The solvent was evaporated *in vacuo* and traces of pyridine and acetic anhydride were removed by azeotropic distillation of toluene. The polyacetate **14** was obtained as a syrup (443 mg, quantitative yield) which did not crystallize.

Compound **14** (400 mg, 0.83 mmole) was dissolved in methanolic ammonia (40 ml) and allowed to stand overnight at room temperature. Removal of the solvent under reduced pressure yielded a sirupy residue which was shaken for 5 min with 20 ml of chloroform and allowed to stand overnight at room temperature. The insoluble tacky crystalline material was separated by filtration and recrystallized from water–ethanol. The yield of **15** was 203 mg (80%), mp 202–225° (sintered), 233–235° (effervescent). The ultraviolet spectrum of the compound was similar to that for cytidine, and an infrared spectrum indicated the lack of ester linkages. A ninhydrin test on **15** was negative.

Anal. Calcd for $C_{12}H_{18}N_4O_5 \cdot {}^3/_2H_2O$: C, 42.23; H, 6.16; N, 16.42. Found: C, 42.33; H, 6.39; N, 16.41.

Methyl 3-Acetamido-3-deoxy-tri-*O*-acetyl-α-D-mannopyranoside (18).—Compound **13** (97 mg, 0.31 mmole) was hydrogenated at room temperature in 20 ml of water with 89 mg of platinum oxide for a period of 60 hr. The catalyst was filtered and the alkaline filtrate was evaporated to dryness. The hexahydro pyrimidine nucleoside **16**, obtained as a syrup, was dissolved in 15 ml of methanol and the solution was saturated with hydrogen chloride at 0°. The mixture was refluxed gently for 8 hr. The solvent was evaporated under reduced pressure and the resultant syrup was azeotropically dried with three portions of toluene. The residue (containing **17**) was dissolved in a mixture of pyridine (8 ml) and acetic anhydride (2 ml) and was allowed to remain overnight at room temperature. The solvent was evaporated to dryness under reduced pressure followed by an azeotropic removal of traces of acetic anhydride with toluene. The residue was dissolved in chloroform (5 ml) and placed on an acid-washed alumina column packed with benzene. Elution was performed with 150 ml of benzene (which yielded 20 mg of material), followed by 100 ml of a 1:1 benzene–ethyl acetate mixture (which yielded 78 mg of material) and finally with 100 ml of ethyl acetate (which yielded 28 mg of material). Upon evaporation of the second fraction followed by refrigeration, the residue yielded colorless needles. These were recrystallized from ethanol–petroleum ether to give colorless needles of methyl 3-acetamido-3-deoxy-2,4,6-tri-*O*-acetyl-α-D-mannoside (**18**), mp 150–151°. A mixture melting point with an authentic sample[23] showed no depression and their infrared spectra were identical.

1-(3-Deoxy-3-nitro-β-D-glucopyranosyl)-N^4-benzoylcytosine (19).—*N*-Benzoylcytidine[24] (7.0 g, 0.02 mole) was oxidized with sodium metaperiodate (4.28 g, 0.02 mole) in 150 ml of 50% aqueous ethanol. Sufficient additional metaperiodate was added to ensure complete oxidation of the glycol (as indicated by a positive starch–iodide test). The precipitate formed was filtered and washed with ethanol, and the combined filtrates were evaporated *in vacuo*. To a solution of the dialdehyde in 100 ml of 75% ethanol was added nitromethane (1.2 ml, 0.02 mole). Sodium hydroxide (10 ml of 1 *N* solution) was added dropwise and the mixture was stirred for an additional 15 min. Dowex 50 (H^+) was added with stirring along with 25 ml of water. Enough resin was added to lower the pH to *ca.* 4–5. The resin was removed by filtration and washed with 50 ml of water and 75 ml of ethanol. The combined filtrates were concentrated to a small volume. Ethanol was added and removed *in vacuo* repeatedly until crystallization occurred in the yellow solution. (If allowed to evaporate to dryness, the product undergoes decomposition). The mixture was cooled overnight and the precipitate was removed by filtration, washed with ethanol, cooled in a Dry Ice–acetone bath, and then thoroughly washed with ether and dried. The yield of product was 2.0 g (25%), mp 174–177°. Silica gel thin layer chromatography (chloroform–methanol, 5:1) indicated only one spot.

Anal. Calcd for $C_{17}H_{18}N_4O_8 \cdot {}^1/_2H_2O$: C, 49.16; H, 4.62; N, 13.48. Found: C, 48.70; H, 4.89; N, 13.03.

