benzene–ligroin, m.p. 144.5–145.5°, λ_{max} 229.5 (12,000), 289.5 (7120), and 310 mμ (9100).

Anal. Calcd. for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.64; H, 7.05; N, 5.22.

Further elution of the column with methanol gave 220 mg. (19%) of 6-(6-methoxy-1,2,3,4-tetrahydro-2-naphthyl)-2-(1*H*)-pyridone (VIII) which was recrystallized from 95% ethanol, m.p. 239–239.5°, λ_{max} 227 (13,820), 289 (8275), 306 (9350), and 361 mμ (605).

Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.43; H, 6.70; N, 5.50.

The infrared spectra of the three methylation products are fully consistent with the structural assignments.

In a different methylation experiment a solution prepared from 500 mg. of 6-(6-hydroxy-1,2,3,4-tetrahydro-2-naphthyl)-2(1*H*)-pyridone, 75 mg. of sodium hydride, and 25 ml. of methanol was cooled and treated with 5 ml. of dimethyl sulfate, and the resulting mixture was refluxed for 2 hr. Work-up of the reaction mixture gave, on evaporation of the chloroform, 330 mg. (64%) of 6-(6-methoxy-1,2,3,4-tetrahydro-2-naphthyl)-2(1*H*)-pyridone (VIII), m.p. 236.5–238°.

6-(6-Hydroxy-1,2,3,4-tetrahydro-2-naphthyl)-1-methyl-2-(1H)-pyridone (Xb). A solution of 900 mg. of 6-(6-methoxy-1,2,3,4 - tetrahydro - 2 - naphthyl) - 1 - methyl - 2(1*H*)-pyridone (Xa) and 15 ml. of 48% hydrobromic acid was refluxed for 3 hr., cooled, and filtered to give 1.08 g. of the crude pyridone hydrobromide, m.p. 232–235° dec. The hydrobromide was stirred with warm concd. ammonium hydroxide, and the resulting solid was collected on a filter to give 716 mg. of product, m.p. 251–253°. The analytical sample of Xb crystallized from aqueous acetic acid in white platelets, m.p. 254°, λ_{max} 225 (10,800), 230 (10,750), and 310 mμ (9230) with an inflection at 294 mμ (7650). The infrared spectrum is consistent with the structural assignment.

Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71. Found: C, 74.79; H, 6.72.

CAMBRIDGE 39, MASS.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF CALIFORNIA, DAVIS]

Amines Derived from Dihalopropenes. II. Synthesis of (±)- and (−)-1-(2-Methylene-1-aziridinyl)-3-buten-2-ol[1]

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Treatment of *N*-(2-bromoallyl)-2-hydroxy-3-butenylamine (IV) with sodium amide in liquid ammonia has been found to yield 1-(2-methylene-1-aziridinyl)-3-buten-2-ol (III) together with a small amount of 1-(2-propynylamino)-3-buten-2-ol (V). (±)-IV was prepared from 2-bromoallylamine and butadiene monoxide, and (−)-IV was prepared from 2,3-dibromopropene and (−)-1-amino-3-buten-2-ol. The relationship of III to Tetramin (I), the broad spectrum antineoplastic agent, is discussed.

The finding that Tetramin[2a] (I) has a broad spectrum of antineoplastic activity[2b] is striking in that the vast majority of "alkylating agents" that have shown promise as antineoplastic agents are capable of functioning as dialkylating agents,[3] whereas the components of I appear to be capable of acting only as a monoalkylating agent. Thus, the action of Tetramin in rapidly multiplying cells may be quite different from that of dialkylating agents, or one of the components of I may be converted in these cells to another compound which can function in a manner similar to that of a dialkylating agent. It is noteworthy that biological oxidation of the hydroxyl group of Ia would yield the amino ketone (II). II can function as a dialkylating agent because of the possibility of Michael-type addition to the α,β-unsaturated ketone part of the molecule as well as through a nucleophilic displacement reaction at one of the ring carbons.[4]

It has been found that the DPN (diphosphopyridine nucleotide) concentration in various animal tumors is depressed by the addition of I, and the reduction in DPN concentration parallels the curative action of I.[5] It is interesting to speculate that I is oxidized by DPN, and the oxidation product—*i.e.*, II—reacts with the reduced DPN in such a manner that reoxidation of the reduced

(1) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. This research was also supported in part by Cancer Research funds of the Cancer Research Coördinating Committee, University of California.

(2)(a) Although Tetramin, the product from the reaction of aziridine and butadiene monoxide, was assigned the 1-(1-aziridinyl)-3-buten-2-ol (Ia) structure,[3] Tetramin is a two to one mixture of Ia and 2-(1-aziridinyl)-3-buten-1-ol (XIIe, R_1R_2 = —CH_2CH_2—). The isomers have been separated and characterized by NMR spectroscopy. (Private communication from E. M. Chamberlin.)

