sulfate. After the addition was complete, stirring was continued for 1 hr. The mixture was then further dried over additional anhydrous magnesium sulfate before filtration. The methylene chloride was then removed from the solution and the remaining liquid was distilled to yield 5.0 g. (38%) of yellow liquid **6**, b.p. 87–88° (145 mm.), $n^{25}D$ 1.4591, $\lambda_{max}^{EtOH\ 95\%}$ 248 mμ (ϵ 8300). The infrared spectrum of the compound was similar to the other α,β-unsaturated azo compounds. The n.m.r. spectrum of **6** exhibited numerous peaks consisting of a vinyl quartet centered at 6.5 two NCH$_3$ peaks at 3.78 and 3.85 (3:1), two superimposed doublets of different intensities at 1.98 and 2.10 (*cis-* and *trans-β-CH$_3$*), and a quartet at 1.7 p.p.m. (*α-CH$_3$*), indicative of a mixture of *cis* and *trans* isomers in a ratio of approximately 1:3.

Anal. Calcd. for $C_5H_{10}N_2$: C, 61.18; H, 10.27; N, 28.55. Found: C, 61.00; H, 10.08; N, 28.42.

Reaction of Methylhydrazine with α-Chlorodeoxy-benzoin. Eleven grams (0.05 mole) of α-chlorodeoxybenzoin was dissolved in methylene chloride and this solution was added dropwise to a solution of 6.0 g. (0.11 mole) of methylhydrazine and 6.0 g. (0.06 mole) of triethylamine in methylene chloride with magnesium sulfate also present to take up the water formed. The addition was carried out so as to maintain a slow reflux. The mixture was stirred for several hours after the addition was complete. The magnesium sulfate was then removed by filtration and the solvent was removed, whereby, 12.9 g. of light yellow crystals appeared. Upon recrystallization from methanol, 8.8 g. (77%) of material, m.p. 135–137°, was obtained. This proved to be benzil monomethylhydrazone.[15]

The infrared spectrum of the material was superimposable with that of authentic benzil monomethylhydrazone prepared from methylhydrazine and benzil.

Reaction of α-Chloroacetophenone with Methylhydrazine. Ten grams (0.069 mole) of α-chloroacetophenone was dissolved in benzene and added to 7.0 g. (0.15 mole) of methylhydrazine also dissolved in benzene. An ammoniacal odor could be detected during the addition. The mixture was refluxed for 2 hr. since the initial reaction appeared to be slow. The benzene was removed and the residual mixture was distilled at reduced pressure. Very little volatile material was present. The undistilled material in the distillation flask (8.1 g.) was dissolved in methanol and recrystallized several times. A colorless solid, m.p. 201–202°, was obtained and was shown to be 2,5-diphenylpyrazine[16] by comparison with an authentic sample prepared by heating α-chloroacetophenone in concentrated ammonia for 2 hr. A mixture melting point of the former sample with the product of the latter reaction showed no melting point depression.

Reaction of Methylhydrazine with α-Bromoisobutyrophenone. When 34.0 g. (0.15 mole) of α-bromoisobutyrophenone was added to 14.7 g. (0.32 mole) of methylhydrazine in benzene very little heat was evolved, and no yellow color or any other color appeared. The mixture was then heated at reflux overnight. Upon distillation no material of the expected volatility resulted.

(15) M. O. Forster and D. Cardwell, *J. Chem. Soc.*, 861 (1913), reported m.p. 138°.

(16) H. O. House and E. J. Grubbs, *J. Am. Chem. Soc.*, 81, 4733 (1959), reported m.p. 197.3–198°.

Symmetrical SN2 Reactions Using Iodide-131 Tracer. Kinetic Studies in Carbohydrates[1]

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Two isomeric iodo sugars were shown to have the structures of methyl-4,6-dideoxy-2,3-di-O-benzyl-4-iodo-α-D-gluco- and -galactopyranosides by conversion of each to known sugar derivatives. The rates of reaction of these sugars with iodide ion were determined using iodide-131 tracer under pseudo-first-order kinetic conditions. The galacto isomer was found to react 2.8 and 2.4 times as fast as the gluco isomer with iodide ion in acetone at 62.8 and 82.0°, respectively. Activation parameters for both reactions were obtained from the rate data, and the significance of the differences noted is discussed.

The isolation of 4-amino-4,6-dideoxyaldohexoses and their N-alkyl derivatives as components of antibiotics,[3,4] and from cell wall lipopolysaccharides of *Chromobacterium violaceum*[5] and several strains of *Escherichia coli* as sugars linked to thymidine diphosphate,[6,7] stimulated interest in the syntheses of these naturally occurring compounds.[3,8–10] Syntheses of

(1) (a) Abstracted in part from the Ph.D. Dissertation of John A. Valicenti, Wayne State University, 1965. (b) For previous work using radioactive halogen in mechanistic studies, *cf.* C. L. Stevens and John A. Valicenti, *J. Am. Chem. Soc.*, 87, 838 (1965).

