

Optical Rotatory Dispersion and Circular Dichroism. Part LXXIX.¹ Circular Dichroism of some Carbohydrate Azides

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C.d. data are presented for fifty monosaccharides and disaccharides containing the azide chromophore. The azide Cotton effects near 280 nm are discussed in terms of the octant rule for azides.

THE u.v. absorption spectrum of alkyl azides exhibits a weak transition (ϵ ca. 30) in the region 280—290 nm. Cotton effects corresponding to this transition were first investigated in 1967 by Djerassi and his colleagues,² who recorded o.r.d. and c.d. data for a series of steroidal azides. These workers suggested that the sign of the azide Cotton effect should be related to the geometry of the chromophore's environment by an octant rule analogous to that for ketones. Subsequently this octant

rule was tested for a number of carbohydrate azides by Paulsen,³ who concluded that there was agreement between the octant rule prediction and the observed sign of the Cotton effect in the majority of cases.

Djerassi suggested that if a compound was viewed along the line of the azide chromophore, with the lone pair of electrons on N-1 upward and in the vertical plane,

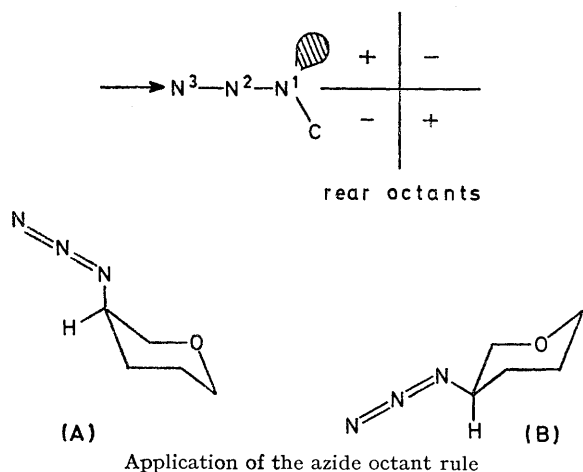
¹ Part LXXVIII, D. N. Kirk, P. M. Scopes, and B. M. Tracey, *Tetrahedron Letters*, 1973, 1355.

² C. Djerassi, A. Moscovitz, K. Ponsold, and G. Steiner, *J. Amer. Chem. Soc.*, 1967, **89**, 347.

³ H. Paulsen, *Chem. Ber.*, 1968, 1571.

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then the region around the chromophore could be divided into octants analogous to those for ketones. Atoms in a



given octant make a contribution to the Cotton effect of the same sign as would be expected for a ketone viewed

attached to a carbonyl group; the oxygen atom of the carbonyl representing the lone pair of the nitrogen atom N-1.) Paulsen emphasised³ that for each configuration of the azide group, there are several possible conformations around the C-N₃ bond to be considered. He suggested that the conformation determining the sign of the Cotton effect is that in which the linear azide group is coplanar with the adjacent C-H bond, and pointing away from the pyranose ring [(A) and (B) for axial and equatorial azides, respectively].

The availability of a large number of monosaccharide and disaccharide azides has enabled us to test the octant rule more extensively and to record Cotton effects for carbohydrates with an azide group in positions other than those discussed previously.³ In this paper we have assumed the preferred conformations shown in the Figure for those compounds in which the azide group is directly attached to the six-membered ring.

The results (Tables 1–3) show that the azide Cotton effects are generally very small, with $\Delta\epsilon$ values of ± 0.3 or less. The same range of values ($\theta \pm 1000$ or less) was

