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STUDIES ON CYCLITOLS—XII

NEW SYNTHESES OF 2-DEOXYSTREPTAMINE AND TRIAMINOCYCLOHEXANEDIOLS*

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Abstract—The previously reported method for conversion of cyclopentanoid cyclitols into cyclohexanoid aminocyclitols has been applied to (1,2/3,5)-3,5-diacetamidocyclopentane-1,2-diol **4a**, to produce acetylated derivatives of (1,3/2,4,6)-4,6-diaminocyclohexane-1,2,3-triol(deoxystreptamine) **24**, the epimeric (1,2,3/4,6)-diaminotriol **9** and the corresponding 2,4,6-triaminocyclohexane-1,3-diols **11** and **10**. The well known *cis*-3,5-dibromo-1-cyclopentene **1** was converted by treatment with sodium azide into *cis*-3,5-diazido-1-cyclopentene **2**; oxidation of **2** with $KMnO_4$ gave (1,2/3,5)-3,5-diazidocyclopentane-1,2-diol **3a**, which was acetylated to the di-O-acetyl derivative **3b**. Hydrogenation with Pd-C catalyst and acetylation gave (1,2/3,5)-3,5-diacetamido-1,2-di-O-acetylcyclopentane-1,2-diol **4b** and selective deacetylation with methanolic NH_3 gave the diacetamidodiol **4a**. The NMR spectra of **2**, **3b** and **4b** were consistent with the proposed structures. Oxidation of **4a** with periodate gave *erythro*-2,4-diacetamidocyclopentanedial **5** which was treated with nitromethane under alkaline conditions to give a mixture of diacetamidonitrocyclohexanediols whose principal components were (1,3/2,4,6)-4,6-diacetamido-2-nitrocyclohexane-1,3-diol **6a** and the epimeric (1,2,3/4,6) compound **7a**. Hydrogenation of **6a** with Raney nickel T4 catalyst gave (1,3/2,4,6)-4,6-diacetamido-2-aminocyclohexane-1,3-diol **8**, which was acetylated to (1,3/2,4,6)-2,4,6-triacetamido-1,3-di-O-acetylcyclohexane-1,3-diol **11b**; the NMR spectrum of **11b** showed the presence of 3 equatorial acetamido groups, two of which are isochronous, and two equivalent equatorial acetoxyl groups. Selective acetylation of **8** gave (1,3/2,4,6)-4,6-diacetamido-1,3-di-O-acetyl-2 aminocyclohexane-1,3-diol **11d**. Treatment of the hydrochloride (or hydrobromide) of both **8** and **11d** with $AgNO_2$ and acetylation of the deaminated product gave (1,2,3/4,6)-4,6-diacetamido-1,2,3-tri-O-acetylcyclohexane-1,2,3-triol **9c**. The NMR spectrum showed the presence of two isochronous equatorial acetamido groups, two isochronous equatorial acetoxyl groups and one axial acetoxyl group. Hydrogenation of **7a** followed by acetylation gave (1,2,3/4,6)-2,4,6-triacetamido-1,3-di-O-acetylcyclohexane-1,3-diol **10c**; the NMR spectrum of **10c** showed the presence of two isochronous equatorial acetamido groups, one axial acetamido group and two isochronous equatorial acetoxyl groups. Confirmation of some of the configurational assignments was obtained when di-N-acetyldeoxystreptamine **24a** was oxidized by periodate to give a diacetamidopentanedial which was proved to be identical with **5** when it reacted with nitromethane to give the same cyclohexanoid products. When **11d** was deaminated as described and the product treated with CrO_3, a ketonic compound (1,3/4,6)-4,6-diacetamido-1,3-di-O-acetyl-2-oxocyclohexane-1,3-diol **25** was obtained; reduction of **25** with $NaBH_4$ and acetylation of the product gave a mixture of pentaacetyl deoxystreptamine **24b** and the epimeric compound **9c**. By the use of $^{14}CH_3NO_2$, **10c** and **11b** specifically labeled in carbon-2 were obtained.

CYCLOHEXANOID aminocyclitols are known as components of many carbohydrate antibiotics.[1,2] Recently Nakajima *et al.* have synthesized several diastereoisomeric

