Studies on Cyclic Polyols. XI. New Syntheses of Inosadiamines[1-3]

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DL-1,2-O-Isopropylidene-(1,2/5)-5-acetamido-3-cyclopentene-1,2-diol (**3**) has been prepared and has been converted, by permanganate hydroxylation and acetylation, into DL-1,2-di-O-acetyl-3,4-O-isopropylidene-(1,2,5/3,4)-5-acetamidocyclopentane-1,2,3,4-tetrol (**4a**). Selective removal of either the O-acetyl groups or the O-isopropylidene group converts **4a** into **5** and **6**, respectively, each of which is susceptible to glycol cleavage by periodate. Treatment of **5** with periodate produces DL-*lyxo*-4-acetamido-2,3-O-isopropylidenedioxypentanedial (**11**), whereas **6** is converted into DL-*ribo*-4-acetamido-2,3-diacetoxypentanedial (**17**). DL-1,2-Di-O-acetyl-(1,5/2)-5-acetamido-3-cyclopentene-1,2-diol (**8**) has been hydroxylated with permanganate to produce DL-3,4-di-O-acetyl-(1,2,4/3,5)-5-acetamidocyclopentane-1,2,3,4-tetrol (**10**). On treatment with periodate, **10** is converted into DL-*xylo*-4-acetamido-2,3-di-O-acetoxypentanediol (**21**). Treatment of the dialdehydes **11**, **17**, and **21** with nitromethane under alkaline conditions leads to the formation of mixtures of partially acetylated derivatives of acetamidonitrodideoxyinositols. By catalytic hydrogenation in the presence of Raney nickel T-4, followed by acetylation, the latter are converted into the corresponding diacetamidodideoxyinositols (inosadiamines). By chromatography on alumina, nine pure compounds were isolated and identified, of which six were previously unreported. From the *lyxo*-dialdehyde **11** four inosadiamine hexaacetates were obtained: 4,6-diacetamido-1,2,3,5-tetra-O-acetyl-4,6-dideoxy-*myo*-inositol (**13**); DL-2,6-diacetamido-1,3,4,5-tetra-O-acetyl-2,6-dideoxy-*epi*-inositol (**14**); DL-1,3-diacetamido-2,4,5,6-tetra-O-acetyl-1,3-dideoxy-*allo*-inositol (**15**); and 1,3-diacetamido-2,4,5,6-tetra-O-acetyl-1,3-dideoxy-*neo*-inositol (**16a**) or DL-2,4-diacetamido-1,3,5,6-tetra-O-acetyl-2,4-dideoxy-*chiro*-inositol (**16b**). The corresponding monoisopropylidene derivatives were obtained by a minor modification of the procedure; these were DL-4,6-diacetamido-1,5-di-O-acetyl-4,6-dideoxy-3,4-O-isopropylidene-*myo*-inositol (**13**-Ip); DL-2,6-diacetamido-1,3-di-O-acetyl-2,6-dideoxy-4,5-O-isopropylidene-*epi*-inositol (**14**-Ip); and DL-1,3-diacetamido-2,4-di-O-acetyl-1,3-dideoxy-5,6-O-isopropylidene-*neo*-inositol (**16**-Ip-a) or DL-2,4-diacetamido-1,3-di-O-acetyl-2,4-dideoxy-5,6-O-isopropylidene-*chiro*-inositol (**16**-Ip-b). From the *ribo*-dialdehyde **17** three inosadiamine hexaacetates were obtained: DL-2,6-diacetamido-1,3,4,5-tetra-O-acetyl-2,6-dideoxy-*epi*-inositol (**14**); DL-1,5-diacetamido-2,3,4,6-tetra-O-acetyl-1,5-dideoxy-*myo*-inositol (**19**); and 1,5-diacetamido-2,3,4,6-tetra-O-acetyl-1,5-dideoxy-*epi*-inositol (**20a**) or DL-1,3-diacetamido-2,4,5,6-tetra-O-acetyl-1,3-dideoxy-*epi*-inositol (**20b**). From the *xylo*-dialdehyde **21** three previously known isomers were obtained: 1,3-diacetamido-2,4,5,6-tetra-O-acetyl-1,3-dideoxy-*scyllo*-inositol (hexaacetyl streptamine, **23**); 1,3-diacetamido-2,4,5,6-tetra-O-acetyl-1,3-dideoxy-*myo*-inositol (**24**); and DL-1,3-diacetamido-2,4,5,6-tetra-O-acetyl-1,3-dideoxy-*chiro*-inositol (**25**). When ^{14}C-labeled nitromethane was used in the condensation reactions, ^{14}C-labeled **13**, **14**, **15**, **19**, **20**, **23**, and **24** were isolated.

Current interest in the chemistry of cyclohexane aminocyclitols is due largely to the occurrence of such substances as components of certain antibiotics.[2,5] The inosamines have been investigated in many laboratories and thirteen of the twenty theoretically possible isomers have been synthesized and characterized in the past twenty years. On the other hand, only ten of the fifty-four theoretically possible diasteroisomeric inosadiamines have been synthesized.[6-9] Our interest in this problem has come from synthetic studies in this laboratory[10,11] on cyclopentane aminocyclitols.

The present communication describes the synthesis of several isomeric inosadiamines, starting from cyclopentane aminocyclitols. Suitable derivatives of the 5-acetamido-3-cyclopentene-1,2-diols previously reported[11] have been converted into acetamidocyclopentanetetrols (see Chart I). Selective derivatization followed by periodate oxidation has yielded the corre-

(1) (a) Supported in part by U. S. Public Health Service Research Grants AM-07719 and GM-13971 from the National Institutes of Health. (b) The nomenclature of cyclitols has been unsettled, and many authors have devised their own systems for indicating configurational relationships (see ref 2 below). Recently an international committee under the auspices of IUPAC and IUB has recommended a set of rules for cyclitol nomenclature, based largely on proposals by Drs. S. J. Angyal and L. Anderson. These recommendations have been adopted as official, tentative rules by the IUPAC/IUB Commission on Biochemical Nomenclature and by the IUPAC Commission on Nomenclature of Organic Chemistry. The cyclitols described in the present study are named by the Angyal–Anderson system. The recommendations of the Joint Cyclitol Nomenclature Subcommittee provide that the basic method of naming and numbering cyclitols shall be the IUPAC Rules for Nomenclature of Organic Chemistry, Part C, as published in *Pure Appl. Chem.*, **11**, No. 1 and 2 (1965). Additional stipulations are then given to resolve questions of numbering preference which are unique to the cyclitols and related compounds, and a method for designating absolute configuration is provided. When the IUPAC organic chemistry rules are used, as with the cyclopentane derivatives discussed in this paper, relative configuration is indicated by a fractional prefix (Maquenne) in which the locants (positional numbers) of all the substituents on one side of the plane of the ring are arranged in ascending order in the numerator, and the locants for the substituents on the other side of the plane are in the denominator.

An exception to the IUPAC organic chemistry rules is made for compounds which may be considered to be derived from the inositols (cyclohexanehexols) by replacement of one or two of the hydroxyl groups by other univalent substituents. Such cyclitols are named as substituted inositols; the inosadiamines, for example, become *x,y*-diamino-*x,y*-dideoxyinositols. The relative configuration is designated by the prefix used for the parent inositol, and the positions are numbered as in the parent inositol. There are alternative ways of numbering each of the inositols, but replacement of –OH by $-NH_2$ may eliminate some of the alternatives. The alternative used is the one which gives the amino groups the lower numbers; *e.g.*, in the present work (see Chart II) the amino groups of compound **15** are numbered 1,3 rather than 2,4 and the amino groups of compound **16a** are numbered 1,3 rather than 4,6. One new name must also be mentioned. The optically active and racemic inositols are now designated as D-, L- and DL-*chiro*-inositol, respectively. This name is used in the present work.

In the representation of the various compounds in the charts, the same enantiomer is not always shown. We feel that by showing the correct configurational relationships between starting material and products we will add to the clarity of the presentation.

(2) S. J. Angyal and L. Anderson, *Advan. Carbohyd. Chem.*, **14**, 184 (1959).

(3) Part X: H. Z. Sable and H. Katchian, *Carbohyd. Res.*, **5**, 109 (1967).

(4) Author to whom correspondence and requests for reprints should be addressed.

(5) K. L. Rinehart, Jr., "The Neomycins and Related Antibiotics," John Wiley and Sons, Inc., New York, N. Y., 1964.

(6) (a) M. L. Wolfrom, S. M. Olin, and W. F. Polglase, *J. Amer. Chem. Soc.*, **72**, 1724 (1950); (b) H. Straube-Rieke, H. A. Lardy, and L. Anderson, *ibid.*, **75**, 694 (1953); (c) K. Heyns and H. Paulsen, *Chem. Ber.*, **89**, 1152 (1956).

