complete elution of the diglyceride fraction. The alkenyl-acylglycerol fraction contained about 220 μmoles of alkenyl ether (88% yield) and 360 μmoles of ester suggesting that it was 75% pure, the other 25% being diglyceride that was not removed by chromatography.

Preparation of Alkenylglycerol.—To 15 ml. of methanol-chloroform (4:1) containing 198 μmoles of alkenyl-acylglycerol, 1 ml. of water and 1 ml. of 1 N NaOH in methanol were added. This mixture was incubated for 1 hour at 37°; then 25 ml. of chloroform and 7 ml. of water were added. The water layer was discarded. The chloroform layer was evaporated to dryness under nitrogen, the residue dissolved in 10% diethyl ether in petroleum ether, and put on a 20-g. silicic acid column (diameter, = 2 cm.). The column was washed with 100 ml. of 10% diethyl ether, 100 ml. of 25% diethyl ether, 100 ml. of 40% diethyl ether, and the alkenylglycerol was then eluted with about 300 ml. of 60% diethyl ether until the fractions gave a negative test for total aldehyde. The alkenylglycerol fractions were combined, evaporated to dryness, and the residue washed three times with cold hexane, yielding 185 μmoles of alkenylglycerol (93% yield).

Preparation of Alkenylglycolaldehyde and Hexadecylglycolaldehyde.—To 88 ml. of ethanol, containing 99 μmoles of alkenyl-glycerol, were added 20 ml. of 0.01 M NaIO₄ and 2 ml. of 0.1 M potassium phosphate buffer, pH 7.0. The mixture was let stand at room temperature in the dark. The extent of the reaction was determined by the decrease in optical density of the reaction mixture at 300 mμ. When the reaction was 95% complete on this basis (about 4 hours), 160 ml. of chloroform and 30 ml. of water were added. The water layer was discarded. The chloroform layer was evaporated to dryness, the residue dissolved in petroleum ether and put on a 10-g. silicic acid column (diameter, 1.5 cm.). The column was washed with 100 ml. of 1% diethyl ether in petroleum ether and then the alkenylglycolaldehyde was eluted with 100 ml. of 4% diethyl ether. The elution of the alkenylglycolaldehyde was rapidly completed as the column was washed with 100 ml. of 10% diethyl ether. Unreacted alkenyl-glycerol (20 μmoles) was then eluted from the column with diethyl ether. The elution of both these compounds was readily followed by analyzing the tubes for total aldehyde. The yield of alkenylglycolaldehyde was 76 μmoles.

In a similar manner, 16.2 mg. of hexadecylglycerol (51 μmoles) was treated with periodate and isolated by silicic acid chromatography. Although this compound contains no alkenyl ether group, the compound reacts with the fuchsin reagent for aldehydes because of the periodate-produced aldehyde group. About 53 μmoles of hexadecylglycolaldehyde was eluted from the column, based on the total aldehyde analysis.

Preparation of Methyl α-Chlorododecyl Ether.—Dodecanal (56.5 g., 0.307 mole) was dissolved in 60 ml. of hexane in a two-necked flask equipped with a magnetic stirrer. Gaseous HCl was bubbled through this mixture for 1 minute; then 9.8 g. of methanol (0.307 mole) was added dropwise over the next 3 minutes. The HCl ebullition was continued during this addition and for the remaining course of the reaction. No attempt was made to control the temperature during the reaction. Aliquots were removed at various times and analyzed by G.L.C. to determine the extent of reaction. After 40 minutes, 90% of the aldehyde had been converted to the chloro ether which was present in the upper phase of the reaction mixture.

Preparation of Methyl 1-Dodecenyl Ether.—The upper phase from the above reaction was added to 64 g. (0.528 mole) of dimethylaniline and this mixture was heated on the steam-bath for 60 minutes. The mixture was allowed to cool for 2.5 hours, and the upper layer was decanted and filtered. The filtrate was then distilled under a pressure of about 1 mm. Two fractions were collected: fraction 1, 49–60°, was mostly dimethyl-aniline; fraction 2, 60–100° (90 ml. of distillate, mostly collected between 80–100°) contained cis- and trans-methyl 1-dodecenyl ether, dodecanal, dimethylaniline, and dimethylaniline hydrochloride. An air condenser was used during the collection of fraction 2 to permit operation of the condenser at a higher temperature and thereby avoid troublesome gels due to dimethyl-aniline· HCl which tends to sublime at that temperature.

Separation and Purification of cis (VII) and trans (VIII) Methyl 1-Dodecenyl Ethers.—Twenty ml. of fraction 2 was put on a column containing 1600 g. of alumina (column diameter, 4.5 cm.). Elution was carried out as shown in Fig. 1. Fractions 16–52 were combined, concentrated under nitrogen and distilled at 55° under a pressure of 0.045 mm. to obtain the cis isomer. Fractions 57–75 were treated similarly to obtain the trans isomer. The yields were 3.0 g. of VII and 2.9 g. of VIII. Had all of the original distillate, fraction 2, been processed in this way, the over-all yield would be 43%.

Anal.[29] Calcd. for C₁₃H₂₆O: C, 78.68; H, 13.21; OCH₃, 15.67; iodine no., 127.9, Found: for VII: C, 79.0; H, 13.6; OCH₃, 13.2; iodine no., 128. For VIII: C, 79.3; H, 13.7; OCH₃, 13.7; iodine no., 129.[30]

(29) Elemental analyses were performed by Weiler and Strauss Micro-analytical Laboratory, Oxford, Eng.

(30) Note Added in Proof.—Additional evidence for the cis-alkenyl configuration of beef heart plasmalogen has been provided recently by Norton, et al., J. Lipid Res., 3, 456 (1962).

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Stereospecific Total Synthesis of Two 5-Amino-5,6-dideoxy-DL-hexonic Acids, a Novel Class of Aminosugar Related Compounds[1]

By B. Belleau and Yum-Kin Au-Young

The stereospecific total synthesis of 5-amino-5,6-dideoxy-DL-allonic acid XVII and 5-amino-5,6-dideoxy-DL-gulonic acid XXVI is described. The reaction sequence involves a Diels–Alder condensation between methyl sorbate and 1-chloro-1-nitrosocyclohexane V to give the adduct VI. The structure and configuration of the latter was established by its conversion to the new aminoacid XI and to 6-methyl-3-piperidinol XIII, which was shown to possess the trans configuration by n.m.r. spectroscopy. Hydroxylation of the N-benzoyl-adduct IX with osmium tetroxide followed by hydrolysis and catalytic hydrogenolysis afforded the aminoacid XVII of the allose series. Epoxidation of the N-benzoyladduct IX with peroxytrifluoroacetic acid gave in high yield a 1:1 mixture of the epoxides XIX and XX which were easily separated by crystallization. Reaction of these epoxides with hydriodic gave the pure iodohydrins XXX and XXXI. Structural and configurational assignments to these iodohydrins and the precursor epoxides were made on the basis of the course of the methanolysis of the iodohydrins. Reaction of the epoxides with formic acid gave the diol monoformates XXI and XXII which underwent ready methanolysis to XXIII and XXIV and hydrolysis to a single tetrahydro-1,2-oxazine-carboxylic acid XXV. Hydrogenolysis of the methanolysis products gave an aminoacid XXVI of the gulose series. Treatment of the epoxide XIX with hydrogen chloride in methanol gave the chlorohydrin XXVII, whereas the oxide XX afforded a mixture of the N-debenzoylated chlorohydrin XXVIII and the corresponding lactone XXIX. Spectroscopic properties (infrared and n.m.r.) of several intermediates are reported.

Introduction.—A variety of aminosugars are known to occur in antibiotics,[2] antigenic polysaccharides,[3]

cell wall constituents,[4] etc. The major efforts in their synthesis has dealt with alteration of naturally occurring sugars. Their possible availability by total synthesis appears more remote and constitutes a prob-

(1) This work was supported by the National Research Council of Canada and represents a portion of the thesis submitted by Y.-K. Au-Young in partial fulfillment of the requirements for the M.Sc. degree.

(2) E. E. van Tamelen, Fortschr. Chem. Org. Naturstoffe, 16, 90 (1958); A. B. Foster and D. Horton, Adv. Carbohydrate Chem., 4, 213 (1953); W. G. Overend, Ann. Rep. Chem. Soc. (London), 56, 286 (1959).

(3) K. Heyns, G. Kussling, W. Lindenberg, H. Paulsen and M. E. Webster, Chem. Ber., 92, 2435 (1959).

