).

(6) (a) J. T. Thurston, *et al.*, THIS JOURNAL, **73**, 2981 (1951); (b) D. W. Kaiser, *et al.*, *ibid.*, **73**, 2984 (1951).

(7) By calculation from the *p*H at half-neutralization, K_B = *ca.* 5×10^{-7}.

(8) F. C. Schaefer, THIS JOURNAL, **77**, 5922 (1955).

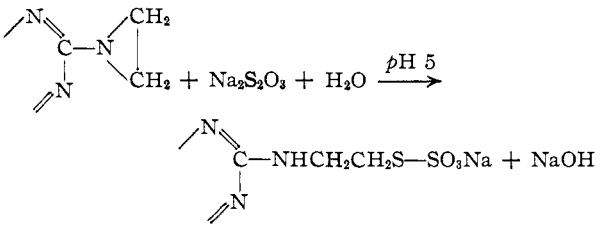


Method 1 has the advantages of deferring the complicating influences of the ethylenimine group until the last step and presumably of being more economical of ethylenimine. However, by this route the temperatures required for the final step may be too high to be operable with this low-boiling imine at atmospheric pressure, or serious loss through decomposition may ensue. The use of anhydrous ethylenimine as may be necessary in some cases is also a disadvantage on a larger than laboratory scale. Method 2 has the advantages of allowing the reaction with ethylenimine to take place at low temperature and in an aqueous system so that crude ethylenimine[9] may be used. Also, the intermediate (1-aziridinyl)-chloro-*s*-triazines have greater reactivity than is usual for aminochloro-*s*-triazines, judging from the very mild conditions which suffice for the preparation of triethylenemelamine.[9]

Six intermediate mono- and dichloro-*s*-triazines were successfully converted to mono- and bis-1-aziridinyl-*s*-triazines. The intermediate (1-aziridinyl)-chloro-*s*-triazines, I and II, were prepared from cyanuric chloride and were utilized for the preparation of five other mono- and bis-(1-aziridinyl)-*s*-triazines. In two cases, products were prepared by both methods 1 and 2. The preparation of II was found to be fairly satisfactory, and this compound was reasonably stable in storage. Compound I, however, could not be isolated in stable condition. Pertinent data on the products obtained are given in Tables I and II.[9a]

Several reactions which were tried did not yield crystalline products although they appeared to proceed as expected. In some of these cases failure may have been the result of unfavorable physical properties of the products. However, further work has indicated that in many experiments where amines were used as hydrogen chloride acceptors in organic solutions rearrangement of 1-aziridinyl-*s*-triazine groups probably occurred destroying the desired products.[8]

It was found useful to have a semi-quantitative method for estimating the 1-aziridinyl-*s*-triazine structure in various products and solutions. The reaction with sodium thiosulfate[10] serves this purpose. Figure 1 shows the rate of reaction and the extent to which several of our products and triethylenemelamine reacted with this reagent.