(2) Detroit News Fellow, 1964–1965.

(3) C. L. Stevens, P. Blumbergs, and F. A. Daniher, *J. Am. Chem. Soc.*, 85, 1552 (1963); C. L. Stevens, K. Nagarajan, and T. Haskell, *J. Org. Chem.*, 27, 2991 (1962).

(4) C. L. Stevens, Abstracts, 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965, p. 15C.

(5) R. W. Wheat, E. L. Rollins, and J. M. Leatherwood, *Biochem. Biophys. Res. Commun.*, 9, 120 (1962).

(6) J. L. Strominger and S. S. Scott, *Biochim. Biophys. Acta*, 35, 552 (1959).

(7) R. Okazaki, T. Okazaki, and Y. Kuriki, *ibid.*, 38, 384 (1960).

five of the eight diastereomeric 4-amino-4,6-dideoxy sugars have been accomplished in this laboratory[11a,c] including the naturally occurring amosamine,[3] bamosamine,[4] viosamine,[8,10] and thomosamine.[9] A 4,6-dideoxy-4-thio sugar has also been reported.[11b] The synthetic routes to such 4-substituted-4,6-dideoxy sugars are long (14–18 steps) and involve important displacement reactions at C-4 and C-6 with nucleophiles such as iodide, azide, benzoate, and thiocyanate ions. Little quantitative data are available on the reactivities at hexose carbon atoms other than positions 1 and 6.[12]

Eliel has studied the relative rates of displacement of axial and equatorial groups in the cyclohexane ring system[13,14] and the conformational equilibrium of monosubstituted halocyclohexanes.[15] Berlin and Jensen used low-temperature n.m.r. methods to determine the conformational equilibrium of iodocyclohexane isomers.[16]

The use of radioiodide for kinetic tracer studies is well known, including the classical work of Hughes and Ingold on the S_N2 reaction mechanism.[17]

Work in this laboratory has shown that the reaction of methyl 6-deoxy-2,3-di-O-benzyl-4-O-methanesulfonyl-α-D-glucopyranoside (I) with sodium iodide gave a mixture of isomeric 4-iodo-substituted pyranosides.[18] A study was undertaken using radioactive iodide-131 tracer under suitable kinetic conditions to determine the relative reactivity toward displacement of the equatorial and axial 4-iodo substituents of these pyranose sugars.

Results

The reaction of methyl-6-deoxy-2,3-di-O-benzyl-4-O-methanesulfonyl-α-D-glucopyranoside[9,10] (I) with excess sodium iodide at high temperature gave a mixture of isomeric 4,6-dideoxy-4-iodopyranosides II and III with the empirical formula, $C_{21}H_{25}IO_4$. The compounds II, an oil, and III, crystalline, m.p. 104–105°, were separated by means of alumina chromatography and had significantly different infrared spectra and thin layer chromatographic behavior.[18] Optical rotation data suggested the gluco configuration for II and the
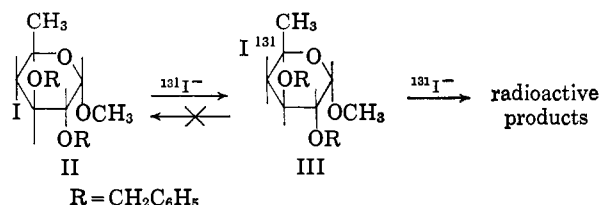
(8) C. L. Stevens, P. Blumbergs, F. A. Daniher, R. W. Wheat, A. Kiyomoto, and E. L. Rollins, *J. Am. Chem. Soc.*, **85**, 3061 (1963).

(9) C. L. Stevens, P. Blumbergs, D. Otterbach, J. L. Strominger, M. Matsuhashi, and D. Dietzler, *ibid.*, **86**, 2937 (1964).

(10) C. L. Stevens, P. Blumbergs, F. A. Daniher, J. L. Strominger, M. Matsuhashi, D. Dietzler, S. Suzuki, T. Okazaki, K. Sugimoto, and R. Okazaki, *ibid.*, **86**, 2939 (1964).

(11) Abstracts, 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965: (a) C. L. Stevens, P. Blumbergs, J. Lickerson, and D. Chitharanjan, p. 5C; (b) C. L. Stevens, W. E. Dennis, P. Blumbergs, and K. G. Taylor, p. 1C; (c) to be published.