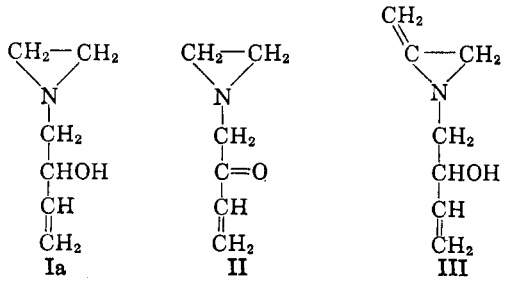
(2)(b) See *Cancer Chemotherapy Reports*, issued by the Cancer Chemotherapy National Service Center, National Institutes of Health, Bethesda 14, Md., August 1959, p. 52, for a summary of the clinical data on Tetramin, compiled by F. R. White.

(3) D. A. Karnofsky, *Ann. N. Y. Acad. Sci.*, **68**, 1261 (1958).

(4) E. J. Reist, I. G. Junga, and B. R. Baker, *J. Org. Chem.*, **25**, 1674 (1960), have pointed out that the relatively selective antineoplastic activity and lesser toxicity of Tetramin (I), as compared with analogs of the components of I which contain hydroxyl groups that are less readily oxidized, might be due to oxidation of I in normal cells to a relatively nontoxic substance (presumably II). The antineoplastic activity and toxicity of II are of obvious interest.

(5) H. Holzer and H. Kröger, *Klin. Wochschr.*, **36**, 677 (1958); H. Kröger, B. Ulrich, and H. Holzer, *Arzneimittel-Forsch.*, **9**, 598 (1959).

coenzyme is greatly impeded. The fact that several biological oxidations of alcohols in which DPN takes part are known to be stereospecific[6] indicated that the preparation of an optically pure form of Ia or a suitable analog would most likely be of value in correlating the activity of Ia with its structure. As preparation of one of the enantiomorphs of Ia appeared to require a rather lengthy synthetic procedure, we first directed our efforts to the synthesis of the "allenimine" (2-methyleneaziridine) analog 1-(2-methylene-1-aziridinyl)-3-buten-2-ol (III).



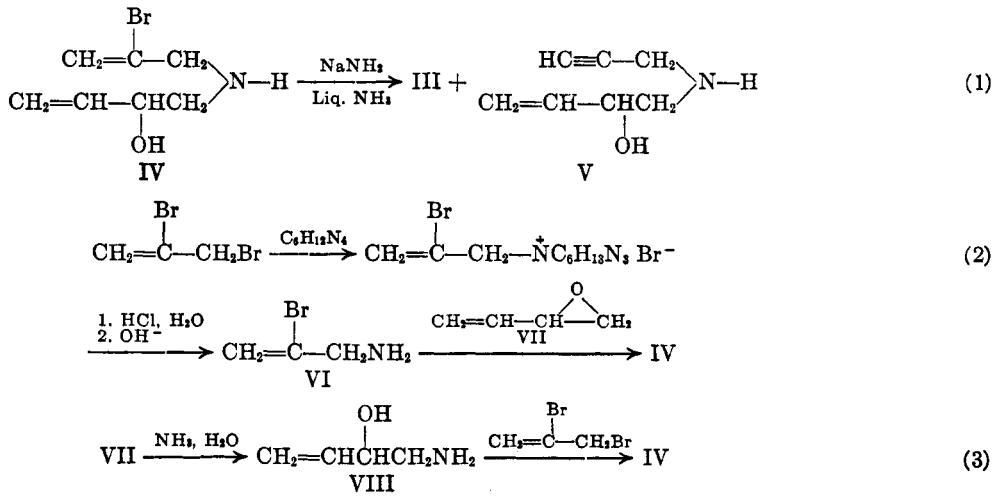
Ia II III

An *N*-alkylallenimine is prepared by treatment of the corresponding *N*-(2-bromoallyl)alkylamine with an alkali-metal amide in liquid ammonia.[7] Also formed in the reaction is some of the corresponding *N*-alkylpropargylamine.[7b-d] Thus, synthesis of III required preparation of *N*-(2-bromoallyl)-2-hydroxy-3-butenylamine (IV); treatment of IV with sodium amide in liquid ammonia was expected to give a mixture of III and 1-(2-propynylamino)-3-buten-2-ol (V) (Equation 1).

ammonium bromide obtained from 2,3-dibromopropene and hexamethylenetetramine, followed by treatment of the mixture of the hydrochlorides with base, gave an 80% yield of 2-bromoallylamine (VI). (*VI must be handled with extreme caution! Contact with 2-bromoallylamine can cause severe skin and eye irritation.*) VI was treated with butadiene monoxide (VII) in the same manner as that used for the preparation of I from aziridine and VII,[8] to form IV in 74% yield. Addition of IV to a slurry of sodium amide in liquid ammonia gave a 66% yield of a three to one mixture of III and 1-(2-propynylamino)-3-buten-2-ol (V). V, m.p. 59–60°, was separated from III by cooling an ether solution of the mixture, and III, essentially free of V, was obtained by distillation of the mother liquor.

(−)-1-(2-Methylene-1-aziridinyl)-3-buten-2-ol (III) was prepared by treatment with sodium amide in liquid ammonia of (−)-IV, which was prepared as shown in 3. VII and 28% ammonium hydroxide solution gave a mixture of 1-amino-3-buten-2-ol (VIII) and 2-amino-3-buten-1-ol, and the isomeric amino alcohols were separated by fractional crystallization of their oxalate salts.[9] (−)-VIII, obtained *via* the (+)-camphor-10-sulfonic acid salt,[9] was treated with 2,3-dibromopropene in absolute ethanol to give (−)-IV in 63% yield.

