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.]

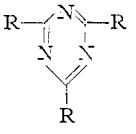
Homologs of Triethylenemelamine

BY FRED C. SCHAEFER

RECEIVED JUNE 1, 1955

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 $CH_3\underset{\text{R}}{C}HCH_2N$—

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

(1) V. P. Wystrach, D. W. Kaiser and F. C. Schaefer, THIS JOURNAL, **77**, 5915 (1955).
(2) F. C. Schaefer, J. T. Geoghegan and D. W. Kaiser, *ibid.*, **77**, 5918 (1955).
(3) F. C. Schaefer, *ibid.*, **77**, 5922 (1955).
(4) G. D. Jones, *J. Org. Chem.*, **9**, 484 (1944).
(5) C. C. Howard and W. Marckwald, *Ber.*, **32**, 2031 (1899).
(6) H. C. Brown and M. Gerstein, THIS JOURNAL, **72**, 2926 (1950).
(7) Y. M. Yanbikow, *J. Gen. Chem.* (*U.S.S.R.*), **8**, 1545 (1938).

36% yield. In the procedure described below, a large excess of sodium (12 g. atoms per mole of the sulfonamide) was used in amyl alcohol at 115–120°, and the azetidine produced was distilled directly from the reaction mixture as a solution in amyl alcohol. The yield of distilled base was 42%. For the present purpose, it was not necessary to separate it from the alcohol, with which it formed a constant boiling mixture. This could be done, however, by extraction of the base with hydrochloric acid followed by regeneration with concentrated caustic and distillation, as employed in the recovery of 2-methylaziridine.

Before the unpromising procedure of Howard and Marckwald was attempted, some attention was given to alternative reactions which might be used for the preparation of azetidine. Although these were unsuccessful, brief mention of the results may be of interest. Gabriel and Weiner[8] obtained a 60% yield of a steam distilled mixture of azetidine and its dimer by reaction of 3-bromopropylamine with alkali but, although the two compounds were isolated in pure form, their ratio was not stated. Ruzicka, Salomon and Meyer[9] have used this method but likewise give no yield data. In the present work, it was found that only 6–26% yields of steam-volatile amine were produced by this reaction. Catalytic hydrogenolysis of N-*p*-toluenesulfonylazetidine was attempted but practically no volatile base was produced. It was interesting that a small amount of dimerization took place giving N,N′-bis-*p*-toluenesulfonyl-1,5-diazacycloöctane.[10] Attempts to alkylate cyanamide with trimethylene dibromide in aqueous or substantially dry ethanol in the presence of sodium hydroxide gave little or none of the desired N-cyanoazetidine. In the latter case O-ethyl-N,N-trimethyleneurea appears to have been the major product.

Experimental Section[11]

2-Methylaziridine.—1-Amino-2-propanol (200 g., 2.67 moles) in one liter of ethanol was treated with hydrogen chloride until the solution was acid to methyl orange. **The hydrochloride** was crystallized by chilling the solution. It was washed with cold ethanol and dried over sulfuric acid, yield 237 g. (80%), m.p. 74–76° (lit. 72.5–74°[12]). A suspension of this crude salt (2.12 moles) in 400 cc. of toluene was stirred at 25–30°, and 2.5 moles of thionyl chloride was added gradually. After two hours, during which the temperature rose to 45°, the mixture was heated to 75° during two additional hours and then was boiled briefly. The solid product was filtered in the cold and washed with toluene. Recrystallization from ethanol gave 216 g. of **2-chloropropylamine hydrochloride**,[13] m.p. 187–190°, yield 78%.

A mixture of 214 g. (1.64 moles) of 2-chloropropylamine hydrochloride, 164 g. (4.1 moles) of sodium hydroxide and 400 cc. of water was heated for two hours at 50°. The solution was then distilled at slightly reduced pressure (b.p. approx. 70°) until 178 cc. was collected. This distillate contained 1.55 moles of base (94% yield). It was mixed with 100 g. of sodium hydroxide (two liquid phases), and 2-methylaziridine was distilled through a one-foot glass helices-packed column while 50% sodium hydroxide was fed slowly to the top of the column. The distillate weighed 75 g., b.p. 65–66°, yield 80%. The product was stabilized with a few pellets of sodium hydroxide and stored in a refrigerator until used.