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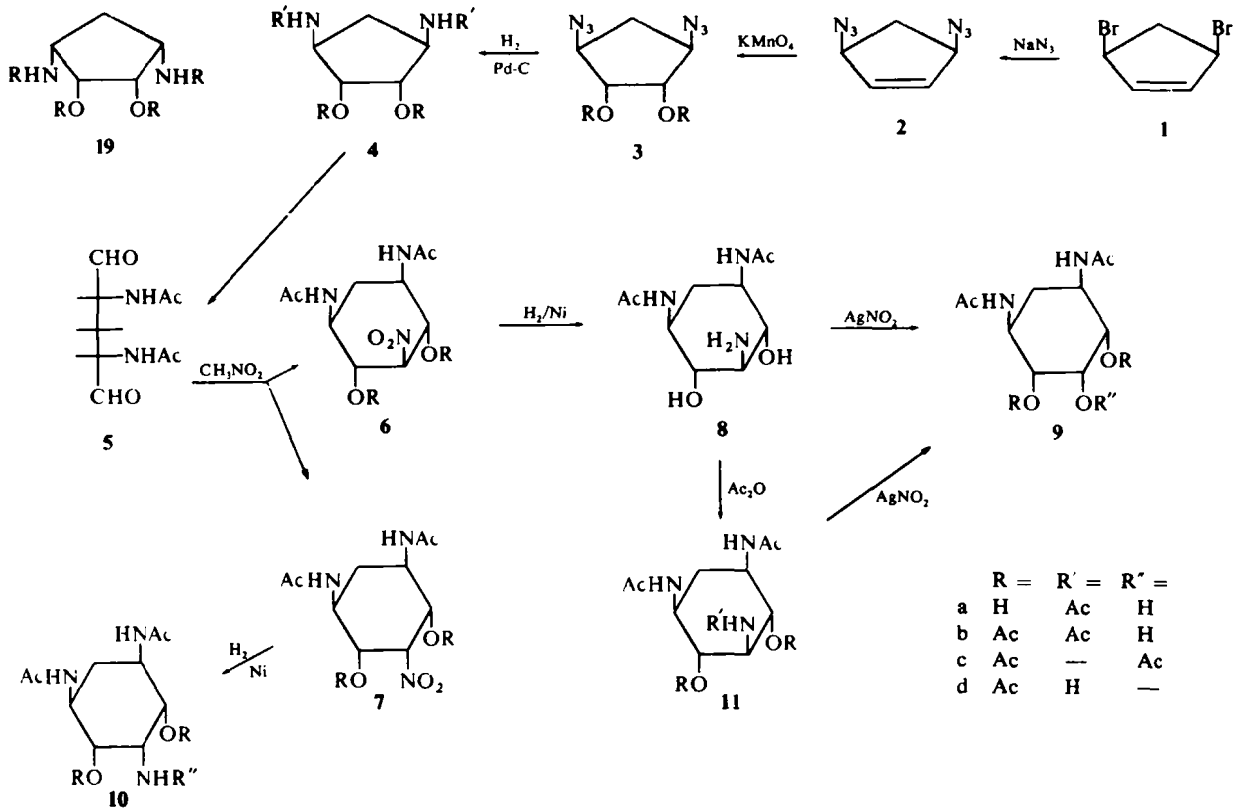
CHART I

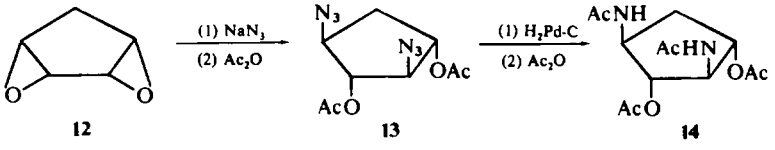


	R =	R' =	R" =
a	H	Ac	H
b	Ac	Ac	H
c	Ac	—	Ac
d	Ac	H	—

deoxyinosamines[3] and deoxyinosadiamines[4] by stereoselective routes, starting from benzene glycol (3,5-cyclohexadiene-1,2-diol). Previously we have reported the syntheses of a number of cyclopentanoid aminocyclitols[5] and the conversion of some of these into inosadiamines[6] by a route involving the formation of pentanedials and cyclization of the latter with nitromethane. The present communication deals with a continuation of these studies. A diaminocyclopentanediol has been synthesized and converted into two triaminocyclohexanediols and two deoxyinosadiamines*; one of the latter is identical with authentic deoxystreptamine. Some of these compounds have also been prepared specifically labeled with ^{14}C, by the use of ^{14}C-nitromethane. The general sequence of reactions leading to a deoxyinosadiamine, e.g. **9**, is shown in Chart 1. The well-characterized[7] *cis*-3,5-dibromocyclopentene **1** was converted by a series of steps into the diacetamidocyclopentanediol **4a**, and the latter oxidized to the *meso*-2,4-diacetamidopentanedial **5** which is the substrate for cyclization with nitromethane. The partially acetylated compound **9b** was oxidized (see below) to a ketone **25**; the latter was reduced and acetylated, yielding a mixture of epimers **9c** and **24b**. One of these (**24b**) was found to be identical with a corresponding derivative of authentic deoxystreptamine.

RESULTS

(1,2/3,5)-3,5-*Diacetamido*-1,2-*di*-O-*acetylcyclopentanediol* **4b**. The reaction sequence **1** → **4b** shown in Chart 1 gave reasonable yields, but several alternative synthetic routes were investigated because of the explosive nature of the intermediate diazido compound **2**. Two of these routes will be mentioned briefly here.[8] In previous studies[9] in this laboratory, diepoxide **12** was found to react with H_2O or Br^- to give products resulting from epoxide-opening reactions (a) at C-1 and C-4 and (b) at C-2 and

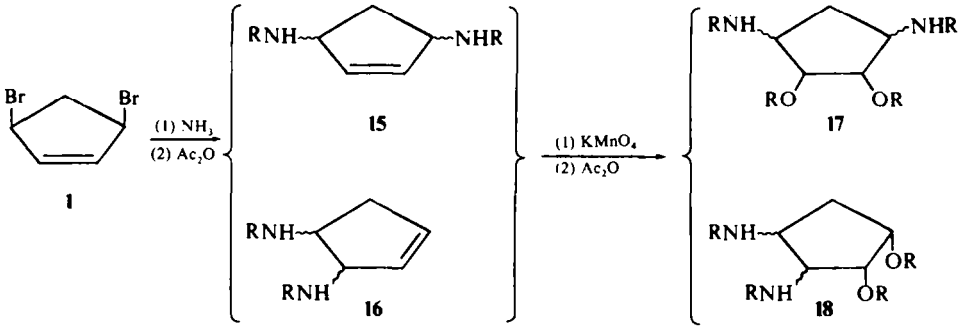


12 **13** **14**

C-4. A sequence of reactions beginning with epoxide-opening by azide was therefore undertaken in the hope that a separable mixture of the diacetamido compounds **4b** and **14** would be obtained. However the work-up gave only a compound which was tentatively identified as **14**, and although some **4b** was probably formed, it could not be isolated in pure form from the reaction mixture. The second alternative route[8] involved the treatment of dibromocyclopentene **1** with ammonia designed to produce 3,5-diaminocyclopentenes **15a**. Actually the product of the ammonolytic reaction was a

