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The Reaction of Methyl 2,3-Anhydro-β-D-lyxofuranoside with Sodium Benzyl Mercaptide [1,2]

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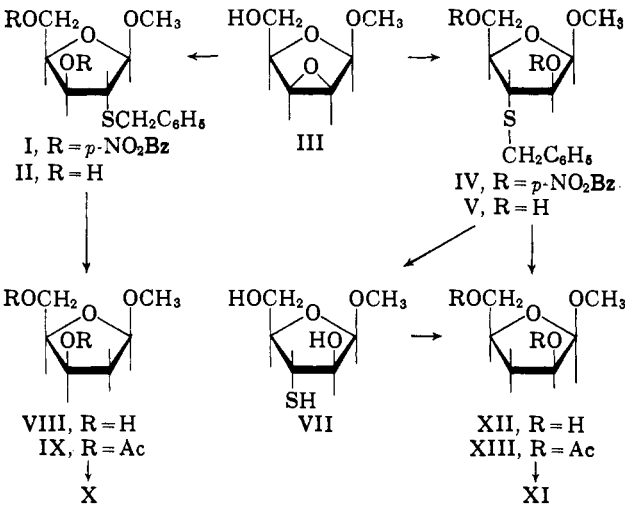
The opening of methyl 2,3-anhydro-β-D-lyxofuranoside with sodium benzyl mercaptide gave the 2-benzylthiodiol II as the major product, this being the first report of ring opening of a 2,3-anhydrofuranoside which did not occur very predominantly at C-3. As proof of structure, the diol II was desulfurized, then hydrolyzed to 2-deoxy-D-*threo*-pentose. The 3-benzylthiodiol V, also isolated in the epoxide opening, by similar treatment was converted to 3-deoxy-D-*threo*-pentose. The diols II and V, after tosylation, gave compounds XV and XVI that reacted with azide ion *via* the common episulfonium ion XIV. The difference in chemical reactivity between the derivatives of II and V is discussed in terms of possible nonplanar conformations of the furanose ring.

A previous paper[4] from these laboratories described the conversion of methyl 2,3-anhydro-β-D-ribofuranoside to 2- and 3-deoxy-D-*erythro*-pentose by a route that utilized an S-ethylepisulfonium ion intermediate. This work established the reaction conditions that permitted syntheses of 2'-[5] and 3'-[6]deoxyadenosine. As part of a program to prepare the C-3' and C-2' epimers, respectively, of 2'- and 3'-deoxyadenosine, it was advantageous to study first the syntheses of the necessary sugars 2-deoxy- (X) and 3-deoxy-D-*threo*-pentose (XI); this manuscript describes these experiments.

The starting material for this work was also a sugar epoxide, methyl 2,3-anhydro-β-D-lyxofuranoside (III).[7] Reaction of III with sodium benzyl mercaptide gave an essentially quantitative yield of a sirup that was treated with *p*-nitrobenzoyl chloride in pyridine. Fractional crystallization of the acylation product afforded two di-*p*-nitrobenzoates, m.p. 91–92° and 139–140°. The assignment of structures I and IV, respectively, to these esters was based on n.m.r. data (see Table II). The comparison of the spectra of I and IV with those of the diols II and V obtained by saponification of I and IV, respectively, and of the diacetates of II and V showed that in the xylose series corresponding to I the coupling constant for the protons on C-1 and C-2 (J_{12}) was 1–1.5 c.p.s., the small value typical for the *trans* coupled C-1–C-2 protons of a pentofuranoside.[8] In the arabinosides related to IV, J_{12} = 4.3–4.5 c.p.s., typical of *cis*-C-1–C-2 protons of a pentofuranoside.[8] The optical rotation of the mixture of *p*-nitrobenzoates derived from the reaction of III and sodium benzyl mercaptide indicated that, approximately, a 60:40 mixture of II and V, respectively, was formed *as a result of predominant attack at C-2 of III.*

In order to provide chemical proof of structure for the diols II and V, the diols were desulfurized with Raney nickel, affording, after acetylation, the diacetates IX, isolated as a liquid by vapor phase chromatography and accompanied by an appreciable quantity of furfuryl acetate (VI), and XIII, as a crystalline solid; no furfuryl acetate was detected in the preparation of XIII. The n.m.r. spectra of the desulfurized compounds were in complete agreement with their assignments as 2-deoxy- and 3-deoxyglycosides, respectively. Thus the C-1 proton signal of IX appeared as a pair of doublets with J_{12} = 1.85 c.p.s. for the C-1–C-2 *trans*-coupled protons and J_{12} = 4.95 c.p.s. for the C-1–C-2 *cis*-coupled protons while the C-1 proton of XIII appeared as a single doublet with J_{12} = 4.1 c.p.s. as predicted for the *cis* situation of the protons at C-1 and C-2.[9] The acetates IX and XIII were converted to the deoxyfuranosides VIII and XII, then hydrolyzed to the free sugars. The α-benzylphenylhydrazone of 2-deoxy-D-*threo*-pentose (X) agreed in properties with the derivative reported in the literature,[10] while the α-benzylphenylhydrazone of 3-deoxy-D-*threo*-pentose (XI), a new sugar, was also a crystalline solid with different properties from that derivative of X.