(4) R. E. Strange and L. H. Kent, Biochem. J., 71, 333 (1959).

lem which has apparently been left unchallenged. Mention should be made, however, that some successful efforts directed at the total synthesis of some carbohydrate related structures have been reported,[5-7] but the method of partial synthesis still constitutes the only practical route. Approach by total synthesis requires for all practical purposes that stereochemical control be achieved in the construction of the four contiguous asymmetric centers normally present in aminosugars. It is the purpose of this communication to describe a novel method of approach which is stereospecific and which gives access to some derivatives of the 5-amino-5-deoxyhexoses, the least studied of the aminohexoses. The most striking feature of our approach lies perhaps in the use of a starting material (sorbic acid) which has no pre-formed asymmetric center.

Method of Approach.—The use of six-membered intermediates in our projected total synthesis was indicated, as they should provide for a much higher degree of stereochemical control than open-chain analogs in the construction of contiguous asymmetric centers. The intermediacy of tetrahydro-1,2-oxazine derivatives (I) appeared best suited to our purposes since this ring system would have cyclohexane-like geometry and would greatly simplify the necessary ultimate transition from cyclic to open-chain geometry owing to the susceptibility of the O–N bond to hydrogenolysis. Several years ago, Dilthey[8] showed that 3,6-dihydro-1,2-oxazines can be obtained through the Diels–Alder reaction of nitrosobenzene with butadiene. This reaction has since been extended to cyclopentadiene by Kresge and Schulz.[9] For our purposes, nitrosobenzene is an unsuitable dienophile because there exist no simple method for the ultimate removal of the N-phenyl substituent in the adducts. This limitation may be circumvented by taking advantage of the dienophilic properties of α-chloronitrosoalkanes (V) which, as shown by Wichterle,[10] lead directly to 3,6-dihydro-1,2-oxazines (II) with an unblocked nitrogen. This interesting extension of the Diels–Alder reaction appeared most attractive for our purposes as it uniquely
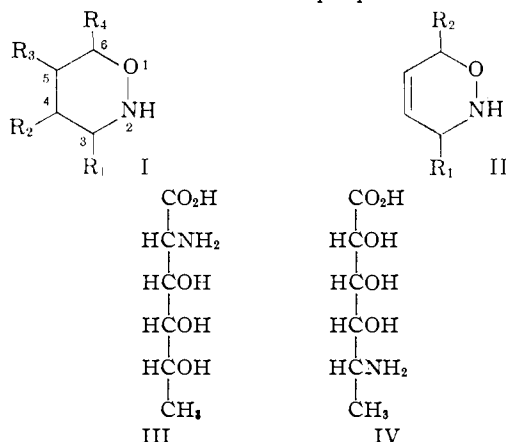
provides *firstly*, for the one-step stereospecific construction of two out of four of the contiguous asymmetric centers normally present in hexosamines and this by virtue of the fact that the Diels–Alder reaction is stereospecific, leading exclusively to *cis*-adducts when the diene has the *trans-trans*-geometry[11]; *secondly*, for

(5) O. Westphal and S. Stern, *Ann.*, **620**, 8 (1959).

(6) M. M. Fraser and R. A. Raphael, *J. Chem. Soc.*, 4280 (1955).

(7) F. Weygand and H. Leube, *Chem. Ber.*, **89**, 1914 (1956).

(8) W. Dilthey, *J. prakt. Chem.*, **156**, 27 (1940); Yu. A. Arbuzov, *Izvest. Akad. Nauk S.S.S.R. Otdel. Khim. Nauk*, 344 (1952).

(9) G. Kresge and G. Schulz, *Tetrahedron*, **12**, 7 (1961).

(10) O. Wichterle, *Collection Czech. Chem. Communs.*, **16**, 33 (1951).

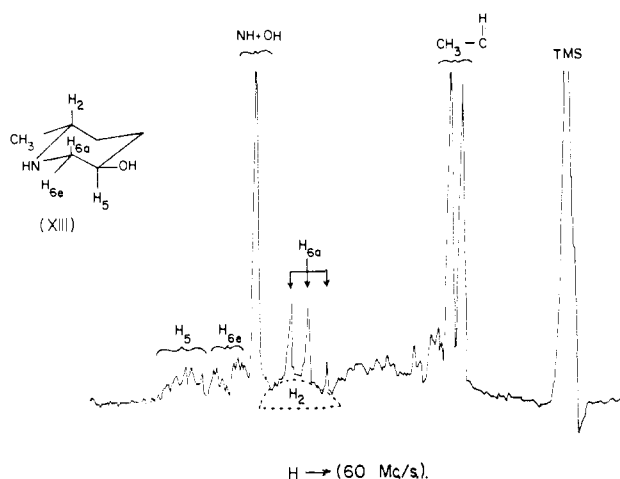(11) G. J. Martin and R. K. Hill, *Chem. Revs.*, **61**, 537 (1961).

Fig. 1.—Spectrum of XIII in chloroform with tetramethylsilane (TMS) as an internal reference.

the introduction in the adduct of two additional functional groups at positions 4 and 5. In view of the probable cyclohexene-like geometry of the adduct II, some degree of stereochemical control may be achieved when attacking the 4,5-double bond with electrophilic reagents; *thirdly*, a potential pathway for the stereoselective synthesis of some or all of the eight possible racemic 5-amino-5,6-dideoxyhexoses or 2-amino-2,6-dideoxyhexoses. The application of suitable equilibration methods to *cis* adducts ought to give an entry into the thermodynamically more stable *trans* series of reduced 3,6-disubstituted-1,2-oxazines, and thus should provide for the preparation of the four racemates not directly derivable from the *cis* adduct.

In order to explore the feasibility of this approach, *trans-trans*-sorbic acid was selected as the diene component and 1-chloro-1-nitrosocyclohexane (V) as the dienophile. An ultimate product resulting from the use of this diene would be a 6-deoxy analog of either a 2-amino-2-deoxy or a 5-amino-5-deoxyhexonic acid (IV or III). Since carbon 5 of sorbate is electrophilic and because the nitrogen of nitrosobenzene can act as an electron donor as evidenced from the course of its dimerization[12] (the resulting dimer having structure (VIII)), one might be justified in expecting that the use

$$C_6H_5N{=}NC_6H_5$$ with two O atoms double-bonded above the N atoms
VIII
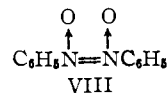
of V with sorbate would result in the formation of adduct VI rather than VII. It does not seem possible to use Wichterle's results[10] as a basis for the prediction of directive effects in this reaction so that it was of some intrinsic interest to ascertain the direction of the addition of V to sorbate.

Discussion of Results.—When 1-chloro-1-nitrosocyclohexane (V) was mixed with sorbic acid in ether–ethanol, reaction did not occur, the starting materials being recovered unchanged. However, substituting methyl sorbate for sorbic acid, a crystalline adduct slowly separated in 70–75% yield after about 10 days at 0°. No reaction occurred, however, when methyl *cis-trans*-sorbate was used. Empirical analysis, infrared (strong peaks at 1740 cm⁻¹ and 1890 cm⁻¹) and n.m.r. spectra (see Experimental) definitely established the gross structural features of the adduct as corresponding to VI or VII; no evidence for the *cis* configuration could be adduced from these data. The adduct was characterized as the N-benzoyl derivative

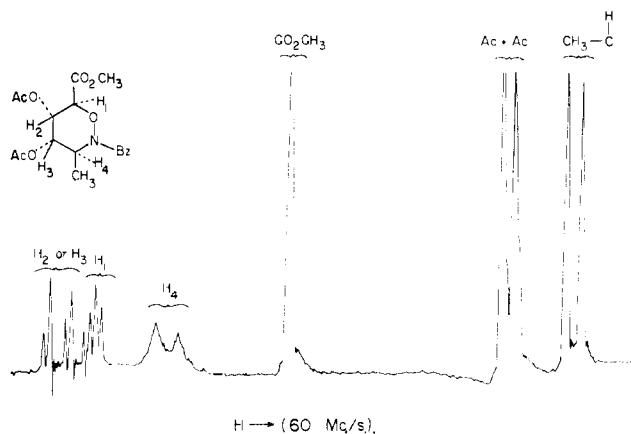(12) B. G. Gowenlock and W. Lütte, *Quart. Revs.*, **12**, 321 (1958).

Fig. 2.—Spectrum of the diacetate of XVI in chloroform; tentative assignment.