Calculation of Molecular Rotation by Summation of Partial Conformational Contributions. Rotations of the Eight 1,6-Anhydro-β-D-hexopyranoses and Their Triacetates[1]

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The optical rotations of the 1,6-anhydro-β-D-hexopyranoses and their triacetates have been correlated. The rotations are expressed as the algebraic sum of a series of empirical rotatory contributions by various conformational elements of asymmetry; close agreement between the calculated and experimentally determined rotations is observed.

It has been shown by Whiffen[2] that the observed rotation of an optically active molecule can be regarded as an algebraic summation of partial rotatory contributions of various conformational elements of asymmetry. Empirical values were determined that permitted calculation of the rotations of various cyclic sugars and cyclitols with fair accuracy. A more extensive treatment bas been presented by Brewster,[3] and it has been applied to various types of optically active organic compounds.[4,5] The best correlations between the calculated and the experimental values have been observed with compounds that are devoid of absorption bands in the near ultraviolet, and which have predictable, fixed conformations, or for which valid estimates of conformational populations can be made.[6] In the carbohydrate field the calculations are particularly simple in the case of the polyhydroxycyclohexanes,[2,5,7] and discrepancies between observed and calculated rotations have been interpreted in terms of equilibria between different conformers.[2,5,8] Similar comparisons have been made for the methyl D-aldopyranosides,[2,5,9] although the correlations between the observed and calculated values are not precise enough to permit detailed treatment in terms of conformational populations.

(1) Supported, in part, by a grant from the National Institutes of Health, Public Health Service, Department of Health, Education, and Welfare, Bethesda, Md. 20014; Grant No. GM-11976-03 (The Ohio State University Research Foundation Project 1820).

(2) D. H. Whiffen, *Chem. Ind.* (London), 964 (1956).

(3) J. H. Brewster, *J. Am. Chem. Soc.*, **81**, 5475, 5483 (1959).

(4) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 401–412.

(5) S. J. Angyal, *in* E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965, pp 381–394.

(6) W. D. Celmer, *J. Am. Chem. Soc.*, **87**, 1797 (1965); **88**, 5029 (1966); Abstracts of Papers, Winter Meeting of the American Chemical Society, Phoenix, Ariz., Jan 1966, pp C13, C14; Abstracts of Papers 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967, p C19.

(7) S. Yamana, *Bull. Chem. Soc. Japan*, **33**, 1741 (1960).

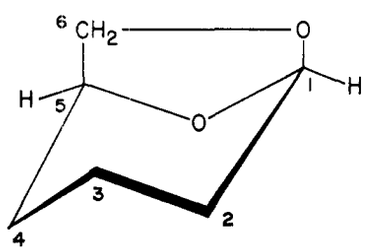
(8) G. E. McCasland, S. Furuta, L. F. Johnson, and J. N. Shoolery, *J. Org. Chem.*, **29**, 2354 (1964).

(9) W. Kauzmann, F. B. Clough, and I. Tobias, *Tetrahedron*, **13**, 57 (1961).

With the synthesis of the last of the 1,6-anhydro-β-D-hexopyranoses, the *talo* isomer (and its triacetate),[10] there is now available a complete set of measured rotations for all eight stereoisomeric triols and their triacetates in this conformationally rigid, bicyclic [3.2.1] system. This series provided the opportunity to determine, essentially by the approach of Whiffen,[2] an empirical set of values for partial rotatory contributions of various conformational elements, in a system wherein the potential ambiguities introduced by possible conformational changes are eliminated.[11]

The present approach is founded upon the basic assumption[2] that the total rotation of the molecule can be expressed as the algebraic sum of the rotatory contributions of a number of conformational elements. A series of conformational elements is defined, the magnitude of the rotatory contribution of each element is expressed as an algebraic term, and the numerical value of each term is calculated from a set of simultaneous equations, in which each equation relates the observed rotation for a given structure to the algebraic sum of the terms.

In the 1,6-anhydro-β-D-aldopyranose skeleton (1), various conformational rotatory elements can be recognized by viewing along each carbon–carbon bond in



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turn and observing the projected relationships between vicinal oxygen or carbon substituents. Interactions that advance as a right-hand screw are defined as positive, and those that have a left-hand screw relationship are defined as negative. Certain elements of asymmetry remain fixed in the parent ring system. Four conformational rotatory elements are proposed, and are defined as follows.