The reaction of III with sodium benzyl mercaptide provides the first example of ring opening of a 2,3-anhydrofuranoside by a nucleophile in which the attack is not very predominantly at C-3.[4] For example, the reaction of epoxide III with ammonia is reported to give only the 3-amino sugar[7] and, in the synthesis of 9-(β-D-arabinofuranosyl)-adenine,[11] the opening of 9-(2',3'-anhydro-β-D-lyxofuranosyl)-adenine with sodium benzoate in N,N-dimethylformamide gave only a trace of the xylose isomer from epoxide opening at C-2'. It

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(2) A preliminary announcement of a portion of this work has appeared: *J. Am. Chem. Soc.*, **85**, 235 (1963).

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(4) C. D. Anderson, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, **81**, 898 (1959).

(5) C. D. Anderson, L. Goodman, and B. R. Baker, *ibid.*, **81**, 3967 (1959).

(6) W. W. Lee, A. Benitez, C. D. Anderson, L. Goodman, and B. R. Baker, *ibid.*, **83**, 1906 (1961).

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

(8) See K. L. Rinehart, Jr., W. S. Chilton, M. Hichens, and W. von Phillipsborn, *ibid.*, **84**, 3216 (1962), for a similar n.m.r. assignment of a pentofuranoside configuration.

(9) *Cf.* C. D. Anderson, W. W. Lee, L. Goodman, and B. R. Baker, *ibid.*, **83**, 1900 (1961), for the use of n.m.r. in differentiating 2-deoxy and 3-deoxy sugars.

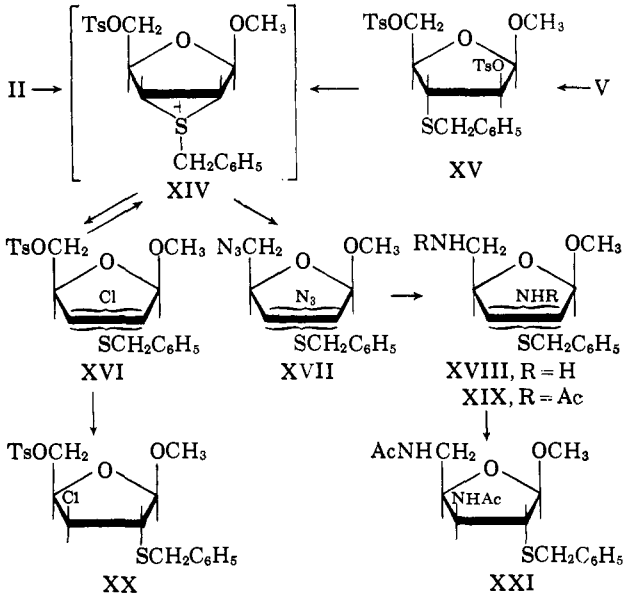
(10) F. Weygand and H. Wolz, *Ber.*, **85**, 256 (1952); G. Rembarz, *ibid.*, **95**, 1565 (1962).

(11) W. W. Lee, A. Benitez, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, **82**, 2648 (1960).

is interesting that the ring opening of the α-anomer of III with sodium benzyl mercaptide gave predominantly the 3-benzylthioarabinoside[12] and that cleavage of methyl 2,3-anhydro-β-D-ribofuranoside with sodium ethyl mercaptide gave exclusively the 3-ethylthioxyloside,[4] both of which results can be rationalized on the basis of steric considerations. The reason for the nonselectivity in the ring opening of III with sodium benzyl mercaptide is obscure, but it must be pointed out that there has been no sound explanation for the observed general predominance of C-3 ring opening with 2,3-anhydrofuranosides.

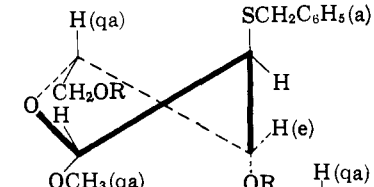
The diol V was reduced with sodium and liquid ammonia giving the mercaptan VII. Treatment of VII with triethyl phosphite under free radical conditions[13] gave the 3-deoxyglycoside XII as shown by vapor phase chromatographic identification of the diacetate XIII from acetylation of the desulfurization mixture. This technique of converting a thiol sugar to a deoxy sugar may have advantages with certain compounds over the conventional Raney nickel desulfurization.

