Hydrolytic Cleavage of 1-Dimethylaminocyclohexene.[27]—When 5 drops of dimethylaminocyclohexene (b.p. 175.5°) was added to 5 ml. of 10% hydrochloric acid in a test-tube and the solution warmed, cyclohexanone was formed. Addition of a solution of 2,4-dinitrophenylhydrazine in sulfuric acid caused the immediate precipitation of the 2,4-dinitrophenylhydrazone derivative which melted at 160°. The reported[16] m.p. of this derivative is 161°.

Alkylation of 1-Dimethylaminocyclohexene with Benzyl Chloride.—A mixture of 12.6 g. (0.1 mole) of the enamine and 12.6 g. (0.1 mole) of benzyl chloride in 25 ml. of methanol was refluxed overnight. It was hydrolyzed with 10% hydrochloric acid and then made basic. Extraction with ether and evaporation of the solvent gave a small amount of liquid residue. This was crudely distilled by the use of a small distillation flask (b.p. 125° (1.5 mm.)). The distillate gave a semicarbazone derivative which melted at 165°. The reported melting point for the semicarbazone of 2-benzylcyclohexanone[28] is 166–167°.

Anal. Calcd. for $C_{14}H_{19}N_3O$: C, 68.54; H, 7.81; N, 17.13. Found: C, 68.45; H, 7.52; N, 17.22.

Attempted Reduction of 1-Dimethylaminocyclohexene.—A reduction (3 hr. duration) of 25.2 g. (0.2 mole) of the enamine was attempted using 2.8 g. (0.4 g. atom) of lithium in methylamine. After acid hydrolysis of the product, distillation yielded 12.4 g. (63%) of cyclohexanone boiling at 154–156° (n^{20}D 1.4510). There was no evidence of any dimethylaminocyclohexane.

Attempted Reduction of 1-Piperidinocyclohexene.—The attempted reduction (3 hr. duration) of 33 g. (0.2 mole) of the enamine with 2.8 g. (0.4 g. atom) of lithium in methylamine gave, upon hydrolysis, and subsequent distillation 3.2 g. of cyclohexanone (b.p. 46–47° (14 mm.), n^{20}D 1.4520; 2,4-dinitrophenylhydrazone m.p. 160°) and 16.4 g. (50%) of starting material (b.p. 120–122° (17 mm.)).

Similar results were noted when the reduction was carried out in ethylamine.

(28) E. Pratt and D. Kubler, THIS JOURNAL, **76**, 52 (1954).

3-Dimethylaminocyclohexene.[29]—This compound was prepared using 90 g. (2 moles) of dimethylamine and 81 g. (0.33 mole) of 1,2-dibromocyclohexane in 310 g. of benzene. Distillation gave 28 g. (83%) of product boiling at 161–163° (n^{20}D 1.4685). The reported boiling point is 161–163° (725 mm.).[30] A styphnate derivative melted at 167–169° (reported m.p. 163–164°).[30]

Reduction of 3-Dimethylaminocyclohexene.—Twelve and one-half grams (0.1 mole) of this olefin in methylamine was reduced for 3 hr. with 1.4 g. (0.2 g. atom) of lithium. Subsequent hydrolysis and distillation gave 4.3 g. of product boiling at 161.5–162.5° (n^{20}D 1.4565). This corresponds to a mixture of starting material and completely saturated amine. A picrate could be isolated from this fraction, which after two recrystallizations melted at 176–178° and did not depress the melting point of the same derivative prepared from authentic N,N-dimethylcyclohexylamine. Likewise an infrared spectra showed that a considerable portion of the original olefin had been reduced.

Attempted Acid Hydrolysis of 3-Dimethylaminocyclohexene.—Twelve and five-tenths grams (0.1 mole) of 3-dimethylaminocyclohexene was dissolved in 50 ml. of 10% hydrochloric acid and the solution was refluxed for 30 minutes. After cooling, the solution was extracted thoroughly with ether. Evaporation of the ether extract left no residue, showing that no cyclohexanone or other acid-insoluble material had formed. The aqueous acid portion then was made basic with sodium hydroxide solution and 11.5 g. of the 3-dimethylaminocyclohexene was recovered.

Acknowledgment.—The authors are grateful to the Lithium Corporation of America whose financial assistance made this work possible.

(29) R. Willstätter and D. Hatt, *Ber.*, **45**, 1467 (1912).

(30) M. Mousseron, R. Jacquier and R. Zagdoun, *Bull. soc. chim. France*, 974 (1953).

LAFAYETTE, IND.

[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL SCIENCES, STANFORD RESEARCH INSTITUTE, AND THE KETTERING-MEYER LABORATORY, SOUTHERN RESEARCH INSTITUTE]

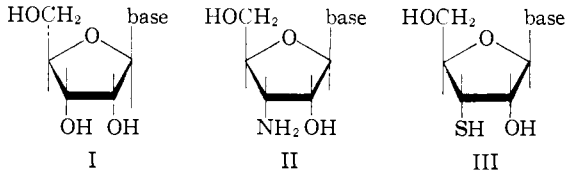
Potential Anticancer Agents.[1] XIII. The Thiourethan Neighboring Group. I. A New Synthesis of Amino Sugars

BY B. R. BAKER, KATHLEEN HEWSON,[2] LEON GOODMAN AND ALLEN BENITEZ

RECEIVED JULY 17, 1958

Reaction of the sodio derivative of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (XII) with phenyl isothiocyanate afforded a 53% yield of the amorphous 2-phenylthiourethan XIII and a 21% yield of the crystalline 3-phenylthiourethan XV, the structures of which were proved unequivocally. Mesylation of the 3-phenylthiourethan XV followed by ring closure with methanolic sodium methoxide, then alkaline hydrolysis, afforded methyl 2-anilino-4,6-*O*-benzylidene-2-deoxy-α-D-mannopyranoside (XIV). The potential use of this new amino sugar synthesis, whereby a 1,2-*trans*-glycol system of a sugar can be converted to a 1,2-*cis*-amino alcohol system, is discussed.