* The official, tentative IUPAC rules for the nomenclature of cyclitols are used in the present study. The application of these rules to compounds of the type considered in this work has been indicated in the previous study (Ref. 6). One point of nomenclature requires comment. Aminocyclohexanepentols and diaminocyclohexanetetrols may be named, according to the rules, as x-amino-x-deoxyinositols, and x,y-diamino-x,y-dideoxyinositols, respectively. However, analogous compounds having fewer than four hydroxylic substituents are not usually named as derivatives of inositols. Consequently, streptamine is named as a 1,3-diamino-1,3-dideoxyinositol, whereas deoxystreptamine must be named as a 4,6-diaminocyclohexane-1,2,3-triol, even though these systematic names do not indicate the close relationship between the two compounds.

complicated mixture containing all the possible isomeric diaminocyclopentenes **15** and **16**, as well as some unexpected products. The purified diacetamido compounds **15b** and **16b** were converted into the acetamidodiol derivatives **17** and **18** and were tentatively identified by NMR* spectroscopy. Since reasonable yields of the desired product could



a: R = H
b: R = Ac

not be obtained by the methods outlined, the procedure involving the diazido compound **2** was used, but its inherent danger must be emphasized.† Compound **2** was used immediately in the next step to produce the diazidodiol derivative **3b** which appears to be less hazardous than **2**.

The structure proposed for the diacetate **3b** is supported by its NMR spectrum, which is typical of the AMX_2Y_2 Spectra we have observed previously[10] in symmetrically tetrasubstituted cyclopentanes. The strongest signal is a singlet at δ2·42, representing the two equivalent acetyl groups. The methylenic protons are represented by two multiplets, centered at δ2·56 and δ1·57. Each of these multiplets is a doublet of triplets, showing $J_{gem} = 14{\cdot}2$ c/s; the lower-field multiplet shows $J_{cis} = 8{\cdot}1$ c/s, and the higher-field multiplet shows $J_{trans} = 6{\cdot}95$ c/s. The N-C-H protons are represented by a multipet at δ3·97, and the O-C-H protons are represented by a multiplet at δ5·08. The lines of the multiplet at δ1·57 are broader than are the corresponding lines of the multiplet at δ2·56, suggesting that the former are involved in long-range coupling[10b] with the O-C-H- protons. The diazido compound **3b** was hydrogenated with Pd-C catalyst to produce the dihydrochloride of **4d**, m.p. 240–245° (dec), and the latter was acetylated to produce **4b**, m.p. 190–191°. The overall yield of the sequence of reactions **1** → **4b** was 20%. The proposed structure of **4b** was based on the method of synthesis and on its NMR spectrum, and eventually on the nature of the deoxyinosadiamines that were obtained (see below). The NMR spectrum of **4b** shows two narrow singlets at δ1·97 and δ2·03. These signals are equal in intensity, and are very much stronger than all the other signals in the spectrum. By analogy with other systems[6,11] in which acetamido protons resonate at higher field than acetoxyl protons, the signal at δ1·97 is assigned to the two

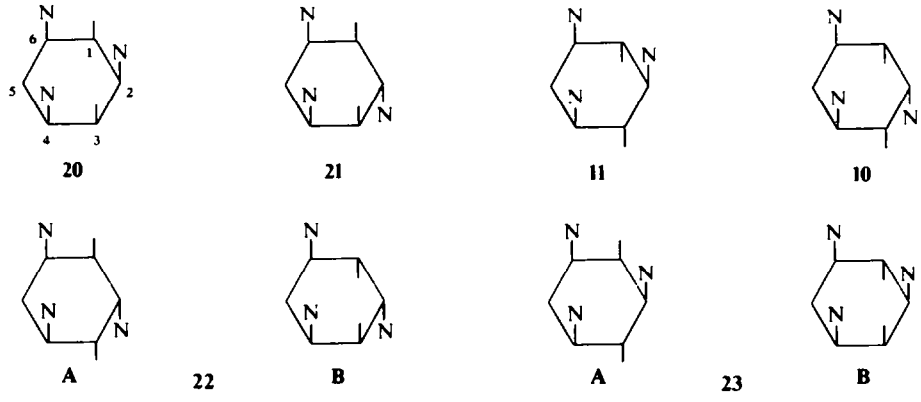
* The following abbreviations are used: Ac_2O, acetic anhydride; DMF, N,N-dimethylformamide; IR, infrared; NMR, nuclear magnetic resonance; TLC, thin-layer chromatography.

