TABLE VI

Reaction	α	T', °K.	T, °K.	2δ, kcal./mole	Obsd. range of $\Delta H^{\ddagger}$, kcal./mole
Decompn. of phenylazotriphenylmethane[8]	0.61	348.0	298.3	11.8	4.5
Decarboxyln. of 3-substd. mesitoic acids in 83% H_2SO_4[14]	.18	344.8	333.8	15.1	6.0
Decarboxyln. of picolinic acid in neut. solvents[15]	.052	446.0	437.7	9.7	9.1
Decarboxyln. of picolinic acid in basic solvents[15]	.064	455.2	447.2	12.9	12.3
Solvolysis in 90% aq. acetone of substd. t-cumyl chlorides[16]	.10	328.2	308.2	4.0	3.5
Dehydrn. of β-hydroxy ketones in 1 M H_2SO_4[17]	.072	318.2	298.2	2.7	2.7
Rearrang. of allyl p-substd. phenyl ethers[18]	.092	473.0	433.0	3.8	3.8
Acid-catalyzed rearrang. of benzhydryl azides[19]	.15	318.2	298.2	5.7	3.3

reproducibility. It is found in such cases, however, that equating the observed range of $\Delta H^{\ddagger}$ values with 2δ leads to a calculated α which is quite reasonable for the experimental technique employed.

Table VI lists some examples for which published data provide some estimate of reproducibility. This list was limited to cases which use $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ rather than Arrhenius or collision theory parameters. It was assumed along with the original authors in each case that the proper kinetic order was observed and that $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were independent of temperature. Each value of α tabulated is equal to or less than the maximum fractional lack of reproducibility which can be computed from the published data. It should be emphasized that this is not a true maximum error, but is necessarily less than the true α. The values of T and T' listed are the temperature extremes employed for that member of the series which yielded the listed α. In each case the value of 2δ is at least as great as the observed range of $\Delta H^{\ddagger}$, and this variation can thus reasonably be attributed to experimental error. These studies were chosen only as examples of the difficulty involved in obtaining a clearly valid relationship between enthalpy and entropy of activation and their selection as examples implies nothing beyond this fact.

In the present work, the effect of non-random errors was minimized by making very precise measurements over a small temperature range in solvents of low vapor pressure. Reproducibility considerations alone suggest a value of less than 0.008 for α. Using this value of α in eq. 7 gives a value for 2δ of 1.38 kcal./mole. This is only a little less than the 1.78 kcal./mole range of observed $\Delta H^{\ddagger}$ values, and non-random errors have not been considered.

On a purely statistical basis, the probable error in rate constants observed in individual runs translates to a probable error of about 0.06 kcal./mole in $\Delta H^{\ddagger}$. As previously described, an evaluation based on this number would lead to the conclusion that the observed linear relationship between enthalpy and entropy was valid, and such an evaluation would be improper.

From considerations based on maximum possible error, it must be concluded that the major part of the observed linear relationship between enthalpy and entropy of activation is very likely the result of experimental error, not only in the present case but in most, if not all, previously published examples of such a relationship. This does not deny the possibility of the existence of such relationships, but rather implies that the positive demonstration of such a phenomenon is extremely difficult due to the inherent nature and magnitude of the experimental errors.

(14) F. M. Beringer and S. Sands, J. Am. Chem. Soc., 75, 3319 (1953).

(15) N. H. Cantwell and E. V. Brown. ibid., 75, 4466 (1953).

(16) Y. Okamoto, T. Inukai and H. C. Brown, ibid., 80, 4969 (1958).

(17) D. S. Noyce and W. L. Reed, ibid., 80, 5539 (1958).

(18) W. N. White, D. Gwynn, R. Schlitt, C. Girard and W. Fife, ibid., 80, 3271 (1958).

(19) C. H. Gudmundsen and W. E. McEwen, ibid., 79, 329 (1957).

Potential Antiradiation Drugs. II. β-Aminomercaptans Derived from D-Allose[1,2]

BY LEON GOODMAN AND JAMES E. CHRISTENSEN

A complex neighboring group approach provided a successful synthesis of methyl 3-amino-2,3-dideoxy-2-mercapto-α-D-allopyranoside hydrochloride (IX). The blocked 3-aminoaltroside (II) afforded, in two steps, the crystalline dithiocarbamoyl mesylate (VI) which, heated in pyridine, cyclized to the thiazoline V, that was reduced to the thiazolidine IV. Compound IV was deblocked and hydrolyzed, via the crystalline mercuric salt VIII, to the aminomercapto glycoside IX.