The substitution of the amino or mercapto group for the hydroxyl groups of natural purines such as hypoxanthine and guanine has led to compounds that inhibit nucleotide metabolism as exemplified by 2,6-diaminopurine, 6-mercaptopurine and thioguanine.[3] It would therefore be logical to assume that substitution of an amino or mercapto group for one of the hydroxyl groups of the sugar moiety of a natural riboside (I) could also lead to active inhibitors. An example of the substitution of amino for one hydroxyl of the ribose moiety is 6-dimethylamino-9-(3′-amino-3′-deoxy-β-D-ribofuranosyl)-purine (II), the "aminonucleoside" derived from the antibiotic puromycin. This aminonucleoside II, active against the adenocarcinoma of the C_3H mouse,[4] Leukemia L-1210[5] and Adenocar-



(1) This program is under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, and is in collaboration with the Sloan–Kettering Institute for Cancer Research. For the preceding paper of this series *cf.* L. Goodman, L. O. Ross and B. R. Baker, *J. Org. Chem.*, in press.

(2) Southern Research Institute, Birmingham 5, Ala.

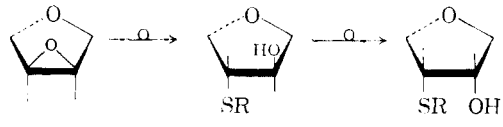
(3) A. Bendich in E. Chargaff and J. N. Davidson, "The Nucleic Acids," Academic Press, Inc., New York, N. Y., 1955, Vol. 1, p. 105.

(4) P. L. Bennett, S. L. Halliday, J. J. Oleson and J. H. Williams, "Antibiotics Annual 1954–1955," Medical Encyclopedia, Inc., New York, N. Y., p. 766.

(5) Unpublished data by Dr. J. H. Burchenal, Sloan–Kettering Institute.

cinoma 755,[6] can be obtained by selective cleavage of puromycin[7] or by total synthesis from D-xylose.[8,9] It may be, therefore, that nucleosides derived from 3-deoxy-3-mercapto-D-ribofuranose (III) will serve as useful antagonists of nucleotide metabolism.

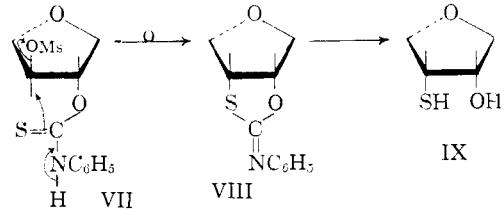
A number of 3-thio derivatives of sugars (V) have been synthesized by the ring opening of 2,3-anhydro sugars (IV) with a mercaptan. The products must have the *trans* orientation of the



IV V VI

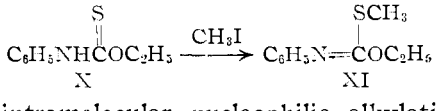
resultant thio and hydroxyl functions because of the mechanism of reaction.[10] Since the desired 3′-deoxy-3′-mercapto-β-D-ribofuranosyl nucleosides (III) have a C_2-C_3-*cis*-configuration, the ring opening of an anhydro sugar with a mercaptide could be of use only if the resultant product (V) with a *trans* configuration could be inverted to *cis* (VI). Although no such conversion of a *trans*-(V) to *cis*-mercapto alcohol (VI) has been described in the literature, it might be possible to obtain such if R were able to participate in a complex neighboring group reaction.[11]

A second, more attractive approach to 3-deoxy-3-mercapto-D-ribosides involves a neighboring group attack by a sulfur-containing function to give the *cis*-mercapto alcohol system directly. For example, a sugar derivative with a phenylthiocarbamoyl group on C_2 and a mesylate group on C_3 (such as in VII) should internally alkylate with Walden inversion and concomitant ring closure. The resultant bicyclic structure VIII of *cis* configuration should be hydrolyzable to IX. Although



H VII VIII IX

such a ring closure has not been described in the literature, bimolecular nucleophilic alkylation of ethyl N-phenylthiourethan (X) on sulfur to give XI has been observed[12] and is a precedent for the



X XI

above intramolecular nucleophilic alkylation to VIII. This behavior[12] of X indicates that the sulfur atom, rather than the nitrogen atom, of VII should be involved in the ring closure. Since this type of intramolecular cyclization[13] has not been studied previously, methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (XII) was selected as a suitable sugar derivative for study of these transformations and the resultant investigation is the subject of this paper.

Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (XII)[14] failed to react with an isothiocyanate in boiling pyridine or toluene. However, when XII was converted to its sodium alcoholate in dimethylformamide, then treated with phenyl isothiocyanate, two isomeric monophenylthiourethans (XIII and XV)[15] were formed. One thiourethan was easily crystallized; it was insoluble in 3% aqueous sodium hydroxide, melted at 210° and was obtained in 21% yield. The other thiourethan was an amorphous solid, soluble in 3% aqueous sodium hydroxide, and was obtained in 53% yield. Both compounds showed infrared absorption bands typical for the NH—C=S group, with NH near 3.03 and 6.52 μ and C=S near 7.30 μ. That neither compound was a 2,3-*O*-di-substituted thiourethan was evident by the presence of OH absorption at 2.91 μ and by combustion analyses. Only the crystalline isomer was used for further study.