Synthesis of either (+)- or (−)-IV by way of 2 requires optically active VII, which is also required for the synthesis of optically active Ia. Several attempts were made to convert 1-(2-hydroxy-3-bu-



(1)

(2)

(3)

IV was first prepared as shown in 2. Hydrochloric acid–catalyzed hydrolysis of the crude quaternary

tenyl)trimethylammonium hydroxide (IX) to VII, as VIII, which has been resolved, can be converted readily to IX. Unfortunately, the only nitrogen-free compounds that could be isolated from the reaction of IX with sodium hydroxide were methanol and methyl vinyl ketone.

The infrared spectra of III and V were in

(6) B. Vennesland and F. H. Westheimer, *Symposium on the Mechanism of Enzyme Action*, McCollum-Pratt Inst., Johns Hopkins University, Contribution No. 70, 357 (1954).

(7) (a) C. B. Pollard and R. F. Parcell, *J. Am. Chem. Soc.*, 73, 2925 (1951); (b) A. T. Bottini and J. D. Roberts, *J. Am. Chem. Soc.*, 79, 1462 (1957); (c) Part I: A. T. Bottini and R. E. Olsen, *J. Am. Chem. Soc.*, 84, 195 (1962); (d) unpublished work of A. T. Bottini, B. J. King, and R. E. Olsen.

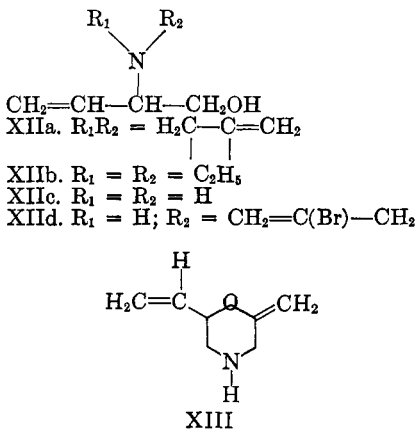
(8) K. Vierling, H. Öttel, and G. Wilhelm, Ger. Patent 1,004,614; *Chem. Abstr.*, 52, 10201 (1958).

(9) M. G. Ettlinger, *J. Am. Chem. Soc.*, 72, 4792 (1950).

complete agreement with the assigned structures. The spectrum of V had a weak band at 2100 cm.$^{-1}$, characteristic of monosubstituted carbon-carbon triple bonds,[10a] as well as bands at 3300–3400 cm.$^{-1}$, characteristic of acetylenic carbon-hydrogen bonds[10a] and oxygen-hydrogen bonds,[10b] and 1650 cm.,$^{-1}$ characteristic of carbon-carbon double bonds.[10c] The infrared spectrum of III had strong bands at 1785 cm.$^{-1}$ and 830 cm.$^{-1}$, and a weak band at 1660 cm.$^{-1}$, characteristic of allenimines[7a, b] and methylenecyclopropane,[11] as well as a strong band at 3400 cm.$^{-1}$ and a sharp, medium intensity band at 1650 cm.$^{-1}$.

The structure of III was confirmed by comparison of its nuclear magnetic resonance NMR spectrum with the NMR spectra of 1-ethyl-2-methyleneaziridine (X)[7b] and 1-diethylamino-3-buten-2-ol (XI).[12] The spectra of III and X had similar patterns of lines centered about $\tau = 5.33 \pm 0.07$[13] and $\tau = 8.14 \pm 0.04$, characteristic of the exocyclic- and endocyclic methylene hydrogens, respectively. The spectra of III and XI had in common numerous lines from $\tau = 3.93$ to 5.20, due to the vinyl and hydroxyl hydrogens of III and the vinyl hydrogens of XI,[14] and a poorly resolved set of lines centered about $\tau = 5.96 \pm 0.03$, due to the allylic hydrogens. The spectrum of III also had a doublet at $\tau = 7.69$, $J = 6.2 \pm 0.2$, due to the C-1-hydrogens of the nitrogen substituent. It is noteworthy that this last set of lines was split only into a doublet by the C-2 hydrogen and did not show the more complex pattern of the AB[15] portion of an ABX system as is sometimes observed for lines due to methylene hydrogens on a carbon bonded to an asymmetric center.[16] The lines due to the corresponding C-1-hydrogens of XI, which were centered at $\tau = 7.45$ and were coincident in part with the lines due to the methylene hydrogens of the ethyl groups, showed the more complex AB pattern, $J = 6.3$, $\delta = 17.9$.[15b]