2,4,6-Tris-(2-methyl-1-aziridinyl)-*s*-triazine (I).—A mixture of 40.7 g. (0.221 mole) of cyanuric chloride, 77 g. (0.73 mole) of sodium carbonate and 600 cc. of ice-water was stirred and held at 5–8° while a solution of 39.0 g. (0.68 mole) of 2-methylaziridine in 100 cc. of water was added during 15 minutes. The temperature was then allowed to rise to 25° during 45 minutes and the reaction mixture was stirred at room temperature for one hour longer. The solution obtained was filtered and extracted with 400 cc. of chloroform in four portions. The chloroform extract was evaporated at reduced pressure to a sirup, which crystallized when diluted with hexane. The product weighed 39.5 g. after being washed with hexane and air-dried, m.p. 95–97° (73%). An additional 16% yield of lower melting material was recovered from the mother liquor. Recrystallization from cyclohexane gave material melting at 98–100°.

Anal. Calcd. for $C_{12}H_{18}N_6$: C, 58.51; H, 7.37; N, 34.12. Found: C, 58.37; H, 7.59; N, 34.18.

Azetidine.—A solution of 84.4 g. (0.40 mole) of N-*p*-toluenesulfonylazetidine[10] in 2 l. of amyl alcohol was heated to 115°, and 37 g. (1.6 g. atoms) of sodium metal was added in 2–4 g. pieces over a period of one hour at that temperature. The reaction mixture was distilled at reduced pressure until 171 cc. of distillate was collected. Titration showed that this contained 55 meq. of base, a 14% yield. In two additional treatments with sodium at 115–125°, carried out in this manner, a total of 4.8 g. atoms of sodium was used and the yield of distilled base was increased to 42%. At this point the residual mixture was quite viscous and reacted only very sluggishly with sodium. Separation of the azetidine (b.p. 63°[5]) from the amyl alcohol by distillation was not possible. Careful fractionation gave a well defined azeotrope boiling at 77.0–78.5° and containing 47% azetidine. This product was used for the reaction with cyanuric chloride described below.

Catalytic hydrogenolysis of N-*p*-toluenesulfonylazetidine with copper chromite in dioxane and in methanol was attempted at 5000 p.s.i. and 250°. No evidence of hydrogen uptake was observed. Examination of the charge after treatment showed that less than a 3.5% yield of azetidine could have been obtained. In each run dimerization of the azetidine derivative gave a small amount of N,N′-bis-*p*-toluenesulfonyl-1,5-diazacycloöctane, m.p. 215–217° (lit. 215°[10]).

For an attempt to prepare azetidine by cyclization of 3-bromopropylamine hydrobromide,[8] this salt was prepared by reaction of 3-aminopropanol with excess concentrated hydrobromic acid.[14] It was difficult to purify the product, which was very soluble in all solvents from which the crude material did not separate as an oil. A 15% yield of fairly pure hydrobromide, m.p. 169–172° (lit. 162°[8]), was finally obtained by crystallization from acetonitrile and from ethyl acetate. Reaction of the salt with three equivalents of 3.0 *N* sodium hydroxide per mole at 80° was 90% complete in 20 minutes, and no further consumption of alkali was observed in an additional hour. However, when the product solution was distilled, only a 6% yield of base was found in the distillate. When a similar reaction mixture was heated immediately to boiling and distilled for 40 minutes, during which most of the water was volatilized, the base obtained in the distillate amounted to a 26% yield. If this was repeated at 80–85°, at slightly reduced pressure, the yield dropped to 17%. No attempt was made to establish how much of the volatile base was azetidine. It is apparent that azetidine formation was only a minor side reaction accompanying condensation reactions.