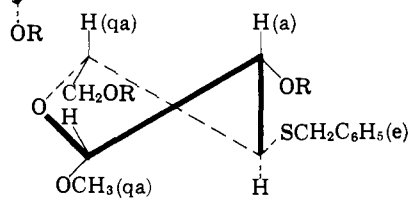
The 3-benzylthiodiol V, under standard tosylation conditions, formed a crystalline ditosylate (XV) while, under the same conditions, the 2-benzylthiodiol II formed



a monochloromonotosylate (XVI) from which a crystalline chlorotosylate, identified as XX by n.m.r. examination, could be obtained. An attempt to convert V to XVI by conducting the tosylation in the presence of a large amount of lithium chloride gave only XV, and an attempt to form XVI by heating XV in pyridine solution at 60–65° with a large quantity of tetramethylammonium chloride for 25 hr. resulted in the recovery of 60% of XV. Since the formation of XVI (and XX) is best rationalized as occurring *via* the episulfonium intermediate XIV, it is evident that XV strongly resists cyclization to XIV. It was of interest in this work to determine whether certain reactions of XV and XVI would proceed through the common intermediate XIV. For this purpose both XV and XVI were treated with sodium azide in hot 2-methoxyethanol giving the azide mixture XVII, qualitatively equivalent from both XV and XVI according to infrared spectra. The azidolysis reaction was not as clean as was desired for this type of study and seemed to be accompanied by some elimination of benzyl mercaptan in the case of both tosylates. Without purification, the azide mixtures (XVII) from both reactions were reduced with sodium borohydride in isopropyl alcohol[14] to the amines XVIII; the basic portion of the product was extracted with cold dilute acid and regenerated, then acetylated to give the solid di-N-acetate mixtures XIX. The final products (XIX) from both XV and XVI had essentially identical infrared spectra (both contained a small amount of O-acetate), n.m.r. spectra (which suggested that XXI was the predominant isomer), melting ranges, and elemental analyses and had optical rotations that were the same within experimental error. Further, the volatile products that remained after extraction of the amines (XVIII) showed nearly the same complex vapor phase chromatography pattern in the case of reactions of both XV and XVI. Recrystallization of the crude diamide XIX provided the pure xyloside XXI whose structure could be verified by n.m.r. analysis. Thus the attack of azide ion on XIV occurred largely at C-3 as might be expected simply on the basis of steric considerations. These data seem best explained by assuming the common intermediate XIV; evidently, under sufficiently forcing conditions, XV can be converted to XIV.

The difference in behavior of II and V to the same tosylation conditions points out the importance of conformational considerations in furanose sugars. Three recent articles have discussed the conformations of furanose sugars on the basis of n.m.r. spectroscopy.[15–17] The difference in chemical behavior between II and V can be rationalized by considering the glycosides to exist in the twist[17] conformation of the sugar ring with C-2 and C-3 out of the plane of the ring as in structures XXII and XXIII.[18] Thus in XXII, the diaxial relationship of the 2-benzylthio group and the 3-O-tosyl





group (where R = Ts) would be very favorable to episulfonium ion formation leading eventually to XX as the major product by diaxial[19] opening by chloride ion

(12) J. E. Christensen and L. Goodman, *J. Org. Chem.*, **28**, 2995 (1963).
(13) C. Walling and R. Rabinowitz, *J. Am. Chem. Soc.*, **81**, 1243 (1959).
(14) P. A. S. Smith, J. H. Hall, and R. O. Kan, *ibid.*, **84**, 485 (1962).
(15) R. U. Lemieux, *Can. J. Chem.*, **39**, 116 (1961).
(16) C. D. Jardetzky, *J. Am. Chem. Soc.*, **84**, 62 (1962).
(17) L. D. Hall, *Chem. Ind.* (London), 950 (1963).
(18) The conformer of XXII (*i.e.*, II) in which C-2 is *endo* and C-3 is *exo* and in which the benzylthio group and the OR group are diequatorial would be the preferred structure on thermodynamic grounds. However, both the chemistry and the n.m.r. data are compatible with conformer XXII (*i.e.*, II) and other factors must be involved that favor that structure.
(19) A. Fürst and Pl. A. Plattner, Abstracts of Papers, 12th International Congress of Pure and Applied Chemistry, New York, N. Y., 1951, p. 409.

TABLE I

COUPLING CONSTANTS (C.P.S.) FOR DERIVATIVES OF II AND V COMPARED WITH CALCULATED VALUES FOR XXII AND XXIII

	$J_{H-1-H-2}$	$J_{H-2-H-3}$	$J_{H-3-H-4}$
Calcd. for XXII	0.32	1.8	4.0
Found for II diacetate	1.5	2.2	5.0
Calcd. for XXIII	4.0	9.2	8.6
Found for V	4.4	8.7	8.7

TABLE II

N.M.R. DATA, CHEMICAL SHIFTS (τ), AND COUPLING CONSTANTS (C.P.S.)