† *cis*-3,5-diazidocyclopentene was unstable at room temperature and is explosive above 90°. More than ten preparations of this material were made without incident, but one preparation on a slightly larger scale was accompanied by a violent and destructive explosion during vacuum distillation.

acetamido groups, and that at δ2·03 to the two acetoxyl groups. All the other tetraacetylated diaminocyclopentanediols[8] show at least three lines for the acetyl protons, therefore the narrowness of the signals is presumptive evidence that the two pairs of acetyl groups are truly isochronous; this can be true only for symmetrical compounds, in this case **4b** and the isomeric all-*cis* compound **19b**. The latter configuration is unlikely, because during the hydroxylation of **2** by permanganate, steric hindrance, due to the azido groups flanking the double bond, directs the reagent to the other side of the plane of the ring, producing **3**. The structures of **3b** and **4b** confirm the conclusion that **2** has the *cis*-configuration, and show that displacement of bromine by the strong nucleophile, N_3^-, has proceeded by a "normal" S_N2 mechanism, without any rearrangement. In the case of the weaker nucleophile NH_3, deep-seated rearrangements must have occurred, as indicated by the mixture of products obtained.

Epimeric 2,4,6-*triaminocyclohexanediols*. The tetraacetylated compound **4b** was partially deacetylated by treatment with methanolic NH_3, and the resulting diol **4a** was oxidized with sodium metaperiodate to the symmetrical diacetamidopentanedial **5**. Under the usual conditions for cyclization this substance reacted with nitromethane to give a mixture of diacetamido-nitro-cyclohexanediols. Since three new asymmetric centers are created from the nitro-carbon and the former aldehyde C atoms, eight nitro compounds are to be expected, and the same number of triaminodiols would be obtained after reduction of the nitro groups. The configurations of these diastereoisomers are shown in Chart 2. Because of the symmetry of the starting material, four of the possible

CHART 2. Possible configurations of triaminocyclohexanediols produced



products form two DL pairs, viz. **22A–22B** and **23A–23B**. Table 1 shows the possible and preferred conformations of these substances. In assigning a preferred conformation, we have assumed that the energetic changes caused by axial acetamido groups are roughly equivalent to those due to axial acetoxyl groups. Since there are five bulky groups to be considered, those conformers with two or fewer axial acetyl groups are considered to be preferred. In an earlier study[6] we proposed that intramolecular H-bonding involving the acetamido H atoms could make an "acetamide-axial" conformation predominate over an apparently equivalent "acetamide-equatorial" conformation.

In the present case such H-bonding might be important in conferring additional stability to an already favored conformation but would probably not be enough of an influence, for example, to make the favored conformation of **20***aeaea* rather than *eaeae* (Table 1).

TABLE 1. CONFORMATIONS OF TRIAMINOCYCLOHEXANEDIOLS DERIVED FROM *meso*-DIACETAMIDOCYCLOPENTANEDIOL

Configuration	Conformation[a]	Disposition of acetyl groups			
		N—Ac		O—Ac	
		axial	equatorial	axial	equatorial
10	*eeaee*	1	2		2
	aaeaa	2	1	2	
11	*eeeee*		3		2
	aaaaa	3		2	
20	*eaeae*		3	2	
	aeaea	3			2
21	*aeeea*	2	1		2
	eaaae	1	2	2	
22	*aeeae*	1	2	1	1
	eaaea	2	1	1	1
23	*eaeee*		3	1	1
	aeaaa	3		1	1

[a] Only the two alternative chair conformations are considered. In each case the more probable conformation is given first. The groups are indicated in the following order: C-6 acetamide, C-1 acetoxyl, C-2 acetamide, etc. See text for discussion of the "preferred" conformation.

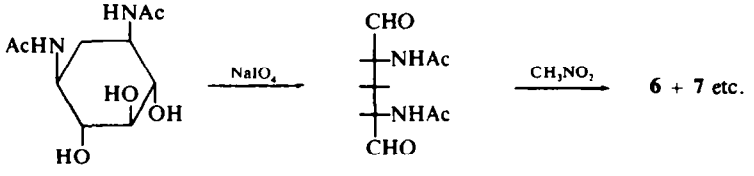
Only two of the six possible nitro compounds were actually isolated. These have been shown to be **6a** and **7a**, with the former predominating. No attempt was made to assign the configuration of these compounds on the basis of the chemical shifts of the acetyl protons, since the presence of the anisotropic nitro group would make the spectral interpretation equivocal. Instead, the nitro compounds were hydrogenated, the resulting triaminodiol derivatives were acetylated, and the peracetylated compounds were used for configurational studies. In our earlier work[6] we observed that catalytic hydrogenation of such compounds could not be carried out with PtO_2, Raney nickel (W-2) or 10% Pd-C; the reduction succeeded, however, when Raney nickel T-4, prepared according to Nishimura[12] was used as the catalyst. The same catalyst was used in the present work.

Reduction of **6a** gave the partially acetylated triaminodiol **8**, which was converted into the fully acetylated derivative **11b**, m.p. 355–357° (dec). The NMR spectrum of **11b** shows three sharp singlets, in the correct ratios for the five acetyl groups, as follows: δ2·00 (6 protons), two equivalent equatorial acetoxyl groups; δ1·90 (6 protons), two equivalent equatorial acetamido groups; δ1·87 (3 protons), one equatorial acetamido group. This spectrum is compatible only with the all-equatorial conformer of **11b**.

Reduction of the crude nitro-compound **7a** and acetylation of the product, gave an additional pentaacetyl-triaminodiol, m.p. 309°, which is assigned structure **10c** on the basis of its NMR spectrum. The spectrum showed two sharp singlets in a ratio of 3:2, due to the indicated groups: δ2·00 (9 protons), two equivalent equatorial acetoxyl groups, one axial acetamido group; δ1·94 (6 protons), two equivalent equatorial acetamido groups. As shown in Table 1, this spectral assignment is compatible only with the preferred conformation of **10c**.

