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.

STAMFORD, CONN.

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

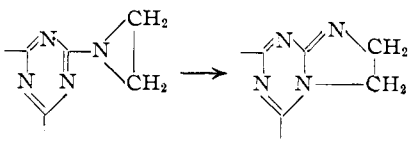
Rearrangement Reactions of 1-Aziridinyl-*s*-triazines; Dihydroimidazo[1,2-a]-*s*-triazines

BY FRED C. SCHAEFER

RECEIVED JUNE 1, 1955

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

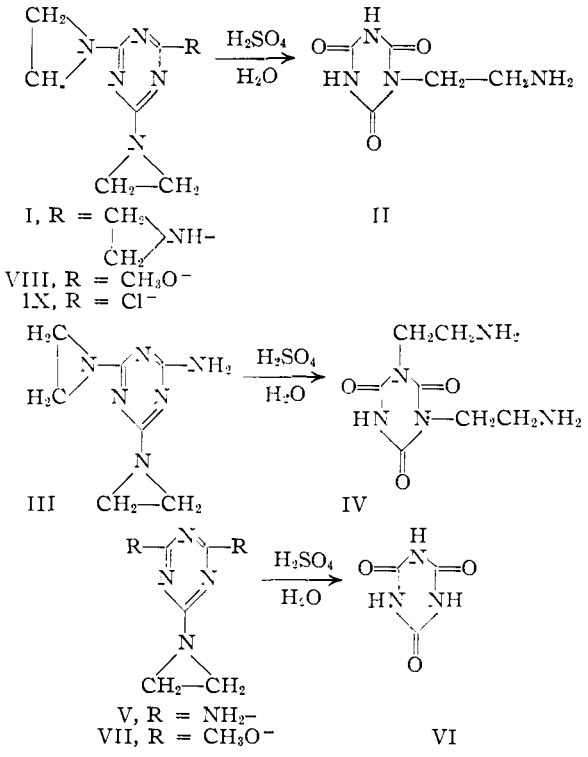
(1) F. C. Schaefer, J. T. Geoghegan and D. W. Kaiser, THIS JOURNAL, **77**, 5918 (1955).

(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).

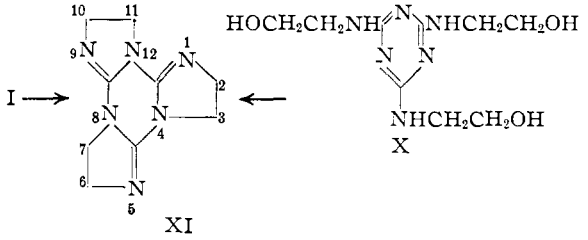
(4) Usually further degradation of the initial hydrolysis products leads to considerable destruction of the triazine ring so that only low yields of informative products are obtained.

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



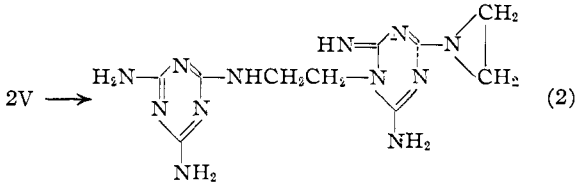
that the hydrolysis products could not be used as proof of structure and that the rearrangement indicated in reaction 1 had occurred prior to hydrolysis in these cases.

Experiments in which catalytic reduction of triethylenemelamine (I) to 2,4,6-trisethylamino-*s*-triazine was attempted provided a further example of this rearrangement. No hydrogen uptake was detectable at 100° in the presence of Raney nickel and hydrogen at 1200 p.s.i. However, an isomer of I was recovered in about 40% yield. This was completely inert to aqueous sodium thiosulfate at *p*H 5 and therefore contained no 1-aziridinyl-*s*-triazine groups.[1] Its synthesis by an alternate route, cyclization of 2,4,6-tris-(2-hydroxyethylamino)-*s*-triazine (X) with phosphorus oxychloride, confirmed its identification as 2,3,6,7,10,11-hexahydrotrisimidazo[1,2-a;1′,2′-c;1″,2″-e]-*s*-triazine (XI).

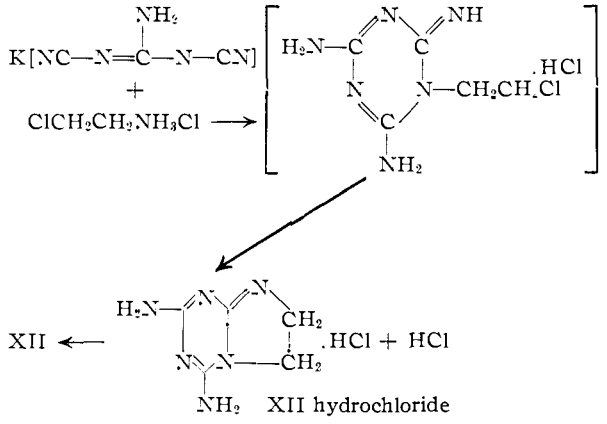


Some study of the conditions required for the rearrangement of I to XI in the particular system employed showed that water, Raney nickel catalyst and hydrogen were simultaneously required for the production of XI in detectable amounts.

Attempts to bring about the rearrangement by heat alone were essentially unsuccessful. It was not possible to rearrange I to XI by heating a dioxane solution at 100° under which conditions I does not polymerize appreciably in several hours. Polymerization which does occur at higher temperatures precluded the study of more strenuous conditions. However, V is much more stable to polymerization, and its stability with respect to rearrangement was investigated in *o*-dichlorobenzene at 130–175°, in chlorobenzene at 132° and in 2-ethoxyethanol at 135°. In no case was the expected rearrangement product, 5,7-diamino-2,3-dihydroimidazo[1,2-a]-*s*-triazine (XII), found in isolable amount. Other reactions did occur in varying degrees, including formation of relatively strongly basic products, probably by intermolecular alkylation reactions such as (2).