IX which gave infrared and n.m.r. spectra in agreement with expectations. That the *cis* adduct VI had resulted was established as follows: catalytic hydrogenation over Adams catalyst led to the rapid uptake of two molar equivalents of hydrogen resulting in the isolation of a crystalline amino acid whose properties agreed with those of an α-hydroxy-δ-amino acid (XI) but not of an α-amino acid. Thus, the amino acid reacted sluggishly with ninhydrin by comparison with the common α-aminoacids, gave only a phenyl ureide and not a hydantoin with phenyl isocyanate and gave pK_1 and pK_2 values of 3.76 and 10.3 instead of 2.0–2.5 and 9.0–9.5 as would be expected if the structure was that of an α-aminoacid. The observed pK's match closely the respective pK's of lactic acid (3.8) and the ε-amino group of lysine (10.5). Finally, the corresponding methyl ester X was smoothly converted to the lactam XII upon heating to 100°, thus conclusively establishing that adduct VI is the sole product of the Diels–Alder reaction. There remained to establish the configuration of the adduct and this could be done by reducing the 6-methyl-3-hydroxy-2-piperidinone (XII) with lithium aluminum hydride and by analyzing the n.m.r. spectrum of the resulting 6-methyl-3-piperidinol (XIII). The spectrum of XIII is shown in Fig. 1 where it can be seen that it is consistent only with a *trans* configuration. For the latter, one would expect[13] J(H$_{6a}$ to H$_{6e}$) = 12 c.p.s., J(H$_{6a}$ to H_5) = 10 c.p.s.; for the alternative *cis* configuration (axial hydroxyl), one should observe J(H$_{6a}$ to H$_{6e}$) = 12 c.p.s. and J(H$_{6a}$ to H$_5$) = 2–4 c.p.s. For H$_{6e}$, in both *cis-* or *trans-* XIII, one would expect J(H$_{ea}$ to H$_5$) = 2–4 c.p.s. From the spectrum (Fig. 1), the following values are obtained: J(H$_{6a}$ to H$_{6e}$) = 10.7 c.p.s.; J(H$_{6a}$ to H$_5$) = 9.2 c.p.s.; J(H$_{6e}$ to H$_5$) = 4.4 c.p.s. It follows that the 6-methyl-3-piperidinol (XIII) has the *trans* configuration and this is possible only if the precursor aminoacid ester has the *erythro* configuration X and the adduct VI the *cis* arrangement. It is of interest to note that it is the nitrogen of the nitroso group of V which acts as the electron donor in the reaction leading to VI and that the stereochemical course of the addition is in line with previous generalizations concerning the Diels–Alder reaction.[11] A stereospecific route to the novel aminoacid XI is therefore provided.

For purposes of comparison and because no tetrahydro-1,2-oxazinecarboxylic acid had as yet been reported, the acid XIV was prepared by catalytic hydrogenation of the N-benzoyl adduct IX, whereupon hy-

drogen uptake stopped after one molar equivalent. Without isolation, the dihydro intermediate was submitted to mild aqueous acid hydrolysis or methanolysis to give the desired *cis*-tetrahydro-1,2-oxazine-3-methyl-6-carboxylic acid (XIV). The infrared spectrum (strong peaks at 1640 cm.$^{-1}$ and 1750 cm^{-1}) agreed with a zwitterionic structure. The pK values of the two dissociating groups (3.0 and 10.2, respectively) indicate some appreciable degree of similarity to the common aminoacids. It will be of interest to examine the metabolism of such novel amino acid related structures.

Having constructed stereospecifically two of the asymmetric centers corresponding to C2 and C5 of hexosamines, there remained to introduce the other two at C4 and C5 of the adduct VI in order to complete the total synthesis. The use of the osmium tetroxide–pyridine complex was indicated for our purposes in view of the usual stereospecificity of its action. Hydroxylation of the N-benzoyl adduct IX by this procedure led in virtually quantitative yield to the *cis*-diol XV which was isolated as the corresponding acid. Attack of the reagent from the least hindered side of the adduct constitutes the only logical steric course for the reaction, an expectation which is well documented in the literature.[14] The diol-N-benzoyl-acid XV was characterized as the methyl ester XVI and methyl ester diacetate. The infrared spectra of these derivatives confirmed the structure, but it must be pointed out that although the n.m.r. spectrum of the diacetate also confirmed the gross structural features it was anomalous in other respects. The spectrum is shown in Fig. 2 and the anomaly rests in the fact that only three of the ring hydrogens give a visible signal. It may be that the fourth hydrogen is masked through interaction with the nitrogen, but no definitive evidence was obtained for this interpretation. Attempts to analyze the n.m.r. spectrum through the use of the methyl ester diacetate deuterated on the carbon alpha to the methoxycarbonyl (prepared from α-deuterated methyl sorbate) were unsuccessful in clarifying this point. Hydrolysis of the diol acid XV under mild conditions followed by hydrogenation over Adams catalyst finally afforded in high yield the aminoacid XVII. Following the carbohydrate nomenclature, this novel structure corresponds to 5-amino-5,6-dideoxy-DL-*allonic* acid (XVII). It should be noted that this is the first time that a 5-amino-5-deoxyhexose related structure becomes available and this through a simple sequence of stereospecific steps. The metabolism of XVII might prove of interest.

In order to gain access to other stereoisomers of XVII, alternative methods of hydroxylation of IX were examined. In theory the *cis*-4,5-diol XVIII epimeric with XVI should be obtainable by hydroxylation with the iodine-silver acetate–wet acetic acid reagent.[15] Several attempts to apply this procedure to the N-benzoyl adduct IX were fruitless, the latter being refractory to the reagent. An indirect approach designed to circumvent this difficulty is described below.

An entry into the 4,5-*trans* series of diols XXV should be provided through epoxidation of the N-benzoyl adduct IX. It was initially observed that the latter was resistant to the action of perbenzoic acid. This lack of reactivity is reminiscent of the failure of 2,5-dimethoxy-2,5-dihydrofuran to consume perbenzoic acid.[16] However, rapid and quantitative epoxidation of IX ensued upon treatment with the more powerful trifluoroacetic acid.[17] However, this reaction completely

(13) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein and W. G. Schneider, *J. Am. Chem. Soc.*, **79**, 1005 (1957); J. A. Pople, W. G. Schneider and H. J. Bernstein, *Can. J. Chem.*, **35**, 1060 (1957). The authors are grateful to Prof. F. A. L. Anet of the Chemistry Department of the University of Ottawa for the interpretation of the n.m.r. spectrum.

(14) E. E. Smissman, J. T. Suh, M. Oxman and R. Daniels, *J. Am. Chem. Soc.*, **81**, 2909 (1959).

(15) R. B. Woodward and F. V. Brutcher, *ibid.*, **80**, 209 (1958).

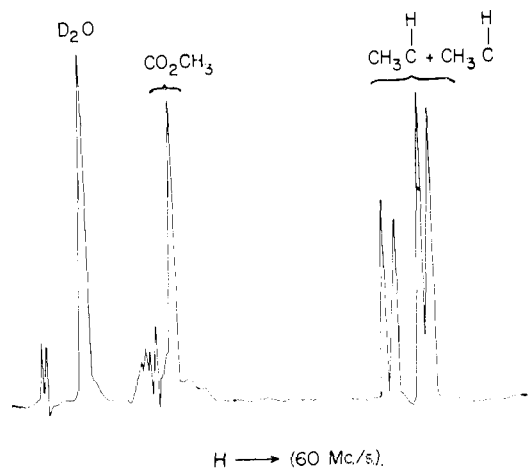(16) J. C. Sheehan and B. M. Bloom, *ibid.*, **74**, 3825 (1952).

Fig. 3.—Spectrum of XXIII + XXIV in D₂O. Peak areas under the methyl doublets and the methyl singlet correspond to a ratio of 1:3.