(12) For recent kinetic studies at position 1, see for example A. M. S. Feather and J. F. Harris, *J. Org. Chem.*, **30**, 153 (1965); also B. Capon, P. Collins, A. Levy, and W. G. Overend, *J. Chem. Soc.*, 3242 (1964); for kinetic studies at position 6, see for example J. M. Sugihara and W. J. Teerlink, *J. Org. Chem.*, **29**, 550 (1964).

(13) E. L. Eliel and R. G. Haber, *J. Am. Chem. Soc.*, **81**, 1249 (1959).

(14) E. L. Eliel and R. S. Ro, *ibid.*, **79**, 5995 (1957).

(15) E. L. Eliel, *Chem. Ind.* (London), 568 (1959).

(16) A. J. Berlin and F. R. Jensen, *ibid.*, 998 (1960).

(17) E. D. Hughes, C. K. Ingold, W. A. Cowdry, S. Masterman, and A. D. Scott, *J. Chem. Soc.*, 1252 (1937). For use of radioiodide, see E. D. Hughes, F. Juliusberger, S. Masterman, and J. Weiss, *ibid.*, 1525 (1935). For more recent work, see S. May and R. Dandel, *J. chim. phys.*, **53**, 274 (1956).

(18) Private communication, Dr. Dieter Otterbach. For other work concerning the introduction of iodide into the 4-position of substituted gluco- and galactopyranosides, *cf.* N. K. Kochetkov and A. I. Usov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **3**, 475 (1964); *Chem. Abstr.*, **60**, 15952g (1964).

galacto configuration for III.[19] Conversion of II and III to the known 4-azido-4,6-dideoxy derivatives[9,10] IV and V, respectively, by displacement with sodium azide in dimethylformamide, confirmed the assignment as shown below.

An extensive study of the reaction of I with sodium iodide indicated that optimum yields were obtained using a 5 M excess of sodium iodide in acetonylacetone solvent at 125° for 3.5 hr. In general, 34% of II, 9% of III, and 10–15% of recovered I were obtained under such conditions (see Table III). Although product stability studies were not done, it was evident that the galacto isomer III was reacting at a faster

I → NaI → II $[\alpha]^{25}D -51.5°$ + III $[\alpha]^{25}D +101.9°$

I, II, III → NaN$_3$ → IV, V

R(I–V) = CH$_2$C$_6$H$_5$
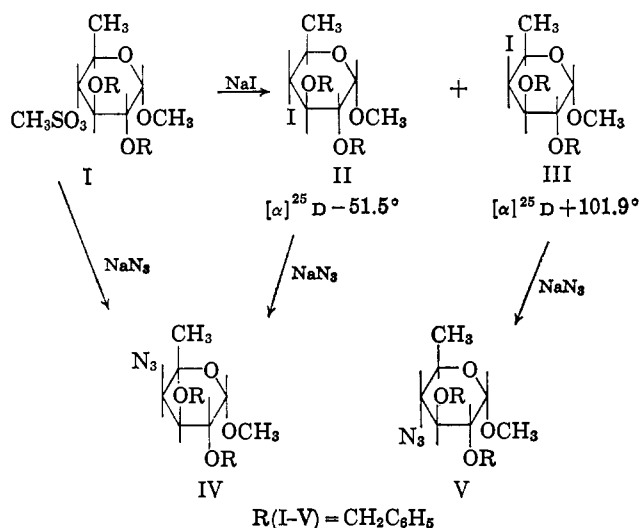
rate with iodide ion to give II than the gluco isomer II to give III. The galacto analog of I yielded 39% of II and 4% of III under similar reaction conditions.

Preliminary studies indicated that interconversions of II and III could be carried out in sodium iodide-acetone solutions at temperatures as low as 60–80°. It was interesting to note that there was little or no reaction with mesylate I and sodium iodide at these lower temperatures. The reaction of II and III with iodide ion at 62.8 and 82.0° provided the basis for a kinetic determination of the relative reactivities toward displacement. Since this is a symmetrical displacement reaction with both the incoming and leaving group the same, the resulting common transition state permits calculation of the ground-state energy differences between the axial and equatorial isomers. By the use of a large excess of iodide ion, pseudomolecular kinetics are achieved. When using radioactive iodide-131 under these conditions, the incorporation of iodide-131 into unlabeled II or III becomes irreversible since, certainly in the early stages of the

II ⇄ $^{131}I^-$ III → $^{131}I^-$ → radioactive products

R = CH$_2$C$_6$H$_5$

(19) Compounds in the gluco configuration prepared in the syntheses of 4-amino-4,6-dideoxy-α-D-gluco- and -galactopyranosides[9,10] had lower optical rotation values than the corresponding galacto isomers. For example, the optical rotation of I is +37.8°, and that of its galacto isomer, +71.4°.

reaction, the large excess of iodide-131 prevents the reverse reaction with the original nonlabeled iodide ion from becoming significant. Pseudo-first-order rate constants are obtained by equating per cent incorporation iodide-131 and per cent reaction.

