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SULPHUR SUBSTITUTION COMPOUNDS OF AMINOSUGARS—VI

THE SYNTHESIS OF 2-AMINO-2, 3-DIDEOXY-3-MERCAPTO-D-ALLOSE DERIVATIVES THROUGH THIAZOLINE INTERMEDIATES

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Abstract—The synthesis of derivatives of 2-amino-2,3-dideoxy-3-mercapto-D-allose starting from a 2-amino-2-deoxy-D-glucose derivative and proceeding *via* neighboring group participation through thiazoline intermediates is described. The identity of these derivatives with similar compounds described in the preceding communication is emphasized.

THE need[1] for an independent and unambiguous synthesis of certain derivatives of 2-amino-2,3-dideoxy-3-mercapto-D-allose, recently obtained by a new displacement reaction,[2] has prompted us to employ a new approach to the preparation of such derivatives. This has involved application of the general method of Crawhall and Elliott[3] for the conversion of hydroxyamino acids into mercaptoamino acids, a method recently utilized by Christensen and Goodman[4] for the conversion of methyl 3-amino-4,6-O-benzylidene-3-deoxy-α-D-altropyranoside into methyl 3-amino-2,3-dideoxy-2-mercapto-α-D-allopyranoside. The main step of this synthesis is the conversion of a *trans*-O-methanesulfonyl-N-dithiocarbomethoxy-β-aminohydroxy sugar into a thiazoline intermediate having a *cis*-arrangement of sulphur and nitrogen atoms, a reaction originating *via* a rear-face attack of a neighbouring —NH—C=S— grouping on a carbon atom carrying a sulphonyloxy group. Under certain conditions it has been found,[4] however, that an attack by the nitrogen atom of the group was preferred over attack by its sulphur atom, thus affording an aziridine derivative instead of the desired thiazoline. When we attempted this reaction with a suitably substituted derivative (III) of 2-amino-2-deoxy-D-glucose (obtainable in two steps from the known[5] starting material I), the action of sodium methoxide at room temperature on III yielded a mixture of two compounds. These exhibited quite similar properties and could be separated only by careful chromatography on alumina. The two products displayed an overall similarity in their infrared spectra except for a striking difference in the C=N absorptions: 6·43 μ (for the initially eluted compound IV, believed to the desired thiazoline) and 6·15 μ (for the more slowly eluted V). The analysis of V indicated it to be an oxygen analog of IV, an assumption which was borne out by comparison of the

