Studies on Cyclic Polyols. VII. The Synthesis of Some Cyclopentaneaminocyclitols[1]

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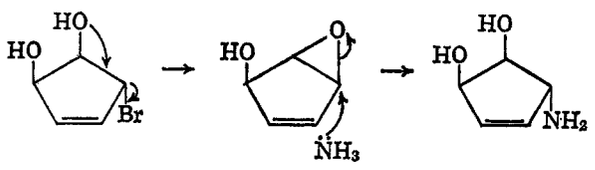
The *cis*- and *trans*-3,4-di-O-acetylcyclopentenediols (Ib and Vb) have been converted into (3,4/5)- and (3,5/4)-5-acetamido-3,4-di-O-acetylcyclopentenediols (IIIb and VIIb) by successive allylic bromination and treatment with NH_3. The corresponding acetamidodiols IIIa and VIIa are converted into DL-(1,2,3/4,5)-1-acetamido-2,3-anhydrocyclopentanetetrol (IXa) and DL-(1,2,3,4/5)-1-acetamido-2,3-anhydrocyclopentanetetrol (XVIIa) by treatment with *m*-chloroperoxybenzoic acid. Treatment with HBr and subsequent acetylation converts the corresponding di-O-acetyl derivatives IXb and XVIIb, respectively, into (1,2,4/3,5)-3-acetamido-1,2,5-tri-O-acetyl-4-bromocyclopentanetriol (Xb) and (1,2,4/3,5)-4-acetamido-1,2,5-tri-O-acetyl-3-bromocyclopentanetriol (XVIIb). Treatment of IIIb and VIIb with HOBr and subsequent acetylation produces, respectively, (1,2,3/4,5)-4-acetamido-1,2,3-tri-O-acetyl-5-bromocyclopentanetriol (XIIIb) and (1,2,4/3,5)-1-acetamido-2,4,5-tri-O-acetyl-3-bromocyclopentanetriol (XVb). Reductive debromination of Xb, XIIIb, and XVIIIb produces the corresponding acetamido-tri-O-acetylcyclopentanetriols. Treatment with $KMnO_4$ and subsequent acetylation converts IIIb into DL-(1,2,3/4,5)-1-acetamido-2,3,4,5-tetra-O-acetylcyclopentanetetrol (XXIIIb). Similar treatment of VIIb produces DL-(1,2,4/3,5)-3-acetamido-1,2,4,5-tetra-O-acetylcyclopentanetetrol (XXVIb). Hydrolysis of XVIIb in dilute acid and subsequent acetylation produces DL-(1,2,4/3,5)-4-acetamido-1,2,3,5-tetra-O-acetylcyclopentanetetrol (XXVIIIb). Similar treatment of IXa produces XXVIb, but IXb is converted into DL-(1,2,3/4,5)-4-acetamido-1,2,3,5-tetra-O-acetylcyclopentanetetrol (XXVb). Partial deacetylation and treatment with acetone converts XXVIIIb into (1,2,4/3,5)-4-acetamido-3,5-di-O-acetyl-1,2-O-isopropylidenecyclopentanetetrol (XXXb). Nucleophilic opening of IXa by N_3^- produces an azido derivative XXXIa which is reduced catalytically with Pd–C and acetylated to DL-(1,2,4/3,5)-3,4-diacetamido-1,2,5-tri-O-acetylcyclopentanetriol (XXXIIIb). Similar treatment of XVIIa produces a different azido derivative XXXVa which by reduction and acetylation also gives XXXIIIb. Influences on epoxide formation and opening are discussed. A strong *cis*-directing effect of an allylic acetamido group on epoxidation by peroxy acids is noted. Steric hindrance, assistance by an adjacent *trans*-acetoxyl group, electronegativity of an adjacent substituent, and relative nucleophilicity of reagents are implicated in the reactions described.

Many stereoisomeric cyclopentane aminocyclitols are theoretically possible: *e.g.*, monoaminocyclopentanetriols (series F), 16 DL pairs; monoaminocyclopentanetetrols G, 6 DL pairs, 4 *meso;* diaminocyclopentanetriols K, 13 DL pairs, 7 *meso, etc.* In the previous paper[3] the synthesis of four racemic pairs of isomeric aminocyclopentanetriols was described. The present communication deals with the continuation of these studies: two monoaminocyclopentenediols, four aminocyclopentanetriols (two of them new, two identical with isomers previously reported[3]), four monoaminocyclopentanetetrols, and one diaminocyclopentanetriol are described. The configurations of all these aminocyclitols have been determined by various criteria (see Chart I).

The reactions by which these compounds were obtained are shown in the flow diagram. Treatment of the unsaturated diol diacetates A with N-bromosuccinimide produces allylic bromocyclitols B which are then converted to the monoaminocyclopentenediols C. The latter compounds can be hydroxylated *cis* or *trans* to produce aminotetrols G; C can be converted directly to bromohydrins E by treatment with HOBr, or indirectly by nucleophilic opening of the epoxide of D with Br^-. The fully acetylated derivatives of these bromohydrins, E, are converted to aminocyclopentanetriols by hydrogenolysis. The epoxide rings of the aminoanhydrotetrols D may be opened[3] with N_3^- and the resulting azido compounds H can be reduced to the diaminotriols K.

Results

Aminocyclopentenediols. A. DL-(3,4/5)-5-Acetamido-3,4-di-O-acetylcyclopentenediol (IIIb).—Allylic bromination of Ib produced a monobromo compound (IIb or IIc) in 87% yield, and treatment of this substance with anhydrous saturated NH_3 in methanol produced the aminodiol, isolated as the triacetate IIIb, mp 139–140°, in 69% yield (see Chart II). Of the other possible structures, IV is excluded, because the acetamidodiol IIIa still contains a vicinal glycol group, as shown by its consumption of 1 molar equiv of periodate. Configuration IIc also is unacceptable, since subsequent reactions (see below) lead to a known aminotriol derivative (XIb) in which the amino group is *trans* to the adjacent OAc group. The formation of IIIb is rationalized as follows. Because of the steric hindrance caused by the acetoxyl group adjacent to the allylic position, *trans* bromination is expected; so structure IIb is preferred, although in the absence of independent proof IIc cannot be excluded from consideration. The over-all retention of configuration has several possible explanations. If a transitory epoxide were formed from IIa or IIb, subsequent attack of NH_3 at the position from which Br^- was expelled would lead to IIIa. If an epoxide is indeed involved, attack at the other end of the oxirane ring did not occur, since the resulting product would have been IV, whose formation has been shown above to be excluded. Alternatively, if the Br is displaced by an SNl reaction, steric hindrance by the adjacent OAc group would cause the NH_3 to enter on the same side from which the Br^- de-

