was controlled by external cooling. After the initial exothermic reaction (1 hr.), the mixture was left shaking for another 24 hr. The homogeneous solution was cooled, methanol added (200 ml.), and the barium salts filtered. The filtrate was dialyzed for 3 days, the solid materials collected by concentrating the dialysate, and the product freeze-dried; yield, 3.2 g.

Anal. Calcd. for $C_6H_7O_2(NHCOCH_3)(OCH_3)_2$: OCH_3, 26.8. Found[20]: OCH_3, 17.2 (66% of theory for fully methylated chitin).

The acetylation and methylation procedures were repeated twice more, followed by reacetylation.

Anal. Calcd. for $C_6H_7O_2(NHCOCH_3)(OCH_3)_2$: OCH_3, 26.8. Found[20]: OCH_3, 24.17 (92% of theory for fully methylated chitin).

Hydrolysis of Permethylated Chitin and Isolation of 2-Acetamido-2-deoxy-3,6-di-*O*-methyl-α-D-glucopyranose.—The above-methylated product (1.5 g.) was hydrolyzed in 6 *N* hydrochloric acid (200 ml.) at 100° for 12 hr. After removal of acid by concentration and codistillation with 1-propanol, the resulting sirup was dissolved in methanol, treated with carbon, the carbon removed by filtering through a sintered glass Büchner funnel covered with a 5-mm. bed of Celite,[22] and the filtrate concentrated to a yellow sirup. The sirup was dissolved in water (5 ml.) and the solution placed on a column (20 × 200 mm.) of Amberlite IR-120 ion-exchange resin (H^+ form). After washing the column to neutrality, the amino sugar derivative was eluted with 1 *N* hydrochloric acid (25 ml.) and sufficient water to give a neutral eluate. The combined eluate and washings were then concentrated to a small volume and the final traces of acid removed by codistillation with 1-propanol; yield 0.6 g. of sirup. Upon concentrating the sirup several times with ethanol, crystals formed, which were filtered and identified by X-ray powder diffraction pattern[24] as 2-amino-2-deoxy-α-D-glucose hydrochloride; yield 68 mg. (12.5%).

The remaining sirup (0.35 g.) was *N*-acetylated by the Roseman and Ludowieg method[6] described above in the preparation of 2-acetamido-2-deoxy-3,6-di-*O*-methyl-α-D-glucopyranose from methylated, carboxyl-reduced heparin. The *N*-acetylated, ninhydrin-negative sirup (148 mg.) was chromatographed by the thin layer technique with 7:3 benzene–methanol.[20] Zones, located with alkaline potassium permanganate spray reagent,[20] corresponded to 2-acetamido-2-deoxyglucose (1.00), $R_{2\text{-acetamido-2-deoxyglucose}}$ 1.8 (strong intensity), 2.62 (medium intensity), and 3.10 (weak intensity). Isolative thin layer chromatography on 19.5 × 19.5 cm. plates with a 0.5-mm. thickness of Silica Gel G yielded on elution of the zone with $R_{2\text{-acetamido-2-deoxyglucose}}$ 2.62 from the silica gel with methanol and concentration, a sirup which crystallized from ethanol–ether–petroleum ether in long needles; yield 21 mg. (14.2% of the sirup chromatographed), m.p. 229–232°, $[\alpha]^{20}D$ +38 ± 5° (final, *c* 0.18, water). For this compound Jeanloz reports[6] $[\alpha]^{25}D$ +90 (15 min.) → +35 ± 5° (24 hr., *c* 0.29, water). This compound was chromatographically homogeneous in solvents A, B, and C and possessed in these solvents the same chromatographic mobility as a sample of 2-acetamido-2-deoxy-3,6-di-*O*-methyl-α-D-glucose obtained from Professor R. Kuhn. The preparation gave an X-ray powder diffraction pattern identical with that of the authentic compound obtained from Professor Kuhn as well as samples of the same compound isolated on hydrolysis of both a methylated disaccharide from carboxyl-reduced heparin[9] and of the permethylated, carboxyl-reduced heparin described above.

Acknowledgment.—This work was supported by the National Science Foundation (Grant G13967; The Ohio State University Research Foundation Project 1164). The heparin used was kindly furnished by the Upjohn Co., Kalamazoo, Michigan. Professor R. Kuhn furnished the reference sample of 2-acetamido-2-deoxy-3,6-di-*O*-methyl-α-D-glucose.