Thus, II and III were subjected to heating in sodium iodide (20 mole excess) acetone solution at 62.8 and 82.0°. At convenient times the organics were reisolated with generally greater than 80% recovery for each sealed tube reaction vessel. Because the iodo sugars are isomeric, separation of product and starting material was not necessary. The γ-activity of the corresponding product mixture was then measured against the original sodium iodide-131 acetone solution as standard. For example, reisolation of products from the reaction of II with iodide-131 at 82.0° for 240 min. gave 0.03544 mmole of a mixture of 4-iodo products with an activity of 1565 c.p.m. or 44,159 c.p.m./mmole. The average activity of the standard iodide-131 counted in the same sequence was 883,-111 c.p.m./mmole. This amounted to a 5.0% incorporation of iodide-131 with a pseudo-first-order rate constant of 2.14×10^{-4} min.$^{-1}$. Another kinetic run under identical conditions gave values of 4.91% incorporation and a rate constant of 2.10×10^{-4} min.$^{-1}$.

Control experiments indicated no loss of radioactivity from mixtures of II and III at 82.0° for up to 10 hr.

Kinetic runs at both temperatures were carried out to 10-12% reaction with sufficient γ-activity for convenient counting above the background count obtained after 0.5% reaction. Table I gives the per cent reaction and pseudo-first-order rate constants for

Table I. Kinetic Data for the Reaction of II and III with Sodium Iodide-131 at 62.8 and 82.0°

Compd. + iodide-131	Temp., °C.	Time, min.	Reaction, %[a]	k,[a] min.$^{-1}$
II	62.8 ± 0.1	180	0.46	2.56×10^{-5}
		471	1.28	2.73
		1359	3.55	2.66
		2562	6.17	2.49
		4040	10.1	2.63
III	62.8 ± 0.1	120	0.79	6.60×10^{-5}
		180	1.42	7.94
		374	2.88	7.81
		1939	11.68	6.41
II	82.0 ± 0.1	60	1.28 (1.39)	2.15 (2.33) $\times 10^{-4}$
		120	2.87 (2.91)	2.43 (2.46)
		180	3.76 (4.01)	2.13 (2.27)
		240	5.00 (4.91)	2.14 (2.10)
		301	6.65 (5.50)	2.29 (1.88)
		479	9.81	2.16
III	82.0 ± 0.1	30	1.69	5.68×10^{-4}
		60	3.10	5.25
		90	4.47	5.08
		120	6.05	5.20
		180	8.98	5.23

[a] Values in parentheses are for identical run at same temperature.

the reaction of II and III with iodide-131 at 62.8 and 82.0°. The rate constant k was calculated from the equation $2.303 \log c_0/c = kt$ with the value c equal to $100 - x\%$ reaction or iodide-131 incorporation.
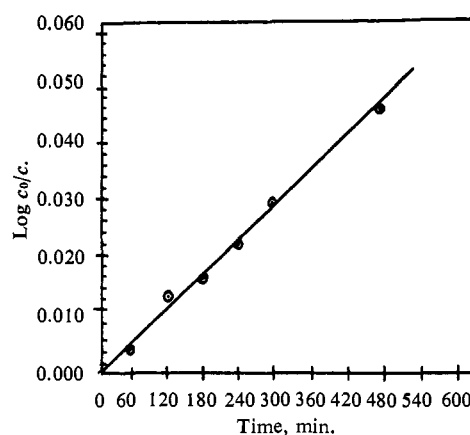

Figure 1. Displacement of II with iodide-131 at 82.0° in acetone.

Figure 1 is a plot of $\log c_0/c$ vs. time for the reaction of II with iodide-131 at 82.0° and its linearity represents a test of the pseudo-first-order kinetics. Excellent linear plots were obtained for all kinetic studies as indicated by the constancy of k values for each reaction.

The average values of the rate constants listed in Table I including average deviation were 2.61 ± 0.07 $\times 10^{-5}$ min.$^{-1}$ and 7.19 ± 0.68 $\times 10^{-5}$ min.$^{-1}$ for II and III at 62.8° and 2.22 ± 0.10 $\times 10^{-4}$ min.$^{-1}$ and 5.29 ± 0.16 $\times 10^{-4}$ min.$^{-1}$ for II and III at 82.0°. Another average value for k for II at 82.0° was 2.21 ± 0.19 $\times 10^{-4}$ min.$^{-1}$.