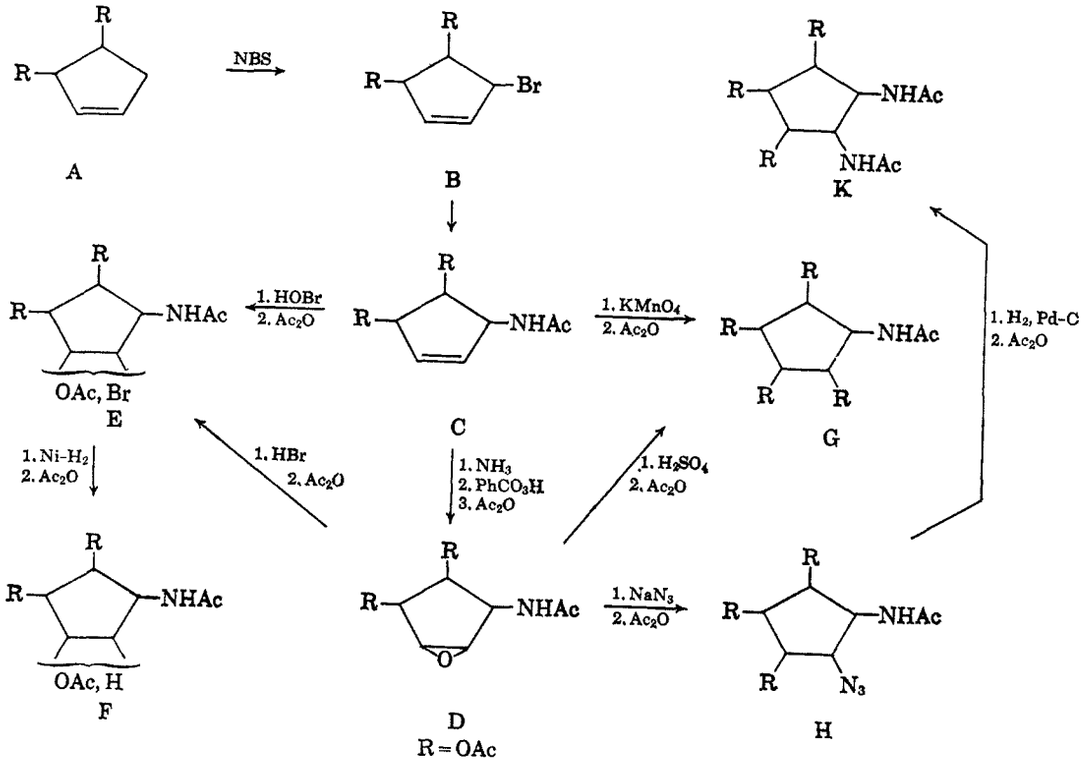


(1) Supported in part by U. S. Public Health Service Research Grant AM-07719 from the National Institutes of Health. For paper VI, see ref 3.

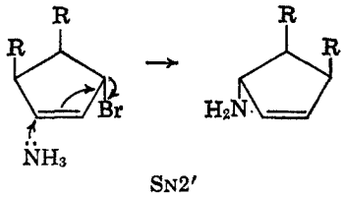
(2) To whom correspondence should be addressed.

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

CHART I
GENERAL REACTION SEQUENCE



parted. Also, although the steric hindrance would preclude an SN2 reaction, an SN2′ mechanism[4] is possible, in which the entering and leaving groups must be on the same side of the plane of the ring. In this case DL-IIb → DL-IIIb, and the net "retention" of configuration is due to conversion of D-II to L-III and of L-II to D-III. Finally, if the bromo compound has structure IIc, an SN2 mechanism is predictable, also leading to IIIb.

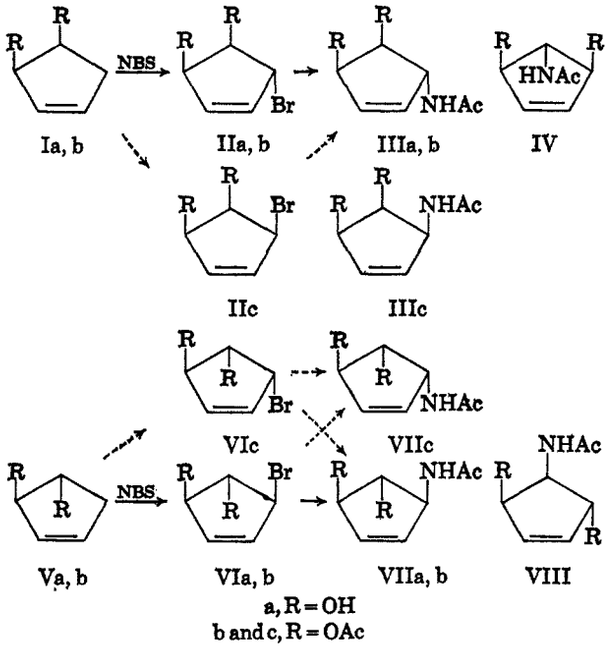


SN2′

B. DL-(3,5/4)-5-Acetamido-3,4-di-O-acetylcyclopentenediol (VIIb).—By similar reasoning, the product of allylic bromination of Vb is assigned structure VIb. An SN2 mechanism leading to VIIc seems unlikely, and, since the acetamidodiol VIIa consumes 1 molar equiv of periodate, structure VIII is untenable. Transitory formation of an epoxide followed by nucleophilic attack by NH_3 would produce VIIb, with over-all retention of configuration, whereas an SN2′ reaction would produce VIIc. Further reactions (see below) convert VII into the (1,2,4/3)-4-acetamidotriol XIX in which the functional groups at positions 2, 3, and 4 are those which were present at positions 5, 4, and 3, respectively, of VII. This excludes configuration VIIc and thereby confirms configuration VIIb. This structure could also arise from VIc by an SN2 mechanism. Finally, as in the previous case, an SN1 reaction in which the amino group enters on the same side from which the Br^- departs would convert VIb to VIIb. Neither in this case nor the previous one, therefore, can the configuration of the aminotriol be used to establish the configuration of the product of allylic bromination.

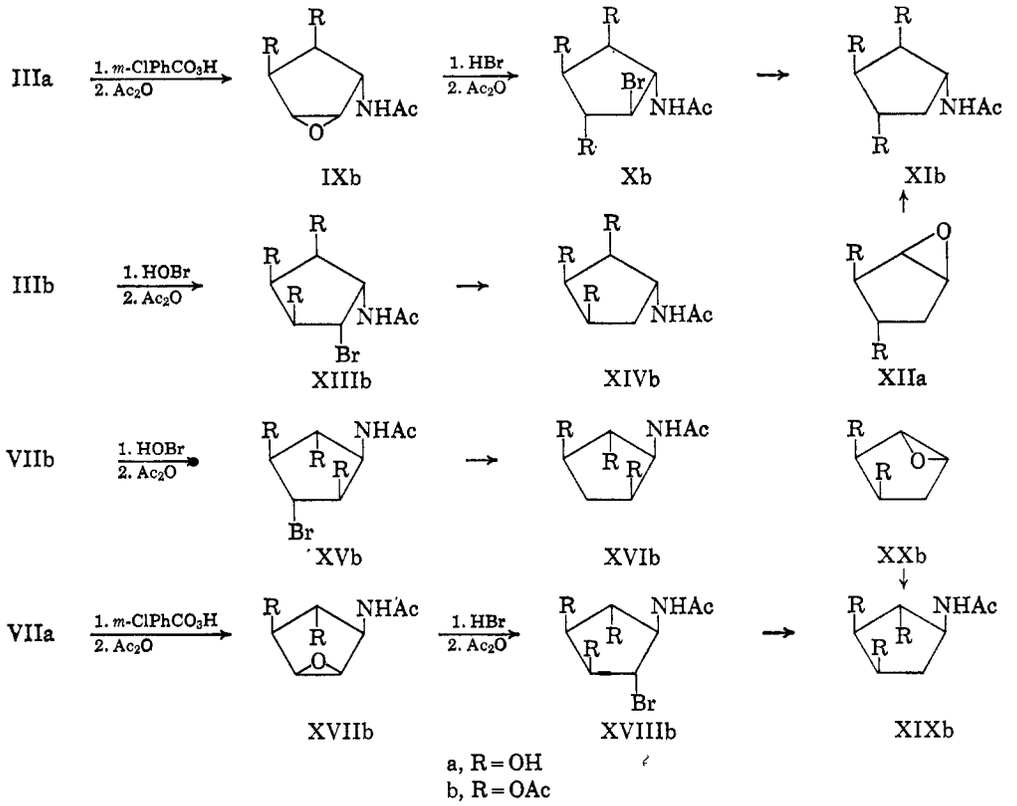
(4) J. D. Roberts and M. C. Caserio, "Basic Principles of Organic Chemistry," W. A. Benjamin, Inc., New York, N. Y., 1964, p 328.

