Synthetic Nucleosides. LXII.[1,2] Facile Displacement Reactions in the D-Mannitol Series. V. Studies on the Selective Conversion of Some Hexitol Derivatives to Aldoses

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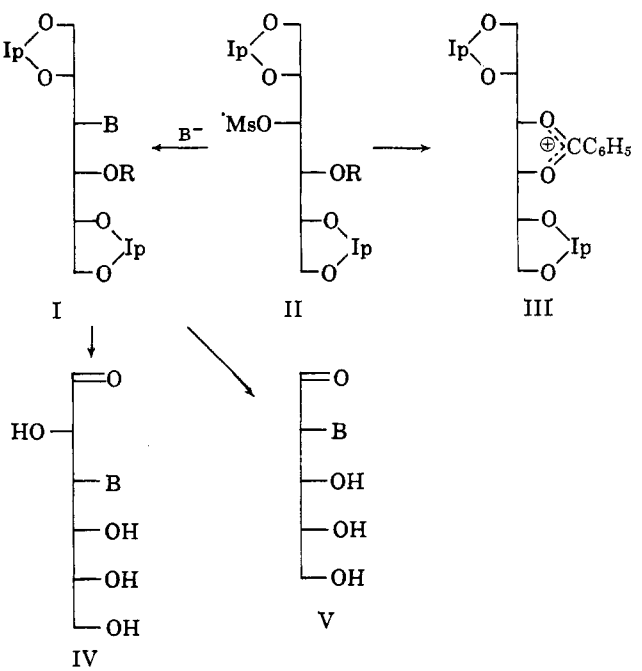
Hydrolysis studies showed there was no selectivity in removing one isopropylidene group from 3-amino-3-deoxy-1,2:5,6-di-*O*-isopropylidene-D-altritol (VIa), its *N*-benzoyl derivative (VIc), or its di-*O*,*N*-benzoyl derivative (VIb), in order that periodate oxidation could give a single pentose. Successful blocking was ultimately achieved by an unsymmetrical blocking technic; 3-amino-4-*O*-benzoyl-*N*-carbophenoxy-3-deoxy-1,2:5,6-di-*O*-isopropylidene-D-altritol (XXXI) could be cyclized by short boiling in pyridine to the unsymmetrical cyclic carbonate, 3-amino-4-*O*-benzoyl-3-deoxy-D-altritol 2,3-carbonate (XXXV), although benzoyl migration to the 6-*O*-benzoyl derivative (XXXIV) was a slower side reaction. As a model series to show the feasibility of the unsymmetrical blocking technic for conversion of a hexitol to a pentose, 4-*O*-benzoyl-3-*O*-carbomethoxy-1,2:5,6-di-*O*-isopropylidene-D-mannitol (XVI) was deacetonated, then cyclized in pyridine to 4-*O*-benzoyl-D-mannitol 2,3-carbonate (XIX); periodate oxidation of XIX and deblocking afforded crystalline D-arabinose.

Earlier work in this area on displacement reactions of the 4-*O*-mesyl group of the D-mannitol derivative (IIa) has shown that the reaction can proceed by direct SN2 reaction (IIa → I) or by anchimeric formation of the ortho ester ion (III)—depending upon the

SCHEME I



a series, R = Bz—
b series, R = CH_3—
c series, R = 2-tetrahydropyranyl-

relative strengths of the anchimeric group and the attacking group (B^-)[3,4] (Scheme I).[5] With a strong nucleophile such as azide ion, formation of I ($B{=}N_3^-$) was favorably competitive; with a weaker nucleophile, such as acetate, the anchimeric reaction predominated. By replacing the benzoate group with an ether function such as methyl (IIb) or 2-tetrahydropyranyl (IIc),[6] only the bimolecular reaction took place, even with a weak nucleophile to give Ib and Ic, respectively. Thus, the use of hexitol derivatives (I) in displacement reactions was successful, whereas the same reactions on displacement of a ring sulfonate of a glycoside were almost always unsuccessful.[7] In order for the greater flexibility in synthetic transformation on hexitol derivatives to be useful for the synthesis of unusual pentoses or hexoses, it would be necessary to find good routes for the selective conversion of the transformed hexitol (I) to pentoses such as V and hexoses such as IV; initial studies on the possible routes for the conversion of I to aldoses (IV and V) are the subject of this paper.