(24) I. Werner, *Mikrochim. Acta*, **39**, 133 (1952).

Stereochemical Effects in the Nucleophilic Displacement Reactions of Primary Carbohydrate Benzenesulfonate Esters with Sodium Iodide[1]

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Reactivities of seven primary benzenesulfonate esters, 1,2,3,4-tetra-*O*-acetyl-6-*O*-(phenylsulfonyl)-β-D-glucopyranose (I), 1,2:3,4-di-*O*-isopropylidene-6-*O*-(phenylsulfonyl)-D-galactopyranose (II), 2,4:3,5-di-*O*-methylene-1-*O*-(phenylsulfonyl)-DL-ribitol (III), 2,4:3,5-di-*O*-methylene-1-*O*-(phenylsulfonyl)-DL-xylitol (IV), 2,4:3,5-di-*O*-benzylidene-1-*O*-(phenylsulfonyl)-L-xylitol (V), 2,4:3,5-di-*O*-methylene-1,6-di-*O*-(phenylsulfonyl)-D-mannitol (VI), and 2,3,4,5-di-*O*-benzylidene-1,6-di-*O*-(phenylsulfonyl)-D-mannitol (VII), toward nucleophilic displacement by sodium iodide in acetonylacetone were determined. Rate constants and activation parameters were established. The data demonstrated that the compounds may be placed into two classes on the basis of ease of reaction. An explanation is proposed based upon the differences in the extent of field interaction of the nucleophilic reagent with electronegative atoms in these as well as other substrates.

In reactions involving displacement of primary iodides with cyanide ion to effect synthesis of deoxynitrile derivatives of carbohydrates, differences in reactivity were observed for the several substrates applied.[2] A rationalization was proposed based upon the degree of interaction of the nucleophilic reagent with the electronegative atmosphere found on the backside of the carbon atom undergoing displacement. An inspection of a summary[3] of data, describing the general reaction applied in carbohydrate chemistry of displacing primary sulfonate esters with iodide ion, suggested the possibility of making the same interpretation for this reaction. Accordingly, a study was made to confirm this observation.

Seven substrates were selected for the kinetic studies described herein. All compounds contained primary benzenesulfonate ester groups so that the departing group could be the same in the displacement reactions studied. 1,2,3,4-Tetra-*O*-acetyl-6-*O*-(phenylsulfonyl)-β-D-glucopyranose (I),[4] 1,2:3,4-di-*O*-isopropylidene-6-*O*-(phenylsulfonyl)-D-galactopyranose (II),[5] 2,4:3,5-di-*O*-methylene-1-*O*-(phenylsulfonyl)-DL-ribitol (III),[6] and 2,4:3,5-di-*O*-methylene-1-*O*-(phenylsulfonyl)-DL-xylitol (IV)[7] were prepared by methods

(1) Abstracted from a portion of the Ph.D. thesis of W. J. Teerlink, University of Utah, August, 1963.

(2) J. M. Sugihara, W. J. Teerlink, R. MacLeod, S. M. Dorrence, and C. H. Springer, *J. Org. Chem.*, **28**, 2079 (1963).

(3) R. S. Tipson, *Advan. Carbohydrate Chem.*, **8**, 181 (1953).

