trace of barium, was 10–12%. A satisfactory analysis could not be obtained even after repeated recrystallizations. The acid decomposed in the neighborhood of 270°. The chloroplatinate, decomposing above 250°, was prepared and recrystallized from alcohol-water.

Anal. Calcd. for $C_9H_{14}N_2O_2Cl_6Pt$: C, 18.31; H, 2.37; Pt, 33.05. Found: C, 18.71; H, 2.57; Pt, 33.19.

The thioureide, m.p. 174–176° dec., was prepared from azobenzene isothiocyanate.[2]

Anal. Calcd. for $C_{22}H_{21}N_5O_2S$: C, 63.01; H, 5.01. Found: C, 63.13; H, 5.29.

N-(β-Picolyl)-β-methylaminopropionitrile. β-Picolylmethylamine (25 g., 0.2 mole) was dissolved in 150 ml. of benzene contained in a three-necked flask fitted with stirrer, dropping funnel, and reflux condenser. Four or five pellets of potassium hydroxide were added and then a solution of 21.2 g. (0.4 mole) of acrylonitrile was added slowly while stirring. After 2 days at room temperature, the mixture was refluxed on the steam bath for several days. The insoluble material was removed by filtration, and the benzene was evaporated. On distillation of the thick residue in vacuum, the nitrile distilled as a slightly turbid liquid at 121–125° (1 mm.). The chloroplatinate, m.p. 228° dec., was recrystallized from alcohol-water.

Anal. Calcd. for $C_{10}H_{15}N_3Cl_6Pt$: C, 20.61; H, 2.58; Pt, 33.50. Found: C, 20.45; H, 2.57; Pt, 33.32.

N-(β-Picolyl)-β-methylaminopropionic acid. The nitrile, prepared above, was hydrolyzed by refluxing with 50% sulfuric acid. The hydrolyzate was treated with barium hydroxide, filtered, and the filtrate treated with carbon dioxide and again filtered to remove the barium. The filtrate was evaporated, and the residue dissolved in chloroform and filtered. Evaporation of the chloroform left the crude product that did not crystallize. Even after standing 6 months in a vacuum desiccator, it remained a viscous liquid. The dihydrochloride was prepared by the method of Liwschitz, Zilkha and Shahak.[3] This compound is a white crystalline solid, melting at 205–206° with slight decomposition.

Anal. Calcd. for $C_{10}H_{16}N_2O_2Cl_2$: C, 45.11; H, 6.01. Found: C, 44.97; H, 5.98.

The chloroplatinate, decomposing without melting, was recrystallized from alcohol-water.

Anal. Calcd. for $C_{10}H_{18}N_2O_2Cl_6Pt$: C, 19.96; H, 2.66; Pt, 32.45. Found: C, 19.61; H, 2.71; Pt, 32.44.

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Chlorination of 2,4-Dioxohexahydro-1,3,5-triazines

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During the course of studying various *N*-halogen compounds, suitable methods of preparing *N*-chlorohexahydro-*s*-triazines became of interest to us.

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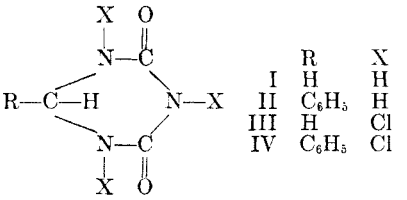
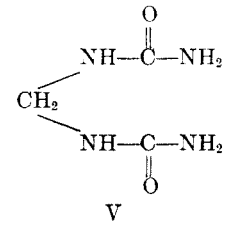


	R	X
I	H	H
II	C_6H_5	H
III	H	Cl
IV	C_6H_5	Cl



V

Our attempts to prepare 2,4-dioxohexahydro-1,3,5-triazine (I) by previously described methods[2,3] were unsatisfactory because of low yield and purity of product. A far more convenient method was devised whereby crude, dry methylenediurea (V) was cyclized in a stirred, refluxing diluent such as nitrobenzene, *n*-hexyl ether, or the dibutyl ether of diethylene glycol (dibutyl Carbitol). Nitrobenzene seemed most convenient to use. The methylenediurea was prepared by a simplification of the method described by Kadowaki.[4] The method of Krassig and Egar[5] was used to prepare 6-phenyl-2,4-dioxohexahydro-1,3,5-triazine (II).

It was found that the efficiency of the halogenation in an aqueous medium was dependent on the *p*H and on the temperature at which the halogenation was carried out. Chlorination of I and II, to the novel III and IV respectively, gave the best results when the reactions were carried out in the range *p*H 1–3 and at ice temperatures. Chlorination at higher *p*H ranges and/or at higher temperatures resulted in diminished yields of product.

1,3,5-Trichloro-2,4-dioxohexahydro-1,3,5-triazine (III), in concentrations as low as 1 p.p.m., completely inhibited the growth of the test organisms *Erwinia amylovora*, *Xanthomonas phaseoli*, *Micrococcus pyrogenes* var. *aureus*, and *Escherichia coli*.[6]

EXPERIMENTAL[7]

Methylenediurea (V). Water (1500 ml.), urea (1200 g., 20 moles), 40% aqueous formaldehyde (250 ml., 3.32 moles),

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(6) Biological data provided by Dr. Paul H. Schuldt of the Boyce Thompson Institute for Plant Research, Inc., Yonkers, N. Y.

(7) All melting points are uncorrected. Elemental analyses by Diamond Alkali Company Research Analytical Laboratory. Available halogen determinations by sodium thiosulfate titration. The theoretical percent available halogen is taken as twice the weight percent of halogen attached to nitrogen.

and concd. hydrochloric acid (25 ml.) were stirred for 24 hr. The resulting solid was filtered and oven dried at 110°. Yields were of the order of 380–420 g. (88–98%) of material, melting at 210–220°, which was suitable for the preparation of I.