Compound	C-1	C-2	C-3	C-4	C-5	OCH_3	$C_6H_5CH_2S$	p-CH_3	CH_3CO	OH
				Xylose isomers						
I	5.1	6.61	4.38	~5.1	5.34	6.61	6.03	..	..	...
	J_{12} ~1	$J_{2,3}$ 1.9	$J_{3,4}$ 5.1							
II	5.35	6.98	5.9	~6.1	6.3	6.73	6.23	..	..	6.5–7.1
	$J_{1,2}$ 1.4									
II diacetate	5.35	6.99	4.86	5.44	~5.9	6.74	6.15	..	7.97	...
	J_{12} 1.5	$J_{2,3}$ 2.2	$J_{3,4}$ 5.0						8.01	
XX	5.23	6.7	5.83	~5.6	~5.6	6.75	6.18	7.55	..	...
	$J_{1,2}$ 1.9	$J_{2,3}$ ~2	$J_{3,4}$ ~5							
XXI	5.25	7.13				6.68	6.18	..	8.02	
	$J_{1,2}$ 1.9								8.08	
IX (2-deoxy)	5.07	~7.6	4.7	5.83	5.83	6.67	..	..	7.97	...
	$J_{1,2}(cis)$ 5.0								8.00	
	$J_{1,2}(trans)$ 1.9									
				Arabinose isomers						
IV	4.96	4.81	6.45	5.84	5.56	6.73	6.11	..	..	...
	$J_{1,2}$ ~5									
V	5.31	~6.05	7.1	~6.05	~6.5	6.58	6.1	..	..	7.45
	$J_{1,2}$ 4.4	$J_{2,3}$ 8.7	$J_{3,4}$ 8.7							7.96
V diacetate	5.08	5.36	~6.9	~6.1	6.05	6.73	6.22	..	7.95	
	$J_{1,2}$ 4.3	$J_{2,3}$ 9.2	$J_{3,4}$ ~9						8.04	
XV	5.37	5.31	6.8	~6.10	~6.10	6.87	6.33	7.53	..	...
	$J_{1,2}$ ~5									
XIII (3-deoxy)	5.13	~5.3	~7.9	~5.9	~5.9	6.68	..	..	7.98	...
	$J_{1,2}$ 4.1									

of the ion XIV. In XXIII, on the other hand, the *trans*-diequatorial relationship of the 2-O-tosyl (R = Ts) group and the 3-benzylthio group would be very unfavorable to formation of the three-membered ion XIV making necessary much more severe reaction conditions in order to convert XV *via* XIV. Further, the formation of XXI as the major product from the series of reactions involving XV and XVI can now be rationalized by the more favorable diaxial opening of XIV by azide ion in the initial reaction. The comparison of the coupling constants calculated by Jardetzsky[16] for maximally puckered five-membered rings with the C-3-*endo*–C-2-*exo* conformation[16] with the values found for derivatives of II and V (Table I) are further evidence in favor of the twist conformations (XXII and XXIII).

Finally, the easy elimination of the elements of water and of methanol from VIII to form, after acetylation, furfuryl acetate (VI) can also be rationalized on the basis of the twist conformation. Representing VIII by structure XXII with the benzylthio group replaced by a proton and R = H, it can be seen that there is an easy path for *trans*-diaxial elimination of water between carbons 3 and 4 and for *trans*-diaxial elimination of methanol between carbons 1 and 2.

Experimental[20]

Methyl 2-Benzyl-3,5-di-O-(*p*-nitrobenzoyl)-2-thio-β-D-xylofuranoside (I) and Methyl 3-Benzyl-2,5-di-O-(*p*-nitrobenzoyl)-3-thio-β-D-arabinofuranoside (IV).—To a solution of 14.6 g. (0.100 mole) of the epoxide III in 30 ml. of dry methanol was added a solution of 5.5 g. (0.102 mole) of sodium methoxide and 12.65 g. (0.102 mole) of benzyl mercaptan in 60 ml. of dry methanol. The resulting solution was heated at reflux under nitrogen for 30 hr., adjusted to pH 7 with glacial acetic acid, then evaporated *in vacuo* leaving a viscous sirup. The residue was dissolved in 100 ml. of water and the solution was extracted with one 100-ml. and two 50-ml. portions of dichloromethane. After being dried, the combined extracts were evaporated *in vacuo* and the residual yellow sirup was boiled with 100 ml. of Skellysolve B (petroleum ether, b.p. 62–70°) leaving, after decantation of the solvent, 25.6 g. (95%) of sirup. Conventional esterification of 23.6 g. of this residue with 47.5 g. of *p*-nitrobenzoyl chloride and 320 ml. of dry pyridine at 0° followed by 18 hr. at room temperature gave 47 g. (95%) of crystalline solid after a standard work-up which included removal of last traces of pyridine by evaporation of a toluene solution of the residue. The solid residue had $[\alpha]^{26}$ $-58.5 \pm 1.1°$ (1%)[20] indicating a 56:44 ratio of I:IV. To 45 g. of the mixture dissolved in 100 ml. of dichloromethane was added 150 ml. of Skellysolve B. The mixture was allowed to stand overnight at room temperature and the separated solid, 11.4 g., m.p. 127–140°, was collected. Further dilution with Skellysolve B led to a succession of solids which were mixtures of I and IV, the first higher-melting fractions being richer in IV and the last lower-melting fractions being enriched with I. The higher melting fractions were recrystallized by dissolving in the ratio of 1 g. per 3 ml. of dichloromethane and diluting the solution with 10 ml. of Skellylsolve B to recover additional IV while the lower-melting solids in solution, 1 g. per 10 ml. of dichloromethane, were precipitated by addition of 50 ml. of Skellysolve B added in small portions to recover, after seeding, additional I. The analytical samples of I and IV were obtained by repeated recrystallizations from dichloromethane–Skellylsolve B. The diester I had m.p. 91–92° and $[\alpha]^{25}$ $-113.6 \pm 1.9°$ (2%).