CHART II



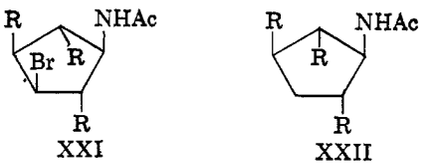
Aminocyclopentanetriols.—The acetamido compounds IIIa,b and VIIa,b were converted into bromohydrin derivatives (X, XIII, XV, XVIII) and the latter were reductively debrominated with Raney nickel catalyst to form the aminotriols (XI, XIV, XVI, XIX) (see Chart III). The bromohydrins were

CHART III



produced either by direct addition of HOBr, or by epoxidation with *m*-chloroperoxybenzoic acid followed by nucleophilic epoxide opening with HBr. By the latter procedure and reduction with Ni, IIIa was converted into DL-XIb which was identical with the product obtained[3] when the epoxydiol XIIa[5] was opened with NaN_3 and then reduced.[6] This identity supports the proposed structures IX and X, for when the epoxide IXb is opened, one would expect the entering Br atom to cause inversion of the attacked carbon, but the configuration of the retained C–O bond would remain the same as it was in the epoxide. Since the retained C–O bond of C-4 is *cis* to the acetamido group, the epoxide must also have been *cis*, and the Br atom was therefore adjacent and *trans* to the acetamido function. The result is also the basis for assigning structure. By the same reaction sequence VIIa is converted to XIXb, mp 112°, identical with the product obtained[3] by opening the epoxide of XXb with NaN_3. By the same reasoning, the proposed configurations of XVII, XVIII, and VII are established.

Addition of HOBr to the double bond of III and VII is expected to produce *trans*-bromohydrins, four configurations being possible in each case, and this assumption is made in the following arguments. Reductive debromination of the product obtained from IIIb leads to an acetamidotriol which consumes 2 molar equiv of periodate, showing that the methylene group is adjacent to the acetamido function. Consequently the possible structures of the bromohydrin are restricted to Xb and XIIIb. However, structure Xb was assigned to the product, mp 157–158°, obtained from the oxirane compound IXb. The product (mp 194–195°) obtained by addition of HOBr is therefore assigned structure XIIIb, and the acetamidotriol obtained by debromination must have structure XIVb. A different situation arises when HOBr is added to VIIb. The acetamidotriol obtained from VIIb consumes only 1 molar equiv of periodate, which proves that its methylene group is not adjacent to the acetamido function. Since the precursor VIIb has an ethylenic function adjacent to the acetamido group, the Br atom must have been attached to the ethylenic carbon atom farther from the acetamido group and only structures XVb or XXI are possible. In the latter case the acetamidotriol produced would have structure XXII, but a compound,



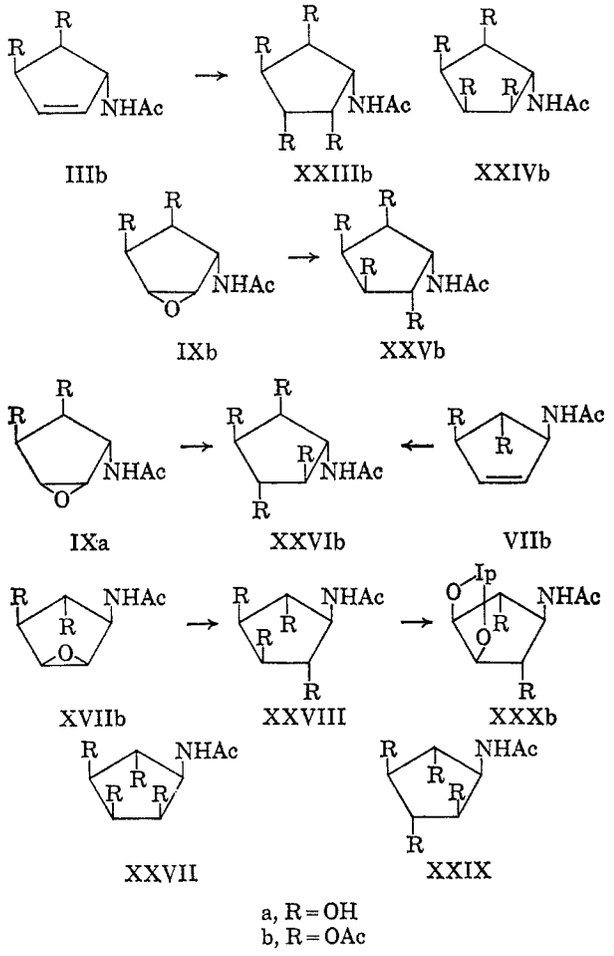
mp 106°, to which configuration XXII is assigned was obtained previously.[3] The acetamidotriol, mp 120–121°, obtained by reductive debromination of the bromohydrin from VIIb is therefore assigned structure XVI, and the bromohydrin must be XV.

Aminocyclopentanetetrols.—The aminocyclopentenediols III and VII can be hydroxylated *cis* and *trans*. *cis* hydroxylation is accomplished by oxidation of the double bond with $KMnO_4$, and *trans* hydroxylation is effected by epoxidation and hydrolysis of the oxirane compounds IX and XVII. *cis* hydroxylation of III may give rise to the isomeric structures XXIII and XXIV. The principal directive influence should be steric hindrance of allylic and homoallylic substituents, since

(5) J. A. Franks, Jr., B. Tolbert, R. Steyn, and H. Z. Sable, *J. Org. Chem.*, **30**, 1440 (1965).

(6) F. D. Cramer in "Methods in Carbohydrate Chemistry," Vol. 1, R. L. Whistler and M. L. Wolfrom, Ed., Academic Press Inc., New York, N. Y., 1962, p 243.

CHART IV



similar treatment of corresponding cyclohexene derivatives[7] led to introduction of the *cis* glycol group in the less hindered position (see Chart IV). The two structures are easily differentiated by examination of the nmr spectrum of the fully acetylated product. This spectrum contains five separate lines corresponding to the five different acetyl groups. Since XXIV is a *meso* compound, the OAc groups flanking the acetamido group would be indistinguishable spectroscopically, and the two distant groups would also be indistinguishable. The spectrum of the acetyl groups of XXIV would therefore consist of two lines corresponding to six protons each, and a third line representing the three protons of the N-acetyl group. The observed spectrum is therefore compatible only with XXIIIb.

trans hydroxylation of III, *e.g.*, by hydrolysis of the epoxide of IX, can produce only two isomers of configuration XXV and XXVI. On the basis of our previous studies,[5,8] we expected that steric hindrance would be the principal directive influence, leading preponderantly to XXVI. Actually two isomers were obtained by hydrolysis in dilute acid, depending on whether the hydroxyl groups in the substrate were free (IXa) or acetylated (IXb). Hydrolysis by 1% H_2SO_4 and subsequent acetylation converted IXa in 54% yield to a pentaacetate, mp 123–125°, tentatively designated as XXVIb. Similar treatment of IXb gave a 66% yield of another pentaacetate, mp 192°, considered to be XXVb. The assignment of configuration XXVIb to the isomer of mp 123–125° was substantiated when the same substance was obtained in 44% yield by *cis* hydroxylation of VIIb with buffered $KMnO_4$. In this case configuration XXVII is also possible, but is not expected to form easily because of steric hindrance by both allylic substituents. Assuming that the epoxide opening of IXa or IXb does not involve any over-all rearrangements, we conclude that in IXa the *trans*-hydroxyl group has shielded the adjacent end of the oxirane ring and has directed the opening to the other end of the ring. On the other hand, IXb has opened at the more hindered position, which may be ascribed to participation of the neighboring *trans*-acetoxyl group in the epoxide opening (see the Discussion).