The NMR spectrum of (±)-III had a low intensity doublet at $\tau = 6.60$, $J = 6.2 \pm 0.2$, that was not present in the spectrum of (−)-III, and the spectrum of XI had a series of low intensity lines resembling the AB portion of an ABX pattern centered about $\tau = 6.60$. These low intensity lines are believed due to the C_1-hydrogens of XIIa and XIIb, respectively. The reaction of butadiene monoxide (VII) with aqueous ammonia yields a significant amount of 2-amino-3-buten-1-ol (XIIc) together with the main product, 1-amino-2-buten-2-ol (VIII),[9] and it seems reasonable that some *N* - (2 - bromoallyl) - 1 - hydroxymethyl - 2 - propenylamine (XIId) would be formed together with IV during the reaction of VII with 2-bromoallylamine (VI), and that some 2-diethylamino-3-buten-1-ol (XIIb) would be formed together with XI during the reaction of VII with diethylamine. Treatment of a mixture of IV and XIId with sodium amide in liquid ammonia would yield a mixture of III and XIIa. (−)-IV, which was prepared from 2,3-dibromopropene and VIII that was free of XIIc, would not be expected to be contaminated with any XIId.



XIII

With the exceptions of the lines at $\tau = 6.60$, the areas of the bands in the NMR spectra of III and XI were in the theoretical ratio. If the lines at $\tau = 6.60$ in the spectra of (±)-III and XI were due to the C-1 hydrogens of XIIa and XIIb, respectively, our samples of (±)-1-(2-methylene-1-aziridinyl)-3-buten-2-ol and 1-diethylamino-3-buten-2-ol were contaminated with from 5–9% of XIIa and XIIb, respectively.[17] Our samples of (±)- and (−)-III contained less than 2% of 1-(2-propynylamino)-3-buten-2-ol (V), as indicated by the absence of lines at $\tau = 6.9 \pm 0.1$, the resonance frequency of the methylene hydrogens of the propargylamino group of V.

It is of interest that no evidence was obtained which indicated that any 3-methylene-5-vinylmorpholine (XIII), or a six-membered ring isomer of XIII, was formed during the reaction of IV with sodium amide in liquid ammonia.

(10) (a) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 2nd Ed., Wiley, New York, 1958, p. 58; (b) p. 96; (c) p. 34.

(11) J. T. Gragson, K. W. Greenlee, J. M. Derfer, and C. E. Boord, *J. Am. Chem. Soc.*, **75**, 3344 (1953).

(12) F. F. Blicke and J. H. Biel, *J. Am. Chem. Soc.*, **79**, 5508 (1957).

(13) G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

(14) This singlet due to the hydroxyl hydrogen of XI appeared at $\tau = 6.08$ in the spectrum of the XI containing 2% tetramethylsilane and 2% methanol.

(15) (a) J. A. Pople, W. G. Schneider, and H. J. Bernstein, *High-resolution Nuclear Magnetic Resonance*, McGraw-Hill, New York, 1959, p. 98; (b) p. 120.

(16) *Cf.* P. M. Nair and J. D. Roberts, *J. Am. Chem. Soc.*, **79**, 4565 (1957).

(17) Identification of the contaminants as XIIa and XIIb gains further support from the fact that the product from the reaction of butadiene monoxide and aziridine is a mixture of Ia and 2-(1-aziridinyl)-3-buten-1-ol (XIIe, $R_1R_2 = —CH_2CH_2—$).[2a]

Antineoplastic activity.[18] In a series of tests with the same set of controls, (±)-III appeared to have greater antineoplastic activity than (−)-III against the mouse tumor Adenocarcinoma 755. (±)-III was less active than I against Adenocarcinoma 755, and doses of (±)-III four times greater than doses of I were required for comparable activity. (±)-III was inactive against the mouse tumors Leukemia L-1210 and Sarcoma 180 at doses twice as great as the range in which I showed activity.

One possible cause for the lesser antineoplastic activity of III as compared with I is that the greater bulk of the exocyclic-methylene group as compared with that of two hydrogens may cause a steric interaction with a group near the site of biological activity which impedes the proper alignment of III in the biological system necessary for antineoplastic activity.

Although the results on the comparative activity of (±)- and (−)-III against Adenocarcinoma 755 must be taken as preliminary,[19] they are most provocative. If they are confirmed by more extensive tests with (+)-III as well as (−)-III, knowledge of the existence of a relationship between antineoplastic activity and the absolute configuration about C-2 of the nitrogen substituent of ethylenimines would provide a new insight into the nature of the sites of biological activity of these substances and make available a more complete template for the building of new antineoplastic agents.

EXPERIMENTAL

All melting points and boiling points are uncorrected. Infrared spectra were obtained with a Beckman IR-4 spectrophotometer. NMR spectra were obtained at 60 mc. with a Varian Associates HR-60 system using samples contained in 5-mm. o.d. tubes. Resonance frequencies in NMR spectra were determined relative to tetramethylsilane as an internal standard using the "side-band" technique with a Packard CD-200 Audio-oscillator. Microanalyses were performed by Mr. V. H. Tashinian, Berkeley, Calif., and by Drs. Weiler and Strauss, Oxford, England.