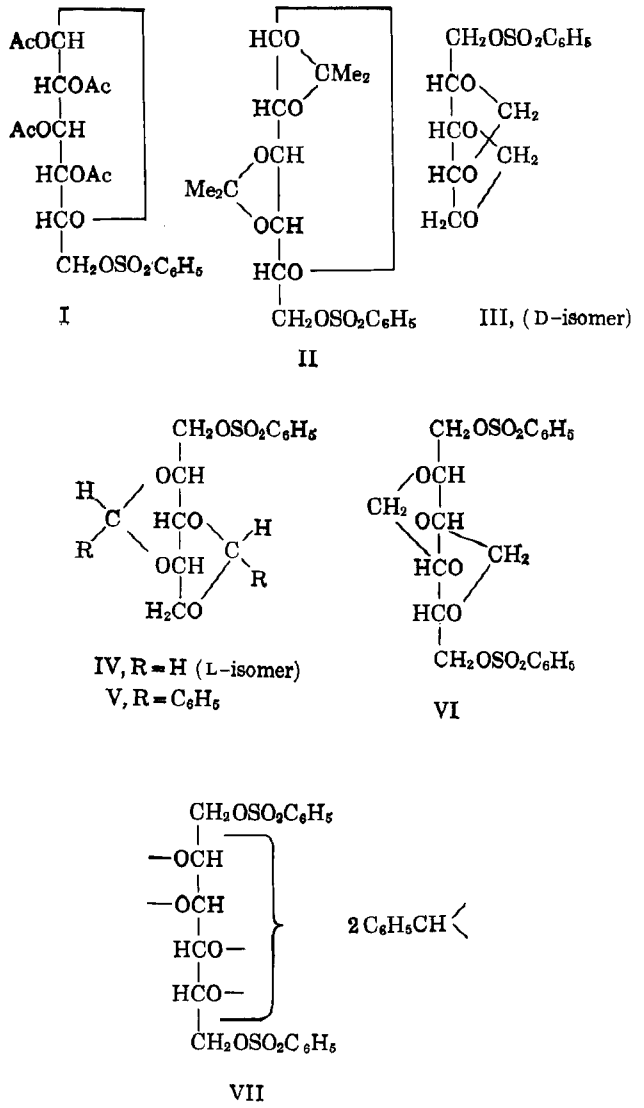
(4) E. Hardegger and R. M. Montavon, *Helv. Chim. Acta*, **29**, 1199 (1946).

(5) A. L. Raymond and E. F. Schroeder, *J. Am. Chem. Soc.*, **70**, 2785 (1948).

(6) R. M. Hann and C. S. Hudson, *ibid.*, **66**, 1906 (1944).

(7) R. M. Hann, A. T. Ness, and C. S. Hudson, *ibid.*, **66**, 670 (1944).

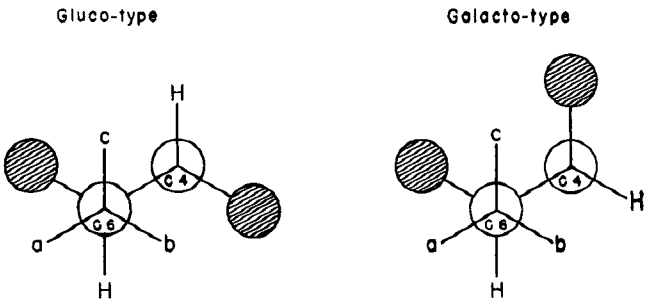
CHART I



used in the synthesis of the corresponding *p*-tolylsulfonyl derivatives. 2,4:3,5-Di-*O*-benzylidene-1-*O*-(phenylsulfonyl)-L-xylitol (V) was synthesized starting from the known 1,3:2,4-di-*O*-benzylidene-D-sorbitol,[8] which was oxidized with periodate to yield 2,4:3,5-di-*O*-benzylidene-L-xylose, which was isolated as its crystalline ethyl hemiacetal. Reduction of the latter with lithium aluminum hydride provided 2,4:3,5-di-*O*-benzylidene-L-xylitol, which was obtained as an intractable gel, and was thus purified by formation of its crystalline acetate. Transesterification with sodium methoxide in methanol gave the purified di-*O*-benzylidene-L-xylitol, which was readily converted into crystalline V by reaction with benzenesulfonyl chloride in pyridine. The preparation of 2,4:3,5-di-*O*-methylene-1,6-di-*O*-(phenylsulfonyl)-D-mannitol (VI) and 2,3,4,5-di-*O*-benzylidene-1,6-di-*O*-(phenylsulfonyl)-D-mannitol (VII) is described in the literature.[9]

Rate measurements were made by following iodide ion concentrations titrimetrically. Second-order rate constants were established for the seven substrates and are given in Table I. The method of least squares was applied in determining slopes of lines from the experimental data. Standard deviations[10] were established. Heats and entropies of activation were calculated from the absolute rate equation.[11a] Relative rate constants at 100° also were calculated to permit direct comparisons in reactivity. These data are given in Table II.