2,4,6-Tris-(1-azetidinyl)-*s*-triazine (II).—A mixture of 36.8 g. of the azetidine–amyl alcohol azeotrope (≈ 0.29 mole of azetidine) and 200 cc. of water was neutralized to the methyl orange end-point with 6 *N* hydrochloric acid, and the amyl alcohol was removed by extraction with ether. The aqueous solution was chilled, and 16.6 g. (0.090 mole) of cyanuric chloride was added. To this slurry was then added 23.2 g. (0.58 mole) of sodium hydroxide dissolved in 150 cc. of water during 30 minutes at 18°. The reaction

(8) S. Gabriel and J. Weiner, *Ber.*, **21**, 2669 (1888).

(9) L. Ruzicka, G. Salomon and K. E. Meyer, *Helv. Chim. Acta*, **20**, 109 (1937).

(10) W. Marckwald and A. F. Droste-Huelshoff, *Ber.*, **31**, 3264 (1898).

(11) Melting points are corrected. Microanalyses were carried out in these laboratories under the direction of Dr. J. A. Kuck. Infrared absorption spectra were obtained and interpreted by Mr. N. B. Colthup.

(12) S. Gabriel and H. Ohle, *Ber.*, **50**, 805 (1917).

(13) G. D. Jones, *et al.*, *J. Org. Chem.*, **9**, 125 (1944).

(14) Similar to the preparation of 2-bromoethylamine hydrobromide, ref. 1.

mixture was stirred for one hour at room temperature. The crystalline product was filtered and washed with water. After drying, it weighed 20 g. (90% yield). Recrystallization of the crude product from alcohol–benzene and from benzene gave 17 g., m.p. 256–259°.

Anal. Calcd. for $C_{12}H_{18}N_6$: C, 58.51; H, 7.37; N, 34.12. Found: C, 58.55; H, 7.19; N, 33.80.

Compound II did not react detectably with sodium thiosulfate under conditions which give rapid, quantitative conversion of 1-aziridinyl-*s*-triazines to the Bunte salts.[2] This test was complicated by the insolubility of II in the reagent, but the conclusion nevertheless seems warranted that the azetidine derivative has a much lower order of reactivity than triethylenemelamine. Compound II could be titrated to a sharp end-point with 0.5 *N* hydrochloric acid thus showing its distinction from triethylenemelamine in reactivity to acids.[3]

Attempted Preparation of N-Cyanoazetidine.—Reaction of trimethylene dibromide with equivalent amounts of cyanamide and sodium hydroxide in 25% aqueous ethanol was 90% complete in 3 hours at 70–75° as judged by the disappearance of the alkali. However, only 15–20% of the expected weight of product could be extracted from the reaction mixture with benzene. Only a small portion of this was distillable below 100° at 6 mm. Thus, the yield of N-cyanoazetidine was negligible.

When this reaction was tried in substantially dry ethanol, slightly better results obtained. A mixture of 39.5 g. (0.44 mole) of sodium acid cyanamide,[15] 89.8 g. (0.44 mole) of trimethylene dibromide and 17.8 g. (0.44 mole) of sodium hydroxide in 200 cc. of ethanol reacted exothermically. After 30 minutes at 50° and one hour at 78° the reaction mixture was filtered. The solution was concentrated, and the residue was distilled at low pressure. Approximately 8 g. of material boiling at 75–85° at 3 mm. was obtained. This had a neutral equivalent of 179 (basic) which corresponded to a mixture of about 29% N-cyanoazetidine and 71% O-ethyl-N,N-trimethyleneurea. This identification was supported by infrared absorption spectra. On this basis, the total yield of these compounds was only 16%.

(15) Commercial 72% sodium acid cyanamide was used. This contained a substantial amount of sodium carbonate.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF IRWIN, NEISLER & CO.]

The Relative Basicities of α-, β- and γ-Carboline Anhydronium Bases

BY ALLAN P. GRAY

RECEIVED JUNE 2, 1955

Dissociation constants have been determined for simple carboline anhydronium bases. The observed order of base strength ($\beta > \gamma > \alpha$) may be rationalized qualitatively in terms of resonance theory.