2-Bromoallylamine (VI). A stirred solution of 154 g. (1.1 moles) of hexamethylenetetramine in 1250 ml. of chloroform was heated at reflux, and 200 g. (1.0 mole) of 2,3-dibromopropene (Columbia Organic Chemicals Co., Inc.) was added dropwise in one hour. Precipitation of the quaternary ammonium salt was noted soon after the first addition of 2,3-dibromopropene. The reaction mixture was heated at reflux for 4 hr., allowed to stand overnight, and cooled in an ice bath. The salt was collected by suction filtration. After air drying, it weighed 308 g. (91%) and had m.p. 185–186.5°. The crude product was used for the preparation of VI. The quaternary ammonium bromide (200 g., 0.59 mole) was dissolved in a warm solution prepared from 400 ml. of water, 2 l. of ethanol, and 480 ml. (5.8 moles) of concentrated hydrochloric acid. Within an hr., a precipitate of ammonium chloride had formed. The mixture was allowed to stand for 2 days and the ammonium chloride was removed by filtration. The filtrate was concentrated in stages to 600 ml. The solid that separated was removed by filtration and was found to be ammonium chloride. The filtrate was evaporated to dryness on a rotary film evaporator.

Because of the toxicity of 2-bromoallylamine, rubber gloves and protective goggles should be worn during the following operations. The residue was taken up in 250 ml. of water, and the mixture was made alkaline with 6*N* sodium hydroxide. The heavy red-brown organic phase was separated; the aqueous solution was saturated with sodium chloride and extracted 3 times with 100-ml. portions of ether. The ether extracts were combined with the organic phase, washed with 100 ml. of saturated sodium chloride, and dried over potassium carbonate. The ether was removed by distillation and 2-bromoallylamine (58 g., 72%) was collected at 65–67° (100 mm.), n_D^{25} 1.5081.

Anal. Calcd. for C_3H_6NBr: C, 26.49; H, 4.45; N, 10.30. Found: C, 26.64; H, 4.57; N, 10.19.

The *p*-bromobenzenesulfonamide derivative[20] had m.p. 90–92°.

Anal. Calcd. for $C_9H_9NO_2SBr_2$: C, 30.44; H, 2.55. Found: C, 31.06; H, 2.58.

1-Bromo-3-buten-2-ol. N-Bromosuccinimide (435 g., 2.5 moles), in a solution of 151 g. (2.8 moles) of 1,3-butadiene and 500 ml. of ether, was added to a vigorously stirred mixture of 200 ml. of ether and 300 ml. of water held at 10°. Vigorous stirring was continued for 6 hr. during which time the *N*-bromosuccinimide dissolved and the 2 phases became clear. The aqueous phase was extracted 3 times with 500-ml. portions of ether. The extracts were combined with the ether solution from the reaction mixture and dried over magnesium sulfate. Most of the ether was removed by distillation at atmospheric pressure. The residue was distilled under nitrogen through a 200 × 25-mm. column packed with glass helices. 1-Bromo-3-buten-2-ol (304 g., 81%) was collected at 54–55° (6 mm.), n_D^{22} 1.5013; lit.[21] b.p. 161–162.5°, n_D^{15} 1.5022.

Anal. Calcd. for C_4H_7OBr: C, 31.81; H, 4.67; Br, 52.92. Found: C, 31.57; H, 4.70; Br, 52.76.

Butadiene monoxide (VII). The butadiene monoxide used was obtained from Columbia Organic Chemicals, Inc., or synthesized as follows. 1-Bromo-3-buten-2-ol (858 g., 5.68 moles) was added in 5 hr. to a stirred solution of 1368 g. (34.2 moles) of sodium hydroxide in 2 l. of water held at 16–18°. When the addition was complete, stirring was continued for 3 hr. The organic phase was separated, and the aqueous layer was extracted 3 times with 200-ml. portions of ether. The ether extracts were combined with the organic solution, dried over sodium hydroxide, and distilled. Butadiene monoxide (224.5 g., 57%) was collected at 65.5–67°, n_D^{28} 1.4129 (lit.[22] b.p. 65–65.8° (739 mm.), n_D^{20} 1.4170).

N-(2-Bromoallyl)-2-hydroxy-3-butenylamine (IV). Butadiene monoxide (10.5 g., 0.15 mole) was added dropwise in 20 min. to a well stirred solution of 63.0 g. (0.46 mole) of 2-bromoallylamine and 2 ml. of water at 15°. The temperature

(18) Samples of (±)- and (−)-III were submitted to the Cancer Chemotherapy National Service Center (CCNSC), and antitumor tests were carried out at the Stanford Research Institute under the auspices of the CCNSC. The opinions expressed in this paper are those of the authors and not necessarily those of the CCNSC.

(19) It is conceivable that the apparent greater activity of (±)-III as compared with (−)-III was due to the presence of some XIIa in our sample of (±)-III. The activity against Adenocarcinoma 755 of XIIa and the analogous component of Tetramin, XIIe, would be of interest. It is noteworthy that J. M. Venditti, A. Goldin, and I. Kline, *Cancer Chemotherapy Reports*, issued by the Cancer Chemotherapy National Service Center, National Institutes of Health, Bethesda 14, Md. April 1961, p. 73, have found that XIIe is inactive against Leukemia L-1210, and XIIe is more toxic than Ia.

(20) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, Wiley, New York, 4th Ed., 1956, p. 227.

