causing an immediate precipitation of sodium methanesulfonate. The reaction mixture was refluxed for 1 hour and then the methanol distilled *in vacuo* to the point of turbidity. The reaction mixture at this stage was diluted with saturated salt solution and extracted with petroleum ether which dissolved VII away from other insoluble organic impurities. The petroleum ether extract was dried and evaporated to a mobile oil with a terpene-like odor. Distillation of this oil afforded 11.1 g. of VII, b.p. 110° at 45 mm. (54%).

Anal. Calcd. for $C_9H_{14}O$: C, 78.26; H, 10.15. Found: C, 78.28; H, 10.28.

(**B**).—A solution of 10 g. of diol VI and 15 g. of *p*-toluenesulfonyl chloride in 50 cc. of ether was treated dropwise with stirring with a solution of 15 g. of potassium hydroxide in 50 cc. of water. After addition was complete the reaction mixture was heated for 1 hour on the steam-bath and worked up as in part A; yield 7 g. (80%) of VII.

Preparation of Diol VIII by Osmium Tetroxide Hydroxylation of Oxide VII.—A solution of 10 g. of oxide VII in 25 cc. of dioxane was treated with 25 g. of osmium tetroxide and allowed to stand at room temperature for 2 days. At the end of this period the dark reaction mixture was decomposed by hydrogen sulfide,[9] filtered through Celite and concentrated to a water-soluble oil, wt. 7.5 g. This oil crystallized on standing and could be recrystallized from ether, m.p. 95–98°.

Anal. Calcd. for $C_9H_{10}O_3$: C, 62.81; H, 9.30. Found: C, 62.60; H, 9.38.

Cleavage of VIII to IX and Formation of the Bicyclic $\Delta^{\alpha,\beta}$-Aldehyde X. (**A**).—A solution of 575 mg. of crystalline diol VIII in 2 cc. of tetrahydrofuran at room temperature was treated with 750 mg. of sodium metaperiodate in 5 cc. of water. The reaction mixture was cooled slightly to offset the heat of reaction which was accompanied by the separation of sodium iodate. The reaction mixture was allowed to stand 1 hour, then concentrated *in vacuo* and the water-soluble keto aldehyde intermediate IX thoroughly extracted with ether. Evaporation of the ether left 360 mg. of a colorless oil which gave an immediate yellow precipitate with 2,4-dinitrophenylhydrazone reagent. This oil was dissolved in 15–20 cc. of benzene treated with 3 drops of pyridine and 2 drops of acetic acid and refluxed with a water separator for 1 hour. The reaction mixture was diluted with ether and washed successively with dilute hydrochloric acid, potassium bicarbonate and saturated salt solution. The dried ether solution was concentrated and distilled at 100° and 0.7 mm. to afford 100 mg. of crude aldehyde X with a $\lambda_{max}^{CH_3OH}$ 248 mμ, *E* 9800, λ_{max} 5.99 μ (conj C=O), 6.08 μ (C=C), 3.67 μ (ald. C–H); n.m.r. 196 ∼.

2,4-Dinitrophenylhydrazone red crystals from ethyl acetate–methanol, m.p. 214–214.5°. *Anal.* Calcd. for $C_{15}H_{16}O_5N_4$: C, 54.22; H, 4.82; N, 16.87. Found: C, 54.48; H, 5.02; N, 16.70.

Semicarbazone from methanol, m.p. 215–220°. *Anal.* Calcd. for $C_{10}H_{10}O_2N_3$: C, 57.42; H, 7.18; N, 20.10. Found: C, 57.45; H, 7.01; N, 19.73.

(**B**).—A solution of 1.72 g. of diol VIII was cleaved in 20 cc. of water with 3 g. of sodium metaperiodate for 1 hour. The reaction solution was made alkaline with potassium hydroxide and warmed on the steam-bath to the appearance of turbidity. Extraction with ether afforded 150 mg. of crude X, $\lambda_{max}^{CH_3OH}$ 244 mμ, *E* 9800.