1. An algebraic value a is assigned to the *gauche* interaction along the C-1–C-2 bond between the substituent at C-2 and one of the oxygen atoms at C-1. The other oxygen atom at C-1 is antiparallel to the C-2 substituent, and this arrangement makes a rotatory contribution of zero.

2. An algebraic value b is assigned to each vicinal diol group in a staggered relationship along the C-2–C-3 bond and the C-3–C-4 bond. It is immaterial whether the substituents are axial or equatorial. Vicinal diols in the *trans* diaxial arrangement of these two bonds give a rotatory contribution of zero.

3. An algebraic value c is assigned to the *gauche* arrangement, along the C-4–C-5 bond, of the C-4 substituent and the ring oxygen atom attached to C-5. The antiparallel arrangement of the C-4 substituent and the O-5 ring oxygen atom makes a contribution of zero.

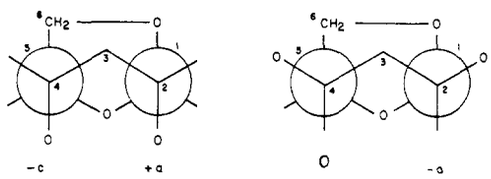

Figure 1.—Rotatory contributions along the C-2–C-1 and C-4–C-5 bonds.

4. An algebraic value d is assigned to the parent ring structure **1**. The sign for **1** is positive; that of the β-L enantiomorph would be negative.

It can be seen (Figure 1) that those 1,6-anhydro-β-D-hexopyranose derivatives that have an equatorial C-2 substituent give a contribution of $-a$, and those having an axial C-2 substituent give a contribution of $+a$, for the C-1–C-2 term. Those derivatives having an axial C-4 substituent give a contribution of $-c$, and those having an equatorial C-4 substituent give a C-4–C-5 contribution of zero (Figure 1). It should be noted that c and d are related, and that the interaction that the C-4 substituent may experience with C-6 is included in the d term as a necessary consequence of defining as zero the contribution of the antiparallel arrangement of the C-4 substituent and the ring oxygen atom attached to C-5. Neglected H–H interactions are also compensated in this term.[12]

With these four terms, eight equations can be set up for the rotations of the eight 1,6-anhydro-β-D-hexopyranoses, and solution of any four of these as a set of simultaneous equations gives numerical values of a, b, c, and d that, when used for calculation of the rotations of the remaining four isomers, give reasonably close agreement with the observed rotations. Similar calculations for the triacetates give a set of numerical values for a, b, c, and d that are valid for this system, and again can be used for calculation of rotations that are in reasonably close agreement with observed values. However, this approach gives identical rotatory magnitudes for the D-*gluco* and D-*allo* configurations, and for the D-*ido* and D-*talo* configurations, whereas the observed rotations differ, in each case, by about 10°. It is possible to refine the calculation by the introduction of an extra term that is related to the number of axial substituents, as follows. (See Table I.)

5. An algebraic value f is assigned as a positive contribution for each substituent at C-2, C-3, or C-4

TABLE I

PARTIAL MOLECULAR ROTATORY CONTRIBUTIONS DETERMINED EMPIRICALLY FOR THE 1,6-ANHYDRO-β-D-ALDOPYRANOSES AND THEIR TRIACETATES

Structure	—Partial molecular rotatory contribution[a,b]— a	b	c	d	f
1,6-Anhydro-β-D-aldopyranoses	6,300	4,400	13,300	−8,600[c]	+1,600[c]
1,6-Anhydro-β-D-aldopyranose triacetates	9,900	3,500	21,500	−12,000[c]	+1,700[c]

[a] The signs of terms a, b, and c are given by the chirality of the screw pattern that they represent. [b] Molecular rotatory values are given as $[M]_D = [\alpha]_D \times$ mol wt. [c] These signs are reversed when 1,6-anhydro-β-aldopyranoses in the L series are considered.

(10) D. Horton and J. S. Jewell, *Carbohydrate Res.*, **5**, 149 (1967).

(11) An alternative approach, based on the method of optical superposition, has been presented by M. Černý, J. Pacák, and J. Staněk, *Chem. Ind.* (London), 1559 (1966). The specific rotation of 1,6-anhydro-β-D-talopyranose was predicted from data on the other seven 1,6-anhydro-β-D-hexopyranoses.

(12) It is, in principle, possible to define the rotatory elements 3 and 4 in a different way, so that element 4 does not include a contribution from the interaction of the C-4 substituent with C-6. Evaluation of the new algebraic terms would require data on 1,6-anhydro-4-deoxy-β-D-hexopyranoses.

