ture melting point, and infrared spectrum. The recrystallized solid weighed 0.10 g. (55%), m.p. 191.5–192.5°.

6-Bromo-3-carbethoxy-5-hydroxy-2-methylbenzofuran (XII).—The reaction apparatus used was that in method B for VI, except that nitrogen was bubbled through the reaction solution, and the exiting vapors were passed through a water-rinsed gas trap. Temperature was kept at 10–15° throughout the reaction. A solution of 22.0 g. (0.10 mole) of III in chloroform was treated with a solution of 16 g. (0.10 mole) of bromine in 100 ml. of chloroform over a period of 70–80 min. The bromine color of the first 75 ml. of this reagent solution was discharged rapidly, but the last 25 ml. were discharged more slowly. The mixture was stirred an additional 20 min., poured into 500 ml. of saturated sodium bicarbonate solution, and, after stirring 10 min. longer, was filtered. The filter crop was triturated with two 100-ml. portions of 5% aqueous sodium thiosulfate solution and with three 100-ml. portions of water. After drying, the solid weighed 24.5 g. (82%). It was dissolved in 600 g. of hot acetone, treated with charcoal, then filtered hot. When cooled, filtered, and air-dried for 4 hr., the microcrystalline white solid, m.p. 191–192°, was recovered from the acetone mother liquor. The total yield of XII melting over 191° was 24.1 g. (81%). The analytical sample was recrystallized from an ethanol–acetone mixture, m.p. 192.5–193°.

Anal. Calcd. for $C_{12}H_{11}BrO_4$: C, 48.18; H, 3.71; Br, 26.72. Found: C, 48.21; H, 3.89; Br, 26.85.

The **methyl ether** of XII was prepared as described under III. Treatment of 3.1 g. of XII gave 3.4 g. of the crude methyl ether; recrystallization from a benzene–pentane mixture (9 g., 20 g.) gave 1.6 g., m.p. 122.5–123.5°. Further recrystallization from carbon tetrachloride gave a granular white solid, m.p. 126.5–127.5°.

Anal. Calcd. for $C_{13}H_{13}BrO_4$: C, 49.86; H, 4.18; Br, 25.52. Found: C, 49.94; H, 4.25; Br, 25.78.

It is interesting that bromination proceeds smoothly in chloroform without added base or catalyst. In ether, or a 3:7 mixture of ether–chloroform, brominated derivatives of III were obtained only in trace quantities, III being recovered nearly quantitatively.

3-Carbethoxy-4,6-dibromo-5-hydroxy-2-methylbenzofuran (XIII).—The same procedure was used as for XII, except that 2 equiv. of bromine were used, and the temperature was kept at 22–26°. When 5.5 g. of III was allowed to react with bromine in this way for 3 hr., a crude product weighing 7.28 g. (77%) was obtained, m.p. 116–118°. Attempted recrystallization from ethanol was accompanied by formation of an orange-brown color. The recovered solid, 6.2 g., m.p. 115–118°, was somewhat orange in color. Further purification was by molecular distillation from a 120–125° oil bath at 0.5 mm. The analytical sample, from carbon tetrachloride, was a white solid, m.p. 118–119°.

Anal. Calcd. for $C_{12}H_{10}Br_2O_4$: C, 38.13; H, 2.66; Br, 42.28. Found: C, 38.07; H, 2.82; Br, 42.10.

The **methyl ether** of XIII was prepared as indicated under III, and recrystallized first from carbon tetrachloride, then from acetone–water (charcoal). The analytical sample was recrystallized from acetone–water (0.48 g. of methyl ether, 4.0 g. of acetone, 1.8 g. of water) to give long white needles (0.38 g.), m.p. 87.5–88.5°.

Anal. Calcd. for $C_{13}H_{12}Br_2O_4$: C, 39.83; H, 3.09; Br, 40.76. Found: C, 40.36; H, 3.44; Br, 40.35.

Acknowledgment.—The authors wish to thank Miss Yvonne Chiang and Dr. Earl Whipple for taking and advising on the interpretation of the n.m.r. spectra.

Degradation and Synthesis of Desosamine

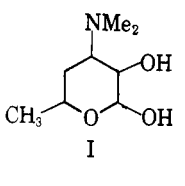
HOWARD NEWMAN[1]

The Chemical Research and Development Laboratories, Agricultural Division, American Cyanamid Company, Princeton, New Jersey

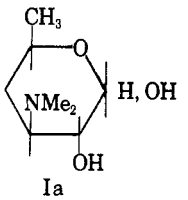
Received December 11, 1963

The degradation of desosamine (I) to 2-ethoxy-3,4-epoxy-6-methyl-tetrahydropyran (IVa) and the reconversion of the latter to desosamine are described. A synthesis of racemic IVa is also presented.

Desosamine (I), the amino sugar component of a considerable number of the macrolide antibiotics,[2,3] has recently evoked considerable interest. Foster, *et al.*, showed it to be a D-hexose.[4] Foster, *et al.*,[5] and Newman[6] presented chemical evidence which established a *trans* relationship between the C-2 hydroxyl and C-3 dimethylamino substituents, while n.m.r. studies by Hofheinz and Grisebach[7] and Woo, *et al.*,[8] established its configuration as D-*gluco* (Ia). Two non-



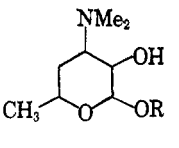
I



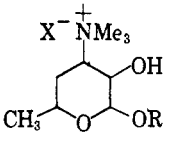
Ia

stereospecific syntheses of I have been described,[6,9] as has its formation from 3-amino-3-deoxy-D-glucose by replacement of the C-4 and C-6 hydroxy substituents with hydrogen from suitably constituted intermediates.[10] In this paper we described, in detail, the degradation of desosamine hydrochloride (I + HCl) to 2-ethoxy-3,4-epoxy-6-methyltetrahydropyran (IVa), the synthesis of racemic IVa, and the reconversion of optically active IVa to desosamine hydrochloride (I + HCl).

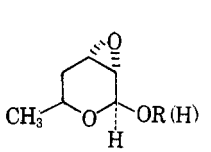
Ethyl desosaminide (IIa) was degraded to the epoxide IVa by pyrolysis of its quaternary hydroxide derivative IIIb which was, in turn, prepared from the corresponding methiodide IIIa. The stereochemical im-



IIa, R = ethyl
b, R = methyl



IIIa, X = I⁻
b, X = OH⁻



IVa, R = ethyl
b, R = methyl

plication of this degradation has already been discussed.[6]

(1) Lederle Laboratories Division, American Cyanamid Co., Pearl River, N. Y.

(2) A. B. Foster and D. Horton, *Advan. Carbohydrate Chem.*, **14**, 213 (1959).

(3) H. Els, W. D. Celmer, and K. Murai, *J. Am. Chem. Soc.*, **80**, 3777 (1958).

(4) C. H. Bolton, A. B. Foster, M. Stacey, and J. M. Webber, *J. Chem. Soc.*, 4831 (1961).

(5) C. H. Bolton, A. B. Foster, M. Stacey, and J. M. Webber, *Chem. Ind.* (London), 1945 (1962).

(6) H. Newman, *ibid.*, 372 (1963).

(7) W. Hofheinz and H. Grisebach, *Tetrahedron Letters*, **No. 9**, 377 (1962).

(8) P. Woo, H. Dion, L. Durham, and H. Mosher, *ibid.*, **No. 17**, 735 (1962).

(9) F. Korte, A. Bilow, and R. Heinz, *Tetrahedron*, **18**, 657 (1962).

(10) A. C. Richardson, *Proc. Chem. Soc.*, 131 (1963).