Anal. Calcd. for $C_{27}H_{24}N_2O_{10}S$: C, 57.0; H, 4.25; N, 4.93; S, 5.64. Found: C, 57.0; H, 4.31; N, 4.87; S, 5.58.

The diester IV had m.p. 139–140° and $[\alpha]^{25}D$ $+11.2 \pm 0.2°$ (2%).

Anal. Found: C, 57.0; H, 4.51; N, 4.89; S, 5.61.

(20) Boiling points and melting points are uncorrected; the latter were obtained with the Fisher–Johns block. The n.m.r. spectra were mainly run in deuteriochloroform using a Varian V-4311 spectrometer operated at 60 Mc.; tetramethylsilane was used as a reference standard. Vapor phase chromatography was carried out on a 5-ft., 0.25-in. butanediol succinate polyester on silanazed Chromosorb (20:80 w./w.) column operated at 150 or 200°. Optical rotations refer to solutions in chloroform at 5890 Å. unless otherwise noted. Magnesium sulfate was used as the drying agent unless otherwise noted.

The two isomers I and IV could be distinguished by thin-layer chromatography on alumina using benzene as an eluent wherein I traveled somewhat faster than IV as shown by detection with ultraviolet light or a potassium permanganate spray. Careful chromatography of a mixture of I and IV on alumina (Brockmann activity III) also served as a means of separating the isomers.

Methyl 2-Benzyl-2-thio-β-D-xylofuranoside (II) and Its Diacetate.—A mixture of 5.45 g. (9.6 mmoles) of the diester I, 3.3 g. (59 mmoles) of potassium hydroxide, 30 ml. of methanol, and 12 ml. of water was heated at reflux for 2 hr., then evaporated *in vacuo*. The residual sirup was dissolved in 25 ml. of water and the solution was extracted with six 40-ml. portions of chloroform. The combined extracts were dried, then evaporated yielding 2.6 g. (100% yield) of an oil, $[\alpha]^{24}$ −45.1° (0.75%).

Anal. Calcd. for $C_{13}H_{18}O_4S$: C, 57.8; H, 6.71; S, 11.9. Found: C, 57.8; H, 7.14; S, 11.6.

A mixture of 0.54 g. (2.0 mmoles) of II, 4 ml. of pyridine, and 0.80 ml. of acetic anhydride was left at room temperature for 18 hr., then diluted with 0.40 ml. of water. After standing 2 hr., the mixture was diluted with 15 ml. of chloroform and extracted with four 5-ml. portions of saturated aqueous sodium bicarbonate. The chloroform solution was dried and evaporated *in vacuo* leaving 0.64 g. (90%) of an oil that was evaporatively distilled. The diacetate boiled at 100–110° (bath temperature) at 0.004 mm. giving a distillate with $[\alpha]^{25}$ −123.8° (0.90%).

Anal. Calcd. for $C_{17}H_{22}O_6S$: C, 57.6; H, 6.26; S, 9.04. Found: C, 57.6; H, 6.19; S, 9.09.

Methyl 3-Benzyl-3-thio-β-D-arabinofuranoside (V) and Its Diacetate.—The hydrolysis of 5.7 g. of IV, using the procedure described for the preparation of II, afforded 2.7 g. (100% yield) of a sirup which, by recrystallization from 300 ml. of boiling Skellysolve B, afforded 2.4 g. (88% yield) of colorless needles, m.p. 52–54°. The analytical sample obtained by recrystallization from Skellysolve B had the same melting range and $[\alpha]^{25}$ −23.5° (2%).

Anal. Found: C, 58.0; H, 6.90; S, 11.7.

The diacetate from V was prepared from 0.54 g. of V by the procedure described for synthesis of the diacetate of II. The product, 0.70 g. (99% yield), was evaporatively distilled at 100–120° (bath temperature) and 0.005 mm. affording a colorless oil, $[\alpha]^{25}$ −22.0° (1.25%).

Anal. Found: C, 57.9; H, 6.31; S, 9.12.