The crystalline thiourethan was shown to be the 3-*O*-thiourethan XV by the following transformations. Reaction of the thiourethan XV with alkaline peroxide[16] afforded crystalline methyl 4,6-*O*-benzylidene-3-*O*-phenylcarbamoyl-α,D-glucopyranoside (XIX). Hydrolysis of the benzylidene group of XIX in 80% aqueous methanol with Amberlite IR-120 (H) ion exchange resin[17] afforded methyl 3-*O*-phenylcarbamoyl-α-D-glucopyranoside (XXIII) as an amorphous solid that was shown to be homogeneous by paper chromatography.[27] That no rearrangement or anomerization had taken place during the hydrolysis was shown by reconverting the amorphous urethan XXIII back to its crystalline benzylidene derivative XIX with benzaldehyde and zinc chloride. That the amorphous urethan XXIII and its precursors possessed the urethan group on the 3-hydroxyl was clearly demonstrated by the fact that XXIII consumed no periodate over a 24-hour period as would be expected for a structure with no contiguous hydroxyl groups. If the crystalline thiourethan had been the 2-*O*-urethan XIII, this sequence would have given rise to methyl 2-*O*-phenylcarbamoyl-α-D-glucopyranoside (XXIV), which can be predicted to consume 1 mole-equivalent of periodate.[18,19]

(6) Unpublished data by Dr. H. E. Skipper, Southern Research Institute.

(7) B. R. Baker, J. P. Joseph and J. H. Williams, THIS JOURNAL, **77**, 1 (1955).

(8) B. R. Baker, R. E. Schaub and J. H. Williams, *ibid.*, **77**, 7 (1955).

(9) B. R. Baker, R. E. Schaub, J. P. Joseph and J. H. Williams, *ibid.*, **77**, 12 (1955).

(10) For a summary of these reactions, see Paper I of this series by L. Goodman, A. Benitez and B. R. Baker, *ibid.*, **80**, 1680 (1958).

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

(12) C. Lieberman, *Ann.*, **207**, 121 (1881).

(13) A closely analogous reaction is the cyclization of i to ii described by J. C. Crawhall and D. F. Elliott, *J. Chem. Soc.*, 2071 (1951); 3094 (1952).

(14) B. R. Baker and R. E. Schaub, *J. Org. Chem.*, **19**, 646 (1954).

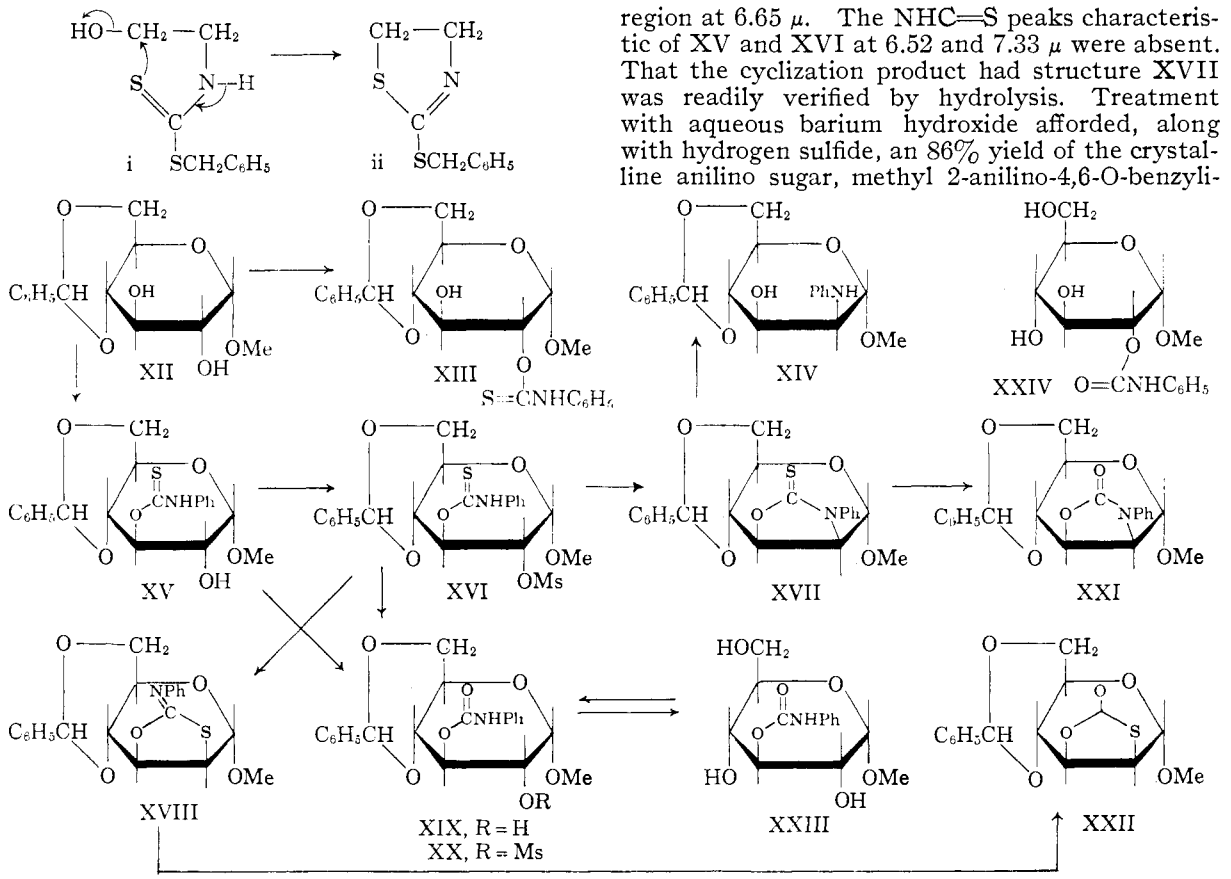
(15) R. W. Bost and E. R. Andrews, THIS JOURNAL, **65**, 900 (1943). prepared *t*-butyl N-phenylthiourethan by reaction of sodium *t*-butoxide with phenyl isothiocyanate in excess *t*-butyl alcohol as the solvent.