2,4-Dioxohexahydro-1,3,5-triazine (I). A stirred mixture of crude, dry methylenediurea (132 g., 1 mole) and 500 ml. of nitrobenzene was heated at a gentle reflux for 4–5 hr. After cooling and filtering, the tan residue was triturated with two 200-ml. portions of ethyl ether. The solid was extracted with three 1-l. portions of boiling water, the combined extracts decolorized with carbon, concentrated until crystals began to form, and cooled. Filtration and drying gave 80 g. (69.5%) of material decomposing above 300°.

Anal. Calcd. for $C_3H_5N_3O_2$: C, 31.3; H, 4.3. Found: C, 31.3; H, 4.4.

1,3,5-Trichloro-2,4-dioxohexahydro-1,3,5-triazine (III). I (23 g., 0.2 mole) was suspended in 500 ml. of water in a 1-l. beaker furnished with a gas dispersion tube, a mechanical stirrer, and an addition funnel, and cooled by an ice bath. The electrodes of a Beckman Model H-2 *p*H meter were so arranged that the *p*H of the contents of the beaker could be followed continuously. Chlorine (46 g., 0.648 mole) was passed in over a 2-hr. period while 6*N* sodium hydroxide was added at such a rate as to maintain the *p*H of the reaction mixture in the range *p*H 2.0–2.5. The solid was filtered, washed with two 50-ml. portions of water, and dried to give 31 g. (69%) of III containing 91% available chlorine (97.5% is theoretical). Recrystallization from chloroform–carbon tetrachloride gave white plates melting at 137–138°.

Anal. Calcd. for $C_3H_2Cl_3N_3O_2$: C, 16.5; H, 0.9; Cl, 48.7; N, 19.2. Found: C, 16.8; H, 0.8; Cl, 47.4; N, 19.4.

1,3,5-Trichloro-6-phenyl-2,4-dioxohexahydro-1,3,5-triazine (IV). II (15.2 g., 0.08 mole) was chlorinated, by the use of 18 g. (0.253 mole) of chlorine, and worked up in the manner described for III to give 21 g. (87%) of IV containing 70% available chlorine (72.4% is theoretical). Recrystallization from chloroform gave a white solid melting at 248–249°.

Anal. Calcd. for $C_9H_6Cl_3N_3O_2$: C, 36.8; H, 2.1; Cl, 36.2; N, 14.3. Found: C, 36.8; H, 3.0; Cl, 35.1; N, 14.5.

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Potential Anticancer Agents.[1] XXXVII. Monofunctional Aziridines Related to Tetramin

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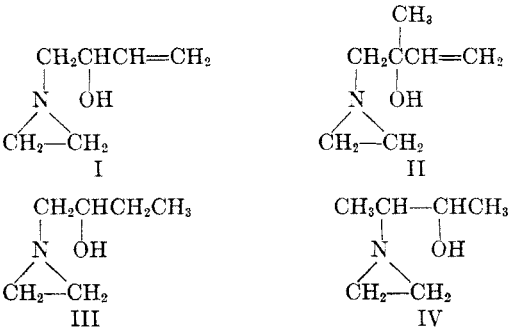
Tetramin [β-(1-aziridinyl)-α-vinylethanol] (I) is a broad spectrum anticancer agent which is active against a variety of transplanted animal tumors[2] as well as several human carcinomas.[2,3] Oettel[2] has reported that both the hydroxyl group and the double bond of Tetramin are necessary in order to maintain anticancer activity but did not cite evidence. Frohberg[4] reported that



β-(1-aziridinyl)-α-methyl-α-vinylethanol (II) showed reduced activity against Ehrlich Ascites-Carcinoma, Sarcoma 37, and Walker-Carcinosarcoma 256, as compared with Tetramin (I).

These results lead us to report our findings on the synthesis and activity of the Tetramin analogs (II–IV). These compounds were tested on the mouse tumors Sarcoma 180, Adenocarcinoma 755, and Leukemia L-1210. Tetramin has a substantial anticancer effect in all three of these systems.[3] However the three analogs (II–IV) were inactive at the maximum tolerated doses which were lower than the range where Tetramin showed activity. It is interesting to speculate that the possibility of biological oxidation of the secondary hydroxyl of Tetramin supplies the normal cell with a mechanism of detoxification which is apparently lacking in the cancer cell, thus accounting for the higher toxicity and resultant lack of activity of II–IV. Allylic alcohols are reported to be more easily oxidized to the carbonyl than the corresponding saturated alcohols,[5] thus offering a possible explanation for failure of the normal cell to detoxify the saturated analog (III) of Tetramin or the isomer (IV) by oxidation. The lowered activity of II compared with Tetramin observed by Frohberg[4] and the absence of selective activity of II observed in our laboratories is also understandable on the basis of an oxidative detoxification of Tetramin by the normal cell.

The synthesis of β-(1-aziridinyl)-α-methyl-α-vinylethanol (II) was accomplished in 70% yield by the addition of ethylenimine to 3,4-epoxy-3-methyl-1-butene. Although there is a possibility of obtaining two isomers from this addition, no isomeric β-(1-aziridinyl)-β-methyl-β-vinylethanol could be detected by vapor phase chromatography.

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, Contract No: SA-43-ph-1892. The opinions expressed in this paper are those of the authors and not necessarily those of the Cancer Chemotherapy National Service Center. For the preceding paper in this series, *cf.* A. Benitez, L. O. Ross, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, in press.

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