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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(3) (a) S. J. Angyal, *Chem. Ind.* (London), 1230 (1954); (b) T. Posternak, "Les Cyclitols," Hermann, Paris, 1962, p 38.

(4) A. Fuerst and P. A. Plattner, Abstracts of Papers, 12th International Congress of Pure and Applied Chemistry, New York, N. Y., 1951, p 409.

(5) (a) M. Nakajima and N. Kurihara, *Chem. Ber.*, **94**, 515 (1961); (b) M. Nakajima, N. Kurihara, and A. Hasegawa, *ibid.*, **95**, 141 (1962); (c) M. Nakajima, A. Hasegawa, and N. Kurihara, *ibid.*, **95**, 2708 (1962); (d) M. Nakajima, A. Hasegawa, and F. W. Lichtenthaler, *Ann. Chem.*, **669**, 75 (1963); (e) *ibid.*, **680**, 21 (1964).

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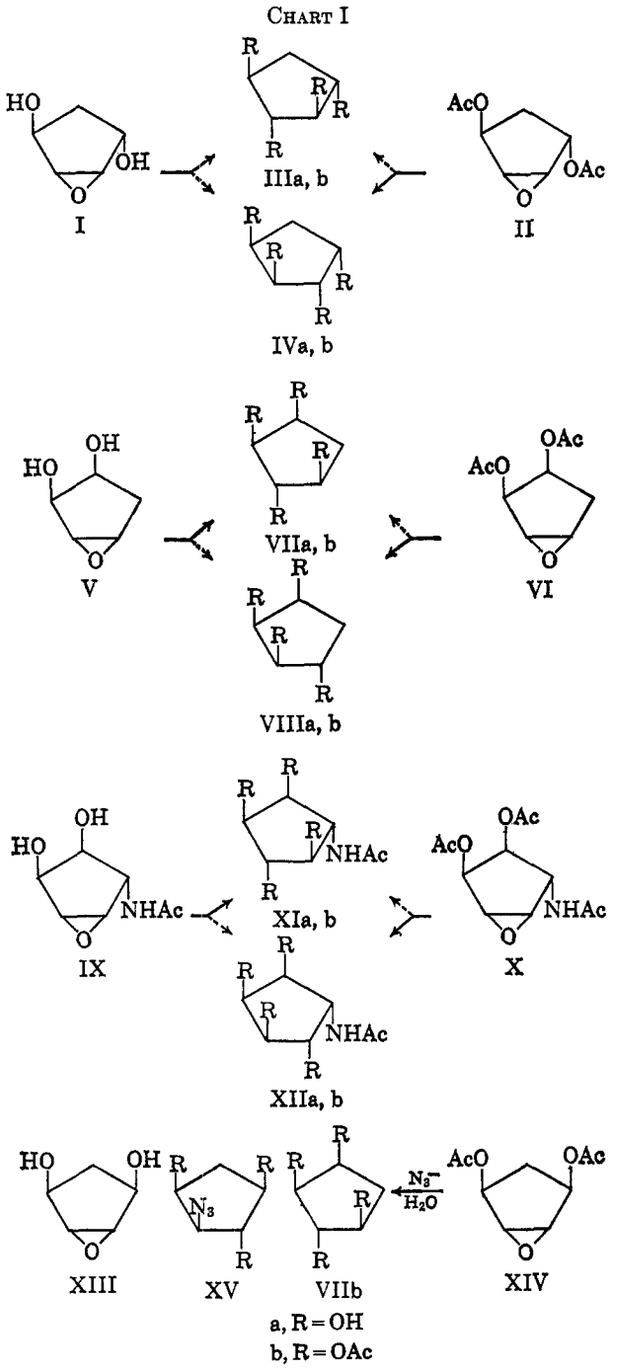
(7) J. A. Franks, Jr., B. Tolbert, R. Steyn, and H. Z. Sable, *J. Org. Chem.*, **30**, 1440 (1965).