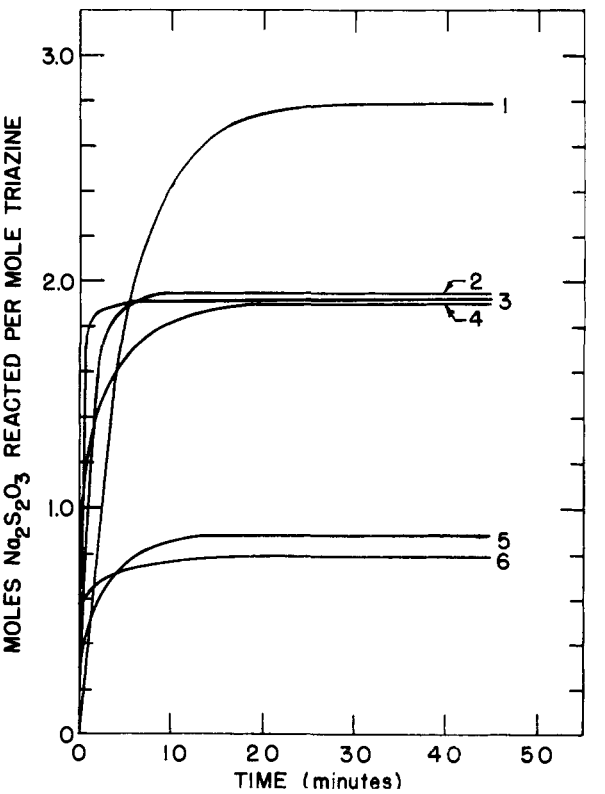


Fig. 1.—Rate of reaction of 1-aziridinyl-*s*-triazines with $Na_2S_2O_3$: 1, triethylenemelamine; 2, 2,4-bis-(1-aziridinyl)-6-methoxy-*s*-triazine; 3, 2,4-bis-(1-aziridinyl)-6-(2-chloroethylamino)-*s*-triazine; 4, 2,4-diamino-6-(1-aziridinyl)-*s*-triazine; 5, 2-amino-4,6-bis-(1-aziridinyl)-*s*-triazine; 6, 2-(1-aziridinyl)-4,6-dimethoxy-*s*-triazine.

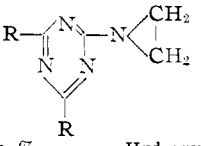
(9) V. P. Wystrach, D. W. Kaiser and F. C. Schaefer, THIS JOURNAL, **77**, 5915 (1955).

(9a) NOTE ADDED TO PROOF.—G. I. Braz (*Zhur. Obshchei Khim.*, **25**, 1413 (1955)) has reported the preparation of compounds II, VII, and VIII and other related 1-aziridinyl-*s*-triazines by reaction of chloro-*s*-triazines with excess ethylenimine in benzene. The properties of his products agree with ours.

(10) This reagent is generally applicable to determination of the nitrogen mustards; C. Golumbic, J. S. Fruton and M. Bergmann, *J. Org. Chem.*, **11**, 518 (1946). We are indebted to Dr. F. S. Philips of the Sloan-Kettering Institute for Cancer Research for communicating to us the conditions which he found suitable in work with triethylenemelamine.

TABLE I

MONO-1-AZIRIDINYL-*s*-TRIAZINES

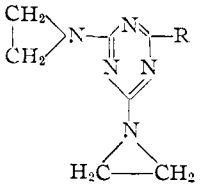


R	Yield, %	M.p.,[a] °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found[15]
NH_2–	34[b]	220 dec.	$C_5H_8N_6$	39.46	38.65	5.30	5.41	55.24	55.34
CH_3O–	69[b]	121–123	$C_7H_{10}N_4O_2$	46.15	46.21	5.53	5.68	30.76	30.52
$(CH_3)_2N$–	<12[c]	55–57	$C_9H_{16}N_6$	51.90	51.42	7.74	7.27	40.36	40.54

[a] For recrystallized compound. [b] Method 1, yield based on intermediate chloro-*s*-triazine. [c] Method 2, yield based on cyanuric chloride.

TABLE II

2-4-BIS-(1-AZIRIDINYL)-*s*-TRIAZINES



R	Yield, %	M.p.,[a] °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found[15]
CH_3NH–	38[b]	128.5–131.0[c]	$C_8H_{12}N_6$	49.98	49.98	6.30	6.41	43.72	43.58
$(CH_3)_2N$–	73[b]	67–69[d]	$C_9H_{14}N_6$	52.41	52.56	6.80	6.82	40.75	40.63
$(C_2H_5)_2N$–	44[b]	66.5–68.0[e]	$C_{11}H_{18}N_6$	56.37	55.30 56.12[f]	7.74	7.65	35.87	36.20
$ClCH_2CH_2NH$–	46[b]	87–88[g]	$C_9H_{13}N_6Cl$	44.91	45.31 45.09[f]	5.41	5.56	34.92	34.92
NH_2–	65[h] 30[b]	231 dec.[i]	$C_7H_{10}N_6$	47.18	47.02	5.66	5.58	47.17	47.75
C_6H_5–	40[h]	142 dec.[j]	$C_{13}H_{13}N_5$	65.25	65.30	5.48	5.53	29.27	29.17
H–	59[h]	147–148	$C_7H_9N_5$	51.52	51.45	5.56	5.47	42.92	43.02
Cl–	47[k]	145 dec.[l]	$C_7H_8N_5Cl$	42.54	42.61	4.08	4.22	35.44	35.71
CH_3O–	44[h] 71[b]	117–119[m]	$C_8H_{11}N_5O$	49.73	49.78	5.74	5.77	36.25	36.23