Although the field of hexitol chemistry has been sufficiently established to warrant a review,[8] surprisingly little work has been done on the selective conversion of hexitols to aldoses. Conversion of a hexitol to a lower aldose is certainly possible when the hexitol is blocked in such a way that only one *vic*-glycol is present; an example is the well-known conversion of 1,2:5,6-di-*O*-isopropylidene-D-mannitol with lead tetraacetate to 2,3-*O*-isopropylidene-D-glyceraldehyde.[9] Furthermore, if all the groups of a hexitol except a primary hydroxyl group are blocked, it should be feasible to convert this primary hydroxyl to an aldehyde function either directly or indirectly. For our initial studies we chose to seek blocked hexitols with only one *vic*-glycol group that could be cleaved with periodate or lead tetraacetate to an aldose; thus, this study is concerned mainly with the selective blocking of appropriate hexitols.

Since several derivatives (VI) of 3-amino-3-deoxy-1,2:5,6-di-*O*-isopropylidene-D-altritol were available[4] by suitable SN2 transformation of the D-mannitol derivative (IIa), the possible selective hydrolysis of these derivatives (VI) to a monoisopropylidene derivative, VII or VIII, was investigated (Scheme II) by

(1) This work was supported generously by Grant No. CY-5845 from the National Cancer Institute, U. S. Public Health Service.

(2) For the previous paper of this series, see B. R. Baker and T. Neilson, *J. Org. Chem.*, **29**, 1063 (1964).

(3) B. R. Baker and A. H. Haines, *ibid.*, **28**, 438 (1963), paper LIV of this series.

(4) B. R. Baker and A. H. Haines, *ibid.*, **28**, 442 (1963), paper LV of this series.

(5) Abbreviations used in structural formulas: Ip is isopropylidene; Bz is benzoyl; Ms is methanesulfonyl.

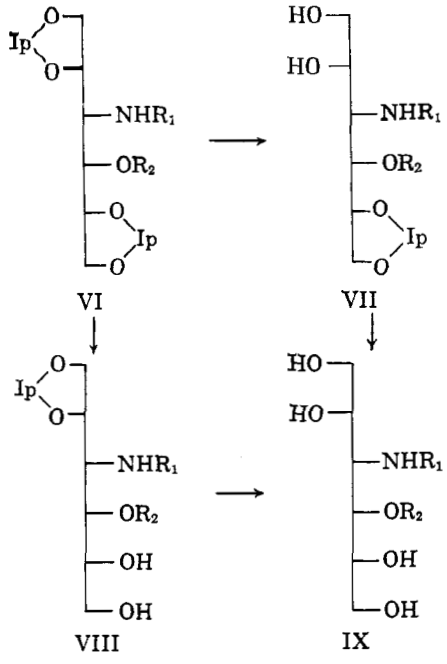
(6) B. R. Baker and H. S. Sachdev, *J. Org. Chem.*, **28**, 2132 (1963), paper LVI of this series.

(7) B. R. Baker and H. S. Sachdev, *ibid.*, **28**, 2135 (1963), paper LVII of this series.

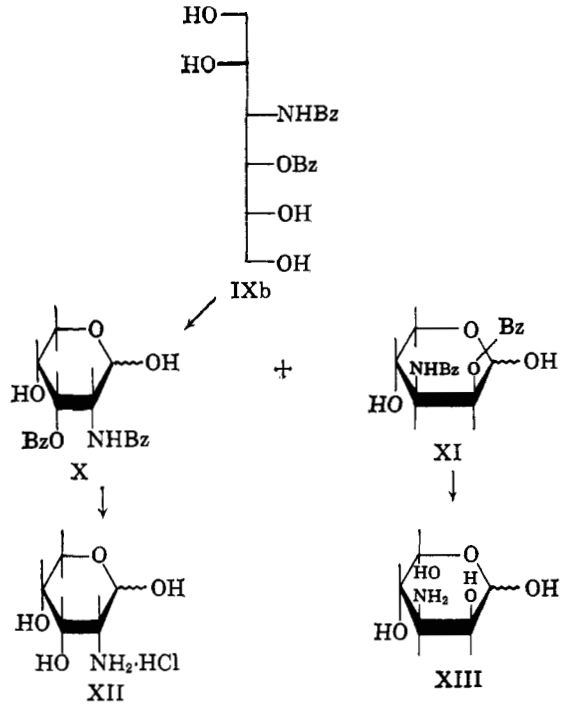
(8) S. A. Barker and E. J. Bourne, *Advan. Carbohydrate Chem.*, **7**, 137 (1952).

(9) E. Baer and H. O. L. Fischer, *J. Biol. Chem.*, **128**, 463 (1939).