Opening of the epoxide XVII is not subject to the directive influences of steric hindrance or assistance by neighboring acetoxyl groups. Under the usual conditions XVIIb was converted in 76% yield to a pentaacetate, mp 147°, which could have configuration XXVIIIb or XXIXb. The structure is assigned on the basis of reactivity with acetone. The product of epoxide opening was converted to the free acetamidotetrol XXVIIIa or XXIXa, which was then treated with acetone and $CuSO_4$, to form a mono-O-isopropylidene ketal, isolated as the triacetate, mp 157°. The cyclopentane ring cannot assume any conformation that will allow a *trans*-1,3-dioxolane ring to form, and mono-O-isopropylidene ketal derivatives of 1,3-cyclopentanediols have never been reported. Consequently the acetamidotetrol almost certainly contains a vicinal *cis*-glycol grouping. Of the two possible alternatives, only XXVIII satisfies this requirement.[9]

Diaminocyclopentanetriols.—The epoxides IX and XVII have been converted into diaminotriol derivatives by means of nucleophilic opening with NaN_3 to give the azido compounds, followed by catalytic reduction[3,6,10] to a diaminotriol. The possibility of acetoxyl assistance in the epoxide opening was eliminated by prior conversion of O-acetyl groups to hydroxyl groups. In each case only one of the two possible isomers has been obtained. By these procedures IXb gave a 68% yield of a diaminotriol pentaacetate, mp 235° which could be XXXIII or XXXIV (see Chart V). Partial deacetylation gave the diacetamidotriol XXXIIIa which consumed 2 molar equiv of periodate. Since XXXIVa is expected to consume only 1 molar equiv of periodate, the nucleophilic opening by NaN_3 must have produced an azido compound whose configuration is XXXI, and the pentaacetate, mp 235°, is XXXIIIb.

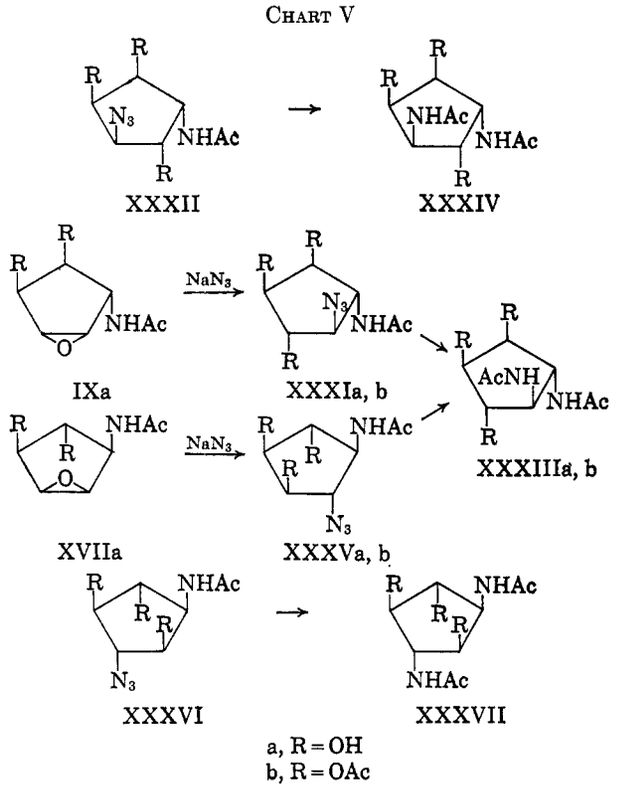
(7) (a) M. Nakajima, A. Hasegawa, and N. Kurihara, *Chem. Ber.*, **95**, 2708 (1962); (b) M. Nakajima, I. Tomida, N. Kurihara, and S. Takei, *ibid.*, **92**, 173 (1959).

(8) H. Z. Sable, T. Adamson, B. Tolbert, and T. Posternak, *Helv. Chim. Acta*, **46**, 1157 (1963).

(9) Although the configurational assignments to the compounds that we have designated XXVIIIb and XXXb are self-consistent with the other data reported in this paper, some uncertainty remains. Dr. Robert Schaffer of the National Bureau of Standards reported (Abstracts of Papers, Winter Meeting of the American Chemical Society, Phoenix, Ariz., Jan 17–19, 1966, Abstract 31C) the synthesis of a compound to which he has assigned structure XXXb, but whose melting point is 183–184°, and also an isomeric substance, mp 157–158°, which he considers to be epimeric at the point of attachment of the acetamido group. After being informed of our results, Schaffer converted his substance of mp 183–184° by hydrolysis and acetylation to a pentaacetate, mp 146.5–147°, in agreement with mp 147° which we observed for XXVIIIb. Our supply of pure XXVIIIb was exhausted and insufficient crude material was available for purification, so that direct comparison of the products has been impossible.

(10) A. Bertho and J. Maier, *Ann. Chem.*, **498**, 50 (1932).

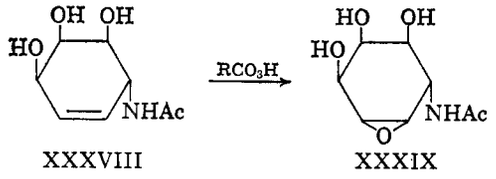
CHART V



The same reaction sequence converted XVIIb into a pentaacetate, mp 247°, in 63% yield. In this case configurations XXXIII and XXXVII are possible. Again the decision has been based on consumption of periodate by the diacetamidotriol. The latter consumed 2 molar equiv of periodate, a result which is only compatible with XXXIIIa. The nucleophilic opening of the oxirane ring has therefore produced XXXVa, and the pentaacetate, mp 247°, must be XXXIIIb, *i.e.*, identical with the pentaacetate, mp 235°. That these are indeed polymorphic crystal forms of the same substance is shown by the identity of the infrared spectra.

Discussion

Previous studies of cyclopentene derivatives[5] have substantiated Henbest's rule[11] for epoxidation by peroxy acids of cycloalkenes having allylic substituents, *i.e.*, a bulky neighboring substituent directs the formation of an oxirane ring *trans* to the substituents, but an exception occurs when the allylic substituent is a hydroxyl group. The latter forms a hydrogen bond with the peroxy acid, and consequently the oxirane ring forms *cis* to this allylic substituent. Goodman, *et al.*,[12] reported that allylic benzamides are also *cis* directing in the epoxidation reaction. In the cyclohexane series[7a] the epoxidation of XXXVIII has been found to produce XXXIX in 85% yield, showing the greater influence of the allylic acetamido group in comparison with one allylic and two homoallylic hydroxyl groups on the other side of the ring. The present study substantiates this conclusion, since IIIa is converted into IXa, rather than the other possible epoxide.



