being complete in a few minutes. The excess barium hydroxide was precipitated with solid carbon dioxide. After being filtered through Celite, the solution was added at the top of a chromatographic column containing about 10 g. of wet Amberlite IRC-50 (H-form). The column was washed with a total of 1150 cc. of 50% aqueous methanol when ultraviolet inspection showed that only a negligible amount of purine was in a 50-cc. cut. The pooled fractions showed a content of 472 mg. of nucleosides calculated for the mol. wt. of starting material.

The column was eluted with 400 cc. of 2 *N* ammonia in 50% aqueous methanol. The last 100-cc. cut showed by ultraviolet inspection only 4.3 mg. of nucleoside. The four 100-cc. aliquots were allowed to stand overnight. The first 100-cc. aliquot was the only one to deposit crystals; yield 245 mg. (17%), m.p. 263° dec. This filtrate was combined with the other three cuts and evaporated to dryness *in vacuo*. Crystallization of the residue from 20 cc. of water gave, after 2 days at 3° to complete crystallization, 366 mg. (total yield 26%) of product, m.p. 260–261° dec.

In a pilot run the yield was 31% (22 mg.), m.p. 259–260° dec., $[\alpha]^{25}D$ −40° (0.4% in dimethylformamide); $\lambda_{max}^{H_2O}$ 259 mμ (ε 15,000); λ_{max}^{KBr} 2.97, 3.12 μ (OH, NH), 5.98, 6.22 μ (C=N), 9.13, 9.24, 9.66 μ (OH and C–O–C).

Anal. Calcd. for $C_{10}H_{14}N_6O_3$: C, 45.1; H, 5.30; N, 31.5. Found: C, 44.8; H, 5.50; N, 31.1.

The β-configuration was established by periodate oxidation in *p*H 4.5 acetic acid–sodium acetate buffer. The resultant solution then had $[\alpha]^{24}D$ −24°, M_D −6400.[14,15] The oxidation was complete in a few minutes and did not change further after an additional 16 hours.

A similar hydrolysis and work-up of pure VIII gave a 46% yield of 9-(3′-amino-3-deoxy-α-D-ribofuranosyl)-adenine (XI) as an amorphous solid which could not be crystallized.

(B).—A mixture of 200 mg. of pure 3′-phthalimido-3′-deoxyadenosine and 1.35 cc. of methyl Cellosolve containing 0.027 cc. of 100% hydrazine hydrate was heated on the steam-bath for 1.5 hours. After 10 minutes solution was complete and after 15 minutes another solid began to separate. The mixture was treated with 0.28 cc. of acetic acid and 1.4 cc. of methyl Cellosolve and heated 10 minutes more. The mixture was evaporated to dryness *in vacuo*. Addition of 5 cc. of water left 73 mg. (89%) of insoluble phthalhydrazide. The solution was chromatographed as in procedure A to give 81 mg. (60%) of product, m.p. and mixed m.p. with preparation A, 264° dec. Both compounds had identical infrared spectra.

Similarly, hydrazinolysis of 200 mg. of crude 3′-phthalimido-3′-deoxyadenosine gave 55 mg. (41%) of product, m.p. 264° dec., identical with preparation A.

PEARL RIVER, NEW YORK

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

Preparation of Ethylenimine and Triethylenemelamine

BY V. P. WYSTRACH, DONALD W. KAISER[1] AND FRED C. SCHAEFER

RECEIVED JUNE 1, 1955

An improved process for preparing triethylenemelamine from ethylenimine and cyanuric chloride has been developed. It features the use of an aqueous reaction medium and the generation of ethylenimine in solution, which obviates the isolation and handling of anhydrous ethylenimine. The rates of formation of ethylenimine from 2-aminoethyl hydrogen sulfate, 2-chloroethylamine hydrochloride, and 2-bromoethylamine hydrobromide have been compared. An improved laboratory preparation of anhydrous ethylenimine is described. Some solubility and stability data on triethylenemelamine are presented.