Fig. 4.—Spectrum of XXVIII + XXIX. Peak areas under the methyl doublets and the methyl singlet correspond to a ratio of 3:1.

lacked stereospecificity, the isomer ratio being 1:1 as ascertained by n.m.r. spectroscopy. This is in marked contrast to the results with osmium tetroxide and the explanation may be that the steric requirements of trifluoroperacetic acid are practically nil due to its much smaller dimensions. Simple crystallization of the mixture from methanol achieved complete separation of the two epimers XIX and XX in good yields. The homogeneity of these isomers was established by n.m.r. spectroscopy which however could not be relied upon for configurational assignments. It was therefore essential to establish their configuration by chemical means, and to this end their reaction with halogen acids as well as the behavior of the resulting halohydrins were examined (see below). In order that the results can be discussed in a logical fashion, the course of the reaction of the epoxides with formic acid will be described first. Brief heating of either epoxide with formic acid readily afforded crystalline mixtures of glycol monoformates. The rule of *trans* diaxial opening[18] cannot be safely applied in the deduction of the structure of the latter because it is not known which conformation the transition state should preferentially adopt. However, on the basis of evidence presented below, reaction with formic acid would lead primarily to XXI and XXII, respectively. Because further changes appeared to be induced by hot formic acid in the primary products, the crystalline mixtures from both epoxides were submitted to acid-catalyzed methanolysis whereupon the *same* crystalline *trans*-diol hydrochloride was obtained in good yield from either diol monoformate. Although the empirical composition of the product supported structure XXIII, the n.m.r. spectrum showed that it consisted of a mixture of two components in the ratio 1:3 (see Experimental). That these two components cannot be simple epimers was evidenced by the fact that the intensity ratio of the C-methyl doublets to the O-methyl singlet of the methoxycarbonyl (Fig. 3) was such that only the minor component could have been a methyl ester. It could be deduced on that basis that the major component was most probably the derived lactone XXIV, the formation of which poses no special theoretical problem. The fact that the empirical composition of this lactone does not differ markedly from that of the methyl ester XXIII and that the crystalline mixture gave rise to two bands at 1750 and 1746 cm.⁻¹ in the infrared supports the conclusion that lactone XXIV is probably the major
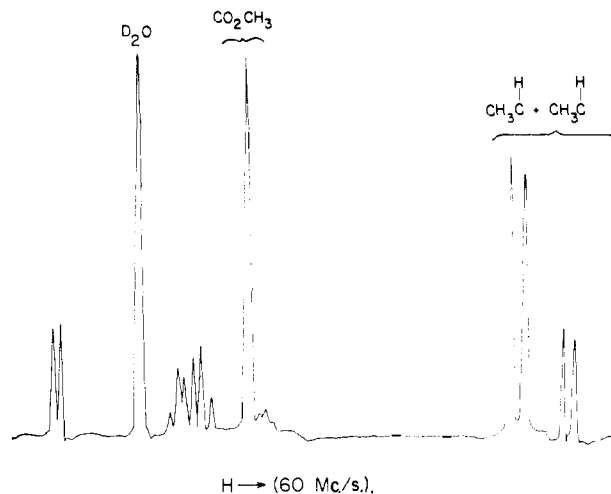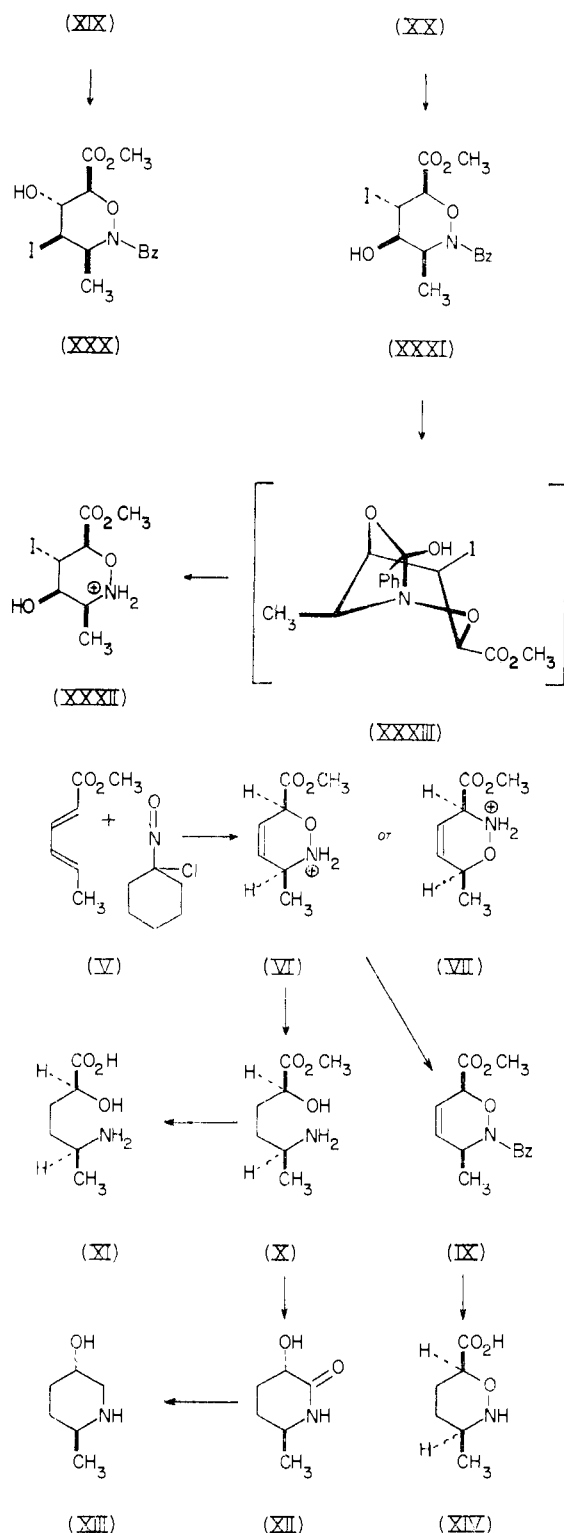
product of the methanolysis reaction. In agreement with this interpretation mild hydrolysis of the mixture gave rise to a single zwitterionic oxazinecarboxylic acid (XXV) (as ascertained by n.m.r.) which was isolated in two crystalline modifications. Catalytic hydrogenolysis of the mixture XXIII + XXIV finally afforded the corresponding trihydroxy-δ-aminoacid XXVI which following the carbohydrate nomenclature may be designated as *5-amino-5,6-dideoxy-*DL*-gulonic acid.*

The formation of the same mixture of products from either glycol monoformate establishes that the isomeric epoxides undergo ring opening at different positions (hence both *trans* - diols have the same configuration), whereas the formation of lactone XXIV requires the configuration XXIII for the diol methyl ester. The positions of attack by formic acid are established if the configurations of the oxides are known. The structures of the latter could be deduced from the course of their reaction with methanolic hydrogen chloride. Whereas the α-epoxide XIX gave rise in high yield to the N-benzoylchlorohydrin XXVII, the β-epimer XX afforded exclusively the N-debenzoylated chlorohydrin under the same conditions. Even though empirical analysis supported formulation XXVIII for the latter, the infrared spectrum exhibited two strong bands at 1770 and 1750 cm.⁻¹ thus suggesting that the isolated crystalline salt consisted of a mixture of the expected methyl ester XXVIII and the corresponding γ-lactone XXIX. The empirical composition of the latter does not differ markedly from that of the methyl ester XXVIII, but n.m.r. spectroscopy clearly confirmed that the salt indeed consisted of a mixture of two components in the ratio 3:1. Moreover, the ratio of the intensities of the methyl doublets (Fig. 4) and the O-methyl peak showed that the latter was 25% lower than the theoretical value. This evidence coupled with the infrared data strongly suggested that the lactone XXIX is produced to the extent of 25% during the course of methanolysis. This may well represent the equilibrium composition of the methanolysis mixture. The formation of lactone XXIX and its corresponding chlorohydrin methyl ester XXVIII establishes the configuration of the oxides as well as the positions of their attack by nucleophiles. Since, as shown above, attack of the epoxides by formic acid involves different positions, it follows that the structure of the glycol monoformates would be correctly represented by XXI and XXII. The resistance of the isomeric chlorohydrin XXVII to undergo debenzoylation under conditions leading

(17) W. D. Emmons and A. S. Pagano, *J. Am. Chem. Soc.*, **77**, 89 (1955).

(18) D. H. R. Barton and R. C. Cookson, *Quart. Revs.*, **10**, 44 (1956);

D. H. R. Barton and J. F. King, *J. Chem. Soc.*, 4398 (1958).

(XIX)   (XX)

(XXX)   (XXXI)

(XXXII)   (XXXIII)

(V)   (VI)   or   (VII)

(XI)   (X)   (IX)

(XIII)   (XII)   (XIV)

(XIX)   (XX)

(XXI)   (XXII)

(XXIII)   (XXIV)

(XXV)   (XXVI)

to loss of the benzoyl group in XXVIII must reflect the operation of a neighboring group participation effect of the type discussed below and confirms the structure assignments to XXVII and XXVIII.