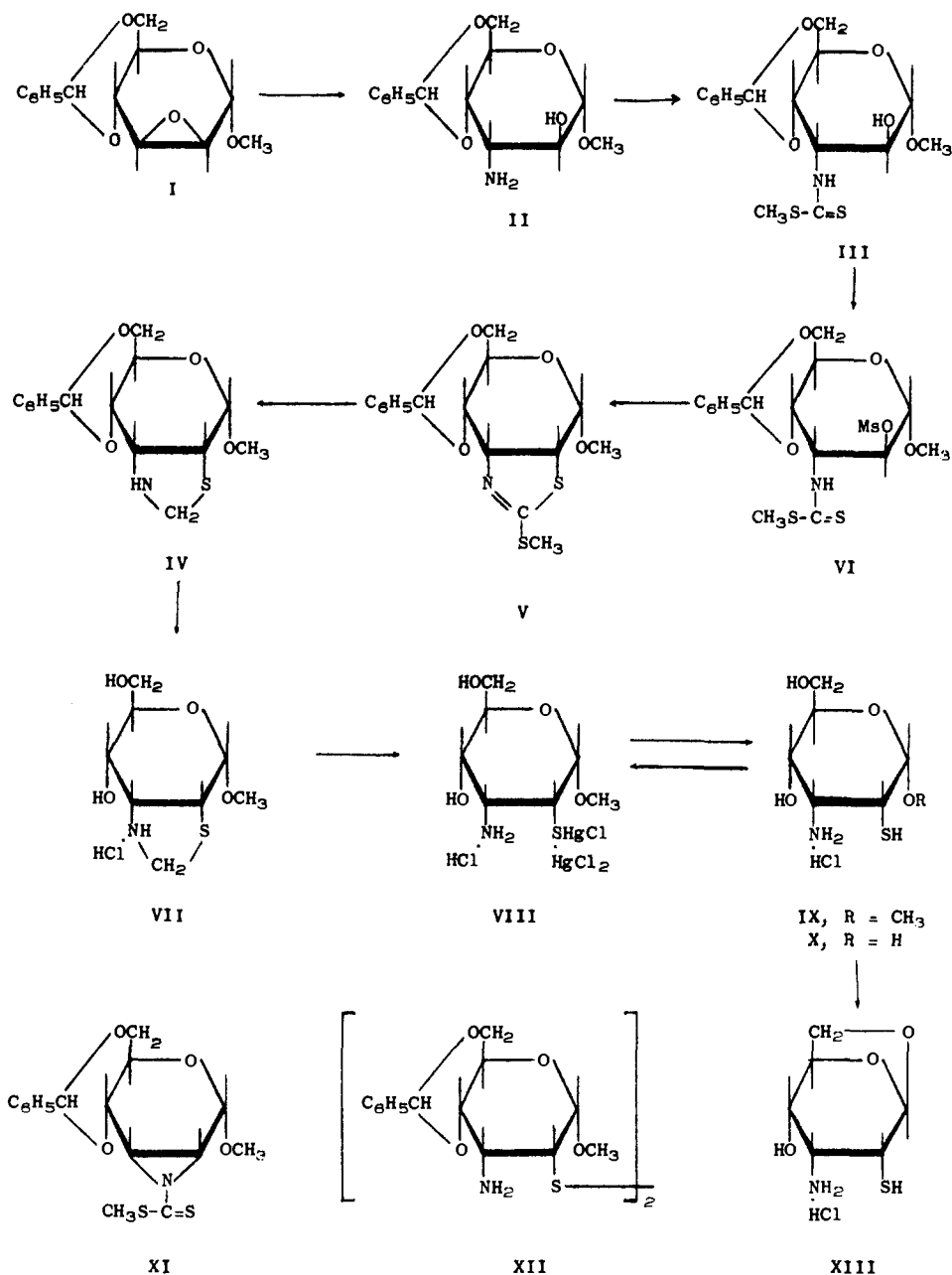A number of chemical compounds protect living systems against the degradation caused by ionizing

radiation.[3] Cysteine was one of the earliest of such compounds reported.[4] This amino acid possesses a combination of thiol and amine groups

(2) For a preliminary announcement of a part of this work, see Paper I of this series, J. E. Christensen and L. Goodman. J. Am. Chem. Soc., 82, 4738 (1960).

(3) For a recent review of the subject which contains an excellent bibliography, see D. R. Kalkwarf, Nucleonics, 18, No. 5, 76 (1960).