(**C**).—A solution of 2 g. of diol VIII was cleaved with 3 g. of sodium metaperiodate for 1 hour and the product continuously extracted with ether. The ether solution was evaporated and the residue treated with 50 cc. of *t*-butyl alcohol containing 0.39 g. of potassium metal dissolved. The reaction mixture turned yellow and finally orange-red. After 15 minutes the reaction was quenched with 10% hydrochloric acid, evaporated and worked up as described above. The product obtained in low yield exhibited $\lambda_{max}^{CH_3OH}$ 248 mμ, *E* 7448.

(**D**).—Results comparable to the foregoing were experienced when the ether solution of the cleavage product IX was allowed to stand several hours on basic alumina and then eluted.

Oxidation of the Bicyclic Aldehyde X to the Acid XI.—A solution of 100 mg. of the aldehyde X in 2 cc. of ethanol was treated with silver oxide freshly prepared from 200 mg. of silver nitrate and 100 mg. of potassium hydroxide. The oxidation was allowed to proceed for 30 minutes with stirring and then filtered, evaporated and dissolved in ether. The acidic material was extracted with potassium bicarbonate. Acidification of the bicarbonate extract precipitated the acid XI in crystalline form. The latter was extracted with ether and crystallized from the same solvent, m.p. 100–102°.

Anal. Calcd. for $C_4H_{12}O_3$: C, 64.29; H, 7.14. Found: C, 64.09; H, 7.08.

RAHWAY, N. J.

(9) Method of D. H. R. Barton and D. Elad, *J. Chem. Soc.*, 2085 (1956).

[CONTRIBUTION FROM CHEMICAL DIVISION, AEROJET-GENERAL CORPORATION]

The Synthesis of 1,1'-Biaziridine. A New Bicyclic System[1]

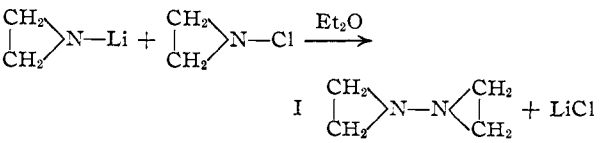
BY ALLEN F. GRAEFE AND RALPH E. MEYER

RECEIVED JANUARY 24, 1958

The preparation of 1-haloaziridines from ethylenimine and hypohalite is described. The reaction of 1-chloroaziridine with 1-lithiumaziridine in ether was investigated, and evidence is presented that the isolated product is 1,1'-biaziridine. Some properties of this new bicyclic compound are presented.

Introduction

During the course of an investigation of the lower alkyl hydrazines in this Laboratory, it became a matter of importance to synthesize the as yet unknown bicyclic compound, 1,1'-biaziridine (I). A method of preparation of the compound became available when it was found that 1-chloroaziridine could be obtained from ethylenimine and aqueous hypochlorite. 1,1'-Biaziridine was then prepared from the reaction of 1-chloroaziridine with the known 1-lithiumaziridine.[2]



To our knowledge, no other hydrazine derivative has been prepared by this method. This may be the result of the ready dehydrohalogenation of alkylchloramines by alkylamide anions since, in an attempt to prepare tetramethylhydrazine from dimethylchloramine and dimethylamidomagnesium halide, Klages and co-workers reported amines as the only basic products.[3] In the present synthesis

(1) This investigation was carried out under a contract with the Office of Naval Research.

(2) H. Gilman, *et al.*, THIS JOURNAL, **67**, 2106 (1945).

(3) F. Klages, *et al.*, *Ann.*, **547**, 1 (1941).

$$(CH_3)_2NMgX + (CH_3)_2NCl \longrightarrow$$

$$(CH_3)_2NH + CH_2{=}NCH_3 \xrightarrow{H_2O} CH_2O + CH_3NH_2$$

of 1,1′-biaziridine, dehydrohalogenation is presumably not favored, because the dehydrohalogenated product would be highly strained, containing a doubly bonded carbon–nitrogen linkage within a three-membered ring.[4]

Experimental[5]

Unless otherwise stated, all operations to be described in the preparation of 1,1′-biaziridine were carried out under oxygen-free, moisture-free conditions. Manipulations of materials were accomplished in a nitrogen-filled box, the nitrogen having been passed successively through towers of alkaline pyrogallol, calcium sulfate, phosphorus pentoxide and soda lime. A purified nitrogen atmosphere also was employed in carrying out all reactions.