From these values of k at the two temperatures, activation parameters and the equilibrium constant for the reactions with iodide-131 were calculated. These are listed in Table II.

The difference in enthalpies of activation between II and III is 1654 cal./mole; in entropies of activation, 2.9 e.u., corresponding to a ground-state free energy difference of 787 cal./mole. The equilibrium constant K for an equilibrium of isomers II and III at 25° is 0.26 indicating 79% of the more stable *gluco* isomer II present.

Discussion

The *irreversible* nature of the exchange reactions studied in this work represent a highly useful approach to the technique of tracer analysis. The accuracy of the experimental procedure is manifested in the 3-10% average deviations of the measured rate constants. These deviations correspond closely to the calculated experimental error for each determination. Reproducibility of the measurements is indicated in the duplicate run of II with iodide-131 at 82.0°. The average rate constants obtained were the same within the limits of experimental error.

The bond lengths, bond angles, and stereochemistry of the pyranose sugar ring system are similar to those of cyclohexane.[20] Thus, certain comparisons can be made between the axial–equatorial energy differences and SN2 displacement reactivities in both ring systems.[21]

From the absolute rate constants in this carbohydrate series, the *galacto* isomer was reacting 2.8 times (62.8°)

(20) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 246.
(21) For correlation of rates and free energies of chemical reactions, see G. S. Hammond, *J. Am. Chem. Soc.*, 77, 334 (1955).

Table II. Activation Parameters and Relative Rate Values

Compd.	Temp., °C.	ΔS^*, e.u.	ΔH^*, kcal./mole	E_a, kcal.	K_{eq}, (k_{III}/k_{II})
II	62.8 ± 0.1	−11.8 ± 1.0			
	82.0 ± 0.1	−11.8	25.6 ± 0.1	26.3	2.8 (62.8°)
III	62.8 ± 0.1	−14.7 ± 1.7			
	82.0 ± 0.1	−14.7	23.9 ± 0.4	24.6	2.4 (82.0°)

and 2.4 times (82.0°) faster than the *gluco* isomer, corresponding to a ground-state free energy difference of about 0.8 kcal./mole. Such a relative rate difference was not unexpected when one considers the ground-state free energy differences of the monosubstituted halocyclohexanes. Berlin and Jensen found the conformational equilibrium of iodocyclohexane to favor the equatorial isomer by only about 2:1, corresponding to a standard free energy difference of 0.4 kcal./mole.[16] This relatively small energy difference was attributed to the ease of distortion of the iodine electron cloud. The energy required for such distortion is small compared to the energy involved in steric interactions of the axial substituent. However, the k_{cis}/k_{trans} rate ratios observed in the bimolecular substitution reactions of the 4-*t*-butylcyclohexyl tosylates[13] and bromides[14] with thiophenolate were 31 and 58, respectively. These were ascribed to the differences in transition states in the unsymmetrical substitution reactions. Interestingly, Eliel discusses the simplified energetics of a hypothetical symmetrical substitution reaction, the displacement of 4-*t*-butylcyclohexyl iodide by radioiodide.[22]

The ground-state enthalpy content of sugar III was greater by 1.7 kcal. than II, probably due to increased steric interactions of the axial iodine atom in III.

The difference of 2.9 e.u. in the entropies of activation for II and III is just beyond the limits of experimental error and indicates a slightly more disordered ground state for III *relative to II*. No single explanation for this is apparent and the difference may well result from a number of small contributions such as, for example, a contribution from the other chair form of III (IIIA in Figure 2). It should be pointed out, certainly, that kinetic data at a third and possibly fourth temperature is needed before the magnitude of the entropy difference can be considered with any great reliability. The values of the entropies of activa-
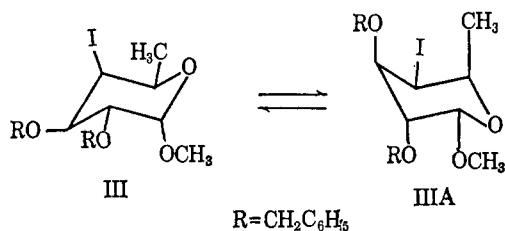

Figure 2.

tion are in agreement with the ordered transition state required in an S~N~2 reaction.

(22) Reference 20, p. 225.

It is tempting to conclude that the activation parameters of the reaction suggest a transition state which more nearly resembles the *galacto* isomer. However, the difference in free energies of activation (*ca.* 0.7 kcal. at 62.8°) is not large enough compared to the energy values themselves (*ca.* 29 kcal.) to make this at all certain.