(4) H. M. Patt, E. B. Tyree, R. L. Strauhe and D. E. Smith, Science, 110, 213 (1949).

OCH₂ ... C₆H₅CH ... O ... OCH₃

I

C₆H₅CH ... OCH₂ ... O ... HO ... OCH₃ ... NH₂

II

C₆H₅CH ... OCH₂ ... O ... HO ... OCH₃ ... NH ... CH₃S–C=S

III

C₆H₅CH ... OCH₂ ... O ... OCH₃ ... HN ... CH₂

IV

C₆H₅CH ... OCH₂ ... O ... OCH₃ ... N=C ... S ... SCH₃

V

C₆H₅CH ... OCH₂ ... O ... MsO ... OCH₃ ... NH ... CH₃S–C=S

VI

HOCH₂ ... O ... HO ... OCH₃ ... NH ... S ... HCl ... CH₂

VII

HOCH₂ ... O ... HO ... OCH₃ ... NH₂ ... SHgCl ... HCl ... HgCl₂

VIII

HOCH₂ ... O ... HO ... OR ... NH₂ ... SH ... HCl

IX, R = CH₃
X, R = H

C₆H₅CH ... OCH₂ ... O ... OCH₃ ... N ... CH₃S–C=S

XI

[C₆H₅CH ... OCH₂ ... O ... OCH₃ ... NH₂ ... S]₂

XII

CH₂—O ... O ... HO ... NH₂ ... SH ... HCl

XIII

which is duplicated in cysteamine (β-mercaptoethylamine),[5,6] one of the most extensively studied and one of the most effective of the radiation protective compounds. Although cysteamine is a compound of relatively low toxicity, its absolute toxicity restricts the amount that can be used to afford radiation protection. The incorporation of the β-mercaptoethylamine moiety in a sugar or in other physiologically important molecules might result in a compound with a better ratio of protective effect to toxicity than that of cysteamine. This article is concerned with the synthesis of a compound of this class, a β-aminomercaptan derived from D-allose.

There is ample precedent in the literature for the conversion of a trans-β-aminoalcohol system in a sugar to the corresponding cis-β-aminohydroxy sugar by way of neighboring group participation.[7] The preparation of a cis-β-aminomercapto sugar could be similarly visualized as proceeding from a trans-β-aminohydroxy sugar via a sulfur-containing "complex neighboring group."[8] This approach has been employed successfully by Crawhall and Elliott in the conversion of certain hydroxyamino acids to mercaptoamino acids[9] and was successful in the preparation of the cis-aminomercapto sugar IX described here.

(5) Z. M. Bacq in "Proceedings of the International Conference on the Peaceful Uses of Atomic Energy," Vol. II, United Nations, New York, N. Y., 1956, p. 332.

(6) L. Eldjarn, A. Pihl and B. Shapiro, in ref. 5, p. 335.

(7) (a) B. R. Baker and R. E. Schaub, J. Org. Chem., 19, 646 (1954); (b) B. R. Baker, R. E. Schaub and J. H. Williams, J. Am. Chem. Soc., 77, 7 (1955); (c) B. R. Baker and R. E. Schaub, ibid., 77, 2396 (1955).

(8) S. Winstein and R. Boschan, ibid., 72, 4669 (1950).

(9) J. C. Crawhall and D. F. Elliott, J. Chem. Soc., 2071 (1951).

The anhydromannoside I[10] was opened with ammonia to give the 3-aminoaltroside II.[11] The almost exclusive opening of I at C.3 to give the *trans*-diaxial product II, in accordance with the Fürst–Plattner rule,[12] has been adequately demonstrated.[11] Reaction of the amine II with carbon disulfide and iodomethane in pyridine containing triethylamine[9] afforded a quantitative yield of the crude, crystalline dithiocarbamate III. The reaction of III with thionyl chloride, the reagent used by Crawhall and Elliott[9] in the work that was cited above, probably yielded a cyclized product but partial loss of the benzylidene blocking group also occurred, resulting in a material that could not be purified. The mesylate VI of III, however, was a stable crystalline compound that could be prepared in excellent yield by conventional sulfonylation procedures. Compound VI showed two modes of ring closure. The use of sodium methoxide resulted in the formation of the thioacylated ethylenimine XI[13] by way of nitrogen participation.[2] When the mesylate VI was heated at reflux in pyridine solution, the crystalline thiazoline V was isolated in reasonable yield. The thiazoline V had a strong C=N infrared band at 6.4 μ which distinguished it from isomeric XI. This sharp distinction in the course of the reaction of VI with the two base treatments was surprising, since, logically, five-membered ring formation would be expected to be favored over three-membered ring formation.