(16) A. F. McKay, M. Skulski and O. L. Garmaise, *Can. J. Chem.*, **36**, 147 (1958); A. Kjaer, *Acta Chem. Scand.*, **6**, 327 (1952).

(17) J. Honeyman and T. C. Stening, *J. Chem. Soc.*, 537 (1958).

(18) E. L. Jackson in R. Adams, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1944, Vol. 2, p. 341.

(19) The conversion of the thiourethan XV to a urethan XIX was considered an essential step since a thiourethan such as methyl 3-*O*-



Treatment of the crystalline thiourethan XV with methanesulfonyl chloride in pyridine gave the mesylate XVI as a glass. That the OH group of XV had been mesylated was shown by S→O infrared absorption at 7.40 and 8.48 μ as well as lack of OH absorption near 2.9 μ. The thiourethan group was still present, as shown by characteristic absorption at 6.52 and 7.33 μ. However, the reaction formed other side products, as shown by relatively weak bands in the double bond region at 5.74 and 6.08 μ.

Reaction of the crude mesylate XVI with methanolic sodium methoxide gave a 67% yield of crystalline product,[20] analysis showing the loss of elements of methanesulfonic acid. The loss of the mesyl group was also indicated by the lack of sulfonate infrared absorption bands in the product near 7.40 and 8.48 μ. The product could have either structure XVII or structure XVIII, depending upon whether nitrogen or sulfur, respectively, had participated in the neighboring group displacement reaction. The lack of absorption near 6.1 μ, characteristic of C=N in XVIII, indicated that the product was XVII, formed by neighboring group participation of nitrogen. The infrared spectrum of the product contained a new, strong band at 7.02 μ as well as enhanced absorption in the phenyl region at 6.65 μ. The NHC=S peaks characteristic of XV and XVI at 6.52 and 7.33 μ were absent. That the cyclization product had structure XVII was readily verified by hydrolysis. Treatment with aqueous barium hydroxide afforded, along with hydrogen sulfide, an 86% yield of the crystalline anilino sugar, methyl 2-anilino-4,6-O-benzylidene-2-deoxy-α-D-mannopyranoside (XIV), which gave appropriate combustion values and was free of sulfur. That the cyclization product had the structure of XVII was further confirmed by selective hydrolysis of its C=S to C=O with mercuric acetate[21] in ethanol. The resultant cyclic urethan XXI contained no sulfur and showed infrared absorption at 5.65 μ, typical of the carbonyl group of a five-membered cyclic urethan.[22]

In view of Lieberman's results[12] of the S-alkylation of ethyl N-phenylthiourethan (X) to XI, it is surprising that the alkylation of XVI proceeded by nitrogen attack to XVII rather than by sulfur attack to XVIII. One noticeable difference in the two procedures is Lieberman's use of the silver salt of X, in contrast to the sodium salt used in the cyclization of XVI. However, this difference could not be exploited; although XVI readily reacted with silver carbonate to form an insoluble silver salt that lacked the typical NH band of XVI at 6.52 μ, this silver salt was recovered unchanged when refluxed in ethanol or methyl ethyl ketone.

With the establishment of the principal infrared absorption bands for the amino sugar intermediates XVII and XXI it became possible to offer an explanation for some of the extraneous bands in the double bond region present in the crude mesylation product XVI, as well as in the crude material in the mother liquor from the cyclic thiourethan XVII.

phenylthiocarbamoyl-α-D-glucopyranoside could be expected to consume periodate by oxidation of the sulfur function.

(20) In some runs a small amount of highly insoluble by-product was obtained that had infrared absorption bands in agreement with the structure XX, caused by hydrolysis of the C=S to C=O. This by-product was most probably formed during the mesylation reaction, as discussed later.

(21) A. Kjaer, *Acta Chem. Scand.*, **6**, 1374 (1952), has used this procedure to convert thioacylated α-amino acids to the corresponding acylated α-amino acids.

(22) B. R. Baker and J. P. Joseph, THIS JOURNAL, **77**, 15 (1955).

The base-catalyzed cyclization of the mesyl thiourethane XVI could possibly give as a minor product some oxathiolane XVIII formed by participation of sulfur in the neighboring group reaction. The anilino group of XVIII, being part of an imino ester, would be expected to undergo facile hydrolysis to the cyclic thiolcarbonate XXII. The material in the mother liquor from XVII showed strong absorption at 5.74 μ, most probably a carbonyl in a five-membered ring. Since the C=O of the cyclic urethan XXI had carbonyl absorption at 5.65 μ, the most likely possibility for the 5.74 μ band was the C=O of the thiolcarbonate XXII. This mother liquor also contained a band at 6.08 μ, assigned to the C=N of the anil XVIII.