[a] For recrystallized compound. [b] Based on compound II. [c] Recrystallized from toluene–cyclohexane; reference 5 gives m.p. 127°. [d] From benzene; reference 5 gives m.p. 75–76°. [e] From hexane. [f] Van Slyke method. [g] From toluene. [h] For reaction of the dichloro-*s*-triazine with ethylenimine. [i] According to ref. 5 the compound does not melt below 420°. [j] Reference 5 gives m.p. 146–148°. [k] Based on cyanuric chloride. [l] Reference 5 gives m.p. 135°. [m] Reference 5 gives m.p. 121°.

Pharmacological data[11] and the results of testing the compounds in Tables I and II against cancer have been reported by others.[1b,e,f,g,12] Additional evaluation data on a few of these compounds have also been published by the English team who also report animal testing of several other 1-aziridinyl-*s*-triazines.[13]

Experimental Section[14,15]

2-Amino-4,6-bis-(1-aziridinyl)-*s*-triazine (III).—A slurry of 330 g. (2.000 moles) of 2-amino-4,6-dichloro-*s*-triazine[6a] in 1600 cc. of ice-water was prepared, and to it was added during 1.5 hours a solution of 175 g. (4.1 moles) of ethylenimine,[9] 176 g. (4.4 moles) of sodium hydroxide and 1500 cc. of water. Reaction was moderately exothermic, but the mixture was held at 25 ± 2°. Titration of an aliquot showed the reaction to be 87% completed by the end of the addition and 97% completed after one hour longer at 25°. The product was filtered at 10° and was washed with a little cold water, with methanol, and then with acetone. After air drying at room temperature the crude product weighed 231 g. (65%), m.p. 210–220° dec. This contained 6% of material insoluble in boiling water. The soluble portion could not be recovered from boiling water by cooling or by addition of methanol, a non-solvent for III. The compound could be recrystallized satisfactorily (about 60% recovery) from 45 cc. of 2:1 methanol–water per gram, m.p. 231° dec.

2,4-Diamino-6-(1-aziridinyl)-*s*-triazine (IV).—A mixture of 73.0 g. (0.50 mole) of 2,4-diamino-6-chloro-*s*-triazine,[6a] 21.5 g. (0.50 mole) of ethylenimine, 20.0 g. (0.50 mole) of sodium hydroxide and 500 cc. of water was heated to 85° in 10–15 minutes and was maintained at 85 ± 2° for 20 minutes. The mixture was filtered hot, and the solid product was washed with cold water. The damp filter cake was added to 1500 cc. of boiling water, and the mixture was boiled two minutes and filtered. The filtrate was immediately chilled. Filtration after about 1.5 hours gave 25.6 g., m.p. 220–225° dec., yield 34%. Only infusible material could be recovered by cooling the filtrate from the reaction mixture or from the recrystallization mother liquor. An 11.3-g. sample of the product was further recrystallized for analysis from 250 cc. of boiling water with 75% recovery, m.p. *ca.* 220° dec.

In other experiments it was shown that no appreciable reaction occurred below 80° and also that at 95° the monoethylenemelamine formed was unstable. The yield decreased with longer reaction time.

The following work was done to evaluate the possible extent of contamination of the product by III, arising from 2-

(11) (a) F. S. Philips, *et al.*, *J. Pharmacol. Exptl. Therap.*, **100**, No. 4, Pt. 1, 398 (1950); (b) J. J. Biesele, *Nature*, **166**, 1112 (1950).

(12) S. M. Buckley, *et al.*, *Cancer*, **5**, 144 (1952).

(13) J. A. Hendry, R. F. Homer, F. L. Rose and A. L. Walpole, *Brit. J. Pharmacol.*, **6**, 357 (1951); A. L. Walpole, *et al.*, *ibid.*, **9**, 306 (1954).