Materials.—Ethylenimine, b.p. 55 to 57°, was obtained from Chemirad Corporation, Port Washington, L.I., N. Y. Mallinckrodt anhydrous (0.01% water) diethyl ether was used throughout the experiments. Methyllithium was prepared from lithium wire and methyl bromide in ether solution according to the method of Pierce.[6] At the end of the reaction any unreacted methyl bromide was removed from the reaction mixture by refluxing until the exit vapors from the condenser did not form a precipitate within ten minutes when bubbled into 25% trimethylamine in methanol. The resulting solution was analyzed for methyllithium, as described by Pierce, by acid titration and by measuring the volume of methane liberated on hydrolysis. The concentration of methyllithium as determined by the two methods was found to agree to within 0.01 mole/liter. 1-Lithiumaziridine was prepared from ethylenimine and ethereal methyllithium by the method of Gilman.[2] The amount of methane collected during the reaction was 94% of the theoretical amount, based on methyllithium. The resulting ether suspension of the product was used directly in the preparation of 1,1′-biaziridine, as described below.

1-Chloroaziridine.—A solution of 92.4 g. (2.20 moles) of sodium hydroxide pellets (assay 97%) in 385 g. of water was maintained at −5 to −10° while 80.3 g. (1.1 moles) of chlorine was introduced. The addition of chlorine was followed by a gain in weight of the solution. To the resulting hypochlorite solution 43.0 g. (1.00 mole) of cold (−10°) ethylenimine was added rapidly with swirling. The crude 1-chloroaziridine separated as a colorless upper layer, with the simultaneous decoloration of the hypochlorite solution. The layers were separated, and the organic layer was washed with 30-ml. portions of distilled water until the washings were no longer basic (four to six washings required). The product was dried over anhydrous magnesium sulfate and was then distilled at reduced pressure through a 12-in. column packed with glass helices. The 1-chloroaziridine, which distilled at 37.5° to 38.3° at 245 mm., was a mobile, colorless, strongly lachrymatory liquid, $n^{20}D$ 1.4433, d^{24} 1.11 g./ml., immiscible with water, and miscible with ethanol and organic solvents. The yield was 80% of the theoretical, based on ethylenimine.

Anal. Calcd. for C_2H_4NCl: C, 30.99; H, 5.20; N, 18.07; Cl, 45.74. Found: C, 30.98; H, 5.13; N, 18.09; Cl, 45.72.

An analysis for positive halogen was carried out by dissolving the compound in ethylene chloride, adding excess potassium iodide, acidifying with glacial acetic acid, and titrating the liberated iodine with standard sodium thiosulfate; found, Cl, 45.69. Although 1-chloroaziridine could be redistilled at 38° without change, an infrared spectrum of material which was redistilled at 70 to 71° (749 mm.) showed new bands in the infrared at 5.88 and 7.36 μ.

1-Bromoaziridine.—The procedure described above for the preparation of 1-chloroaziridine was followed, with the substitution of molecular bromine for chlorine. Addition of ethylenimine to the hypobromite solution resulted in the separation of a straw-colored oil which, when washed with water, dried, and distilled, boiled at 48° at 131 mm., $n^{25.5}D$ 1.5095, d^{24} 1.70. The compound was too unstable for analysis. In every preparation an explosion or a fume-off occurred either during distillation or within a few hours thereafter.

