Amines Derived from Dihalopropenes. IV. The Absolute Configurations of the 1-(2-Methylene-1-aziridinyl)-3-buten-2-ols[1]

ALBERT T. BOTTINI, VASU DEV, AND MYRNA STEWART

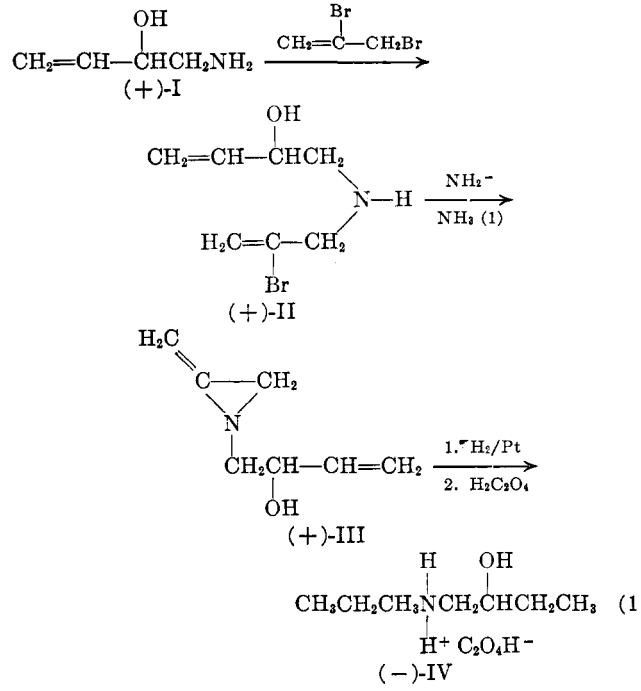
Chemistry Department, University of California, Davis, California

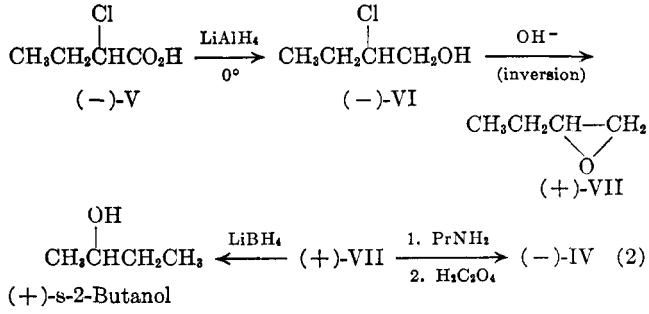
Received July 27, 1962

Hydrogenation of (+)-1-(2-methylene-1-aziridinyl)-3-buten-2-ol (III) yields the same enantiomer of 1-propylamino-2-butanol as is obtained from treatment of s-(+)-2-ethyloxirane with *n*-propylamine. Since neither of these reactions affects the asymmetric center, (+)-III must have the R-configuration.

We reported recently that racemic 1-(2-methylene-1-aziridinyl)-3-buten-2-ol, the allenimine analog of the active component of Tetramin,[2] is more active against Adenocarcinoma 755 than (−)-III.[3] The absolute configurations of the 1-amino-3-buten-2-ols, which are used in the preparation of (+)- and (−)-III, were unknown. Therefore, to establish the absolute configurations of the enantiomers of III, it was necessary to relate the configuration of an optically active III to that of a compound whose absolute configuration was known.

Hydrogenation of (±)-III over Adams' catalyst, using the same conditions that convert N-alkylallenimines to the corresponding N-alkyl-*n*-propylamines,[4] was found to yield 1-propylamino-2-butanol, which could also be prepared in excellent yield from *n*-propylamine and 2-ethyloxirane (VII). As the absolute configurations of the 2-ethyloxiranes could be assigned with a high degree of certainty,[5] and as formation of 1-propylamino-2-butanol from either III or VII takes place without affecting the asymmetric center, it was decided to relate the configuration of an optically active III to that of an enantiomer of IV. The sequences of reactions used to establish the absolute configurations are shown as equations 1 and 2.