Synthesis of XII by reaction of 2-chloroethylamine hydrochloride with potassium dicyanoguanidine provided this compound for comparison with the products obtained in these attempted rearrangement experiments.

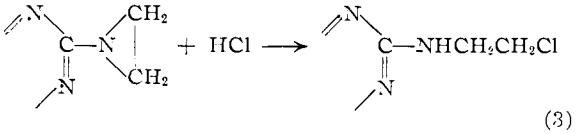


In an experiment in which condensation of 2,4-bis-(1-aziridinyl)-6-chloro-*s*-triazine (IX) with octadecylamine in methanol was attempted in the presence of triethylamine as an acceptor, it had been observed that most of the 1-aziridinyl-*s*-triazine groups were destroyed.[1] Further work showed that IX is essentially stable in boiling methanol, but that in the presence of triethylamine hydrochloride, the 1-aziridinyl-*s*-triazine structure was rapidly lost. Catalyzed polymerization or methanolysis might have taken place, but rearrangement reactions could have been responsible for the observed effect. This last possibility was supported when it was found that both I and V rearranged in good yield to XI and XII, respectively, when heated with triethylamine hydrochloride in boiling acetonitrile. A suspension of triethylamine hydrochloride in a boiling solution of I in benzene caused essentially no rearrangement. This was consistent with the fact that I can be prepared in over 70% yield by reaction of cyanuric chloride with ethylenimine in benzene solution.[6] It is probable, how-

(6) R. A. Pingree and M. A. Dahlen, "Textile Finishing Treatments" (P.B. 1576), published by the Office of Technical Sales, Department of Commerce, Washington, D. C., 1945, p. 53.

ever, that rearrangement is to be expected whenever a soluble amine salt is formed in a reaction involving a 1-aziridinyl-*s*-triazine. These conditions were obtained in several reactions which had been attempted.[1]

Additional, somewhat obscure examples of the rearrangement reactions were found in the behavior of 1-aziridinyl-*s*-triazines toward dilute hydrochloric acid. 2,4-Diamino-6-(1-aziridinyl)-*s*-triazine (V) and ethylenimine itself can be titrated potentiometrically in water without difficulty, giving sharp end-points and no indication of instability during the few minutes required. However, attempts to conduct titrations of I and III with an intermittent-reading *p*H meter failed, no break being observed. When a continuous-reading meter was used, it was found that at about *p*H 3–4 the acid was consumed as fast as it is normally added. Compound V reacted quite sluggishly by comparison. It was thought that formation of the 2-chloroethylamino derivatives by reaction 3 might be responsible for these results, this being a general reaction of aziridine compounds.[7] However, some additional work disclosed unexpected complexity in these reactions. The data obtained did not permit an unequivocal interpretation, but when considered in the light of the results discussed above regarding the hydrolysis of these compounds with strong sulfuric acid, they led to the conclusion that more or less the same reactions were caused by dilute hydrochloric acid as by the sulfuric acid.

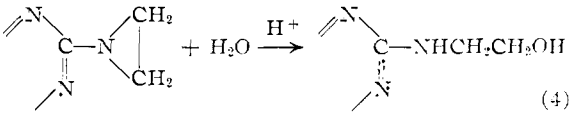


(3)

Samples of I, III and V were allowed to react to completion with dilute aqueous hydrochloric acid, and the product solutions were examined by potentiometric titration with alkali. In each case distinct end-points were found which showed the amount of acid consumed. In addition, in the case of III and V clear second end-points were obtained representing neutralization of the hydrochlorides of weak bases (pK_a *ca.* 5.0). Only general buffering in the low *p*H range was observed in the case of I. The data showed that I, III and V consumed approximately 1.1, 0.85 and 0.5 mole of hydrochloric acid per mole, respectively, in about one hour, after which these values did not change. After the same period, the solutions from III and V contained 0.85 and 1.0 mole of weak base hydrochloride per mole, respectively. Analysis of the reaction solutions by the thiosulfate method showed that all aziridinyl groups in I and III had been destroyed by the time of these titrations. After 40 hr. longer, the amount of weak base hydrochloride in the solution from V had decreased to 0.66 mole per mole. Attempts to recover a product from the reaction of I failed. However, after hydrolysis of the products with strong sulfuric acid, a trace of 2-aminoethyl isocyanurate (II) was isolated; no cyanuric acid was obtained. In the somewhat simpler case of V, it was possible to recover XII from the reaction products, but much larger amounts of material were not identified.

(7) (a) S. Gabriel and R. Stelzner, *Ber.*, **28**, 2933 (1895); (b) H. Bestian, *Ann.*, **566**, 210 (1950).

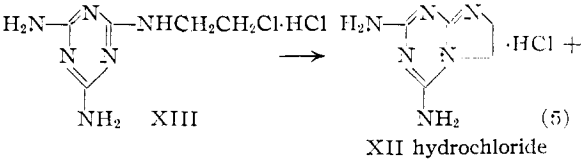
The following reactions might account for the loss of aziridinyl groups under the conditions used: ring opening by reaction 3; rearrangement, reaction 1; hydrolytic ring opening to give 2-hydroxyethylamino groups, reaction 4; and polymerization. Polymerization seems excluded since I and III did not yield insoluble products. Acid consumption



(4)

could be caused by either reaction 3 or 1 since in the latter case the rearrangement product can be a strong base (*e.g.*, XII; pK_a *ca.* 10.7).