(21) A. A. Petrov, *J. Gen. Chem. U.S.S.R.*, **8**, 142 (1938); *Chem. Abstr.*, **32**, 5370 (1938).

(22) R. G. Kadesch, *J. Am. Chem. Soc.*, **68**, 41 (1946).

of the reaction mixture was raised slowly to 100° and held at that temperature for 6 hr. Most of the unchanged 2-bromoallylamine (41 g.) was collected at 52–54° (30 mm.). The product (23.0 g. 74%) was collected at 107–109° (2 mm.), $n_D^{25.5}$ 1.5128.

Anal. Calcd. for $C_7H_{12}NOBr$: C, 40.80; H, 5.87; N, 6.80. Found: C, 40.10; H, 5.93; N, 6.21.

1-(2-Methylene-1-aziridinyl)-3-buten-2-ol (III). To a well stirred slurry of 4.1 g. (0.105 mole) of sodium amide (Roberts Chemical Co.) in 200 ml. of liquid ammonia contained in a 500-ml., 3 necked flask equipped with a mechanical stirrer, Dry Ice reflux condenser, and dropping funnel was added dropwise in 30 min. a solution of 10.3 g. (0.050 mole) of *N*-(2-bromoallyl)-2-hydroxy-3-butenylamine in 30 ml. of dry ether. The solution was stirred under reflux for 6 hr. Stirring was continued and the ammonia was allowed to evaporate. Water (50 ml.) was added cautiously to the residue; the aqueous solution was saturated with sodium chloride and extracted 5 times with 30-ml. portions of ether. The ether extracts were combined, washed with 30 ml. of saturated sodium chloride, and dried over potassium carbonate. The ether was removed by distillation and the residue was distilled under nitrogen to yield 4.1 g. (66%) of product with b.p. 50–68° (1 mm.), n_D^{25} 1.4840. When the distillation flask was allowed to cool, crystals formed in the arm of the flask. The infrared spectrum of the product possessed a weak band at 2100 cm.$^{-1}$ and an intense band at 1785 cm.$^{-1}$ indicating that the distillate was a mixture of III and 1-(2-propynylamino)-3-buten-2-ol (V). The distillate was taken up in 40 ml. of dry ether and cooled to −10° to deposit 0.9 g. of shining white needles with m.p. 59–60°. The infrared spectrum of the solid indicated that it was V essentially free of III.

Anal. Calcd. for $C_7H_{11}NO$: C, 67.17; H, 8.86. Found: C, 66.53; H, 8.60.

The mother liquor was concentrated, and a second crop (0.2 g.), which was a liquid at room temperature, was taken by cooling the solution at −25° and removing the mother liquor by suction through a fritted disk. The infrared spectrum of the second crop indicated that it was a mixture of the two products. The mother liquor was dried over a small amount of potassium carbonate and distilled to yield 2.5 g. of 1-(2-methylene-1-aziridinyl)-3-buten-2-ol (III), b.p. 50–52° (1.5 mm.), $n_D^{33.5}$ 1.4827, that was essentially free of its isomer as determined by NMR spectroscopy.

Anal. Calcd. for $C_7H_{11}NO$: C, 67.17; H, 8.86; N, 11.19. Found: C, 67.12; H, 8.87; N, 11.30.

The products from another run, in which 20.6 g. (0.10 mole) of IV was treated with 8.2 g. (0.21 mole) of sodium amide, were fractionally distilled under nitrogen. The fraction with b.p. 65–68° (3 mm.), n_D^{29} 1.4845, weighed 6.4 g. (51%). The infrared spectrum of this fraction had no band at 2100 cm.$^{-1}$, thus indicating that it contained little, if any, V. The fraction contained less than 2% of V as determined by NMR spectroscopy. A second fraction (2.0 g., 16%), b.p. 68–86° (3 mm.), n_D^{29} 1.4824, consisted mainly of V.

(−)-*1-Amino-3-buten-2-ol* [(−)-VIII]. *l*-1-Amino-3-buten-2-ol *d*-camphor-10-sulfonate, m.p. 147.5–148.5°, $[\alpha]_D^{27}$ +14.4° (0.160 g./10 ml. of water), lit.[9] m.p. 148.5–150°, $[\alpha]_D$ +14° (in water) was prepared as described by Ettlinger.[9,23] A solution of 54.2 g. (0.17 mole) of the salt in 300 ml. of absolute ethanol was treated with a solution of 9.5 g. (0.17 mole) of potassium hydroxide in 150 ml. of absolute ethanol. The solid that separated was removed by suction filtration and washed with a small amount of absolute ethanol. The filtrate was concentrated by distillation at 50 mm. to yield a semisolid mass which was mixed with 50 ml. of absolute ethanol. The solid was removed by suction filtration, washed with 25 ml. of absolute ethanol, and the filtrate was distilled. (−)-1-Amino-3-buten-2-ol (9.5 g., 64%) had b.p. 77–79° (10 mm.), m.p. 52–53°, $[\alpha]_D^{22}$ −28.0° (0.199 g./10 ml. of water); lit.[9] b.p. 72° at 8 mm. for the *d,l*-amino alcohol.