(14) Melting points are corrected. Most 1-aziridinyl-*s*-triazines decomposed with resinification at about 140°. Those having melting points above this temperature bad to be heated rapidly or introduced to the heating bath slightly below their melting points if these were to be observed. Some inaccuracy is therefore quite possible although reproducibility was good.

(15) The microanalyses were carried out in these laboratories under the direction of Dr. J. A. Kuck. The Dumas method for nitrogen analysis was usually more reliable than the pressure Kjeldahl method. Infrared absorption spectra were obtained and interpreted by Mr. N. B. Colthup.

amino-4,6-dichloro-*s*-triazine, a possible contaminant in the starting material. A 2.1-g. sample of IV was extracted with 200 cc. of cold water. The undissolved material was redried (1.3 g.), and the extract was evaporated to a dry residue (0.8 g.) in an evacuated desiccator over sulfuric acid in the presence of sodium hydroxide. Infrared examination of the two fractions showed them to be identical with each other and with the original material. Comparison with a synthetic mixture containing 92% IV and 8% III showed that not over 2% of III could have been present in the extract and, therefore, not over 1% in the original product. There was no actual indication of any contamination.

2,4-Bis-(1-aziridinyl)-6-phenyl-*s*-triazine (V).—A solution of 12.9 g. (0.30 mole) of ethylenimine and 33.3 g. (0.33 mole) of triethylamine in 100 cc. of benzene was added in 35 minutes to 33.9 g. (0.15 mole) of 2,4-dichloro-6-phenyl-*s*-triazine[16] in 80 cc. of benzene while the mixture was held at 15–20°. The temperature was then allowed to rise to 35°, and the mixture was held there for one hour and then at 50° for 30 minutes. The triethylamine hydrochloride which crystallized was filtered from the solution, and the latter was evaporated at reduced pressure to about 100 cc. from which 14.5 g. of crystals separated on cooling (40% yield). This product was recrystallized from 80 cc. of benzene plus 50 cc. of heptane giving 10.9 g., m.p. 142° dec.

2,4-Bis-(1-aziridinyl)-*s*-triazine (VI).—A 0.40-mole batch of aqueous ethylenimine was prepared by heating at 50° for 80 minutes a mixture of 46.4 g. (0.400 mole) of 2-chloroethylamine hydrochloride,[9] 280 cc. of water, 32.0 g. (0.80 mole) of sodium hydroxide and 42.4 g. (0.40 mole) of sodium carbonate (mixed in the order given). The ethylenimine solution was cooled to 3°, and during 40 minutes a solution of 30.0 g. (0.20 mole) of 2,4-dichloro-*s*-triazine[17] in 100 cc. of acetonitrile was added at 3–4°. The mixture was then allowed to warm to 19° in 80 minutes. The insoluble salts, mainly sodium bicarbonate, were filtered and washed with a little cold water and with chloroform. The combined filtrate and washings were extracted with 300 cc. of chloroform in four portions, and the chloroform solution was evaporated to dryness. The crystalline residue was recrystallized from benzene giving 19.4 g. (59%), m.p. *ca.* 120° dec. Further recrystallization from benzene gave 6.5 g., m.p. 147–148° dec.

2,4-Bis-(1-aziridinyl)-6-chloro-*s*-triazine (II).—A finely divided suspension was prepared by running a warm solution of 46.1 g. (0.25 mole) of cyanuric chloride in 100 cc. of dioxane into 500 cc. of stirred ice-water. To this at 0–2° was added during 25 minutes a solution of 22.0 g. (0.51 mole) of ethylenimine and 69.1 g. (0.50 mole) of potassium carbonate in 500 cc. of water. The thick slurry produced was stirred 10 minutes longer at 1° and then was filtered. The pasty product was washed with water and dried at 60° in a forced draft oven. The crude, dry product (34.5 g.) was extracted with a boiling mixture of 300 cc. of carbon tetrachloride and 200 cc. of chloroform. From the solution was recovered 23.5 g., m.p. 132–135° dec. (47% yield). Further recrystallization from benzene gave material melting at 135° with dec. Rather surprisingly, the compound was found to be stable in boiling methanol, and recrystallization from this solvent raised the melting point to 145° dec.