(7) M. Nakajima, N. Kurihara, A. Hasegawa, and T. Kurokawa, *Ann. Chem.*, **689**, 243 (1965).

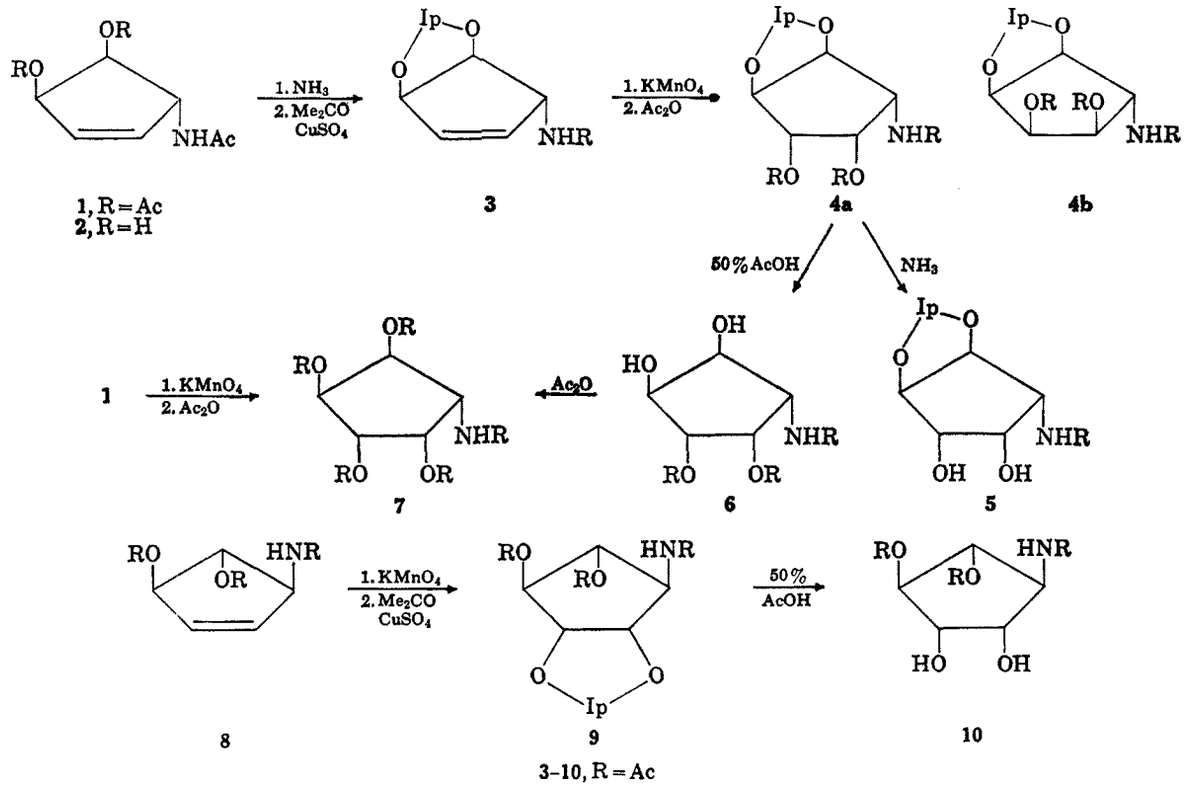
(8) M. Nakajima, A. Hasegawa, and F. W. Lichtenthaler, *ibid.*, **669**, 75 (1963).

(9) (a) G. Quadbeck and E. Röhm, *Chem. Ber.*, **89**, 1645 (1956); (b) M. L. Wolfrom, F. Radell, R. M. Husband, and G. E. McCasland, *J. Amer. Chem. Soc.*, **79**, 160 (1957); (c) F. W. Lichtenthaler and H. O. L. Fischer, *ibid.*, **83**, 2005 (1961); (d) F. W. Lichtenthaler, *Angew. Chem. Intern. Ed. Engl.*, **3** 211 (1964); (e) V. Brocca and A. Dansi, *Ann. Chim.* (Rome) **44**, 120 (1954); *Chem. Abstr.*, **49**, 8821 (1955).

(10) A. Hasegawa and H. Z. Sable, *J. Org. Chem.*, **31**, 4149 (1966).

(11) A. Hasegawa and H. Z. Sable, *ibid.*, **31**, 4154 (1966).

CHART I



sponding trisubstituted pentanedials. The latter compounds, on treatment with nitromethane[9d,e] followed by catalytic reduction and acetylation, gave mixtures of hexaacetyl *m*-inosadiamines. The mixtures were separated by chromatography and fractional crystallization. Configurational assignments are based on the known configuration of the starting materials and the chemical shifts of the methyl protons of the acetyl groups.[8,12-14] Altogether, nine inosadiamines (six of them previously unreported) have been characterized. Some of the syntheses were repeated with ^{14}C-labeled nitromethane, to give specifically labeled inosadiamines.

Results

Selectively Blocked Acetamidocyclopentanetetrols.—The 5-acetamido-3-cyclopentene-1,2-diols[11] **1** and **8** (Chart I) have yielded three different dialdehydes, as shown in Charts I and II. DL-1,2-di-O-acetyl-(1,2/5)-5-acetamido-3-cyclopentene-1,2-diol (**1**) was first transformed into the corresponding O-isopropylidene derivative **3**; hydroxylation with permanganate, and acetylation then gave a product which could have been either **4a** or **b**. However, by two reactions not involving the asymmetric centers the substance was converted into the known pentaacetate[11] **7**, and structure **4a** is therefore correct. Selective removal of either the O-acetyl groups or the O-isopropylidene group then gave, respectively, glycols **5** and **6**. In the case of the all-*trans* compound DL-1,2-di-O-acetyl-(1,5/2)-5-acetamido-3-cyclopentene-1,2-diol (**8**), a previous study[11] had shown that the di-O-acetylacetamidotetrol produced by treatment with permanganate was **10**. In order to obtain a pure sample of **10**, the syrupy crude product was converted into the crystalline O-isopropylidene derivative **9** which was purified and then hydrolyzed with 50% acetic acid to give **10**.

Treatment of the glycols with periodate converts **5** into DL-*lyxo*-4-acetamido-2,3-isopropylidenedioxypentanedial (**11**); **6** is converted into DL-*ribo*-4-acetamido-2,3-diacetoxypentanedial (**17**); and **10** is converted into DL-*xylo*-4-acetamido-2,3-diacetoxypentanedial (**21**) (see Chart II).

Inosadiamines from *lyxo* Dialdehyde 11.—Treatment of the dialdehyde **11** with nitromethane under alkaline conditions[9d] produced a mixture of stereoisomeric deoxynitroinosamines **12** (see Chart II). Attempted catalytic hydrogenation of **12** with PtO_2, Raney nickel (W-2), or 10% palladium on carbon, under various conditions, was unsuccessful. Raney nickel T-4, prepared according to Nishimura,[15] however, was found to be effective, as shown by the disappearance of the nitro group. The reduced material, after acid hydrolysis of the isopropylidene group and peracetylation, was fractionated by chromatography. Six different hexaacetylinosadiamine fractions were obtained, apparently in pure state, as shown by sharpness of the melting points. Configurational assignments were based on nmr spectroscopy, by which the numbers of axial and equatorial acetoxy and acetamido groups could be determined[8,12-14] as shown in Table I. These results were then compared with the predicted preferred conformation of each of the products that could have arisen from the sequence of reactions employed. Because three new asymmetric centers are created in the condensation of a dialdehyde with nitromethane, eight inosadiamines could be formed. The configurations

(12) R. U. Lemieux and R. J. Cushley, *Can. J. Chem.*, **41**, 858 (1963).

(13) (a) F. W. Lichtenthaler, *Chem. Ber.*, **96**, 845 (1963); (b) *ibid.*, **96**, 2047 (1963); (c) F. W. Lichtenthaler and H. Leinert, *ibid.*, **99**, 903 (1966); (d) F. W. Lichtenthaler and P. Emig, *Tetrahedron Lett.*, 577 (1967).

(14) M. Nakajima, A. Hasegawa, and F. W. Lichtenthaler, *Ann. Chem.*, **680**, 21 (1964).

(15) S. Nishimura, *Bull. Chem. Soc. Jap.*, **32**, 61 (1959).