TABLE 1
C.d. of carbohydrate derivatives with an axial azide chromophore

	$\Delta\epsilon$	λ/nm
(a) Compounds with a <i>trans</i> -benzylidene substituent		
1 Methyl 3-azido-4,6- <i>O</i> -benzylidene-3-deoxy- α -D-altropyranoside (I; R = H)	+0.20m	282
2 Methyl 3-azido-4,6- <i>O</i> -benzylidene-3-deoxy-2- <i>O</i> -methyl- α -D-altropyranoside (I; R = Me)	+0.20m	284
3 Methyl 3-azido-4,6- <i>O</i> -benzylidene-3-deoxy-2- <i>O</i> -tosyl- α -D-altropyranoside (I; R = Ts)	+0.22m	274
4 Methyl 3-azido-2- <i>O</i> -benzyl-4,6- <i>O</i> -benzylidene-3-deoxy- α -D-altropyranoside (I; R = Bz)	+0.20m	281
5 3-Azido-4,6- <i>O</i> -benzylidene-3-deoxy- α -D-altropyranosyl 3-azido-4,6- <i>O</i> -benzylidene-3-deoxy- α -D-altropyranoside	+0.28m	277
6 3-Azido-4,6- <i>O</i> -benzylidene-3-deoxy-2- <i>O</i> -mesyl- α -D-altropyranosyl 3-azido-4,6- <i>O</i> -benzylidene-3-deoxy-2- <i>O</i> -mesyl- α -D-altropyranoside	+0.26m	280
7 3-Azido-4,6- <i>O</i> -benzylidene-3-deoxy- α -D-altropyranosyl 4,6- <i>O</i> -benzylidene- α -D-glucopyranoside	+0.13m	283
8 Methyl 3-azido-4,6- <i>O</i> -benzylidene-3-deoxy- α -D-allopyranoside	+0.05m	286
9 Methyl 3-amino-2-azido-4,6- <i>O</i> -benzylidene-2,3-dideoxy- α -D-altropyranoside (II; R = NH ₂)	-0.04m	286
10 Methyl 2-azido-4,6- <i>O</i> -benzylidene-2-deoxy-3- <i>O</i> -tosyl- α -D-altropyranoside (II; R = OTs)	-0.28m	274
11 2-Azido-4,6- <i>O</i> -benzylidene-2-deoxy-3- <i>O</i> -mesyl- α -D-altropyranosyl 2-azido-4,6- <i>O</i> -benzylidene-2-deoxy-3- <i>O</i> -mesyl- α -D-altropyranoside	-0.14m	278–280
12 2-Azido-4,6- <i>O</i> -benzylidene-2-deoxy- α -D-altropyranosyl 2-azido-4,6- <i>O</i> -benzylidene-2-deoxy- α -D-altropyranoside	None detected	
(b) Compounds with a <i>cis</i> -benzylidene substituent		
13 Methyl 2-azido-4,6- <i>O</i> -benzylidene-2-deoxy- α -D-idopyranoside (III; R ¹ = R ² = H, R ³ = OMe)	+0.03m	284
14 Methyl 2-azido-4,6- <i>O</i> -benzylidene-2-deoxy-3- <i>O</i> -tosyl- α -D-idopyranoside (III; R ¹ = Ts, R ² = H, R ³ = OMe)	-0.12m	285
15 Methyl 3-azido-4,6- <i>O</i> -benzylidene-3-deoxy- α -D-idopyranoside (IV; R ¹ = R ² = H, R ³ = OMe)	+0.21m	281
16 Methyl 3-azido-4,6- <i>O</i> -benzylidene-3-deoxy-2- <i>O</i> -tosyl- α -D-idopyranoside (IV; R ¹ = Ts, R ² = H, R ³ = OMe)	-0.11m	274
(c) Compounds lacking fused rings		
17 Methyl 2,6-di- <i>O</i> -acetyl-3-azido-3-deoxy-4- <i>O</i> -(2,3,4,6-tetra- <i>O</i> -acetyl- α -D-glucopyranosyl)- β -D-allopyranoside	-0.18m	282
18 Benzyl 4- <i>O</i> -(4-azido-4-deoxy- β -D-galactopyranosyl)- β -D-glucopyranoside	+0.17m	280–288

along the O-C bond (see Figure).* (This situation can be simulated in Dreiding models by an acetylene unit

* The derivation of the octant rule for azides follows immediately from the octant rule for the carbonyl chromophore because of the analogy between the orbitals involved in the $n\text{-}\pi^*$ transitions of the two chromophores, as noted in the paragraph beginning on the bottom of p. 347 of ref. 2, and is correctly stated in that work. However, we are informed by one of the authors of ref. 2 (A. M.) that the statement on the bottom of the left hand column of p. 348 beginning, 'This follows from the fact that . . . ' and ending ' . . . no sign changes at all.', is specious as stated. The error arose because of changes in subsequent drafts of the original manuscript. He informs us that a more appropriate statement would be: 'This follows from

recorded by Paulsen³ for sugar azides and by Djerassi² for steroidal azides. The absorption bands are also small ($\epsilon < 1000$) and occur in the region 268–274 nm for typical monoazides, at 268 nm for diazides with an azide group at C-1, and at 280 nm for the triazide.