In the case of V essentially all acid consumption probably was due to reaction 3, producing 2,4-diamino-6-(2-chloroethylamino)-*s*-triazine hydrochloride (XIII), since very close to 1.0 mole of weak base hydrochloride remained after 0.5 mole of acid had disappeared. Although it was not shown by a thiosulfate analysis that all aziridinyl groups had been destroyed at this point, substantial evidence for this is that a maximum amount of acid consumption had taken place. The other 50% of V presumably was converted to the hydrochloride of 2,4-diamino-6-(2-hydroxyethylamino)-*s*-triazine (XIV) by reaction 4. The subsequent decrease in the amount of the weak base hydrochloride is believed to be evidence for a relatively slow cyclization reaction



(5)

XII hydrochloride

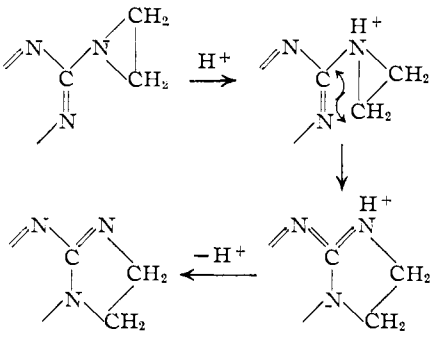
Evidently, the principal initial products would lead to cyanuric acid in the hydrolysis with strong sulfuric acid.

In the cases of I and III the basic strengths of the possible rearrangement products are not known, and the acid consumption data cannot be interpreted easily. However, the rearrangement reaction 1 is a plausible explanation for the complete loss of aziridinyl groups in the time required for consumption of approximately one mole of hydrochloric acid per mole of triazine. The ring opening reactions 3 and 4 probably compete to a considerable extent.

With one notable exception[8] all of the rearrange-

(8) The rearrangement of 1 to XI under the influence of conditions for hydrogenation is not easily classed as an acid-catalyzed process. Although there has been evidence presented that positively charged hydrogen is present on or in a nickel catalyst, this is a small effect, and the dipole moment of the H–Ni bond has been found to be very slight. Nevertheless, the hydrogen–nickel system has been shown to catalyze hydrogen exchange reactions and isomerizations of the butenes which are known to be catalyzed by certain acids. These effects have not been clarified in detail, but it appears that hydrogen bond formation with chemisorbed hydrogen is involved. This might also take place to bring about rearrangement of 1. Leading references on this subject are: (a) D. D. Eley, *J. Phys. Colloid Chem.*, **55**, 1017 (1951); (b) T. I. Taylor and V. H. Dibeler, *ibid.*, **55**, 1036 (1951); (c) H. J. Bernstein, *ibid.*, **56**, 351 (1952); R. Suhrmann, *Z. Elektrochem.*

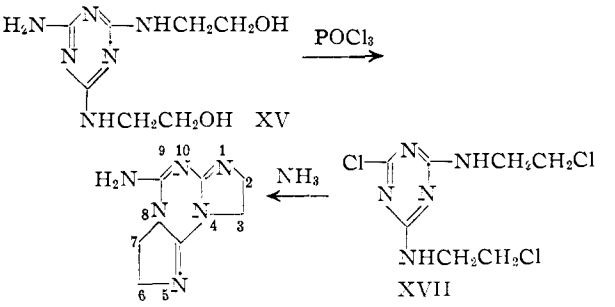
ment reactions reported here clearly were acid catalyzed. A mechanism may be indicated as shown.



Acid catalysis is of predominant importance in the reactions of ethylenimine derivatives.[9] Reactions with amines do take place sluggishly[7] but a base may usually be considered a stabilizer. The rapid rearrangement of 1-aziridinyl-*s*-triazines under acidic conditions is, therefore, of considerable practical importance. Not only does it cause difficulties in the preparation of this group of compounds, but it is apt to be a serious side reaction whenever a sluggish reagent is treated with a 1-aziridinyl-*s*-triazine under even mildly acid conditions. An example of this is the reaction of I with dilute hydrochloric acid at *p*H 3–4. On the other hand, powerful nucleophilic reagents, *e.g.*, the thiosulfate ion, may react satisfactorily.[1,10] The influence of acidic conditions is perhaps of greatest practical importance in the chemotherapeutic application of I. The possibility of reaction of this compound with acidic substances in the stomach has been recognized, and it has become the practice to give the drug to fasting patients one hour before breakfast along with sodium bicarbonate.[11]

We had hoped to prepare one or more (2-chloroethyl)-2,4,6-triamino-*s*-triazines for comparison with the corresponding 1-aziridinyl-*s*-triazines, but this did not prove possible. Although intermediates containing the 2-chloroethylamino-*s*-triazine group were obtained satisfactorily, subsequent reactions gave dihydroimidazo[1,2-a]-*s*-triazines rather than the compounds desired (similar to reaction 5). Similarly, synthetic routes based on introduction of the 2-chloroethyl group in the final step were invariably unsuccessful. In several instances, the cyclized products were isolated in satisfactory purity and their structures were established with assurance. In other cases, the products could not be properly characterized although they were readily seen to be of the same nature.