Reactivities of the seven substrates fall into two distinct groups. Compounds I, III, VI, and VII were found to be more reactive than II, IV, and V. The fiftyfold difference in reactivity exhibited by the diastereoisomers, 2,4:3,5-di-*O*-methylene-1-*O*-(phenylsulfonyl)-DL-ribitol (III) and the DL-xylitol derivative (IV), is very significant. A rationalization of these differences may be made by a conformational analysis of the substrates. As proposed earlier,[2] the difference in reactivity of the glucose derivative (I) and the galactose derivative (II) may be related to the difference in location of the oxygen atom at C-4. In II, the C-6



phenylsulfonyloxy bond would be expected to be oriented predominantly near a or b, as described in the Newman projection formula given, while in I all staggered conformations appear essentially equally probable. The backside approach of the nucleophilic reagent on substrate I would be impeded only by the ring oxygen. With substrate II, both the ring oxygen and the oxygen at C-4 would influence approach of the nucleophilic reagent in the two most probable staggered conformations.[11b] The ketal ring on C-3 and C-4 of II should tend to distort the C-4–O bond away from a true axial position.

Six-membered acetal rings also may be classified into the same two categories. The fused ring in III is of the *trans*-decalin type with the primary sulfonyloxymethyl group in an equatorial position in much the same environment as in I. Relative rate constants for displacement are very similar for the two. IV has a fused ring of the *cis*-decalin type, which allows two all-chair conformations. The "O-inside"[12] conformation depicted, with the function undergoing displacement in an atmosphere of the galacto-type, is more likely than the "H-inside"[12] form because of its greater stability,[13] and because the bulky sulfonyloxymethyl group would not be placed inside the folded portion.

(8) J. K. Wolfe, R. M. Hann, and C. S. Hudson, *J. Am. Chem. Soc.*, **64**, 1493 (1942).

(9) G. S. Skinner, L. A. Henderson, and C. G. Gustafson, Jr., *ibid.*, **80**, 3788 (1958).

(10) W. J. Youden, "Statistical Methods for Chemists," John Wiley and Sons, Inc., New York, N. Y., 1951, p. 42.

(11) (a) S. Glasstone, K. J. Laidler, and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941, p. 14. (b) A referee suggested that the difference in reactivity could be more readily explained on the basis of steric-type nonbonded interactions. We propose that the geometry of the transition state for the gluco- and galacto-types need not be the same. On this basis, eclipsing effects would be different and would be dependent upon the degree of interaction of the incoming and departing anions with oxygen atoms in the substrate. For these reasons, an explanation based upon field effects appears more logical to us.

(12) J. A. Mills, *Advan. Carbohydrate Chem.*, **10**, 1 (1955).

(13) R. U. Lemieux and J. Howard, *Can. J. Chem.*, **41**, 393 (1963).

TABLE I

RATE CONSTANTS FOR REACTION OF PRIMARY CARBOHYDRATE SULFONATES WITH SODIUM IODIDE

Compound	$k_r \times 10^4$, l. mole^{-1} sec.$^{-1}$						
	65°	70°	75°	80°	85°		
1,2,3,4-Tetra-*O*-acetyl-6-*O*-(phenylsulfonyl)-β-D-glucopyranose (I)	2.24 ± 0.05	3.52 ± 0.03	5.63 ± 0.06	8.81 ± 0.24	13.75 ± 0.08		
2,4:3,5-Di-*O*-methylene-1-*O*-(phenylsulfonyl)-DL-ribitol (III)	2.91 ± 0.10	4.64 ± 0.03	7.41 ± 0.07	11.48 ± 0.08			
2,4:3,5-Di-*O*-methylene-1,6-di-*O*-(phenylsulfonyl)-D-mannitol (VI)		7.25 ± 0.05	11.72 ± 0.11	18.78 ± 0.15	29.3 ± 0.14		
2,3,4,5-Di-*O*-benzylidene-1,6-di-*O*-(phenylsulfonyl)-D-mannitol (VII)		7.94 ± 0.11	13.77 ± 0.36	22.0 ± 0.27	34.3 ± 0.24		
	110°	115°	120°	125°	130°	135°	145°
1,2:3,4-Di-*O*-isopropylidene-6-*O*-(phenylsulfonyl)-D-galactopyranose (II)		1.55 ± 0.05	2.35 ± 0.11	3.64 ± 0.07	5.22 ± 0.11	7.60 ± 0.05	
2,4:3,5-Di-*O*-methylene-1-*O*-(phenylsulfonyl)-DL-xylitol (IV)	2.79 ± 0.08	4.10 ± 0.08	6.16 ± 0.18	9.75 ± 0.10			
2,4:3,5-Di-*O*-benzylidene-1-*O*-(phenylsulfonyl)-L-xylitol (V)			1.65 ± 0.08	2.43 ± 0.07	3.67 ± 0.03	5.47 ± 0.13	12.3 ± 0.44