Because iodohydrins were required as potential precursors of the epimeric 4,5-cis-diol XVIII, the action of aqueous hydriodic acid on the epoxides was studied. This reaction proceeded smoothly in the cold and led in virtually quantitative yields to the pure isomeric iodohydrins which were assigned the respective structures XXX and XXXI by analogy with the course of the reactions with hydrogen chloride and formic acid. Confirmation of these assignments was obtained using as a basis the remarkable difference in the reactivity of
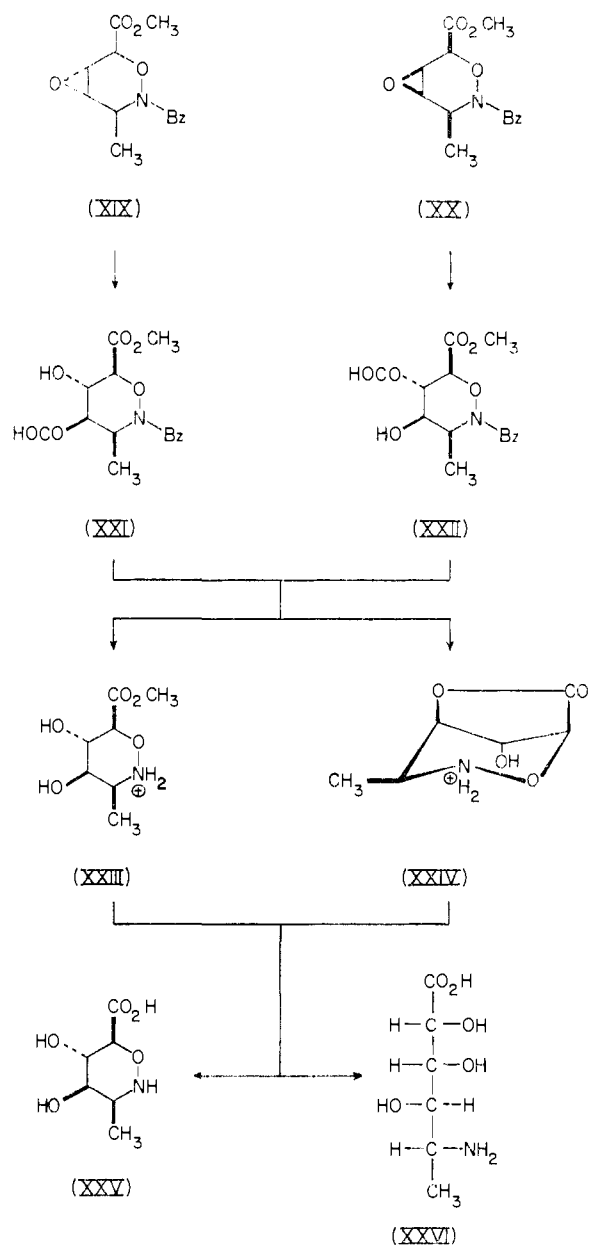
the iodohydrins toward methanolysis. Whereas iodohydrin XXX was left unchanged after treatment with cold methanolic hydrogen chloride, the isomeric XXXI was smoothly converted under the same conditions to the corresponding debenzoylated product XXXII. This latter behavior suggests the operation of a neighboring group participation effect which is commonly described as an N→O acyl migration.[19] Conformational analysis requires N→O benzoyl group migration to take place much more readily from either of the two possible epimeric iodohydrins which can form from the epoxide XX than from either of those from XIX. In the case of iodohydrin XXXI the formation of the required five-membered cyclic intermediate XXXIII is readily accommodated, whereas iodohydrin XXX would require the formation of a six-membered cyclic intermediate. Thus, the experimental results agree with expectations based on the assigned structures and confirm the assignments. A similar interpretation applies to the contrasting behavior of the epoxides toward hydrogen chloride (see above).

(19) G. Fodor and J. Kiss, Nature, 163, 287 (1949); G. Fodor and J. Kiss, J. Am. Chem. Soc., 72, 3495, 5807 (1950); G. Fodor and K. Nador, J. Chem. Soc., 721 (1953).

(XVIII)

(XV, R = H)
(XVI, R = CH₃)

(XVII)

(XIX) ⟶

(XXVII)

(XX) ⟶

(XXVIII)   (XXIX)
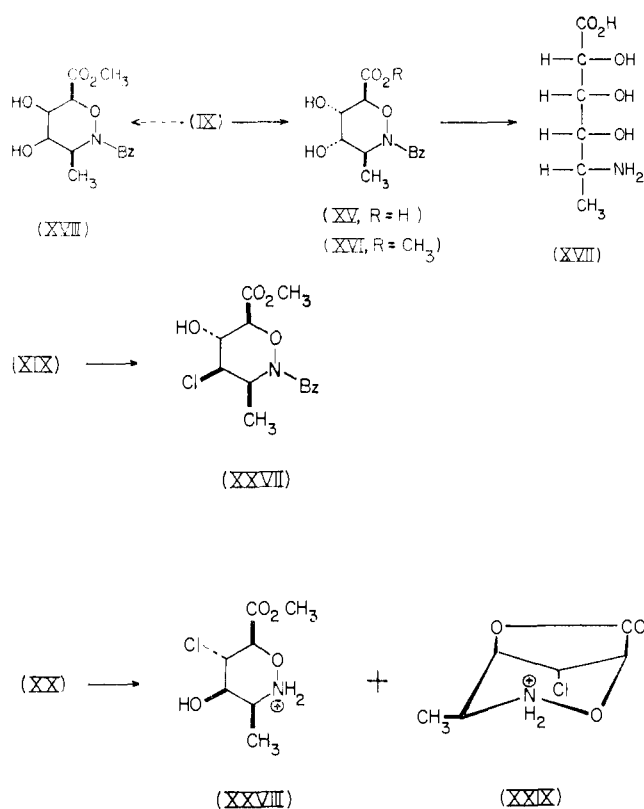
It is worthwhile mentioning that whereas the iodo-hydrin XXX readily gave an O-acetate, the isomeric XXXI gave only the starting epoxide XX under the same conditions, a result which cannot be easily explained. Finally, attempted solvolysis of the iodohydrin acetate derived from XXX in the presence of silver acetate in wet acetic acid led to products which are as yet unidentified.

The configuration assignments to XVII and XXVI should be valid as long as no epimerization of the asymmetric centers took place in the various intermediates. We have verified that some of those transformations which might have been suspected to cause epimerization led in fact to retention of configurational integrity in the products. This was done by carrying such reactions VI → IX and IX → XV → XVII in the appropriate deuterated solvents and analyzing the products for deuterium by n.m.r. No incorporation of deuterium (in stable positions) in the resulting products was noticeable, thus suggesting that epimerization may not be a complicating factor in the interpretation of results. A final definitive proof of the configurational assignments might be provided through partial synthesis from known carbohydrate sources.

This work suggest that the Diels–Alder reaction of suitable dienes with nitrosoalkanes constitutes a worthwhile approach to novel carbohydrate derivatives of difficultly accessible configurations.

Acknowledgments.—Financial support of this work by the National Research Council of Canada is gratefully acknowledged. Appreciation is expressed to Dr. R. R. Fraser and Professor F.A.L. Anet for the interpretation of the n.m.r. data and to Mrs. Liselotte Westland for the determination of the n.m.r. spectra. Thanks are due also to two Referees for their constructive criticisms.

Experimental[20]

cis-3-Methyl-6-methoxycarbonyl-3,6-dihydro-1,2-oxazine Hydrochloride (VI).—To a solution of 41 g. (0.28 mole) of 1-chloro-

(20) Melting points were determined on a Kofler hot-stage and are corrected. Microanalyses were by Miss E. Busk, Department of Chemistry,

1-nitrosocyclohexane in 105 ml. of ether and 41 ml. of ethanol was added 105.8 g. (0.84 mole) of freshly distilled methyl sorbate and the mixture kept at 0° for 2 weeks; 36.3 g. (67% yield) of colorless crystals, m.p. 151–152°, was collected. This material could be recrystallized from ethanol without change in the m.p.; λ_{max} 1730 and 1580 cm.$^{-1}$; lines in the n.m.r. (D₂O as solvent) at: 9.4 and 15.68 c.p.s. (C₆-methyl), 156.75 (methoxy), 183.92 (H₃), 256.03 (H₆), 296.78 c.p.s. (olefin H) (reference, *t*-butyl alcohol).