Triethylenemelamine, 2,4,6-tris-(1-aziridinyl)-*s*-triazine (I) was first prepared during World War II in Germany.[2,3] Called Persistol Hö 1/193, it was found to be very effective as a cross-linking agent for wool and as a hydrophobizing agent for regenerated cellulose. More recently it has shown promise as a chemotherapeutic agent against certain types of cancer.[4]

In the German method for preparing I,[2,3,5] ethylenimine is condensed with cyanuric chloride in benzene solution using triethylamine as hydrogen chloride acceptor. This process has several disadvantages. The use of benzene is objectionable on a large scale because of its inflammability. Also, its relatively low solvent power for the product I results in small yields per unit volume. Triethylamine is expensive to use as well as to recover. Finally, anhydrous ethylenimine is costly to prepare, is highly toxic, and can polymerize explosively.[6]

We have been successful in using water as the reaction medium for the preparation of I and have circumvented the use of anhydrous ethylenimine. In so doing, the disadvantages of the German process have been overcome.[7]

The use of an aqueous reaction medium has been possible because of the remarkable speed of the reaction at low temperatures and the unusual solubility properties of I (Table I).

TABLE I

APPROXIMATE SOLUBILITY OF TRIETHYLENEMELAMINE IN VARIOUS SOLVENTS AT 26°

Solvent	Solubility % by wt.	Solvent	Solubility % by wt.
Water	40.0	Ethanol	7.7
Chloroform	28.1	Benzene	5.6
Methylene chloride	19.7	Dimethyl cellosolve	4.8
Methanol	12.5	Methyl ethyl ketone	4.7
Nitromethane	(11.5)	Ethyl acetate	4.5
Acetone	10.6	Carbon tetrachloride	3.6
Dioxane	9.6		

(1) Olin Mathieson Chemical Corp., New Haven, Conn.

(2) R. A. Pingree and M. A. Dahlen, "Textile Finishing Treatments," PB-1576, Office of Technical Sales, Department of Commerce, Washington, D. C. Also published in Great Britain as B.I.O.S. Miscellaneous Report No. 18.

(3) H. Bestian, *Ann.*, **566**, 210 (1950), has published the chemistry of ethylenimine as investigated in the laboratories of I. G. Farbenindustrie A.G.

(4) F. C. Schaefer, J. T. Geoghegan and D. W. Kaiser, THIS JOURNAL, **77**, 5918 (1955). References to the literature pertaining to the use of triethylenemelamine in cancer therapy are cited.

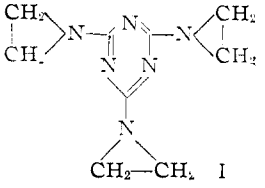
(5) J. Heyna and W. Weibezahn, German Patent 859,025 (July 8, 1949).

(6) The hazards of handling ethylenimine are discussed by Pingree and Dahlen, ref. 2, Appendix XVI, p. 3.

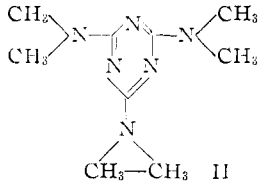
(7) *Cf.* (a) V. P. Wystrach and D. W. Kaiser, U. S. Patent 2,520,619 (August 29, 1950); (b) D. W. Kaiser and F. C. Schaefer, U. S. Patent 2,653,934 (Sept. 29, 1953).

Ethylenimine was found to displace all three chlorine atoms in cyanuric chloride very rapidly at about 0° in aqueous solution in the presence of inorganic bases. This was quite surprising in view of the considerably higher temperature required with dimethylamine in aqueous systems[8]; however, the usual stepwise formation of the intermediate condensation products could be achieved by close control of the reaction conditions.[4]

The solubility of I in water is extraordinary. It dissolves to the extent of 40% at 26° whereas hexamethylmelamine (II), which is superficially at least very similar in structure, is virtually insoluble in water. This would be disadvantageous for the isolation of the product from the aqueous reaction mixture were it not that extraction of I with chloroform is remarkably efficient in dilute solution and is further enhanced by dissolved salts in the aqueous phase. The extraction provided a valuable stage of purification so that complete evaporation of the extract gave a product of high quality.



I



II

The hazards involved in using anhydrous ethylenimine for producing triethylenemelamine have been substantially reduced and the processing simplified by the discovery that usable aqueous solutions of ethylenimine can be prepared conveniently in high yield by treating a precursor of ethylenimine, $XCH_2CH_2NH_2$, with aqueous alkali under mild conditions. Only 2-chloroethylamine, 2-bromoethylamine and aminoethyl hydrogen sulfate were considered to be feasible ethylenimine precursors. Table II summarizes the rates of formation of ethylenimine when these materials are treated with aqueous alkali. The results are presented as half-time and total-time values taken from plots of percentage of ethylenimine formed *vs.* time.