TABLE II

ACTIVATION PARAMETERS AND RELATIVE RATE CONSTANTS AT 100°

Compound	ΔH^*, kcal.	ΔS^*, e.u.	Relative rate constant at 100°
1,2,3,4-Tetra-*O*-acetyl-6-*O*-(phenylsulfonyl)-β-D-glucopyranose (I)	21.2 ± 0.22	−12.9 ± 0.6	1.00
1,2:3,4-Di-*O*-isopropylidene-6-*O*-(phenylsulfonyl)-D-galactopyranose (II)	24.2 ± 0.45	−14.1 ± 1.1	0.00902
2,4:3,5-Di-*O*-methylene-1-*O*-(phenylsulfonyl-DL-ribitol (III)	20.2 ± 0.14	−15.3 ± 0.4	1.14
2,4:3,5-Di-*O*-methylene-1-*O*-(phenylsulfonyl)-DL-xylitol (IV)	24.6 ± 0.96	−11.2 ± 2.4	0.0235
2,4:3,5-Di-*O*-benzylidene-1-*O*-(phenylsulfonyl)-L-xylitol (V)	25.2 ± 0.41	−12.2 ± 1.0	0.00581
2,4:3,5-Di-*O*-methylene-1,6-di-*O*-(phenylsulfonyl)-D-mannitol (VI)	22.2 ± 0.18	−8.5 ± 0.5	2.13
2,3,4,5-Di-*O*-benzylidene-1,6-di-*O*-(phenylsulfonyl)-D-mannitol (VII)	23.0 ± 1.02	−5.8 ± 2.9	2.84

The relative rate constant of IV is distinctly less than that for the gluco-type and even less than that of III for which slight distortion of the C-4–O bond was proposed. V should be very similar to IV but with a slightly more rigid ring conformation resulting from the presence of the phenyl groups. These interpretations accord with the relative rate constants. The fused ring in VI is again of the *cis*-decalin type. The "H-inside" form places both sulfonyloxymethyl groups equatorial, and the "O-inside" places both axial as shown by the conformational formulas. Based on these considerations, Mills[12] suggested that the former may be more stable. However, in this instance the conformational instability may allow boat and skew conformations. The "H-inside" and a boat–boat conformation place the carbon undergoing displacement in the gluco-type configuration. The axial location of the group in the "O-inside" conformation does not allow a comparison with compounds I–V. The high reactivity of the compound suggests a minimum of field interaction to the approach of the nucleophilic reagent. The ring sizes in 2,3,4,5-di-*O*-benzylidene-1,6-di-*O*-(phenylsulfonyl)-D-mannitol (VII) have not been established. Since the relative reactivity is of the same order of magnitude as that of VI, the same ring structures and conformations are suggested. (See Chart II).

The difference of approximately 4 kcal. per mole in activation enthalpy between the compounds of the gluco-type and those of the galacto-type provides evidence that an unfavorable disposition of oxygen atoms has an appreciable effect on the transition state energy. Making the likely assumption that inductive effects vary little with change in geometry of the molecule, then the difference must be attributed to variances in field effects in the reactions of the two groups of compounds. The availability of the several stereoisomeric forms of monosaccharide derivatives thus provides this possibility of obtaining experimental evidence separating inductive and field effects in SN2 displacement reactions, generally most difficult to realize.[14] Extending this rationale to other nucleophilic displacement reactions, an explanation for the

(14) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, p. 203.