In the case of *cis* hydroxylation by permanganate, the directive influence is steric hindrance: in the conversions IIIb → XXIIIb, and VIIb → XXVIb, the new glycol function is introduced on the less hindered side of the ring, in agreement with results in the cyclohexane series.[7]

At least four factors are concerned in determining the direction of epoxide opening observed in the present studies. These factors are steric hindrance, assistance by a neighboring acetoxyl group, electronegativity of groups adjacent to the oxirane ring, and "nucleophilicity" of the attacking group. The different direction of opening of IXa and IXb by water exemplifies the first two influences. Acetoxyl-assisted opening of epoxide rings in substituted hexoses has been reported by Buchanan, *et al.*,[13] and further examples and a more detailed discussion of this effect are presented elsewhere.[14] A definite difference is observed between the strong nucleophile, N_3^-, and the weak nucleophile, H_2O, in opening the epoxide ring of IXb. With the weak nucleophile, the intramolecular reaction, *i.e.*, the acetoxyl-assisted opening, predominates over direct attack of the nucleophile on the unhindered face of the oxirane ring. The competition between attack of the strong nucleophile with the acetoxyl-assisted opening has not been measured, but N_3^- competes successfully with the weaker nucleophile, H_2O, since the azido compound XXXI is formed in at least 68% yield. It would be interesting to compare the rates of opening of the strong nucleophile in competition with the intramolecular reaction in a series of partially hindered epoxides having one adjacent *trans*-acetoxyl group, such as IXb.

We have emphasized[5] the directive influence on epoxide opening of an electronegative substituent adjacent to the oxirane ring, under conditions in which a transition state carbonium ion may be assumed. The stereoselective hydrolysis of XVIIb to XXVIII may be rationalized by an extension of the explanation offered previously.[5,15] The developing carbonium ion of the transition state is destabilized by the adjacent electronegative substituent, and the opening occurs at the other end of the oxirane ring. In the present example the ester is more effective than the amide in destabilizing the developing carbonium ion. This observation is consistent with other known differences between acetoxy and acetamido derivatives, *e.g.*, acetic acid has a much larger acid dissociation constant than has acetamide.

Experimental Section

Physical Constants.—Melting points were determined on a Kofler micro hot stage (Arthur H. Thomas and Co.) and are corrected. Boiling points are uncorrected. Refractive index was measured with an Abbe refractometer.

(11) H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1958 (1957).

(12) L. Goodman, S. Winstein, and R. Boshan, *J. Am. Chem. Soc.*, **80**, 4312 (1958).

(13) (a) J. G. Buchanan and R. M. Saunders, *J. Chem. Soc.*, 1791 (1964); (b) *ibid.*, 1796 (1964); (c) J. G. Buchanan and J. C. P. Schwarz, *ibid.*, 4770 (1962); (d) J. G. Buchanan, *ibid.*, 2511 (1958).

(14) Part VIII, A. Hasegawa and H. Z. Sable, *J. Org. Chem.*, **31**, 4161 (1966).

(15) R. U. Lemieux, R. K. Kullnig, and R. Y. Moir, *J. Am. Chem. Soc.*, **80**, 2237 (1958).

Microanalyses.—Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Special Reagents.—*m*-Chloroperoxybenzoic acid[16] was used for epoxidations. The commercially available reagent was used without further purification. Acid-washed alumina (Merck) was used for chromatography.

Spectra.—Nmr spectra were recorded on samples dissolved in $CDCl_3$ with a Varian Associates A-60 nmr spectrometer. Infrared spectra were measured with a Perkin-Elmer Model 237B spectrophotometer.

DL-(3,4/5)-5-Acetamido-3,4-di-O-acetylcyclopentenediol (IIIb).—To a solution of 3.6 g (1.96 mmoles) of *cis*-3,4-di-O-acetyl-1-cyclopentenediol[3] (Ib) in 70 ml of anhydrous carbon tetrachloride 4.0 g (2.25 mmoles) of freshly recrystallized N-bromosuccinimide was added and the reaction mixture was refluxed for 2 hr. After cooling, succinimide was filtered off and the filtrate was washed with saturated $NaHCO_3$ and water and dried over Na_2SO_4. Evaporation under reduced pressure gave 4.5 g (87%) of crude DL-(3,4/5)-3,4-di-O-acetyl-5-bromocyclopentenediol (IIb). Attempts to distil IIb were unsuccessful. Compound IIb (3.0 g) was dissolved in 150 ml of methanol saturated with dry ammonia gas and left for 2 days at room temperature. The reaction mixture turned red. Solvent and acetamide were evaporated under reduced pressure, leaving a black syrup, which was acetylated by adding acetic anhydride (20 ml) and pyridine (20 ml) and leaving for 2 days at room temperature. The crude IIIb was chromatographed twice over Al_2O_3 (30 g, 1.0 cm in diameter) with chlorofom to give a crystalline substance which was recrystallized from ether, 1.88 g (69%) of colorless prisms, mp 139–140°.

Anal. Calcd for $C_{11}H_{15}NO_2$ (241.24): C, 54.77; H, 6.23; N, 5.81. Found: C, 54.53; H, 6.24; N, 5.98.

DL-(1,2,3/4,5)-1-Acetamido-4,5-di-O-acetyl-2,3-anhydrocyclopentanetetrol (IXb).—Compound IIIb (723 mg, 3.0 mmoles) was dissolved in 30 ml of methanol saturated with dry ammonia gas and 15 ml of absolute ethanol, and the mixture was left overnight at room temperature. Solvent and acetamide were evaporated under reduced pressure to give 470 mg (3.0 mmoles) of crystalline substance (IIIa), mp 156–158°. This product was dissolved in 20 ml of chloroform and 10 ml of acetic acid and 1.6 g (9.25 mmoles) of *m*-chloroperoxybenzoic acid was added. After 7 days in the dark at room temperature the solution was concentrated to dryness at reduced pressure. Water (30 ml) was added, and *m*-chlorobenzoic acid and excess *m*-chloroperoxybenzoic acid were filtered off. The filtrate was washed with two 50-ml portions of ether and concentrated *in vacuo* to a yellow syrup. This material was acetylated by the usual procedures, standing for 2 days at 5°. The crude black acetylation mixture was concentrated at reduced pressure to a syrup which was dissolved in 20 ml of ethanol and decolorized by active carbon. The solvent was evaporated to give a yellow syrup, which crystallized from ether during several days at −10°, yielding 670 mg (87%) of IXb, recrystallized from ether–ethanol (1:1) as needles, mp 155°.

Anal. Calcd for $C_{11}H_{15}NO_6$ (257.24): C, 51.36; H, 5.82; N, 5.44. Found: C, 51.16; H, 5.65; N, 5.41.

DL-(3,5/4)-3-Acetamido-4,5-di-O-acetylcyclopentenediol (VIIb).—To a solution of 10.0 g (5.43 mmoles) of DL-*trans*-3,4-di-O-acetylcyclopentenediol[3] (Vb) in 180 ml of anhydrous carbon tetrachloride was added 11.6 g (6.51 mmoles) of N-bromosuccinimide. The reaction mixture was refluxed for 2.5 hr and was then worked up as above, to give 15.7 g of reddish oil (VIb). The bromo compound could not be distilled. Crude VIb (15.0 g) was dissolved in 700 ml of methanol saturated with dry ammonia gas and the mixture was left for 2 days at room temperature. The solvent and acetamide were evaporated and the resulting black syrup was acetylated (50 ml of pyridine and 30 ml of acetic anhydride, 2 days at room temperature). The black acetylation mixture was concentrated under reduced pressure to a syrup, which was chromatographed three times over Al_2O_3 (150 g, 2.0 cm in diameter) with chloroform–benzene (1:1) to give a crystalline substance VIIb, yielding 900 mg (7.0%). Recrystallization from ether gave needles, mp 123°.

Anal. Calcd for $C_{11}H_{15}NO_2$ (241.24): C, 54.74; H, 6.23; N, 5.81. Found: C, 54.65; H, 6.21; N, 5.80.