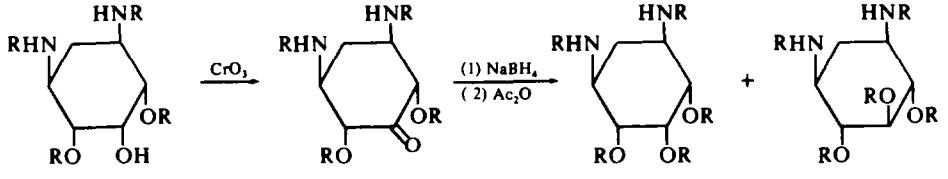
An epimer of deoxystreptamine was obtained when the partially acetylated triaminodiol **8** was deaminated by treatment with $AgNO_2$ in the presence of HBr. Acetylation of the product of this reaction gave a pentaacetate, m.p. 250–255° (dec), whose NMR spectrum showed two equivalent equatorial acetamido groups at δ1·93, two equivalent equatorial acetoxyl groups at δ2·00 and one axial acetoxyl group, δ2·20. This is compatible only with the preferred chair conformer of **9c**. The same compound was obtained when **11d**, in which the amino function is flanked by acetoxyl rather than by OH groups, was the substrate of the deamination reaction. Such inversion of configuration during deamination of aminocyclitols was observed originally by Posternak,[13] and also appears to occur in the case of 3′-aminoglucopyranosyluracil.[14] (See Discussion).

Further confirmation of the proposed configurations of the intermediates was obtained in two ways. First, di-N-acetyldeoxystreptamine **24a** was oxidized with periodate to yield a dialdehyde, and the latter reacted with nitromethane to give the same mixture of nitro compounds, **3** and **7** which were obtained when **4a** was the starting



24a **5**

material. The yield in this reaction was 3·4 g of **6a** and 2·0 g of amorphous **7a** from 4·2 g of pentanedial **5**. Second, the partially acetylated triol **9b** was selectively oxidized and the ketonic product **25** was reduced and acetylated to give a mixture from which were



9b: R = Ac **25** **9c** **24b**

isolated **9c** and a second pentaacetyl derivative melting above 350°, whose IR and NMR spectra were identical[4] with those of the corresponding derivative of deoxystreptamine **24b**.

In view of the inversion of configuration which occurred when **8** and **11d** were deaminated, the deamination of **10a** or **10b** seemed to offer a reasonable route for the

synthesis of deoxystreptamine. However, the attempt was unsuccessful. In several experiments, in which the hydrochloride of **10a** was treated with $AgNO_2$, no product was isolated. When the hydrobromide of **10b** was used the only product isolated, in poor yield, was **9c** (see Discussion).

DISCUSSION

In our earlier study[6] the total yeild in the cyclization reaction was of the order of 15%, and no conclusions could be drawn about "major" and "minor" products. In the present work the experiment in which di-N-acetyldeoxystreptamine was the starting material permits such conclusions, in view of the good yield of **6** and **7**. Approximately two-thirds of the product was the all-*trans* substance **6a**; this is expected for two reasons: first, in the transition state the nitro group and the developing hydroxyl groups can be disposed in a 1,2,3-triaxial-*trans* orientation, whereas in the transition state for **7a** such an orientation is impossible. Probably the latter transition state would be of higher energy than that for **6a**. Second, if the energy of the product has any bearing on the course of the reaction, the all-equatorial compound **6a** is, again, of lower energy than is its epimer **7a**. The sizable amount of **7a** which is formed shows that the difference in energies between the two transition states, though appreciable, is still not more than 0·5–1·0 kcal, probably because in the 1,2,3-triaxial disposition, the nitro group of **6a** encounters serious *syn*-diaxial interaction with both acetamido groups; the nitro group of **7a** cannot be involved in such interaction, and this decreases the difference in energy of the two transition states. The negligible yield of the other possible diastereoisomers is in agreement with the expected higher energies of both their transition states and ground states.*

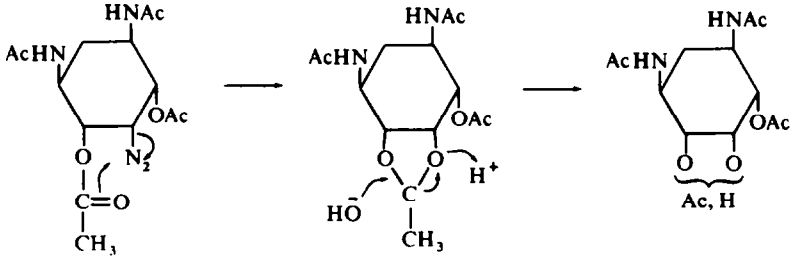
The conformational assignments, based on chemical shifts of the acetamido and acetoxyl groups, are made with the implicit assumption that nonchair conformations may be ignored. Fetizon *et al.*[15a] propose that substituted cyclohexanones exist in twisted or flattened chair conformations; on the other hand, Stolow *et al.*[15b] believe that nonchair conformations are relatively unimportant. The applicability of such conclusions to the present case is uncertain, but this type of information will be necessary in any future attempts to assess the contribution of intramolecular NH···O H-bonding[16] to the conformational equilibrium.