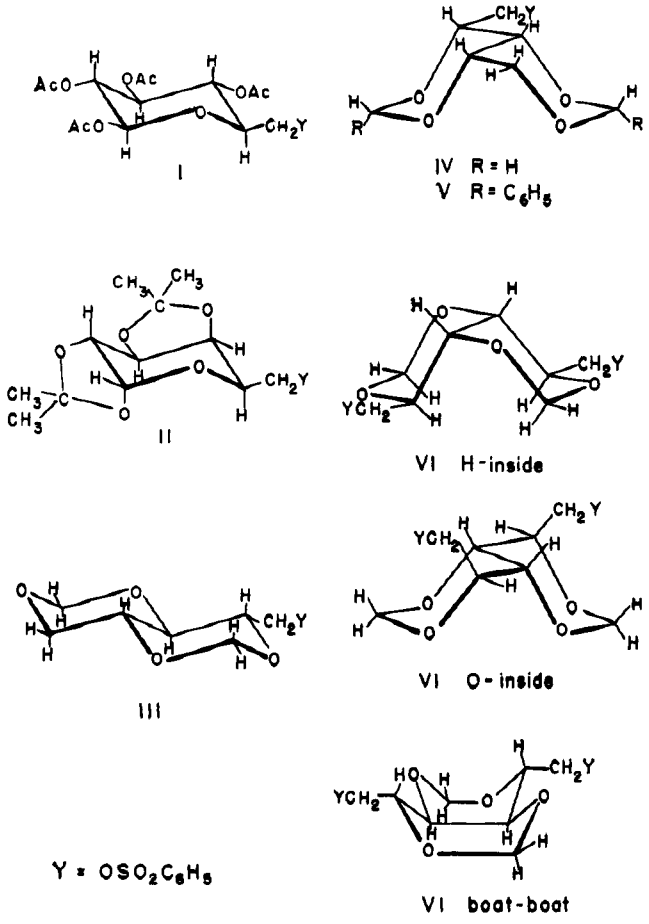
TABLE III

PROPERTIES OF BENZENESULFONATE ESTERS

Compound	Yield, %	M.p., °C.	[α]D	Analysis, % Calcd. C	Calcd. H	Calcd. S	Found C	Found H	Found S
1,2,3,4-Tetra-*O*-acetyl-6-*O*-(phenylsulfonyl)-β-D-glucopyranose (I)	21 from D-glucose	179–180	+24.5°[a] (*c* 1.73, $CHCl_3$)	49.18	4.95	6.56	48.74	4.99	6.36
1,2:3,4-Di-*O*-isopropylidene-6-*O*-(phenylsulfonyl)-D-galactopyranose (II)	89 from 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose	79.0–79.5	−51.6°[b] (*c* 0.73, $CHCl_3$)	53.99	6.04		53.63	6.06	
2,4:3,5-Di-*O*-methylene-1-*O*-(phenylsulfonyl)-DL-ribitol (III)	96 from 2,4:3,5-di-*O*-methylene-DL-ribitol	144–145		49.36	5.10	10.14	49.94	5.08	10.06
2,4:3,5-Di-*O*-methylene-1-*O*-(phenylsulfonyl)-DL-xylitol (IV)	82 from 2,4:3,5-di-*O*-methylene-DL-xylitol	152.5–153		49.36	5.10		49.76	5.23	

[a] Temperature was 23°. [b] Temperature was 31°.

CHART II



alternation effect[15] and for the divergent opinions, which in one case states that electron-withdrawing groups decrease reactivity[16] and the other that electron-releasing groups decrease reactivity,[17] may be given. Clearly, the preferred staggered conformation of a compound containing electron-rich substituents on adjacent carbon atoms is that in which these entities are *trans*. When the rotational barrier in the C–C bond is sufficiently high, the same type of field effect would be expected as described for the carbohydrate derivatives. Accordingly, depressed reactivity would follow for compounds with electron-withdrawing groups in the β-position as a result of the field effect, but at a more remote site the field effect becomes minimal and induction provides for enhancement in the rate of displacement.

(15) E. L. Eliel, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 138.

(16) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., 2nd Ed., New York, N. Y., 1962, p. 175.

(17) I. Dostrovsky, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 173 (1946); P. B. D. de la Mare, L. Fowden, E. D. Hughes, C. K. Ingold, and J. D. H. Mackie, *ibid.*, 3200 (1955); C. K. Ingold, *Quart. Rev.* (London), **11**, 1 (1957).

Experimental[18]

2,4:3,5-Di-*O*-benzylidene-L-xylose Ethyl Hemiacetal.—A suspension of 38.2 g. of 1,3:2,4-di-*O*-benzylidne-D-sorbitol,[8] m.p. 220–221°, in 160 ml. of ethanol, 40 ml. of water, and 22.2 g. of sodium metaperiodate was stirred for 1 hr. and then allowed to stand overnight. The solid product was filtered, washed with water, and air-dried. Two recrystallizations from ethanol–chloroform gave 16.1 g. (41%) of 2,4:3,5-di-*O*-benzylidene-L-xylose ethyl hemiacetal, m.p. 189–189.5°, $[\alpha]^{31}D$ +35.5° (*c* 0.27, pyridine).

Anal. Calcd. for $C_{21}H_{24}O_6$: C, 67.73; H, 6.50. Found: C, 67.62; H, 6.62.