Anal. Calcd. for C₇H₁₂ClNO₃: C, 43.4; H, 6.2; Cl, 18.0. Found: C, 43.7; H, 6.5; Cl, 18.0.

The N-benzoyl derivative IX was obtained by treating 10 g. of the adduct in 100 g. of ice and water with 8.8 g. of sodium bicarbonate and with 7.3 g. of benzoyl chloride added in three portions while stirring vigorously. After 30 min., the crystalline precipitate was collected, washed with ice-cold water, dried, and recrystallized from ether–pentane; m.p. 43–44°, yield 13 g. (84%); λ_{max} (CHCl₃) 1640 and 1750 cm.$^{-1}$.

Anal. Calcd. for C₁₄H₁₅NO₄: C, 64.36; H, 5.74. Found: C, 64.27; H, 5.57.

The N-acetyl and N-carbobenzoxy derivatives were obtained as uncrystallizable oils in nearly quantitative yields.

erythro-5-Amino-2-hydroxycaproic Acid (XI).—A solution of 6 g. (0.03 mole) of the adduct hydrochloride VI in 250 ml. of acetic acid was hydrogenated at 50 p.s.i. of hydrogen over 0.8 g. of Adams catalyst. Hydrogen uptake had stopped after 3 to 4 hr., but in several instances hydrogenating conditions were maintained for up to 16–17 hr. The catalyst was removed, the solvent evaporated *in vacuo* and the residue treated with 15 ml. of ice-cold concd. hydrochloric acid. After standing in the cold for 16–17 hr., the solution was diluted with water and evaporated to dryness *in vacuo*. The residue was taken up in 300 ml. of water and the solution treated with 100 g. of Dowex 50-X8 resin in the acid form. The suspension was shaken for 30 min., and the resin washed with two 250-ml. portions of 2N-triethylamine in methanol-water 1:4.[21] Evaporation of the combined eluates *in vacuo* left a sirup which crystallized from 2-propanol. Recrystallization from water-ethanol afforded 2.5 g. of colorless crystals, m.p. 192°. It gave a deep blue color with ninhydrin when the test was performed at 100° for 5 min. It traveled on Whatman paper No. 1 (ethanol, water, pyridine, 80:20:4) to give a sharp spot (ninhydrin), R_f of 0.64; pK_1 and pK_2 (water): 3.7 and 10.2; λ_{max} 3200, 1640 and 1580 cm.$^{-1}$.

Anal. Calcd. for C₆H₁₃NO₃: C, 48.97; H, 8.84. Found: C, 48.62; H, 8.69.

Occasionally, hydrogenation was incomplete and the first crop of crystals from the initial crystallization from 2-propanol consisted of the tetrahydro-1,2-oxazine-acid (XIV), the preparation of which is described below. The mother liquor usually deposited the aminoacid after removal of the first crop.

The N-phenyl ureide of XI was obtained by treating the crude methyl ester hydrochloride after hydrogenation with saturated sodium bicarbonate followed by extraction with chloroform and evaporation of the solvent. To 0.47 g. of oily residue was added 0.36 g. of phenyl isocyanate; the mixture was warmed to 45° for 10 min., then excess 5% aqueous hydrochloric acid added followed by heating to 100° for 1 hr. On cooling, a solid separated with was recrystallized from methylene dichloride-ether to give colorless crystals, m.p. 178°. λ_{max} 3400, 1725, 1620, 1590, 1540 cm.$^{-1}$.

Anal. Calcd. for C₁₃H₁₈N₂O₄: C, 58.64; H, 6.76. Found: C, 58.78; H, 6.84.

trans-3-Hydroxy-6-methyl-2-piperidinone (XII).—An 8-g. portion of the adduct hydrochloride VI was hydrogenated as described above and after removal of the catalyst and the solvent, the residual methyl ester hydrochloride X was converted to the free base by treatment with silver carbonate in dry methanol. Evaporation of the methanol solution after removal of the silver chloride left a liquid which was kept at 100° for 2–3 hr. Addition of ether to the oil led to the crystallization of the lactam XII in 42% yield. Recrystallization from isopropyl alcohol gave the analytical sample, m.p. 154°; λ_{max} 3350, 3210 and 1650 cm.$^{-1}$.

Anal. Calcd. for C₆H₁₁NO₂: C, 55.81; H, 8.52; N, 10.82. Found: C, 56.19; H, 8.41; N, 10.97.

trans-6-Methyl-3-piperidinol (XIII).—A 0.3-g. quantity of the lactam described above (XII) was placed in a Soxhlet thimble and continuously extracted for 36 hr. with ether containing 0.26 g. of lithium aluminum hydride. The ether solution was worked up in the usual manner, using 5% aqueous sodium hydroxide to decompose the salts and excess hydride. Crystallization of the product from ether gave colorless needles, m.p. 96°; λ_{max} 3300

(21) C. K. Harris, E. Tigane and C. S. Hanes, *Can. J. Biochem. Phys.*, 39, 439 (1961).

and 3100 cm.$^{-1}$. The n.m.r. spectrum of the compound (in CHCl$_3$) is reproduced in Fig. 1.

Anal. Calcd. for C$_8$H$_{13}$NO: C, 62.60; H, 11.30. Found: C, 62.22; H, 11.10.

cis-3-Methyl-tetrahydro-1,2-oxazine-6-carboxylic Acid (XIV).— A methanolic solution (100 ml.) of 13 g. of the N-benzoyl adduct IX was hydrogenated over 0.5 g. of 10% palladium-on-charcoal under 50 p.s.i. of hydrogen. One equivalent of hydrogen was absorbed within 10–15 min., after which time the mixture was filtered and the filtrate treated with excess dry hydrogen chloride at 0°. The solution was allowed to stand for 3 days, evaporated *in vacuo* and the residue washed with ether in order to remove methyl benzoate. The residue was dissolved in 5% aqueous hydrochloric acid and the solution allowed to stand overnight. It was evaporated *in vacuo*, the residue taken up in water and the pH adjusted to 7.0 with aqueous sodium hydroxide. The solution was evaporated to dryness *in vacuo*, and the re idue extracted with several portions of hot 2-propanol. The itered hot ex tracts deposited 5.5 g. of the free oxazinecarboxylic acid XIV which when recrystallized from large volumes of methanol gave colorless prisms, m.p. 178–180° dec., negative ninhydrin test, pK_2 10.1 (water), λ_{max} 3021 and 1625 cm.$^{-1}$. Its n.m.r.spectrum (in pyridine) showed it to be homogeneous (single methyl doublet at high field).

Anal. Calcd. for C$_6$H$_{11}$NO$_3$: C, 49.65; H, 7.58; N, 9.65. Found: C, 49.54; H, 7.66; N, 9.52.

N-Benzoyl-*cis*-3-methyl-6-methoxycarbonyl-*cis*-4α,5α-dihydroxytetrahydro-1,2-oxazine (XVI).—A solution of 1.2 g. of the N-benzoyl adduct IX in 100 ml. of anhydrous ether was treated with 1 g. of osmium tetroxide and 1 ml. of pyridine. After 12 hr. at room temperature, the brown crystalline material (2.5 g. or 96% yield) was collected and resuspended in aqueous methanol (1:4 v./v.) containing 2.5 g. of sodium carbonate. After shaking for 48 hr., the mixture was filtered and the filtrate evaporated to dryness *in vacuo;* the residue was dissolved in 200 ml. of water and the solution acidified with concd. hydrochloric acid, whereupon a grayish crystalline mass separated (1 g.). The crude product was dissolved in excess 8 N ammonium hydroxide, the solution decolorized with some Norit and the product reprecipitated by acidification; m.p. 202–203° dec.; the yield was nearly quantitative. This product was the free acid XV; λ_{max} 3450, 1740 and 1630 cm.$^{-1}$.

Anal. Calcd. for C$_{13}$H$_{15}$NO$_6$: C, 55.51; H, 5.33. Found: C, 55.71; H, 5.09.

The methyl ester XVI was obtained by treating a solution of the acid in dimethylformamide with an excess of ethereal diazomethane. It crystallized from methanol as colorless needles, m.p. 213°; λ_{max} 3600, 3300, 1750, 1640 cm.$^{-1}$.

Anal. Calcd. for C$_{14}$H$_{17}$NO$_6$: C, 56.94; H, 5.76. Found: C, 56.82; H, 5.89.

