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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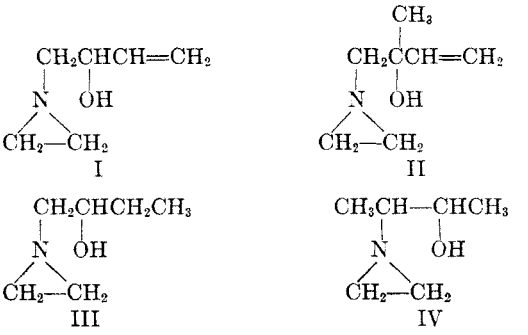
Tetramin [β-(1-aziridinyl)-α-vinylethanol] (I) is a broad spectrum anticancer agent which is active against a variety of transplanted animal tumors[2] as well as several human carcinomas.[2,3] Oettel[2] has reported that both the hydroxyl group and the double bond of Tetramin are necessary in order to 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.

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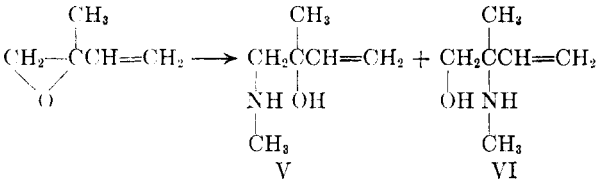
(4) H. Frohberg, *Arch. exp. Pathol. Pharmakol.*, **236**, 280 (1959).

(5) (a) H. Adkins, R. M. Elofson, A. G. Rossow, and C. C. Robinson, *J. Am. Chem. Soc.*, **71**, 3622 (1949). (b) M. Harfenist, A. Bavley, and W. A. Lazier, *J. Org. Chem.*, **19**, 1608 (1954).

This is somewhat surprising in view of the recent report[6] that the reaction of 3,4-epoxy-3-methyl-1-butene with methylamine gave a mixture of the primary (V) and secondary (VI) addition products in the ratio of 10 to 1. The addition of ethylenimine to 1,2-epoxybutane followed by distillation of the product, gave a 50% yield of a material which was 98% pure as shown by vapor phase chromatography and which is presumed to be β-(1-aziridinyl)-α-ethylethanol (III). Similarily, 2,3-epoxybutane gave a 45% yield of β-(1-aziridinyl)-α,β-dimethylethanol (IV) which was 93% pure according to vapor phase chromatography.



V VI

EXPERIMENTAL[7]

3,4-Epoxy-3-methyl-1-butene. To a vigorously stirred suspension of 67.3 g. (0.99 mole) of isoprene in 250 ml. of water was added 176.1 g. (0.99 mole) of *N*-bromosuccinimide at a rate which kept the temperature between 18–25°. After the addition (about 0.5 hr.) was complete, the mixture was stirred at 18–25° for 2–3 hr. by which time all of the *N*-bromosuccinimide was in solution and the solution gave a negative test with potassium iodide paper.

The organic layer was extracted with three 90-ml. portions of diethyl ether. The combined ether layers were dried over magnesium sulfate, then evaporated to dryness *in vacuo* to yield 151 g. of the crude bromohydrin of isoprene.

The isoprene bromohydrin was added over 20–30 min. to 270 g. of 30% aqueous sodium hydroxide which had been cooled to 10–15° in an ice bath. After the addition was complete, the reaction was stirred at about 10° for 2 hr., then the organic phase was separated from the aqueous layer. The aqueous layer was washed with 50 ml. of ether. The ether layer and organic layer were combined, dried over magnesium sulfate, then distilled through a small Vigreux column to yield 33.7 g. (41%) of 3,4-epoxy-3-methyl-1-butene, b.p. 78–82°, n_D^{26} 1.4139, which was 91% pure as shown by vapor phase chromatography;[8] $\lambda_{max(\mu)}^{film}$ 6.07 (C=C), 7.20 (CH_3), 10.08, 10.85 (—CH=CH_2), 11.25, 12.75 (epoxide).

Pummerer and Reindel[9] prepared this compound in 30–40% yield by the reaction of isoprene with perbenzoic acid. They reported b.p. 81° (735 mm.) and n_D^{19} 1.4179. Petrov[10] reported b.p. 78.5–79° and n_D^{20} 1.4142 for 3,4-epoxy-3-methyl-1-butene prepared using *N*-bromoacetamide, then 80% potassium hydroxide.