The direct acid hydrolysis of 2-alkylmercaptothiazolines such as V has been shown to proceed only to the dithiocarbonate which results from cleavage of the C=N bond,[14] so that compound V did not appear to represent a direct precursor of the desired *cis*-aminomercaptan IX. Therefore, methods were sought to reduce V to a thiazolidine which should be convertible to the aminomercaptan IX by mild hydrolytic procedures. Reaction of V with lithium aluminum hydride in refluxing tetrahydrofuran gave back only starting material. This resistance to reduction of V may be attributable to the presence of the 2-methylthio group, since the lithium aluminum hydride reductions of some Δ^3-thiazolines and of one 2-alkyl-Δ^2-thiazoline were reported recently to give good yields of N - alkyl - β - mercaptoamines.[15] Sodium borohydride also failed to reduce V, but the combination of sodium borohydride and aluminum chloride[16] gave a product which had no C=N absorption in the infrared: no discrete thiazolidine, however, could be isolated from this product. Aluminum amalgam has been used to convert 2-alkylthio-Δ^2-thiazolines, analogous to V, to the cor-

responding 2-noralkylthiothiazolidines.[17,18] This reduction applied to V afforded a good yield of the crystalline thiazolidine IV. When the reaction time and temperature were increased, the yield of IV was lower and the disulfide XII of the aminomercaptan derived from IV was isolated as a byproduct. Refluxing 1% methanolic hydrogen chloride removed the benzylidene blocking group of IV, giving a high yield of the crystalline thiazolidine salt VII whose recrystallization behavior and melting point behavior suggested that little, if any, anomerization had occurred in the deblocking.

Treatment of VII with hot aqueous mercuric chloride gave formaldehyde as a volatile product plus a high yield of a sharply melting crystalline solid with elemental analyses compatible with structure VIII; the sharp melting point of VIII is an indication of anomeric purity in VIII, and, therefore, also in VII. The infrared spectrum of the mercuric salt designated as VIII suggested that the amine group in the molecule was not protonated; structure VIII must be regarded as tentative. The decomposition of the mercaptide salt VIII with hydrogen sulfide gave an excellent yield of the *cis*-β-aminomercapto glycoside (IX) as a hygroscopic solid, again probably the quite pure α-anomer as shown by the large positive optical rotation. When IX was heated with 6 N hydrochloric acid in an effort to prepare the free sugar X, it was converted to a crystalline solid which is probably the 1,6-anhydride XIII. The large negative rotation of the solid is in accord with its formulation as XIII.[19] When the hydrolysis was conducted for a shorter time there was evidence from microanalytical data that a mixture of X and XIII was formed, but it could not be resolved by paper chromatography nor by separation *via* derivatives. The situation encountered here in the hydrolysis of IX seems to be similar to that encountered by Jeanloz and Jeanloz[21] in the synthesis of 3-amino-3-deoxy-D-gulose where both the free sugar and the 1,6-anhydride were formed in the hydrolysis of a glycoside. The factors which determine the equilibrium between free hexoses and their 1,6-anhydrides have been discussed in a recent review.[22]

Experimental[23]

Methyl 4,6-O-Benzylidene-3-deoxy-3-(dithiocarbomethoxy)-amino-α-D-altropyranoside (III).—To a chilled (0–5°), stirred solution of 7.00 g. (24.9 mmoles) of the 3-aminoaltroside II[11] in 35 ml. of dry pyridine was added 3.46 ml. (24.9 mmoles) of triethylamine, then 1.65 ml. (27.4 mmoles) of carbon disulfide, the temperature being maintained below 10°. The solution was stirred at ice-bath temperature for 1 hour, then 1.58 ml. (25.4 mmoles) of iodomethane was added at such a rate that the temperature

(10) H. R. Bolliger and D. A. Prins, *Helv. Chim. Acta*, **28**, 465 (1945).

(11) W. H. Myers and G. J. Robertson, *J. Am. Chem. Soc.*, **65**, 8 (1943).

(12) A. Fürst and Pl. A. Plattner, Abstracts of Papers, 12th International Congress of Pure and Applied Chemistry, New York, 1951, p. 405.

(13) The transformations of XI will be discussed in detail in a later paper.

(14) J. C. Crawhall and D. F. Elliott, *J. Chem. Soc.*, 3094 (1952).

(15) M. Thiel, F. Asinger, K. Häussler and T. Körner, *Ann.*, **622**, 107 (1959).

(16) H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **77**, 3164 (1955).