1-*O*-Acetyl-2,4:3,5-di-*O*-benzylidene-L-xylitol.—A mixture of 4.2 g. of lithium aluminum hydride and 1100 ml. of tetrahydrofuran, which had been freshly distilled over lithium aluminum hyride, was stirred 1 hr. to disperse the reagent. To this was added slowly while stirring 25 g. of 2,4:3,5-di-*O*-benzylidene-L-xylose ethyl hemiacetal. The reaction was stirred 2 hr. and then allowed to stand overnight. The following day wet tetrahydrofuran was added dropwise with stirring to destroy the excess lithium aluminum hydride. The inorganic products were removed by filtration and washed several times with acetone. The combined filtrate and washings were evaporated under reduced pressure on a steam bath to obtain 19 g. of a powder melting at 190–196°. A solution of 5.0 g. of the latter was dissolved in 100 ml. of pyridine and 10.0 ml. of acetic anhydride was added. The reaction mixture was allowed to stand for 2 hr. and then poured into 500 ml. of ice and water. Crystalline 1-*O*-acetyl-2,4:3,5-di-*O*-benzylidene-L-xylitol was obtained which after recrystallization from chloroform–ethanol weighed 3.8 g. (58% over-all yield), m.p. 170–171°, $[\alpha]^{31}D$ +41.4° (*c* 0.76, chloroform).

Anal. Calcd. for $C_{21}H_{22}O_6$: C, 68.10; H, 5.99. Found: C, 68.02; H, 6.04.

2,4:3,5-Di-*O*-benzylidene-1-*O*-(phenylsulfonyl)-L-xylitol (V).—To a solution of 10 g. of 1-*O*-acetyl-2,4:3,5-di-*O*-benzylidene-L-xylitol in 50 ml. of chloroform was added 4 ml. of 0.2 *N* sodium methoxide in methanol, and the resulting mixture was left for 6 hr. at room temperature. The solid obtained was triturated with 200 ml. of ethanol, filtered, and dried to give 8.60 g. of 2,4:3,5-di-*O*-benzylidene-L-xylitol, m.p. 194–195°. A solution of 5.0 g. of the latter in 50 ml. of anhydrous pyridine was cooled to 0°, and 4 ml. of benzenesulfonyl chloride in 10 ml. of anhydrous pyridine was added dropwise while stirring. The reaction mix-

(18) All melting points are corrected. Microanalyses were made by K. W. Zimmerman, Australian Microanalytical Service, University of Melbourne.

ture was left at 0° for 2 hr. and then allowed to warm to room temperature overnight. The reaction mixture was then cooled in an ice bath, and 10 ml. of water was added dropwise over a period of 1 hr. The reaction mixture was then poured into 500 ml. of ice and water to produce a crystalline solid which upon recrystallization from chloroform–ethanol weighed 4.76 g. (65% over-all yield), m.p. 131–132°, $[\alpha]^{23}D$ +10° (*c* 1.19, chloroform).

Anal. Calcd. for $C_{25}H_{24}O_7S$: C, 64.09; H, 5.16; S, 6.84. Found: C, 63.95; H, 5.18; S, 6.69.

Other Materials.—The benzenesulfonate esters, I,[4] II,[5] III,[6] and IV,[7] were prepared by methods used in the synthesis of the corresponding *p*-toluenesulfonate esters. Data obtained are given in Table III. Compounds VI and VII previously were characterized.[9] Acetonylacetone was fractionally distilled through a 40-cm. Vigreux column. The fraction boiling at 101–102° at 46 mm. or 82° at 23 mm. was collected. Standard solutions (0.100 *M* or 0.080 *M*) of sodium iodide, Baker and Adamson analyzed, dried at 110° overnight, in acetonylacetone were prepared. Standard solutions (0.100 *M* or 0.080 *M* in sulfonate) of each of the benzenesulfonate esters in acetonylacetone were prepared. A standard solution, approximately 0.03 *M*, of silver nitrate, Baker and Adamson analyzed, dried overnight at 110°, was used in Volhard[19] or argentimetric[20] titrations for iodide ion.