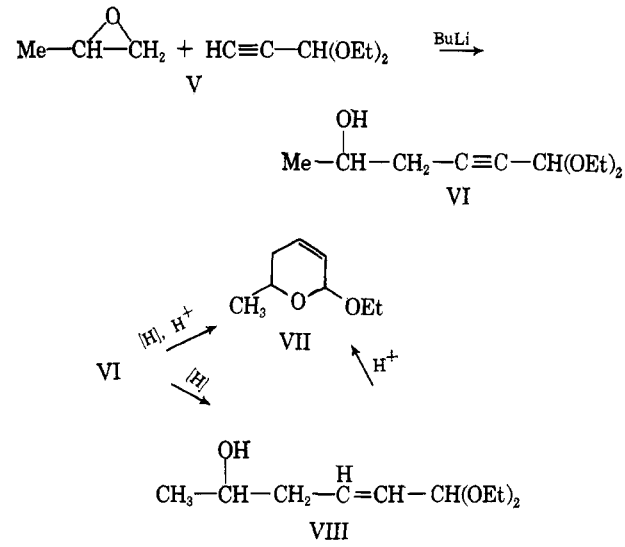
Vapor phase chromatographic analysis of the epoxide IVa indicated the presence of both the α- and β-anomers. The fact that desosamine (I) was known to be a D-hexose[4] permitted the assignment of configuration to the two anomeric components on the basis of their optical rotations and the application of Hudson's Isorotation Rule.[11] The lower retention time component exhibited the more negative rotation and was consequently assigned the β-configuration.

Methyl desosaminide (IIb) was also degraded to the corresponding epoxide IVb, and here, too, the lower retention time component exhibited the more negative rotation and was assigned the β-configuration.

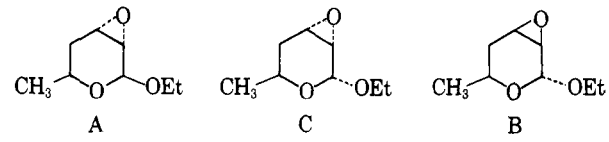
The nuclear magnetic resonance spectra of the two anomeric methyl glycosides IVb support the configurational assignment made. Thus, the C-1 proton resonance of the lower retention time component appeared at τ 5.25 ($J_{12} \cong 0$), while this signal for the higher retention time component appeared at τ 5.09 (J_{12} = 2.5 c.p.s.). This observation parallels the commonly observed phenomenon[8,12-14] that axial protons in the chair form of cyclohexane and pyranose derivatives resonate at higher field than their equatorial counterparts.[15]

The racemic modifications of the α- and β-anomers of IVa were synthesized as follows. The lithium salt of propargyl aldehyde diethylacetal[17] (V) reacted with propylene oxide to give 1,1-diethoxy-5-hydroxyhex-2-yne (VI) in 60% yield. VI could be converted directly to 2-ethoxy-6-methyl-5,6-dihydro-2H-pyran (VII) by reduction over 10% palladium on charcoal until a molar equivalent of hydrogen was consumed, followed by the addition of a small amount of concentrated hydrochloric acid and shaking for an additional short period. Omission of the acid treatment permits the isolation of the acyclic olefin, 1,1-diethoxy-5-hydroxyhex-2-ene (VIII), which can, in turn, be cyclized to VII by treatment with acid. Traces of acid must be rigorously excluded from the hydrogenation system if it is desired to prevent cyclization of the initially formed VIII. In one experiment (see Experimental), VII was the only product isolated, although no acid was added; this was presumably due to traces already present.

The amounts of the two isomers of VII (*cis* and *trans*)[18] present could be extrapolated from the composition of the epoxide mixture IX obtained from it by perbenzoic acid oxidation (see below), with the result that, in all preparations of VII but one, the *trans* isomer largely ($\geq$85%) predominated. In the one exception, VII was inadvertently obtained in an attempt to convert VI to VIII by hydrogenation over 10% palladium on charcoal in the absence of acid. The *cis–trans* isomer ratio of VII obtained in this preparation was roughly 1:2, a considerable amount of *cis* isomer having been formed.



Epoxidation of VII with perbenzoic acid was investigated first. (The same results were subsequently obtained with commercially available *m*-chloroperbenzoic acid.) The epoxide IX obtained was a three-component mixture, A, B, and C (in order of increasing retention time), separable by gas chromatography. The infrared spectra of components A and C were identical with those of the β- and α-anomers, respectively, of epoxide IVa obtained by the degradation of desosamine. A and C must, therefore, be the *cis* and *trans*[18] 2-ethoxy-3,4-epoxy-6-methyltetrahydropyran isomers, respectively, in which the epoxide ring is *trans* to the C-5 methyl substituent, while B must be the isomeric epoxide in which the oxide ring and the C-5 methyl group are *cis* oriented.[19] The *trans* (methyl, ethoxyl) configuration is assigned to B on the basis of the variation in the A:B ratio in the various preparations of IX obtained from different preparations of VII (1:30 to 1:1.5) as compared to the essential constancy of the B:C ratio in those same cases (3.5:1 to 2.5:1).[20] This is indicative of a common precursor for B and C, which must be *trans*[19] VII since the methyl and ethoxyl substituents in C are known to be *trans*.



The homogeneity of B follows from its n.m.r. spectrum in which only a single peak at τ 5.05 ($J_{12} \cong 0$) due

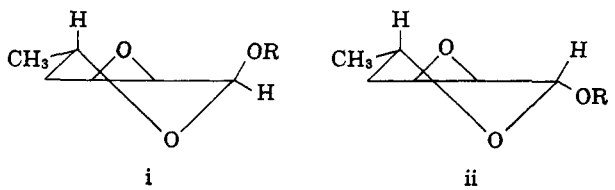
(11) C. S. Hudson, *J. Am. Chem. Soc.*, **31**, 66 (1909).

(12) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *ibid.*, **80**, 6098 (1958); R. U. Lemieux and J. W. Lown, *Can. J. Chem.*, **41**, 889 (1963).

(13) J. van der Veen, *J. Org. Chem.*, **28**, 564 (1963).

(14) A. H. Lewin and S. Winstein, *J. Am. Chem. Soc.*, **84**, 2464 (1962).

(15) It is assumed that the conformations of the α- and β-anomers of IVb are represented by i and ii, respectively. The basis for this expectation will



be discussed later in the paper. (The chair conformations are taken to be more stable than the boat by analogy with the preferred chair conformation for cyclohexene oxide.[16])

(16) B. Ottar, *Acta Chem. Scand.*, **1**, 283 (1947).

(17) J. C. Sheehan and C. A. Robinson, *J. Am. Chem. Soc.*, **71**, 1436 (1949).

(18) *cis* and *trans* refer to the relative configuration of the methyl and ethoxyl substituents.

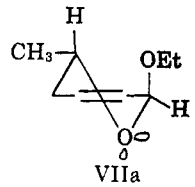
(19) The possibility that component B is a positional isomer is ruled out by the product of its reaction with dimethylamine described later.

(20) Considering the fact that the retention times of the components were such that peak separation was not complete, no significance is attached to the 3.5:1 to 2.5:1 variation. (Peak areas were approximated by multiplying the peak width at half-height by the peak height.)

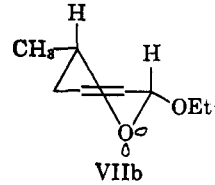
to the C-1 proton was present. If B was, in fact, a mixture, epimeric at C-1, one would expect to see the C-1 proton n.m.r. signals corresponding to both epimers by analogy with the behavior of the α- and β-anomer mixture IVb, in which two C-1 protons signals at τ 5.09 ($J_{12} \cong 2.5$ c.p.s.) and 5.25 ($J_{12} \cong 0$) were clearly visible. The essential coincidence in τ-values between the C-1 proton signal of the α-anomer of IVb and that of component B is further support for the *trans*[18] configuration assigned to the latter.

Thus, of the four possible epoxides that could be formed from the two epimers of VII, only three were obtained, two (B and C) corresponding to *trans* VII and one (A) to *cis* VII.