TABLE II
OBSERVED AND CALCULATED ROTATION OF 1,6-ANHYDRO-β-D-HEXOPYRANOSES AND THEIR TRIACETATES

Configuration	Sum of partial rotatory contributions	1,6-Anhydro-β-D-hexopyranoses in water: [α]D, degrees[a] Obsd	Calcd	[M]D, degrees[a,b] Obsd	Calcd	1,6-Anhydro-β-D-hexopyranose triacetates in chloroform: [α]D, degrees[a] Obsd	Calcd	[M]D, degrees[a,b] Obsd	Calcd
allo	$a - c + d + 2f$	−75.8[c]	−76	−12,280	−12,400	−70.8[c]	−70	−20,390	−20,200
altro	$-a - 2b - c + d + f$	−213[d]	−218	−34,506	−35,400	−172[d]	−169	−49,536	−48,700
gluco	$a - c + d + 3f$	−66.2[d]	−66	−10,724	−10,800	−65.5[d]	−64	−18,864	−18,500
manno	$-a + b - c + d + 2f$	−127.6[d]	−127	−20,671	−20,600	−123.6[d]	−126	−35,597	−36,500
gulo	$a + 2b + d + f$	+50.4[e]	+50	+8,165	+8,100	+22.1[e]	+23	+6,365	+6,600
ido	$-a + d$	−92.6[f]	−92	−15,001	−14,900	−75.1[f]	−76	−21,629	−21,900
galacto	$a - b + d + 2f$	−21.9[d]	−21	−3,548	−3,500	−5.7[d]	−7	−1,642	−2,200
talo	$-a + d + f$	−80[g]	−82	−12,960	−13,300	−73[g]	−70	−21,024	−20,200

[a] Determined for temperatures in the range 14–20°. [b] [M]D values give [α]D × mol wt. [c] J. Pratt and N. K. Richtmyer, *J. Am. Chem. Soc.*, **77**, 1906 (1955). [d] N. K. Richtmyer and C. S. Hudson, *ibid.*, **63**, 1727 (1941). [e] L. C. Stewart and N. K. Richtmyer, *ibid.*, **77**, 1021 (1955). [f] E. Sorkin and T. Reichstein, *Helv. Chim. Acta*, **28**, 1 (1945). [g] See ref 10.

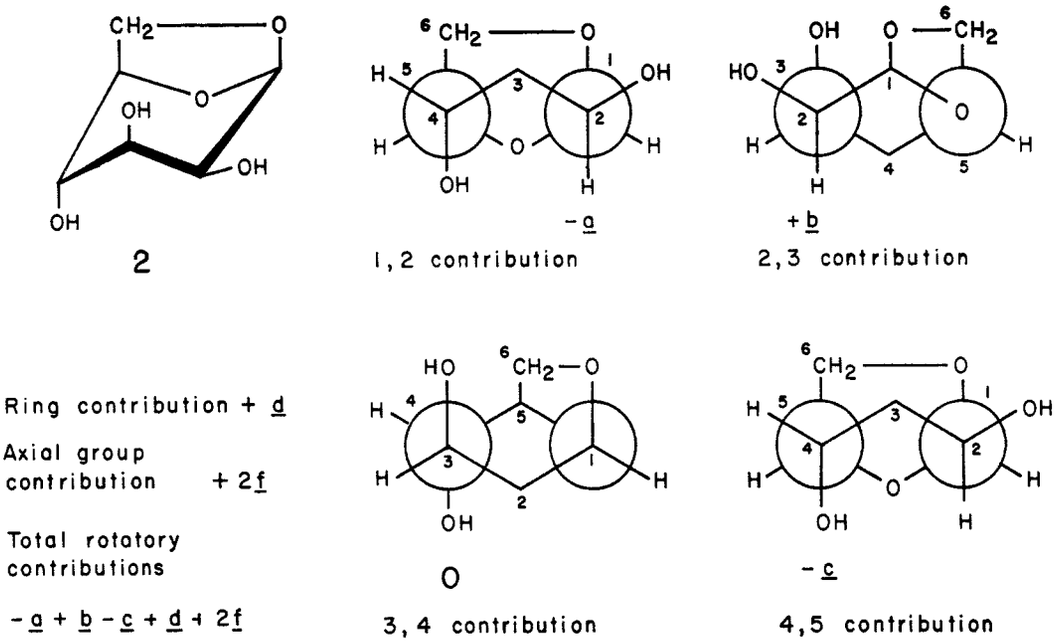

Figure 2.—Summation of rotatory contributions in 1,6-anhydro-β-D-mannopyranose (2).

that is axial. This contibution would be negative for the 1,6-anhydro-β-L-hexopyranoses.