Compounds with an azide group at position 2, 3, 4, or 6

the fact that the analogous viewpoint for C=O would be along the C-O bond from C toward O, with the carbonyl group in its usual orientation. This corresponds to an interchange of the left-front with the right-rear octant, *etc.*, *i.e.* to a double change in signs which is, of course, equivalent to no sign changes at all.' The erroneous statement was noted by a referee, and we thank him for calling the point to our attention.

in the pyranose ring show a Cotton effect near 280 nm (range 274–286 nm), but for compounds with an azide group at C-1, the maximum is observed near 268 (range 264–272 nm). No significant difference has been detected between the wavelengths of the maxima for axial and equatorial azides. Data in Table 3 show that diazides

benzylidene ring lies in the back lower right octant and therefore a positive Cotton effect would be predicted for compounds 1–8 of general formula (I). Compounds 1–4 with a variation in the group R all have very similar small Cotton effects. Compounds 5 and 6 are non-reducing disaccharides with two identical monosaccharide

TABLE 2
C.d. of carbohydrate derivatives with an equatorial azide chromophore

	$\Delta\epsilon$	λ/nm
(a) Compounds with a <i>trans</i> -benzylidene substituent		
19 Methyl 3-azido-4,6- <i>O</i> -benzylidene-3-deoxy- α -D-glucopyranoside (V; R = OH)	–0.10m	282
20 Methyl 3-azido-4,6- <i>O</i> -benzylidene-2,3-dideoxy- α -D-glucopyranoside (V; R = H)	–0.10m	270
21 Methyl 3-azido-4,6- <i>O</i> -benzylidene-3-deoxy-2- <i>O</i> -tosyl- α -D-glucopyranoside (V; R = OTs)	+0.20m	274
22 Methyl 2-azido-4,6- <i>O</i> -benzylidene-2-deoxy- α -D-allopyranoside (VI)	+0.06m	286
(b) Compounds lacking fused rings		
23 2,3,4,6-Tetra- <i>O</i> -acetyl- β -D-glucopyranosyl azide (VII; R ¹ = OAc, R ² = Ac)	+0.23m	268
24 2,3,4,6-Tetra- <i>O</i> -mesyl- β -D-glucopyranosyl azide (VII; R ¹ = OMs, R ² = Ms)	+0.37m	268
25 2-Acetamido-3,4,6-tri- <i>O</i> -acetyl-2-deoxy- β -D-glucopyranosyl azide (VII; R ¹ = NHAc, R ² = Ac)	+0.21m	264
26 2-Acetamido-3,4,6-tri- <i>O</i> -acetyl-2-deoxy- β -D-galactopyranosyl azide	+0.11m	267
27 2,3,6-Tri- <i>O</i> -acetyl-4- <i>O</i> -(2,3,4,6-tetra- <i>O</i> -acetyl- β -D-glucopyranosyl)- β -D-glucopyranosyl azide	+0.32m	269
28 2,3,6-Tri- <i>O</i> -acetyl-4- <i>O</i> -(2,3,4,6-tetra- <i>O</i> -acetyl- β -D-galactopyranosyl)- β -D-glucopyranosyl azide	+0.28m	270
29 2,3,6-Tri- <i>O</i> -acetyl-4- <i>O</i> -(2,3,4,6-tetra- <i>O</i> -acetyl- α -D-glucopyranosyl)- β -D-glucopyranosyl azide	+0.28m	270
30 Methyl 3-acetamido-2-azido-2,3-dideoxy- α -D-idopyranoside (VIII; R ¹ = NHAc, R ² = OH, R ³ = H)	–0.14m	285
31 Methyl 2-azido-2-deoxy- α -D-altropyranoside (VIII; R ¹ = R ³ = OH, R ² = H)	–0.02m	282
32 Methyl 2-azido-2-deoxy-3,4,6-tri- <i>O</i> -mesyl- α -D-allopyranoside (IX)	+0.11m	280
33 Methyl 3-azido-3,6-dideoxy-4-tosyl- α -D-idopyranoside (X)	–0.04m	278
34 Methyl 6-acetoxy-3-azido-3-deoxy-4- <i>O</i> -(2,3,4,6-tetra-acetyl- α -D-glucopyranosyl)- β -D-glucopyranoside	+0.10m	280
(c) Compounds with a boat conformation		
35 Methyl 3-azido-4,6- <i>O</i> -benzylidene-3-deoxy- β -D-idopyranoside (IV; R ¹ = R ³ = H, R ² = OMe)	+0.05m	279
36 Methyl 3-azido-4,6- <i>O</i> -benzylidene-3-deoxy-2- <i>O</i> -mesyl- β -D-idopyranoside (IV; R ¹ = Ms, R ² = OMe, R ³ = H)	–0.06m	285
37 Methyl 2-azido-4,6- <i>O</i> -benzylidene-2-deoxy- β -D-idopyranoside (III; R ¹ = R ³ = H, R ² = OMe)	–0.05m	290