The optical rotation differences of II and III offered a second means for following their interconversion. However, kinetic analysis by this technique would have required determination of the II–III equilibrium constants at each temperature employed. Further, the lower precision of the optical method would not have lent itself to use of the method of initial rates at low temperatures. Using higher interconversion temperatures (or prolonged reaction times) for obtaining accurate optical kinetic data was not deemed feasible in view of the poor recoveries of products in the preparation of II and III from I (at 125°).

The simplicity and accuracy of the tracer technique employed here and its suitability to the method of initial rate determinations would appear to make it a useful kinetic tool in the carbohydrate area and certainly others as well.

Experimental Section

All melting points are uncorrected. Microanalyses were performed by the Midwest Microanalytical Laboratory, Indianapolis, Ind. A Nuclear-Chicago Corporation scintillation counter was employed for counting in combination with an NRD Instrument Co. Model L-6 well. Standard iodide-131 was counted in 3.0 ml. of water while iodide-131 labeled organic products were counted in 2.0-ml. chloroform solutions. All counting values reported are corrected for background which averaged about 215 c.p.m.

Methyl-4,6-dideoxy-2,3-di-O-benzyl-4-iodo-α-D-gluco- and -galactopyranosides (II and III). An acetonylacetone solution (15 ml.) containing methyl-6-deoxy-2,3-di-O-benzyl-4-O-methanesulfonyl-α-D-glucopyranoside[10] (I) (5.0 g., 11.4 mmoles) was added to a mechanically stirred solution of sodium iodide (8.0 g., 53 mmoles) in acetonylacetone (25 ml.) at 125° over a period of 0.5 hr. After 3 hr. under nitrogen atmosphere at this temperature, the reaction mixture was cooled and diluted with 150 ml. of water. The aqueous solution was then extracted with petroleum ether (b.p. 50–70°; five 200-ml. portions). The petroleum ether extract was washed with water (two 200-ml. portions) and then was dried over anhydrous magnesium sulfate. Upon removal of solvent *in vacuo*, the residual oil, 4.55 g., partially crystallized on standing at room temperature. Trituration with petroleum ether followed by filtration yielded 585 mg. of a white solid which

was identified as I by mixture melting point determination. Removal of solvent from the triturate gave 3.87 g. of an oil which contained three major components as indicated by thin layer chromatography (solvent system A, 50:50 ether–petroleum ether mixture) with R_f values of 0.43, 0.52, and 0.73. The component with R_f 0.43 was starting material I.

The above oily mixture was then chromatographed over 110 g. of Woelm Grade 1 alumina as outlined below. (a) Seven 200-ml. fractions of 10–15% ether–petroleum ether yielded 1.67 g. of a colorless oil, R_f system A, 0.73. (b) Seven 200-ml. fractions of 50–80% ether–petroleum ether mixtures yielded 485 mg. of a white crystalline solid after recrystallization from ethanol, m.p. 104–105°, R_f system A, 0.52. (c) Two 150-ml. fractions of 20% chloroform–ether mixtures yielded 230 mg. of I, R_f system A, 0.43, after recrystallization from ethanol.

The colorless oil, R_f 0.73, $[\alpha]^{25}$D −51.5° (c 1.01, chloroform), and the crystalline solid, R_f 0.52, $[\alpha]^{25}$D +101.9° (c 1.07, chloroform), were found to have the same empirical formula by elemental analysis.[18]

Anal. Calcd. for $C_{21}H_{25}IO_4$: C, 53.53; H, 5.34; I, 27.56. Found (for oily iodo isomer): C, 53.83; H, 5.55; I, 27.51. Found (for crystalline isomer): C, 53.80; H, 5.52; I, 27.83.

The infrared spectra of both iodo compounds differed considerably in the 8.0–11.0-μ region. As described below, the oily iodo isomer was shown to be in the *gluco* configuration, II, and the crystalline iodo compound, the *galacto* configuration, III. Yield data for the preparation of II and III from I are given in Table III. Varying amounts of I were used but the molar ratio of sodium iodide to I (5:1) was maintained. All reactions were carried out in acetonylacetone at 125 ± 5° except when indicated.

Table III. Displacement of I with Sodium Iodide

Amount of I, g.	Yield, % II	Yield, % III	Recovered I, %
0.20	34	9	
0.20[a]	34	9	
1.26	34	9	
3.00	34	11	10
5.00	32	9	16
10.0[b]	10	12	33

[a] Reaction carried out in acetic anhydride at 140° for 18 hr.
[b] Reaction temperature was 115°.

The reaction of methyl-6-deoxy-2,3-di-O-benzyl-4-O-methanesulfonyl-α-D-galactopyranoside[10] with sodium iodide under the identical conditions described above yielded 39% of II and 4% of III after the usual work-up and purification.