2,4-Bis-(1-aziridinyl)-6-methoxy-*s*-triazine (VII).—A solution of 17.2 g. (0.40 mole) of ethylenimine and 17.6 g. (0.44 mole) of sodium hydroxide in 125 cc. of water was added at 20–25° to a slurry of 36.0 g. (0.20 mole) of 2,4-dichloro-6-methoxy-*s*-triazine[18] in 125 cc. of ice-water. Reaction was mildly exothermic. The reaction mixture was stirred at room temperature for 25 minutes during which time the chlorotriazine dissolved practically completely and the sodium hydroxide was nearly completely consumed. The solution was filtered and was extracted with about 250 cc. of chloroform in three portions. The chloroform solution was evaporated at low temperature leaving a crystalline residue weighing 17 g. (44% crude yield). Recrystallization from benzene–heptane gave material melting at 117–119°.

Preparation of this compound in benzene solution in essentially the manner described in reference 5 gave approximately the same yield as above.

2-(1-Aziridinyl)-4,6-dimethoxy-*s*-triazine (VIII).—To a slurry of 35.1 g. (0.20 mole) of 2-chloro-4,6-dimethoxy-*s*-triazine[18] in 200 cc. of water was added gradually a solution of 8.6 g. (0.20 mole) of ethylenimine and 8.8 g. (0.22 mole) of sodium hydroxide in 100 cc. of water. There was a mildly exothermic reaction, but the mixture was held at 25–30° during the addition and for 30 minutes longer. It was then warmed briefly at 55°. The crude product was filtered at 5° and was air-dried. It weighed 25.0 g. (69%) and melted at 118–122°. Recrystallization from a mixture of 250 cc. of benzene and 50 cc. of heptane gave 7.5 g., m.p. 121–123°.

Attempted Preparation of 2,4-Bis-(1-aziridinyl)-6-methylphenylamino-*s*-triazine.—2,4-Dichloro-6-methylphenylamino-*s*-triazine[6a] did not react with ethylenimine in water at 0–25° in the presence of sodium hydroxide. In benzene in the presence of triethylamine reaction appeared to proceed smoothly in a distinctly stepwise fashion, one equivalent of ethylenimine reacting at 10–15° and the second at about 25°. However, no product could be isolated. The desired compound would be expected to have a very low melting point and high solubility.

2-(1-Aziridinyl)-4,6-bis-(dimethylamino)-*s*-triazine (IX).—A hot solution of 46.1 g. (0.25 mole) of cyanuric chloride in 50 cc. of acetone plus 75 cc. of dioxane was run into 200 cc. of rapidly stirred ice-water to prepare a finely divided suspension of cyanuric chloride. This was cooled to −10°, and to it was added during 10 minutes at −8 to −10° a mixture of 10.8 g. (0.25 mole) of ethylenimine, 34.5 g. (0.25 mole) of potassium carbonate and 200 cc. of water (two liquid phases). The reaction mixture was stirred for 20 minutes at −10°. To the slurry of I thus obtained was added a mixture of 55.0 g. of 41% aqueous dimethylamine (0.50 mole), 69.0 g. (0.50 mole) of potassium carbonate and 175 cc. of water (two liquid phases). During this addition the temperature was held below 10°. After another 1.5 hours at 10–20°, it was heated to 50° for a few minutes, cooled to 25°, and filtered to remove a little flocculent solid. The two-phase filtrate was extracted with about 400 cc. of chloroform in three portions, and the chloroform solution was evaporated to a sirup at low temperature. This was extracted with benzene, leaving 3.0 g., m.p. >250° undissolved. Re-evaporation to a sirup and crystallization of this from hexane gave approximately 6 g. of waxy crystals. Further recrystallization from hexane gave 4.2 g., m.p. 55–57°.

Attempted Isolation of 2-(1-Aziridinyl)-4,6-dichloro-*s*-triazine (I) and Related Experiments. Attempts to isolate this intermediate, formed as described above for the preparation of IX, were unsuccessful. An insoluble product melting at 90–110° was obtained, but this could not be worked up to give I in pure form. Attempted recrystallizations from carbon tetrachloride or benzene at low temperatures yielded only decomposed products.