The results can be rationalized on the basis of conformations VIIa and VIIb for *trans* and *cis* VII, respectively, which would be expected to be very largely preferred based on a consideration of pertinent steric



VIIa

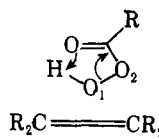


VIIb

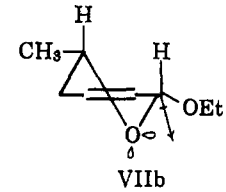
and electronic factors. Thus, for *trans* VII (conformation VIIa) the difference in A-values[14] between methyl[14] and ethoxyl[21] (0.7 kcal.) plus the "anomeric effect"[22] (preferred axial orientation for the anomeric oxygen of a pyranose, 1.1 kcal.[22]) would result in a free-energy difference of 1.8 kcal. in favor of the conformer shown, corresponding to a 95% equilibrium concentration ($\Delta F = -RT \ln K$) of VIIa. Similarly for *cis* VII (conformation VIIb) the sum (since, in the other chair conformer, both substituents become axial) of the A-values for methyl and ethoxyl (2.7 kcal.) minus 1.1 kcal. for the "anomeric effect" leads to a 1.6-kcal. difference in favor of conformer VIIb, which corresponds to an equilibrium concentration of 94% (see ref. 15). The above values are, of course, only crude estimates, since the A-values used were determined for cyclohexane, and the "anomeric effect" value is also only approximate[22]; however, they do indicate that it is not unreasonable to interpret the observed results in terms of conformations VIIa and VIIb.

On this basis then, peracid attack of *trans* and *cis* VII takes place predominantly (*ca.* 75%) and exclusively, respectively, from the side opposite the ethoxyl substituent, which is quasi-axial in *trans* VII and quasi-equatorial in *cis* VII.

If it is assumed that the transition state for olefin epoxidation with peracid is of the type proposed by Bartlett[23] (see diagram), the results can be explained as follows. The epoxidation of *trans* VII from the side opposite the quasi-axial ethoxyl substituent is favored



because of the adverse steric factor involved in a *cis* approach. A possible unfavorable electronic factor resulting from the interaction of the electron pairs on the ethoxyl oxygen with those of O-1 and/or O-2 of the peracid will be assumed to be cancelled, more or less, by a similar effect operating between the axially oriented pair of electrons on the ring oxygen[24] and the oxygen electrons of the peracid on the other side of the ring plane. In the case of *cis* VII, exclusive attack from the topside of VIIb is suggested to be the result of an adverse electronic effect which is a combination of the interaction of the oxygen electrons of the peracid with the axially oriented electron pair of the ring oxygen and the dipole–dipole interaction (see diagram) of the type proposed by Henbest[25] to explain predominant *trans* attack of peracid on 4-methoxy and 4-cyano cyclopentene.[26] (The dipole–dipole interaction would not



VIIb

(Approach of an electrophile is expected to take place from the side opposite the resultant dipole vector which in this case extends below the ring plane)

seem to apply to *trans* VII where the resultant dipole vector would be pretty much in the plane of the ring.)

That the *cis–trans* isomer distribution of olefin VII may be obtained directly from the composition of the epoxide IX follows from the fact that IX is recovered unchanged from glacial acetic acid after 72 hr. at room temperature. If epimerization of IX by the generated benzoic acid accompanied the epoxidation, one would have expected to observe the replacement of ethoxyl by acetoxyl.

It was thought that the observed preferential attack of peracid from the side opposite the ethoxyl substituent in *trans* VII might be turned to good advantage by substituting acetyl hypobromite for the peracid. Assuming the primary factor responsible for the direction of peracid attack on *trans* VII is steric in origin, the positive bromine initiating the attack[27] would then approach predominantly from the side opposite ethoxyl, and *trans* opening[28] of the resulting bromonium ion would yield an acetoxy bromide which, on base treatment, would give, as the major product, the epoxide of opposite configuration to that predominantly obtained with peracid, and one which is configurationally correct for opening to desosamine.

In actual fact, reaction of a mixture of *cis* and *trans* VII with acetyl hypobromite in carbon tetrachloride and subsequent base treatment of the resulting acetoxy

(21) D. S. Noyce and L. J. Dolby, *J. Org. Chem.*, **26**, 3619 (1961).

(22) J. T. Edwards, P. F. Morand, and I. Puskas, *Can. J. Chem.*, **39**, 2069 (1961), and references cited there.

(23) P. D. Bartlett, *Record Chem. Progr.* (Kresge-Hooker Sci. Lib.), **11**, 47 (1950).

(24) C. A. Coulson, "Valence," Oxford University Press, London, 1952, p. 209.

(25) See H. B. Henbest, *Proc. Chem. Soc.*, 159 (1963), for a review of his work relating to the directive effects of substituents on additions to cyclic olefins.

(26) Since the question of the relative size of hydrogen *vs.* a pair of electrons is unsettled [A. R. Katritzky, *et al.*, *J. Chem. Soc.*, 2637 (1962), and references cited therein], the relative steric environment above and below the ring plane cannot be assessed. It is assumed, for purposes of discussion, that there is little, if any, difference between them.

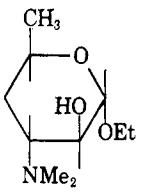
(27) See W. A. Waters, "Organic Chemistry: An Advanced Treatise," Vol. IV, H. Gilman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1953, p. 1230.

(28) G. E. McCasland and E. C. Horswill, *J. Am. Chem. Soc.*, **76**, 1654 (1954).

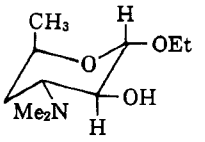
bromide mixture gave a mixture of four components, A, B, C (identical with A, B, and C obtained from peracid treatment of VII), and D (highest retention time, not previously obtained). The ratios of A to D and of B to C remained approximately 1:1, while the relative amounts of A (or D) to B (or C) varied depending on the *cis–trans* ratio of VII. These results may be explained by a nonselective attack of *cis* VII as a common precursor leading to A and D and of *trans* VII as a precursor to B and C.

The nonselectivity of the acetyl hypobromite reaction is compatible with the extreme rapidity (in contrast to the peracid reaction) with which it occurs.[29a]

Treatment of the epoxide mixture IX obtained from perbenzoic acid oxidation of VII with saturated aqueous dimethylamine gave, after recrystallization of the initially obtained oily solid from petroleum ether (b.p. 30–60°), a crystalline dimethylamino alcohol, m.p. 42.5–45.5°. Its hydrolysis product rapidly consumed a molar equivalent of periodate. [The hydrolysis product of the material obtained from the petroleum ether mother liquor (40% of the total dimethylamino alcohol) consumed 0.73 of a molar equivalent.] The n.m.r. spectrum of the compound, m.p. 42.5–45.5°, showed a single doublet centered about τ 5.43 (J_{12} = 6.1 c.p.s.) due to the proton at C-1. Comparison of its n.m.r. spectrum with that of authentic ethyl desosaminide (IIa, 3:1 mixture of α- and β-anomers from extrapolation of the composition of the epoxide mixture obtained from it) indicated that the synthetic material contained *no* α-ethyl desosaminide, the latter showing a single doublet centered about τ 5.07 (J_{12} = 3.6 c.p.s.). The signal due to the C-1 proton of the β-anomer was obscured by a complex multiplet at higher field and could not be unequivocally assigned. However, since the amount of component A (the only possible precursor of β-ethyl desosaminide) present in the starting epoxide mixture was less than 10%, and since, as will be pointed out, the epoxide corresponding to desosamine reacts with dimethylamine to give roughly a 1:1.5 mixture of 2- and 3-dimethylamino sugar glycosides, the synthetic material, m.p. 42.5–45.5°, could not contain more than 6% of β-ethyl desosaminide.[29a] The compound of m.p. 42.5–45.5° must, therefore, be a 3,4,6-trideoxy-3-dimethylamino sugar glycoside with an *altro* configuration (X). The α-configuration assigned to the ethoxyl substituent in X follows from its formation from component B of epoxide mixture IX. The relatively large value of the C-1–C-2 proton coupling