SCHEME II



SCHEME III



time–product studies using thin layer chromatography (t.l.c.) or paper chromatography.

The glycoside linkage of methyl 2-amino-2-deoxy-D-glucopyranoside is stable to acid hydrolysis, presumably owing to the protonation of the amino group repelling further protonation of the acetal linkage[10]; it was, therefore, considered possible that the protonated 3-amino group of VIa would slow the hydrolysis of the 1,2-*O*-isopropylidene group compared to the 5,6-*O*-isopropylidene which should result in a favored formation of VIIIa. A solution of VIa in 70% aqueous ethanol containing 0.24 *N* hydrochloric acid was allowed to react at 20°; aliquots were removed at appropriate times and quenched with excess sodium bicarbonate. When the aliquots were investigated by t.l.c. (acetone–chloroform, 2:3), four spots could be detected by ninhydrin. After 60–240 min., the fastest moving spot was starting material (VIa), the slowest moving spot (at the origin) was the fully hydrolyzed product (IXa), and the intermediate spots were presumably VIIa and VIIIa. By the time the intermediate spots were detectable (60 min.), the fully hydrolyzed product was already detectable and later times showed no accumulation of a mono-*O*-isopropylidene derivative. Apparently both isopropylidene groups hydrolyze at similar rates; presumably the acetal-oxygen at C-1 can still be protonated even though the amino group is protonated, thus resulting in no appreciable selective hydrolysis. Complete hydrolysis of VIa with 0.4 *N* hydrochloric acid to IXa required 7 hr. at 0°.

Similar time studies on the hydrolysis of the dibenzoyl derivative (VIb) or the *N*-benzoyl derivative (VIc) showed that selective hydrolysis to VII or VIII was not feasible, since none of the intermediate mono-*O*-isopropylidene derivative accumulated and the final product (IX) began to appear soon after VII–VIII. The fully de-acetonated products (IXb and IXc) were isolated in crystalline form in 79 and 76% yields, respectively, when hydrolysis was allowed to go to completion.

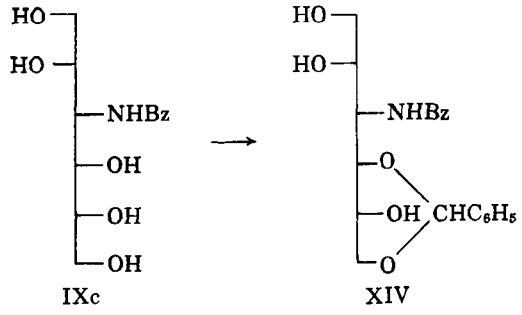
When the dibenzoyl derivative (IXb) was treated with periodate in aqueous dimethylformamide, 1 mole of periodate was consumed in less than 15 min.; about 2 days is necessary for a 2nd mole of periodate to be consumed. Thus, when IXb consumes 1 mole of periodate, the resultant pentose immediately cyclizes to X or XI (Scheme III); the ratio of X to XI is of course dependent upon the relative rate of cleavage of the two *vic*-glycol groups in IXa. The resultant X or XI or mixture of the two could then be expected to react with periodate slowly, since only the open-chain forms of X and XI have a *vic*-glycol system. The oxidation product(s) moved as a single spot (detected by aniline phthalate) on paper chromatography; however, hydrolysis of X–XI did not give a single aminopentose (XII or XIII), but a mixture as shown by paper chromatography.

When the di-*O*-isopropylidenealtritol (VIb) hydrolysis was quenched when the largest quantity of VIIb and VIIc were present and then the mixture subjected to periodate oxidation followed by acid hydrolysis, the same two spots (XII and XIII) were obtained. Thus neither route was considered to be sufficiently selective to be of preparative utility.

By use of the "Barker and Bourne rules," [11] it might be anticipated that IXc would react preferentially with benzaldehyde to give a mono-4,6-*O*-benzylidene derivative (XIV), which then has a single *vic*-glycol system oxidatively cleavable to a derivative of 2-amino-2-deoxy-D-ribose. Unfortunately—owing to its insolubility—IXc failed to react appreciably when only 1 mole of benzaldehyde was present in reaction mixtures; with excess benzaldehyde in benzene on the presence

(10) R. C. G. Maggride and A. Neuberger, *J. Chem. Soc.*, 745 (1938).

(11) S. A. Barker and E. J. Bourne, *ibid.*, 905 (1952).