Attempts to prepare IV by reaction of 28% aqueous ammonia with I were unsuccessful. Likewise attempts to prepare VIII by reaction of I with sodium methoxide in methanol did not give the desired product.

Reaction of 2,4-Bis-(1-aziridinyl)-6-chloro-*s*-triazine (II) with Amines and Ammonia.—Methylamine, dimethylamine, diethylamine and 2-chloroethylamine were condensed with equimolar amounts of II in water at 0–10° in the presence of potassium carbonate. The products were isolated by chloroform extraction of the solutions obtained followed by evaporation of the extract and recrystallization from suitable solvents. A large amount of water-insoluble material containing considerable II was obtained in each case. The products (X–XIII) are summarized in Table I. Under the same conditions II did not react appreciably with β,β′-iminodipropionitrile or with ammonia. If about 15% of acetone was present in the reaction mixture and a large excess of ammonia was used reaction did take place but did not give an isolable product. Similar experiments with octadecylamine, aniline and sodium sulfanilate were also unsuccessful.

Reaction of allylamine or diethylamine with II in benzene with excess amine or triethylamine present appeared to

(16) A. Ostrogovich, *Chem. Zentr.*, **36**, 739 (1912). We prepared this compound by heating a mixture of 2,4-dihydroxy-6-phenyl-*s*-triazine with three times its weight of phosphorus oxychloride at reflux for 20 hours, decomposing the excess oxychloride with ice-water, and recrystallizing the crude product from benzene. The yield was 72%, m.p. 121–123°. This procedure was developed by R. A. Gadea in our Bound Brook Laboratories.

(17) I. Hechenbleikner, THIS JOURNAL, **76**, 3032 (1954).

(18) J. R. Dudley, *et al.*, *ibid.*, **73**, 2986 (1951).

proceed as expected at 25–50°, but the products were not sufficiently pure to be crystallized. *p*-Chloroaniline did not react appreciably under these conditions.

By reaction of a threefold excess of 28% aqueous ammonia with II in methanol at 50–60°, III was obtained in 30% yield. However, attempted reactions with β-naphthylamine, *p*-chloroaniline and *p*-toluidine in boiling methanol in the presence of triethylamine did not give isolable products.

The instability of the 1-aziridinyl group under the conditions of these experiments was clearly shown by the following experiments. A solution of 0.10 mole each of II, octadecylamine and triethylamine in 220 cc. of methanol was boiled for 1.5 hours. Analysis of an aliquot of the reaction solution by the thiosulfate method showed that only 25% of the original 1-aziridinyl groups remained after this time. When the reaction was attempted in methanol at room temperature with sodium hydroxide present as the hydrogen chloride acceptor, 90% of the alkali was used up in 18 hours, but again only about 25% of the 1-aziridinyl groups remained.

Other Reactions of 2,4-Bis-(1-aziridinyl)-6-chloro-*s*-triazine (II).—Compound VII was prepared in 71% by reaction of II with sodium methoxide in methanol at 30°. The product crystallized readily after partial evaporation of the filtrate from the reaction mixture and melted at 116–118°. Its identity was confirmed by infrared comparison with the product from 2-chloro-4,6-dimethoxy-*s*-triazine.

Reaction products prepared similarly from sodium phenoxide and sodium isopropylmercaptide could not be isolated in crystalline form.

Reaction of 1-Aziridinyl-*s*-triazines with Sodium Thiosulfate.—An approximately 1.5-meq. sample of the 1-aziridinyl-*s*-triazine was dissolved in 50 cc. of water at 25°. To the solution was added 25.00 ml. of 0.100 *N* sodium thiosulfate. With the *p*H of the solution measured continuously with a Beckman model H2 *p*H meter, 0.100 *N* hydrochloric acid was added from a buret to hold the *p*H at 5.2 ± 0.2 as reaction proceeded with the liberation of sodium hydroxide. After a stable *p*H reading was obtained, the solution was allowed to stand 30 minutes longer. The unreacted thiosulfate was then titrated with standard iodine solution to determine the extent of reaction. The results of determinations made in this way are presented graphically in Fig. 1. The curves are plotted on the assumption that the rate of hydrochloric acid consumption is proportional to the rate of reaction. This approximation is close enough for the present purpose, although in general the amount of hydrochloric acid needed was greater than the amount of alkali liberated by an amount depending on salt formation and buffering effects.