Methyl 3,5-Di-O-acetyl-2-deoxy-β-D-*threo*-pentofuranoside (IX).—A well stirred mixture of 2.6 g. (9.7 mmoles) of the diol II, about 26 g. of Raney nickel[21] (thoroughly washed with absolute ethanol), and 50 ml. of absolute ethanol was heated at reflux for 6 hr., then filtered through Celite. The filter cake was washed with several portions of boiling absolute ethanol and the filtrate and the washes were evaporated at 30° and 20 mm. leaving 1.20 g. of a colorless sirup whose infrared spectrum showed that some of the S-benzyl group was still present. The product was acetylated with 15 ml. of pyridine and 3.5 ml. of acetic anhydride and worked up conventionally, the pyridine being removed with ice-cold 0.5 *N* hydrochloric acid. The acetylated product, 1.7 g., had the distinctive odor of a simple acetate ester. Evaporative distillation of the product at 20 mm. furnished two fractions: (a) 0.05 g. boiling at 60–95° (bath temperature) which was identified as furfuryl acetate (VI) by infrared and gas chromatographic comparison with authentic material, and (b) 0.80 g. collected at 100–140° which was still contaminated with some furfuryl acetate but which was mainly the diester IX. The diacetate IX was collected by preparative gas chromatography of fraction b at 200°[20] giving a colorless oil with $[\alpha]^{25}$ −79.5° (0.75%).

Anal. Calcd. for $C_{10}H_{16}O_6$: C, 51.7; H, 6.94. Found: C, 52.0; H, 6.83.

The gas chromatographic pattern of the crude product (after acetylation) of another desulfurization of II indicated an over-all yield from II of 5.5% of VI and 32% of IX.

Methyl 2,5-Di-O-acetyl-3-deoxy-β-D-*threo*-pentofuranoside (XIII).—Using the conditions described for the desulfurization of II, 1.0 g. of crystalline V was converted to 0.45 g. (82% yield) of a yellow sirup which was acetylated as described for the preparation of IX, affording 0.55 g. of product that was evaporatively distilled at 100–120° (bath temperature) and 20 mm. The distillate crystallized and was recrystallized from a small volume of Skellysolve B giving the analytical sample, m.p. 63–64°, $[\alpha]^{25}$ −111.4° (1.85%).

Anal. Found: C, 51.5; H, 6.75.

(21) Sponge nickel catalyst, Davison Chemical Co., Cincinnati 29, Ohio.

Compound XIII showed a slightly greater retention time on gas chromatography[20] at 200° than did IX but the difference was not sufficient for a chromatographic separation. Gas chromatography showed the absence of furfuryl acetate (VI) from the product and indicated an over-all yield of 46% of XIII from V.

2-Deoxy-D-*threo*-pentose (X) 1-Benzyl-1-phenylhydrazone.—A solution of 80 mg. of IX in 3 ml. of dry methanol was treated with a trace (1–2 mg.) of sodium methoxide. After the solution had stood overnight at room temperature, it was evaporated *in vacuo* and the residue was dissolved in 3 ml. of water. The aqueous solution was neutralized by stirring with 100 mg. of IRC-50 (H) and, after filtration, the neutral solution was evaporated *in vacuo* leaving 35 mg. of sirup (VIII). The glycoside VIII was dissolved in 5 ml. of 0.01 *N* aqueous acetic acid and the solution, under nitrogen, was heated at reflux 1.75 hr., then evaporated *in vacuo* leaving 30 mg. of sirupy free sugar (X). Compound X was dissolved in 0.2 ml. of isopropyl alcohol, 0.10 g. of 1-benzyl-1-phenylhydrazine as the free base was added, and the mixture was left at room temperature for 4 days, then evaporated *in vacuo*. The residue was triturated with 2 ml. of dry ether, the ether was decanted and, on standing, the ethereal solution deposited a crystalline solid. Two recrystallizations from benzene–petroleum ether (30–60°) afforded 15 mg. of the analytical sample, m.p. 115–116°, $[\alpha]^{24}$ +11.7° (1% in pyridine) [lit.[10] gives m.p. 115–117° and $[\alpha]^{20}$ +13.1° (1.10% in pyridine)].

3-Deoxy-D-*threo*-pentose (XI) 1-Benzyl-1-phenylhydrazone.—Crystalline diacetate XIII, 0.14 g., was converted to 90 mg. of XII, as a sirup, by the method described for preparation of VIII. The glycoside XII in 5 ml. of 0.01 *N* hydrochloric acid was heated at reflux for 1 hr., then the solution was stirred with 50 mg. of Dowex 2 (CO_3), filtered, and evaporated *in vacuo*, leaving 80 mg. of XI as a sirup. Treatment with 1-benzyl-1-phenylhydrazine by the procedure used in derivatizing X gave 30 mg. of crystalline solid, m.p. 85–88°. Two recrystallizations from dry ether afforded the analytical sample, m.p. 86.0–86.5°, $[\alpha]^{24}$ +16.2° (1%).

Anal. Calcd. for $C_{18}H_{22}N_2O_3$: C, 68.8; H, 7.05; N, 8.91. Found: C, 68.7; H, 6.90; N, 9.08.