CHART II

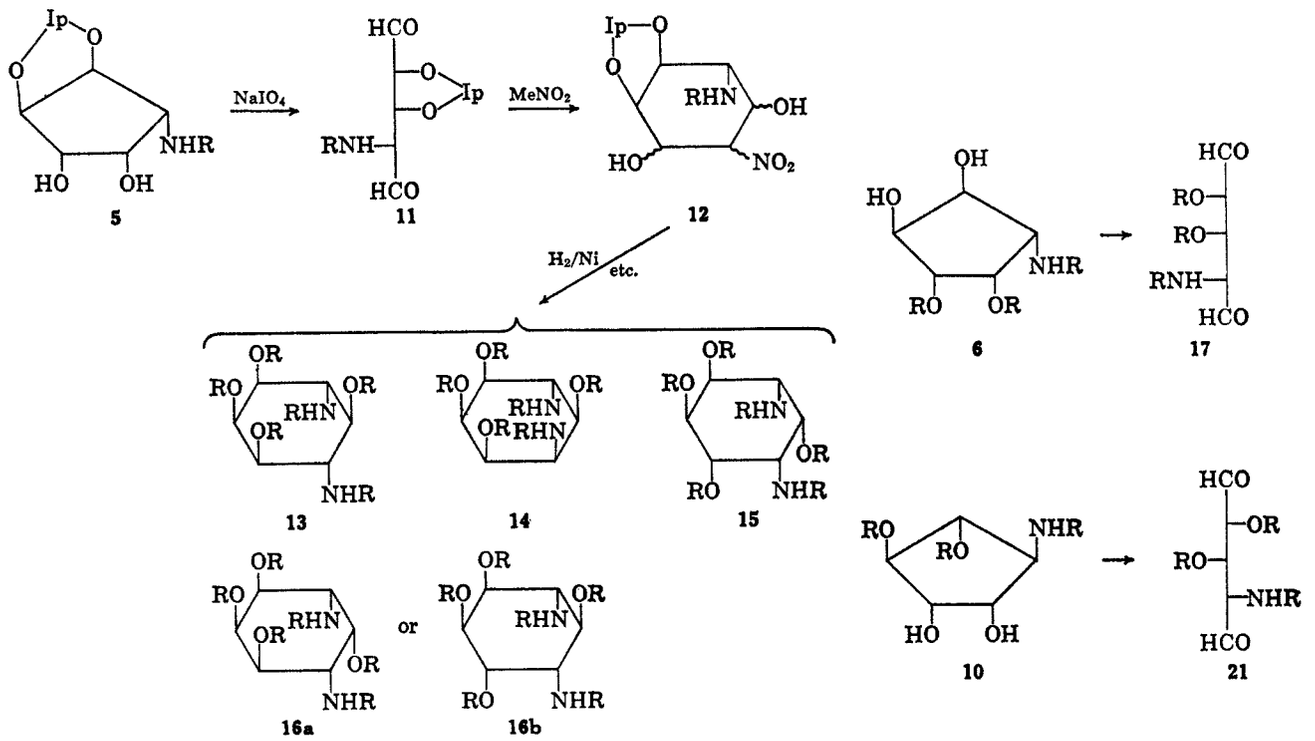


TABLE I

CHEMICAL SHIFTS OF ACETYL METHYL GROUPS OF INOSADIAMINES[a]

Compd	Trivial designation	Preferred conformation	Acetoxyl protons		Acetamido protons	
			Axial	Equatorial	Axial	Equatorial
13	*myo*-4,6	eaeeee	2.18 (3)	1.99 (9)		1.87 (6)
14	*epi*-2,6	eaeaee	2.20 (3)	2.00 (3), 1.93 (3), 1.89 (3)	2.00 (3)	1.87 (3)
15	*allo*-1,3	aeaeea	2.21 (3)	2.01 (3), 1.98 (6)	2.01 (6)	
16a or	*neo*-1,3	eaeeae	2.22 (6)	2.01 (6)		1.92 (6)
16b	*chiro*-2,4	eaaeee				
19	*myo*-1,5	eaeeee	2.16 (3)	2.08 (3), 2.01 (3), 1.97 (3)		1.90 (6)
20a or	*epi*-1,5	eaeaee	2.10 (6)	1.97 (3), 1.88 (3)		1.85 (6)
20b	*epi*-1,3					
23	*scyllo*-1,3	eeeeee		2.00 (12)		1.87 (6)
24	*myo*-1,3	eaeeee	2.24 (3)	2.01 (6), 2.00 (3)		1.90 (6)
25	*chiro*-1,3	eaaeee	2.19 (3)	2.00 (3), 1.98 (3), 1.97 (3)	2.00 (3)	1.95 (3)

[a] Spectra were measured on solutions in $CDCl_3$–CD_3OD (2:1 or 1:1). Values are reported on the δ scale. Numbers in parentheses refer to number of protons.

TABLE II

PREFERRED CONFORMATIONS OF INOSADIAMINES

Configuration	Root name	Conformation
1,2,3,4,5,6/0	*cis*-	aeaeae or eaeaea
1,2,3,4,5/6	*epi*-	eaeaee
1,2,3,4/5,6	*allo*-	aeaeea or eaeaae
1,2,3,5/4,6	*myo*-	eaeeee
1,2,4,5/3,6	*muco*-	eeeaaa or aaaeee
1,2,3/4,5,6	*neo*-	eaeeae
1,2,4/3,5,6	*chiro*-	aeeeea
1,3,5/2,4,6	*scyllo*-	eeeeee

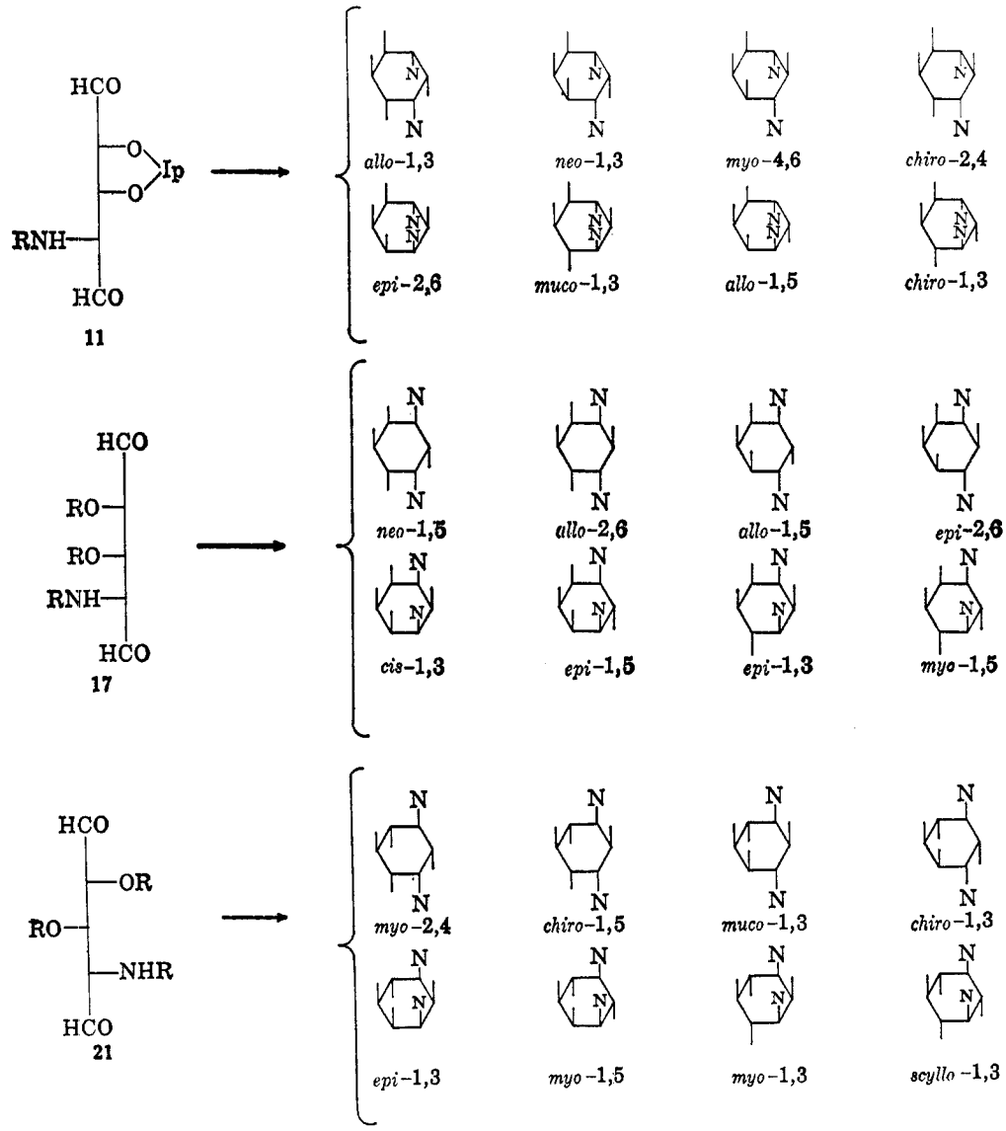
and conformations of these are indicated in Table II and Chart III. The total yield of pure products was 12%; so one cannot refer to "principal" or "minor" products of the cyclization reaction (see Experimental Section). The most abundant product isolated was considered to have configuration **13**, *i.e.*, *myo*-4,6, since it had one axial acetoxyl group, whereas the other three acetoxyl groups and both acetamido groups were equatorial. The two next most abundant products were assigned configurations **14** (DL-*epi*-2,6) and **15** (DL-*allo*-1,3). A fourth product, **16**, mp 296–299°, had two axial and two equatorial acetoxyl groups and two equatorial acetamido groups. This restricts the possible configuration to *neo*-1,3 (**16a**) and DL-*chiro*-2,4 (**16b**) but does not distinguish between these two possibilities. Two additional products of this reaction have not been identified.