(17) A. H. Cook and J. R. A. Pollock, *J. Chem. Soc.*, 1898 (1950).

(18) F. Winternitz, M. Mousseron and R. Dennilauler, *Bull. soc. chim. France*, 1228 (1956).

(19) In the analogous case of the conversion of methyl 3-amino-3-deoxy-α-D-altropyranoside to 3-amino-1,6-anhydro-3-deoxy-α-D-altropyranoside the specific rotations (measured in water) of the two compounds were +109.9° and —171.9°, respectively.[20]

(20) L. F. Wiggins, *J. Chem. Soc.*, **18** (1947).

(21) R. W. Jeanloz and D. A. Jeanloz, *J. Org. Chem.*, **26**, 537 (1961).

(22) R. J. Ferrier and W. G. Overend, *Quart. Revs. (London)*, **13**, 265 (1959).

(23) Melting points are uncorrected and were obtained with the Fisher–Johns apparatus. Optical rotations were measured with a Standard polarimeter model D attachment to the Beckman DU spectrophotometer calibrated with standard sucrose solutions.

remained below 10°. After being stirred for 30 minutes more at 0-5°, the mixture was stored for 15 hours at 5°, then poured, with stirring, into 200 ml. of ice-water. The aqueous mixture was extracted with three 50-ml. portions of dichloromethane, the combined extracts were washed with 70 ml. of saturated aqueous sodium bicarbonate and two 70-ml. portions of water, then dried over magnesium sulfate. Evaporation *in vacuo* yielded a residue which was freed from pyridine by dissolving in toluene and re-evaporating *in vacuo*. The white solid, 9.39 g. (102%), was recrystallized from 120 ml. of ethyl acetate and 100 ml. of petroleum ether (30-60°) to yield 7.50 g. (81%) of white crystals, m.p. 179-188°. Three more recrystallizations of a portion (0.50 g.) of this material afforded 0.35 g. of the analytical sample, m.p. 187-190°, $[\alpha]^{26}D$ +45° (1% in chloroform); $\lambda_{max(\mu)}^{Nujol}$ 3.01 and 3.03 (OH, NH), 6.68 (NH), 9.04 (C=S), 13.18 and 14.12 (monosubstituted benzene).

Anal. Calcd. for $C_{16}H_{21}NO_5S_2$: C, 51.8; H, 5.70; S, 17.3. Found: C, 52.2; H, 5.57; S, 17.2.

Methyl 4,6-O-Benzylidene-3-deoxy-3-(dithiocarbomethoxy)-amino-2-O-methylsulfonyl-α-D-altropyranoside (VI).—To a chilled (0°), stirred solution of 4.00 g. (10.8 mmoles) of the thioacylated amine III in 55 ml. of reagent pyridine was added dropwise 1.40 ml. (18.1 mmoles) of methanesulfonyl chloride. The solution was stirred at ice-bath temperature for 1 hour, then left overnight at room temperature. Pouring the reaction mixture into 200 ml. of ice-water with stirring caused the precipitation of a white semisolid, which was collected and dissolved in 120 ml. of chloroform. The chloroform solution was washed with three 40-ml. portions of water, dried over magnesium sulfate and evaporated *in vacuo*. The solid residue was freed of pyridine by dissolving in toluene and re-evaporating *in vacuo*, leaving 4.65 g. (96%) of a pale yellow solid. This was recrystallized from 100 ml. of benzene and 50 ml. of petroleum ether (30-60°) to give 3.65 g. (75%) of product, m.p. 170-172°. The analytical sample was obtained by two more recrystallizations and had m.p. 171-173°, $[\alpha]^{26}D$ +42° (1% in chloroform); $\lambda_{max(\mu)}^{Nujol}$ 3.03 and 6.53 (NH), 8.44 (—OSO_2—), 8.98 (C=S), 13.34 and 14.20 (monosubstituted benzene).

Anal. Calcd. for $C_{17}H_{23}NO_7S_3$: C, 45.4; H, 5.16; S, 21.4. Found: C, 46.2; H, 5.29; S, 21.2.