DL-(1,2,3,4/5)-1-Acetamido-4,5-di-O-acetyl-2,3-anhydrocyclopentanetetrol (XVIIb).—Compound VIIb (670 mg, 2.78 mmoles) was dissolved in 20 ml of methanol saturated with dry ammonia gas and 10 ml of absolute ethanol, and the mixture was left overnight. The solvents and acetamide were evaporated under reduced pressure to give crystalline substance VIIa, mp 135°. To a solution of 430 mg (2.74 mmoles) of VIIa in 8 ml of chloroform and 15 ml of acetic acid, 1.5 g (8.43 mmoles) of *m*-chloroperoxybenzoic acid was added, and the solution was left for 7 days in the dark at room temperature. Solvent was removed at reduced pressure and the product was worked up as described under IXb. The material was acetylated (5 ml of pyridine, 3 ml of acetic anhydride, overnight at room temperature). The crude black acetylation mixture was concentrated to a syrup, which was dissolved in 5 ml of ethanol and decolorized with active carbon. After several days at −10° the solution deposited 458 mg (64%) of XVIIb. Recrystallization from ether–ethanol (1:1) gave colorless prisms, mp 148°.

Anal. Calcd for $C_{12}H_{15}NO_6$ (257.24): C, 51.36; H, 5.84; N, 5.44. Found: C, 51.18; H, 5.92; N, 5.60.

DL-(1,2,3/4,5)-4-Acetamido-1,2,3-tri-O-acetyl-5-bromocyclopentanetriol (XIIIb).—To a solution of 241 mg (1.0 mmoles) of IIIb in 5 ml of 20% acetic acid, 9 ml of 2% bromine water solution (Br_2, 176 mg, 1.1 mmoles) was slowly added, with cooling in ice water. The reaction mixture was left for 2 hr at room temperature and concentrated under reduced pressure to a yellow syrup, which was acetylated (5 ml of pyridine, 2 ml of acetic anhydride, overnight at room temperature). The reaction mixture was concentrated under reduced pressure to give a red, crystalline residue, which was recrystallized from ethanol, yielding 260 mg (70%) of colorless needles, mp 194–195°.

Anal. Calcd for $C_{13}H_{18}BrNO_7$ (380.20): C, 41.07; H, 4.77; N, 3.69. Found: C, 41.27; H, 4.90; N, 3.86.

DL-(1,2,3/4)-4-Acetamido-1,2,3-tri-O-acetylcyclopentanetriol (XIVb).—Compound XIIIb (130 mg, 0.32 mmole) was dissolved in 10 ml 50% ethanol, 500 mg of Raney nickel and 2.0 g of Amberlite IR-4B were added, and hydrogen was bubbled through while the mixture was stirred magnetically for 5 hr at 65–70°. Catalyst and resin were removed by filtration and washed with 10 ml of water and the combined filtrate was evaporated under reduced pressure to give a syrup, which was chromatographed over Al_2O_3 (10 g, 0.8 cm in diameter) with chloroform. The first 10 ml of eluate gave 90 mg (87%) of white crystals. Recrystallization from ether gave colorless plates, mp 132°.

Anal. Calcd for $C_{13}H_{19}NO_7$ (301.29): C, 51.82; H, 6.36; N, 4.65. Found: C, 51.88; H, 6.52; N, 4.47.

DL-(1,2,4/3,5)-3-Acetamido-1,2,5-tri-O-acetyl-4-bromocyclopentanetriol (Xb).—Hydrogen bromide gas was vigorously bubbled for 1 min through a solution of IXb (230 mg, 0.89 mmole) in 10 ml of absolute ethanol. After standing for 2 hr at room temperature, the solution was concentrated at reduced pressure to a yellow syrup, which was acetylated (5 ml of pyridine and 2 ml of acetic anhydride, overnight at room temperature). The resulting syrup was chromatographed over Al_2O_3 (20 g, 1.0 cm in diameter) with chloroform to give 256 mg (75%) of Xb. Recrystallization from ethanol gave colorless needles, mp 157–158°.

Anal. Calcd for $C_{13}H_{18}BrNO_7$ (380.20): C, 41.07; H, 4.77; N, 3.69. Found: C, 40.95; H, 4.75; N, 3.81.

DL-(1,4/2,3)-1-Acetamido-2,3,4-tri-O-acetylcyclopentanetriol (XIb).—Compound Xb (100 mg, 0.26 mmole) was dissolved in 10 ml of 50% ethanol; 500 mg of Raney nickel and 1.5 g of Amberlite IR-4B were added. Reduction and work-up were carried out as described under XIVb. The syrup obtained was acetylated (2 ml of pyridine and 1 ml of acetic anhydride). The acetylated product was chromatographed over Al_2O_3 (10 g, 0.8 cm in diameter with chloroform as eluent. The first 20 ml of eluate gave 60 mg (60%) of starting material (Xb). The second 20 ml of eluate contained 20 mg (25%) of XIb. Recrystallization from ether gave plates, mp 135–136°, showing no melting point depression with the authentic sample[3] and identical infrared spectrum.

DL-(1,2,4/3,5)-1-Acetamido-2,4,5-tri-O-acetyl-3-bromocyclopentanetriol (XVb).—To a solution of 100 mg (0.41 mmole) of VIIb in 4 ml of 50% acetic acid, 4 ml of 2% bromine water (Br_2, 80 mg, 0.5 mmole) was slowly added with cooling in ice water. The mixture was left for 2 hr at room temperature and then concentrated under reduced pressure to a yellow syrup, which was acetylated by the procedure described above. The acetylated substance was chromatographed over Al_2O_3 (20 g, 1.0 cm in diameter) with chloroform. The first 40 ml of eluate gave 153 mg (97%) of XVb as needles, mp 132–133°.

(16) Purchased from FMC Corp., Carteret, N. J.

Anal. Calcd for $C_{13}H_{18}BrNO_7$ (380.20): C, 41.07; H, 4.77; N, 3.69. Found: C, 41.13; H, 4.90; N, 3.80.

DL-(1,2,4/3)-2-Acetamido-1,3,4-tri-O-acetylcyclopentanetriol (XVIb).—Compound XVb (100 mg, 0.26 mmole) was dissolved in 10 ml of 50% ethanol; 500 mg of Raney nickel and 1.5 g of Amberlite IR-4B were added, and reduction and work-up were carried out as above. After acetylation (1.0 ml of pyridine and 0.5 ml of acetic anhydride) the product was chromatographed over Al_2O_3 (20 g, 1.0 cm in diameter) with chloroform. From the first 60 ml of eluate 52 mg (65%) of XVIb was isolated as prisms, mp 120–121°.

Anal. Calcd for $C_{13}H_{19}NO_7$ (301.29): C, 51.82; H, 6.36; N, 4.65. Found: C, 51.88; H, 6.52; N, 4.47.

DL-(1,2,4/3,5)-4-Acetamido-1,2,3-tri-O-acetyl-5-bromocyclopentanetriol (XVIIIb).—Hydrogen bromide gas was vigorously bubbled for 1 min through a solution of XVIIb (75 mg, 0.29 mmole) in 5 ml of absolute ethanol. The reaction mixture was left for 60 min at room temperature and concentrated to a yellow syrup, which was acetylated (2 ml of pyridine and 1 ml of acetic anhydride) and the acetylated product was chromatographed over Al_2O_3 (10 g, 0.8 cm in diameter) with chloroform. The first 20 ml of eluate contained 104 mg (70%) of XVIIIb. Recrystallization from ethanol gave needles, mp 150–151°.