Methyl 3-Thio-β-D-arabinofuranoside (VII) and Its Triacetate.—A solution of 1.00 g. (3.70 mmoles) of the diol V in 8 ml. of 1,2-dimethoxyethane was added dropwise and with stirring to a solution of 0.425 g. (18.5 mg.-atoms) of sodium in 20 ml. of liquid ammonia. The mixture was stirred at −70° for 0.5 hr., then 5 ml. of ethanol was added dropwise. The suspension was evaporated with a nitrogen stream, 10 ml. of water was added to the residue, and the solution was adjusted to pH 7 with glacial acetic acid and extracted with 5 ml. of chloroform. The aqueous phase was evaporated *in vacuo* and the residue was partitioned between 4 ml. of water and 40 ml. of chloroform. The aqueous solution was extracted with five 20-ml. portions of chloroform; the combined chloroform solutions were dried and evaporated leaving 0.46 g. (69%) of a colorless sirup (VII) which gave a strong positive nitroprusside test and whose infrared spectrum showed thiol absorption at 3.92 μ.

Acetylation of 50 mg. of VII by the conventional procedure using pyridine and acetic anhydride gave an oily triacetate whose infrared spectrum showed O-acetate absorption at 5.72 μ and S-acetate absorption at 5.84 μ in a ratio of about 2:1.

Anal. Calcd. for $C_{12}H_{18}O_7S$: C, 47.1; H, 5.92; S, 10.5. Found: C, 46.7; H, 5.76; S, 9.53.

A mixture of 0.18 g. (1.0 mmoles) of VII, 0.20 ml. (1.15 mmoles) of triethyl phosphite, 1 ml. of dioxane, and a trace of azobisisobutyronitrile was heated at 70° for 1 hr. and then, with ice cooling, treated with 3 ml. of pyridine and 0.6 ml. of acetic anhydride. The mixture was left overnight at room temperature, treated with 0.2 ml. of water, stirred at room temperature 2 hr., then diluted with 10 ml. of chloroform, and extracted with four 4-ml. portions of saturated aqueous sodium bicarbonate. The chloroform solution was dried and used directly for gas chromatography.[20] The triethyl phosphite peak was weak and strong peaks with the same retention times as triethyl thionophosphate and methyl 2,5-di-O-acetyl-3-deoxy-β-D-*threo*-pentofuranoside (XIII) were noted. Evaporation of the chloroform solution *in vacuo* gave a residue whose infrared spectrum was comparable to that of an equimolar mixture of triethyl thionophosphate and XIII; there was no S-acetyl absorption at 5.84 μ.

Acetylation of a mixture of triethyl phosphite and triethyl thionophosphate by the method described above and analysis of the reaction product by gas chromatography showed that the two components were not changed by the reaction conditions.

Methyl 3-Benzyl-3-thio-2,5-di-O-(*p*-tolylsulfonyl)-β-D-arabinofuranoside (XV).—To a chilled (0°) stirred solution of 0.54 g. (2.00 mmoles) of the diol V in 10 ml. of dry pyridine was added, in small portions, 1.90 g. (10.00 mmoles) of *p*-toluenesulfonyl chloride. The mixture was stirred at room temperature for 66 hr., 0.5 ml. of water was added, and stirring was continued for 4 hr.; then the mixture was evaporated *in vacuo*. Water, 20 ml., was added to the residue and the brown oil which resulted was separated by extraction with three 10-ml. portions of chloroform. The combined extracts were washed twice with 4 ml. of water, dried, and evaporated *in vacuo* affording 1.33 g. (115% yield) of a brown oil that crystallized on standing. The solid was recrystallized from benzene–Skellysolve B giving, after four recrystallizations, the analytical sample, m.p. 80°, $[\alpha]^{25}$ +27.0° (1.9%).

Anal. Calcd. for $C_{27}H_{30}O_8S_3$: C, 56.0; H, 5.22; S, 16.6. Found: C, 56.0; H, 5.20; S, 16.8.

Another crystal form of XV, m.p. 87.5–91°, was isolated in later work.

Anal. Found: C, 56.5; H, 5.22; S, 16.6.

When the tosylation of V was conducted in the presence of 20 mmoles of lithium chloride with the quantities and conditions as described above, 0.86 g. (74%) of crystalline tosylate XV was obtained. When 0.29 g. of XV in 20 ml. of dry pyridine containing 0.60 g. of dry tetramethylammonium chloride was heated at 61–64° for 25 hr. and the mixture worked up as in the tosylation, 0.18 g. of the ditosylate was recovered.

Methyl 2(3)-Benzyl-3(2)-chloro-3(2)-deoxy-2(3)-thio-5-O-*p*-(tolylsulfonyl)-β-D-xylo-(arabino)-furanoside (XVI) and Methyl 2-Benzyl-3-chloro-3-deoxy-2-thio-5-O-(*p*-tolylsulfonyl)-β-D-xylofuranoside (XX).—Treatment of 1.08 g. (6.00 mmoles) of the diol II with 3.80 g. of *p*-tolylsulfonyl chloride by the procedure described for tosylation of V gave 2.0 g. (75%) of a brown sirup which darkened on standing. From another similar run the product was analyzed.