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[CONTRIBUTION FROM THE STAMFORD LABORATORIES, RESEARCH DIVISION, AMERICAN CYANAMID CO.]

Rearrangement Reactions of 1-Aziridinyl-*s*-triazines; Dihydroimidazo[1,2-a]-*s*-triazines

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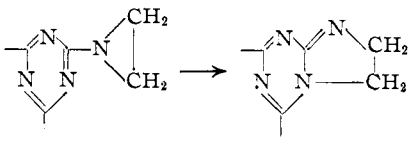
1-Aziridinyl-*s*-triazines rearrange in the presence of acidic catalysts to form dihydroimidazo[1,2-a]-*s*-triazines. Several examples of this rearrangement reaction have been found and the necessary conditions studied to a limited extent. Alternative routes to the dihydroimidazo[1,2-a] *s*-triazine structure by various cyclization reactions also have been investigated.

In the course of work on the preparation of 1-aziridinyl-*s*-triazines[1] and a limited examination of their chemical properties, several anomalous results were obtained. Further study has disclosed that a facile intramolecular rearrangement was responsible.[2]



(1)

The first observations of this isomerization were made in the course of degradation studies intended to substantiate the structure of 2,4,6-tris-(1-aziridinyl)-*s*-triazine (I).

Hydrolysis of substituted amino-*s*-triazines with strong mineral acids[3] has often been used in our laboratory as an effective aid in the elucidation of their structures. Ample evidence has shown that hot 50–85% sulfuric acid will hydrolyze C-amino or imino groups to C-hydroxy or oxo groups while alkyl or aryl substituents on ring nitrogen atoms are not affected.[4] Therefore, isolation of an isocyanurate (a ring nitrogen substituted *s*-triazine) from among the hydrolysis products has been considered to establish the presence of a substituent on ring nitrogen prior to hydrolysis. Several 1-aziridinyl-*s*-triazines were hydrolyzed in this way with very interesting (and misleading) results. Thus, compound I gave mono-2-aminoethyl isocyanurate, 1-(2-aminoethyl)-2,4,6-trioxohexahydro-*s*-triazine (II), as the only isolable hydrolysis product; 2-amino-4,6-bis-(1-aziridinyl)-*s*-triazine (III) gave bis-2-aminoethyl isocyanurate, 1,3-bis-(2-aminoethyl)-2,4,6-trioxohexahydro-*s*-triazine (IV); and 2,4-diamino-6-(1-aziridinyl)-*s*-triazine (V) gave cyanuric acid (VI).[5] 2-(1-Aziridinyl)-4,6-dimethoxy-*s*-triazine VII) also gave VI, while 2,4-bis-(1-aziridinyl)-6-methoxy-*s*-triazine (VIII) gave II.

It appeared unlikely that the hydrolysis products II and IV correctly reflected ring N-substitution in I, III and VIII in view of the apparent nitrogen mustard-like reactivity of these compounds. When it was possible to prepare both III and VIII from the common intermediate, 2,4-bis-(1-aziridinyl)-6-chloro-*s*-triazine (IX),[1] it became obvious

(1) F. C. Schaefer, J. T. Geoghegan and D. W. Kaiser, THIS JOURNAL, **77**, 5918 (1955).

(2) S. Gabriel and R. Stelzner, *Ber.*, **28**, 2929 (1895), reported the analogous rearrangement of 1-benzoylaziridine at its boiling point to form 2-phenyloxazoline.

(3) (a) A. W. Hofmann, *ibid.*, **18**, 2787 (1885); (b) F. C. Schaefer, J. R. Dudley and J. T. Thurston, THIS JOURNAL, **73**, 2996 (1951).

(4) Usually further degradation of the initial hydrolysis products leads to considerable destruction of the triazine ring so that only low yields of informative products are obtained.

(5) Alternative tautomeric structures for these cyanuric acid derivatives are possible, of course. Spectroscopic evidence favors the carbonyl structures in the solid state.