Kinetic Studies.—A constant temperature bath containing mineral oil with temperature control of ±0.05° in the vicinity of 75° and of ±0.1° in the vicinity of 125° was used. For a run at a given temperature, nineteen 18 × 150 mm. Pyrex test tubes were used. Aliquots of 5.00 ml. of a standard sulfonate ester solution were introduced at room temperature. Then 5.00 ml. of the standard iodide solution was introduced into each tube at room temperature and immediately immersed into the bath. Tubes were withdrawn at varying intervals and quickly immersed in a mixture of ice and water. The contents of each tube were transferred, using distilled water or acetone to effect quantitative removal, into an erlenmeyer flask and titrated for unreacted iodide.

Acknowledgment.—A University of Utah Research Committee Fellowship to W. J. Teerlink during the summer of 1962 is gratefully acknowledged.

(19) J. R. Caldwell and H. V. Moyer, *Ind. Eng. Chem., Anal. Ed.*, **7**, 38 (1935).

(20) I. M. Kolthoff and E. B. Sandell, "Textbook of Quantitative Inorganic Analysis," 3rd Ed., The Macmillan Co., New York, N. Y., 1952, p. 544.

The Synthesis of Some 5′-Thiopentofuranosylpyrimidines[1]

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The synthesis of 5′-thiothymidine (XIIIa), 2′-deoxy-5-fluoro-5′-thiouridine (XIIIb), 5′-thiouridine (III), and a number of acylated derivatives of XIIIa and XIIIb is described. The tendency of XIIIa, XIIIb, and III to form cyclonucleosides by addition of the thiol group across the uracil carbon–carbon double bond was studied. No evidence could be obtained for cyclonucleoside formation from 5′-thiothymidine (XIIIa) at pH 1 or 7. At pH 13, disulfide formation occurred. The fluoronucleoside (XIIIb) formed disulfide quite rapidly at pH 13. At pH 7, an equilibrium which exists between the open-chain nucleoside (XIIIb) and the cyclonucleoside (XVb) is ultimately displaced to the open-chain form by disulfide formation. At pH 1, the open-chain nucleoside (XIIIb) appears stable. A solution of 5′-thiouridine (III) at pH 7 exists in equilibrium with the cyclonucleoside (IVb). At pH 1, there was no evidence for cyclonucleoside formation, while at pH 13 disulfide formation occurred.

Bannister and Kagan[2a] recently reported on their efforts to prepare 5′-thiouridine (III) and its acetonide (II). They observed[2a] that treatment of 5′-S-acetyl-2′,3′-O-isopropylidine-5′-thiouridine (I) with methanolic ammonia gave, instead of the expected acetonide (II) of 5′-mercaptouridine, a product in which the thiol group of II had added across the uracil double bond to give the isomeric cyclic sulfide (IVa). (See Scheme I.)

The formation of the cyclic sulfide was suggested by the disappearance of the characteristic uridine ultraviolet absorption peak in the 260-mμ region. Their work indicated that, under alkaline conditions, this cyclization was reversible and that the "normal" structure (II) was regenerated. More recently, Chambers and Kurkov[2b] observed ready formation of the cyclonucleoside (IVa) at neutral pH. In one experiment, crystalline II was isolated by rapid acidification of an alkaline solution of II. In subsequent attempts to repeat this, however, invariably the cyclonucleoside (IVa) separated although the presence of acetone 5′-thiouridine in solution was suggested from the ultraviolet spectrum. We recently prepared a series of acylated derivatives of 5′-thiothymidine (XIIIa) and 2′-deoxy-5-fluoro-5′-thiouridine (XIIIb) for another purpose and thought it would be interesting to investigate the possibility of a similar cyclonucleoside formation with the free thiols.

The synthetic approach that was used to prepare the thionucleosides is outlined in the sequence (V → XIII). Thus treatment of thymidine (Va) with 1.2 moles of *p*-tolylsulfonyl chloride in pyridine at 0° gave 63% of the 5′-tosylate (VIa). That VIa was the desired 5′-tosylate of thymidine and not the isomeric 3′-tosylate was demonstrated by the preparation of the same compound by the unequivocal five-step synthesis described by Michelson and Todd[3] for the preparation of VIa.

Treatment of the tosylate (VIa) with acetic anhydride in pyridine gave the 3′-O-acetate (VIIa) as a sirup. Displacement of the tosyl group was accomplished by means of potassium thioacetate in acetone at room temperature affording 3′,5′-O,S-diacetyl-5′-thiothymidine (Xa) as a crystalline compound in 45% yield. In a similar fashion, VIa was treated with benzoyl chloride and propionyl chloride to give the benzoate (IXa) and propionate (VIIIa), respectively. Subsequent displacement of the appropriate

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