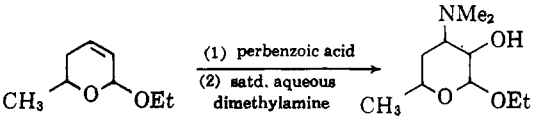
X



Xa

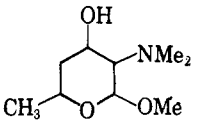
constant (6.1 c.p.s.). is compatible with conformation Xa in which the H-1–H-2 dihedral angle is approximately 180°.[8,12,13,30]

In view of the n.m.r. data which unequivocally establish the structure of the dimethylamino sugar glycoside obtained from perbenzoic acid oxidation of IX as X (possibly contaminated with not more than 6% of β-ethyldesosaminide), it is of interest that Korte and coworkers[9] were able to convert their dimethylamino sugar glycoside, obtained as indicated, which melted at 45° (presumably a purer sample than ours), to a 13%



yield of crystalline 3-dimethylamino sugar hydrochloride, which, on further purification, gave racemic desosamine hydrochloride (I + HCl, unspecified yield) identical (infrared and paper chromatography[31]) with an authentic specimen.

Ring opening of the epoxide IVa obtained by the degradation of ethyl desosaminide (IIa) gave a mixture of 2- and 3-dimethylamino-4,6-dideoxyglycosides XI and IIa in roughly a 1:1.5 ratio. This is in sharp con-



XI

trast to the essentially exclusive opening of the epoxide mixture IX obtained from the peracid oxidation of VII to the 3-dimethylaminoglycoside X. [Since the epoxide mixture IX consisted of 70–75% of component B, the other two components, A and C, being identical with the two anomeric epoxides obtained from desosamine, the consumption of 0.89 equiv. of periodate ($0.6 \times 1.00 + 0.4 \times 0.73$, see above) by the hydrolysate of the dimethylamino alcohol mixture obtained from epoxide IX indicates that component B underwent essentially exclusive attack at C-3.]

The difference in behavior of component B and the epoxide mixture IV obtained from the degradation of desosamine [conformation XII and XIII, respectively (see discussion above)] may be explained on the basis that both electronic factors (attack at the position furthest removed from C-1)[32] and stereoelectronic factors (*trans* diaxial ring opening)[33] favor attack at C-3

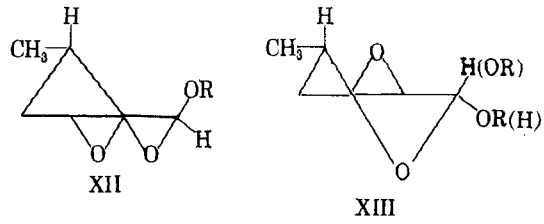
(29) (a) G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955). (b) As noted by a referee, the maximum arithmetic yield possible for β-ethyl desosaminide in the *crystalline* material obtained is 17%. This, however, would require the assumption that the β-ethyl desosaminide is completely insoluble in petroleum ether (solvent of crystallization, see Experimental). It has been our experience that the petroleum ether (and other solvent) solubilities of the anomeric mixture of ethyl glycosides obtained from desosamine and the ethyl glycoside X are quite similar. It is our feeling, therefore, that, while the 17% figure is arithmetically possible, the 6% figure has the advantage of being both arithmetically possible and physically probable.

(30) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); R. U. Lemeiux, J. Stevens, and R. Fraser, *Can. J. Chem.*, **40**, 1955 (1962).

(31) We found essentially identical R_f values for X methiodide and ethyl desosaminide methiodide (0.42 and 0.43, respectively) on Whatman No. 1 paper with the upper phase of a *n*-butyl alcohol–ethanol–water mixture (4:1:5) as the developing solvent.

(32) This is in accord with previous observations on the direction of ring opening of epoxides containing polar substituents [R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959)].

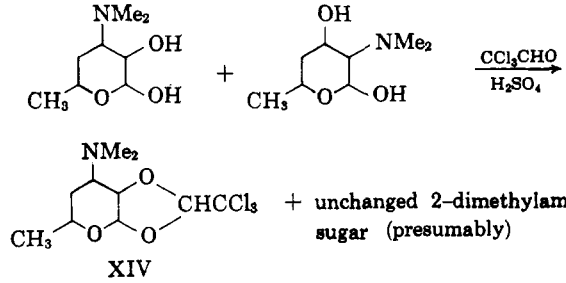
(33) D. H. R. Barton and R. C. Cookson, *Quart. Rev.*, **10**, 44 (1956).



XII XIII

in XII, whereas, in XIII, the favorable electronic effect for attack at C-3 is counteracted by an unfavorable stereoelectronic effect (diequatorial opening). Component B is, therefore, attacked exclusively at C-3 while IV undergoes attack at both C-2 and C-3.

The mixture of 2- and 3-dimethylamino-4,6-dideoxyglycosides obtained from the epoxide mixture IVb could be separated by treating its hydrolysis product with chloral in the presence of concentrated sulfuric acid at room temperature. Only the 3-dimethylamino sugar



XIV

+ unchanged 2-dimethylamino sugar (presumably)

(desosamine) formed a trichloroethylidene derivative XIV, which was identical with that formed from authentic desosamine.

The trichloroethylidene derivative XIV was converted to methyl desosaminide in refluxing methanolic hydrogen chloride; XIV was, however, unaffected by conditions which readily hydrolyze isopropylidene and benzylidene derivatives.[34]

The hydrolysate obtained from the reaction of the 2- and 3-dimethylamino-4,6-dideoxyglycoside mixture with dilute hydrochloric acid deposited a 5% yield of desosamine hydrochloride (I + HCl) from ethanol–ether–acetone, in the cold, identical (melting point, mixture melting point, optical rotation, and infrared spectrum) with an authentic sample.

Experimental[35]

Ethyl Desosaminide (IIa). **A.**—The procedure of Flynn, *et al.*,[36] was followed. A solution of 7.8 g. (0.037 mole) of desosamine hydrochloride (obtained as described in ref. 4) in 125 ml. of saturated absolute ethanolic hydrogen chloride was heated under reflux for 17 hr. and evaporated. Chloroform was added to the dark yellow sirupy residue and the mixture was made basic with 10% sodium hydroxide solution to pH 12 (alkacid test paper). The aqueous phase was extracted with chloroform and the combined chloroform extracts were dried and evaporated. The red sirupy residue was distilled *in vacuo* to give 3.7 g. (42%) of ethy desosaminide, b.p. 55–63° (0.1 mm.), lit.[36] b.p. 65–67° (0.2 mm.).

B.—A solution of 21 g. (0.029 mole) of erythromycin[37] in 400 ml. of absolute ethanol was heated under reflux for 2.5 hr. with gaseous hydrogen chloride bubbling through the reaction mixture. (The reaction mixture turned black almost immediately after refluxing began.) The ethanolic hydrogen chloride was removed *in vacuo*, the black residue was dissolved in chloroform, and the chloroform solution was extracted twice with water. The aqueous solution was made basic (pH 11–12) and the resulting turbid solution was extracted with chloroform. Drying and evaporating the chloroform extracts yielded an orange liquid residue which was distilled to give 3.6 g. (61%) of ethyl desosaminide, b.p. 63–64.5° (0.1–0.3 mm.). (The ethanolysis could be conveniently run on six times this scale, ethyl desosaminide being obtained in comparable yield.)

Methyl Desosaminide (IId).—A solution of 4 g. (0.02 mole) of ethyl desosaminide in 100 ml. of saturated methanolic hydrogen chloride was heated under reflux for 2.75 hr., the methanolic hydrogen chloride was evaporated *in vacuo*, and the residue was distilled to yield 3 g. (79%) of methyl desosaminide, b.p. 76–77° (0.7–0.8 mm.), lit.[36] b.p. 61–62° (0.3 mm.).