Anal. Calcd. for $C_{20}H_{23}ClO_5S_2$: C, 54.2; H, 5.23; Cl, 8.00; S, 14.5. Found: C, 54.0; H, 5.32; Cl, 9.12; S, 14.9.

After standing at 5° for 2 months the, by-now-black, sirup largely crystallized. The crystalline material was dissolved in a small volume of cold benzene and the solution decanted from the insoluble black tar. The benzene solution was treated at room temperature with Norit A and filtered, and the filtrate was diluted with Skellysolve B to give colorless crystals, m.p. 75–80°. Two more such recrystallizations afforded material, m.p. 80–81°, $[\alpha]^{24}$ −33.8° (2%), which gave a positive Beilstein test for halogen and which gave a mixture melting point of 60–65° with the polymorph of XV, m.p. 80°.

Anal. Found: C, 55.4; H, 5.93; Cl, 7.92; S, 14.9.

Conversion of XV and XVI to Methyl 3(2),5-Diacetamido-2(3)-benzyl-3(2),5-dideoxy-2(3)-thio-β-D-xylo-(arabino)-furanoside (XIX).—A stirred mixture of 1.00 g. (1.73 mmoles) of ditosylate XV, 1.40 g. (21.6 mmoles) of sodium azide, and 12 ml. of 95% aqueous 2-methoxyethanol was heated at 105–110°, under nitrogen, for 17 hr., then cooled and evaporated *in vacuo*. The residue was dissolved in 50 ml. of water and extracted with three 45-ml. portions of chloroform; the combined extracts were washed with 50 ml. of water and dried adding Norit A during the drying. Evaporation *in vacuo* gave 0.40 g. of dark, viscous sirup (XVII) whose infrared spectrum showed strong azide absorption at 4.72 μ and no tosyl absorption. From 0.80 g. (1.78 mmoles) of the chlorotosylate XVI, by an identical procedure, was obtained 0.48 g. of brown oil which showed some tosyl absorption at 8.50 μ but strong azide absorption at 4.72 μ.

The crude azide XVII, 0.40 g., from XV was dissolved in 15 ml. of isopropyl alcohol, 0.20 g. of sodium borohydride was added, and the stirred mixture was heated at reflux, under nitrogen for 17 hr., then evaporated *in vacuo*. The residue was dissolved in 12 ml. of water and extracted with three 15-ml. portions of dichloromethane; the combined extracts were washed with 15 ml. of water and dried, then evaporated *in vacuo*. The infrared spectrum of the residue which smelled strongly of benzyl mercaptan showed that only a trace of azide remained. The residue was dissolved in 15 ml. of dichloromethane and extracted with 12 ml. of ice-cold 1 *N* hydrochloric acid giving the nonbasic chloroform fraction B and the acid extract A. The extract A was made strongly basic with 12 ml. of ice-cold 5 *N* aqueous potassium hydroxide and extracted with three 15-ml. portions of dichloromethane. The combined extracts were washed with 10 ml. of water and dried, then evaporated *in vacuo* to give 0.17 g. of yellow sirup whose infrared spectrum showed the absorptions at 2.95, 3.02, and 6.22 μ expected for the amino groups and which was almost identical with the spectrum of the similar material derived from XVI (see below). Acetylation of this sirup with 2 ml. of dry pyridine, 1 ml. of acetic anhydride, and 3 drops of triethylamine yielded 0.21 g. of a yellow sirup (XIX) that crystallized on standing, m.p. 85–110°, $[\alpha]^{25}$ −131.4 ± 11.3° (1.13%). Its infrared spectrum showed a small O-acetate band at 5.72 μ.

Anal. Calcd. for $C_{17}H_{24}N_2O_4S$: C, 57.9; H, 6.86; N, 7.95; S, 9.10. Found: C, 58.3; H, 6.59; N, 7.32; S, 8.82.

The crude azide XVII, 0.48 g., from XVI was treated in the same way to give 0.25 g. of a sirup (XIX) that crystallized on standing, m.p. 90–115°, $[\alpha]^{24}$ −146.4 ± 12.6° (1.15%). Its infrared spectrum was almost identical with that of the product from XV as was its n.m.r. spectrum.

Anal. Found: C, 58.5; H, 6.85; N, 7.39; S, 9.32.

The chloroform extracts B from the sodium borohydride reduction products in both cases were acetylated, affording, in each case, about 0.10 g. of dark viscous oil which gave a similar and complex pattern on gas chromatography[20] at 200°. The infrared spectra of the fractions B from XV and XVI were not identical but showed generally the same functional groups including both O-acetate and N-acetate absorptions.

Methyl 3,5-Diacetamido-2-benzyl-3,5-dideoxy-2-thio-β-D-xylofuranoside (XXI).—Recrystallization of the mixed diamides XIX derived from both XV and XVI from benzene–hexane and finally from carbon tetrachloride–Skellysolve B gave a product with m.p. 118.5–120.0°, $[\alpha]^{25}$ −181° (1.025%).

Anal. Found: C, 57.8; H, 6.90; N, 8.02; S, 9.11.

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