2-Chlorobutanoic acid (V), prepared by the action of sulfuryl chloride on butyric acid,[9] was fractionated, and the center cut was partially resolved by crystallization of its cinchonidine salt from methanol.[10] The levorotatory acid that was isolated was reduced with lithium aluminum hydride to (−)-2-chloro-1-butanol (VI),[10] and compound (−)-VI was treated with sodium hydroxide to give s-(+)-2-ethyloxirane (VII).[5]

One portion of compound s-(+)-VII, which had a specific rotation of $[\alpha]^{30}D$ +10.7° in benzene (*c* 6.5), was converted to 1-propylamino-2-butanol acid oxalate (IV) with a specific rotation of $[\alpha]^{26}D$ −9.6° in 50% ethanol (*c* 4.4), and another portion was converted with lithium borohydride to s-(+)-2-butanol,[7] which had a specific rotation of $[\alpha]^{26}D$ +6.3° (neat). As optically pure s-(+)-2-butanol has a specific rotation of $[\alpha]^{26}D$ +13.6° (neat),[11] and the preparations of IV and 2-butanol from 2-ethyloxirane take place without affecting the asymmetric center, specific rotations of $[\alpha]^{30}D$ ±23.1° and $[\alpha]^{26}D$ ±20.7° can be calculated, respectively, for the optically pure 2-ethyloxiranes in benzene and the optically pure 1-propylamino-2-butanol acid oxalates in 50% ethanol.

As both (+)-2-ethyloxirane and (+)-2-butanol are known to have the s-configuration, the (−)-1-propyl-

(1) Presented at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962. 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 by Grant CY-5528 from the National Cancer Institute of the Public Health Service. Part III: A. T. Bottini, B. J. King, and J. M. Lucas, *J. Org. Chem.*, **27**, 3688 (1962).

(2) For a summary of early clinical data on Tetramin, compiled by F. R. White, see *Cancer Chemotherapy Rept.*, **4**, 52 (1959), Cancer Chemotherapy National Service Center, Bethesda, Md. See also, J. M. Venditti, A. Goldin, and J. Kline, *ibid.*, **11**, 73 (1961).

(3) A. T. Bottini and V. Dev, *J. Org. Chem.*, **27**, 968 (1962). The results of tests of (+)-III and (−)-III against Adenocarcinoma 755 using the same sets of controls should be received soon from the Cancer Chemotherapy National Service Center (CCNSC). Test data received from the CCNSC may be obtained from the authors on request.

(4) C. B. Pollard and R. F. Parcell, *J. Am. Chem. Soc.*, **73**, 2925 (1951); A. T. Bottini and R. E. Olsen, *ibid.*, **84**, 195 (1962).

(5) (−)-3-Heptanol, which has been assigned the R-configuration,[6,7] is the product of the reaction of (+)-2-ethyloxirane and propylmagnesium bromide.[8] Thus, (+)-2-ethyloxirane can be assigned the s-configuration.[7]

(6) J. A. Mills and W. Klyne, "Progress in Stereochemistry," Vol. I, W. Klyne, ed., Academic Press, Inc., New York, N. Y., 1954, p. 205.

(7) R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956).

(8) P. A. Levene and A. Walti, *J. Biol. Chem.*, **94**, 367 (1931).

(9) G. Steinbrun, German Patent 1,014,092; *Chem. Abstr.*, **53**, 15981 (1959).

(10) K. Freudenberg and W. Lwowski, *Ann.*, **597**, 141 (1955).

(11) R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, **99**, 45 (1911).

amino-2-butanol acid oxalate (IV) obtained from s-(+)-VII must have the R-configuration. Therefore, (+)-1-(2-methylene-1-aziridinyl)-3-buten-2-ol (III), which also yielded (−)-IV, as well as the intermediates used in the preparation of (+)-III, (+)-1-amino-3-buten-2-ol (I)[12] and (+)-N-(2-bromoallyl)-2-hydroxy-3-butenylamine (II), must also possess the R-configuration. Further, the (+)-I used in the sequence of reactions leading to (+)-III was 87% resolved, and the observed specific rotation of $[\alpha]^{26}D$ −16.8° in 50% ethanol (*c* 4.2) for (−)-IV prepared from (+)-I was 81% of the specific rotation calculated for optically pure (−)-IV. This agreement indicates that less than 7% racemization accompanies the reactions used for the preparation of II, III, and IV.