Methyl-4-azido-4,6-dideoxy-2,3-di-O-benzyl-α-D-galactopyranoside (IV). The oily iodo compound II (0.1336 g., 0.28 mmole) was heated with sodium azide (0.100 g., 1.5 mmoles) in dimethylformamide (3 ml. containing 6 drops of water) at 140° for 5.5 hr. The slightly yellow solution was then diluted with 50 ml. of water and extracted with petroleum ether (three 50-ml. portions). After drying, the solvent was removed *in vacuo* yielding 92.8 mg. of a heavy oil. A pentane–hexane solution containing the oil gave 56.4 mg. of

crystals upon cooling, m.p. 52.0–52.5°. The mixture melting point with an authentic sample of IV[9] was undepressed. Infrared spectra of the two compounds were superimposable and their thin layer chromatographic behavior was identical (R_f system A, 0.41). The infrared spectrum and thin layer R_f value of the 4-azido compound prepared in this experiment were distinctly different from those of methyl-4-azido-4,6-dideoxy-2,3-di-O-benzyl-α-D-glucopyranoside (R_f system A, 0.58).[23]

Reduction of IV prepared in this experiment with lithium aluminum hydride in dioxane led to the 4-amino compound which was identical with the known methyl-4-amino-4,6-dideoxy-2,3-di-O-benzyl-α-D-galactopyranoside[9] and its N-acetate derivative[9] by thin layer chromatography. Thin layer chromatographic behaviors of the analogous 4-amino and 4-acetamido *gluco* derivatives[10] were substantially different from those of the *galacto* derivatives prepared in this experiment.

Methyl-4-azido-4,6-dideoxy-2,3-di-O-benzyl-α-D-glucopyranoside (V).[10,22] Following the procedure described above, III was converted to V with sodium azide in dimethylformamide. The oily product V had identical infrared spectrum and thin layer R_f value (0.58) as an authentic sample[23] and differed in such respects from IV.

Radioactive Iodide-131.[24] A standard solution of iodide-131 in acetone was prepared by inoculation of an acetone solution of sodium iodide (8.0068 g.) with 0.5 ml. of aqueous sodium iodide-131 and dilution to 50.00 ml. The standard solution thus contained 1.068 mmoles of sodium iodide-131/ml. Four 25-μl. aliquots of this inoculated stock solution served as primary counting standards for the remainder of the experiment.

Kinetic Studies at 62.8°. Displacement of II with Sodium Iodide-131. To a 10.00-ml. volumetric flask containing II (0.1053 g., 0.2248 mmole) was added 4.0 ml. of the standard sodium iodide-131 acetone solution which was subsequently diluted to volume. Four 2.0-ml. aliquots, each containing 0.854 mmole of sodium iodide-131 and 0.0449 mmole of II, and one 1.0-ml. aliquot with the same 19.3 M excess of sodium iodide-131 were placed in small combustion tubes, sealed, and immersed in a constant temperature bath at 62.8 ± 0.1°. Sample tubes were removed at specified times, quenched by cooling, opened, and diluted with 10 ml. of water. Ether extraction (three 10-ml. portions) was followed by drying over anhydrous potassium carbonate and the removal of solvent *in vacuo* in a tared flask. Recovery of products was generally greater than 80%. Results are shown in Table IV with the counting of each sample, standard, and background done in sequence for 5-min. periods and three times each. Average counting values are given.

Displacement of III with Sodium Iodide-131 at 62.8°. The identical procedure was followed as described

(23) The authentic sample was prepared according to the procedure of Stevens.[10] *Anal.* Calcd. for $C_{21}H_{25}N_3O_4$: C, 65.77; H, 6.57; N, 10.96. Found: C, 66.01; H, 6.64; N, 10.78.

(24) Radioactive iodide-131, a γ-emitter with a half-life of 8.0 days, was obtained as 1.0 ml. of aqueous sodium iodide-131 with an initial activity of 1 mc./ml. The aqueous iodide-131 used for inoculation in each standard solution preparation had an activity of 0.1 mc. Each standard solution thus had a specific activity in the range of 1,000,000 counts/ml.

Table IV. Reaction of II with Sodium Iodide-131 at 62.8 ± 0.1°

Time, min.	Amount of reisolated sample, mmole	Activity of reisolated sample, c.p.m.	Activity of reisolated sample, c.p.m./ mmole	Activity of standard iodide-131 c.p.m./ mmole
180	0.04441	207	4,661	1,010,961
471	0.04078	501	12,285	962,322
1359	0.04249	1451	34,149	962,322
2562	0.04462	2503	56,095	908,614
4040	0.01921	1668	84,226	834,082

above including use of the same iodide-131 standard solution. III (0.1037 g., 0.2214 mmole) and a 4.0-ml. aliquot of the standard iodide-131 solution resulted in a 19.0 M excess of sodium iodide-131 in each reaction vessel. Table V gives experimental counting data.