TABLE 3

C.d. of carbohydrate derivatives with an azide chromophore at C-6 and of compounds with more than one azide group

	$\Delta\epsilon$	λ/nm
(a) 6-Azido-derivatives		
38 1,2,3,4-Tetra- <i>O</i> -acetyl-6-azido-6-deoxy- α -D-glucose	–0.07m	279
39 2,3,4-Tri- <i>O</i> -acetyl-6-azido-6-deoxy- β -D-glucosyl benzyl hydrogen phosphate	–0.11m	282
40 1,3,4-Tri- <i>O</i> -acetyl-6-azido-6-deoxy-2- <i>O</i> -tosyl- α -D-glucose	–0.10m	274
41 Methyl 2,3,4-tri- <i>O</i> -acetyl-6-azido-6-deoxy- α -D-glucopyranoside	–0.04m	279
42 Methyl 2,3-di- <i>O</i> -acetyl-6-azido-6-deoxy-4- <i>O</i> -(2,3,4-tri- <i>O</i> -acetyl-6-azido-6-deoxy- α -D-glucopyranosyl)- β -D-glucopyranoside	–0.16m	275
(b) Diazides		
43 2,3,4-Tri- <i>O</i> -acetyl-6-azido-6-deoxy- α -D-glucopyranosyl azide	+0.27m	268
44 3,4-Di- <i>O</i> -acetyl-6-azido-6-deoxy-2- <i>O</i> -tosyl- β -D-glucopyranosyl azide	+0.35m	267
45 6-Azido-6-deoxy-2,3,4-tri- <i>O</i> -mesyl- β -D-glucopyranosyl azide	+0.33m	268
46 Benzyl 4- <i>O</i> -(4,6-diazido-4,6-dideoxy- β -D-galactopyranosyl)- β -D-glucopyranoside	+0.19m	282
47 4,6-Diazido-4,6-dideoxy- α -D-galactopyranosyl 4,6-diazido-4,6-dideoxy- α -D-galactopyranoside	+0.33m	282
48 4,6-Diazido-3,4,6-trideoxy- α -D-galactopyranosyl 4,6-diazido-3,4,6-trideoxy- α -D-galactopyranoside	+0.26m	284
49 Methyl 2,3-diazido-4,6- <i>O</i> -benzylidene-2,3-dideoxy- α -D-mannopyranoside	–0.41m	286
(c) Triazide		
50 3,4,6-Triazido-2,3,4,6-tetradeoxy- α -D-galactopyranosyl 3,4,6-triazido-2,3,4,6-tetradeoxy- α -D-galactopyranoside	+0.60m	283

with one of the two azide substituents at C-1 have a Cotton effect near 268 nm, *i.e.* the influence of the C-1 azide is dominant. Other diazides have Cotton effects at longer wavelengths near 280 nm.

Compounds with an Axial Azide Group.—Table 1 gives c.d. data for eighteen compounds in which the azide group is axial with respect to a pyranose ring. For twelve of these compounds the conformation of the pyranose ring is rigidly fixed by the *trans*-benzylidene substituent (*cf. trans*-decalin).