It is of interest that the specific rotation of $[\alpha]^{26}D$ −25.0 ± 0.4° calculated by us for optically pure (−)-2-chloro-1-butanol (VI) is in fair agreement with the value of $[\alpha]^{25}D$ −23.9° calculated by Freudenberg and Lwowski.[10] For the purpose of these calculations, we assumed that conversion of VI to 2-butanol occurs without racemization, and Freudenberg and Lwowski assumed that the specific rotation of optically pure 2-chlorobutanoic acid (V) is $[\alpha]^{25}D$ −17.5° and that reduction of V with lithium aluminum hydride at 0° occurs without racemization. However, it must be noted that whereas the refractive indices observed by us for (−)-V and (−)-VI are in excellent agreement with values reported for (±)-V[13] and (±)-VI,[14] they are in only fair agreement with the values reported for (−)-V and (−)-VI.[10]

Experimental[15]

(+)-1-Amino-3-buten-2-ol (I).—The filtrates remaining[8] after the fractional crystallization of the (+)-camphor-10-sulfonate salt of (−)-I were concentrated to dryness with a rotary film evaporator. From the residue was obtained[8] 72.3 g. [68% based on the camphor-10-sulfonate salt] of (+)-enriched I, which had a boiling point of 78–79° (10 mm.); lit.,[12] b.p. 72° (8 mm.). A solution of 72.0 g. (0.827 mole) of (+)-enriched I was added to a cold solution of 192 g. (0.827 mole) of (−)-enriched camphor-10-sulfonic acid[16] dissolved in 300 ml. of absolute ethanol. To this solution was added 1.3 l. of anhydrous ethyl acetate, and the resulting solution was allowed to stand at room temperature for 24 hr. The white crystalline solid that separated was collected by suction filtration and washed with 100 ml. of ethyl acetate. It had a melting point of 141–143°. The salt was recrystallized four times from absolute ethyl acetate–absolute ethanol to yield 130.5 g. [49% based on (+)-enriched I] of (+)-1-amino-3-buten-2-ol-(−)-camphor-10-sulfonate, which had a melting point of 146.5–148.5°; lit.,[12] m.p. 148.5–150°.

(+)-Enriched I (27.6 g., 78%), with a boiling point of 84–85° (18 mm.), was regenerated from 130 g. of the sulfonate salt with potassium hydroxide. The material had a specific rotation of $[\alpha]^{30}D$ 25.3° (0.196 g./5 ml. of absolute ethanol). As optically pure (−)-I has a specific rotation of $[\alpha]^{30}D$ −29.0° (0.210 g./5 ml. of absolute ethanol),[8] the (+)-I obtained was 87% optically pure.

(+)-N-(2-Bromoallyl)-2-hydroxy-3-butenylamine (II).—A solution of 31.0 g. (0.155 mole) of 2,3-dibromopropene in 50 ml. of absolute ethanol was added dropwise to a cold (0°), mechanically stirred solution of 27 g. (0.31 mole) of (+)-I in 100 ml. of absolute ethanol. When the addition was complete, the reaction mixture was allowed to warm to room temperature and after 6 hr. was heated at reflux for 3 hr. The reaction mixture was worked up in essentially the same manner as described in the preparation of (−)-II.[3] (+)-II (23.1 g., 72%) was collected at 108–109° (1 mm.). The product had $n^{28}D$ 1.5130, $[\alpha]^{30}D$ 6.0° (0.368 g./5 ml. of absolute ethanol).

Anal. Calcd. for $C_7H_{12}NOBr$: C, 40.80; H, 5.87; N, 6.80; Br, 38.78. Found: C, 40.77; H, 5.81; N, 6.74; Br, 38.58.

Optically pure (−)-II has m.p. 34–36°, $[\alpha]^{23}D$ −6.2° (0.263 g./10 ml. of absolute ethanol), and not $[\alpha]^{23}D$ −3.5° as reported earlier.[3]

(+)-1-(2-Methylene-1-aziridinyl)-3-buten-2-ol (III).—Compound (+)-II (20.6 g., 0.10 mole)was treated with 9.75 g. (0.25 mole) of sodium amide in essentially the same manner as described in the preparation of (−)-III.[3] The product from the reaction was distilled under nitrogen through a semimicro Vigreux column, and four fractions were taken. The first three fractions (5.4 g., 43%) were collected at 68–71° (2 mm.). They possessed identical infrared spectra and refractive indices ($n^{25}D$ 1.4871), and the center fraction had $[\alpha]^{30}D$ 27.7° (0.247 g./5 ml. of absolute ethanol); lit.,[3] $[\alpha]^{20}D$ −30.5° (0.837 g./20 ml. of absolute ethanol) for optically pure (−)-III. The fourth fraction (4.7 g., 27%) was collected at 75–95° (2 mm.), with a sizeable fraction distilling at 94–95° (2 mm.), $n^{25}D$ 1.4873. Examination of the infrared spectrum of the fourth fraction indicated that it contained about two thirds of (+)-III and one third 1-(2-propynylamino)-3-buten-2-ol.[3]