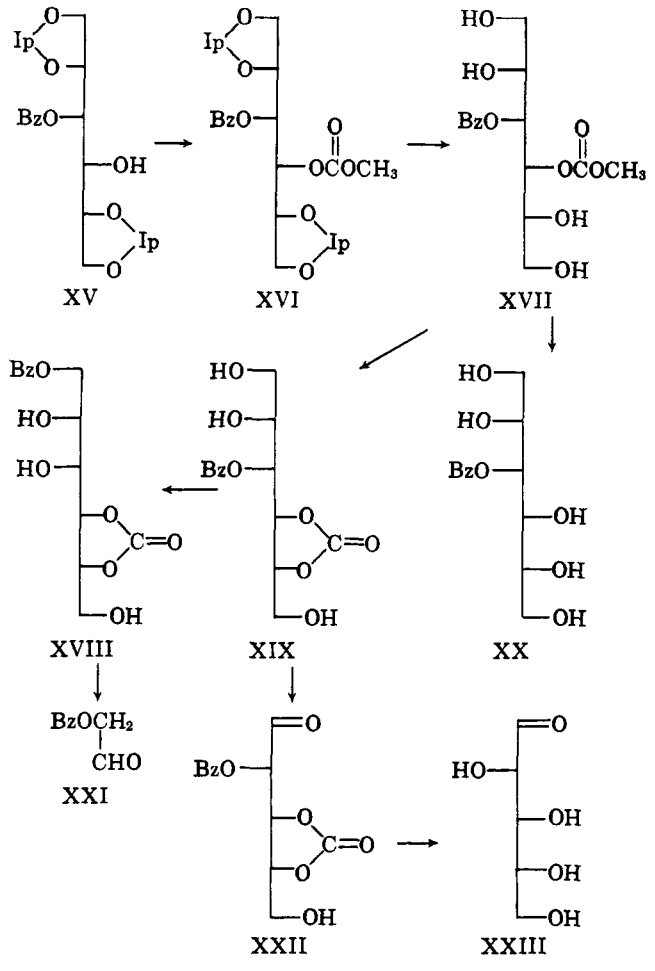
of *p*-toluenesulfonic acid or cupric sulfate, a non-crystalline product was obtained which had properties expected for a di-*O*-benzylidene derivative.

From the preceding studies on derivatives of VI and IX, it was clear that selective reactions involving the 1, 2, 4, and 5 hydroxyls were not likely to be found that would lead to suitable preparative methods. We, therefore, turned our attention to derivatives of I with an R group that could be cyclized onto the 4-hydroxyl group after the isopropylidene groups had been removed; such an unsymmetrical cyclization would then give a system with only one remaining *vic*-glycol. A model series starting with 3-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-D-mannitol (XV)[12] was first explored to see if the key cyclization step (XVII → XIX), followed by oxidation to the D-arabinose derivative (XXII), was feasible.

Reaction of XV with methyl chlorocarbonate in pyridine to give the crystalline mixed carbonate (XVI) was sluggish. The best conditions found were 1:1 chloroform–pyridine as solvent with excess methyl chlorocarbonate at 65° for 2 days; under these conditions, 46% of XVI was obtained and 33% of unchanged XV was recovered. When XVI was hydrolyzed under excessively strenuous conditions, not only were the isopropylidene groups removed, but the carbomethoxy group also was lost and crystalline 3-*O*-benzoyl-D-mannitol (XX) was obtained. As a result, it was necessary to do a time study of the hydrolysis; 0.5 *N* hydrochloric acid in 56% aqueous tetrahydrofuran at 23° was chosen as the hydrolysis medium and neutralized aliquots were subjected to t.l.c. After 9 hr., only a trace of starting material could be detected and only a trace of 3-*O*-benzoyl-D-mannitol (XX) had formed; the main spot (R_f 0.27) appeared to be that of the desired product (XVII). When the reaction was extended to 19 hr., considerable XX had formed (Scheme IV).