This term takes into account the rotatory contribution arising from the presumed slight ring distortion produced by interactions of axial substituents.

Solution of any five of the eight equations for the 1,6-anhydro-β-D-hexopyranoses provides numerical values for the five terms (Table I). The calculated rotations for the remaining isomers are then in excellent agreement with the values determined by experiment (Table II). A similarly consistent set of values was calculated (Table II) for the triacetates; the numerical magnitudes of the five terms differed somewhat from those determined for the parent triols.

The method is illustrated with 1,6-anhydro-β-D-mannopyranose (**2**) as the example (Figure 2). The C-2 hydroxyl group has a left-hand screw relation to O-6 (oxygen atom of the anhydro bridge) and gives a contribution of $-a$; the antiparallel arrangement of O-5 and the C-2 hydroxyl group gives a contribution of zero. Along the C-2–C-3 bond there is a right-hand screw relation of hydroxyl groups, giving a contribution of $+b$. Along the C-3–C-4 bond the two groups are *trans* diaxial and the contribution is zero. There is a *gauche* relation along the C-4–C-5 bond between the C-4 hydroxyl group and O-5, which defines a left-hand screw and therefore givs a contribution of $-c$. When the skeletal contribution ($+d$) and the contributions ($+2f$) for the two axial substituents are included, summation of the terms gives the following equation.

$$\text{total rotation} = -a + b - c + d + 2f$$

Corresponding summations are given in Table II for the other configurations. The parameters calculated for the triacetates were of like sign and similar order of magnitude to those calculated for the parent triols, and indicate that the anisotropy of the acetyl substituent does not introduce serious complications into the calculation of rotation by summation of partial conformational contributions.

The self-consistency of the data presented herein for the 1,6-anhydro-β-D-hexopyranoses and their triacetates lends strong support to the view, also endorsed by nmr data,[13] that all of these compounds adopt chairlike conformations, even the D-*gluco* structure, which has all substituents axial.

The observed specific rotations of those 1,6-anhydro-3-deoxy-β-hexopyranoses (and their diacetates) that have been reported in the literature are in good agree-

(13) L. D. Hall and L. Hough, *Proc. Chem. Soc.*, 382 (1962).

ment with those calculated by using the partial molecular rotatory contributions given in Table I. Good correlations for the 1,6-anhydro-4-deoxy-β-hexopyranoses and their diacetates can be obtained[12] by taking into account the interaction of the C-4 substituent with C-6. The 2,7-anhydro-β-heptulopyranoses can be accommodated by inclusion of an additional term for the hydroxymethyl group. Details of these calculations, together with calculations on aminodeoxy derivatives of 1,6-anhydro-β-hexopyranoses, will be given in a separate report.

Registry No.—I (*allo*), 14059-68-8; I (*altro*), 10339-41-0; I (*gluco*), 498-07-7; I (*manno*), 14168-65-1; I (*gulo*), 14274-90-9; I (*ido*), 10339-42-1; I (*galacto*), 644-76-8; I (*talo*), 14059-73-5; II (*allo*), 14661-09-7; II (*altro*), 14661-10-0; II (*gluco*), 13242-55-2; II (*manno*), 13242-48-3; II (*gulo*), 14661-13-3; II (*ido*), 14661-14-4; II (*galacto*), 4132-24-5; II (*talo*), 14661-16-6.

Oxidations of Amines. IV. Oxidative Fragmentation[1]

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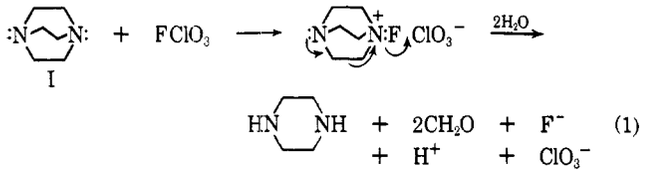
Oxidation of a representative group of β-amino and β-hydroxy amines with either chlorine dioxide or sodium hypochlorite resulted in carbon–carbon cleavage to give formaldehyde along with ammonia or the corresponding primary or secondary amine. The obvious relationship of this reaction to the fragmentation reactions described by Grob and co-workers[2] suggested the term "oxidative fragmentation."