Anal. Calcd for $C_{13}H_{18}BrNO_7$ (380.20): C, 41.07; H, 4.77. Found: C, 41.27; H, 4.63.

DL-(1,2,4/3)-4-Acetamido-1,2,3-tri-O-acetylcyclopentanetriol (XIXb).—Compound XVIIIb (60 mg, 0.16 mmole) was dissolved in 10 ml of 50% ethanol; 500 mg of Raney nickel and 1.5 g of Amberlite-IR-4B were added. Reduction and work-up were carried out as described above. The crude acetylated product was chromatographed over Al_2O_3 (15 g, 0.8 cm in diameter) with chloroform. The first 30 ml of eluate gave 33 mg (70%) of XIXb, mp 112°. Mixture melting point with the authentic sample[3] (mp 112°) did not shown any depression and the infrared spectra of both compounds were identical.

DL-(1,2,3/4,5)-1-Acetamido-2,3,4,5-tetra-O-acetylcyclopentanetetrol (XXIIIb).—To a solution of 300 mg (1.24 mmoles) of IIIb in 40 ml of 95% ethanol, 0.8 g of $MgSO_4 \cdot 7H_2O$ was added; 35 ml of 1% $KMnO_4$ solution was slowly added with stirring for 30 min at −20°. The reaction mixture was left overnight at room temperature and filtered. The filtrate was treated with active carbon and concentrated under reduced pressure to give a white, amorphous substance, which was acetylated (5 ml of pyridine and 5 ml of acetic anhydride, heating for 2 hr at 70–80°). The reaction mixture was filtered to remove inorganic substances and the filtrate was concentrated under reduced pressure to a syrup. The acetylated product was chromatographed over Al_2O_3 (20 g, 1.0 cm in diameter) with chloroform to give 292 mg of crude XXIIIb. Recrystallization from ether gave 207 mg (46%) of needles, mp 119°.

Anal. Calcd for $C_{15}H_{21}NO_9$ (359.33): C, 50.14; H, 5.89; N, 3.89. Found: C, 50.07; H, 5.81; N, 3.84.

DL-(1,2,3/4,5)-4-Acetamido-1,2,3,5-tetra-O-acetylcyclopentanetetrol (XXVb).—Compound IXb (200 mg, 0.76 mmole) was dissolved in 10 ml of 1% H_2SO_4 and the solution was heated for 2 hr at 100°. Amberlite IR-4B was added to remove H_2SO_4 and after filtration the solution was concentrated to a slightly yellow syrup, which was acetylated (5 ml of pyridine and 2 ml of acetic anhydride) and the acetylated product was chromatographed over Al_2O_3 (15 g, 0.8 cm in diameter) with chloroform. The first 30 ml of eluate gave 185 mg (66%) of XXVb, mp 192°.

Anal. Calcd for $C_{15}H_{21}NO_9$ (359.33): C, 50.14; H, 5.89; N, 3.89. Found: C, 49.96; H, 5.89; N, 3.93.

DL-(1,2,4/3,5)-3-Acetamido-1,2,4,5-tetra-O-acetylcyclopentanetetrol (XXVIb). A. From Acetamidoepoxydiol IXa.—Compound IXa (100 mg, 0.39 mmole) was dissolved in 5 ml of methanol solution saturated with dry ammonia gas and 10 ml of absolute ethanol, and left overnight at room temperature. Solvents and acetamide were removed under reduced pressure to give a syrupy substance, which was dissolved in 10 ml of 1% H_2SO_4 and heated for 1 hr at 80–100°. Sulfuric acid was removed with Amberlite IR-4B and the filtrate was concentrated to a slightly yellow syrup, which was acetylated (5 ml of pyridine and 2 ml of acetic anhydride) and the acetylated product was chromatographed over Al_2O_3 (15 g, 1.8 cm in diameter) with chloroform. The first 20 ml of eluate gave 75 mg (54%) of crystals (XXVIb). Recrystallization from ether gave colorless needles, mp 123–125°.

B. From Acetamidodiol Diacetate VIIb.—To a solution of 482 mg (2.0 mmoles) of VIIb in 60 ml of 95% ethanol, 1.2 g of $MgSO_4 \cdot 7H_2O$ was added and 50 ml of 1% $KMnO_4$ solution was added with stirring over 30 min at −10°. After filtration the solution was treated with active carbon and concentrated under reduced pressure to give a white, amorphous substance. One-third of this product was acetylated (5 ml of pyridine and 2 ml of acetic anhydride) and the crude acetylated product was chromatographed over Al_2O_3 (10 g, 0.8 cm in diameter) with chloroform to give 106 mg (44%) of XXVIb, mp 122–124°. Recrystallization from ether gave colorless needles melting at 123–125°; mixture melting point with the substance obtained from IXa (mp 123–125°) was not depressed and the infrared spectra of both compounds were identical.

Anal. Calcd for $C_{15}H_{21}NO_9$ (359.33): C, 50.14; H, 5.89; N, 3.89. Found: C, 50.30; H, 6.04; N, 4.00.

DL-(1,2,4/3,5)-4-Acetamido-1,2,3,5-tetra-O-acetylcyclopentanetetrol (XXVIIIb).—A solution of 250 mg (0.93 mmole) of XVIIb dissolved in 15 ml of 1% H_2SO_4 was heated for 2 hr at 80–90° and the product was worked up as described for XXVIb. After acetylation (10 ml of pyridine and 10 ml acetic anhydride, heating for 2 hr at 60–70°) the product was chromatographed over Al_2O_3 (20 g, 1.0 cm in diameter) with chloroform. The first 30 ml of eluate contained 265 mg (76%) of XXVIIIb. Recrystallization from ether gave needles, mp 147°

Anal. Calcd for $C_{15}H_{21}NO_9$ (359.33): C, 50.14; H, 5.89; N, 3.89. Found: C, 50.20; H, 6.02; N, 4.01.

DL-(1,2,4/3,5)-4-Acetamido-3,5-di-O-acetyl-1,2-O-isopropylidenecyclopentanetetrol (XXXb).—Compound XXVIIIb (200 mg, 1.56 mmoles) was dissolved in 5 ml of methanol saturated with dry ammonia gas and 5 ml of absolute ethanol, and left overnight at room temperature. The solvents and acetamide were evaporated under reduced pressure to give a crystalline substance (XXVIIIa, mp 148°), which was stirred for 48 hr in a stoppered flask with anhydrous acetone (50 ml), methanol (5 ml), anhydrous $CuSO_4$, and one-half drop of 98% H_2SO_4. The green reaction mixture was neutralized to pH 7 with Amberlite IR-4B and filtered. The residue was washed with acetone (50 ml), and the combined filtrate was evaporated under reduced pressure to give a syrupy substance, which was acetylated (5 ml of pyridine and 2 ml of acetic anhydride, heating for 2.5 hr at 60–70°). The reaction mixture was concentrated under reduced pressure to give a brown syrup, which was decolorized with active carbon in hot ethanol (50 ml). Solvent was evaporated, the residue was dissolved in ether, and the solution was stored at −10°. Crystals deposited over a period of several days. Recrystallization from ether gave 105 mg (59%) of needles (XXXb), mp 157°.

Anal. Calcd for $C_{14}H_{21}NO_7$ (315.32): C, 53.32; H, 6.71; N, 4.44. Found: C, 53.22; H, 6.47; N, 4.50.