4',6'-O-Benzylidene-1'-O-methyl-2-(methylthio)-α-D-allopyrano[3',2':4,5]-2-thiazoline (V).—A solution of 1.00 g. (2.22 mmoles) of the mesylate VI in 10 ml. of reagent pyridine was heated at reflux for 15 hours in a nitrogen atmosphere. The dark mixture was evaporated *in vacuo*, maintaining the bath temperature below 30°. The residue was extracted with two 10-ml. portions of warm (50°) benzene, leaving a residue of 0.35 g. (57%) of crystalline solid whose infrared spectrum indicated it to be pyridinium mesylate. The benzene solution was evaporated *in vacuo*, yielding 0.60 g. (76%) of a brown foam which crystallized on standing. Recrystallization from 5 ml. of isopropyl alcohol afforded 0.40 g. (51%) of solid, m.p. 132-134°, and a second recrystallization from 4 ml. of isopropyl alcohol gave the analytical sample, m.p. 134-136°, $[\alpha]^{26}D$ +160° (1% in chloroform); $\lambda_{max(\mu)}^{Nujol}$ 6.42 (C=N), 13.02 and 14.30 (monosubstituted benzene); there was no –OH or –NH absorption near 3.0 μ.

Anal. Calcd. for $C_{16}H_{19}NO_4S_2$: C, 54.4; H, 5.42; N, 3.96; S, 18.1. Found: C, 54.2; H, 5.33; N, 4.09; S, 18.0.

4',6'-O-Benzylidene-1'-O-methyl-α-D-allopyrano[3',2':4,5]thiazolidine (IV).—Aluminum foil (1.0 g.) was amalgamated according to the directions of Vogel[24] and to the aluminum amalgam was added 25 ml. of tetrahydrofuran and 0.500 g. (1.41 mmoles) of the thiazoline V. To this stirred mixture water (7 ml.) was added dropwise, resulting in a vigorous evolution of gas. The resulting mixture was stirred for 20 hours at 55° (bath temperature), then filtered through Celite. The filtrate was evaporated to dryness *in vacuo*, leaving 0.45 g. (103%) of a white foam which crystallized on standing. Recrystallization from 5 ml. of isopropyl alcohol afforded 0.29 g. (66%) of crystalline solid, m.p. 141-143°, and a second recrystallization from 3 ml. of isopropyl alcohol gave 0.25 g. of the analytical sample, m.p. 143-144°, $[\alpha]^{26}D$ +99°(1% in chloroform);

(24) A. I. Vogel, "Textbook of Practical Organic Chemistry," Longmans, Green and Co., Ltd., London, Eng., 1956, p. 198.

$\lambda_{max(\mu)}^{Nujol}$ 3.04 (NH), 13.03 and 14.22 (monosubstituted benzene); there was no C=N absorption near 6.4 μ.

Anal. Calcd. for $C_{16}H_{19}NO_4S$: C, 58.2; H, 6.19; N, 4.53; S, 10.4. Found: C, 58.2; H, 6.51; N, 4.53; S, 10.2.

When a larger quantity (6.76 g.) of the thiazoline V was reduced using the above procedure, except that the reaction mixture was heated at reflux for about 30 hours, there was isolated, after one recrystallization from isopropyl alcohol, 3.16 g. (53%) of product, m.p. 133-145°. The broad melting range probably resulted from the presence of a small amount of the blocked β-aminomercaptan derived from IV, since, after the crude product had stood about 1 day, a portion (0.40 g., m.p. 212-220° dec.) of the solid had become insoluble in hot isopropyl alcohol as a result of air oxidation to the disulfide XII. This high-melting solid was recrystallized twice from chloroform-petroleum ether (30-60°) to give the analytical sample of XII, m.p. 229-236° dec.; $\lambda_{max(\mu)}^{Nujol}$ 3.00 (NH_2, weak), 13.10, 13.22 and 14.33 (monosubstituted benzene).

Anal. Calcd. for $C_{28}H_{36}N_2O_8S_2$: C, 56.7; H, 6.11; N, 4.73; S, 10.8. Found: C, 57.0; H, 6.18; N, 4.85; S, 10.8.

1'-O-Methyl-α-D-allopyrano[3',2':4,5]thiazolidine Hydrochloride (VII).—A solution of 0.590 g. (1.91 mmoles) of the blocked thiazolidine IV in 20 ml. of 1% methanolic hydrogen chloride was heated at reflux for 1 hour, then evaporated *in vacuo*. The residual white foam was recrystallized by dissolving it in methanol and adding ether to the point of turbidity, affording 0.40 g. (82%) of white crystals, m.p. 174-179° dec. Two more recrystallizations from methanol-ether gave 0.32 g. of the analytical sample, m.p. 178-183° dec., $[\alpha]^{25}D$ +103° (1% in methanol); $\lambda_{max(\mu)}^{Nujol}$ 2.91 and 3.09 (OH), 3.75, 3.90, 4.12 and 6.31 (NH_2^+); there was essentially no phenyl absorption in the 13-15 μ region.