Reaction of 2-amino-4,6-bis-(2-hydroxyethylamino)-*s*-triazine (XV) with phosphorus oxychloride produced a compound (XVIa) which was recovered in low yield. This highly water-soluble substance behaved as a strongly acidic dihydrochloride of a compound having two basic groups of widely differing strength (pK_a's approximately 3.0 and 9.0). Analysis gave data substantially in agreement with the composition of 9-amino-2,3,6,7-tetrahydrobisimidazo-[1,2-a;1′,2′-c]-*s*-triazine dihydrochloride (XXIa). By treatment with ex-

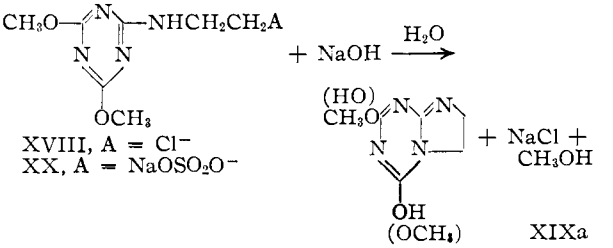


XVIa, dihydrochloride
XVIb, monohydrochloride

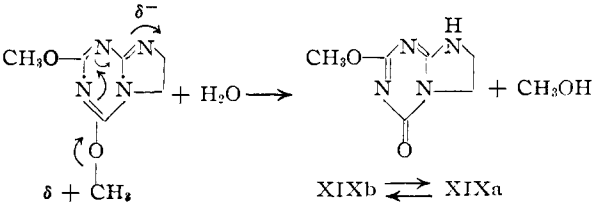
cess sodium hydroxide in a little water, XVIa was converted to a somewhat less soluble hydrochloride (XVIb) which was nearly neutral and analyzed approximately for the monohydrochloride of 9-amino-2,3,6,7-tetrahydrobisimidazo[1,2-a;1′,2′-c]-*s*-triazine. The latter was identical (by infrared inspection) with the product obtained by condensation of 2-chloro-4,6-bis-(2-chloroethylamino)-*s*-triazine (XVII) with excess ammonia at 90°. However, compound XVIa could not be regenerated by recrystallization of the monohydrochloride from excess hydrochloric acid.

The reaction of X with phosphorus oxychloride to produce XI has been mentioned above. This reagent apparently did not cause cyclization of 2,4-diamino-6-(2-hydroxyethylamino)-*s*-triazine (XIV) to a significant degree.

Reaction of 2-chloroethylamino-4,6-dimethoxy-*s*-triazine (XVIII) with sodium hydroxide in aqueous ethanol led to the formation of 5(7)-hydroxy-7(5)-methoxy-2,3-dihydroimidazo[1,2-a]-*s*-triazine (XIXa) (or a tautomer such as XIXb) which was recovered in about 70% yield.



Compound XIX was also isolated from among the products of reaction of sodium 2,4-dimethoxy-6-(2-sulfatoethylamino)-*s*-triazine (XX) with aqueous sodium hydroxide. The demethylation which occurred in these reactions is noteworthy since ordinary alkoxy-*s*-triazines are quite stable under comparable conditions. No evidence is available to show which methyl group is lost, but it is likely that



(9) G. D. Jones, *J. Org. Chem.*, **9**, 484 (1944).

(10) Potassium thiocyanate (0.04 *N*) reacted with I at *p*H 5–6 and 25–40° to the extent of almost exactly 2.0 moles per mole of I. The fate of the third aziridinyl group in I was not established.

(11) R.W. Rundles, *J. Am. Pharm. Assoc.*, **15**, 432 (1954); see also D. A. Karnofsky, *et al.*, *Arch. Internal. Med.*, **87**, 477 (1951).

the sensitivity is at the 5-methoxy group which is at the end of a long conjugated system.

Experimental Section[12]

Hydrolytic Degradation of 1-Aziridinyl-*s*-triazines with Sulfuric Acid. Triethylenemelamine (I).—Fourteen grams of I[13] was added cautiously to 100 cc. of 65% sulfuric acid causing a vigorous reaction and formation of an insoluble mass. The mixture was heated at 145° for 20 hr., and the black solution obtained was poured on 500 g. of ice. No cyanuric acid crystallized as the solution was allowed to stand for one hour. Sulfate was then precipitated quantitatively by treatment with barium hydroxide. The solution obtained was weakly alkaline and gave a faint test for barium ion. It was evaporated to a sirup at low temperature. Addition of a little methanol promoted the crystallization of 2.3 g., m.p. 239° dec. After recrystallization from aqueous ethanol and from water, this product melted at 280–281°. This compound was a weak base (pK_a *ca.* 6.8). Analysis established its structure as 1-(2-aminoethyl)-2,4,6-trioxohexahydro-*s*-triazine (II).

Anal. Calcd. for $C_5H_8N_4O_3$: C, 34.88; H, 4.69; N, 32.55; neut. equiv., 172.1. Found: C, 34.72; H, 4.72; N, 32.59; neut. equiv., 172.5.

Synthesis of this substance by an independent route provided final confirmation of its structure (see below).

Several hydrolyses of I with sulfuric acid of other concentrations were tried. In no case could cyanuric acid be found among the products and no better yields of II were obtainable.

2-Amino-4,6-bis-(1-aziridinyl)-*s*-triazine (III).—Hydrolysis of 15 g. of III[1] with 85% sulfuric acid in the manner described for I yielded no cyanuric acid but approximately 4 g. of a basic compound (pK_a *ca.* 6.6) which melted at 213.0–214.0° (from water). This was identified by analysis as 1,3-bis-(2-aminoethyl)-2,4,6-trioxohexahydro-*s*-triazine (IV).

Anal. Calcd. for $C_7H_{13}N_5O_3$: C, 39.06; H, 6.09; N, 32.55. Found: C, 39.13; H, 6.10; N, 32.70.

2,4-Diamino-6-(1-aziridinyl)-*s*-triazine (V).—A mixture of 10 g. of V[1] and 50 cc. of 65% sulfuric acid was boiled for 18 hr. Crystals separated during the heating period. The mixture was poured on 200 g. of ice, and after a few minutes the crystals were filtered, washed with water and with alcohol, and dried. The crude product weighed 5.1 g. Recrystallization from 140 cc. of water followed by drying at 110° gave 4.6 g., neut. equiv. (acidic) 131 (theory for anhydrous cyanuric acid, 129). Infrared examination confirmed the identification of the product as cyanuric acid (VI).