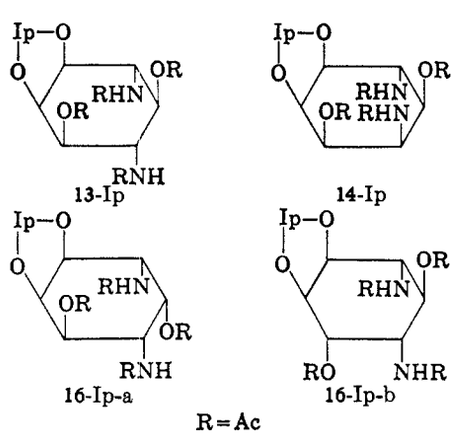
In a separate experiment the sequence of reactions was altered so that the mixture obtained after reduction of the nitro group was not acidified, but was acetylated directly to a mixture of monoisopropylidenetetraacetylinosadiamines. From this mixture four compounds were purified. Three of these correspond to the inosadiamines **13**, **14**, and **16**, since removal of the isopropylidene groups followed by peracetylation yielded compounds identical with the hexaacetyl derivatives previously prepared. The isopropylidene derivatives are designated as **13**-Ip, **14**-Ip, and **16**-Ip.

Inosadiamines from *ribo* Dialdehyde 17.—Three diastereoisomeric inosadiamines were obtained from the

CHART III

POSSIBLE CONFIGURATIONS AND TRIVIAL NAMES OF INOSADIAMINES THAT COULD BE DERIVED FROM THE THREE DIALDEHYDES USED IN THIS STUDY



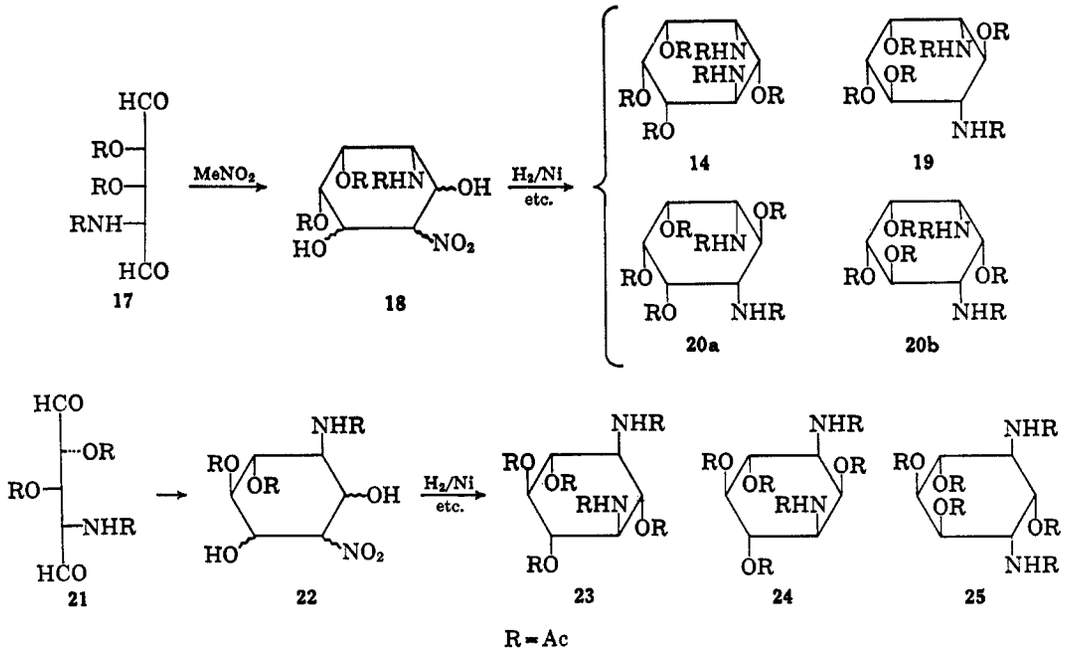


cyclization of the dialdehyde **17** (Chart IV). One of these is identical with the product designated as DL-*epi*-2,6 (**14**) which was obtained from dialdehyde **11**. Another product **19** had one axial acetoxyl group and all the other acetyl groups equatorial. Of the eight possible isomers (Chart III) only DL-*myo*-1,5 can assume such a conformation. The third product, **20**, had two each of axial and equatorial acetoxyl groups and two equatorial acetamido groups. Two of the possible compounds, *epi*-1,5 (**20a**) and DL-*epi*-1,3 (**20b**), could exist in this conformation. No further decision between these possibilities can be based on the available evidence.

Inosadiamines from *xylo* Dialdehyde 21.—Three products were obtained from the condensation of dialdehyde **21** with nitromethane (see Chart IV). In this case, all three of the compounds were previously known.[6-8] The physical and spectral properties of these substances agreed with those reported by the earlier workers. The compounds are the *scyllo*-1,3 (streptamine),[6] the *myo*-1,3,[7] and the DL-*chiro*-1,3[8] (structures **23**, **24**, and **25**, respectively; Chart IV).

Validity of use of Chemical Shift of Acetyl Groups for Configurational Assignments.—The correlations of chemical shift with the axial or equatorial orientation of acetoxyl and acetamido groups were established[8,12-14] on the basis of spectra measured on solutions in chloroform. Most of the new compounds reported here are insufficiently soluble in chloroform for the measurement of nmr spectra. The values reported in Table I are de-