The crude mesylation product XVI also contained bands at 5.74 μ (C=O of XXII) and 6.08 μ (C=N of XVIII). The formation of XVIII could arise from acid-catalyzed (pyridine hydrochloride) cyclization of the thiourethan XV, during mesylation, with generation of an equivalent of water. The water could then hydrolyze some of the imino group of XVIII, resulting in the thiolcarbonate XXII, or hydrolyze the thiourethan XVI to XX. These suggested by-products could then account for the complex double bond absorption in the crude XVI. That the formation of the anil XVIII did not rise by pyridine-catalyzed cyclization of the mesylate XVI was demonstrated by long boiling of an ethylene dichloride–pyridine solution of XVI; no change in the relative intensities of bands in the double bond region at 5.6–7.4 μ was observed.

These results suggested the study of acid-catalyzed ring closure of the thiourethan XV to the anil XVIII. Pyridine hydrochloride would be objectionable because the water formed could complicate the reaction by hydrolyzing the C=S of the thiourethan XV to the C=O of the urethan XIX; concurrent hydrolysis of the anil XVIII to the thiolcarbonate XXII would not be objectionable. Thionyl chloride was considered a better reagent since it would also react with the water generated in the ring closure. In addition, thionyl chloride has been used previously for acid catalysis in other neighboring group ring closures on an adjacent carbon bearing a hydroxyl.[11,13,14,23]

A dilute solution of the thiourethan XV in thionyl chloride was allowed to stand in an infrared cell for liquids, and absorption spectra at 5.5 to 7 μ were run at intervals. A new, strong band appeared at 5.88 μ at the time of the first measurement (5 minutes). This band increased in optical density over 85 minutes and did not change further up to 205 minutes. At about the same rate that this new band began to appear, the NH band of XV at 6.53 μ began to decrease; the rate of decrease ceased after 85 minutes and was then constant up to 205 minutes.[24] These results are compatible with the cyclization of the thiourethan XV to the anil XVIII, provided it is assumed that the infrared absorption at 5.9 μ could be assigned to the C=NH$^+$ of the anil XVIII hydrochloride.

A similar reaction mixture then was processed by evaporation of the thionyl chloride, the residue being partitioned between chloroform and aqueous sodium bicarbonate to convert the hydrochloride to the free base XVIII. The infrared absorption spectrum of the glassy product showed that little, if any, of the starting thiourethan XV was present, in that the bands at 6.52 and 7.3 μ were weak. However, the 5.88 μ band of C=NH$^+$ had disappeared as expected and was replaced by the C=N band of XVIII at 6.08 μ and the less expected C=O band of the thiolcarbonate of XXII at 5.74 μ. Treatment of the mixture with 70% acetic acid at room temperature caused almost complete hydrolysis of the anil XVIII to the thiolcarbonate XXII since the 6.08 μ C=N band was now negligible and the 5.74 μ C=O band was intensified. Unfortunately, these acid conditions also caused loss of some of the benzylidene blocking group, giving rise to mixtures that could not be crystallized.

That the infrared absorption bands assigned to the anil XVIII and the thiolcarbonate XXII are probably correct and that these compounds were formed has been given sturdy support by study of these reactions in the simpler cyclopentane system,[25] where the products could be adequately purified. The application of these reactions to more suitably blocked sugars is also discussed.[25]

Nevertheless, methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (XII) served as an admirable system for study of the thiourethan neighboring group reactions under alkaline conditions, a new process for synthesis of amino sugars having resulted. By use of N-substituted thiourethan groups other than N-phenyl it should be possible to make a variety of N-alkyl-, N-aryl- and N-aralkylamino sugars by this process. In fact, if an N-benzylthiourethan is employed, it should be possible to remove the N-benzyl group from a molecule such as XIV by hydrogenolysis, thus constituting a useful method for the synthesis of amino sugars without a substituent on the amino group, particularly where one wishes to convert a *trans*-glycol system (as in XII) to a *cis*-amino alcohol system (as in XIV).

Experimental[26,27]

Methyl 4,6-*O*-Benzylidene-2(and 3)-*O*-phenylthiocarbamoyl-β-D-glucopyranoside (XIII and XV).—To a solution of 10.0 g. (35.4 mmoles) of dry methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (XII)[14] in 50 ml. of pure dimethylformamide was added a solution of 1.91 g. (35.4 mmoles) of sodium methoxide (Mathieson) in 10 ml. of methanol. The bulk of the methanol and some of the dimethylformamide was evaporated at the water-pump on a spin dryer (bath 80–90°), with a drying tube in the line to prevent moisture

(23) W. S. Johnson and E. N. Schubert, THIS JOURNAL, **72**, 2187 (1950); G. E. McCasland and D. A. Smith, *ibid.*, **72**, 2190 (1950).

(24) The disappearance of the C=S bond at 7.3 μ could not be followed since the S → O vibration of thionyl chloride makes the solvent non-transparent at that wave length.

(25) L. Goodman, A. Benitez, C. D. Anderson and B. R. Baker, the accompanying paper XIV, THIS JOURNAL, **80**, 6582 (1958). The only apparent difference between the cyclopentane and the sugar systems was the shift in infrared to lower wave length when the C=N of the sugar system was protonated.

(26) Rotations were determined with a Keston polarimetric attachment to the Beckman DU spectrophotometer. Melting points are uncorrected.