2-(1-Aziridinyl)-4,6-dimethoxy-*s*-triazine (VII).—Hydrolysis of 10 g. of this compound[1] gave 1.3 g. of cyanuric acid (identified by infrared examination).

2,4-Bis-(1-aziridinyl)-6-methoxy-*s*-triazine (VIII).—Hydrolysis of 10 g. of VIII[1] with 85% sulfuric acid gave 0.4 g. of II, m.p. 270–272°, confirmed by infrared examination.

1-(2-Aminoethyl)-2,4,6-trioxohexahydro-*s*-triazine (II).—N-Benzoylethylenediamine was prepared by the reaction of ethyl benzoate with excess dry ethylenediamine[14] and was converted to the hydrochloride, m.p. 164–166° (from dioxane), yield 48%. This was converted to **2-benzamidoethylisomelamine** by the method of Kaiser and Nagy.[15]

N-Benzoylethylenediamine hydrochloride (30.1 g., 0.15 mole), 22.1 g. (0.15 mole) of potassium dicyanoguanidine and 8.03 g. (0.15 mole) of ammonium chloride in 120 cc. of 2-ethoxyethanol were heated for 10 hr. at 127–132° while a slow stream of air was bubbled through the mixture to sweep out ammonia. The insoluble product was filtered, washed with 2-ethoxyethanol and with methanol, and air-dried. The solid was then extracted with warm water which left undissolved 32 g. of crude 2-benzamidoethylisomelamine hydrochloride (68% yield). This was converted to the free base by treatment with excess 3% sodium hydroxide at 30–50°. The 2-benzamidoethylisomelamine was recrystallized from 2-methoxyethanol, m.p. 240–241°.

Anal. Calcd. for $C_{12}H_{15}N_7O$: N, 35.9. Found: N, 35.3.

Fifteen grams of the isomelamine was heated with about 80 cc. of 50% sulfuric acid for 16 hr. at 115°. The clear solution obtained deposited crystals of benzoic acid on cooling. The mixture was poured on ice and extracted with chloroform to remove the benzoic acid. The aqueous solution was freed of sulfuric acid by exact neutralization with barium hydroxide. Evaporation then yielded 1.5 g. of a basic compound, m.p. 270–272° dec., which was apparently II, identical with the hydrolysis product from I. This identity was confirmed by infrared comparison.

Rearrangement of I to 2,3,6,7,10,11-Hexahydrotrisimidazo[1,2-a;1′,2″-c;1″,2″-e]-*s*-triazine (XI) under Reducing Conditions.—The best of 12 preparations is reported: A mixture of 10.2 g. (0.050 mole) of I, 100 cc. of pure dioxane, 0.90 g. (0.050 mole) of water and approximately 4 g. of Raney nickel catalyst was heated to 100° under 1200 p.s.i. hydrogen pressure for 7 hr. The reaction mixture was then filtered, and the solids were extracted with ethanol. The ethanol and dioxane solutions were united and evaporated to a small partly crystalline residue. This was diluted with water and the crystals were filtered. The 4.3 g. obtained melted at 308–309°. Most of the remainder of the starting material was recovered as an uncrystallized sirup by re-evaporation of the aqueous mother liquor. Recrystallization of the solid from water gave needles of a dihydrate which were reduced to an anhydrous powder by long drying at 105°. This material (XI) melted at 322–324° without decomposition. Analysis showed it to be isomeric with I. It was inert toward aqueous sodium thiosulfate at *p*H 4.0–5.2.

Anal. Calcd. for $C_9H_{12}N_6$: C, 52.92; H, 5.92; N, 41.15; neut. equiv., 204. Found: C, 52.63; H, 6.19; N, 41.67; neut. equiv., 202; pK_a *ca.* 5.8.

In variations of the process described, it was demonstrated that water, Raney nickel and hydrogen were simultaneously required for the formation of XI in isolable amounts, although in no case was hydrogen absorption observed. No alternative solvents or catalysts were investigated. Compound I was found to be stable in dioxane at 100° at atmospheric pressure.

Preparation of XI from 2,4,6-Tris-(2-hydroxyethylamino)-*s*-triazine.—Phosphorus oxychloride (200 cc., 2.1 moles) was added to 94.0 g. (0.36 mole) of 2,4,6-tris-(2-hydroxyethylamino)-*s*-triazine[16] during 30 minutes. Reaction was vigorous. Hydrogen chloride was evolved, and the temperature rose to about 100°. The mixture was then boiled for two hours. Most of the excess phosphorus oxychloride was distilled during another 1.5 hr., and the residual sirup was poured on ice. Excess sodium hydroxide was added to make the mixture strongly alkaline. The solid which crystallized was filtered, washed with water, and dried at 100°. The product weighed 42 g. (57.5%), m.p. *ca.* 320°. Material recrystallized from water melted at 320–325°. Elemental analysis, potentiometric titration, and comparison of infrared spectra showed this product to be identical with the isomer XI obtained from triethylenemelamine.

Reaction in benzene at 20–30° was very incomplete. However, if no solvent was used a 25% yield of XI was obtained after 2.5 hr. at this temperature, showing the remarkable ease with which this cyclization takes place.