When a preparative-sized hydrolysis of XVI was run for 12 hr. in aqueous tetrahydrofuran at 20–25°, the resultant oily product showed both cyclic and linear carbonate carbonyls at 1780 and 1740 cm.$^{-1}$, corresponding to XIX and XVII, respectively. This sirup was treated further with boiling pyridine, 5 hr. being required to complete the cyclization of XVII to XIX—as shown by the loss of the 1740-cm.$^{-1}$ linear carbonate carbonyl band.[13] From this syrup could then be isolated 3% of crystalline 3-*O*-benzoyl-D-mannitol (XX), and a varying amount (depending on the hydrolysis conditions) of a crystalline benzoyl

SCHEME IV



carbonate derivative also was isolated which was ultimately shown to be the 6-benzoate (XVIII) by periodate oxidation to glycol aldehyde benzoate (XXI); the major product was still a sirup, presumably XIX. If the reaction temperature was raised to 35°, then the yields of XVIII and XX were increased to 17 and 11%, respectively, but cyclization to XIX was nearly complete without pyridine treatment; after removal of the crystalline 6-benzoate (XVIII), the remaining crude 3-benzoate (XIX) was treated with pyridine, oxidized with periodate to XXII, then deblocked to give crystalline D-arabinose. Although the yield of D-arabinose was low, the feasibility of the method was shown; rather than spend further development time on this sequence, we turned our attention back to the more important 3-amino-D-altritol derivative (VIa).

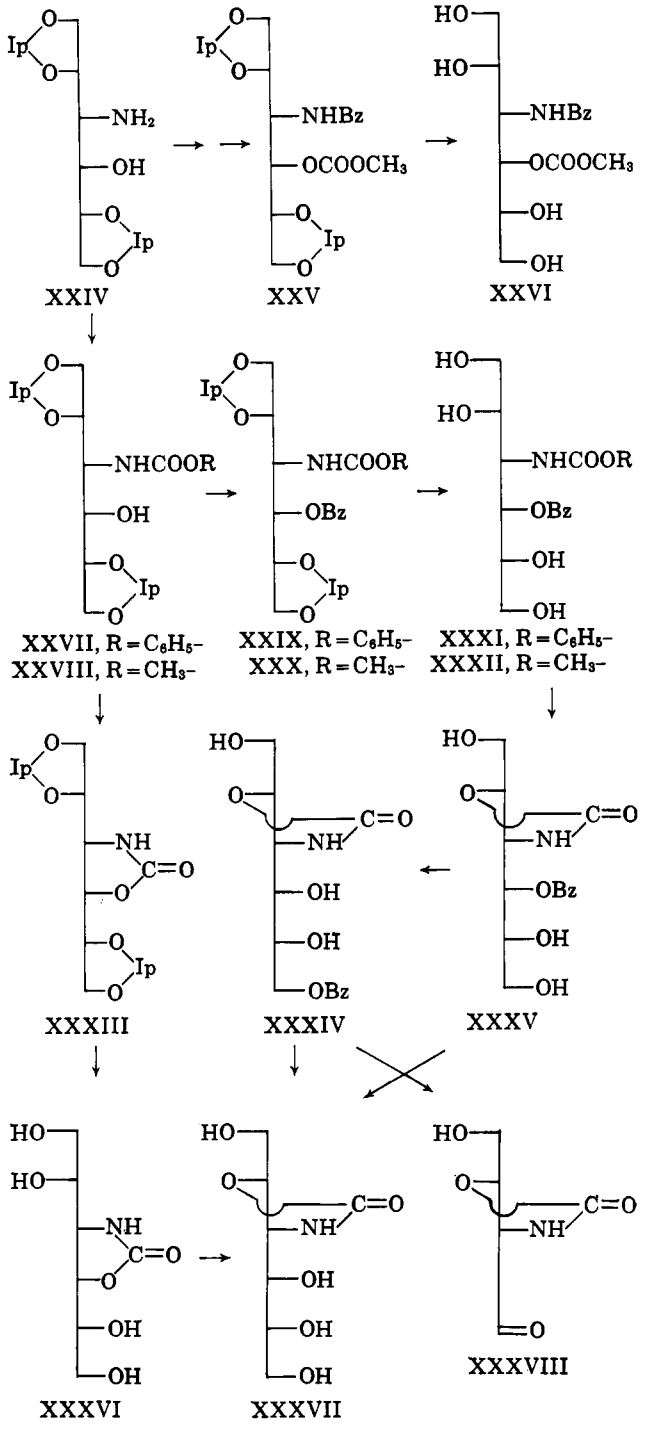
Dependent upon whether the carbomethoxy function is placed on the 3-amino group (XXXII) or on the 4-hydroxyl group (XXVI) of the 3-amino-D-altritol system (XXIV), it should be possible to obtain 3-amino-D-lyxose *via* XXXV or 2-amino-D-ribose, respectively, under controlled conditions. Initial attention was directed towards the *N*-carbomethoxy series. Reaction of XXIV with methyl chloroformate in methylene chloride in the presence of triethylamine afforded a 66% yield of crystalline XXVIII (Scheme V). Benzoylation to crystalline XXX proceeded smoothly with pyridine–benzoyl chloride.