CHART IV



R = Ac

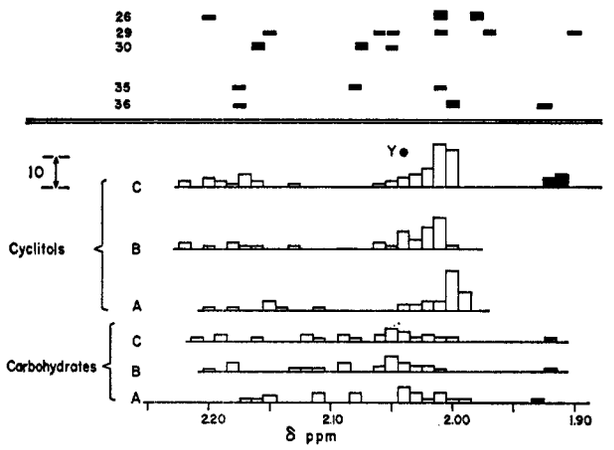


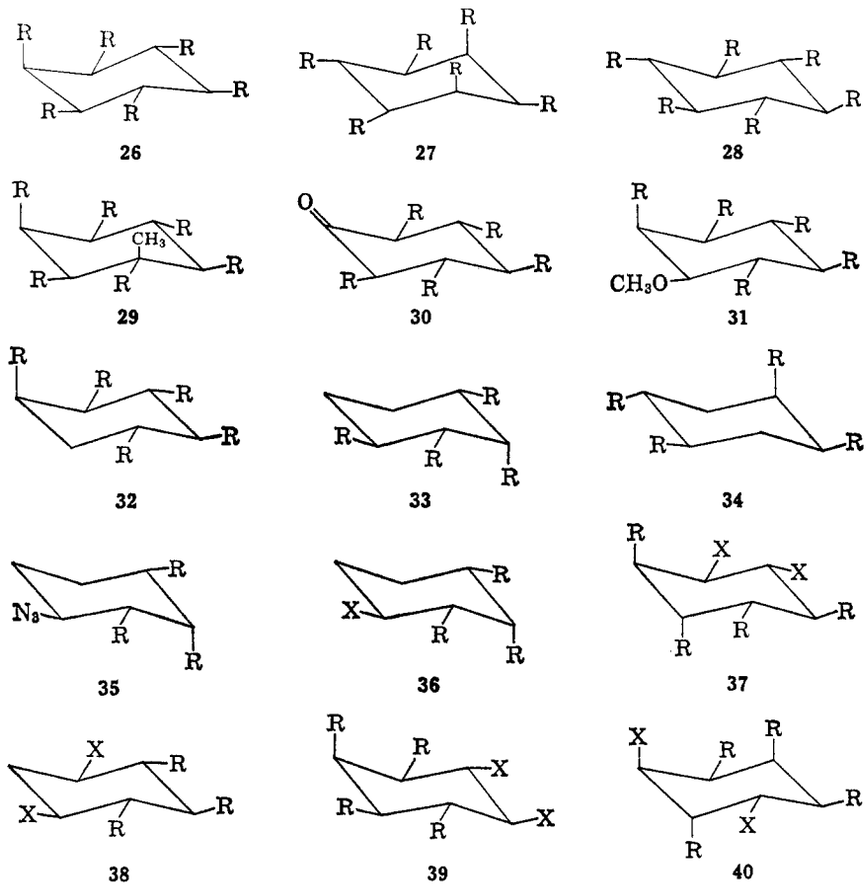
Figure 1.—Chemical shifts of acetyl protons of acetoxy and acetamido groups of carbohydrates and cyclitols. The diagonally hatched areas represent equatorial acetamido groups. Point Y represents an axial acetamido group in compound **40**. The remaining data refer to acetoxyl groups. The vertical axis in each case represents the number of signals observed at the indicated chemical shift, and the double arrow marked 10 shows the height equivalent to 10 signals in the histogram. A, B, and C indicate that the data are derived from spectra measured on solutions in $CDCl_3$, $CDCl_3$–CD_3OD (2:1), and $CDCl_3$–CD_3OD (1:1), respectively. The upper part of the figure shows the influence of magnetically anisotropic functional groups on chemical shifts of compounds with similar configurations. Not shown in the figure are the chemical shifts of the C-CH_3 group of laminitol (δ 1.56–1.58) and the O-CH_3 group of bornesitol (δ 3.36–3.38).

rived from spectra measured on solutions in a mixed solvent, either 2:1 or 1:1 (v/v) mixtures of $CDCl_3$ and CD_3OD. In view of the well-known influence of solvent composition on chemical shift, we considered a reexamination of the chemical shifts of acetyl groups in the mixed solvents essential. The results of such a study are shown in Figure 1. Five fully acetylated carbohydrates and fifteen fully acetylated cyclitols (including aminocyclitols) were studied. A definite solvent shift is observed when 2:1 or 1:1 $CDCl_3$–CD_3OD is substituted for pure $CDCl_3$. However, the shift is small and in no case does any ambiguity arise. The data for the carbohydrates and the cyclitols are reported separately in Figure 1 because the carbohydrate derivatives have two types of groups not found in the cyclitols, *viz.*, anomeric and primary acetoxyl groups. The axial anomeric acetoxyl signals are those at lowest field,[16,17] and the signals of equatorial anomeric acetoxyl groups are the only ones that may overlap with the "axial" region and may thus cause confusion in the assignments. In the case of the cyclitols, Figure 1 shows that the generalizations previously established[8,12–14] are still valid when the mixed solvent is used in place of pure $CDCl_3$.

The data for laminitol **29** and 2,4,6/3,5-pentahydroxycyclohexanone (*scyllo-ms*-inosose) **30** (Chart V) are given separately because both contain magnetically anisotropic groups. *Scyllo-ms*-inosose contains no axial acetoxyl groups but two of the groups give nmr signals at δ 2.16, *i.e.*, in the middle of the "axial" spectral region. This is due to a strong deshielding effect exerted by the ring carbonyl group, and these low-field signals probably represent the acetoxyl groups adjacent to the ring carbonyl. In the case of laminitol, the C-methyl group shields some and deshields other acetoxyl groups relative to the equatorial acetoxyl groups of *myo*-inositol. Even so, in spite of the presence of the anisotropic group the assignments seem unambiguous. On the basis of the results of Lichtenthaler and Emig[13d] the signal at δ 1.89 is assigned to the C(CH_3)–acetoxyl group. The anisotropic effect of the azido group is seen when the data for the azidotriol triacetate **35** are compared with those for the acetamidotriol triacetate **36**. One of the equatorial acetoxyl groups of **35** is deshielded by 0.08 ppm relative to **36**, whereas the other equatorial group and the axial group are unaffected. Similar observations on the effects of anisotropic groups have been published recently by Horton, *et al.*,[17] and by Cushley,

(16) D. Horton, J. B. Hughes, J. S. Jewell, K. D. Philips, and W. N. Turner, *J. Org. Chem.*, **32**, 1073 (1967).
(17) D. Horton, W. E. Mast, and K. D. Philips, *ibid.*, **32**, 1471 (1967).

CHART V
CYCLITOLS OF KNOWN CONFIGURATION USED IN STUDY OF CHEMICAL SHIFTS OF ACETYL GROUPS



et al.[18] Since the new aminocyclitols listed in Table I contain the same type and number of substituents, the assignment of configuration based on chemical shifts appears to be safe.

^{14}C-Labeled Inosadiamines.—When the nature of the products was established, each of the condensation reactions was repeated as described, except that the nitromethane was labeled with ^{14}C. The usual procedures then gave a series of specifically labeled inosadiamines. A similar type of reaction was used by Drummond, *et al.*,[19] to prepare specifically labeled inosamines, which were then deaminated to give labeled inositols.

Discussion

The hexaacetyl derivative of the *allo*-1,3-diamine **15** can exist in two chair conformations in which nonbonded repulsions might be assumed to be nearly equivalent. The data in Table I suggest, however, that one of the conformers predominates, specifically the one in which the acetamido groups are axial. Two possible explanations of this finding are (a) that the combination of two axial acetamido groups and one axial acetoxyl group is sterically less demanding than are three axial acetoxyl groups and (b) that, when the acetamido groups are axial, one or both amide hydrogen atoms can more easily form hydrogen bonds. This hydrogen bonding would then make the "acetamide axial" conformer more stable. Study of Dreiding models shows that each amide hydrogen atom can approach within H-bonding distance of several potential electron-pair donors, including the carbonyl oxygen and the nitrogen atom of the other acetamido group, as well as the carbonyl oxygen atoms of adjacent equatorial acetoxyl groups. A situation which would be formally analogous to a dimeric form of acetic acid or acetamide, *i.e.*, that in which both amide hydrogens would be bonded simultaneously to the opposite carbonyl oxygens, appears to be excluded because of interference between the acetyl methyl groups. Further experimental work will be required to establish whether such hydrogen bonds are indeed present, and, if so, what acceptor atoms participate in the bonding. Similar arguments involving H bonding of the acetamide hydrogen atom can be used to justify the assignment of a favored conformation for the *muco*-inosadiamine **40** as shown in Chart V. The three *myo*-inosadiamines reported in Table I could also exist in chair conformations with *syn*-diaxial acetamido groups, but these conformations would have five substituents axial and only one equatorial, a most unfavorable situation. In a related study, Lichtenthaler and Leinert[13c] find that in the case of hexaacetyl-*cis*-inosatriamine-(1,3,5) the "acetamide equatorial" conformation is favored, rather than the axial conformations proposed in the present work. The conformation of the triamino compound is deduced from the nmr spec-

(18) R. J. Cushley, K. A. Watanabe, and J. J. Fox, *J. Amer. Chem. Soc.*, **89**, 394 (1967).
(19) G. I. Drummond, J. N. Aronson, and L. Anderson, *J. Org. Chem.*, **26**, 1601 (1961).

trum of a sample dissolved in D_2O, whereas in the present study spectroscopy was carried out on solutions in $CDCl_3$–CD_3OD whose polarity is much lower. Undoubtedly, the aqueous environment would have a greater tendency to disrupt intramolecular H bonds, so that this stabilizing factor would be absent. Furthermore, because of the greater polarity of acetamide groups relative to acetoxyl groups, one may postulate the existence of a solvent cage of D_2O molecules associated with the acetamido groups. Such a solvent cage would make these groups much larger than the acetoxyl groups, and thus would favor the "acetamide equatorial" conformation.

The chemical shifts observed in the case of the *epi*-2,6 isomer **14** are not easy to interpret, since the signals are at higher field than those of all the other compounds. By elimination of other possibilities we have arrived at the conclusion presented, but some reservations may be necessary, and the configurational assignment in this case, although reasonable, is only tentative.