Attempted Thermal Rearrangement of V to XII.—Samples of V were heated for 2–3 hr. (a) at 175° in *o*-dichlorobenzene, (b) at 132° in chlorobenzene, and (c) at 135° in 2-ethoxyethanol. The solid products, which were recovered practically quantitatively in (a) and (b) but not in (c), were titrated potentiometrically to find any change in base strength or neutral equivalent. It was found that about 10 mole per cent. of the starting material was converted to a relatively strong base by processes a and c, but that no significant change occurred in (b). Infrared absorption spectra showed that the products from (a) and (b) contained large amounts of V and possibly some of XII, the desired rearrangement product. Neither V nor XII were present in the product from (c).

(12) Melting points are corrected. Microanalyses were carried out in these laboratories under the direction of Dr. J. A. Kuck. Infrared spectra were obtained and interpreted by Dr. J. E. Lancaster and Mr. R. J. Francel. Pressure reactions were carried out by Mr. W. H. Montgomery and Mr. O. Rorso.

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(14) A. J. Hill and S. R. Aspinall, *ibid.*, **61**, 822 (1939); S. R. Aspinall, *J. Org. Chem.*, **6**, 895 (1941).

(15) D. W. Kaiser and D. Nagy, U. S. Patent, 2,481,758 (1949).

(16) D. W. Kaiser, *et al.*, THIS JOURNAL, **73**, 2984 (1951).

5,7-Diamino-2,3-dihydroimidazo[1,2-a]-*s*-triazine (XII).—The method of Kaiser and Nagy[16] for the preparation of isomelamines was employed.

A mixture of 116 g. (1.00 mole) of 2-chloroethylamine hydrochloride,[13] 147 g. (1.00 mole) of potassium dicyanoguanidine, 53.5 g. (1.00 mole) of ammonium chloride and 750 cc. of 2-ethoxyethanol was heated at reflux for 18 hr. The reaction mixture was filtered cold, and the solid product was washed with acetone and water and was dried at 100°. The dry product weighed 202 g., m.p. above 360°. After two recrystallizations from water, a sample gave the analysis below, identifying the compound as the hydrochloride of XII. It was essentially neutral in water and therefore could not be isomeric 2-chloroethylisomelamine.

Anal. Calcd. for $C_5H_9N_6Cl$: C, 31.83; H, 4.81; N, 44.56; Cl, 18.8. Found: C, 31.63; H, 4.94, N, 44.65; Cl, 18.3.

Treatment of the hydrochloride with excess warm aqueous potassium hydroxide liberated the base which melted at 308–310°.

Anal. Calcd. for $C_5H_8N_6$: C, 39.49; H, 5.30; N, 55.24. Found: C, 39.38; H, 5.24; N, 55.25.

Potentiometric titration showed that the basic dissociation constant of XII (K_B) is approximately 5×10^{-4} (pK_a, 10.7) which is typical for an aliphatic isomelamine.[17] Under the usual conditions for reaction of 1-aziridinyl-*s*-triazines with sodium thiosulfate,[1] the free base was completely inert. Hydrolysis with 10 *N* sulfuric acid yielded II, m.p. 285° dec., which was shown by infrared comparison to be identical with the hydrolysis product from I.

Triethylamine Hydrochloride Catalyzed Rearrangements of 1-Aziridinyl-*s*-triazines.—A solution of 1.30 g. of 2,4-bis-(1-aziridinyl)-6-chloro-*s*-triazine (IX)[1] in 50 cc. of methanol was boiled for 1.5 hr. Analysis of the solution by the thiosulfate method[1] then showed that at least 85% of the original 1-aziridinyl groups remained. This experiment was then repeated with an equimolar amount of triethylamine hydrochloride present. The product solution had *p*H 11.0 in water and potentiometric titration showed that approximately 35 mole % of a strong base had been generated in the initially neutral mixture. Analysis by the thiosulfate method showed that only 18% of the original 1-aziridinyl groups remained.

To rearrange I to XI, 2.6 g. of the former and 1.0 g. of triethylamine hydrochloride were heated together in 60 cc. of boiling acetonitrile for 1.5 hr. Gradual deposition of a crystalline product took place. Further crystallization in the cold gave a total of 2.0 g. of solid which was completely soluble in water. Recrystallization from 15 cc. of hot water gave 1.3 g. of fine needles which dried to a powder at 100°, m.p. *ca.* 320°. This material was identical with XI prepared from I under reducing conditions.

Triethylamine hydrochloride suspended in a boiling benzene solution of triethylenemelamine did not cause formation of more than a trace of XI.

Rearrangement of V was accomplished by heating 1.65 g. with 1.0 g. of triethylamine hydrochloride and 25 cc. of acetonitrile at reflux for 2.5 hr. After the reaction mixture was cooled, filtration gave 1.90 g. of a neutral, water-soluble material which contained chloride ion. Infrared examination showed that the product was largely the expected 5,7-diamino-2,3-dihydroimidazo[1,2-a]-*s*-triazine hydrochloride together with a smaller amount of V. Analysis by the thiosulfate method showed the presence of approximately 38% of the original V.

Reaction of 1-Aziridinyl-*s*-triazines with Dilute Hydrochloric Acid. Triethylenemelamine (I).—A solution of 10.2 g. (0.050 mole) of I in 50 ml. of water was prepared. To this was added slowly (30 minutes) 300 ml. of 0.5 *N* hydrochloric acid (0.150 mole). Forty-five minutes later a 10.0-ml. aliquot was removed and titrated potentiometrically. The curve obtained showed clearly that approximately 1.1 moles of hydrochloric acid had been consumed per mole of I. No further change was detectable by another titration 18 hr. later. At the time of the first titration, another 10.0-ml. aliquot (*p*H 2) was mixed with 25.0 ml. of 0.100 *N* sodium thiosulfate. No observable *p*H change occurred in 10 minutes. Titration with standard iodine solution 45 minutes later confirmed that no thiosulfate had been consumed. This was repeated with a sample adjusted to *p*H 5, again with no thiosulfate consumption.