Reaction of 1-Chloroaziridine with 1-Lithiumaziridine.—Six liters of ether was cooled to −50°, and 990 g. (12.79 moles) of 1-chloroaziridine in 5 liters of ether was added dropwise with stirring simultaneously with an ethereal suspension of 1-lithiumaziridine (prepared from 7 liters of 1.83 *M* ethereal methyllithium (12.79 moles of methyllithium) and 550 g. (12.79 moles) of ethylenimine in 5 liters of ether). The reaction mixture was maintained at about −50° during the 3.5-hour addition period. Too rapid addition or a higher reaction temperature resulted in the formation of a brown color, with attendant loss in yield of product. The reaction mixture was allowed to warm to room temperature overnight, and the solution was filtered by withdrawal through a coarse filter stick. The light-yellow ether filtrate contained no appreciable amount of the desired product, as determined by the titration of an acidified aliquot with standard potassium iodate, and was discarded. The yellow-orange solid[7] was washed four times with 1.5-liter portions of ether.[8] The solid was decomposed by addition to 8.5 liters of ice-water, and an ether layer which separated at this point was set aside for combination with the ether extracts to be obtained later in the workup. Analysis of an aliquot of the aqueous solution with standard potassium iodate indicated a maximum yield of 1,1′-biaziridine of 2.56 moles or 20%.

The separation of 1,1′-biaziridine as a crude oil from the water solution was effected by the portionwise addition of 10 lb. of powdered potassium carbonate. The temperature was maintained in the range 25 to 35° by external cooling during the salting-out process. Both the aqueous layer and the black oil which separated were extracted several times with ether (9.5 liters total). The combined ether extracts, which contained a maximum of 15.7% (2.01 moles) of the theoretical amount of 1,1′-biaziridine (of which three-fourths came from the oil), was dried over anhydrous potassium carbonate and then flash-distilled.

The clear, colorless distillate contained, in addition to a maximum of 2.01 moles of 1,1′-biaziridine, a maximum of 2.10 moles of ethylenimine. That ethylenimine was present in the distillate at this point was shown in another run, in which direct fractionation of the dry ethereal extracts (see above paragraph) afforded a fraction, b.p. 54.6 to 54.9° (749 mm.), which was determined to be nearly pure ethylenimine on the basis of its boiling point (lit.[9] 56°), specific gravity, 0.836 (lit.[9] 0.832), acid equivalence (93.6% of the theoretical for ethylenimine), and infrared spectrum (identical with that of pure ethylenimine). That a maximum of 2.10 moles of ethylenimine was present in the ethereal solution in the present run was shown by titration with standard acid, the 1,1′-biaziridine being too feebly basic to titrate.

Isolation of 1,1′-Biaziridine.[8]—The ethereal solution containing 1,1′-biaziridine, ethylenimine and residual water was passed repeatedly through a vertical column packed with 14.8 lb. of molecular sieve (Linde Air Products, Type 4A, 1/16-in. pellets) until the ethylenimine (and water) had been removed completely, as determined by acid titration. The sieve was washed with additional ether to minimize loss of 1,1′-biaziridine. Only 5 to 6% of the 1,1′-biaziridine originally present in the ether solution was lost during the removal of ethylenimine in this manner. Ether was removed from the solution by distilling through an Oldershaw column (reflux ratio, 1.5:1) until the 11 liters of solution had been reduced to a volumn of 300 ml., and the residue was then fractionated through a 12-in. Widmer spiral column (reflux ratio, 10:1). After removal of additional ether, the following cuts were collected (data include percentage purity by titration with potassium iodate, calculated as 1,1′-biaziridine): I, b.p. 82.0–83.0° (750 mm.), 1.25 g., 96.3%; II, b.p. 83.0–83.2° (750 mm.), 119.3 g., $n^{20.9}D$ 1.4387, 100.8%;

(4) D. J. Cram and M. J. Hatch, THIS JOURNAL, **75**, 33 (1953).

(5) Analyses were performed by Elek Microanalytical Laboratories, Los Angeles, Calif.

(6) O. R. Pierce, *et al.*, THIS JOURNAL, **76**, 474 (1954).