Pertinent reports, from the laboratories of Baer and Lichtenthaler, have appeared recently. Baer and Yu[17] have described the synthesis of three diastereoisomers of deoxystreptamine, by catalytic hydrogenation of 4,6-dinitropyrogallol. Lichtenthaler *et al.*[18] have reported that pentanedial reacts with nitromethane and benzylamine to produce 1,5-dibenzylamino-6-nitrocyclohexane, which can be hydrogenated to give 1,2,3-cyclohexanetriamine.

The retention of configuration which is observed when **10b** is deaminated is not

* A referee has suggested that it is possible that there is only one cyclization product prior to the acidification of the reaction mixture, namely the aci-nitro salt corresponding to both **6a** and **7a**. In this case, the proportions might be kinetically controlled, but by the relative rates of isomerization of the aci-nitro compound (formed by acidification) in the two possible ways. Alternatively **6a** and **7a** may be in equilibrium via the aci-nitro salt. In this case the relative ground state energies of the two products would govern. We thank the referee for this valuable addition to our discussion.

unprecedented. When Cron *et al.*[19] deaminated a preparation of O-acetylated kanosamine (3-amino-3-deoxy-D-glucose), reacetylation gave pentaacetyl-α-D-glucopyranose. In contrast, as noted above, Watanabe *et al.*[14] observed that deamination of an unacetylated derivative of the same aminosugar proceeds with inversion of configuration. It is possible that elimination of N_2 from the diazonium intermediate is assisted by participation of nearby acetoxyl groups, and involves an intermediate orthoester. In the case of O-acetylkanosamine, the participating group would be the 6-acetoxyl group. According to this explanation, the configurational inversion observed in the deamination of **11d** would be due to the participation of the adjacent *trans* acetoxyl groups. The



explanation is incomplete, however, since it does not account for the inversion that occurs in the deamination of non-acetylated carbohydrates and cyclitols.

Addendum. After submitting this manuscript we became aware of the recent report by Suami *et al.*[20] of a new partial synthesis of deoxystreptamine from *myo*-inosadiamine-1,3, in which the first step is a replacement of the C-2 OH group by bromine. The authors rationalize the stereoselectivity of this reaction by front-side participation[21] similar to the one we propose for the deamination.

EXPERIMENTAL

M.ps were determined on a Kofler Micro hot stage (A. H. Thomas and Co.) or on a Yangimoto Co. micro M.p. apparatus and are corrected. B.ps are uncorrected. NMR spectra were recorded with a Varian Associates A-60 NMR Spectrometer. The spectra of cpds **4b** and **24b** were measured on solns in $CDCl_3$, and those of cpds **9c**, **10c**, and **11b** on solns in $CDCl_3$:CD_3OD (1:1). IR spectra were recorded with a Perkin-Elmer Model 237B or with a Shimadzu AR-275 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.

For column chromatography, Merck aluminum oxide, acid washed, was used. TLC was carried out with silica gel G as the backing material, and $CHCl_3$:MeOH 5:1 as developing agent. After drying, the plates were sprayed with NH_4vanadate in 50% H_2SO_4. Proportions indicated for mixed solvents refer to volume per volume ratios.

cis-3,5-*Diazidocyclopentene* **2**. Compound **1** (45·0 g, 200 mmole) was dissolved in 100 ml of DMF and 5 ml water; 45·0 g NaN_3 were added, with stirring, at room temp. The temp rose to 70° and the mixture was then left for 3 hr, with occasional shaking; the ppt was removed by filtration and washed with DMF, and the soln evaporated *in vacuo* in a rotary evaporator. During this operation the bath temp was maintained below 45°. The residue was dissolved in 200 ml of $CHCl_3$, the soln was washed with water, dried over Na_2SO_4 and then evaporated. The red, oily product was distilled *in vacuo*, giving 24·0 g (160·4 mmole, 80·2%) of **2**, b.p. 64–67°, 0·75 torr. This substance cannot be stored at room temp and may be explosive when heated (see footnote above).

(1,2/3,5)-1,2-*Di*-O-*acetyl*-3,5-*diazidocyclopentane*-1,2-*diol* **3b**. A soln of 24·0 g (160 mmole) of **2** in 1 liter 95% EtOH was chilled and maintained at −20°; a soln of 120 g $MgSO_4 \cdot 7H_2O$ in 200 ml water was added, and then 1600 ml 2% $KMnO_4$ aq were added, with continuous stirring, over a 3 hr period. After

standing overnight at room temp the mixture was filtered, the filtrate was treated with active carbon and concentrated, leaving a red residue which was acetylated (100 ml pyridine, 90 ml Ac_2O, left overnight at room temp). A ppt which formed was removed, and the reagents were evaporated; the brown, oily product was dissolved in ether, the soln was washed with 2N HCl, 2N NaOH and water, and dried over Na_2SO_4. The ether was removed and the yellow oil (30 g) was distilled giving 24·5 g (59%) of **3b**, b.p. 138–142°, 0·6–0·7 torr.

(1.2/3.5)-1.2-*Di*-O-*acetyl*-3.5-*diaminocyclopentane*-1.2-*diol dihydrochloride* **4d**. To 12·0 g (44·8 mmole) of **3b** dissolved in 400 ml abs EtOH were added 12·0 g of 10% Pd-C catalyst, and H_2 was bubbled through while the mixture was stirred at room temp. After 4 hr the mixture was made slightly acidic by addition of 2N HCl, and hydrogenation continued for 3 hr. After removal of the catalyst, the filtrate was evaporated to give a crystalline substance; recrystallized from EtOH gave 8·2 g (61·7%) of **4d**, plates, m.p. 240–245° dec. (Found: C, 37·30; H, 6·41; N, 9·51. $C_9H_{18}O_4N_2Cl_2$ (289·2) requires: C, 37·38; H, 6·27; N, 9·69%).