Anal. Calcd. for $C_9H_{19}NO_3$: C, 57.11; H, 10.12; N, 7.40. Found: C, 56.84; H, 10.09; N, 7.47.

Ethyl Desosaminide Methiodide.—A solution of 3.2 g. (0.016 mole) of ethyl desosaminide prepared as in A in 10 ml. of acetone was cooled in ice–water and 5 ml. (0.08 mole) of methyl iodide was added. After cooling for an additional 3 min., the reaction mixture was permitted to warm to room temperature and kept there for 1 hr. The acetone and excess methyl iodide were evaporated and the partially solid residue was triturated with ethyl acetate to yield 5.2 g. (95%) of the colorless, solid methiodide, m.p. 153–176°.

The analytical sample was prepared by permitting a partial suspension of the methiodide in hot acetone to cool to room temperature. After keeping overnight, the methiodide was collected, washed with two small portions of acetone then ethyl acetate, and dried *in vacuo* overnight, m.p. 186–188°.

Anal. Calcd. for $C_{11}H_{24}INO_3$: C, 38.27; H, 7.00; I, 36.76; N, 4.06. Found: C, 38.31; H, 6.99; I, 37.01; N, 4.14.

Methyl Desosaminide Methiodide.—The procedure used was essentially that employed for the ethyl analog. After evaporating the excess acetone and methyl iodide, the residue was suspended in ethyl acetate. The methiodide began to crystallize within 30–45 min. After standing at room temperature overnight, 5 g. (95%) of methiodide, m.p. 142–148°, was collected.

The analytical sample was prepared by permitting a hot suspension of the methiodide in acetone–ethyl acetate to cool to room temperature and keeping overnight. The collected solid was dried *in vacuo* at 78° for 1 hr., m.p. 148–155°.

Anal. Calcd. for $C_{10}H_{22}INO_3$: C, 36.26; H, 6.69; I, 38.32; N, 4.22. Found: C, 36.95; H, 6.82; I, 38.60; N, 4.42.

2-Ethoxy-3,4-epoxy-6-methyltetrahydropyran (IVa).—A solution of 5 g. (0.014 mole) of ethyl desosaminide methiodide in 100 ml. of water was stirred with silver oxide (from 26 g., 0.15 mole, of silver nitrate) for 23 hr. at room temperature. The silver oxide was removed by filtration, washed with water, and the combined aqueous filtrates were evaporated *in vacuo* below 35°. Final traces of moisture were removed by pumping (vacuum pump) for 3 hr. The light yellow, hygroscopic residual glass was pyrolyzed at 80–170° (15 mm.), the pyrolysate being collected in a Dry Ice-cooled side arm test tube receiver. The pyrolysate was dissolved in ether, washed successively with two small portions of dilute hydrochloric acid, water, and saturated sodium bicarbonate solution, dried, and evaporated to yield 1.2 g. (55%) of nearly colorless, neutral liquid residue. A temperature programmed (25–200°) vapor chromatographic analysis of the product on a 3-ft. 20% DEGS-on-Chromosorb W column (helium flow rate, *ca.* 120 cc./min.) indicated it to be a mixture of two components, A and B (appearing at 140° and 160°, respectively), in a 1:3 ratio which were separately collected (column temperature, 150°; helium flow rate, *ca.* 120 cc./min.): component A (lower retention time), $[\alpha]^{25}D$ −73° (*c* 0.52, chloroform); component B (higher retention time), $[\alpha]^{25}D$ +57° (*c* 0.79, chloroform).

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found for A: C, 60.47; H, 9.15. Found for B: C, 60.45; H, 9.06.

(34) This is presumably due to the electron-withdrawing effect of the trichloromethyl group which makes oxygen protonation and the subsequent cleavage of the oxygen carbon bond more difficult.

(35) Melting points are corrected. Microanalyses are by Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were taken either neat (liquids) or as mulls in Nujol (solids) with a Perkin-Elmer Infracord or 421 spectrophotometer. N.m.r. spectra were determined on a Varian Associates DP60 spectrometer at 56.4 Mc. in deuteriochloroform with tetramethylsilane as an internal standard. Solutions were dried over magnesium sulfate.

(36) E. H. Flynn, M. V. Sigal, P. F. Wiley, and K. Gerzon, *J. Am. Chem. Soc.*, **76**, 3121 (1954).

(37) Kindly supplied by Abbott Laboratories.

The infrared spectra of components A and B were identical with the first and third components, respectively, of the ternary epoxide mixture IX obtained by the synthesis described below.

2-Methoxy-3,4-epoxy-6-methyltetrahydropyran (IVb).—The procedure followed was that outlined for the ethyl analog. The epoxide IVb was obtained in 50% yield and its two components, A′ and B′ (lower retention time and higher retention time components, respectively), present in a 1:1.8 ratio, were separated on a 3-ft. 20% DEGS-on-Chromosorb W column at 150° (helium flow rate, *ca.* 150 cc./min.): component A′, $[\alpha]^{25}D$ −83° (*c* 1.15, chloroform), C-1 proton chemical shift τ 5.25 ($J_{12} \cong 0$); component B′, $[\alpha]^{25}D$ +73.3° (*c* 0.81, chloroform), C-1 proton chemical shift τ 5.09 (J_{12} = 2.5 c.p.s.).

Anal. Calcd. for $C_7H_{12}O_3$: C, 58.31; H, 8.39. Found for A′: C, 58.58; H, 8.75. Found for B′: C, 58.44; H, 8.61.

Reaction of 2-Ethoxy-3,4-epoxy-6-methyltetrahydropyran (IVa) with Dimethylamine.—A solution of 0.46 g. (0.003 mole) of IVa in 10 ml. of saturated aqueous dimethylamine was heated at 75–80° for 18 hr. The colorless reaction mixture was diluted with water, thoroughly extracted with chloroform, and the chloroform extracts were dried and evaporated. The residue obtained was distilled to yield 0.4 g. (66%) of a colorless liquid, b.p. 85–90° (bath temperature) at 0.3 mm. The 3000–2700- and 1500–1000-cm.$^{-1}$ regions of its infrared spectrum were essentially identical with that of authentic ethyl desosaminide; the 1000–600-cm.$^{-1}$ region in the two were, however, different.

Anal. Calcd. for $C_{10}H_{21}NO_3$: C, 59.08; H, 10.41; N, 6.89. Found: C, 58.81; H, 10.18; N, 6.76.

Hydrolysis of the Product Obtained from IVa and Dimethylamine. Periodic Acid Titration of the Hydrolysate.—A solution of 0.29 g. (0.0014 mole) of the dimethylamino alcohol in 2 ml. of 2 *N* hydrochloric acid was heated on the steam bath for 20 min.[9] and evaporated to dryness at room temperature (high vacuum pump, Dry Ice-cooled rotary trap). The residue was evacuated (under high vacuum) over potassium hydroxide for 2 hr. at room temperature, triturated with anhydrous ether, and then evacuated (high vacuum) over potassium hydroxide at room temperature for 3 days to yield 0.31 g. of a colorless glass. Approximately 0.275 g. of this material was dissolved in a small amount of ethanol and ether was added until the solution became turbid. After standing overnight at −10°, a colorless solid separated accompanied by an oil. The oily substance was dissolved by the addition of a small amount of acetone, and, after an additional 4 hr. at −10°, the solid was collected and dried *in vacuo* at 100° for 5 hr., yielding 13 mg. (*ca.* 5%), m.p. 178–179° dec.; mixture melting point with an authentic specimen of desosamine hydrochloride (recrystallized from ether–ethanol–acetone, m.p. 178–179° dec.) was 175.5–178° dec.; $[\alpha]^{25}D$, authentic desosamine hydrochloride, +61.5° (*c* 1.32, ethanol); $[\alpha]^{25}D$, "synthetic" desosamine hydrochloride, +63.7° (*c* 0.66, ethanol).