(7) The appearance of the 1,1′-biaziridine in the *solid* at this point was to some extent unexpected. It is suggested that an intermediate complex containing 1,1′-biaziridine and lithium chloride is formed, and that this complex breaks down in the presence of water.

(8) Subsequent steps in the workup to the section "Isolation of 1,1′-Biaziridine" were carried out without the presence of a nitrogen atmosphere.

(9) S. Gabriel and R. Stelzner, *Ber.*, **28**, 2929 (1895).

III, b.p. 83.2–90.0° (750 mm.), 11.0 g., $n^{20.9}$D 1.4388, 99.6%; and IV, b.p. 90–98° (750 mm.), 1.0 g., $n^{20.9}$D 1.4365, 95.2%. Cut II was a colorless, mobile liquid, freezing at −11°, $n^{28.6}$D 1.4356, d^{24} 0.901 g./ml., net heat of combustion 710 kcal./mole,[10] miscible with water, ethanol, methylhydrazine, benzene and hexane, and immiscible with hydrazine, yield 11.1% (from 1-chloroaziridine). This cut was found to be extremely explosive when heated in an oxygen atmosphere.[11]

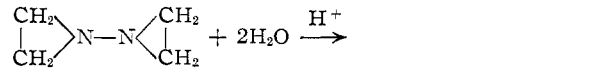
Anal. of Cut II: Calcd. for $C_4H_8N_2$: C, 57.14; H, 9.52; N, 33.33; mol. wt., 84.12; *MR*, 24.83. Found for $C_4H_8N_2$: C, 56.90; H, 9.96; N, 33.12; mol. wt., 84.2 (cryoscopic in benzene), 84.5 (potentiometric with potassium iodate); *MR*, 24.39.

1,1′-Biaziridine, in contrast to the simple alkyl hydrazines, is feebly basic, and could not be titrated with aqueous acid. However, a picric acid derivative of 1,1′-biaziridine was prepared in ether solution. After recrystallization from ethanol the compound slowly decomposed on heating without melting. An analysis with potassium iodate indicated that the oxidation of this compound involves a 6.12 electron change (theory 6.00).

Discussion

Proof of Structure of 1,1′-Biaziridine.—Several pieces of evidence have been obtained which indicate that the isolated product is 1,1′-biaziridine. Strong absorption in the infrared spectrum at 8.25 and 11.5 μ was interpreted to be convincing evidence that the compound contained at least one ethylenimine ring, since these frequencies have been assigned as the vibration frequencies of the ethylenimine ring itself.[12] The infrared spectrum also indicated the absence of N–H bonding (at 3.0 μ) and C=N bonding (at approximately 6.0 μ).[13]

When oxidized in 6 *N* hydrochloric acid solution with aqueous potassium iodate, the compound was found to undergo a six-electron change, which is characteristic of symmetrically disubstituted alkylhydrazines.[14] The observed electron change is explained readily in terms of the usual acid-catalyzed ring opening of ethylenimine derivatives, in this case to form *sym*-bis-β-hydroxyethylhydrazine



$$HOCH_2CH_2NHNHCH_2CH_2OH$$

The calculated molar refraction of the compound is also in keeping with the assigned structure. A nuclear magnetic resonance spectrum indicated that all of the hydrogen atoms are equivalent.[15] The method of preparation and these physical and chemical properties support the proposed 1,1′-biaziridine structure assigned to the compound.

Proof of Structure of the 1-Haloaziridines.—The compounds isolated from the reaction of sodium hypohalite with ethylenimine are considered to be the desired 1-haloaziridines on the basis of their method of preparation, immiscibility with water, infrared spectra (which show absorption at 8.25 and 11.5 μ), and the use of the chloro compound in the preparation of 1,1′-biaziridine.

(10) The authors are indebted to Mr. A. L. Parrette and to Mr. C. A. Leonard for heat of combustion data.

(11) Private communication from Dr. Adalbert Elek, Elek Microanalytical Laboratories, Los Angeles, Calif.

(12) H. T. Hoffman, Jr., THIS JOURNAL, **73**, 3028 (1951).