The reaction was repeated as described. The solution was then evaporated to a sirup, and this was hydrolyzed with 65% sulfuric acid. No cyanuric acid was formed in isolable amount. However, a small amount of II, m.p. *ca.* 279°, was recovered.

2-Amino-4,6-bis-(1-aziridinyl)-*s*-triazine.—To 1.671 g. (0.00939 mole) of III dissolved in 20 cc. of water was added during 30 minutes 60.0 ml. of 0.500 *N* hydrochloric acid (0.030 meq.). The solution was stirred 30 minutes longer. It was then diluted to 100.0 ml. and a 10.0-ml. aliquot was titrated potentiometrically. A well-defined titration curve was obtained which showed that 0.85 mole of hydrochloric acid had been consumed per mole of III and that approximately another 0.85 mole was present as the salt of a weak base (pK_a, *ca.* 5.0). Analysis of another aliquot by the thiosulfate method showed that all 1-aziridinyl groups had been destroyed.

2,4-Diamino-6-(1-aziridinyl)-*s*-triazine.—A small scale reaction, conducted as described for III, demonstrated that after one hour *ca.* 0.51 mole of hydrochloric acid had been consumed per mole of V, and that 1.0 mole was present as the salt of a weak base. The acid consumption did not change in an additional 40 hr., but the amount of weak base hydrochloride present decreased to 0.66 mole per mole of V used.

An attempt was made to recover the reaction products in the following way. Two hundred cc. of 3.0 *N* hydrochloric acid was added during 10 minutes to a solution of 30.4 g. (0.20 mole) of V in one liter of water. After 30 minutes at room temperature, the solution was filtered to remove 1–2 g. of insolubles, made basic to phenolphthalein, and evaporated at low temperature to 100 cc. Crystallization gave 22.1 g., m.p. 360° dec. Neutralization of the mother liquor to *p*H 7 with hydrochloric acid caused precipitation of 11.2 g., m.p. 330–340° dec. Both of these solids were found to be mixtures of XII and its hydrochloride. No indication of the presence of 6-(2-chloroethylamino)-2,4-diamino-*s*-triazine among the reaction products was found.

Reaction of 2-Chloro-4,6-bis-(2-chloroethylamino)-*s*-triazine (XVII) with Ammonia.—Compound XVII was prepared as follows: A solution of 8.0 moles of sodium hydroxide in one liter of water was slowly added at 0–5° to a mixture of 2.0 moles of cyanuric chloride and 4.0 moles of 2-chloroethylamine hydrochloride[13] in 650 cc. of acetone and 2.5 l. of water. The reaction mixture was then stirred at 45–50° for 3.5 hr. The solid product was filtered, washed with water, and dried at 100°. The crude dry product was recrystallized from dioxane, m.p. 163° dec., yield 334 g. (62%).

Anal. Calcd. for $C_7H_{10}N_5Cl_3$: Cl, 39.3. Found: Cl, 39.4.

Reaction of excess ammonia with XVII in dioxane at 90° under pressure gave an easily water-soluble product. After two recrystallizations from water, an approximately 25% yield of material was obtained, m.p. 350°. Analysis, although unsatisfactory, indicated that this could be the **hydrochloride of 9-amino-2,3,6,7-tetrahydroimidazo[1,2-a;1′,2′-c]-*s*-triazine (XVIb).**

Anal. Calcd. for $C_7H_{11}N_6Cl$: C, 39.2; H, 5.13; N, 39.2; Cl, 16.6. Found: C, 38.83; H, 5.47; N, 38.39; Cl, 14.75.

Cyclization of 2-Amino-4,6-bis-(2-hydroxyethylamino)-*s*-triazine (XV).—Reaction of 20.0 g. (0.094 mole) of XV[16] with 75 cc. (0.72 mole) of phosphorus oxychloride, followed by distillation of excess oxychloride and dilution of the residue with ethanol, produced a solid product. This was filtered and dissolved in a small amount of warm water. Solution was accompanied by a vigorous reaction and evolution of hydrogen chloride. Approximately 7 g. of a granular solid was recovered by dilution of the aqueous solution with methanol, m.p. *ca.* 340° dec. A sample recrystallized from water, in which it was very soluble, melted with dec. at 340–345°. The compound was a strongly acidic hydrochloride. Potentiometric titration indicated that it was the dihydrochloride of a compound having two basic groups whose pK_a's were approximately 3.0 and 9.0. Analytical data were somewhat unsatisfactory but suggested the structure XVIa.

Anal. Calcd. for $C_7H_{12}N_6Cl_2$: C, 33.48, H, 4.82; N, 33.47; Cl, 28.24. Found: C, 33.22; H, 5.02; N, 32.84, Cl; 27.97.

(17) J. R. Dudley, THIS JOURNAL, **73**, 3007 (1951).

This dihydrochloride was converted to a less soluble material by treatment with sodium hydroxide at *p*H 6–8 in a little water. Infrared examination showed this derivative to be virtually identical with XVIb, obtained from XVII. Recrystallization of this monohydrochloride from excess hydrochloric acid did not regenerate XVIa.

Attempted Cyclization of 2,4-Diamino-6-(2-hydroxyethylamino)-*s*-triazine (XIV).—Compound XIV, m.p. 225–227°, was prepared by condensation of 2,4-diamino-6-chloro-*s*-triazine with ethanolamine following a general method described in reference 16.

Anal. Calcd. for $C_5H_{10}N_6O$: N, 49.38. Found: N, 49.0.

Neither XII nor its hydrochloride could be isolated from the reaction product obtained by heating XIV with three equivalents of phosphorus oxychloride.