(±)-2-Chlorobutanoic Acid (V).[9]—To a well stirred solution of 528 g. (6.0 moles) of butyric acid and 10 ml. of dimethylformamide at 80–85° was added dropwise 1215 g. (9.0 moles) of sulfuryl chloride in 6 hr. The resulting yellow solution was held at 90–95° for 2 hr. and distilled through a 600 × 8 mm. Poddielniak column fitted with a total reflux head. The weights, boiling points, and refractive indices of the fractions are given below. Only the third fraction was used in subsequent work. The reported refractive index for (±)-V is $n^{20}D$ 1.4411.[13]

Fraction	Weight, g.	B.p., °C.	(Mm.)	$n^{23}D$
1	117	107–111	(28)	1.4374
2	34	116–119	(32–35.5)	1.4389
3	153	122–123.5	(34)	1.4398
4	57	114.5–115	(18)	1.4438

(−)-2-Chlorobutanoic Acid (V).—The salt (m.p. 148.5–150°) obtained from evaporation of a solution prepared from 353 g. (1.2 moles) of cinchonidine (Fluka AG., Buchs, SG, Switzerland), 147 g. (1.2 moles) of (±)-V, and 300 ml. of methanol was suspended in 1500 ml. of boiling acetone and enough methanol (*ca.* 100 ml.) was added slowly to give complete solution. The solution was allowed to cool to room temperature and stand for 6 hr. The white crystals that separated were collected, and after four additional recrystallizations from acetone–methanol, they weighed 370 g. and had a melting point of 149.5–152°. This material was dissolved in 200 ml. of methanol, and the solution was allowed to stand at 0° for 2 weeks. The solid that separated weighed 107 g. (21%) and melted at 153.5–154.5°. To a mixture of 400 g. of crushed ice and 170 g. of 60% perchloric acid covered with 150 ml. of ether was added 107 g. (1.26 moles) of the above cinchonidine salt. The mixture was shaken vigorously, and after about 10 min., all of the cinchonidine salt had disappeared. The ether phase was separated, and the aqueous phase was extracted three times with 100-ml. portions of ether. The ether extracts were combined, washed twice with 20-ml. portions of water, and dried over magnesium sulfate. The ether was removed by distillation at atmospheric pressure, and distillation of the residual oil yielded 29.3 g. (93%) of (−)-2-chlorobutanoic acid, b.p. 93–94° (9 mm.), $n^{26}D$ 1.4377, $[\alpha]^{25}D$ −9.1° (0.374 g./5 ml. of chloroform); lit.,[10] b.p. 98.5° (14 mm.), $n^{25}D$ 1.4414, $[\alpha]^{25}D$ 17.2° (neat) for (+)-V.

(−)-2-Chloro-1-butanol (VI).—Following the procedure described by Freudenberg and Lwowski,[10] 29 g. (0.24 mole) of (−)-

(12) M. G. Ettlinger, *J. Am. Chem. Soc.*, **72**, 4792 (1950). Our results allow the assignment of the s-configuration to (−)-5-vinyl-2-thioöxazolidone, the antithyroid factor isolated from numerous plants of the *Brassicaceae* and synthesized by Ettlinger.

(13) E. Schjanberg, *Z. physik. Chem.* (Leipzig), [A] **172**, 197 (1935).

(14) H. M. Waddle and H. Adkins, *J. Am. Chem. Soc.*, **61**, 3361 (1939).

(15) All melting points and boiling points are uncorrected. Infrared spectra were obtained with a Beckman IR-4 spectrophotometer. Rotations were taken with a Rudolph and Sons Model No. 251 polarimeter in 2-dm. tubes. Microanalyses were performed by Mr. V. H. Tashinian, Berkeley, Calif.

(16) The (−)-camphor-10-sulfonic acid, which had a specific rotation of $[\alpha]^{31}D$ −24.6° (0.562 g./50 ml. of water), was obtained using the procedure of H. Burgess and C. S. Gibson, *J. Soc. Chem. Ind.*, **44**, 496T (1925). They reported a specific rotation of $[\alpha]^{20}D$ −28.15° in water for optically pure (−)-camphor-10-sulfonic acid, which indicates that our material was more than 87% optically pure.