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

(9) See discussion of this point in ref 7.

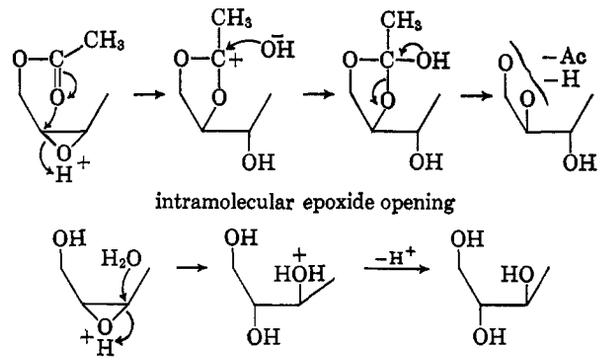
(10) (a) Part VI, A. Hasegawa and H. Z. Sable, *J. Org. Chem.*, **31**, 4149 (1966); (b) part VII, *ibid.*, **31**, 4154 (1966).

CHART I



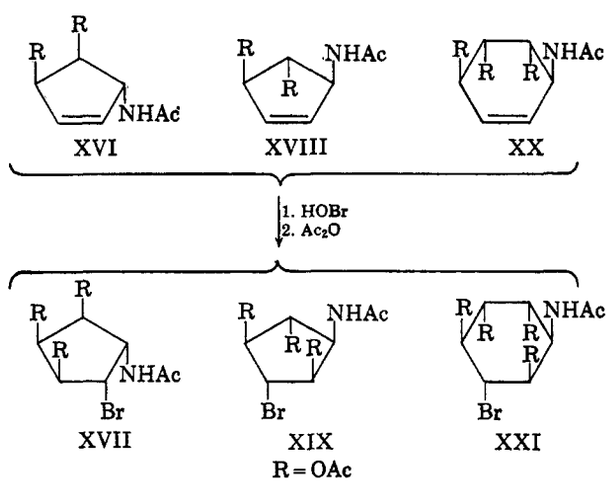
of IVa is also present. When II is hydrolyzed, the opposite result is obtained; in this case IVa is the principal product and the semiquantitative chromatographic analysis suggests that only about 1–2% of III is formed. Similarly, opening the epoxide of V and VI can yield only tetrols VII or VIII. Hydrolysis of V produces approximately 90–95% VIIa, whereas VI is converted almost entirely to VIIIa, only 2% or less of VIIa being formed.

The complete reversal of selectivity between the free and acetylated anhydrotetrols can be explained by assuming that the acetoxyl group participates in opening the adjacent end of the oxirane ring. The carbonyl oxygen atom attacks the adjacent end of the ring causing rupture of the epoxide with simultaneous formation of the transient ortho ester like acetoxonium intermediate; the latter is then attacked by water or hydroxyl ion, forming the final product. Since the un-

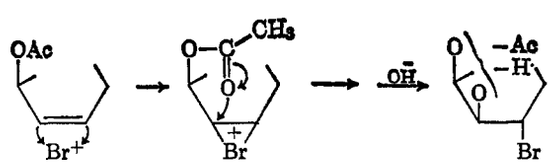


assisted opening hardly affects the hindered site, one may assume that the intramolecular opening reaction is at least 50–100 times as fast as the intermolecular opening.

Addition of HOBr to Allylic Cycloalkenes.—Treatment of cyclopentenes having allylic acetoxyl and acetamido groups[10b] with 2% bromine water has given high yields of one of the four possible, isomeric *trans*-bromohydrins, in agreement with similar results[5e] with the analogous cyclohexene derivatives. DL-(3,4/5)-5-Acetamido-3,4-di-O-acetylcyclopentenediol (XVI) was converted in 70% yield into bromohydrin XVII; the



(3,5/4) isomer XVIII was converted in 97% yield into bromohydrin XIX. These observations may be explained on the basis of different controlling factors for the two steps of the addition of HOBr. The first step, the addition of a bromonium ion to the double bond, generating a transient epibromonium ion, is governed by steric hindrance, the addition occurring on the less hindered side of the ring. The second step, addition of OH^-, occurs by assistance of the neighboring *trans*-acetoxyl or -acetamido group, analogous to the process shown for the intramolecular epoxide-opening reaction.