Preparation of XIX by Reaction of 2-Chloroethylamino-4,6-dimethoxy-*s*-triazine (XVIII) with Sodium Hydroxide.—2,4-Dichloro-6-(2-chloroethylamino)-*s*-triazine, m.p. 111.5–113°, was prepared in 83% yield by reaction of equimolar amounts of cyanuric chloride with 2-chloroethylamine and sodium hydroxide in aqueous acetone at 0–5°.[18]

Anal. Calcd. for $C_5H_5N_4Cl_3$: Cl, 46.8. Found: Cl, 46.3.

This intermediate was converted in 89% yield to XVIII, m.p. 95–97°, by reaction with methanol containing an equivalent amount of sodium hydroxide.[19]

Anal. Calcd. for $C_7H_{11}N_4O_2Cl$: N, 25.6. Found: N, 25.4.

A mixture of 69.6 g. (0.32 mole) of XVIII, 105 cc. of 3.06 *N* sodium hydroxide (0.32 mole) and 300 cc. of ethanol was refluxed for 2 hr. At the end of this time, no alkalinity remained. Crystallization of the solution on cooling and partial evaporation gave 37.6 g. (70%). Material recrystallized from water (87% recovery) melted at 229–231°. (The observed m.p. was exceptionally dependent on the rate of heating. Rapid heating was necessary to get a clear melt and the highest m.p.) Analytical data were in substantial agreement with structure XIX.

Anal. Calcd. for $C_6H_8N_4O_2$: C, 42.85; H, 4.80; N, 33.52. Calcd. for $C_7H_{10}N_4O_2$: C, 46.1; H, 5.49; N, 30.7. Found: C, 42.89; H, 5.13; N, 32.88.

Degradation of the XIX with 65% sulfuric acid gave II.

Preparation of XIX from Sodium 2,4-Dimethoxy-6-(2-sulfatoethylamino)-*s*-triazine (XX).—Compound XX, m.p. 166–168° (from 90% ethanol; dried at 110°) was prepared in 82% yield by condensation of 2-chloro-4,6-dimethoxy-*s*-triazine[19] with 2-aminoethyl hydrogen sulfate and sodium hydroxide in water at 35°.

Anal. Calcd. for $C_7H_{11}N_4O_6SNa$: N, 18.54; Na, 7.61. Found: N, 18.2; Na, 7.4.

A solution of 30.2 g. (0.100 mole) of XX and 4.40 g. (0.110 mole) of sodium hydroxide in 280 cc. of water was heated at reflux. Titration of aliquots showed that the reaction was 78% completed in 30 minutes. After 55 minutes (80% reaction) residual alkalinity was neutralized, and the solution was evaporated to dryness. Extraction of the residue with boiling ethanol and fractional crystallization of the extract gave small amounts of XIX, identical with the product from XVIII, and another substance, m.p. 157.0–157.5°, which could not be identified. It was interesting that the reaction of XX with alkali was much faster than release of ethylenimine from 2-aminoethyl hydrogen sulfate under similar conditions.[13]

STAMFORD, CONN.

(18) J. T. Thurston, *et al.*, THIS JOURNAL, **73**, 2982 (1951).
(19) J. R. Dudley, *et al.*, *ibid.*, **73**, 2986 (1951).

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

Homologs of Triethylenemelamine

BY FRED C. SCHAEFER

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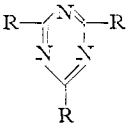
2,4,6-Tris-(2-methyl-1-aziridinyl)-*s*-triazine and 2,4,6-tris-(1-azetidinyl)-*s*-triazine have been prepared from cyanuric chloride. Improved procedures are reported for the preparation of the required imines, 2-methylaziridine and azetidine.

Concurrently with our investigations of triethylenemelamine (2,4,6-tris-1-aziridinyl-*s*-triazine)[1] and other 1-aziridinyl-*s*-triazines,[2,3] the synthesis of homologs of triethylenemelamine was undertaken, principally to provide these compounds for comparative testing in the chemotherapy of cancer. The reaction of aqueous 2-methylaziridine with cyanuric chloride at 25° to give 2,4,6-tris-(2-methyl-1-aziridinyl)-*s*-triazine (I) was accomplished very successfully by the procedure developed for the preparation of triethylenemelamine.[1] Under very similar conditions, azetidine was converted to



I CH_3CHCH_2N— (R)

II $CH_2CH_2CH_2N$—

2,4,6-tris-(1-azetidinyl)-*s*-triazine (II) in excellent yield. A few tests demonstrated that the latter product did not have appreciable reactivity of the nitrogen mustard type.

2-Methylaziridine was prepared from 1-amino-2-propanol *via* 2-chloropropylamine hydrochloride by the procedure we have found most satisfactory for aziridine itself.[1] The over-all yield was 62%. This simple process is highly recommended, although we have not had experience with Wenker's method, which appears to be much better for the preparation of 2-methylaziridine than for aziridine itself.[4]

Azetidine was prepared by a modification of the method of Howard and Marckwald.[5] This procedure may make this compound more attractive for laboratory use in the future. Although Howard and Marckwald reported that a nearly quantitative yield of azetidine was obtained by reduction of 1-*p*-toluenesulfonylazetidine with sodium in isoamyl alcohol, most subsequent reports of the method have been very discouraging. Thus, Jones[4] obtained only a 14% yield, and Brown and Gerstein reported their yield as "low and insufficient to permit fractionation in an efficient column."[6] Yanbikow,[7] however, was more successful, and has reported a

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(3) F. C. Schaefer, *ibid.*, **77**, 5922 (1955).
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(7) Y. M. Yanbikow, *J. Gen. Chem. (U.S.S.R.)*, **8**, 1545 (1938).