At 100° and an aminoethyl hydrogen sulfate concentration of 1.42 *M* (*ca.* 20%) reaction was essentially complete in 2.5 hr. If the ethylenimine was allowed to distil as it formed, the maximum yield was 70–76% of theoretical. Thus, about 25–30% decomposed before it could be distilled. Excess alkali increased the reaction rate only moderately; it also catalyzed the polymerization or hydrolysis of ethylenimine. The relatively small effect of large excesses of alkali on the reaction rate is in agreement with the concept that the rate-controlling step is intramolecular quaternization of sodium 2-aminoethyl sulfate.[9]

TABLE II

RATES OF FORMATION OF ETHYLENIMINE FROM VARIOUS INTERMEDIATES

Expt.	Molar ratio[a] NaOH/ AEHS	Temp., °C.	Ethylenimine formed, % At 75 min.	At 150 min.	Analysis method
2-Aminoethyl hydrogen sulfate (AEHS)					
1	2[a]	100[b]	44.5	77	Titration
2	2	100	60	98	Titration
3	2	100	42.5	70	Distln.
4	3	100	71	98	Titration
5	3	100	56.5	76	Distln.
6	5[c]	100	52	61	Distln.
	NaOH/ CEA·HCl[d]		At 25 min.	At 50 min.	
2-Chloroethylamine hydrochloride (CEA·HCl)					
7	2.2[c]	29	10.5	14	Titration
8	3.1	50	78.5	96	Titration
	NaOH/ BEA·HBr[e]		At 25 min.	At 50 min.	
2-Bromoethylamine hydrobromide (BEA·HBr)					
9	3	3	7.5	14.5	Titration
10	3	33	93	98	Titration

[a] [AEHS] = 1.42 *M*, except in expt. 1 where [AEHS] = 0.71 *M*. [b] No detectable reaction at 70°. [c] KOH. [d] [CEA·HCl] = 1.25 *M*. [e] [BEA·HBr] = 1.0 *M*.

An essentially complete reaction was obtained with 2-chloroethylamine hydrochloride in about 50 minutes at 50°. The ethylenimine could be distilled from the reaction mixture at reduced pressure (at <50°) practically quantitatively, showing that polymerization or hydrolysis was not appreciable at this temperature. The reaction rate was low at 29°. The rate of formation of ethylenimine from 2-bromoethylamine hydrobromide was even more rapid. Reaction was 93% complete in 25 minutes at 33° and was appreciable even at 3°. Either of these 2-haloethylamines is satisfactory for the present purpose.

The preferred process for preparing triethylenemelamine is described under method C in the Experimental section. An aqueous solution of ethylenimine, prepared by the action of alkali on 2-chloroethylamine hydrochloride, is added directly to a slurry of cyanuric chloride in cold water. The yields are somewhat lower and the reaction is considerably slower than in method A, wherein distilled ethylenimine in alkaline solution is added to a cyanuric chloride slurry in water, or method B, wherein anhydrous ethylenimine is added to an alkaline slurry of cyanuric chloride. However, these shortcomings are of minor importance compared with the avoidance of handling anhydrous ethylenimine.

Before the technique of preparing aqueous ethylenimine solutions was perfected, it was necessary to have available large quantities of anhydrous ethylenimine. The procedure for the preparation of this material described in the Experimental section is believed to be more rapid and efficient than others

(8) We have previously reported data on the preparation of hexamethylmelamine which bears this out, D. W. Kaiser, *et al.*, THIS JOURNAL, **73**, 2984 (1951). Because of a somewhat ambiguous statement by W. M. Pearlman and C. K. Banks, *ibid.*, **70**, 3726 (1948), to the effect that dimethylamine reacted readily with cyanuric chloride at 25° to give hexamethylmelamine, this reaction has now been attempted in water at 25° to show clearly the greater reactivity of ethylenimine. A 100% excess of dimethylamine was used and 4 hours time was allowed. The yield of 2-chloro-4,6-bis-(dimethylamino-*s*-triazine approached quantitative and no hexamethylmelamine was found. As will be shown in a later paper, however, unhydrated secondary amines, *e.g.*, piperidine or morpholine in non-aqueous media, do give the corresponding melamines at 25°.

(9) (a) H. Freundlich and W. Neumann, *Z. physik. Chem.*, **87**, 69 (1914); (b) G. D. Jones, *J. Org. Chem.*, **9**, 125 (1944).

published previously.[10,11] Only simple equipment is required, and 150–300 g. of ethylenimine can be prepared conveniently in a few hours.