The cyclopentane cyclitols and aminocyclitols[10,11] are convenient starting materials for the preparation of cyclohexane aminocyclitols. The disadvantage of these compounds is that so far none of the racemates has been resolved. However, methods exist for resolution of amino compounds, and this disadvantage can be overcome. The total synthesis of inosadiamines from cyclopentadiene represents the conversion of a petroleum by-product into compounds related to antibiotics, which are of potential interest in biological and medicinal chemistry. The same approach has been used for preparing deoxyinosadiamines,[20] and should be a useful step in the synthesis of labeled or modified antibiotics.

Experimental Section[21]

DL-1,2-O-Isopropylidene-(1,2/5)-5-acetamido-3-cyclopentene-1,2-diol (3).—A 10.4-g (43.2 mmol) sample of DL-1,2-di-O-acetyl-(1,2/5)-5-acetamido-3-cyclopentene-1,2-diol[11] (**1**) was dissolved in 100 ml of methanol saturated with dry NH_3 and 50 ml of absolute ethanol and left overnight at room temperature. The solvent and acetamide were evaporated under reduced pressure to give the syrupy acetamidodiol **2**. The latter was stirred 3 days with anhydrous acetone (450 ml), anhydrous $CuSO_4$ (50 g), and 0.5 ml 98% H_2SO_4. The green reaction mixture was neutralized with saturated methanolic NH_3 and filtered. Evaporation of solvent gave a syrup which crystallized from ether. Recrystallization from ether gave 6.74 g (79%) of plates (**3**), mp 98°. *Anal.* Calcd for $C_{10}H_{15}O_3N$ (197.24): C, 60.89; H, 7.67; N, 7.10. Found: C, 60.60; H, 7.52; N, 6.89.

DL-1,2-Di-O-acetyl-3,4-O-isopropylidene-(1,2,5/3,4)-5-acetamidocyclopentane-1,2,3,4-tetrol (4a).—To a solution of 2.8 g (14.2 mmol) of **3** in 400 ml of 95% ethanol, 10.5 g of $MgSO_4 \cdot 7H_2O$ was added; then 400 ml of 2% aqueous $KMnO_4$ was added, with stirring, over a period of 2 hr at −20°. The mixture was then left overnight at room temperature, filtered, treated with active carbon, and filtered again. Concentration in a rotary evaporator gave an amorphous substance, which was extracted with 100 ml of hot absolute ethanol. The ethanolic solution was evaporated to a yellow syrup; this was acetylated (10 ml of pyridine, 10 ml of acetic anhydride) overnight at room temperature. Removal of the reagents by evaporation gave a syrup which was chromatographed over Al_2O_3 (60 g, 1.8-cm diameter) with chloroform to give 2.93 g of crude **4a**. Recrystallization from ether gave 2.41 g (54%) of colorless needles, mp 108°. *Anal.* Calcd for $C_{14}H_{21}O_7N$ (315.32): C, 53.32; H, 6.71; N, 4.44. Found: C, 53.46; H, 6.58; N, 4.45.

DL-3,4-O-Isopropylidene-(1,2/3,4,5)-5-acetamidocyclopentane-1,2,3,4-tetrol (5).—Compound **4a** (1.267 g, 4.02 mmol) was dissolved in 50 ml of methanol saturated with NH_3 and 10 ml of methanol and left overnight at room temperature. Solvent and acetamide were evaporated. The crystalline residue was recrystallized from absolute ethanol–ether to give **5**, 675 mg (73%), as needles, mp 144–145°. *Anal.* Calcd for $C_{10}H_{17}O_5N$ (231.25): C, 51.94; H, 7.41; N, 6.06. Found: C, 51.84; H, 7.60; N, 6.12.

DL-1,2-Di-O-acetyl-(1,2,5/3,4)-5-acetamidocyclopentane-1,2,-3,4-tetrol (6).—Compound **4a** (860 mg, 3.12 mmol) was dissolved in 60 ml of 50% acetic acid and heated for 1 hr at 100°. Removal of solvent gave a crystalline substance which was recrystallized from absolute ethanol–ether to yield 508 mg (68%) of **6** as colorless needles, mp 133°. *Anal.* Calcd for $C_{11}H_{17}O_7N$ (275.27): C, 47.99; H, 6.23; N, 5.09. Found: C, 47.48; H, 6.26; N, 5.18.

DL-1,2,3,4-Tetra-O-acetyl-(1,2,5/3,4)-5-acetamidocyclopentane-1,2,3,4-tetrol (7).—Compound **6** (40 mg, 0.14 mmol) was acetylated (2.0 ml of pyridine, 1.0 ml of acetic anhydride, 2 days at room temperature) and worked up as usual. Ether (2 ml) was added to the syrupy residue, and after standing at −10° for several days the product crystallized. Recrystallization from ether gave plates (48 mg, 89%), mp 119°. A mixture melting point with authentic[11] **7** was not depressed, and the infrared spectra were identical.

DL-3,4-Di-O-acetyl-1,2-O-isopropylidene-(1,2,4/3,5)-5-acetamidocyclopentane-1,2,3,4-tetrol (9).—To a solution of 2.5 g (10.4 mmol) of DL-1,2-di-O-acetyl-(1/2,5)-5-acetamido-3-cyclopentene-1,2-diol[11] (**8**) in 250 ml of 95% ethanol, 7.5 g of $MgSO_4 \cdot 7H_2O$ was added. The solution was stirred and maintained at −20° for 1 hr while 272 ml of 1% aqueous $KMnO_4$ was added. After standing overnight at room temperature the mixture was filtered; the filtrate was treated with active carbon, refiltered, and then concentrated. The amorphous residue was extracted with 100 ml of hot absolute ethanol, and the syrupy product obtained after evaporation of the ethanol was treated with 450 ml of anhydrous acetone, 10 g of anhydrous $CuSO_4$, and 0.2 ml of 98% H_2SO_4, and stirred for 2 days. The product was worked up as usual, and the syrup obtained was chromatographed over Al_2O_3 (80 g, 1.8-cm diameter) with chloroform to give crude **9** (1.46 g, 44%). Crystallization from ether gave needles, mp 147–150°. *Anal.* Calcd for $C_{14}H_{21}O_7N$ (315.31): C, 53.32; H, 6.71; N, 4.44. Found: C, 53.10; H, 6.58; N, 4.35.

DL-3,4-Di-O-acetyl-(1,2,4/3,5)-5-acetamidocyclopentane-1,2,-3,4-tetrol (10).—The isopropylidene derivative **9** (150 mg, 0.48 mmol) was dissolved in 10 ml of 50% acetic acid and heated for 2 hr at 100°. After removal of solvents a slightly yellow syrup (**10**) was obtained. Attempts to crystallize this product were unsuccessful.

4,6-Diacetamido-1,2,3,5-tetra-O-acetyl-4,6-dideoxy-*myo*-inositol (13), DL-2,6-Diacetamido-1,3,4,5-tetra-O-acetyl-2,6-dideoxy-*epi*-inositol (14), DL-1,3-Diacetamido-2,4,5,6-tetra-O-acetyl-1,3-dideoxy-*allo*-inositol (15), and 1,3-Diacetamido-2,4,5,6-tetra-O-acetyl-1,3-dideoxy-*neo*-inositol (16a) or DL-2,4-Diacetamido-1,3,5,6-tetra-O-acetyl-2,4-dideoxy-*chiro*-inositol (16b).—The acetamido isopropylidene compound **5** (630 mg, 2.72 mmol) was dissolved in 15 ml of water containing 600 mg of $NaIO_4$ and the solution was left overnight at room temperature. After evaporation of water, the residue was extracted with 50 ml of hot ethanol–chloroform (1:1). When this solvent was evaporated a yellowish syrup (*lyxo*-dialdehyde **11**) was obtained, which was used without further purification for the next reaction. The syrup was dissolved in 10 ml of absolute ethanol, and 750 mg of nitromethane was added. The solution was cooled and maintained between 0 and −5° while 7 ml of "2% sodium alcoholate" (2 g of Na in 100 ml of ethanol) was added dropwise over a period of 10 min with stirring; the stirring was continued for 2 hr. The mixture was then left overnight at 5°. Yellow crystals separated; these were dissolved in 100 ml of methanol and the solution was treated with Amberlite IRC-50-H^+ to remove sodium ions. The solvent was evaporated, leaving a yellow syrup **12** whose infrared spectrum showed absorption at frequencies characteristic of the following functional groups: OH (3400 cm^{-1}), NO_2 (1541 cm^{-1}),

(20) A. Hasegawa and H. Z. Sable, unpublished data.