The early, pioneering researches of Robinson and his co-workers did much to clarify the then obscure properties of the carboline anhydronium bases.[1,2] Largely as a result of the finding of this system in a number of naturally occurring alkaloids, β-carboline anhydronium bases have lately been subjected to intensive study,[3] whereas their α- and γ-analogs have been relatively neglected.[4]

In connection with an attempt to correlate the chemical with biological properties of some bis-carboline salts,[5] we had occasion to determine the approximate dissociation constant of α-carboline methiodide and noted the pK_a value to be markedly lower than values that had been reported for certain β-carboline derivatives.[6] The β-carboline salts for which data are available[6] are all alkaloids of quite complex structure, and apparently no measurements have been reported for other carboline systems. It thus appeared of interest to determine and compare the dissociation constants of simple α-, β- and, also, γ-carboline anhydronium bases. Since the ionization of acids and bases is a thermodynamically controlled equilibrium process, such data would permit insight into the relative stabilities of these anhydronium bases and their corresponding conjugate acids.

α-Carboline methiodide, norharman (β-carboline) methobromide and harman methobromide were at hand from the earlier study.[5] γ-Carboline was synthesized by the method of Robinson and Thornley[4] with the exception that the required intermediate, 4-chloropyridine, was obtained from the reaction of phosphorus oxychloride with pyridine N-oxide.[7] The dissociation constants were determined by potentiometric titration (Beckman, glass electrode *p*H meter) with 0.1 *N* sodium hydroxide of carbon dioxide-free, 60% ethanol solutions of the carboline methohalide salts. The alcoholic solvent was used owing to the tendency of the β-carboline derivatives (but not the α- or γ-isomers) to precipitate during the course of titration in water. The *p*H at 50% neutralization was taken without refinement to represent the pK_a value. The point of 50% neutralization was readily determinable in the case of α-carboline methiodide which afforded a titration curve with a sharp inflection at the end-point, but had to be calculated for the β- and γ-isomers, the curves of which showed no such clear breaks.[8] The results listed in Table I

(1) J. W. Armit and R. Robinson, *J. Chem. Soc.*, **127**, 1604 (1925), adopted the general term *anhydronium base* for "the anhydro derivatives of aromatic onium hydroxides," important resonance forms of which are (a) aromatic with complete separation of charge and (b) quinonoid.

(2) *Chemical Abstracts* nomenclature is 9-pyrid-2,3b-indole for α-carboline, 9-pyrid-3,4b-indole for β-carboline and 5-pyrid-4,3b-indole for γ-carboline. The trivial names are used for convenience.

(3) *Cf.* B. Witkop, THIS JOURNAL, **75**, 3361 (1953); and H. Schwarz and E. Schlittler, *Helv. Chim. Acta*, **34**, 629 (1951), for recent investigations of these interesting substances and for an introduction to the literature.

(4) *Cf.* R. H. Freak and R. Robinson, *J. Chem. Soc.*, 2013 (1938), for studies on α-carboline; R. Robinson and S. Thornley, *ibid.*, **125**, 2169 (1924), for γ-carboline.

(5) A. P. Gray, E. E. Spinner and C. J. Cavallito, THIS JOURNAL, **76**, 2792 (1954).

(6) V. Prelog, *Helv. Chim. Acta*, **31**, 558 (1948), reported a pK_a of 10.6 for sempervirine. H. Schwarz and E. Schlittler[3] reported values of from 10.4–10.7 for serpentine, alstonine and two related alkaloid derivatives. Measurements were made in 40% methanol solution by titration of the salts with tetramethylammonium hydroxide.

(7) *Cf.* M. Murakami and E. Matsumura, *J. Chem. Soc. Japan*, **70**, 236 (1949), *C. A.*, **45**, 4698d (1951), T. Kato and M. Ohta, *J. Pharm. Soc. Japan*, **71**, 217 (1951), *C. A.*, **46**, 4541a (1952).

(8) Presumably, this is a result of the titration of extremely weak acids in dilute solution.