V was reduced with 14.5 g. (0.38 mole) of lithium aluminum hydride to yield 20.5 g. (79%) of (−)-VI, which had b.p. 58–59° (22 mm.), $n^{25}D$ 1.4410, $[\alpha]^{26}D$ −12.0° (0.248 g./5 ml. of benzene), $[\alpha]^{26}D$ −11.6° (neat); lit.,[10] b.p. 53–54° (15 mm.), $n^{25}D$ 1.4442, $[\alpha]^{25}D$ +23.9° (neat), calculated for optically pure (+)-VI; lit.,[14] $n^{25}D$ 1.4410 for (±)-VI.

(+)-2-Ethyloxirane (VII).—To a vigorously stirred solution of 22.2 g. (0.56 mole) of sodium hydroxide and 40 ml. of water at 100° was added dropwise 20.0 g. (0.184 mole) of (−)-VI. The distillate that resulted was collected over a few pellets of sodium hydroxide and then distilled from fresh sodium hydroxide pellets. (+)-2-Ethyloxirane (10.1 g., 76%) was collected at 62–63°. It had $n^{25}D$ 1.3813, $[\alpha]^{30}D$ +10.7° (0.325 g./5 ml. of benzene) and an infrared spectrum superimposable on that of redistilled (±)-VII obtained from Farchan Laboratories.[17]

(+)-s-Butanol.[18]—2-Ethyloxirane (3.6 g., 0.05 mole) dissolved in 15 ml. of anhydrous ether was added dropwise to a well stirred mixture of 1.1 g. (0.05 mole) of lithium borohydride[19] in 30 ml. of ether. When the addition was complete, the mixture was heated at reflux for 2 hr. and allowed to stand overnight at room temperature. Water (10 ml.) was added slowly to the reaction mixture, and the phases were separated. The aqueous phase was saturated with sodium chloride and extracted twice with 15-ml. portions of ether. The ether extracts were combined and dried over potassium carbonate. Distillation yielded 2.70 g. (75%) of a fraction boiling at 88–91°. This fraction was dried over calcium oxide and then distilled to yield 1.6 g. of s-(+)-2-butanol, b.p. 97–99°, $n^{26}D$ 1.3922, d_4^{25} 0.8033, $[\alpha]^{26}D$ +6.3° (neat); lit.,[11] b.p. 99°, $n^{20}D$ 1.3954, d_4^{27} 0.8025, $[\alpha]^{27}D$ 13.52° (neat).

(±)-1-Propylamino-2-butanol Acid Oxalate (IV). A. From 2-Ethyloxirane (VII) and *n*-Propylamine.—(±)-2-Ethyloxirane (21.6 g., 0.30 mole) was added dropwise to a stirred, ice-cold solution of 35.4 g. (0.60 mole) of *n*-propylamine and 5.4 ml. of water. The solution was allowed to stand overnight at room temperature. The excess *n*-propylamine and water were removed by distillation, and the residual oil was distilled to yield 28.5 g. (73%) of 1-propylamino-2-butanol, b.p. 72–74° (7 mm.), $n^{25}D$ 1.4390.

Anal. Calcd. for $C_7H_{17}NO$: C, 64.07; H, 13.06; N, 10.68. Found: C, 64.13; H, 13.12; N, 10.54.

(17) Levene and Walti[3] reported the preparation of (+)-VII, which had a specific rotation of $[\alpha]^{26}D$ +8.75° (neat), from (−)-1-bromo-2-butanol.

(18) Reduction of (±)-VII with lithium borohydride was reported by R. Fuchs and C. A. VanderWerf, *J. Am. Chem. Soc.*, **76**, 1631 (1954).

(19) The lithium borohydride was prepared as described by H. I. Schlesinger, H. C. Brown, and E. K. Hyde, *ibid.*, **75**, 209 (1953).

The amino alcohol (1.3 g., 0.010 mole) was dissolved in 5 ml. of absolute ethanol, and the resulting solution was added to a solution of 1.26 g. (0.010 mole) of oxalic acid dihydrate in 10 ml. of absolute ethanol. The precipitate that formed was dissolved by warming the mixture. The white plates that separated when the solution was allowed to stand at room temperature for 3 hr. weighed 1.4 g. (64%) and melted at 159–160°. After one recrystallization from absolute ethanol, the acid oxalate melted at 159.5–160.0°.

Anal. Calcd. for $C_9H_{19}NO_5$: C, 48.86; H, 8.65; N, 6.33. Found: C, 49.07; H, 8.49; N, 6.27.