(13) Aliphatic Schiff bases of the type RN=CHR′ where R = CH_3, C_2H_5, C_3H_7, *i*-C_3H_7 and C_4H_9, and R′ = CH_3, C_2H_5 and C_3H_7 all absorb strongly in the region 1666 to 1674 cm.$^{-1}$ (approximately 6.0), which has been assigned as the characteristic absorption frequency for the C=N bond (L. Kahovec, *Acta Phys. Austria*, **1**, 307 (1958)). Acetaldazine, CH_3CH=NN=$CHCH_3$ (an isomer of 1,1′-biaziridine), absorbs strongly at 1627 cm.$^{-1}$ (W. West and R. B. Kellingsworth, *J. Chem. Phys.*, **6**, 1 (1938)).

(14) W. R. McBride, *et al.*, *Anal. Chem.*, **25**, 1042 (1953).

(15) J. D. Roberts, unpublished work.

AZUSA, CALIFORNIA

[CONTRIBUTION FROM PARKE, DAVIS & COMPANY'S MULTIPLE FELLOWSHIP IN MEDICINAL CHEMISTRY, MELLON INSTITUTE]

6-Diazo-5-oxo-L-norleucine, a New Tumor-inhibitory Substance.[1a] Preparation of L-, D- and DL-Forms[1b]

BY HORACE A. DEWALD[2] AND ALEXANDER M. MOORE[2]

RECEIVED DECEMBER 18, 1957

6-Diazo-5-oxonorleucine has been prepared by several methods. The synthesis was achieved by covering the amino and α-carboxyl functions of glutamic acid with appropriate protecting groups, converting the γ-carboxyl of glutamic acid to a diazo ketone and then removing the protecting groups by selective hydrolysis; and in crude form by the diazotization of the aminoketone, 5-oxolysine.

6-Diazo-5-oxo-L-norleucine has been prepared by several methods and has been submitted for biological tests which indicated it to be effective *in vitro* in inhibiting the growth of the bacterium *Escherichia coli*[3b] and the fungus *Torulopsis albida*[3a] and, in mice, in inhibiting the growth of the Crocker sarcoma-180 tumor.[4]

One method used to prepare 6-diazo-5-oxo-L-norleucine (VIII) involved using the 1-methyl ester of N,N-phthaloyl-L-glutamic acid (II) as the starting material. Sheehan and Bolhofer had prepared N,N-phthaloyl-L-glutamic anhydride (I) of unknown optical purity.[5] Subsequently, Tipson[6] showed Sheehan and Bolhofer's product to contain 88% of the L- and 12% of the DL-forms, based on the optical rotation reported by them. We found that treatment of the 88%–12% mixture with sodium methoxide at 5° gave a mixture of the 1-methyl esters II of N,N-phthaloyl-L(and DL)-

(1) (a) For paper II of this series, see H. W. Dion, S. A. Fusari, Z. L. Jakubowski, J. G. Zora and Q. R. Bartz, THIS JOURNAL, **78**, 3075 (1956). (b) Presented before the Division of Medicinal Chemistry at the 129th National Meeting of the American Chemical Society, Dallas, Texas, April, 1956.

(2) Parke, Davis & Co., Detroit, Mich.

(3) (a) J. Ehrlich, G. L. Coffey, M. W. Fisher, A. B. Hillegas, D. L. Kohberger, H. E. Machamer, W. A. Rightsel and F. R. Roegner, *Antibiotics & Chemotherapy*, **6**, 487 (1956); (b) R. E. Maxwell and V. E. Nickel, *ibid.*, **7**, 81 (1957).

(4) D. A. Clarke, H. C. Reilly and C. C. Stock, Abstracts of Papers 129th Meeting, American Chemical Society, Dallas, Texas, April, 1956, p. 12-M.

(5) J. C. Sheehan and W. A. Bolhofer, THIS JOURNAL, **72**, 2469 (1950).

(6) R. S. Tipson, *J. Org. Chem.*, **21**, 1353 (1956).