(27) The paper chromatograms were run on Whatman No. 1 paper with water-saturated butanol: the spots were located either by inspection under ultraviolet light (when a phenyl group was present) or by silver nitrate spray or by both.

back-up. The remainder of the solvent was then removed by use of an oil-pump. During the evaporation the sodio derivatives of XII separated as a semi-gelatinous mass. The dry residue was suspended in 100 ml. of dry dimethylformamide, then treated with 4.98 ml. (42.0 mmoles) of phenyl isothiocyanate. The mixture was heated, protected from moisture, with occasional swirling, in a bath at 80° until solution was essentially complete (75 minutes). After acidification with 4.98 ml. (87.0 mmoles) of acetic acid, the mixture was diluted with 500 ml. of water and extracted with 100 ml. of chloroform. The chloroform extract, washed with water and dried with magnesium sulfate, was evaporated to dryness *in vacuo*. The residue[28] was crystallized from 25 ml. of chloroform by the addition of 50 ml. of hexane. The product was collected and washed with 1:2 chloroform–hexane; yield 3.16 g. (21%) of XV, m.p. 206–209°. Evaporation of the mother liquor to dryness *in vacuo* left 13.1 g. of a glass containing XIII, which was treated further as described below.

In a pilot run on 0.72 g. of XII, the yield of XV was 0.20 g. (19%), m.p. 208–209°. Recrystallization from chloroform–hexane afforded white crystals, m.p. 210°, $[\alpha]^{26}D$ −77° (0.6% in $CHCl_3$); λ_{max}^{KBr} (μ) 2.91, 3.03 (OH, NH), 6.25, 6.66 (phenyl), 6.53 (NH), 7.30 (C=S), 9.20, 9.55 (C–O–C and C–O–H), 13.3, 14.4 (monosubstituted phenyl).

Anal. Calcd. for $C_{21}H_{23}NO_5S$: C, 60.4; H, 5.55; N, 3.36. Found: C, 60.6; H, 5.90; N, 3.35.

An aliquot (993 mg.) of the above 13.1 g. of glass containing XIII was dissolved in 10 ml. of benzene and extracted with ice-cold 3% aqueous sodium hydroxide (8 × 10 ml.). Each extract was immediately run into dilute acetic acid; 95% of the material was obtained in the first three extracts. The combined, acidified extracts were filtered and the amorphous, granular solid was washed with water; yield 567 mg. of XIII (53% based on XII). For analysis, a sample was dissolved in chloroform and the product precipitated with hexane. The amorphous XIII had λ_{max}^{KBr} (μ) 2.93 (OH), 3.07 and 6.65 (NH), 6.28, 6.70, 13.4 and 14.4 (monosubstituted phenyl), 7.25 (C=S), 9.02, 9.52 and 9.75 (C–O–C and C–O–H). Analysis showed that this amorphous XIII was nearly pure.

Anal. Calcd. for $C_{21}H_{23}NO_5S$: C, 60.4; H, 5.55; N, 3.36. Found: C, 59.6; H, 5.58; N, 3.62.

A check on the solubility in 3% sodium hydroxide then showed that XV was insoluble and XIII was soluble; separation was, therefore, easy. The yield of XV, starting with pure XII, was 31%.

Methyl 4,6-*O*-Benzylidene-3-*O*-phenylcarbamoyl-α-D-glucopyranoside (XIX).—To a solution of 2.00 g. (4.79 mmoles) of XV in 120 ml. of 95% ethanol containing 0.80 g. (20 mmoles) of sodium hydroxide was added, dropwise over a period of 5 minutes, 5.0 ml. (49 mmoles) of 30% hydrogen peroxide. After being stirred for 4 hours, the solution containing a suspended white solid was concentrated *in vacuo* to about 60 ml., then diluted with 300 ml. of water. The white crystals were collected on a filter and washed with 100 ml. of water. This crude product, containing both XII and XIX, melted at 200–204° and weighed 0.92 g. The mother liquor contained XII, but no XIX, as shown by evaporation and lack of C=O absorption of the residue in the infrared. Recrystallization of the 0.92 g. from 40 ml. of 95% ethanol gave 0.30 g. (16%) of XIX, m.p. 246–250°; no attempt was made to recover additional material from the filtrate. In another run, the yield was 25%, m.p. 248–250°. Several recrystallizations from 95% ethanol gave white crystals, m.p. 245–247°, $[\alpha]^{27}D$ +50° (0.4% in pyridine); λ_{max}^{KBr} (μ) 2.92 (OH, NH), 5.80 (urethan C=O), 6.49 (NH), 8.15 (urethan C–O–C), 9.21, 9.30, 9.51 (C–O–), 13.37, 14.35 (monosubstituted phenyl). A paper chromatogram[27] showed a single spot with R_f 0.84.

Anal. Calcd. for $C_{21}H_{23}NO_7$: C, 62.8; H, 5.78; N, 3.49. Found: C, 63.0; H, 5.84; N, 3.36.

Attempts to convert XV to XIX with mercuric acetate in ethanol[21] surprisingly gave mainly XII; only occasionally were even small amounts of XIX present.

Methyl 3-*O*-Phenylcarbamoyl-α-D-glucopyranoside (XXIII).—A solution of 0.600 g. (1.49 mmoles) of XIX in 100 ml. of 80% aqueous methanol was stirred and refluxed with 2.2 g. of Amberlite IR-120 (H) for 4.5 hours.[17] The mixture was filtered and the resin washed with 25 ml. of methanol. The combined filtrate and washings were evaporated to dryness *in vacuo*, leaving 0.58 g. of amorphous residue, m.p. about 100–115°. The residue was extracted with hot benzene (6 × 10 ml.). The combined extracts, on cooling, deposited 0.256 g. (55%) of amorphous XXIII, m.p. about 80–90°. The material insoluble in benzene was dissolved in methanol and the solution clarified with Celite; then the solution was evaporated *in vacuo*, giving an additional 0.223 g. (47%) of amorphous XXIII. That both fractions were identical was shown by infrared absorption spectra and paper chromatography.[27] In each case, a single spot with R_f 0.75 was obtained and no XII (R_f 0.19) or XIX (R_f 0.84) could be detected. The 0.256-g. fraction was characterized further; it had λ_{max}^{KBr} (μ) 2.94 (OH, NH), 5.84 (urethan C=O), 6.47 (NH), 8.12 (urethan C–O–C), 9.58 (broad C–O–); $[\alpha]^{25}D$ +136° (0.7% in 95% EtOH); it failed to consume periodate in aqueous solution over a period of 24 hours. The analysis, on material dried over phosphorus pentoxide at 56° *in vacuo*, still showed the presence of 5% of benzene.