The hydrolysate (17.0 mg., 8.1×10^{-5} mole) obtained was dissolved in 1 ml. of 0.5 M sodium periodate solution (pH of reaction mixture *ca.* 4) and four 50-λ aliquots were assayed by titration with 0.02 *N* arsenious oxide[38] at the intervals indicated in Table I.

TABLE I

Time	15 min.	150 min.	4 days
As_2O_3 consumed by blank (av. value), ml.	2.410		2.405
As_2O_3 consumed by sample (av. value), ml.	2.150	2.177	1.987
Moles of IO_4^-/mole of compound consumed	0.64	0.57	1.03

Since desosamine hydrochloride is reported[36] to consume 2 molar equiv. of periodate in weakly acidic solution, the first rapidly and the second slowly, the consumption of a total of 1 molar equiv. of periodate by the hydrolysate would appear to indicate that the 2-dimethylamino sugar component is unaffected under the conditions employed, perhaps owing to the formation of an unreactive 1,3-cyclic periodic acid ester.

1,2-O-Trichloroethylidene Desosaminide.—To a suspension of 1.0 g. (0.0047 mole) of desosamine hydrochloride in 10 ml. of chloral was added 2 ml. of concentrated sulfuric acid. In quick succession the desosamine hydrochloride dissolved, the solution became turbid, then cleared. After stirring for 4.5 hr., the excess chloral was removed under reduced pressure at *ca.* 35°, and the residue was partitioned between methylene chloride and 2 *N* sodium hydroxide solution. The methylene chloride extracts were washed, dried, and evaporated to yield 1.2 g. (84%) of the trichloroethylidene derivative as a pale yellow, fairly viscous liquid which slowly solidified on standing. The compound was purified by evaporative distillation, two fractions being collected. The first distilled at 50–65° (0.005 mm.), and the second at 65–75° (0.005 mm.). Both fractions solidified on the cold finger of the molecular still (it was necessary to interrupt the distillation to collect the first fraction). The first melted at 49–57° (softening at *ca.* 44°) and the second at 53–61° (softening at *ca.* 44°). (The infrared spectra of the two fractions were virtually identical.) A sample of the second fraction was submitted for analysis.

Anal. Calcd. for $C_{10}H_{16}Cl_3NO_3$: C, 39.43; H, 5.30; Cl, 34.92; N, 4.60. Found: C, 39.26; H, 5.19; Cl, 35.03; N, 4.57.

Reduction of the reaction time to 1 hr. gave the trichloroethylidene derivative in 70% yield.

Methiodide was prepared by treating a solution of the trichloroethylidene derivative in acetone with excess methyl iodide for 0.5 hr. at room temperature. The solid, m.p. 218–224° dec., obtained by evaporating the acetone and excess methyl iodide, was purified by heating in boiling acetone, cooling, and filtering. The solid obtained melted at 231–237° dec.

Anal. Calcd. for $C_{11}H_{19}Cl_3INO_3$: C, 29.58; H, 4.29; N, 3.14. Found: C, 29.78; H, 4.23; N, 2.99.

Methanolysis of 1,2-O-Trichloroethylidene Desosaminide.—A solution of 1.05 g. (0.0034 mole) of the trichloroethylidene derivative in saturated methanolic hydrogen chloride was heated under reflux for 19 hr. and the excess solvent was removed *in vacuo*. The residue was taken up in water and the aqueous solution was washed with methylene chloride, made basic (pH 12–13) with 2 *N* sodium hydroxide solution, and extracted with methylene chloride. The methylene chloride extracts were washed, dried, and evaporated to yield 0.55 g. (85%) of product identical with methyl desosaminide as indicated by comparison of its infrared spectrum and that of its methiodide with those of authentic specimens.

When the reflux time was reduced to 2.5 hr., only partial conversion to methyl desosaminide was observed (infrared analysis).

Attempted Room Temperature Hydrolysis of 1,2-Trichloroethylidene Desosaminide.—The optical rotation of a 1% solution of the trichloroethylidene derivative in 6 *N* hydrochloric acid was unchanged after 20 hr. at room temperature.

Reaction of 2-Methoxy-3,4-epoxy-6-methyltetrahydropyran (IVb) with Dimethylamine Followed by Hydrolysis.—A solution of 0.32 g. (0.002 mole) of IVb in 8 ml. of saturated aqueous dimethylamine was kept at room temperature for 26 hr. and evaporated under reduced pressure. A colorless, basic liquid residue (0.23 g., 53%) was obtained which was hydrolyzed directly with 2 ml. of 2 *N* hydrochloric acid on a steam bath for 20 min.[9] Evaporation of the aqueous solution to dryness *in vacuo* left a colorless residue which was kept under high vacuum over potassium hydroxide at room temperature for 48 hr. to yield 0.25 g. of a colorless glass. The material rapidly (within 30 min.) consumed roughly 0.5 molar equiv. of periodate, in reasonably good agreement with previous results (see above).

Reaction of the Hydrolysate with Chloral.—A suspension of 0.184 g. (8.7×10^{-4} mole) of the hydrolysate obtained in the previous experiment in 2 ml. of chloral was treated with 0.4 ml. of concentrated sulfuric acid. After stirring the reaction mixture for 1 hr., it was worked up as described under "1,2-O-Trichloroethylidene Desosaminide." The 0.16 g. of crude liquid product obtained was converted to its methiodide, m.p. 237–240° dec., as described for 1,2-O-trichloroethylidene desosaminide. The methiodides of both authentic and "synthetic" trichloroethylidene desosaminide were recrystallized by partially dissolving in hot acetone, cooling, and permitting most of the acetone to evaporate slowly at room temperature. The infrared spectra of the two were identical.

1,1-Diethoxy-5-hydroxyhexyne-2 (VI).—To a stirred solution of 97.9 g. (0.76 mole) of propiolaldehyde diethyl acetal[17] in 1.5 l. of anhydrous ether under nitrogen was added, rapidly, 487 ml. (0.75 mole) of a 1.6 *M* solution of *n*-butyllithium in hexane (Mineral Foote Co.). The addition of roughly the last 60 ml. of the butyllithium solution was accompanied by an abrupt color change in the reaction mixture from orange to dark brown. After stirring and heating under reflux for 1.25 hr., 87 g. (1.5 moles) of commercial grade propylene oxide was added rapidly

(38) H. Willard and L. Greathouse, *J. Am. Chem. Soc.*, **60**, 2869 (1938).

followed by an additional 100 ml. of anhydrous ether, and stirring and refluxing under nitrogen was continued for 16 hr. The cooled reaction mixture was washed with water until neutral (three washings), dried, and evaporated to yield 114 g. of a dark brown liquid which was distilled *in vacuo*. After a 1.6-g. forerun, 89 g. (61%) of 1,1-diethoxy-5-hydroxyhexyne-2 was collected, b.p. 84–86° (0.1–0.2 mm.), $n^{25}D$ −1.4493. The analytical sample had b.p. 95–96° (0.5 mm.), $n^{25}D$ −1.4531, ν_{max}^{film} 2.80 (m) and 4.97 μ (w).

Anal. Calcd. for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.40; H, 9.94.

1,1-Diethoxy-5-hydroxyhexene-2 (VIII).—A solution of 5 g. (0.027 mole) of 1,1-diethoxy-5-hydroxyhexyne-2 in 50 ml. of hexane was hydrogenated over 0.5 g. of 10% palladium on charcoal in a Parr apparatus (initial pressure, 17 p.s.i.) until a molar equivalent of hydrogen (*ca.* 2.5 p.s.i.) was consumed (5 min., the reaction was moderately exothermic). The catalyst was removed by filtration and the hexane filtrate was evaporated to yield a 4.8-g. liquid residue which was distilled *in vacuo* to give 4.1 g. (80%) of 1,1-diethoxy-5-hydroxyhexene-2, b.p. 58–65° (0.2 mm.). The analytical sample had b.p. 60–62° (0.1 mm.), $n^{25}D$ −1.4572, ν_{max}^{film} 2.8 and 6.01 μ.