B. From III.—A mixture of 2.5 g. (0.020 mole) of 93% (±)-1-(2-methylene-1-aziridinyl)-3-buten-2-ol (III) and 7% (±)-2-(2-methylene-1-aziridinyl)-3-buten-1-ol[3] in 100 ml. of absolute ethanol to which had been added 0.20 g. of platinic oxide was shaken under 30–35 p.s.i. of hydrogen for 5 hr. The reduction appeared to be complete within 1 hr. The catalyst was removed by filtration, and 2.5 g. (0.020 mole) of oxalic acid dihydrate was dissolved in the filtrate by warming. The solution was concentrated to a volume of 25 ml. and cooled. The first crop of crystals that separated (2.3. g., 52%) melted at 132–137°. After three recrystallizations from ethanol, the acid oxalate (1.7 g.) melted at 157–158°, and the melting point was not depressed by the addition of (±)-IV prepared from (±)-2-ethyloxirane (VII) and *n*-propylamine.

Anal. Calcd. for $C_9H_{19}NO_5$: C, 48.86; H, 8.65; N, 6.33. Found: C, 48.58; H, 8.25; N, 6.10.

(−)-IV. A. From (+)-VII and *n*-Propylamine.—Using the same procedure described for the preparation of (±)-IV from (±)-VII, 3.6 g. (0.050 mole) of (+)-2-ethyloxirane and 5.9 g. (0.10 mole) of *n*-propylamine, in the presence of 1 ml. of water, were converted to 3.3 g. (50%) of (−)-1-propylamino-2-butanol, b.p. 74–76° (9 mm.), $n^{25}D$ 1.4388. The first crop of acid oxalate melted at 157.5–158.5°. After one recrystallization from absolute ethanol, the acid oxalate melted at 158.5–159.0° and had a specific rotation of $[\alpha]^{26}D$ −9.6° (0.220 g./5 ml. of 50% aqueous ethanol by weight).

B. From (+)-III and (+)-1-(2-Propynylamino)-3-buten-2-ol.—The fourth fraction (4.6 g. 0.037 mole) was hydrogenated as described for (±)-III. The first crop of acid oxalate (4.2 g., 51%) melted at 157–158°. After one recrystallization from absolute ethanol, the acid oxalate had a melting point of 158.5–159.0° and a specific rotation of $[\alpha]^{26}D$ −16.8° (0.211 g./5 ml. of 50% aqueous ethanol by weight). Admixture of the acid oxalate with (−)-IV obtained from (+)-VII did not depress its melting point.

Preparation of a Glycoside of 2-Amino-2,3-dideoxy-3-mercaptoaltrose[1]

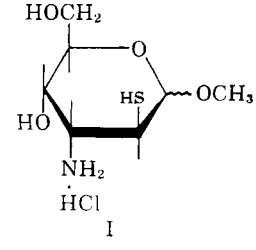
LEON GOODMAN AND JAMES E. CHRISTENSEN

Life Sciences Research, Stanford Research Institute, Menlo Park, California

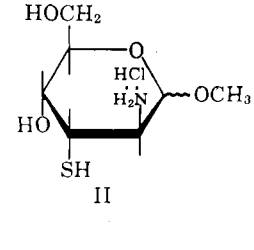
Received August 13, 1962

The synthesis of methyl 2-amino-2,3-dideoxy-3-mercapto-D-altropyranoside hydrochloride (II) is described.

An earlier paper in this series[2] described the synthesis of methyl 3-amino-2,3-dideoxy-2-mercapto-D-altropyranoside hydrochloride (I), prepared as a possible antiradiation drug. This synthesis utilized the conversion of a benzylthio group to the mercaptan function with sodium in liquid ammonia and required that the sugar blocking group be changed from the labile benzylidene to the stable (to sodium–liquid ammonia) ethylidene group prior to the debenzylation in order to permit



I



II

an easy isolation of the derived β-mercaptoamine. In order to circumvent this awkward deblocking-reblocking sequence, it was desirable to use an appropriate ethylidene-blocked sugar as the starting material. This manuscript describes the conversion of methyl 2,3-anhydro-4,6-O-ethylidene-α-D-mannopyranoside (IX) to the title compound (II).

(1) The work reported in this paper (no. 4 of the series) was carried out under the joint auspices of the Office of the Surgeon General, Medical Research and Development Command, under Contract no. DA-49-193-MD-2068 and of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, under Contract no. SA-43-ph-1892. The opinions expressed in this article are those of the authors and not necessarily those of either sponsoring agency.

(2) J. E. Christensen and L. Goodman, *J. Am. Chem. Soc.*, **83**, 3827 (1961).