A kinetic study on the hydrolysis of the isopropylidene groups in XXX was run in acidic aqueous tetrahydrofuran as described for the mannitol series

(12) J. M. Sugihara and G. U. Yuen, *J. Am. Chem. Soc.* **79**, 5780 (1957).

(13) The cyclization of a linear carbonate to a cyclic carbonate in boiling pyridine has been demonstrated previously by E. J. Reist, R. R. Spencer, and B. R. Baker, *J. Org. Chem.* **23**, 1958 (1958).

SCHEME V



(XVI → XVII); t.l.c. in benzene–methanol (5:1) showed that all the starting material was gone after 12 hr. at room temperature in the presence of 0.4 *N* hydrochloric acid, resulting in a major product with R_f 0.21. Further reaction time did not cause appearance of further cleavage products as in the case of XX. The product from a 12-hr. preparative run was a sirup that showed broad infrared absorption of the carbonyls of benzoate and linear urethane at 1720 cm.$^{-1}$ and NH deformation of a linear urethane at 1510 cm.$^{-1}$. Gomper and Herlinger[14] have indicated that the infrared spectra of oxazolones show carbonyl absorption at 1740–1750 cm.$^{-1}$, but show no amide–NH bond near 1510 cm.$^{-1}$. It was concluded that this hydrolysis product was mainly the linear urethane (XXXII) which was further substantiated by the presence of 0.6 equiv. of O–CH_3 in the n.m.r.

When the linear urethane (XXXII) was boiled in pyridine for 5 hr.—conditions used for cyclization of XVII to XIX—no reaction occurred as shown by the unchanged infrared spectrum. Although XXXII could be cyclized initially to XXXV in the higher boiling collidine—as shown by the appearance of a 1740-cm.$^{-1}$ band of a cyclic urethane and the disappearance of the 1510-cm.$^{-1}$ NH band—the t.l.c. pattern showed a series of spots indicating acyl migration under these strenuous conditions.

Attempted cyclization of XXXII with a catalytic quantity of solid sodium methoxide in dimethylformamide[15] was successful, as shown by the appearance of the 1740-cm.$^{-1}$ band, but again t.l.c. indicated acyl migration. With methanolic sodium methoxide cyclization of XXXII took place, but the benzoyl group simultaneously was removed as could be anticipated; the resultant crystalline product was later shown unequivocally to have structure XXXVII.

Since the linear urethane (XXXII) cyclized so slowly to XXXV that acyl migration appeared to be a serious side reaction, the more base-reactive *O*-phenylurethane (XXXI) was synthesized and its cyclization studied. Reaction of the amino-D-altritol derivative (XXIV) with phenyl chloroformate in dichloromethane containing triethylamine gave 86% yield of the carbophenoxy derivative (XXVII) in two dimorphic forms. Benzoylation with pyridine–benzoyl chloride afforded the crystalline benzoate (XXIX) in 94% yield. A time study on acid hydrolysis of the isopropylidene group of XXIX under the now standard conditions by use of the t.l.c. technic showed that hydrolysis was complete in 18 hr. at room temperature and that no further reaction occurred in 24 hr. A preparative run afforded the crystalline carbophenoxy-amino hexitol (XXXI) in 70% yield.

Since benzoyl migration during cyclization of XXXI to XXXV in boiling pyridine was a probable side reaction, a time–product study was made of aliquots by use of t.l.c. and infrared spectra. At the end of 30-min. reflux, t.l.c. in benzene–methanol (4:1) showed that starting material (R_f 0.44) had disappeared and a new major product with R_f 0.35 appeared along with a minor product at R_f 0.40; the infrared spectrum showed the loss of the 1510-cm.$^{-1}$ amide–NH band. At the end of 10 min., starting material and some product at R_f 0.35 were present; the side product at R_f 0.40 was not apparent. At the end of 9-hr. reflux, only one spot (R_f 0.40) was detectable; these results indicated that the desired cyclization to XXXV was probably taking place followed by a slower benzoate migration. When the reaction mixture was processed at the end of 30 min., no crystalline product could be isolated; however, at the end of 3-hr. reflux, a crystalline benzoate could be isolated in 62% yield.

That this benzoate had the rearranged structure, XXXIV, was shown as follows. There are four possible monobenzoates of XXXVII, including XXXIV and XXXV. If the cyclic urethane also rearranged to XXXVI, then there are four more possible mono-

(14) R. Gomper and H. Herlinger, *Ber.*, **89**, 2825 (1956).