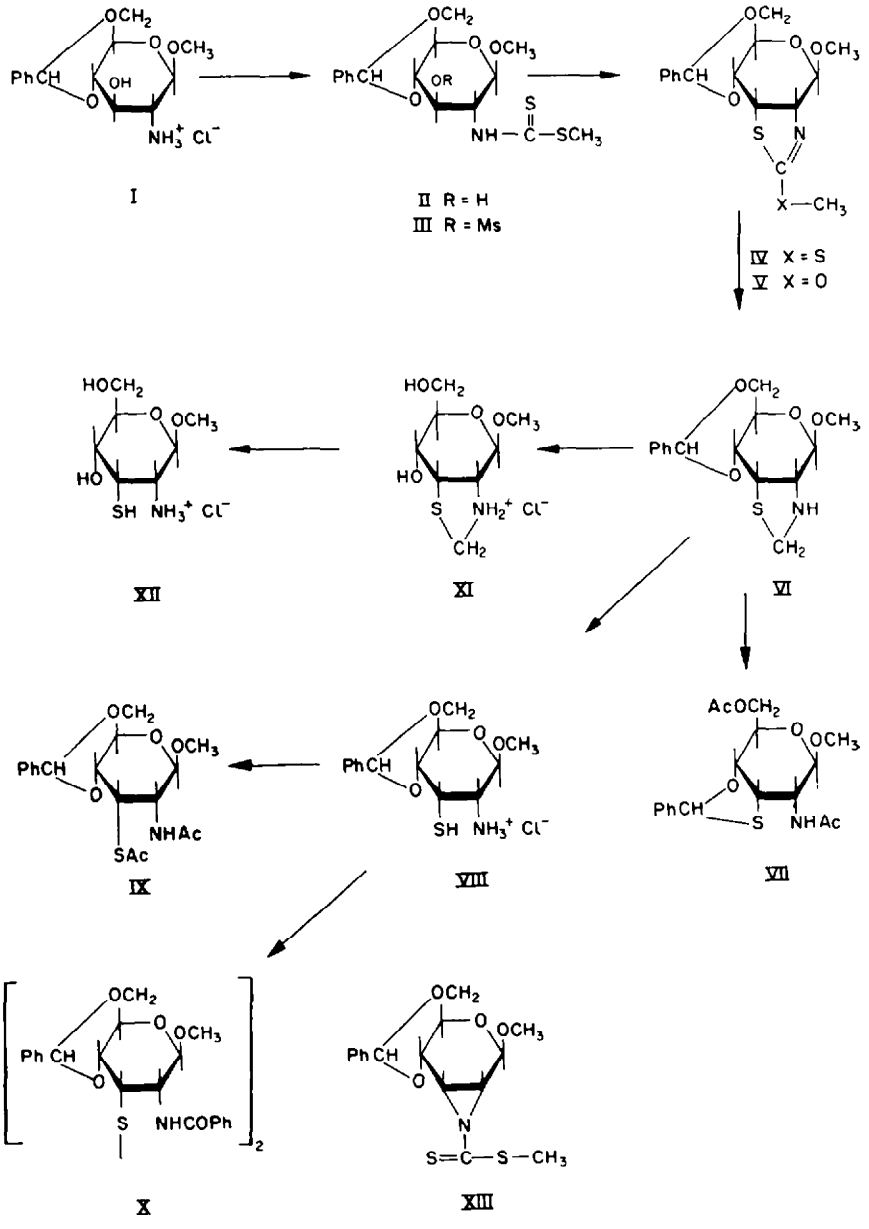
[1] A preliminary account of this work has been given: W. Meyer zu Reckendorf and W. A. Bonner, *Proc. Chem. Soc.* 429 (1961).

[2] W. Meyer zu Reckendorf and W. A. Bonner, *Tetrahedron* **19**, (1963). [Preceding manuscript.]

[3] J. C. Crawhall and D. G. Elliott, *J. Chem. Soc.* 2071 (1951).

[4] J. E. Christensen and L. Goodman, *J. Amer. Chem. Soc.* **82**, 4738 (1960); L. Goodman and J. E. Christensen, *Ibid.*, **83**, 3823 (1961).

[5] W. Meyer zu Reckendorf and W. A. Bonner, *Chem. Ber.* **94**, 3293 (1961).



N.M.R. spectra of both compounds. The signal of the S-methyl group in IV appeared as a strong peak at 154 c.p.s. whereas V showed a strong absorption at 236 c.p.s. a signal corresponding to the chemical shift of a carbomethoxy group.[6] Furthermore, both IV and V were readily reducible by aluminium amalgam[7] to the same thiazolidine VI.

[6] N.M.R. spectra were obtained with a Varian A-60 N.M.R. Spectrometer, and were measured in deuterochloroform against tetramethylsilane as an internal standard. We are indebted to Dr. Lois Durham for the N.M.R. spectra and their interpretation.

[7] A. H. Cook, G. D. Hunter and I. R. A. Pollock, *J. Chem. Soc.* 1892 (1950).

Formation of an aziridine isomer such as XIII has not been observed among our products, whereas Christensen and Goodman obtained such a compound and did not find an oxygen analog (similar to V) of their thiazoline. We suggest that steric factors are responsible for the different behaviour towards methoxide of Goodman's 2-amino-2-deoxy-D-altrose derivative and our 2-amino-2-deoxy-D-glucose derivative, but clearly these differences deserve further exploration.