DL-(1,2,4/3,5)-3,4-Bis(acetamido)-1,2,5-tri-O-acetylcyclopentanetriol (XXXIIIb). A. From Acetamidoanhydrotetrol IXa.—Compound IXb (140 mg, 0.54 mmole) was dissolved in 10 ml of methanol half-saturated with dry ammonia gas and the mixture was left overnight at room temperature and concentrated under reduced pressure. The crude product IXa was dissolved in 4 ml of 2-methoxyethanol and 1 ml of water. Sodium azide (250 mg) and 130 mg of ammonium chloride were added and the mixture was refluxed for 3 hr and concentrated under reduced pressure. Acetylation was carried out with 1 ml of pyridine and 0.5 ml of acetic anhydride, 20 ml of chloroform was added, and the precipitate was removed by filtration. The chloroform was evaporated and the crude azido compound XXXIa (180 mg) was dissolved in 10 ml of absolute ethanol, 70 mg of 10% Pd–C catalyst was added, and hydrogen was bubbled through while the mixture was stirred at 60–65° for 1 hr. The solution was made slightly acidic by addition of 2 *N* HCl and then hydrogen was passed in for 2 hr. After removal of catalyst by filtration, the filtrate was evaporated under reduced pressure, the residual syrup was acetylated (1 ml of pyridine, 0.5 ml of acetic anhydride), and the product was chromatographed over Al_2O_3 (10.0 g, 0.8 cm in diameter) with chloroform. There was obtained 170 mg (87%) of crystalline XXXIIIb. Recrystallization from ether gave 133 mg (68%) of prisms, mp 235°.

Anal. Calcd for $C_{15}H_{22}N_2O_8$ (358.35): C, 50.72; H, 6.19; N, 7.82. Found: C, 50.56; H, 6.30; N, 8.06.

B. From Acetamidoanhydrotetrol XVIIa.—Compound XVIIb (150 mg, 0.58 mmole) was dissolved in 15 ml of methanol two-thirds saturated with dry ammonia gas and the mixture was left overnight at room temperature. Solvent was then evaporated and the product (XVIIa) dissolved in 4 ml of 2-methoxyethanol and 1 ml of water. Sodium azide (250 mg) and 130 mg of am-

monium chloride were added, and the mixture was refluxed for 3 hr and then worked up as before. The crude azido compound XXXVa (130 mg) was reduced, acetylated, and purified as described above. Chromatography gave 130 mg (63%) of a crystalline substance XXXIIIb. Recrystallization from ether gave 101 mg of needles, mp 247°. The infrared spectrum was identical with that of the product obtained from IXa, mmp 239–243°.

Anal. Calcd for $C_{15}H_{22}N_2O_8$ (358.35): C, 50.72; H, 6.19; N, 7.82. Found: C, 50.47; H, 6.32; N, 8.08.

Studies on Cyclic Polyols. VIII. Neighboring-Group Effects in Epoxide Opening and in Addition of Hypobromous Acid[1]

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The direction of hydrolytic opening of partially hindered epoxides of cyclopentane may be governed by steric hindrance or neighboring group participation. When the *trans* substituent adjacent to one end of the oxirane ring is a hydroxyl group, the weak nucleophile H_2O attacks the less hindered end of the ring. In this way DL-(1,2,3/4)-2,3-anhydrocyclopentanetetrol (I) is converted in high yield into DL-(1,3/2,4)cyclopentanetetrol (III); DL-(1,2/3,4)-1,2-anhydrocyclopentanetetrol (V) is converted into DL-(1,2,4/3)cyclopentanetetrol (VII), and DL-(1,2,3/4,5)-1-acetamido-2,3-anhydro-2,3,4,5-cyclopentanetetrol (IX) is converted into (1,2,4/3,5)-5-acetamidocyclopentanetetrol (XI). On the other hand, when the *trans* substituent is an acetoxyl group, the oxirane ring opens at the more hindered end: DL-(1,2,3/4)-1,4-di-O-acetyl-2,3-anhydrocyclopentanetetrol (II) is converted almost exclusively into DL-(1,2/3,4)cyclopentanetretrol (IV), DL-(1,2/3,4)-3,4-di-O-acetyl-1,2-anhydrocyclopentanetetrol (VI) is converted into DL-(1,2,3/4)cyclopentanetetrol (VII), and DL-(1,2,3/4,5)-1-acetamido-4,5-di-O-acetyl-2,3-anhydrocyclopentanetetrol (X) is converted into DL-(1,2,3/4,5)-5-acetamidocyclopentanetetrol (XII). The stereoselectivity associated with acetylation of the adjacent hydroxyl group is ascribed to an opening of the epoxide ring by assistance of the acetoxyl group instead of by direct attack of water on the oxirane ring. When both ends of the oxirane ring are hindered by acetoxyl groups as in *meso*-(1,4/2,3)-1,4-di-O-acetyl-2,3-anhydrocyclopentanetetrol (XIV) even the strongly nucleophilic N_3^- is unable to attack, and instead XIV is converted into VII by the acetoxyl-assisted reaction. A similar effect is seen in the addition of HOBr to hindered cycloalkenes. The first step, addition of a bromonium ion to form an intermediate epibromonium derivative, is governed by steric hindrance, the addition occurring on the less hindered side of the ring. When a *trans*-acetoxyl or -acetamido group is adjacent to the double bond, the second step, addition of OH^-, occurs at the more hindered location, because of participation of the neighboring group. When both an acetamido and an acetoxyl group are present, the effect of the former predominates over that of the latter; *e.g.*, DL-(3,5/4)-3-acetamido-4,5-di-O-acetylcyclopentenediol (XVIII) is converted in 97% yield into DL-(1,2,4/3,5)-1-acetamido-2,4,5-tri-O-acetyl-3-bromocyclopentanetriol (XIX).

The stereoselective rupture of one of the C–O bonds of an epoxide by a nucleophilic reagent may be governed by conformational factors,[3–5] electrostatic effects,[6,7] and steric effects.[7,8] In the cyclohexane series diaxial ring opening of a preferred half-chair form of the epoxide appears to be the predominant effect. An electrostatic effect of an adjacent electronegative substituent has also been proposed.[6,9] In the cyclopentane series steric and electrostatic effects appear to explain most of the examples so far studied[7,8,10] except for two compounds (X and XIV) in which one or both ends of the oxirane ring have an adjacent *trans*-acetoxyl group. Treatment with NaN_3 converted II and VI to the corresponding azidotriol derivatives, the less hindered position of each compound being attacked by the nucleophilic reagent;[10a] under identical conditions, however, XIV was not converted to the expected azidotriol derivative XV (see Chart I). Instead, the only product recovered was the tetrol derivative VIIb, and this result is ascribed to epoxide opening by participation of the adjacent acetoxyl groups. In the other example, hydrolysis in dilute aqueous acid led to opening of the epoxide of IX at the less hindered position, but under the same experimental conditions X was opened at the more hindered position,[10b] and this result also was explained on the basis of acetoxyl-assisted epoxide opening. The present communication describes two more examples in which epoxide opening occurs at the more hindered position, adjacent to a *trans*-acetoxyl group, and a closely related effect in which the direction of addition of HOBr appears also to be governed by participation of an adjacent acetoxyl or acetamido group.

Results

Acetoxyl-Assisted Epoxide Opening.—Since epoxide opening occurs with a single Walden inversion, only two tetrols (III and IV) can be produced by hydrolysis of either I or II. We have reported previously that hydrolysis of I by 0.1–1.0 *N* H_2SO_4 gave III almost exclusively, presumably owing to shielding of the adjacent end of the oxirane ring by the *trans*-hydroxyl group. This result has been confirmed by analysis of the hydrolysate by thin layer chromatography (Figure 1). The principal product is IIIa but a small proportion

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