Anal. Calcd. for $C_{14}H_{19}NO_7 + 5\%\ C_6H_6$: C, 55.6; H, 6.19; N, 4.25. Found: C, 55.5, 55.5; H, 6.40, 6.31; N, 3.94.

Reaction of 0.186 g. (0.594 mmole) of XXIII with 0.186 g. (1.36 mmoles) of zinc chloride in 1.2 ml. (12 mmoles) of benzaldehyde[17] at room temperature for 40 hours gave, after processing and crystallization from 95% ethanol, a 78% yield of XIX, identified by m.p., mixture m.p., infrared absorption spectra and paper chromatography (R_f 0.84).

Methyl 2-Anilino-4,6-*O*-benzylidene-2-deoxy-α-D-mannopyranoside 2,3-Thiocarbonate (XVII).—To a solution of 275 mg. (0.659 mmole) of XV in 1.4 ml. of reagent pyridine cooled in an ice-bath was added 0.23 ml. of methanesulfonyl chloride. After standing in a stoppered container for 24 hours at room temperature, the mixture was poured onto 7 ml. of iced water and extracted twice with chloroform. The combined chloroform extracts were washed with water, then with saturated aqueous sodium bicarbonate. Dried with magnesium sulfate, the chloroform solution was evaporated to dryness *in vacuo*, leaving 320 mg. (98%) of XVI as a glass that could not be crystallized. Inspection of its infrared absorption spectrum (KBr disk) showed the NH and C=S of NH–C=S at 6.52 and 7.33 μ as well as the S → O of sulfonate at 7.40 and 8.48 μ. In addition, relatively weak bands present at 6.08 and 5.74 μ were attributed to the C=N of XVIII and the C=O of XXII, respectively.

To a solution of 320 mg. (0.646 mmole) of the crude XVI in 13.9 ml. of methanol was added 1.06 ml. (1.06 mmoles) of 1 *N* methanolic sodium methoxide. After standing overnight at room temperature in a stoppered flask, the solution was seeded with XVII (or the walls of the flask scratched until crystallization started), then allowed to stand 4 hours more. The product was collected and washed with methanol; yield 130 mg. (50% based on XV) of XVII as white crystals, m.p. 205–207°.

The combined filtrate and washings were evaporated to dryness *in vacuo*. The residue was partitioned between water and chloroform. Dried with magnesium sulfate, the chloroform layer was evaporated to dryness *in vacuo*. Crystallization of the residue from methanol gave an additional 43 mg. (total 67%) of XVII, m.p. 192–201°. A mixture with a sample of the above 130 mg. melted at 200–204°. Recrystallization of a similar preparation from methanol gave white crystals, m.p. 208°, $[\alpha]^{24}D$ −111° (2% in $CHCl_3$). In the infrared (KBr disk), this compound showed no NH–OH absorption near 3 μ, no S → O absorption near 7.4 or 8.5 μ, but did show monosubstituted phenyl absorption at 6.27, 13.2 and 14.4 μ, phenyl plus N–C=S at 6.65 μ, and C=S at 7.02 μ rather than at 7.3 μ as is characteristic of XV, XVI and XIII. This compound also gave a positive test for sulfur after sodium fusion.

Anal. Calcd. for $C_{21}H_{21}NO_5S$: C, 63.1; H, 5.30; N, 3.51. Found: C, 62.9; H, 5.21; N, 3.38.

With 10 g. of pure XV, the yield was 87%. The cyclization of XVI to XVII could also be carried out at the b.p. of methanol; the reaction was complete within 20 minutes and the yield of XVII was 58%. When XV was converted to XVI by a three-day mesylation, then cyclized to XVII at room temperature, the over-all yield of XVII was 60%. In one run a 10% yield of highly insoluble, crystalline by-

(28) If all the residual dimethylformamide is not removed, crystallization is difficult.

product was isolated, m.p. 234–235° dec., that appeared to be XX, based on its infrared spectrum.

Methyl 2-Anilino-4,6-*O*-benzylidene-2-deoxy-α-D-mannopyranoside (XIV).—A solution of 130 mg. (0.325 mmole) of XVII in 3.2 ml. of methoxyethanol was added to a hot solution of 255 mg. (0.808 mmole) of barium hydroxide octahydrate in 3.2 ml. of water. After being refluxed for 18 hours, the mixture was cooled, diluted with about 10 ml. of water, then neutralized with solid carbon dioxide, causing evolution of hydrogen sulfide as evidenced by odor and a positive reaction with lead acetate paper. The solids were collected on a filter and washed with water. The mixture of barium carbonate and product was extracted with boiling ethanol (2 × 5 ml.). Evaporation of the combined ethanol extracts to dryness *in vacuo* gave 100 mg. (86%) of product, m.p. 148–150°. Recrystallization from alcohol–water afforded white crystals, m.p. 148–150°, $[\alpha]^{24}D$ −18° (2% in $CHCl_3$). In the infrared (KBr disk), this compound showed OH–NH absorption at 2.91, 2.95 and 3.03 μ, phenyl at 6.25 and 6.67 μ (only bands between 5 and 6.8 μ), C–O–C and C–O–H at 9.12, 9.34 and 9.95 μ, and monosubstituted phenyl at 13.3 and 14.3 μ.