We subsequently found that the preparation of the thiazoline IV could be simplified by merely suspending the crude mesylate III in aqueous pyridine at room temperature for 2–3 hr, under which conditions almost quantitative conversion of III into IV took place. The same facile conversion into the thiazoline was observed during an attempted chromatographic purification of III by alumina chromatography. Only IV could be eluted from the column.

In order to obtain comparison samples for compounds synthesized *via* the potassium thiolacetate displacement reaction described in the foregoing paper[2] we have opened the thiazolidine ring of VI with mercuric chloride. The resulting complex was decomposed with hydrogen sulphide, affording crystalline methyl 2-amino-4,6-O-benzylidene-2,3-dideoxy-3-mercapto-β-D-allopyranoside hydrochloride (VIII) which was characterized by its I.R. spectrum. This compound was immediately acetylated to give the N,S-diacetyl compound IX, which was identical in every respect with the compound obtained by our previous route.[2] Preparation and acylation of the hydrochloride VIII must be conducted immediately and carefully, avoiding oxidation and excess acidity. When these latter conditions prevailed accidentally, a material was obtained, the I.R. spectrum of which showed the presence of one O-acetyl and a benzylidene group, but no absorption corresponding to a sulphur function. We assume that the latter product possessed the hemithioacetal structure VII, in analogy to a similar compound previously described.[2] Benzoylation of the hydrochloride VIII followed by S-benzoyl saponification with ammonia in methanol afforded the N-benzoyl disulphide X. This sample was identical with the corresponding compound of unknown configuration described before,[2] thus establishing that our earlier sample possessed the D-allose configuration.

Acidic hydrolysis of the thiazolidine VI removed the benzylidene residue to give the nicely crystalline hydrochloride XI. When treated with mercuric chloride followed by hydrogen sulphide this substance yielded methyl 2-amino-2,3-dideoxy-3-mercapto-β D-allopyranoside hydrochloride XII as a hygroscopic white powder which was homogeneous on thin layer chromatograms.

EXPERIMENTAL

Uncorrected m.p.s have been determined in capillaries using a Thomas–Hoover apparatus. Thin layer and column chromatography has been carried out as described in the preceding manuscript.

Methyl 2-amino-4,6-O-benzylidene-2-deoxy-N-(dithiocarbomethoxy)-β-D-glucopyranoside (II).

A solution of 6·2 g hydrochloride I in 40 ml pyridine was treated with 4·4 ml triethylamine under cooling with ice water. After 15 min 2·4 ml carbon disulphide was added and the mixture stirred with cooling for 1·5 hr, after which 1·8 ml methyl iodide was added and the solution was kept at 0° overnight. Addition of ice and water caused precipitation of an oil which was washed with water by decantation, then was dissolved in chloroform. The solution was extracted twice with water, dried and evaporated *in vacuo* to give a sirup. This was crystallized by addition of ether and ligroin to its methanolic solution, affording 4·6 g (65%) pale brownish needles, m.p. 123–135° (dec) after another crystallization from the same solvent mixture. $[\alpha]_D^{23}$ −106° (*c*, 1·02; chloroform). (Found: C, 50·9; H, 6·0; N, 3·8; S, 16·9. $C_{16}H_{21}NO_5S_2$ requires: C, 51·7; H, 5·7; N, 3·8; S, 17·2%).

Methyl 2-amino-4,6-O-benzylidene-N-(dithiocarbomethoxy)-2-deoxy-3-O-methanesulfonyl-β-D-glucopyranoside (III)

A solution of 2·5 g II in 20 ml pyridine was cooled in a dry ice–acetone bath and 2·5 ml methanesulphonyl chloride was added with stirring. The mixture was kept at −5° overnight and then was poured into ice water, whereupon the precipitated product was recrystallized from ethanol, yield 1·5 g (49%), m.p. 188–189°, $[\alpha]_D^{23}$ −17·5° (*c*, 1·03; chloroform). (Found: C, 45·4; H, 4·9; N, 3·3; S, 21·5. $C_{17}H_{23}NO_7S_3$ requires: C, 45·4; H, 5·1; N, 3·1; S, 21·4%).