(−)-*N-(2-Bromoallyl)-2-hydroxy-3-butenylamine* [(−)-IV]. A solution prepared from 8.7 g. (0.10 mole) of (−)-1-amino-3-buten-2-ol, 10.0 g. (0.050 mole) of 2,3-dibromopropene, and 75 ml. of absolute ethanol was heated at reflux for 4 hr. The reaction mixture was concentrated by distillation at 50 mm. until the pot temperature reached 55°. Dry ether (100 ml.) was added to the cool residual oil. The solid that separated was removed by suction filtration and washed twice with 50 ml. portions of dry ether. The filtrate was distilled and 6.45 g. (63%) of (−)-IV was collected at 95–97° (1 mm.), m.p. 34–36°, $[\alpha]_D^{23}$ −3.5° (0.263 g./10 ml. in absolute ethanol). The infrared spectra of (−)- and (±)-IV were indistinguishable.

Anal. Calcd. for $C_7H_{12}NOBr$: C, 40.80; H, 5.87; N, 6.80; Br, 38.78. Found: C, 40.78; H, 5.78; N, 6.98; Br, 38.62.

(−)-*1-(2-Methylene-1-aziridinyl)-3-buten-2-ol* [(−)-III] was prepared from 5.15 g. (0.025 mole) of (−)-IV and 2.05 g. of sodium amide as described for the preparation of racemic III. The product was distilled under nitrogen, and 2 fractions were collected. The first fraction (0.98 g., 31%) had b.p. 51–53° (1.5 mm.), n_D^{21} 1.4878, $[\alpha]_D^{20}$ −30.5° (0.0837 g./20 ml. of absolute ethanol). The infrared spectra of this fraction and (±)-III were indistinguishable. No crystals separated when an ether solution of this material was cooled at −20°, thus indicating that it was essentially free of active 1-(2-propynylamino)-3-buten-2-ol (V). The first fraction contained less than 2% of active V as determined by NMR spectroscopy.

Anal. Calcd. for $C_7H_{11}NO$: C, 67.17; H, 8.86; N, 11.19. Found: C, 67.29; H, 9.01; H, 11.41.

The second fraction (1.05 g., 33%) had b.p. 54–67° (1.5 mm.). Refractionation yielded 0.4 g. of (−)-III which was essentially free of active V. The remainder of the fraction was lost due to a polymerization reaction which took place in the distillation apparatus.

1-Dimethylamino-3-buten-2-ol. A mixture of 14.0 g. (0.2 mole) of butadiene monoxide and 144 ml. of 25% aqueous dimethylamine containing 36 g. (0.8 mole) of dimethylamine was heated at reflux for 6 hr. in a flask equipped with a Dry Ice reflux condenser. The reaction mixture was cooled in an ice bath and made strongly alkaline with 50 g. of sodium hydroxide. The organic layer was separated, and the aqueous solution was extracted with 25 ml. of ether. The ether extract and organic layer were combined, dried over potassium carbonate, and distilled. 1-Dimethylamino-3-buten-2-ol (13.9 g., 61%) was collected at 66–67° (33 mm.), n_D^{23} 1.4472 (lit.[11] b.p. 67–68° at 32 mm.).

1-(2-Hydroxy-3-butenyl)trimethylammonium iodide. To a cold solution of 28.8 g. (0.25 mole) of 1-dimethylamino-3-buten-2-ol in 250 ml. of acetone was added slowly 39.1 g. (0.28 mole) of methyl iodide. The mixture was heated at reflux for 3 hr. and then cooled at −20° for 3 hr. The white, crystalline solid that separated was collected by suction filtration, washed with 25 ml. of cold, dry acetone, and dried in a vacuum desiccator. The product (56.0 g., 87%) had m.p. 70–79°.

Anal. Calcd. for $C_7H_{16}INO$: C, 32.70; H, 6.27; N, 5.45. Found: C, 32.56; H, 6.41; N, 5.54.

Attempts to prepare butadiene monoxide from 1-(2-hydroxy-3-butenyl)trimethylammonium iodide. A. Moist silver oxide, freshly prepared[24] from 34 g. (0.2 mole) of silver nitrate and 8 g. (0.2 mole) of sodium hydroxide, was added to a solution of 12.85 g. (0.05 mole) of 1-(2-hydroxy-3-butenyl)trimethylammonium iodide in 20 ml. of water. The mixture was agitated throughly and filtered. The precipitate was washed 3

(23) During the resolution of 78 g. (0.9 mole) of VIII, 7 g. of a compound with m.p. 242–244° was isolated because of its low solubility in 4:1 ethyl acetate–absolute ethanol. The compound is believed to be the sulfonamide formed from the amino alcohol and *d*-camphor-10-sulfonic acid.

Anal. Calcd. for $C_{14}H_{23}NO_4S$: C, 55.79; H, 7.69; N, 4.65; S, 10.64. Found: C, 55.97; H, 7.73; N, 4.68; S, 10.76.