Although the homoallylic groups offer some steric hindrance, the double bond of XVIII is more hindered on one side, and less hindered on the other side of the plane of the ring than is the double bond of XVI.

The higher yield of bromohydrin XIX relative to XVII may therefore be due to the greater stereoselectivity of addition of Br^+ to XVIII than to XVI. In the sequence XVIII → XIX both ends of the intermediate epibromonium species are hindered by adjacent *trans* groups, and the selective formation of XIX shows that the acetamido group is very effective in the intramolecular reaction, and furthermore that this group is even more effective as a participating neighboring group than the acetoxyl group. This is not unexpected; since the amide nitrogen atom is less electron attracting than the ester oxygen atom, the carbonyl oxygen atom of the amide is more basic than that of the ester. The present situation is analogous to a case in the cyclohexane series, XX → XXI, which was reported elsewhere[5e] by one of us.

Discussion

The mechanisms proposed to explain the directive influence of neighboring acetoxyl and acetamido groups in addition and substitution reactions are derived from the basic principles elucidated primarily by Winstein and his associates.[11,12] Related examples of participation of neighboring groups are found in the steroid field. Addition of bromine to an ethylenic bond in a ring with a homoallylic carboxyl substituent leads to the formation of bromolactones[13] instead of to dibromides. The formation of oxazolines by treatment of *trans*-1,2-acylamido alcohols[14] with $SOCl_2$ is another closely related phenomenon. The mechanism proposed for addition of HOBr is related to that proposed by Woodward and Brutcher[15] for hydroxylation with silver halogenoacetates.

Buchanan, *et al.*, proposed participation of neighboring acetoxyl groups in ring opening of epoxides of hexose derivatives.[16] The large contribution of conformational factors makes the relative importance of other factors more difficult to assess when six-membered rings are involved. In the case of cyclopentane, however, conformational factors are much smaller and the results obtained are more reliable indicators of steric hindrance, acetoxyl assistance, electrostatic effects, etc. Although the reported reversal of stereoselectivity of epoxide opening is most easily explained by invoking the participation of the adjacent *trans*-acetoxyl group, a kinetic study is still required to support this explanation. The acetoxyl-assisted reaction should be sufficiently faster than the unassisted reaction to account for the observed change in product distribution, and in the absence of such evidence the conclusion that the acetoxyl group participates in the reaction can only be tentative.

(11) (a) S. Winstein, C. Hanson, and E. Grunwald, *J. Am. Chem. Soc.*, **70**, 812 (1948); (b) S. Winstein, E. Grunwald, R. E. Buckles, and C. Hanson, *ibid.*, **70**, 816 (1948); (c) S. Winstein, E. Grunwald, and L. L. Ingraham, *ibid.*, **70**, 821 (1948); (d) S. Winstein and E. Grunwald, *ibid.*, **70**, 828 (1948); (e) L. Goodman, S. Winstein, and R. Boschan, *ibid.*, **80**, 4312 (1958).

(12) B. R. Baker and A. H. Haines, *J. Org. Chem.*, **28**, 438 (1963).

(13) (a) A. Winterstein and G. Stein, *Z. Physiol. Chem.*, **202**, 217 (1931); (b) H. Wieland and G. Hänke, *ibid.*, **241**, 93 (1936).

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(15) R. B. Woodward and F. V. Brutcher, *J. Am. Chem. Soc.*, **80**, 209 (1958).