Anal. Calcd. for $C_{20}H_{23}NO_5$: C, 67.2; H, 6.49; N, 3.92. Found: C, 67.2; H, 6.50; N, 4.06.

Methyl 2-Anilino-4,6-*O*-benzylidene-2-deoxy-α-D-mannopyranoside 2,3-Carbonate (XXI).—To a warm solution of 200 mg. (0.501 mmole) of XVII in 200 ml. of absolute ethanol was added a warm solution of 162 mg. (0.508 mmole) of mercuric acetate in 10 ml. of absolute ethanol.[21] A white, gelatinous precipitate separated and gradually became dark gray. After standing for about 18 hours, the mixture was filtered. The filtrate was treated with excess hydrogen sulfide, then filtered through Celite and evaporated to dryness *in vacuo*. The residue was dissolved in 10 ml. of hot absolute ethanol, filtered from some mercuric sulfide, then cooled at 3°. White needles separated gradually over 3 days. The product was collected and washed with cold ethanol; yield 54 mg. (28%), m.p. 168°. Crystals could be isolated from the mother liquor, but were obviously a mixture and were not investigated further.

Recrystallization of the 54 mg. from ethanol did not raise the m.p. The compound had $[\alpha]^{27}D$ −108° (0.1% in $CHCl_3$) and λ_{max}^{KBr} (μ) 5.65 (C=O of five-membered urethan ring), 8.28 (urethan C–O–C), 13.2 and 14.3 (mono substituted phenyl), no OH–NH near 3.0.

Anal. Calcd. for $C_{21}H_{21}NO_6$: C, 65.8; H, 5.52; N, 3.65. Found: C, 65.1; H, 5.33; N, 3.80.

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[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL SCIENCES, STANFORD RESEARCH INSTITUTE]

Potential Anticancer Agents.[1] XIV. The Thiourethan Neighboring Group. II. Synthesis of *cis*-2-Mercapto- and *cis*-2-Anilinocyclopentanols

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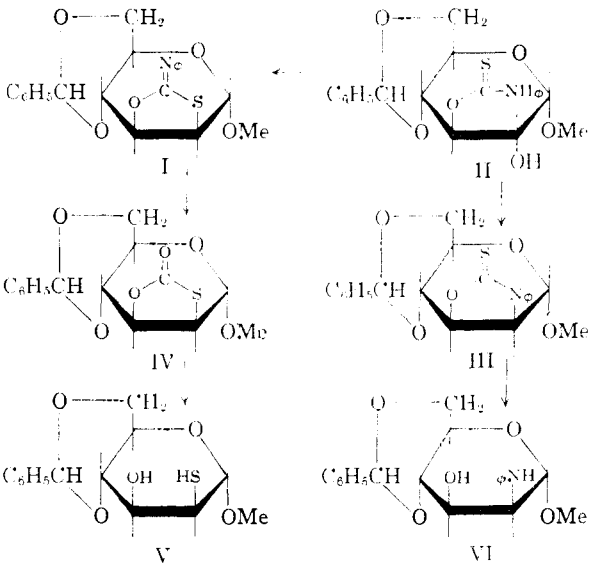
trans-1,2-Cyclopentanediol can be converted to either *cis*-2-mercaptocyclopentanol (X) or to *cis*-2-anilinocyclopentanol (XVI), depending upon the conditions selected for cyclization of the monophenylthiourethan VII of the diol. These transformations have been carried out under conditions that should be compatible with the stability of nucleosides and should allow synthesis of nucleosides containing 3′-deoxy-3′-mercapto- or 3′-anilino-3′-deoxy-D-ribofuranose moieties. In order to establish the structure of *cis*-2-mercaptocyclopentanol (X) prepared by the neighboring group method, this substance was also synthesized from 1-cyclopentenyl acetate through the addition of thiolacetic acid and subsequent hydrolysis.

In the preceding paper of this series,[2] the use of the thiourethan group for the synthesis of anilino sugars and mercapto sugars and nucleosides of such sugars was discussed. Mesylation of the thiourethan II followed by treatment with sodium methoxide afforded the crystalline cyclic thiourethan III, which in turn could be hydrolyzed to crystalline methyl 2-anilino-4,6-*O*-benzylidene-2-deoxy-α-D-mannopyranoside (VI). When the thiourethan II was treated with thionyl chloride, an oily product (I) was obtained that readily lost aniline to give another oil that was presumably the cyclic thiocarbonate IV. The presence of both I and IV in their respective reaction mixtures was highly probable in view of the characteristic infrared absorption bands. Since neither I nor IV could be adequately purified, this thionyl chloride ring closure has now been investigated with the simpler cyclopentane system. The successful conversion of a *trans*-1,2-glycol to a *cis*-2-mercaptoalcohol and to a *cis*-2-anilinoalcohol in the cyclopentane series is the subject of this paper.

The conversion of *trans*-1,2-cyclopentanediol to the monophenylthiourethan, *trans*-2-(phenylthiocarbamoyloxy)-cyclopentanol (VII), was best accomplished by refluxing the dried diol dissolved in toluene with an equimolar quantity of phenyl isothiocyanate.[3] Although the yield of VII was



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(2) B. R. Baker, K. Hewson, L. Goodman and A. Benitez, THIS JOURNAL, **80**, 6577 (1958).

(3) The benzoylthiourethan group was regarded as another interesting neighboring group whose utility could be visualized as similar to