Anal. Calcd. for $C_3H_{16}ClNO_4S$: C, 37.3; H, 6.26; Cl, 13.8; S, 12.4. Found: C, 37.0; H, 6.37; Cl, 13.6; S, 12.5.

Mercuric Chloride Complex of Methyl 3-Amino-2-chloromercurithio-2,3-dideoxy-α-D-allopyranoside Hydrochloride (VIII). A. From the Thiazolidine VII.—To a solution of 0.09 g. (0.35 mmole) of the thiazolidine hydrochloride VII in 2 ml. of water was added dropwise a saturated aqueous solution of mercuric chloride until no more precipitate formed. The reaction mixture was heated on the steam-bath for 1 hour, during which time the precipitate dissolved and formaldehyde was evolved. The solution was allowed to cool slowly to room temperature, causing the formation of 0.20 g. (76%) of a white, crystalline precipitate, m.p. 193-196° dec. This was recrystallized from 3 ml. of water to afford 0.07 g. (27%) of the analytical sample, m.p. 199-201°; $\lambda_{max(\mu)}^{Nujol}$ 2.82, 2.87 and 3.16-3.20 (OH, NH_2), 6.35 (NH_2).

Anal. Calcd. for $C_7H_{15}Cl_4Hg_2NO_4S$: C, 11.2; H, 2.01; Cl, 18.9; N, 1.86; S, 4.26. Found: C, 11.4; H, 2.07; Cl, 18.1; N, 1.60, 1.80; S, 4.22.

B. From the Glycoside IX.—To a solution of 0.100 g. (0.407 mmole) of the glycoside hydrochloride IX (see below) in a few ml. of water was added 15 ml. of a saturated aqueous solution of mercuric chloride. The cloudy suspension was heated on the steam-bath until complete solution resulted, then was cooled, causing the precipitation of 0.11 g. (36%) of crystalline VIII, m.p. 196-197° dec., which had an infrared spectrum identical with that of the analytical sample (see above) and gave no mixed melting point depression with that material.

Methyl 3-Amino-2,3-dideoxy-2-mercapto-α-D-allopyranoside (IX).—The thiazolidine hydrochloride VII (1.00 g., 3.88 mmoles), was converted to 2.53 g. (87%) of the mercuric chloride complex VIII by the procedure described above. This solid VIII was suspended in 50 ml. of reagent methanol and the stirred suspension was treated with a rapid stream of hydrogen sulfide for 15-20 minutes. The mixture was filtered through Celite and the filtrate evaporated to dryness *in vacuo*, affording 0.82 g. (86%) of a hygroscopic, white solid. This was purified by dissolving the solid in methanol and precipitating by the addition of excess ether, yielding a gum which solidified on prolonged pumping in high vacuum. The solid gave a strong, positive nitroprusside test and in the infrared had $\lambda_{max(\mu)}^{Nujol}$ 3.0-3.3

(OH), 3.5–3.9 and 6.25–6.35 (NH_4^+), 3.9–4.0 (SH); these were broad bands and not well resolved; $[\alpha]^{25}D$ +103° (1% in methanol). On paper chromatography[25] in solvents A and B, the compound traveled as a single spot with R_{ad} 0.81 and 1.38, respectively.

Anal. Calcd. for $C_7H_{16}ClNO_4S$: C, 34.2; H, 6.56; Cl, 14.4; N, 5.70; S, 13.1. Found: C, 33.9; H, 6.66; Cl, 14.1; N, 5.24; S, 13.0.

3-Amino-1,6-anhydro-2,3-dideoxy-2-mercapto-D-allopyranose Hydrochloride (XIII).—A solution of 0.390 g. (1.59 mmoles) of the glycoside IX in 20 ml. of 6 N hydrochloric acid was heated at 120° (bath temperature) for 1.5 hours. The slightly yellow solution was decolorized with Norit, filtered through Celite and the filtrate evaporated to dryness *in vacuo* giving a partially crystalline pale yellow sirup. The residue was triturated with several portions of ether, then evaporated *in vacuo* affording 0.34 g. (100%) of

(25) Paper chromatography was run by the descending technique on Whatman No. 1 paper using the solvent systems A, isopropyl alcohol–2 N hydrochloric acid (65:35) and B, 1-butanol–acetic acid–water (5:2:3). Spots were detected with the sodium azide–iodine spray[26] and were located relative to adenine (R_f adenine = 1.00).