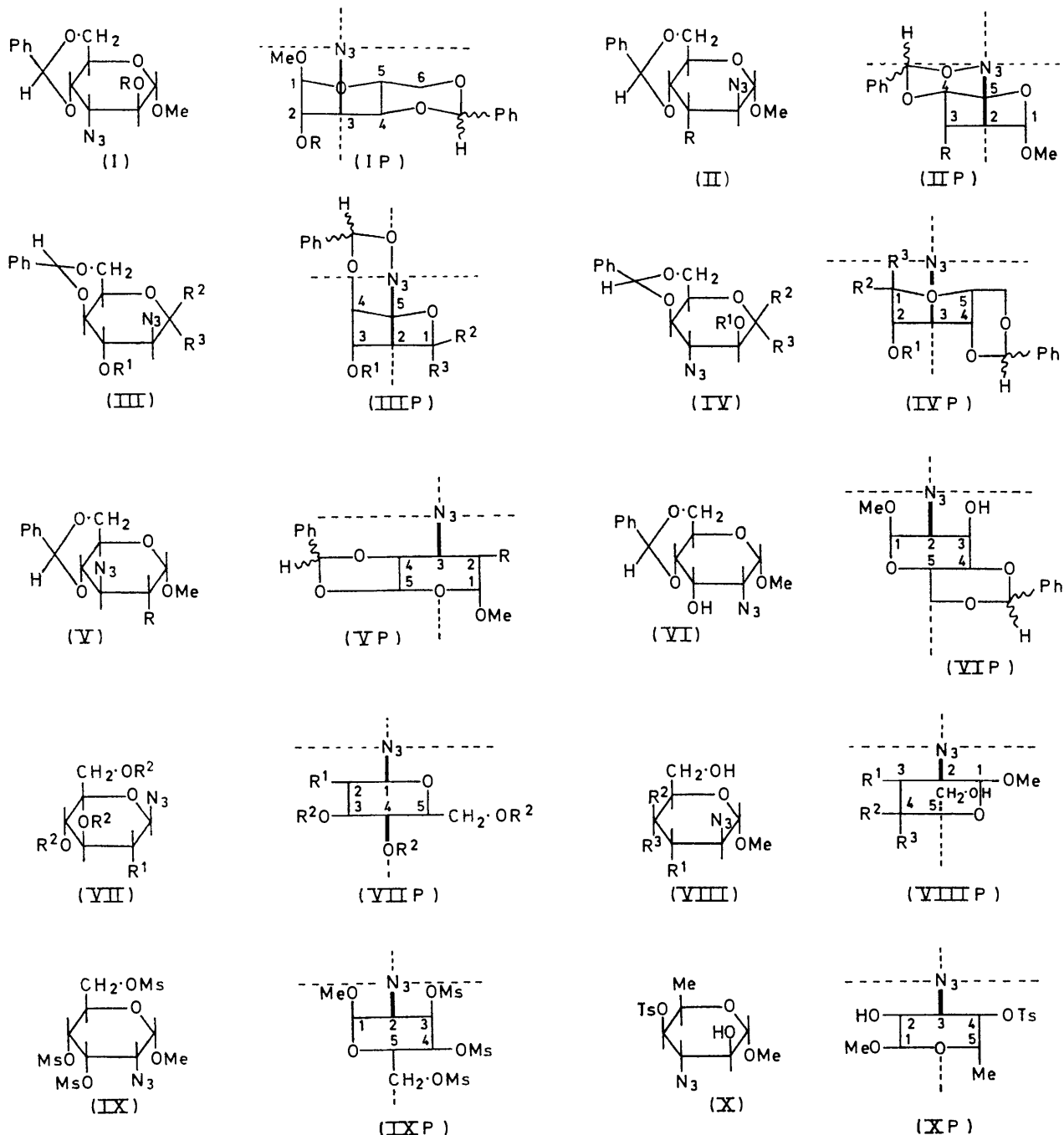
According to the octant projection (IP) the entire

units, and with an azide chromophore in each; these have slightly larger positive Cotton effects. It is interesting that compound 7, a similar disaccharide with the azide chromophore in only one sub-unit, has a $\Delta\epsilon$ value approximately half that of the other two disaccharides 5 and 6. Compound 8 in the allose series has the alternative configuration at C-2; the Cotton effect is of the same sign as for the rest of the group.

For compounds 9–12 [general formula (II)] the benzylidene ring lies in the back lower left region and the octant diagram (IIP) predicts a negative Cotton effect;

this is in accordance with experimental observation. It is interesting, in comparison with later examples, that compound 10 (II; R = OTs) has $\Delta\epsilon$ larger by 0.22 units than compound 9 (II; R = NH₂).

formation in carbohydrates, see ref. 5.) The corresponding octant projection (IIIP) is fairly symmetrical but on balance a positive Cotton effect might be predicted. A very small positive Cotton effect is in fact observed for



Pyranose sugars with a *cis*-fused benzylidene substituent are analogous to *cis*-decalins in that the two *cis*-fused six-membered rings can take up two alternative all-chair conformations. N.m.r. evidence⁴ suggests that compounds 13 and 14 of general formula (III) adopt the ⁴C₁ conformation in which the 1 α -, 2 β -, and 3 α -substituents are all axial. (For a general discussion of con-

formation in carbohydrates, see ref. 5.) The corresponding octant projection (IIIP) is fairly symmetrical but on balance a positive Cotton effect might be predicted. A very small positive Cotton effect is in fact observed for

⁴ H. Paulsen and M. Friedmann, *Chem. Ber.*, 1972, 705, 718.
⁵ J. E. Stoddart, 'Stereochemistry of Carbohydrates,' Wiley-Interscience, New York, 1971.

the change from OH to OTs. The same pattern can be seen for compounds 15 and 16 of general formula (IV) which probably exist in the 4C_1 conformation and for which projection (IVP) predicts a positive Cotton effect. Compound 15 shows a positive Cotton effect but for compound 16 the effect of the tosyl group in the back lower left octant is dominant and the sign becomes negative, with $\Delta(\Delta\epsilon)$ ca. 0.32 for the change OH to OTs.