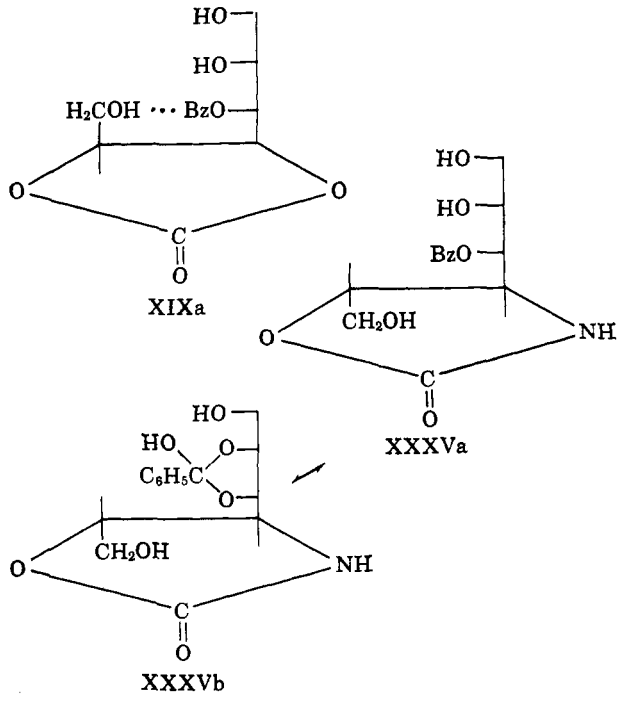
(15) B. R. Baker and J. P. Joseph, *J. Am. Chem. Soc.*, **77**, 15 (1955).

benzoates. A quantitative periodate tetration showed the uptake of a single mole (complete in 24 hr.), and *O*-benzoylglycolaldehyde (XXI) could be isolated as the 2,4-dinitrophenylhydrazone in 44% yield; only structure XXXIV is compatible with this data.

Debenzoylation of the crystalline monobenzoyl urethane (XXXIV) with methanolic sodium methoxide afforded a cyclic urethane, identical with that obtained, as described earlier, from treatment of XXXII under the same conditions; this urethane could have structure XXXVII if no rearrangement of the oxazolidone had occurred, or it could have structure XXXVI if the oxazolidone did rearrange. That the debenzoylation product had structure XXXVII was shown by synthesis of the isomeric XXXVI by an alternate route and comparison of their n.m.r. spectra.

When the *O*-phenylurethane (XXVII) was refluxed in pyridine, cyclization to the crystalline oxazolidone (XXXIII) occurred in 56% yield; this compound also could be prepared by direct fusion of XXIV with diphenyl carbonate. Acid hydrolysis of XXXIII afforded 83% of the deacetonated oxazolidone (XXXVI), clearly isomeric to XXXVII. In order to show that the structural assignments were not the reverse as a result of acid-catalyzed rearrangement, the oxazolidone (XXXVII) was shown to be stable under the conditions used for the preparation of XXXVI—unequivocal proof for the structural assignments.

Attempted confirmation of the structural assignment by n.m.r. was equivocal. The proton of the carbinyl group of an ester—in this case the oxazolidone proton on the carbon bearing the cyclic acyloxyl group—usually gives a signal downfield from a proton attached to the carbinyl group of an alcohol. It can be calculated that the splitting pattern of the proton in question by adjacent protons should be simpler in the case of the *cis*-oxazolidone (XXXVI) than the *trans*-oxazolidone (XXXVII). In deuterium oxide, resolution was insufficient at 20–80° to make an unequivocal assignment of structure by J values, but XXXVI appeared to give a simpler spectrum than XXXVII in this carbinyl region.



Although XXXVI and XXXVII were both stable to dilute acid at room temperature, such was not the case with base. Treatment of XXXVI with methanolic sodium methoxide readily rearranged it to XXXVII, presumably *via* a linear methyl urethane. Thus, the *trans* conformation (XXXVII) is apparently more stable than the *cis* conformation XXXVI.

An interesting contrast is the ready migration of the *O*-benzoate of XXXVa in boiling pyridine compared to the stability of the *O*-benzoate (XIXa) under the same conditions. Benzoyl migration to the 5-hydroxyl could occur readily in XXXVa *via* the ortho ester (XXXVb), then migrate further to the 6-hydroxyl by the same mechanism.[16] Although XIXa could form a similar ortho ester with the adjacent 5-hydroxyl group, the *cis*-hydroxymethyl of XIXa could hydrogen bond to the 4-benzoate, hence competing with the tendency to form an ortho ester; in contrast, the *trans*-hydroxymethyl group of XXXVa cannot hydrogen bond intramolecularly with the 4-benzoate.