(26) E. Chargaff, C. Levine and C. Green. *J. Biol. Chem.*, **175**, 67 (1948).

a pale yellow crystalline solid, m.p. 175–190° dec., $[\alpha]^{25}D$ −112° (1% in water); $\lambda^{Nujol}_{max(\mu)}$ 3.07 (OH); 3.65–3.80, 6.32, and 6.59 (NH_3^+); 3.94 (SH). On paper chromatography in solvents A and B, the material moved as a single spot with R_{ad} 0.77 and 1.30, respectively, not cleanly separated from IX.

Anal. Calcd. for $C_6H_{12}ClNO_3S$: C, 33.7; H, 5.66; Cl, 16.6; S, 15.0. Found: C, 33.1; H, 6.24; Cl, 17.0; N, 6.12; S, 14.6.

Acetylation of the anhydride XIII with acetic anhydride and sodium acetate gave an amorphous solid whose infrared spectrum showed the O-acetyl, S-acetyl and N-acetyl carbonyl absorptions in an approximately 1:1:1 ratio. The material, however, could not be obtained as a crystalline solid.

Potential Antiradiation Drugs. III. β-Aminomercaptans Derived from D-Altrose[1,2]

BY JAMES E. CHRISTENSEN AND LEON GOODMAN

Two methods were explored for the preparation of a glycoside of 3-amino-2,3-dideoxy-2-mercapto-D-altrose. In the first, unsuccessful approach, a synthesis for the unique sugar episulfide VI was developed. Ammonolysis of VI, however, afforded polymeric products containing amino and mercaptan groups. The successful approach employed a *trans*-benzylthiotosylate (XVII) which was converted to a *trans*-benzylthioazide (XIX). A change of blocking groups gave the *trans*-benzylthioazide XXIII, which, treated with sodium and liquid ammonia and the product XXII deblocked with methanolic hydrogen chloride, afforded the desired aminomercapto glycoside (XXI, R = CH_3).

The preceding article[3] described the synthesis as a potential antiradiation drug of a β-aminomercaptan derived from D-allose. It was of interest to study the effect, if any, of the sugar stereochemistry on the radiation protection properties of these sugar β-aminomercaptans; this report describes the synthesis of a β-aminomercapto glycoside derived from D-altrose which is closely related to the compounds described in the previous paper.[3]

Ammonolysis of a sugar episulfide was visualized as the first approach to the preparation of the desired *trans*-β-aminomercapto sugar system. The ring opening of aliphatic episulfides with primary and secondary amines has been reported by several groups[4,5] to give good yields of aminomercaptans. By analogy with the ammonolysis of epoxides, the

aminomercaptans derived from cyclic episulfides should have the new functional groups in the *trans* configuration.

The synthesis of an appropriate sugar episulfide was accomplished starting from the available anhydromannoside I.[6] Reaction of I with ammonium thiocyanate in aqueous 2-methoxyethanol gave an excellent yield of a crystalline solid whose infrared spectrum showed the thiocyanate band at 4.66 μ. The initial reaction product had a wide melting range and required several recrystallizations to afford the narrowly melting analytical sample. However, a widely melting sample gave correct analyses for the expected thiocyanohydrin. These facts indicated that ring-opening of I had taken place at both C.2 and C.3 to give a mixture of two thiocyanohydrins. A fair yield of a sharply melting compound was easily obtained from the mixture by recrystallization and was assumed to be the thiocyanohydrin II by analogy with the predominant opening of I at C.3 by other nucleophiles.[7] The *trans*-diaxial structure II would be the product predicted by the Fürst–Plattner rule.[8] Proof of structure II was provided by desulfuri-

(1) This work 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-268 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) For a preliminary announcement of a part of this work, see J. E. Christensen and L. Goodman, *J. Am. Chem. Soc.*, **82**, 4738 (1960).

(3) L. Goodman and J. E. Christensen, *ibid.*, **83**, 3823 (1961).

(4) H. R. Snyder, J. M. Stewart and J. B. Ziegler, *ibid.*, **69**, 2672 (1947).

(5) P. Iu. Rachinskii, N. M. Slavachevskaia and D. V. Ioffe, *J. Gen. Chem. U.S.S.R. (Eng. Transl.)*, **28**, 3027 (1958).

(6) H. R. Bolliger and D. A. Prins, *Helv. Chim. Acta*, **28**, 465 (1945).

(7) W. H. Myers and G. J. Robertson, *J. Am. Chem. Soc.*, **65**, 8 (1943).

(8) A. Fürst and Pl. A. Plattner, Abstracts of Papers, 12th International Congress of Pure and Applied Chemistry (New York), 1951, p. 409.