Compounds 17 and 18 are not restricted in conformation by the presence of fused rings; the most probable conformation is that in which the azide group is the sole axial substituent. The corresponding octant projections are almost symmetrical and no prediction can be made.

Compounds with an Equatorial Azide Group (Table 2).—For the first examples 19–22 with a *trans*-fused benzylidene system, general formula (V), the octant diagram (VP) shows the second ring lying in a negative region and predicts a negative Cotton effect. In fact, two of the three examples of this type show negative Cotton effects, but compound 21 (V; R = OTs) shows a positive effect. As before the tosyl group outweighs the effect of other substituents when they are present in opposing octants, with $\Delta(\Delta\epsilon)$ ca. 0.30 units for the change for OH to OTs.

The octant diagram (VIP) predicts a positive Cotton effect in accordance with observation for compound 22 (VI).

Compounds 23–29 [general formula (VII)] lack any conformational constraint from fused rings. Their most probable conformation is that in which the azide and the substituents at C-2, C-3, and C-5 are all equatorial. Positive Cotton effects are observed for all seven, in accordance with the projection (VIIP) and in agreement with results obtained for two 1β -azidoglucopyranosyl derivatives listed by Paulsen. Presumably the bulky CH_2OAc substituent in the lower right octant outweighs the effect of OAc in the back lower left octant.

For compounds 30 and 31 [general formula (VIII)] the most probable conformation appears to be 1C_4 , in which the azide group is equatorial. In contrast, both possible chair conformations for compound 32 have a 1,3-diaxial interaction. For the 1C_4 conformation (with an axial azide) this interaction is between the azide group and MeO at C-4; for the alternative conformation with an equatorial azide (4C_1) the interaction is between the methoxy-group (1α) and the mesyl group at 3α . This is the more probable conformation. The octant projections (VIIP) and (IXP) show that the dispositions of the ring oxygen and substituents are quasienantiomeric when the azide groups are equatorial. The observed

Cotton effects, which are of opposite sign, therefore add weight to the suggestion that the 1C_4 conformation is preferred for compounds of formula (VIII).

The octant projection (XP) for compound 33 (X) predicts a negative Cotton effect in accordance with observation. However, the magnitude of the Cotton effect is very small, suggesting that the bulk of the very large tosyl group in the bottom right octant nearly outweighs the OH and OMe substituents in the bottom left octant.

Compounds with a Boat Conformation.—On the basis of n.m.r. evidence,⁴ β -D-idopyranosides are believed to exist in the boat conformation; c.d. data for three compounds of this type (35–37) are included in Table 2 but no prediction can be made about the sign of the Cotton effect.

Other Azides.—Table 3 gives c.d. data for some other carbohydrate azides. Compounds 38–42, which have an azide substituent at the terminal methyl group (C-6) all show small negative Cotton effects near 280 nm. The Cotton effects of the $1\beta,6$ -diazides are apparently dominated by the 1β -azide group, both in sign and magnitude and in the wavelength of the maximum (near 268 nm); for the remaining diazides, the maximum occurs near 280 nm.

Conclusion.—The data recorded confirm that compounds with the azide group substituted on the six-membered ring at C-1, -2, -3, or -4 follow the octant rule as proposed by earlier workers.^{2,3} The large number of possible conformations make it difficult to draw any correlation between the sign of the observed Cotton effect and the stereochemistry of the diazides or of the 6-azido-derivatives.

EXPERIMENTAL

The azides were prepared at Queen Elizabeth College, London, or at the University of Sussex by standard methods of carbohydrate synthesis. C.d. curves were measured at Westfield College on a Roussel-Jouan Dichrograph-185 for solutions in methanol, at a concentration of 1 mg ml⁻¹ or less and with a path length of 1 cm.

We thank the M.R.C. for a postdoctoral fellowship (to D. R. D.) and Professor R. D. Guthrie (University of Sussex) for a gift of many azide samples. We also thank Professor L. Hough and Professor W. Klyne for their interest, and the S.R.C. for a research grant (to Professor Klyne).

[3/699 Received, 3rd April, 1973]