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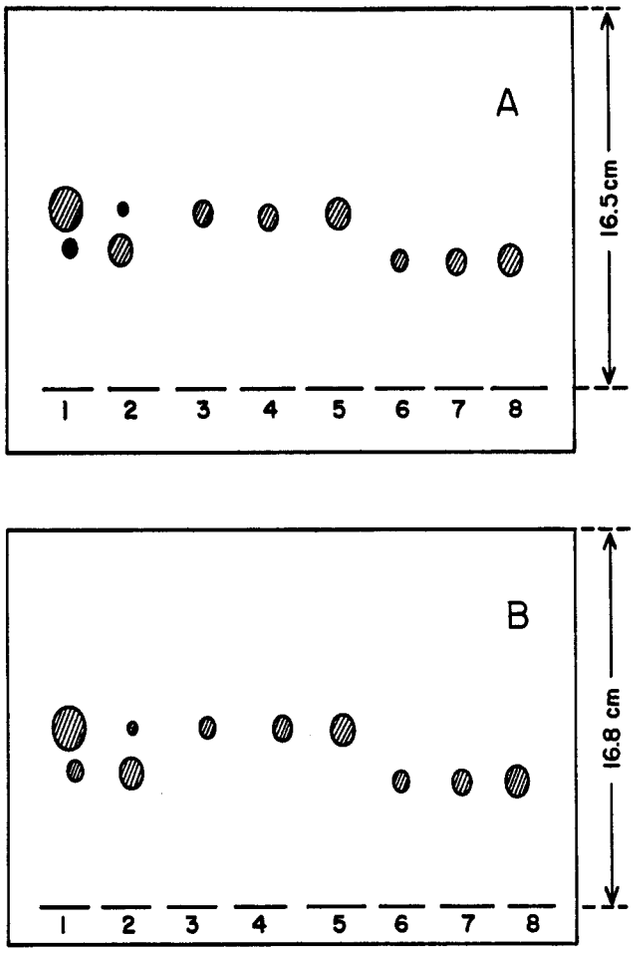

Figure 1.—Thin layer chromatographic analysis of products of epoxide opening: (A) 1, hydrolysate of 0.4 mg of I; 2, hydrolysate of 0.4 mg of II; 3, 4, and 5, 0.03, 0.1, and 0.3 mg, respectively, of IIIa; 6, 7, and 8, 0.03, 0.1, and 0.3 mg, respectively, of IVa; (B) 1, hydrolysate of 0.4 mg of V; 2, hydrolysate of 0.4 mg of VI; 3, 4, and 5, 0.03, 0.1, and 0.3 mg, respectively, of VIIa; 6, 7, and 8, 0.03, 0.1, and 0.3 mg, respectively, of VIIIa.

The failure of XIV to be converted into an azido compound by N_3^- under conditions in which related compounds[17] (I, II, V, VI) do react might be ascribed to simple hydrolysis. Such an explanation is unlikely, since it implies that the weak nucleophile H_2O can attack the ring when the strong nucleophile N_3^- is excluded. When steric hindrance is absent or small the attack of strongly nucleophilic reagents (Br^-, N_3^-) predominates over the attack of water,[7,10] and it is therefore more reasonable to conclude that because of steric hindrance by the two acetoxyl groups flanking the oxirane ring neither nucleophile can have direct access to the bridgehead carbon atoms and the only possible first step is the intramolecular attack at either end of the ring.

Experimental

Melting Points.—Melting points were determined on a Kofler micro hot stage (A. H. Thomas and Co.) and are corrected.

Spectra.—Infrared spectra were measured with a Perkin-Elmer Model 237B spectrophotometer.

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

(17) The related nonacetylated compound XIII has not been tested because we have been unable to prepare it in a pure state.

Chromatography.—Thin layer chromatography was carried out with silica gel G (Brinkmann Instruments, Inc., Westbury, Long Island, N. Y.) as backing; the developing solvent was *n*-butyl alcohol–acetone–water (4:5:1, v/v/v). After drying, the plates were sprayed with the permanganate–periodate reagent of Lemieux and Bauer.[18] R_f values follow: IIIa, 0.51; IVa, 0.41; VIIa, 0.44; VIIIa, 0.32.