(1.2/3.5)-3.5-*Diacetamido*-1.2-*di*-O-*acetylcyclopentane*-1.2-*diol* **4b**. Diacetate **4d** (1·0 g, 3·46 mmole) was acetylated (10 ml pyridine, 5 ml Ac_2O, room temp overnight); the product was chromatographed over a column of Al_2O_3 (50 g, 1·0 cm diam) and eluted with $CHCl_3$. Removal of solvent gave a residue which was crystallized from EtOH-Et_2O and recryst from EtOH: 568 mg (54·7%), plates, m.p. 190–191°. (Found: C, 52·19; H, 6·93; N, 9·40. $C_{13}H_{20}O_6N_2$ (300·3) requires: C, 51·97; H, 6·71; N, 9·33%).

(1.2/3.5)-3.5-*Diacetamidocyclopentane*-1.2-*diol* **4a**. Tetraacetate **4b** (2·5 g, 8·3 mmole) was dissolved in 50 ml MeOH half-saturated with dry NH_3 and the soln was left overnight at room temp. MeOH and acetamide were evaporated leaving crystalline **4a** which was recrystallized from EtOH, giving 1·67 g (93%) of needles, m.p. 273–275°. (Found: C, 50·22; H, 7·67; N, 13·05. $C_9H_{16}O_4N_2$ (216·2) requires: C, 49·99; H, 7·46; N, 12·96%).

(1.3/2.4.6)-4.6-*Diacetamido*-2-*nitrocyclohexane*-1.3-*diol* **6a** and (1.2.3/4.6)-4.6-*diacetamido*-2-*nitrocyclohexane*-1.3-*diol* **7a**. A soln of 2·62 g $NaIO_4$ in 30 ml water was chilled to 5° and 1·8 g (8·33 mmole) of **4a** was added. The resulting soln was left overnight at room temp and then concentrated *in vacuo*. The residue was extracted with hot abs EtOH and the filtrate concentrated to give a slightly yellow syrup **5**. The crude dialdehyde was dissolved in 30 ml abs EtOH, 1·5 g CH_3NO_2 was added, the soln was maintained below 0°, and 15 ml of 2% NaOEt (2 g Na in 100 ml EtOH) were added slowly, with continuous stirring. The soln was then stirred for 2 hr at 0° and left overnight at room temp. The soln was treated with Amberlite IRC-50-H^+ resin to remove Na ions, and was then evap to give a syrupy product. Crystallization from abs EtOH gave 1·0 g (43·3%) of **6a**, m.p. 225–235° dec. The filtrate gave 900 mg of crude **7a**, which was not crystallized.

(1.2.3/4.6)-2.4.6-*Triacetamido*-1.3-*di*-O-*acetylcyclohexane*-1.3-*diol* **10c**. Crude compound **7a** (900 ml) was dissolved in 70 ml 50% EtOH, 4·0 g Raney Ni T-4 catalyst[12] were added and H_2 was bubbled through while the mixture was stirred at room temp; after 2 hr the soln was made slightly acidic with HCl and hydrogenation continued for 5 hr. The catalyst was removed and the filtrate concentrated to a red syrup, which was acetylated (15 ml pyridine, 10 ml Ac_2O, overnight at room temp). The reagents were removed as usual and the products chromatographed on Al_2O_3 (100 g, 1·8 cm diam) with $CHCl_3$-abs EtOH 1:1, as the solvent. The crystalline residue was recrystallized from EtOH; needles (302 mg, 23·0%) m.p. 308–309°. (Found: 51·56; H, 6·67; N, 11·20. $C_{16}H_{25}O_7N_3$ (371·4) requires: C, 51·74; H, 6·79; N, 11·32%).

(1.3/2.4.6)-4.6-*Diacetamido*-3-*aminocyclohexane*-1.3-*diol* **8** and (1.3/2.4.6)-2.4.6-*triacetamido*-1.3-*di*-O-*acetylcyclohexane*-1.3-*diol* **11b**. Nitro compound **6a** (900 ml) was dissolved in 70 ml 50% EtOH, 4·0 g Ni T-4 catalyst were added, and the mixture hydrogenated as described above. Evaporation of solvent gave the hydrochloride of **8** (860 mg)as an amorphous product; treatment of the latter material (215 mg, 0·98 mmole) with pyridine (5 ml) and Ac_2O (3 ml) at 70° for 4 hr gave a crude pentaacetyl derivative which was chromatographed over Al_2O_3 (30 g, 0·8 cm diam) with $CHCl_3$-EtOH 1:1. Evaporation of the eluate gave 150 mg (41%) of **11b**; which recrystallized from EtOH, 137 mg of needles, m.p. 355–357° dec. (Found: C, 51·88; H, 6·95; N, 11·29. $C_{16}H_{25}O_7N_3$ (371·4) requires: C, 51·74; H, 6·79; N, 11·32%).

^{14}C-*labeled pentaacetyltriaminocyclohexanediols* **10c** *and* **11b**. The sequence of reactions described in the previous sections was repeated, radioactive nitromethane* being used. The pentanedial obtained from

* ^{14}C-labeled nitromethane with an indicated specific activity af 240 μ Ci/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 μ Ci/g. The radioactivity is reported in cpm (counts per min above background) and not converted into the Curie scale.