The methyl ester diacetate was obtained by treatment with acetic anhydride in pyridine in the usual manner. It crystallized from ether as colorless needles, m.p. 97°, λ_{max} 1750 and 1650 cm.$^{-1}$. The n.m.r. spectrum of this compound is reproduced in Fig. 2 (see text for discussion).

Anal. Calcd. for C$_{18}$H$_{21}$NO$_8$: C, 56.84; H, 5.54. Found: C, 56.65; H, 5.48.

5-Amino-5,6-dideoxy-DL-allonic Acid.—A suspension of 0.5 g. of the N-benzoyl acid XV described earlier in 20 ml. of concd. hydrochloric acid was heated to 100° until a clear solution resulted. At this point, it was essential to cool rapidly the solution to 20° as otherwise extensive decomposition appeared to take place. After standing at room temperature for 48 hr., the solution was diluted with water and washed with ether. The aqueous phase was taken to dryness *in vacuo* and the residue dissolved in a mixture of 25 ml. of ethanol and 5 ml. of concd. hydrochloric acid. The solution was shaken under 50 p.s.i. of hydrogen for 16 hr. after the addition of 100 mg. of platinum oxide. The catalyst was removed, the filtrate evaporated to dryness *in vacuo* and the residue taken up in water. Excess silver carbonate was added to the solution which was then filtered and the filtrate saturated with hydrogen sulfide. The mixture was filtered through a thick bed of Celite, the clear and colorless filtrate evaporated to dryness *in vacuo* and the residual sirup crystallized from water-ethanol to give colorless prisms, m.p. 230° dec., yield 250 mg. (78%); deep blue color with ninhydrin at 100°; λ_{max} 3500, 3250, 1650, 1600 cm.$^{-1}$.

Anal. Calcd. for C$_6$H$_{13}$NO$_5$: C, 40.22; H, 7.26. Found: C, 40.10; H, 7.32.

Epimeric N-Benzoyl-*cis*-3-methyl-6-methoxycarbonyl-4,5-oxidotetrahydro-1,2-oxazines (XIX) and (XX).—To an ice-cold suspension of 1.5 ml. (0.066 mole) of 90% hydrogen peroxide in 6.1 ml. of ethylene dichloride was added over a 15-min. period, 9.2 ml. (0.08 mole) of trifluoroacetic anhydride. The resulting solution was added dropwise over a 50-min. period to a stirred and cooled solution of 8 g. of the N-benzoyl-adduct IX in 37 ml. of ethylene dichloride containing 30.6 g. of suspended disodium hydrogen

phosphate. The mixture was stirred for 1 hr., followed by the addition of 88 ml. of water. The organic phase was collected and the aqueous phase extracted several times with chloroform. The combined dried extracts were evaporated to give a crystalline mixture (6.5 g.) of the epimeric epoxides after trituration with ether-pentane. The n.m.r. spectrum (in pyridine) of this mixture showed two methyl doublets of equal intensities at high field (as expected for a 1:1 mixture of epimers).

The β-oxide XX was obtained by dissolving the crude mixture in hot methanol and allowing the solution to stand at *room temperature* overnight, whereupon 3.5 g. of colorless cubes, m.p. 137°, separated. Further recrystallizations did not alter the m.p. The n.m.r. spectrum (pyridine) showed only one methyl doublet at high field; λ_{max} (CHCl$_3$) 1750 and 1640 cm.$^{-1}$.

Anal. Calcd. for C$_{14}$H$_{15}$NO$_5$: C, 60.65; H, 5.41. Found: C, 60.40; H, 5.36.

The α-oxide XIX was readily obtained by simple allowing the β-oxide mother liquor to stand overnight at 0°. In this way, colorless needles deposited which when twice recrystallized from methanol had m.p. 95°. The n.m.r. spectrum of this epimer also showed it to be homogeneous (single methyl doublet at high field); λ_{max} (CHCl$_3$) 1750 and 1640 cm.$^{-1}$.

Anal. Calcd. for C$_{14}$H$_{15}$NO$_5$: C, 60.65; H, 5.41. Found: C, 60.80; H, 5.70.

Iodohydrins XXX and XXXI and their Methanolysis. (A) From the β-Oxide.—A mixture of 1.4 g. of the β-oxide XX and 1.5 ml. of 50% aqueous hydriodic acid was stirred vigorously for 15 min. and then allowed to stand a further 10 min. The crystalline mass was collected, washed with water and recrystallized from methanol or ethyl acetate to give colorless crystals of XXXI, m.p. 180–181°, yield 2.0 g. or 98%; λ_{max} 3350, 1750 and 1630 cm.$^{-1}$.

Anal. Calcd. for C$_{14}$H$_{16}$INO$_5$: C, 41.48; H, 3.95. Found: C, 41.80; H, 4.10.

Attempted acetylation of this product in dry dimethylformamide–pyridine with acetic anhydride led to the isolation of the starting β-oxide.

Methanolysis of this iodohydrin XXI was accomplished by dissolving the product (158 mg.) in 20 ml. of methanol followed by the dissolution of dry hydrogen chloride (rapid bubbling for 8 min). at ice temperature. After standing overnight, the solution was evaporated to dryness *in vacuo* to give a residue which solidified when triturated with ether. Recrystallization from 2-propanol gave 125 mg. (96% yield) of colorless needles of XXXII, m.p. 138–140° dec.; λ_{max} 3600, 1750 and 1565 cm.$^{-1}$. The n.m.r. spectrum showed only one sharp methyl doublet at high field.

Anal. Calcd. for C$_7$H$_{13}$ClINO$_4$: C, 24.88; H, 3.85. Found: C, 25.05; H, 3.96.

(B) From the α-Oxide.—Application to the α-oxide XIX of the same procedure described above for the preparation of the iodohydrin from the β-oxide, gave the isomeric iodohydrin XXX in 91% yield. It crystallized from methanol; m.p. 215–217°; λ_{max} 3350, 1750 and 1630 cm.$^{-1}$.

Anal. Calcd. for C$_{14}$H$_{16}$INO$_5$: C, 41.48; H, 3.95. Found: C, 41.20; H, 4.23.

The acetate was obtained by treating the iodohydrin in dry dimethylformamide with excess acetic anhydride and a few drops of pyridine. After standing overnight, the mixture was worked up in the usual manner to give the acetate, m.p. 177–178°, in 81% yield; λ_{max} 1775, 1750 and 1650 cm.$^{-1}$. The n.m.r. spectrum of this compound showed it to be homogeneous (sharp methyl doublet at high field).

Anal. Calcd. for C$_{16}$H$_{18}$INO$_5$: C, 42.90; H, 4.02. Found: C, 42.89; H, 4.03.

Methanolysis conditions identical to those described above for the isomeric iodohydrin XXXI derived from the β-oxide led to quantitative recovery of unchanged N-benzoyl iodohydrin XXX, m.p. 215–217° (identity established by mixed m.p. and infrared.

Attempted solvolysis of the preceding acetate (m.p. 177–178°)) in wet acetic acid containing silver acetate led to precipitation of silver iodide, but no pure product could be isolated from the dark colored mixture.

N-Benzoyl-3β-methyl-4β-hydroxy-6β-methoxycarbonyl-5α-formoxytetrahydro-1,2-oxazine (XXII).—A solution of 1.0 g. of the β-oxide XX in 15 ml. of 90% formic acid was heated to 100° for 45 min. The mixture was evaporated *in vacuo* leaving a solid residue which was recrystallized from 2-propanol to give colorless needles, m.p. 187–189° (yield 0.68 g.); λ_{max} 3300, 1770, 1725 and 1640 cm.$^{-1}$.

Anal. Calcd. for C$_{15}$H$_{17}$NO$_7$: C, 55.72; H, 5.26. Found: C, 55.62; H, 5.31.

Methanolysis of this product was carried out as described above in the case of iodohydrin XXXI. In this way, colorless crystals, m.p. 78–85° dec., separating from 2-propanol–ether were obtained. λ_{max} 3300, 1750, 1746, 1570 cm.$^{-1}$. The n.m.r. spectrum

(Fig. 3) showed that it consisted of a mixture of two components (see text) in a ratio of 1:3. The major component appeared to be the lactone XXIV, whereas the minor product was the corresponding methyl ester XXIII.

Anal. Calcd. for $C_7H_{14}ClNO_5$: C, 36.92; H, 6.15. Found: C, 36.97; H, 6.02.