DL-(1,3/2,4)Tetra-O-acetylcyclopentanetetrol (IIIb). A. From DL-(1,3/2,4)Cyclopentanetetrol.—DL-(1,3/2,4)Cyclopentanetetrol[8] (50 mg, 0.37 mmole) was acetylated by adding 3 ml of pyridine and 2 ml of acetic anhydride and allowing the mixture to stand overnight at room temperature. The reagents were evaporated under reduced pressure to give a yellow syrup, 10 ml of water was added, and the mixture was extracted with ether. The ether solution was washed with 2 *N* HCl, 2 *N* NaOH, and water, dried over Na_2SO_4 and evaporated to a colorless syrup, (III, 80 mg, 71%) which crystallized slowly from ethanol, mp 68°.

Anal. Calcd for $C_{13}H_{18}O_8$ (302.27): C, 51.65; H, 6.00. Found: C, 51.47; H, 6.08.

B. From DL-(1,2,3/4)-2,3-Anhydrocyclopentanetetrol (I).—Sulfuric acid (20 ml, 1%) was added to I prepared from II (500 mg, 2.5 mmoles) by hydrolysis with dilute ammonia–methanol solution (10% saturated) and the mixture was refluxed for 1 hr. The solution was cooled and Amberlite IR-4B was added to remove sulfuric acid; the resin was filtered off and washed with water. The combined filtrate was concentrated at reduced pressure to slightly yellow syrup, which was acetylated (5 ml of pyridine and 5 ml of acetic anhydride, heating for 3 hr at 60°). The usual procedures yielded a colorless syrup of III (550 mg, 73%). The infrared spectra of the substances obtained by both methods were identical.

DL-(1,2/3,4)Tetra-O-acetylcyclopentanetetrol (IVb). A. From DL-(1,2/3,4)Cyclopentanetetrol.—DL-(1,2/3,4)Cyclopentanetetrol[8] (20 mg, 0.15 mmoles) was acetylated (pyridine, 3 ml; acetic anhydride, 2 ml) as described above, yielding 30 mg (68%) of colorless syrup (VI).

Anal. Calcd for $C_{13}H_{18}O_8$ (302.27); C, 51.68; H, 6.00. Found: C, 51.92; H, 6.17.

B. From DL-(1,2,3/4)-1,4-Di-O-acetyl-2,3-anhydrocyclopentanetetrol (II).—Compound II (500 mg, 2.50 mmoles) was hydrolyzed in 1% H_2SO_4 and the hydrolysate was worked up and acetylated by the usual procedures, yielding 520 mg (69%) of IV. The infrared spectra of the substances obtained by both methods were identical.

DL-(1,2,4/3)Tetra-O-acetylcyclopentanetetrol (VIIb). A. From DL-(1,2,4/3)Cyclopentanetetrol.—DL-(1,2,4/3)Cyclopentanetetrol[8] (50 mg, 0.37 mmole) was acetylated with pyridine (3 ml) and acetic anhydride (2 ml) according to the procedure described above. There was obtained 80 mg (71%) of white crystals (VIIb). Recrystallization from ethanol gave colorless needles, mp 81–82°.

Anal. Calcd for $C_{13}H_{18}O_8$ (302.27): C, 51.65; H, 6.00. Found: C, 51.39; H, 5.98.

B. From DL-(1,2/3,4)-1,2-Anhydrocyclopentanetetrol (V).—Compound VI (500 mg, 2.50 mmoles) was treated with dilute ammonia–methanol solution (10%). The product was hydrolyzed with 20 ml of 1% H_2SO_4 and the usual procedures then yielded 490 mg (65%) of white crystals. Recrystallization from ethanol gave needles, mp 81–82°; mixture melting point with the authentic sample showed no depression; and the infrared spectra of both products were identical.

DL-(1,2,3/4)Tetra-O-acetylcyclopentanetetrol (VIIIb). A. From DL-(1,2,3/4)Cyclopentanetetrol).—DL-(1,2,3/4)Cyclopentanetetrol[8] (30 mg, 0.22 mmole) was acetylated by the procedure described above, yielding 60 mg (88%) of colorless syrup (VIIIb).