Anal. Calcd. for $C_{10}H_{20}O_3$: C, 63.79; H, 10.71. Found: C, 63.93; H, 10.86.

The reduction was also effected using Lindlar catalyst.[39] However, both catalysts behaved erratically, the product of the reduction being, in some cases, the cyclic olefin, 2-ethoxy-6-methyl-5,6-dihydro-2H-pyran (VII). This is attributed to the fortuitous presence of traces of acid in the system. Indeed, when the reduction was conducted in the presence of a trace of quinoline (the catalyst actually used in those experiments was the Lindlar catalyst; however, it is felt that 10% palladium on charcoal would behave similarly), the acyclic olefin VIII was obtained consistently.

2-Ethoxy-6-methyl-5,6-dihydro-2H-pyran (VII). A.—A cooled solution (the reduction was moderately exothermic) of 14.2 g. (0.076 mole) of 1,1-diethoxy-5-hydroxyhexyne-2 in 80 ml. of hexane was hydrogenated over 1.4 g. of palladium on charcoal in a Parr apparatus (initial pressure, 10 p.s.i.) until a molar equivalent of hydrogen (*ca.* 7 p.s.i.) was consumed (30 min.). After shaking for an additional 15 min. (the pressure gage had dropped to zero by this time), 5 drops (Pasteur pipet) of concentrated hydrochloric acid was added and shaking was continued for 0.75 hr. The catalyst was removed by filtration, the filtrate was evaporated, and the yellow liquid residue was rapidly distilled at 25–30° (0.2 mm.), the distillate (4.2 g.) being collected in a Dry Ice-cooled receiver. This procedure was repeated with five 14.2-g. samples of 1.1-diethoxy-5-hydroxyhexyne-2, the yields of crude, colorless distillate ranging between 39 and 54%. The combined distillates were redistilled *in vacuo* (foaming), three fractions being collected: fraction 1 (0.25 g.), b.p. 25–72° (40 mm.), $n^{25}D$ −1.4321; fraction 2 (22 g.), b.p. 72–76° (40 mm.), $n^{25}D$ −1.4321; and fraction 3 (2.6 g.), b.p. 76–81° (40 mm.), $n^{25}D$ −1.4338. Fraction 1 was discarded. Fractions 2 and 3 represented a combined yield of 39%; their infrared spectra were practically identical.

The vapor phase chromatogram of fraction 2 on a 3-ft. 20% DEGS-on-Chromosorb W column at 65° (injection port temperature, 50°) with helium as the carrier gas showed a single broad peak accounting for *ca.* 85% of the total material in the chromatogram along with four other minor components. Conduction of the vapor chromatography at higher column and injection port temperatures (135 and 120°, respectively) resulted in decomposition (probably partial) of the compound.

Anal. of fraction 2. Calcd. for $C_8H_{14}O_2$: C, 67.57; H, 9.93. Found: C, 68.12; H, 10.22.

The major component in the vapor chromatogram of fraction 2 was collected (rechromatography indicated it to be ≥95% pure) and submitted for analysis (Found: C, 67.80; H, 10.50).

A still more acceptable analysis was obtained on a sample of VII, b.p. 71–74° (37 mm.), $n^{25}D$ −1.4348, prepared by the same procedure in another experiment (Found: C, 67.45; H, 10.06). The infrared spectra of the three analytical samples were essentially identical.

In one experiment, the cyclic olefin VII was obtained directly from the hydrogenation of VI (35.8 g., 0.19 mole) over 10% palladium on charcoal (3.5 g.), although no acid was added to effect ring closure. The crude product obtained in this experiment was separated into two fractions by distillation *in vacuo*, the first, b.p. 57–61° (17 mm.), 11.6 g., and the second, b.p. 25–30° (0.5 mm.), 3.3 g. The infrared spectra of the two were practically identical.

B.—To a solution of 2.5 g. (0.02 mole) of benzoic acid in 50 ml. of chloroform over magnesium sulfate (the solvent was kept over the drying agent for 1.5 days prior to use) was added 15 g. (0.08 mole) of 1,1-diethoxy-5-hydroxyhexene-2. After 25 hr. at room temperature, the magnesium sulfate was removed by filtration and more chloroform added; the solution was washed twice with dilute sodium hydroxide solution, dried, and evaporated. The yellow liquid residue was distilled *in vacuo* (foaming) to yield 6.25 g. (56%) of VII, b.p. 54–58° (17 mm.). The infrared spectrum of the material obtained was essentially identical with that prepared by the catalyst–hydrochloric acid cyclization method A.

2-Ethoxy-3,4-epoxy-6-methyltetrahydropyran (IX). A. Peracid Oxidation of VII.—A solution of 2.1 g. (0.015 mole) of VII in 50 ml. of 0.61 *M* perbenzoic acid[40] (0.03 mole) in benzene (93% peracid) was kept at room temperature for 8 days. The essentially colorless reaction mixture was poured into methylene chloride and the excess peracid was removed by washing with 2 *N* sodium hydroxide solution (two washings). The organic phase was washed with saturated salt solution, dried, and evaporated to yield a colorless liquid residue which was distilled *in vacuo* to give 2.1 g. (90%) of IX as a colorless liquid, b.p. 77–78° (7 mm.), $n^{25}D$ −1.4390.

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.63; H, 8.87.

With another preparation of perbenzoic acid (0.54 *M*, 84% peracid), VII was converted to IX in 2 days, at room temperature, in 56% yield.

Using *m*-chloroperbenzoic acid (FMC Corp.), VII was converted to IX in 2 days and 8 days at room temperature in yields (crude) of 68 and 77%, respectively. The composition of IX obtained with both peracids was the same.

The vapor chromatogram of the epoxide IX (3-ft. 20% DEGS-on-Chromosorb W column at 150°; injection port temperature, 150°; carrier gas, helium at *ca.* 150 cc./min.) indicated it to be a mixture of three components, A, B, and C (in order of increasing retention times between roughly 1–2 min.). The ratio of A to B varied between 1:30 and 1:5 in various preparations of IX using different preparations of VII obtained by either method A or B. In the case of IX obtained from fraction 2 of VII prepared by reduction of VI *without* the addition of acid (see above), the A–B ratio was inordinately low, being 1:1.5. The B–C ratio, on the other hand, varied between 3.5:1 and 2.5:1 (the B–C ratio in the case in which A–B was 1:1.5, was 2.5:1).[20]

The three components were separated and collected by vapor chromatography (column and conditions employed were essentially the same as for analysis). The infrared spectra of components A and C were identical with the β- and α-anomers, respectively, of epoxide IVa.

B. Reaction of VII with Acetyl Hypobromite Followed by Base.—To an acetyl hypobromite solution prepared by adding 0.18 ml. (0.0035 mole) of bromine to a stirred, cooled (0 to 2°) suspension of 0.66 g. (0.004 mole) of silver acetate in 10 ml. of carbon tetrachloride and stirring for an additional 10 min., was added a solution of 0.5 g. (0.0035 mole) of VII (fraction 2 of the material obtained from the palladium-on-charcoal reduction of VI *without* added acid, see above)[41] in *ca.* 2 ml. of carbon tetrachloride dropwise with stirring at 0–3° (reaction was exothermic). After the addition was complete, the reaction mixture was stirred at 0° for 15 min. and then permitted to warm to room temperature with stirring (*ca.* 15 min.). (A reaction mixture color change from yellow-orange to light yellow accompanied the addition of VII.) The silver salts were removed by filtration and the filtrate was poured into methylene chloride. The organic solution was washed with dilute sodium bisulfite solution and water, dried,

(39) H. Lindlar, *Helv. Chim. Acta*, **35**, 446 (1952).