Hydrolysis of the preceding mixture of lactone and methyl ester of m.p. 78–85° by 10% hydrochloric acid at room temperature for 15 hr. followed by evaporation *in vacuo* gave a sirup which was processed with the resin Dowex-50-X8 as described above in the case of the aminoacid XI. Evaporation of the combined eluates gave in 75% yield 3β-methyl-4β-hydroxy-6β-carboxy-5α-hydroxy-tetrahydro-1,2-oxazine (XXV), m.p. 133° after recrystallization from water; when recrystallized from pyridine, it had m.p. 173°. Both crystalline forms are interconvertible and had identical n.m.r. spectra which in addition showed the compound to be homogeneous (single sharp methyl doublet at high field). The compound gave only a faint color when heated with ninhydrin. It had pK_2 10.2; λ_{max} (form of m.p. 133°) 3500, 3200 and 1620 cm.$^{-1}$; λ_{max} (form of m.p. 173°) 3400, 1620 and 1590 cm.$^{-1}$.

Anal. Calcd. for $C_6H_{11}NO_5$: C, 40.67; H, 6.21; N, 7.90. Found: C, 40.31; H, 6.23; N, 7.80.

N-Benzoyl-3β-methyl-4β-formoxy-6β-methoxycarbonyl-5α-hydroxytetrahydro-1,2-oxazine (XXI).—Using 0.28 g. of the α-oxide XIX and applying the procedure described above for the preparation of XXII, there was obtained 0.15 g. of colorless crystals, m.p. 180–184° after recrystallization from 2-propanol; λ_{max} 3400, 1770, 1725, 1640 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{17}NO_7$: C, 55.72; H, 5.26. Found: C, 55.44; H, 5.08.

Methanolysis of this product under the same conditions described above for XXII gave in 83% yield a crystalline diol hydrochloride, m.p. 78–85°, consisting of the same mixture of components XXIII and XXIV already obtained starting from the β-oxide. The identity of the two mixtures was ascertained by mixed m.p., infrared and n.m.r. spectroscopy.

Hydrolysis of this crystalline mixture with dilute hydrochloric acid at room temperature also afforded the same oxazine carboxylic acid XXV.

5-Amino-5,6-dideoxy-DL-gulonic Acid (XXVI).—A 600-mg. sample of the above described mixture of hydrochlorides XXIII and XXIV in 25 ml. of acetic acid was hydrogenated over Adams catalyst under 50 p.s.i. of hydrogen for 16–17 hr. The catalyst was removed, the solvent evaporated *in vacuo* and the residue hydrolyzed with excess concd. hydrochloric acid at room temperature for 20 hr. The solution was taken to dryness *in vacuo* and

the residue converted to the free aminoacid by treatment with Dowex-50-X8 as described above for the aminoacid XI. A sirup was obtained which crystallized from water–methanol as small colorless needles, m.p. 125°. Three crystals gave a deep blue color with ninhydrin when the test solution was warmed briefly; λ_{max} 3300 and 1600 cm.$^{-1}$. The compound was homogeneous as judged from its n.m.r. spectrum.

Anal. Calcd. for $C_6H_{13}NO_5$: C, 40.22; H, 7.26. Found: C, 39.92; H, 7.57.

3β-Methyl-4β-hydroxy-6β-methoxycarbonyl-5α-chloro-tetrahydro-1,2-oxazine Hydrochloride (XXVIII) and its Lactone, XXIX.—A rapid stream of dry hydrogen chloride was passed for 10 min. at 0° into a solution of 1.02 g. of the β-oxide in 100 ml. of methanol. After standing overnight at room temperature, the solution was evaporated *in vacuo* to leave an oil which crystallized when triturated with ether (yield 0.6 g. or 68%). Recrystallization from 2-propanol gave colorless needles, m.p. 138–145° dec.; λ_{max} (C = O region) 1770 and 1750 cm.$^{-1}$.[1] The n.m.r. spectrum (Fig. 4) showed that it consisted of a mixture of two products in a ratio of 1:3. The ratio of the relative intensities of the methyl doublets to the methyl singlet (CO_2CH_3) showed that the minor component was the lactone XXIX and the major one the methyl ester XXVIII.

Anal. Calcd. for $C_7H_{13}Cl_2NO_4$: C, 34.14; H, 5.28. Found: C, 34.14; H, 5.07.

The N-acetyl-O-acetate derivative was prepared in the usual manner (pyridine, acetic anhydride). It crystallized from ether as long colorless needles, m.p. 150–152°. The infrared spectrum showed that the N-acetyl lactone had co-crystallized as evidenced by the presence of the band at 1770 cm.$^{-1}$. Chromatography on neutral alumina (Woelm, Activity II) gave only oily fractions which resisted crystallization and which proved heterogeneous (n.m.r.); λ_{max} 1770 and 1730 cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{16}O_6NCl$: C, 44.97; H, 5.45. Found: C, 44.72; H, 5.60.

N-Benzoyl-3β-methyl-4β-chloro-6β-methoxycarbonyl-5α-hydroxytetrahydro-1,2-oxazine (XXVII).—A solution of 0.8 g. of the α-oxide in 25 ml. of methanol was treated with dry hydrogen chloride as described in the preceding case. A nearly quantitative yield of colorless crystals, m.p. 203°, was obtained after recrystallization from 2-propanol. The infrared showed the expected bands at 1750 and 1630 cm.$^{-1}$ but no band at 1770 cm.$^{-1}$ as in the preceding case.

Anal. Calcd. for $C_{14}H_{16}ClNO_5$: C, 53.58; H, 5.10. Found: C, 53.30; H, 5.20.

[Contribution from the Department of Chemistry, Duke University, Durham, N. C.]

Base-catalyzed Hydrogen–Deuterium Exchange at the α-Carbon of Ethyl Cinnamate and Certain Related Compounds[1]

By Mary F. Zinn, Thomas M. Harris, Douglas G. Hill and Charles R. Hauser

Deuterations of ethyl cinnamate, ethyl β-phenylcinnamate, chalcone and *trans*-cinnamonitrile were effected with deuterioethanol by means of a catalytic amount of sodium ethoxide. The first three reactions were shown to involve replacement of the α-vinyl hydrogen by deuterium, and the last was assumed to occur similarly. *trans*-Cinnamonitrile afforded a mixture of the *cis* and *trans* isomers. Two possible mechanisms are considered.

Although certain 1,2-dihaloethenes have been observed to undergo vinyl hydrogen–deuterium exchange with deuterium oxide in the presence of sodium methoxide,[2,3] ethyl cinnamate has been reported[2] not to exhibit such exchange under similar conditions.[2] Neither was exchange observed when this ester was treated with deuterium oxide and potassium *t*-butoxide.[2] Unsuccessful attempts have also been made to effect similar deuterations of chalcone and other α,β-unsaturated ketones with deuterium oxide by means of a pyridine base.[4]

In the present investigation successful base-catalyzed deuterations of these and certain other α,β-unsaturated

compounds were realized by employing deuterioethanol instead of deuterium oxide. Thus ethyl cinnamate was deuterated with a tenfold excess of deuterioethanol by means of 10 mole per cent of sodium ethoxide to form the α-deuterio derivative Ia. The ester, recovered in 91% yield, contained 0.82 D atom/molecule.

$$C_6H_5CH{=}CDCOOC_2H_5 \qquad C_6H_5CD{=}CHCOOC_2H_5$$
$$\text{Ia} \qquad\qquad\qquad \text{Ib}$$
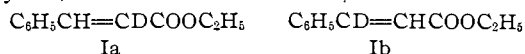
That the deuterated ester was Ia, not the possible Ib, was supported by nuclear magnetic resonance spectra. Thus, whereas the spectrum of non-deuterated ethyl cinnamate contained two doublets caused by the two vinylic hydrogens, that of the deuterated ester showed only a trace of the doublet at higher field while the lower doublet was replaced by a single broader band. The higher field doublet in the spectrum was evidently caused by the α-vinyl hydrogen, since, of the two analogous doublets observed previously for the two vinylic

(1) Supported in part by the National Science Foundation, NSF-G14527.

(2) S. I. Miller and W. S. Lee, *J. Am. Chem. Soc.*, **81**, 6313 (1959).

(3) L. C. Leitch and H. J. Bernstein, *Can. J. Research*, **B28**, 35 (1950); J. E. Francis and L. C. Leitch, *Can. J. Chem.*, **35**, 348 (1957).

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