Anal. Calcd for $C_{13}H_{18}O_8$ (302.27): C, 51.65; H, 6.00. Found: C, 51.66; H, 5.94.

B. From DL-(1,2/3,4)-3,4-Di-O-acetyl-1,2-anhydrocyclopentanetetrol (VI).—Compound VI (500 mg, 2.50 mmoles) was hydrolyzed in 1% H_2SO_4 as above. The usual procedures then yielded a colorless syrup (VIIIb, 510 mg, 67%). The infrared spectra of the substances obtained by both methods were identical.

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Hydrogen Bonding and Conformational Analysis of 3-Piperidinol Derivatives

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The conformational equilibrium of 1-methyl-3-piperidinol showed that intramolecular hydrogen bonding of the hydroxyl group with the heteronitrogen decreased the apparent steric requirement of the axial hydroxyl. The strength of the hydrogen bond was estimated. Evaluation of several approaches to the conformational analysis of the two isomers of 1-methyl-4-phenyl-3-piperidinol is given.

Conformational analysis, which has proven to be essential for the description of alicyclic chemistry,[2] has only sparingly been applied to similar heterocyclic systems.[3] The similarity of the bond angles and bond lengths of C–C–C in alicyclic rings and the C–N–C in cyclic amines allows some direct applications of the techniques applied to cyclohexane derivatives to be employed in the study of piperidine and piperazine analogs.[3] The obvious difference in the alicyclic and heterocyclic systems is the tercovalent, heteronitrogen atom, and numerous approaches have been employed to evaluate the conformation of substituents on this atom.[4] An all-important feature of the electron pair, the ability to form a hydrogen bond with acidic protons, has not been used in a quantitative treatment of the conformation of nitrogen heterocycles, nor has the role of the hydrogen bond in determining the preferred conformation been established.[5] The formation and detection of such a hydrogen bond have been used to assign nonchair conformations to 1,2,2,6,6-pentamethyl-4-

(1) (a) On leave from the University of New Hampshire, 1965–1966, at Harvard and Oxford Universities as a Special Postdoctoral Fellow (1-F3-GM-30,140-01) of the National Institutes of Health. (b) This research is taken from the theses offered in partial fulfillment of the requirements for the Ph.D. Degree at the University of New Hampshire. (c) Public Health Service Predoctoral Fellow, 1962–1965 (GPM-18974).

(2) (a) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962; (b) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965, p 44; (c) M. Hanack, "Conformational Theory," Academic Press Inc., New York, N. Y., 1965.

(3) (a) Series by A. R. Katritzky and co-workers; see R. J. Bishop, G. Fodor, A. R. Katritzky, F. Soti, L. E. Sutton, and F. J. Swinbourne, *J. Chem. Soc.*, 74 (1966); (b) series by R. J. W. Le Fevre and co-workers; see C. Y. Chen and R. J. W. Le Fevre, *Tetrahedron Letters*, 4057 (1965); M. J. Aroney, C. Y. Chen, R. J. W. Le Fevre, and A. N. Singh, *J. Chem. Soc.*, 98 (1966); (c) series by H. O. House; see H. O. House, B. A. Tefertiller, and C. G. Pitt, *J. Org. Chem.*, **31**, 1073 (1966); (d) series by J. McKenna; see J. McKenna, J. M. McKenna, and J. White, *J. Chem. Soc.*, 1733 (1965).

(4) Reference 2b, pp 244–255, gives a summary of all but the most recent work which is given in ref 3.

(5) See p 471 of ref 2b for illustrations of lack of quantitative data; however, during the preparation of this manuscript the review chapter on the hydrogen bond [M. Tichy, *Advan. Org. Chem.*, **5**, 115 (1965)] appeared. This article contains reference to unpublished work relative to this question on p 155.