Table V. Reaction of III with Sodium Iodide-131 at 62.8 ± 0.1°

Time, min.	Amount of reisolated sample, mmole	Activity of reisolated sample, c.p.m.	Activity of reisolated sample, c.p.m./ mmole	Activity of standard iodide-131, c.p.m./ mmole
120	0.03267	262	8,019	1,010,861
180	0.02989	429	14,352	1,010,861
374	0.03587	995	27,739	962,322
1939	0.02199	2334	106,139	908,614

Kinetic Studies at 82.0 ± 0.1°. A standard 50.00-ml. sodium iodide-131 acetone solution was prepared as previously described by inoculation of an acetone solution containing 7.998 g. of sodium iodide with 0.5 ml. of aqueous sodium iodide-131 with an activity of 0.1 mc.

Displacement of II with Sodium Iodide-131 at 82.0°. To II (0.0992 g., 0.2118 mmole) in a 10.00-ml. volumetric flask was added a 4.0-ml. aliquot of the standard iodide-131 solution which contained 1.067 mmole sodium iodide-131/ml. Upon dilution to volume, each reaction tube (another 1.0-ml. aliquot used in this experiment) contained a 20.2 M excess of iodide-131. Table VI lists experimental data.

Table VI. Reaction of II with Sodium Iodide-131 at 82.0 ± 0.1°

Time, min.	Amount of reisolated sample, mmole	Activity of reisolated sample, c.p.m.	Activity of reisolated sample, c.p.m./ mmole	Activity of standard iodide-131, c.p.m./ mmole
60	0.03736	423	11,322	883,111
120	0.03288	832	25,304	883,111
180	0.03694	1225	33,161	883,111
240	0.03544	1565	44,159	883,111
301	0.01686	996	58,726	883,111
479	0.01729	1424	82,359	839,512

A duplicate run was made using II (0.1001 g., 0.2137 mmole) and the same standard iodide-131 solution in 19.9 M excess. Results are shown in Table VII.

Table VII. Duplicate Run of II with Sodium Iodide-131 at 82.0 ±0.1°

Time, min.	Amount of reisolated sample, mmole	Activity of reisolated sample, c.p.m.	Activity of reisolated sample, c.p.m./ mmole	Activity of standard iodide-131, c.p.m./ mmole
60	0.03843	541	14,077	1,013,083
120	0.03672	1082	29,466	1,013,083
180	0.03715	1508	40,592	1,013,083
240	0.03566	1774	49,747	1,013,083
300	0.02080	1160	55,769	1,013,083

Displacement of III with Sodium Iodide-131 at 82.0°. To III (0.1001 g., 0.2137 mmole) was added 4.0 ml. of the sodium iodide-131 standard solution which contained 1.067 mmole sodium iodide-131/ml. Dilution to 10.00 ml. yielded aliquots for kinetic studies with a 19.9 M excess sodium iodide-131. Counting data are expressed in Table VIII.

Table VIII. Displacement of III with Iodide-131 at 82.0 ± 0.1°

Time, min.	Amount of reisolated sample, mmole	Activity of reisolated sample, c.p.m.	Activity of reisolated sample, c.p.m./ mmole	Activity of standard iodide-131, c.p.m./ mmole
30	0.03993	667	16,704	985,791
60	0.04227	1290	30,518	985,791
90	0.04249	1871	44,033	985,791
120	0.04014	2395	59,666	985,791
180	0.01921	1701	88,547	985,791

Stability of II and III at 82.0°. Two counting samples from the reaction of II with sodium iodide-131 at 82.0 (see Table VII; sample A, $t = 180$ min., sample B, $t = 240$ min.) were heated in 2.0 ml. of acetone each for 300 and 614 min., respectively. Upon reisolation, the samples were counted against the original sodium iodide-131 standard used in the displacement reaction. No loss or gain in specific activity of the 4-iodo product mixture was observed within the experimental error. Results are tabulated in Table IX.

Table IX. Stability of II and III at 82.0 ± 0.1°[a]

Reisolated sample (after heating at 82.0°)	Activity of reisolated sample, c.p.m./ mmole	Activity of standard iodide-131, c.p.m./ mmole	Incorp. iodide-131 % (after heating at 82.0°)	Original % incorp. iodide-131
A (300 min.)	32,871	839,512	3.92	4.01
B (614 min.)	40,677	839,512	4.85	4.91

[a] Samples A and B were obtained from kinetic run of II with sodium iodide-131 at 82.0 ± 0.1°. (See Tables I and VII.)