When 27 g II were processed by scaling up the above process tenfold, the crude product being left suspended in the pyridine–water mixture for 2–3 hr, we isolated 13 g thiazoline IV on recrystallization from ethanol, besides a small amount of III.

4′,6′-O-Benzylidene-1′-O-methyl-2-(methylthio)-β-D-allopyrano [2′,3′:4,5]-2-*thiazoline* (IV) *and the 2-methoxy analog* (V)

Mesylate III (5 g) was stirred with 120 ml 0·1 N sodium methoxide solution in absolute methanol at room temp overnight. The clear solution was evaporated *in vacuo* to give a sirup which crystallized on trituration with water, yield 2·9 g (74%). Thin layer chromatography on silica gel with a 1:1 mixture of ethyl acetate and ligroin showed the product to consist of two components; 2·5 g was subsequently separated by chromatography on 200 g alumina, elution with benzene yielding 508 mg pure IV, m.p. 109–110°, $[\alpha]_D^{23}$ −116·6° (*c*, 1·21; chloroform) after recrystallization from ethanol. (Found: C, 54·7; H, 5·3; N, 4·1; S, 17·8. $C_{16}H_{19}NO_4S_2$ requires: C, 54·4; H, 5·4; N, 4·0; S, 18·1%).

Further elution with benzene gave 661 mg of a mixture of IV and V, followed by 660 mg pure V. The latter was recrystallized from cyclohexane, m.p. 108–110°, $[\alpha]_D^{23}$ +45·6° (*c*, 1·03; chloroform). (Found: C, 56·9; H, 5·6; N, 4·1; S, 9·5. $C_{16}H_{19}NO_5S$ requires: C, 56·9; H, 5·7; N, 4·1; S, 9·5%).

4′,6′-O-Benzylidene-1′-O-methyl-β-D-allopyrano [2′,3′:4,5]-*thiazolidine* (VI).

Aluminium foil (2 g) was treated with 100 ml 3% aqueous solution of mercuric chloride, washed with water and ethanol and added to a solution of 1 g thiazoline IV, its oxygen analog V, or a mixture of both. After stirring for about 3 hr at room temp the aluminium hydroxide was filtered with the aid of celite and the clear solution was evaporated *in vacuo* to give 0·7 g (88%) crude crystalline product. This was recrystallized twice from 2-propanol, m.p. 167–168°, $[\alpha]_D^{23}$ −4·9° (*c*, 1·43; chloroform). (Found: C, 58·5; H, 6·2; N, 4·5; S, 10·3. $C_{15}H_{19}NO_4S$ requires: C, 58·4; H, 6·2; N, 4·5; S, 10·3%).

Methyl 2-acetamido-4,6-O-benzylidene-2,3-dideoxy-3-thioacetyl-β-D-allopyranoside (IX)

In a centrifuge tube 250 mg VI was dissolved in hot methanol and a 5% aqueous solution of mercuric chloride added until no more precipitate appeared. This was centrifuged, washed twice with water and dried. It was then suspended in methanol, 3 drops of conc ammonium hydroxide was added and the product was decomposed by passing a stream of hydrogen sulphide through the suspension for 10 min. Mercuric sulphide was centrifuged and the supernatant solution was evaporated to give crystalline methyl 2-amino-4,6-O-benzylidene-2,3-dideoxy-3-mercapto-β-D-allopyranoside hydrochloride (VIII) in admixture with ammonium chloride. The mixture was dissolved immediately in 2·5 ml pyridine and 1·5 ml acetic anhydride, left at room temp for 4 hr and finally decomposed with ice water. The main portion of the product crystallized on standing and was filtered. The mother liquors were extracted with chloroform to give a second crop after usual processing. The combined product was recrystallized from 2-propanol, yield 232 mg. (73%), m.p. 232–233°, mixed m.p. with the corresponding previous compound of unknown configuration[2] 231–232°, $[\alpha]_D^{23}$ −122° (*c*, 1·06; chloroform). (Found: C, 56·7; H, 6·2; N, 3·9; S, 8·6. $C_{18}H_{23}NO_6S$ requires: C, 56·7; H, 6·1; N, 3·7; S, 8·4%).