(40) L. Silbert, E. Siegel, and D. Swern, *J. Org. Chem.*, **27**, 1336 (1962). The yield of perbenzoic acid reported could not be reproduced using the quoted ratio of peroxide to benzoic acid, but was obtained when the ratio was increased to 3:1 (see Table II, *loc. cit.*).

(41) This particular sample is singled out, since, as already noted, its epoxidation with peracid gave an exceptionally large amount of component A relative to that obtained in other preparations of VII, thus indicating it to be inordinately rich in *cis*[18] isomer. It would, therefore, be expected that the fourth possible epoxide, which would be isomeric with component A with respect to the configuration of the oxide ring, would also be formed in relatively large amount, since it too must necessarily arise from *cis* VII.

and evaporated. A colorless liquid residue (0.9 g.) was obtained which showed strong carbonyl absorption at 5.72 μ in the infrared.

The analytical sample of the acetoxy bromide prepared in a similar manner using a sample of VII from another preparation had b.p. 78° (0.2 mm.), $n^{25}D$ −1.4662.

Anal. Calcd. for $C_{10}H_{17}BrO_4$: C, 42.72; H, 6.01; Br, 28.43. Found: C, 42.70; H, 6.08; Br, 28.43.

Treatment of the 0.9 g. of crude acetoxy bromide obtained with 5 ml. of 5% methanolic potassium hydroxide at room temperature for 1.83 hr., followed by pouring the reaction mixture into methylene chloride, washing the organic solution with saturated salt, drying, and evaporating, yielded a 0.35-g. yellow liquid residue. Its infrared spectrum showed no carbonyl absorption and its vapor phase chromatogram on a 3-ft. 20% DEGS-on-Chromosorb W column at 150° (injection port temperature, 150°; helium flow rate, *ca.* 150 cc./min.) showed four peaks between roughly 1–2 min. (The amount of material in this region represented 35–40% of the total material in the chromatogram, the rest being of higher (≥3 min.) retention times. The two major peaks (≥90%), present in roughly equal amounts at retention times 0.95 and 1.6 min., corresponded to components A and C, respectively, of epoxide mixture IX obtained by method A, as indicated by comparison of their respective retention times and infrared spectra. Of the two minor components also present in roughly equal amounts, one, at retention time 1.2 min., was identical (infrared spectrum, v.p.c. retention time) with component B of IX obtained by method A, while the second, at retention time 2.0 min., component D, was not observed in any of the preparations of IX by method A.

The crude product (100 mg.) obtained from the room temperature base treatment was heated under reflux in 2 ml. of 2% methanolic potassium hydroxide, and the reaction mixture was worked up as already described. The vapor chromatogram of the product (70–75% of which consisted of the four epoxides) now showed greatly enhanced intensity in the peaks corresponding to components B and D, all four, A, B, C, and D, now being present in roughly equal amounts. The increase in intensity of the B and D component peaks was accompanied by the essential disappearance of a peak at retention time 5.2 min. present in the product from the room temperature base treatment, which presumably corresponds to the bromohydrin precursors of B and D.

Component D was collected (column and conditions used were the same as for analysis except that the column temperature was decreased to 125°) and its infrared spectrum was measured. As indicated by its infrared spectrum, component D is very largely an epoxide (ν_{max}^{neat} 2974 cm.$^{-1}$, strong). The broad absorption observed in the hydroxyl region is due, in large part, to water as indicated by the considerable reduction in the intensity of this absorption when the spectrum was measured with compensation for water. However, there is also some hydroxyl-containing material (compensated spectrum still showed absorption in this region) which is perhaps due to product resulting from ring opening of the epoxide mixture with methoxide.

Because of the paucity of material, component D was analyzed as part of a 1:1 mixture of components C and D collected as one fraction.

Anal. Calcd. for $C_8H_{14}O_3 \cdot 0.5H_2O$: C, 57.63; H, 9.03. Found: C, 56.82; H, 8.92.

Since its infrared spectrum and analytical data (Found: C, 60.35; H, 8.98. $C_8H_{14}O_3$ requires C, 60.74; H, 8.92.) indicate no water to be associated with the previously isolated component C, it would appear reasonable to assume that the water indicated to be present in the 1:1 C–D mixture is associated with D, the analytical data being in reasonable accord with a monohydrate formulation.

Samples of VII from other preparations behaved similarly towards acetyl hypobromite followed by base, except that, in accord with expectation based on the epoxidation of these samples with peracid, components A and D constituted less than 10% of the epoxide mixture.

When fraction 1 of the material obtained from palladium-on-charcoal reduction of VI *without* added acid (see above) was treated with acetyl hypobromite in a similar manner followed by heating the resulting acetoxy bromide with excess 5% methanolic potassium hydroxide (it has been established that none of the four component epoxides is preferentially destroyed by refluxing 5% methanolic potassium hydroxide), the vapor chromatogram of the epoxide mixture obtained in 40% yield showed only *three* components in roughly equal amounts corresponding to A, B, and C. This was the experiment previously reported[6] by us; we have no explanation for this result.

Attempted Reaction of IX with Glacial Acetic Acid at Room Temperature.—A solution of 100 mg. of IX (obtained by peracid oxidation) in 0.5 ml. of glacial acetic acid was kept at room temperature for 72 hr. and poured into cold 2 *N* sodium hydroxide solution. Extraction with methylene chloride and drying and evaporating the extracts yielded a 100-mg. colorless liquid residue whose infrared spectrum and vapor phase chromatogram were identical with those of starting IX.

Reaction of 2-Ethoxy-3,4-epoxy-6-methyltetrahydropyran (IX) with Dimethylamine.—A solution of 1.85 g. (0.012 mole) of epoxide IX prepared by method A in 15 ml. of saturated aqueous dimethylamine was kept at room temperature for 27 hr. and evaporated. The pale yellow liquid residue (1.7 g.) was distilled *in vacuo* to yield 1.4 g. (58%) of a colorless, basic liquid, b.p. 60–67° (0.1 mm.). The product remained liquid even after 18 hr. at room temperature; however, crystallization was induced by cooling in Dry Ice for *ca.* 5 min. The resulting oily crystalline mass was recrystallized from petroleum ether (b.p. 30–60°, the petroleum ether solution was cooled in Dry Ice for *ca.* 2 min. to induce crystallization). The solid collected melted at 42.5–45.5° after subjection to high vacuum pumping at room temperature for 2 hr.

Anal. Calcd. for $C_{10}H_{21}NO_3$: C, 59.08; H, 10.41; N, 6.89. Found: C, 58.90; H, 10.29; N, 6.89.

Evaporation of the petroleum ether mother liquor left a 0.56-g. basic liquid residue.

Hydrolysis of the Product Obtained from IX and Dimethylamine. Periodic Titration of the Hydrolysate.—A solution of 0.225 g. (0.0011 mole) of the amino alcohol in 2 ml. of 2N hydrochloric acid was heated under reflux for 30 min., evaporated to dryness, and the resulting nearly colorless sirup was subjected to high vacuum pumping over potassium hydroxide for 2 days at room temperature. The periodic acid uptake of this material was determined by titrating 50-λ aliquots of a 1-ml. solution of 22.7 mg. of the compound in 0.5 *M* sodium periodate solution (pH of reaction mixture *ca.* 2) with 0.02 *N* arsenious oxide[38] at the intervals indicated in Table II.

TABLE II

	Blank	Sample after 20 min.	Sample after 90 min.
0.02 *N* As_2O_3 consumed (av. of 3 detn.), ml.	2.330	1.807	1.761
Moles of IO_4^-/mole of compound consumed		0.98	1.07

The material isolated from the petroleum ether mother liquor was similarly hydrolyzed and the hydrolysate was assayed for 3-amino sugar content; 73% was present.

Acknowledgment.—We thank Dr. G. Berkelhammer for his continued interest, Dr. J. Lancaster for the n.m.r. spectra, Mr. W. Fulmor for the optical rotation measurements, and Mr. W. Fulmor and Mr. R. Wayne for the infrared spectra.