Experimental Section[12,13]

2-Aminoethyl Hydrogen Sulfate.—Material commercially available from the B. F. Goodrich Chemical Co. was used without further purification.

2-Chloroethylamine Hydrochloride.—The following procedure proved more convenient and efficient for large scale laboratory work than any of the several published variations.[9b,14,15]

One kilogram of technical grade monoethanolamine was dissolved in 7.5 l. of anhydrous 2B-ethanol and hydrogen chloride gas was passed into the solution at 25–30° until the mixture was acidic to methyl orange. The mixture was chilled, and the monoethanolamine hydrochloride separated by filtration. After washing with a limited amount of cold ethanol, the solid was freed of solvent at reduced pressure. The yield of amine salt was 85–90%, m.p. 82–86°. The mother liquor was reused in subsequent runs.

Twelve moles (1180 g.) of monoethanolamine hydrochloride was slurried in 1900 ml. of toluene and 13.0 moles (932 ml.) of thionyl chloride was added during one hour while the temperature was held at 20–35°. The mixture was gradually heated to 75–80° in 45 minutes. After a five-hour heating period at this temperature, about 250 ml. of liquid was distilled under reduced pressure to remove excess thionyl chloride. The residue was cooled to 30° and filtered. The crude 2-chloroethylamine hydrochloride was washed with toluene and pumped free of solvent in a vacuum desiccator. The yield was 1347 g. (97%), m.p. 120–130°. This crude product could be recrystallized from about one-half its weight of ethanol with a 60% recovery of colorless crystals, m.p. 148.5–150°. The product is highly hygroscopic.

Assay of 2-Chloroethylamine Hydrochloride.—This method depends on the disappearance of 1 mole of base per mole of 2-chloroethylamine in the reaction

$$ClC_2H_4NH_2\cdot HCl + 2NaOH \longrightarrow \begin{matrix}CH_2\\ |\\ CH_2\end{matrix}\!\!>\!NH + 2NaCl + 2H_2O$$

An accurately weighed sample of about 11.0 g. of crude salt was mixed with 100 ml. of 3.00 *N* sodium hydroxide solution and heated at 50° for 80 minutes. Total alkalinity of the solution was then determined by titration with 0.5 *N* acid, using methyl orange as indicator, and the mole per cent. of 2-chloroethylamine hydrochloride calculated. Recrystallized 2-chloroethylamine hydrochloride assayed 99.8% by this method; the crude preparations assayed 90–94%. This procedure may also be adapted to determine the purity of 2-aminoethyl hydrogen sulfate and 2-bromoethylamine hydrobromide.

2-Bromoethylamine Hydrobromide.—A modification of the method of Cortese[16] was used. To 5.0 kg. (20–21 moles) of commercial C.P. hydrobromic acid (d. *ca.* 1.38, 40% HBr) held at 10–20° there was added 500 g. (8.2 moles) of cold redistilled monoethanolamine. The solution obtained was slowly stripped with the aid of a 24-inch column packed with small glass cylinders. Water was collected at 100–100.5°. The boiling point then rose sharply and 1100 ml. of constant boiling hydrobromic acid was collected at 125–126°. The residue was cooled to *ca.* 100° and 1650 ml. of acetone was added. The mixture was stirred and chilled for three hours and the crystalline product was filtered and washed with acetone. The 2-bromoethylamine hydrobromide was dried at 50° giving 1220 g. (69% yield) of colorless crystals, m.p. 170–173°. No attempt was made to recover additional product from the mother liquor.

Rates of Formation of Ethylenimine from Various Intermediates.—Alkaline solutions of 2-sulfato-, 2-chloro- and 2-bromoethylamine salts as shown in Table II were maintained at the indicated temperatures and the rate of formation of ethylenimine was measured by following the decrease in total alkalinity by periodic titration of aliquots to a methyl orange end-point. In experiments 3 and 5, which are comparable with 2, 4 and 6 the ethylenimine (and water) was allowed to distil out of the reaction mixture as it formed (b.p. *ca.* 99–100°). The residue volume was held constant by replacing the distillate with water. Rates of formation of the volatile amine were obtained by periodic titration of the distillate.