The observation by Gardner and co-workers[3] of carbon–carbon scission in the perchloryl fluoride oxidation of triethylenediamine (I) (eq 1) led to speculation on the similarity of this phenomenon to the fragmentations reported by Grob, *et al.*[2] The comparison was strengthened by Huisgen and Kolbeck's report[4] of carbon–carbon bond breaking when the mono-N-oxide of I was treated with benzoyl chloride; here the oxidative step had been accomplished as a separate and discrete operation (eq 2). When Higuchi observed[5] that the oxidizing properties of hypochlorous acid disappeared in the presence of I, in contrast to the stability of hypochlorous acid toward quinuclidine,[6] it seemed likely to us that these differences might best be reconciled in terms of the above cited fragmentations; we have termed this "oxidative fragmentation." The objectives of this study were (a) to establish the products and probably nature of the reaction of I with hypochlorous acid, (b) to extend the comparison of reactions of I with oxidizing agents to chlorine dioxide, whose reactivity toward amines had been rather extensively studied by us,[1] and (c) to explore the scope of hypochlorous acid and chlorine dioxide mediated oxidative fragmentations to other vicinally substituted amines. These objectives have been realized to a considerable extent.



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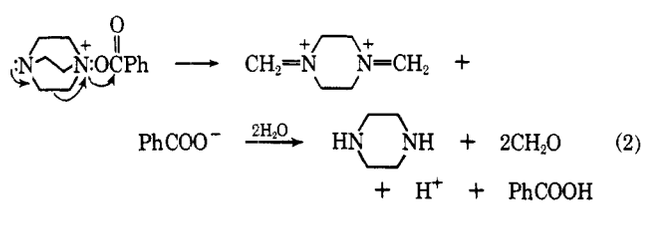
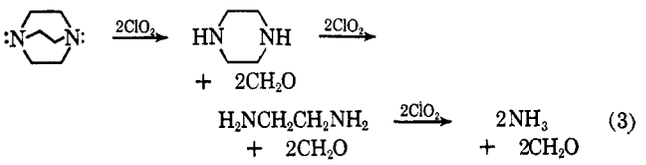


(2)

Results

The amines investigated as candidates for the oxidative fragmentation are compiled in Table I with their proposed oxidation products. The isolation of products from a number of these oxidations posed some difficulties. The formaldehyde formed in the oxidations of amines with chlorine dioxide was rapidly oxidized by chlorite ion to formic acid below pH 6, resulting in very low apparent yields of this aldehyde. Another difficulty encountered in isolation of formaldehyde from solutions occurred when ammonia as well as formaldehyde was an oxidation product. This difficulty was possibly due to the reaction between ammonia and formaldehyde to yield hexamethylenetetramine.[7] Isolation of the amine fragments from the chlorine dioxide oxidations was complicated in that the amine products underwent further degradation with excess chlorine dioxide. An example of such progressive degradation is that of the oxidation of I by chlorine dioxide; in the presence of a large excess of chlorine dioxide, I was observed to degrade to ammonia and formaldehyde (eq 3). In contrast to the extensive degradation of I



(3)

(1) Papers of this series: (a) I, D. H. Rosenblatt, A. J. Hayes, B. L. Harrison, R. A. Streaty, and K. A. Moore, *J. Org. Chem.*, **28**, 2790 (1963); (b) II, D. H. Rosenblatt, L. A. Hull, D. C. DeLuca, G. T. Davis, R. C. Weglein, and H. K. R. Williams, *J. Am. Chem. Soc.*, **89**, 1158 (1967); (c) III, L. A. Hull, G. T. Davis, D. H. Rosenblatt, H. K. R. Williams, and R. C. Weglein, *ibid.*, **89**, 1163 (1967).

(2) P. Brenneisen, C. A. Grob, R. A. Jackson, and M. Ohta, *Helv. Chim. Acta*, **48** (No. 1), 146 (1965), and papers cited therein.

(3) D. M. Gardner, R. Helitzer, and D. H. Rosenblatt, *J. Org. Chem.*, **32**, 1115 (1967).

(4) R. Huisgen and W. Kolbeck, *Tetrahedron Letters*, No. 12, 783 (1965).

(5) T. Higuchi, unpublished results.

(6) T. Higuchi and A. Hussain, submitted for publication.

(7) J. F. Walker, "Formaldehyde," 2nd ed, Reinhold Publishing Corp., New York, N. Y., 1953, p 407.