Methyl 2-acetamido-6-O-acetyl-3,4-S, O-benzylidene-2,3-dideoxy-3-mercapto-β-D-allopyranoside (VII)

This compound was obtained in low yield when the preparation of the above hydrochloride (VIII) was performed without the addition of ammonia, such that the reaction mixture became slightly acidic. After the acetylation step the crude product was purified by chromatography on alumina, eluting with benzene. The homogeneity of the product, m.p. 143–145°, was checked by

thin layer chromatography on silica gel, eluting with 4:1 ethyl acetate–ligroin. (Found: C, 56·7; H, 6·2. $C_{18}H_{23}NO_6S$ requires: C, 56·7; H, 6·1%).

*Methyl 2-benzamido-4,6-O-benzylidene-2,3-dideoxy-3-mercapto-β-*D*-allopyranoside disulphide* (X)

The above crude hydrochloride (VIII) obtained from 250 mg thiazolidine VI was dissolved in 5 ml pyridine (ammonium chloride remained partly undissolved), treated with 0·5 ml benzoyl chloride and allowed to stand for 1 hr at room temp. The crystalline product obtained by adding water was collected, dried, and dissolved in methanol saturated with ammonia, allowing the solution to stand at room temp overnight. Evaporation of the solvent and recrystallization of the residue from ethanol gave 170 mg (53%) disulphide X, m.p. and mixed m.p. with the corresponding previous compound of unknown configuration[2] 239–241°, $[\alpha]_D^{23}$ −14·1° (*c*, 1·4; in dimethyl sulphoxide). (Found: C, 62·8; H, 5·8; N, 3·7; S, 8·0. $(C_{21}H_{22}NO_6S)_2$ requires: C, 63·1; H, 5·5; N, 3·5; S, 8·0%).

*1′-O-Methyl-β-*D*-allopyrano [2′,3′:4,5]-thiazolidine hydrochloride* (XI)

A solution of 1·2 g thiazolidine VI in 100 ml 1% methanolic hydrogen chloride was refluxed for 1 hr, stripped of solvent and the residue was crystallized with absol. ethanol. A second crop of crystalline material was obtained by the addition of absol. ether, yielding a total of 1·0 g (100%). The product was recrystallized from a mixture of ethanol and absol. ether, m.p. 180–181° (dec), $[\alpha]_D^{23}$ −1·9° (*c*, 1·04; water). (Found: C, 37·5; H, 6·3; N, 5·3; S, 12·5; Cl, 13·8. $C_8H_{16}NO_4SCl$ requires: C, 37·3; H, 6·3; N, 5·4; S, 12·4; Cl, 13·8%).

*Methyl 2-amino-2,3-dideoxy-3-mercapto-β-*D*-allopyranoside hydrochloride* (XII)

A mixture of 100 mg thiazolidine salt XI and 250 mg mercuric chloride in 1 ml water was heated at 100° for 1 hr. On cooling the complex salt crystallized. It was collected, suspended in methanol and decomposed by a stream of hydrogen sulphide. The mercuric sulphide was centrifuged and the supernatant was evaporated to give a colourless sirup. This was dried by repeated evaporation of its solution in absol. ethanol, then was dissolved in 2-propanol and the product was precipitated with absol. ether, yielding 74 mg (78%) of an amorphous, very hygroscopic white powder. This was found to be homogeneous by thin layer chromatography on cellulose, employing the solvent systems 2-propanol–2 N hydrochloric acid 65:35 and n-butanol–acetic acid–water 5:2:3 as eluants. $[\alpha]_D^{23}$ −31·2° (*c*, 0·8; in water). (Found: C, 33·2; H, 6·6; N, 5·1; S, 13·3. $C_7H_{16}ClNO_4S$ requires: C, 34·2; H, 6·6; N, 5·7; S, 13·1%).

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