(21) Melting points were determined on a Kofler Micro hot stage (A. H. Thomas and Co.) and are corrected. Boiling points are uncorrected. Nmr spectra were recorded with a Varian Associates A-60 nmr spectrometer. Infrared spectra were recorded with a Perkin-Elmer Model 237B spectrophotometer. Radioactivity was measured on thin samples on steel planchets, with a Nuclear-Chicago Corp. Model 183B counter. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. Proportions indicated for mixed solvents refer to volume per volume ratios. For chromatography, Merck aluminum oxide, acid washed, was used.

acetamido carbonyl (1640 cm^{-1}), and isopropylidenedioxy (842 cm^{-1}). The crude nitro compound **12** was dissolved in 50 ml of 50% aqueous ethanol; 3.0 g of Raney nickel T-4 catalyst[15] was added and hydrogen as bubbled through for 2 hr while the solution was stirred and maintained at 60–65°. The solution was then made slightly acidic by addition of 2 *N* HCl and then hydrogen was passed in for 5 hr. After removal of the catalyst by filtration the solution was acidified with 5 ml of concentrated HCl, the solvents were removed, and the residual syrup was acetylated. The acetylated product was chromatographed over Al_2O_3 (50 g, 1.0-cm diameter) with chloroform and chloroform–ethanol (1:1). The crystalline products obtained from the eluates were recrystallized from absolute ethanol or ethanol–ether (1:1). The first eluate fraction (20 ml of chloroform) yielded 3.5 mg (0.3%) of unidentified needles, mp 250°. A second fraction (50 ml of chloroform) gave 20.5 mg (1.8%) of unidentified prisms (correct analysis for an inosadiamine hexaacetate); these were transformed into needles at 262–263° and melted with sublimation at 300–310°. A third elution (20 ml of chloroform–ethanol) gave 604 mg of syrup which was crystallized from ethanol–ether. Fractional recrystallization of this product from ethanol gave 23 mg (2%) of needles, mp 318–320° dec, identified as **15**, and 48 mg (4.1%) of prisms, mp 250–255° dec, identified as **13**. The combined mother liquors of this fraction were evaporated to a syrup which was dissolved in 10 ml of ethanol–ether and left at 5° for 2 weeks. The crystalline material was fractionally recrystallized from ethanol to give 43 mg (3.7%) of needles, mp 280–283° dec, identified as **14**, and 15 mg (1.3%) of needles, mp 296–299°, identified as **16**. Elemental analysis of **16** was not carried out. *Anal.* Calcd for $C_{18}H_{26}O_{10}N_2$ (430.4): C, 50.19; H, 6.09; N, 6.51. Found for **13**: C, 50.31; H, 6.21; N, 6.59. Found for **14**: C, 50.10; H, 6.17; N, 6.60. Found for **15**: C, 50.39; H, 6.52; N, 6.70. Found for the unidentified prisms: C, 50.28; H, 6.35; N, 6.70.

^{14}C-Labeled Inosadiamines 13, 14, and 15.—The sequence of reactions described in the previous section was repeated, radioactive nitromethane[22] being used. The amounts of starting material were 580 mg of acetamidoisopropylidenetetrol **5** and 750 mg of ^{14}C-nitromethane. The amounts and measured radioactivity of the products were **13**, 45 mg, 3830 cpm/mg; **14**, 33 mg, 4000 cpm/mg; and **15**, 18 mg, 3970 cpm/mg.

DL-4,6-Diacetamido-1,5-di-O-acetyl-4,6-dideoxy-2,3-O-isopropylidene-*myo*-inositol (13-Ip), DL-2,6-Diacetamido-1,3-di-O-acetyl-2,6-dideoxy-4,5-O-isopropylidene-*epi*-inositol (14-Ip), and DL-1,3-Diacetamido-2,4-di-O-acetyl-1,3-dideoxy-5,6-O-isopropylidene-*neo*-inositol (16-Ip-a) or DL-2,4-Diacetamido-1,3-di-O-acetyl-2,4-dideoxy-5,6-O-isopropylidene-*chiro*-inositol (16-Ip-b).—The sequence of reactions used in the previous two sections was repeated with the modifications noted. Crude *lyxo* dialdehyde **11** derived from 580 mg of **5** was dissolved in 15 ml of ethanol and treated with 0.7 ml of nitromethane and 0.7 ml of 2% sodium methylate. The work-up was carried out as described, except that, after removal of the catalyst by filtration, concentrated HCl was not added. Instead the neutral solution was evaporated to a syrup which was acetylated as usual (10 ml of pyridine and 5 ml of acetic anhydride) and the crude product was chromatographed over Al_2O_3 (40 g, 1.8-cm diameter). In each case, removal of the solvent gave a syrup which was crystallized by addition of ether–ethanol (3:1) and recrystallized from ethanol. The first portion of eluate (60 ml of chloroform) gave 35.1 mg of **14-Ip** as needles, mp 246–248°, and 16 mg of an unidentified substance as needles, mp 235–236°. The second eluate (20 ml of chloroform–ethanol, 1:1) gave a residue which was fractionally crystallized from ethanol to give 35.6 mg of **13-Ip** as needles, mp 294–296° dec, and 48.2 mg of **16-Ip** as needles, mp 283–285°. Each of the substances identified had infrared spectra consistent with the functional groups present and the nmr spectra were correct for compounds with two acetoxyl, two acetamido, and two O-isopropylidene methyl groups. Identification was achieved as follows. The isopropylidene derivative (15 mg) was dissolved in 3 ml of 2 *N* HCl and heated at 50° for 30 min, the solvent was evaporated, and the residue was acetylated as usual. The products were crystallized from ethanol–ether and recrystallized from ethanol, to give 10–11 mg of substances whose melting points and infrared and nmr spectra were identical with those of the authentic hexaacetyl compounds **13**, **14**, and **16**.

DL-2,6-Diacetamido-1,3,4,5-tetra-O-acetyl-2,6-dideoxy-*epi*-inositol (14), DL-1,5-Diacetamido-2,3,4,6-tetra-O-acetyl-1,5-dideoxy-*myo*-inositol (19), and 1,5-Diacetamido-2,3,4,6-tetra-O-acetyl-1,5-dideoxy-*epi*-inositol (20a) or DL-1,3-Diacetamido-2,4,5,6-tetra-O-acetyl-1,3-dideoxy-*epi*-inositol (20b).—The *ribo* dialdehyde **17** was prepared from glycol **6** (654 mg, 2.37 mmol) by treatment with $NaIO_4$ (510 mg in 20 ml of water), extraction with hot ethanol, and evaporation to a syrup as described above. The syrupy product was dissolved in 15 ml of absolute ethanol, 600 mg of nitromethane was added, and the solution was maintained between 0 and −5° while 7 ml of 2% sodium ethylate was added (10 min); stirring was continued for 2 hr and the mixture was stored overnight at 5°. The product consisted of a precipitate **18a** and a soluble portion **18b**. These were separated by filtration and were worked up separately as described above, to give hexaacetyl inosadiamines. The product derived from **18a** was chromatographed on Al_2O_3 (50 g, 1.0-cm diameter) with chloroform–ethanol (1:1), and the crystalline product was fractionally recrystallized from ethanol to give 68.5 mg (6.7%) of needles, mp 295–300° dec, identified as **20**, and 11 mg (1.1%) of needles, mp 280–283°, identical with **14** described above. Chromatography of the product from **18b** on Al_2O_3 (20 g, 0.8-cm diameter) with chloroform (20 ml) gave 144 mg of a syrupy substance which was crystallized by addition of 3 ml of ether and 5 ml of ethanol. Fractional recrystallization from ethanol gave 44.2 mg (4.3%) of needles, mp 297–298°, identified as **19**, and an additional 8 mg (0.8%) of **14**. *Anal.* Calcd for $C_{18}H_{26}O_{10}N_2$ (430.4): C, 50.19; H, 6.09; N, 6.51. Found for **19**: C, 50.25; H, 6.31; N, 6.55. Found for **20**: C, 50.31; H, 6.28; N, 6.51.

^{14}C-Labeled Inosadiamines 19 and 20.—The sequence of reactions described in the previous section was repeated, radioactive nitromethane[22] being used. The amounts of starting material used were 486 mg of glycol **6** and 530 mg of nitromethane (12.7 μCi). The amounts and measured radioactivity of the products were **19**, 30 mg, 3900 cpm/mg and **20**, 43 mg, 4600 cpm/mg.