(24) I. A. Pearl, *J. Am. Chem. Soc.*, **68**, 429 (1946).

times with 10-ml. portions of water, and the filtrate and washings were combined. Sodium hydroxide (20 g.) was added to the aqueous solution, and it was distilled slowly to yield a volatile amine (probably trimethylamine) and a colorless liquid with b.p. < 70°. The distillate was dried over potassium hydroxide and redistilled to yield 1.3 g. (84%) of a liquid with b.p. 64.5–65°, n_D^{25} 1.3278, which had an infrared spectrum identical with that of methanol.

B. An aqueous solution of 1-(2-hydroxy-3-butenyl)trimethylammonium hydroxide, prepared from 12.85 g. (0.05 mole) of 1-(2-hydroxy-3-butenyl)trimethylammonium iodide and 0.06 mole of freshly prepared silver oxide, was concentrated at 45° and 100 mm. The syrupy residue was heated in an oil bath at 135°. Vigorous frothing occurred, a volatile amine was evolved, and the distillate with b.p. 55–95° was collected. A polymerization reaction was noted to occur in a portion of the distillate that was collected over sodium hydroxide. Examination of the infrared spectrum of another portion of the distillate that had been dried over sodium sulfate indicated that it consisted of methanol and methyl vinyl ketone.

C. A concentrated aqueous soultion of 1-(2-hydroxy-3-butenyl)trimethylammonium hydroxide, prepared from 12.85 g. of 1-(2-hydroxy-3-butenyl)trimethylammonium iodide, was added to a solution prepared from 40 g. of sodium hydroxide and 30 ml. of water. The mixture became warm and a volatile amine was evolved. The mixture was stirred overnight at 40° during which time a small amount of polymeric substance separated. The mixture was then heated at 110°. More volatile amine was evolved, and more polymer formed, but no distillate was collected with b.p. <100°.

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[CONTRIBUTION FROM THE KETTERING-MEYER LABORATORY,[1] SOUTHERN RESEARCH INSTITUTE]

The Structure of the Tricyclic Purine Derived from the Purin-6-yl Analog of Nitrogen Mustard[2]

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The structure of the ionic product obtained by several investigators from the attempted synthesis of the purin-6-yl analog I of nitrogen mustard has been clarified by an unambiguous synthesis of 9-ethyl-7,8-dihydro-9*H*-imidazo[2,1-*i*]purine (XI). Spectral and chromatographic comparisons of XI and the tricyclic purine derived from I show that ring closure occurred at N_1 of the starting purine.

Recent reports of attempts to synthesize the purin-6-yl analog of nitrogen mustard, N^6,N^6-bis(2-chloroethyl)adenine (I), express conflicting speculations concerning the structure of the apparently identical ionic products obtained.[3,4] Huber[3] proposed a dimeric structure, 1,4-bis(2-chloroethyl)-1,4-dipurin-6-ylpiperazinium dichloride (II), and attributed the low order of toxicity observed to the formation of such a structure, whereas Lyttle and Petering[4] proposed, without preference, one or the other of the quaternary ammonium structures III and IV involving the interaction of one of the 2-chloroethyl groups with either N_1 or N_7 of the purine ring. Di Paco and Tauro[5] presented their product as the covalent structure I without further elaboration.

The facile formation of 7,8-dihydrothiazolo-[2,3-*i*]purine[6] (V) from 6-(2-chloroethylthio)purine[6,7] suggests that a similar ring closure might also be involved with the nitrogen mustard analog I. The activity shown by 6-(2-chloroethylthio)-purine against Sarcoma 180 and Adenocarcinoma 755 in mice was not retained in the cyclized form V.[8] We repeated the synthesis of the water-soluble ionic product derived from I by methods similar to those described previously,[3-5] and by careful treatment of the salt thus formed with sodium hydroxide solution we isolated an an alytical'y and chromatographically pure free base ($C_9H_{10}ClN_5$) to which could be assigned either structure VI or structure VII. The ultraviolet absorption spectra of the base and of the salt in aqueous solutions at *p*H's 1, 7, and 13 are practically identical. The structures III and IV are examples of the several protonated forms that the salts of the free bases VI and VII might assume, depending on the relative basicities of the nitrogen atoms.

2-[(6-Amino-5-nitro-4-pyrimidinyl)ethylamino]-ethanol (VIII), the product of the reaction of 4-amino - 6 - chloro - 5 - nitropyrimidine[9] and 2-ethylaminoethanol, provided a starting point for

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(3) G. Huber, *Angew. Chem.*, **68**, 706 (1956).

(4) D. A. Lyttle and H. G. Petering (to Upjohn Co.), U. S. Patent 2,957,875 (Oct. 25, 1960).

(5) G. Di Paco and C. S. Tauro, *Ann. chim. (Rome)*, **47**, 698 (1957).

(6) R. W. Balsiger, A. L. Fikes, T. P. Johnston, and J. A. Montgomery, *J. Org. Chem.*, **26**, 3446 (1961).

(7) T. P. Johnston, L. B. Holum, and J. A. Montgomery, *J. Am. Chem. Soc.*, **80**, 6265 (1958).

(8) Frank M. Schabel, Jr., *et. al.*, Southern Research Institute, unpublished results.

(9) W. R. Boon, W. G. M. Jones, and G. R. Ramage, *J. Chem. Soc.*, 96 (1951).