Anhydrous Ethylenimine.—A mixture of 694 g. (6 moles) of 2-chloroethylamine hydrochloride, 600 g. (15 moles) of sodium hydroxide and 900 ml. of water was heated at 50° for 2 hr. The solution was then distilled at slightly reduced pressure (b.p. 30–35°) until 680 ml. of distillate had been collected. The cooled distillate was mixed with 350 g. of sodium hydroxide, and the imine was distilled at atmospheric pressure through a one-foot column packed with glass helices. A 50% sodium hydroxide solution was run in slowly at the top of the column during the distillation. The yield of ethylenimine was 187 g. (73%), b.p. 56–57°. The pot temperature did not exceed 70° during the distillation. The ethylenimine was stored over a few pellets of sodium hydroxide. Yields may be improved somewhat by increasing the efficiency of the stripping operation as well as the condensation of the low-boiling distillate.

Caution! Ethylenimine is a very toxic and easily polymerized material and should be handled with extreme care (ref. 14).

Triethylenemelamine. Method A.—A solution of 18.4 g. (0.1 mole) of cyanuric chloride in 35 ml. of dioxane was poured into a vigorously stirred mixture of 100 g. of ice and 100 ml. of water. A solution containing 14.0 g. (0.32 mole) of ethylenimine and 44.5 g. (0.32 mole) of potassium carbonate in the minimum amount (150 ml.) of water was then added to the slurry in 35 min. at 0–5°. At the end of the addition, almost complete solution of the cyanuric chloride had occurred. After treatment with Norite followed by filtration, the reaction solution was extracted five times with a total of 350 ml. of chloroform. Evaporation of the combined chloroform extracts at room temperature gave 20.0 g. (98% yield) of triethylenemelamine as a white, microcrystalline powder, dec. pt. 139°.

Anal. Calcd. for $C_9H_{12}N_6$: N, 41.14. Found: N, 40.80.

Melting (or decomposition) point is not a good criterion of purity for aziridinyl-*s*-triazines. Nitrogen analyses by the Dumas method are satisfactory but the usual Kjeldahl procedure fails with these compounds. A semi-quantitative method for estimating the 1-aziridinyl structure is described in the second paper of this series; *cf.* ref. 4.

Method B.—A solution of 222 g. (1.59 moles) of potassium carbonate in 1150 ml. of water was cooled to 0° and 94 g. (0.5 mole) of powdered cyanuric chloride was slurried in the cold alkaline solution. The dropwise addition of 67.5 g. (1.59 moles) of ethylenimine required 55 minutes at 1–2°, during which time complete solution occurred. The product was recovered as described in method A; a total of 600 ml. of chloroform was used for the extraction. The yield was 89.5 g. (88%). A 91.9% yield was obtained in the same size batch when the cyanuric chloride and ethylenimine were divided into four portions and added successively after the previous portions had reacted.

Method C.—2-Chloroethylamine hydrochloride (111 g., 0.96 mole) was dissolved in a solution containing 126 g. (1.92 moles) of 85% potassium hydroxide, 133 g. (0.96 mole) of potassium carbonate and 600 ml. of water, and the mixture was heated at 50° for one hour. The resulting ethylenimine solution was cooled to room temperature, filtered, and used at once for the next step.

A slurry of 55.3 g. (0.30 mole) of cyanuric chloride in 500 ml. of cold (0–5°) water was prepared as described in method A or B, and the ethylenimine solution was added in 30 minutes at 2°. Stirring was continued at 5° for one hour. The product was recovered by the usual chloroform extraction,

(10) W. A. Reeves, G. L. Drake and C. L. Hoffpauir, THIS JOURNAL, **73**, 3522 (1951).

(11) G. J. Berchet, U. S. Patent 2,212,146 (Aug. 20, 1940).

(12) Due caution should be observed in handling 1-aziridinyl-*s*-triazines. After repeated exposure, sensitive individuals may develop severe allergic reactions to traces of these compounds. A case of dermatitis due to triethylenemelamine therapy has been reported recently by A. M. Frumin and A. I. Rubenstone [*J. Am. Med. Assoc.*, **152**, 914 (1953)].

(13) Melting points are corrected.

(14) Pingree and Dahlen, ref. 2, Appendix XVI.

(15) (a) K. Ward, Jr., THIS JOURNAL, **57**, 914 (1935); (b) G. W. Raiziss and L. W. Clemence, *ibid.*, **63**, 3124 (1941).

(16) F. Cortese, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 91.

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

RECEIVED JUNE 1, 1955

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).