1,3-Diacetamido-2,4,5,6-tetra-O-acetyl-1,3-dideoxy-*scyllo*-inositol (23), 1,3-Diacetamido-2,4,5,6-tetra-O-acetyl-1,3-dideoxy-*myo*-inositol (24), and DL-1,3-Diacetamido-2,4,5,6-tetra-O-acetyl-1,3-dideoxy-*chiro*-inositol (25).—The *xylo* dialdehyde **21** was prepared from the acetamidocyclopentanetetrol derivative **10** (315 mg, 1.14 mmol in 7 ml of water) by treatment with $NaIO_4$ (220 mg) in the usual manner. After removal of water the residue was extracted with 30 ml of hot chloroform, the solvent was evaporated and the syrupy dialdehyde **21** was dissolved in 8 ml of absolute ethanol. This solution was treated with nitromethane (320 mg) and 2% sodium ethylate as described above, except that stirring was continued for 5 hr before storage at 5° overnight. The yellow crystals which formed were collected, dissolved in methanol (50 ml), and worked up as before. The mixture of acetylated inosadiamines was chromatographed on Al_2O_3 (20 g, 0.8-cm diameter). The first eluate (chloroform, 30 ml) yielded 75 mg of syrup which crystallized from ethanol–ether. Recrystallization from ethanol gave 30 mg (6.2%) of **25**, mp 219°. The second eluate (chloroform–ethanol 1:1, 50 ml) gave 90 mg of crystals which were fractionally recrystallized from ethanol to give 15 mg (3.1%) of needles, mp 245–250°, identified as **23**, and 65 mg (13.2%) of needles, mp 270–271°, identified as **24**. The infrared spectra of these compounds were identical with those of authentic samples.[6-8]

^{14}C-Labeled Inosadiamines 23 and 24.—The sequence of reactions just described was repeated, radioactive nitromethane[22] being used. The amounts of starting materials were 250 mg of glycol **10**, 500 mg of nitromethane (12 μCi), and 2.3 ml of sodium ethylate. The amounts and radioactivity of the products were **23**, 9 mg, 4370 cpm/mg and **24**, 48 mg, 4860 cpm/mg.

Acetylation of Cyclitols.—Cyclitols (tetrols and inositols) were acetylated as follows. Cyclitol (60–80 mg) was dissolved in 0.3–0.4 ml of dry pyridine, 0.2–0.3 ml of acetic anhydride was added, and the mixture was left at room temperature for 2 days. The reagents were removed at reduced pressure, a few milliliters of water were added and the mixture was reevaporated. The products were recrystallized from ethanol.

Source of Compounds Used in the Nmr Study. A. Carbohydrates.—The five carbohydrate derivatives used were purchased from commercial sources as follows: α-D-glucopyranose pentaacetate, mp 114–115°, from Eastman Kodak Chemicals; β-D-glucopyranose pentaacetate, mp 133–134°, and β-D-glucos-

(22) ^{14}C-Labeled nitromethane with an indicated specific activity of 240 μCi/g was obtained from Volk Radiochemical Co., Skokie, Ill. In the experiments described this material was diluted to one-tenth the specific activity by addition of nine parts of nonradioactive nitromethane. This diluted material was assumed to have a specific activity of 24 μCi/g. The radioactivity of the products is reported in cpm (counts per minute above background) and not converted into the Curie scale.

amine pentaacetate, mp 182.5–183.5°, from Sigma Chemical Co.; α-D-galactopyranose pentaacetate, mp 94–98°, and β-D-galactopyranose pentaacetate, mp 144–147°, from Aldrich Chemical Co.

B. Cyclitols.[23]—*myo*-Inositol hexaacetate **26**, mp 217–218° (lit.[24] 216°), was prepared by acetylation of *myo*-inositol (General Biochemicals, Inc., Chagrin Falls, Ohio). *epi*-Inositol hexaacetate **27**, mp 183–184° (lit.[25] 188°), was prepared by acetylation of *epi*-inositol kindly supplied by Professor T. Posternak. Hexa-O-acetyl-*scyllo*-inositol (**28**), hexa-O-acetyllaminitol (**29**), penta-O-acetyl-*scyllo*-*ms*-inosose (**30**), penta-O-acetyl bornesitol (**31**), and penta-O-acetyl viburnitol (**32**) were gifts from Professor T. Posternak. Tetraacetates of DL-(1,2,3/4)-tetrol[26a] (**33**), mp 112.5–113.5°, and DL(1,2,4/5)-tetrol[26b] (**34**), mp 91.5–92.5° (lit.[27] 93°), were prepared by acetylation of the corresponding tetrols.[26-28] The azidotriol triacetate[26a] **35**, mp 84–85.5°, was prepared from the corresponding azidotriol, and the acetamidotriol triacetate **36**, mp 157–159°, was prepared by catalytic hydrogenation of the corresponding cyclohexene compound, "conduramine C-4," previously reported by one of us.[29] Inosodiamines **37**, **38**, **39**, and **40** were described previously.[8,29]

Registry No.—**3**, 16019-90-2; **4a**, 16019-91-3; **5**, 16019-92-4; **6**, 16019-93-5; **9**, 16019-91-3; **12**, 16019-95-7; **13**, 6730-22-9; **13**-Ip, 16019-97-9; C-labeled **13**, 16019-98-0; **14**, 16020-12-5; **14**-Ip, 16020-13-6; C-labeled **14**, 16019-99-1; **15**, 16020-00-1; C-labeled **15**, 16020-01-2; **16a**, 16020-02-3; **16b**, 16020-03-4; **16a**-Ip, 16020-04-5; **16b**-Ip, 16020-05-6; **19**, 16020-06-7; **20a**, 16020-07-8; **20b**, 16020-08-9; **23**, 7380-63-4; **24**, 6255-71-6; **25**, 16020-11-4.

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(23) Trivial names are given for most of these compounds.

(24) E. G. Griffin and J. M. Nelson, *J. Amer. Chem. Soc.*, **37**, 1556 (1915).

(25) T. Posternak, *Helv. Chim. Acta*, **19**, 1333 (1936).

(26) Preparation and structure proof of these compounds will be described in subsequent papers in this series: (a) H. Z. Sable, H. Katchian, C. B. Niewoehner, and S. B. Kadlec, manuscript in preparation. (b) H. Z. Sable and A. L. Simonesen, manuscript in preparation.

(27) G. E. McCasland, S. Furuta, L. F. Johnson, and J. N. Shoolery, *J. Org. Chem.*, **28**, 894 (1963).

(28) N. D. Zelinski, Y. I. Denisenko, and M. S. Eventova, *Dokl. Akad. Nauk. USSR*, **1**, 313 (1935).

(29) (a) M. Nakajima, A. Hasegawa, and N. Kurihara, *Chem. Ber.*, **95**, 2708 (1962); (b) *Tetrahedron Lett.* 967 (1964); (c) *Ann. Chem.*, **689**, 235 (1965).

Mass Spectrometry in Structural and Stereochemical Problems. CXLII.[1] Electron Impact Induced Analogies to Thermal Elimination Processes in S-Methyl Xanthates and Esters[2]

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The mass spectra of the epimeric 2-methylcyclohexyl-S-methyl xanthates, acetates, and higher esters have been examined. By a combination of deuterium-labeling techniques and high resolution mass spectrometry, the principal modes of fragmentation of members of these classes have been uncovered. Evidence has been found for the existence of an electron impact induced analog to the thermal Chugaev reaction and, although ring conformational mobility complicates the interpretation of the experimental data, some stereospecificity favoring *cis* elimination appears to exist. Ring conformational freedom obviates any sound stereochemical conclusions in the ester cases. The positional specificity of the analogous elimination processes in all 2-methylcyclohexyl-S-methyl xanthates and esters is found to be high (79–85% 1,2 elimination and independent of the energy of the ionizing electron beam). The corresponding pyrolytic processes have been studied in detail in the epimeric d_0- and 2-d_1-methylcyclohexyl-S-methyl xanthates and acetates and these results are contrasted with those from the electron impact studies. In terms of percentage of the total elimination process, values found for the portion of the electron impact induced elimination which proceeds toward the tertiary center (C-2) are found to be 47% in *cis*-2-methylcyclohexyl-S-methyl xanthate (**5**), 90% in *trans*-2-methylcyclohexyl-S-methyl xanthate (**6**), 42% in *cis*-2-methylcyclohexyl acetate (**7**), and 38% in *trans*-2-methylcyclohexyl acetate (**8**). The corresponding losses in the pyrolytic elimination mode are 29% in **5**, 65% in **6**, 9% in **7**, and 56% in **8**.

In the recent literature[3] have appeared numerous references to analogies existing between thermal and electron impact induced reactions of organic compounds.

It has been pointed out[4] that one of the most general mass spectrometric hydrogen-transfer processes,[5] the McLafferty rearrangement,[6] *i.e.*, electron impact induced β cleavage with concomitant transfer of a γ-hydrogen atom[7] (see a → b), may, in the case of certain esters (c → d),[8] be regarded as the mass spectrometric counterpart to the well-known ester

(1) For paper CXLI, see J. Diekman, J. B. Thomson, and C. Djerassi, *J. Org. Chem.*, **32**, 3904 (1967).

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