β-(1-Aziridinyl)-α-methyl-α-vinylethanol (II). To a mixture of 10.0 g. (0.12 mole) of 3,4-epoxy-3-methyl-1-butene in 5 ml. of water was added dropwise with stirring 10.2 g. (0.24 mole) of ethylenimine dissolved in 5 ml. of water. The temperature was kept at 15–20° during the addition of the ethylenimine and for 3 hr. after the addition was complete. The reaction was left at room temperature for 16 hr. then evaporated to dryness *in vacuo*. The residue was distilled to give 10.6 g. (70%) of II b.p. 40–50° (0.1 mm.), n_D^{27} 1.4672; $\lambda_{max(\mu)}^{film}$ 2.95 (OH), 3.55 (aziridine CH), 6.07 (C=C). The vapor phase chromatogram[11] showed no detectable impurities.

Anal. Calcd. for $C_7H_{13}NO$: C, 66.1; H, 10.3; N, 11.0. Found: C, 66.0; H, 10.5; N, 11.2.

By the same procedure *β-(1-aziridinyl)-α-ethylethanol* (III) was prepared from 10.0 g. of 1,2-epoxybutane[12] and ethylenimine; yield 8.0 g. (50%), b.p. 32–36° (0.1 mm.), n_D^{22} 1.4499; $\lambda_{max(\mu)}^{film}$ 2.97 (OH), 3.55 (aziridine CH). The product was 98% pure according to vapor phase chromatography.[11]

Anal. Calcd. for $C_6H_{13}NO$: C, 62.6; H, 11.4; N, 12.2. Found: C, 62.4; H, 11.4; N, 12.0.

β-(1-Aziridinyl)-α,β-dimethylethanol (IV). A mixture of 10.0 g. (0.14 mole) of 2,3-epoxybutane,[12] 12.0 g. (0.28 mole) of ethylenimine and 5 ml. of water was prepared as described in the preparation of β-(1-aziridinyl)-α-methyl-α-vinylethanol (II), then left for 72 hr. at room temperature. Distillation of the reaction mixture as described for II gave 7.15 g. (45%) of product (IV), b.p. 54–58° (3 mm.), n_D^{22} 1.4515; $\lambda_{max(\mu)}^{film}$ 2.97 (OH), 3.35–3.50 (aziridine CH). The vapor phase chromatogram showed that the distillate was 93% pure.

Anal. Calcd. for $C_6H_{13}NO$: C, 62.6; H, 11.4; N, 12.2. Found: C, 62.2; H, 11.6; N, 12.2.

A reaction time of 16 hr. gave only 5–10% yield.

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(6) V. M. Al'bitskaia and A. A. Petrov, *J. Gen. Chem.*, **28**, 873 (1959), English translation.

(7) Boiling points are uncorrected.

(8) LAC column, 70°.

(9) R. Pummerer and W. Reindel, *Ber.*, **66**, 335 (1933).

(10) A. A. Petrov, *J. Gen. Chem.*, **13**, 481 (1943).

(11) D C-710 column, 170°.

(12) Farchan Research Laboratories, 28915 Anderson Road, Wickliffe, Ohio.

3α-Hydroxy-19-nor-5α-androstan-17-one and 19-Nor-5α-androstane-3α-17β-diol[1,2]

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These compounds were prepared for the purpose of identifying metabolites of 19-nortestosterone.[3,4] 3β-Hydroxy-19-nor-5α-androstan-17-one was converted to the 3β-*p*-toluenesulfonate. The tosylate was treated with potassium acetate in dimethylformamide and the resulting 3α-acetoxy-19-nor-5α-androstan-17-one hydrolyzed in methanolic sodium hydroxide to 3α-hydroxy-19-nor-5α-androstan-17-one. Reduction of 3α-hydroxy-19-nor-5α-androstan-17-one with sodium borohydride yielded 19-nor-5α-androstane-3α,17β-diol.

(1) This work was supported in part by a grant from U.S.P.H.S. No. A-2672.

(2) The C-10 hydrogen in all compounds reported here has the β-configuration.

(3) D. Kupfer and E. Forchielli, *Federation Proc.*, **19**, 1968 (1960).

(4) L. L. Engel, T. Alexander, and M. Wheeler, *J. Biol. Chem.* **231**, 159 (1958).