2·0 g of **4b** was allowed to react with 0·9 g of CH_3NO_2 and the nitro compounds were separated. Reduction of the ^{14}C- **7a**, acetylation and chromatography gave 230 mg of **10c** with a specific activity of 4270 cpm/mg. Reduction of the ^{14}C- **6a** gave 750 mg of the hydrochloride of **8**, and acetylation of 250 mg of the latter gave 155 mg of **11b** with a specific activity of 4400 cpm/mg.

(1,2,3/4,6)-4,6-*Diacetamido*-1,2,3-*tri*-O-*acetylcyclohexane*-1,2,3-*triol* **9c**. A soln of 645 mg (2·3 mmole) of the hydrochloride of **8** in 10 ml of 0·15 N HCl and 3 ml dioxan was maintained at 0°, and 800 mg $AgNO_2$ were added in small portions over a period of 40 min, with continuous stirring; 3 ml dioxan was added, and stirring was continued overnight at room temp. the ppt was removed, the filtrate was concentrated to a yellow syrup which was acetylated (10 ml pyridine, 5 ml Ac_2O, 70° for 4 hr) and the product chromatographed on Al_2O_3 ((60 g, 1·0 cm diam) to give 13 mg of **9c**, prisms, m.p. 250–255° dec. (Found: C, 51·50; H, 6·38; N, 7·44. $C_{16}H_{24}N_2O_8$ (372·4) requires: C, 51·61; H, 6·49; N, 7·52%).

Nitro compounds **6a** *and* **7a**, *starting with deoxystreptamine*. Di-N-acetyldeoxystreptamine (5·0 g) was dissolved in 70 ml water and 8·3 g $NaIO_4$ were added; the diacetamidopentanedial **5** was isolated as described (4·2 g), dissolved in 80 ml MeOH and the condensation carried out as described (4·8 g CH_3NO_2, 30 ml 3% NaOMe). The crude product was recrystallized from 100 ml EtOH, giving 3·4 g of **6a**, and concentration of the mother liquor gave 2·0 g of crude **7a**. The IR spectra of these compounds were identical with those obtained when **4a** was the starting material. Reduction of these nitro compounds and acetylation of the products gave **11b**, m.p. 355–358°, and **10c** m.p. 309–310°; in addition these compounds had the same IR and NMR spectra and the same mobility in TLC as did the corresponding substances derived from **4a**.

(1,2,3/4,6)-4,6-*Diacetamido*-1,3-*di*-O-*acetylcyclohexane*-1,2,3-*triol* **9b**. Nitro compounds **6a** (3·4 g) was hydrogenated as described above. The crude hydrochloride of **8** was added to 100 ml AcOH and 20 ml AcCl and the mixture heated at 60–70° for 3 hr. The reagents were removed by evaporation giving 1·0 g of crude O-acetylated product **11d**; the crude product was dissolved in 20 ml dioxan and 20 ml 0·5% HBr aq. The soln was cooled and maintained at −2°, and 2·5 g $AgNO_2$ was added in small portions over a 90 min period, with continuous stirring. The stirring was then continued for 4 hr, the ppt was filtered off and washed with water. The combined filtrate and washings were treated with Amberlite-IR-120 H^+ resin and then evap to give 2·2 g of crude tetraacetyl **9b**; recrystallized from EtOH gave 880 mg (22%) of **9b**, m.p. 230–240° dec. (Found: C, 51·10; H, 6·51; N, 8·22. $C_{14}H_{22}O_7N_2$ (330·3) requires: C, 50·90; H, 6·71; N, 8·45%).

Acetylation of 30 mg **9b** gave 30 mg **9c**, m.p. 215°. The mother liquor, obtained when **9b** was recrystallized, was evap and the crude product was acetylated giving 350 mg **9c**, m.p. 255°; mixture m.p. with the preceding product was also 255°. The IR and NMR spectra and mobility in TLC showed that this product was identical with that obtained when **4a** was the starting material.

(1,3/4,6)-4,6-*Diacetamido*-1,3-*di*-O-*acetyl*-2-*oxocyclohexane*-1,3-*diol* **25** *and* (1,3/2,4,6)-4,6-*diacetamido*-1,2,3-*tri*-O-*acetyl-cyclohexane*-1,2,3-*triol* (pentaacetyldeoxystreptamine) **24b**. The tetraacetyl **9b** (330 mg) was dissolved in 10 ml AcOH and 60 ml abs acetone; the soln was maintained at 30° and 1·0 ml of a soln of chromic acid (27 g CrO_3, 80 ml H_2O, 20 ml H_2SO_4) was added. The mixture was then stirred at 30° for 20 hr, the insoluble material was separated and washed with acetone. The filtrate and washings were combined and concentrated to a syrup, **25**, which was used without further purification. The crude ketonic **25** was dissolved in 20 ml water, 30 mg $NaBH_4$ were added and the soln was left overnight. Solvent was evaporated, the residual syrup was acetylated (20 ml pyridine, 5 ml Ac_2O) and the product was chromatographed over Al_2O_3 (20 g, 1·5 cm diam) with $CHCl_3$-EtOH 1:1. Evaporation of the solvent left a crystalline product; fractional recrystallization from EtOH gave 54 mg (16%) of **24b**, m.p. above 350°, and 120 mg (34%) of the epimeric **9c**. The IR and NMR spectra of **24b** were identical with the spectra of an authentic sample.[4b,c]

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