Further work will be necessary to see if a *p*-nitrobenzoyl or *p*-chlorobenzoyl blocking group for the 4-hydroxyl of XXXa will be somewhat more stable towards acyl migration or if a *p*-nitrocarbophenoxy group will ring close more rapidly. Since ring closure of XXXI to XXXV is complete in 30 min. in boiling pyridine, whereas benzoyl migration is only about half complete in 3 hr., an acyl blocking group with no more than twice the stability of benzoate or a ring-closing group with no less than twice the reactivity should suffice to complete the synthesis of 3-amino-3-deoxy-D-lyxose *via* an ester such as XXXV. Additional studies on conversion of XXXVII to 2-amino-2-deoxy-D-threose, XXXV to 3-amino-3-deoxy-D-altrose, and 4-amino-D-talose *via* XXVI are worthy of exploration; in this way it could be determined whether or not unusual hexitols derivable by displacement reactions in the D-mannitol series can be converted to unusual tetroses, pentoses, or hexoses by the unsymmetrical blocking technics described in this paper.

Experimental[17]

3-Benzamido-3-deoxy-D-altritol (IXc).—To a solution of 1.5 g. of VIc in 15 ml. of methanol was added 10 ml. of cold 1 *N* aqueous hydrochloric acid. After 7 hr. at 0°, the solution was neutralized by stirring with excess silver carbonate, then clarified by filtration through a Celite pad. The solution was spin evaporated *in vacuo* and the residue was further dried by spin evaporation *in vacuo* of several portions of 1:1 ethanol–benzene. Crystallization of the sirup from ethyl acetate–ethanol gave 0.64 g. (55%)

(16) (a) Base-catalyzed *O*-benzoyl migration directly from the 3-hydroxyl to the 6-hydroxyl has been observed with 1,2-*O*-isopropylidene-D-glucose; *cf.* H. Ohle, *Ber.*, **57B**, 403 (1924), and E. J. Reist, R. R. Spencer, and B. R. Baker, *J. Org. Chem.*, **23**, 1757 (1958). Therefore, direct 4-benzoate migration in XXXVa to the 6-benzoate (XXXIV) is also a possibility; see also (b) E. Pascu, *Advan. Carbohydrate Chem.*, **1**, 109 (1945); and (c) M. L. Wolfrom, E. P. Swan, K. S. Ennor, and A. Chaney, *J. Am. Chem. Soc.*, **81**, 5701 (1959).

(17) Melting points were determined in capillary tubes with a Mel-Temp block and those below 230° are corrected. Infrared spectra were determined in Nujol mull with a Perkin-Elmer Model 137B spectrophotometer. Optical rotations were measured in a 1-dm. microtube in *N,N*-dimethylformamide; per cent concentrations are grams per 100 ml. Thin layer chromatograms were performed with silica gel G in 5:1 benzene–methanol and spots were detected by iodine vapor, unless otherwise indicated. Paper chromatograms were performed on Whatman No. 1 paper with the upper phase of 1-butanol–ethanol–water (4:1:5); spots were detected by ninhydrin if a free amino group was present, by aniline hydrogen phthalate if a reducing sugar was present, or by an ultraviolet lamp if benzoate was present.

of product, m.p. 105–108°. The analytical sample was obtained by recrystallization from the same solvent as white crystals, m.p. 108–110°; ν_{max} 3500, 3350, 3200 (NH, OH), 1640 (amide C=O), 1510 (amide II), and 720, 690 cm.$^{-1}$ (CH of benzoate); $[\alpha]^{23}D$ + 22 ± 3° (0.16%).

Anal. Calcd. for $C_{13}H_{19}NO_6$: C, 54.7; H, 6.73; N, 4.91. Found: C, 54.2; H, 6.68; N, 4.96.

In a later run a different dimorph, m.p. 116–118°, was obtained in 76% yield; ν_{max} 3650, 3400, 3300 (NH, OH), 1625 (amide C=O), 1540 (amide II), 690 cm.$^{-1}$ (CH of benzoate).

Anal. Found: C, 54.7; H, 6.47; N, 4.88.

This compound (IXc) consumed 4.7 moles of periodate in 10 min. and 6 moles in 20 hr., indicating overoxidation.

The possibility of obtaining a monoisopropylidene derivate of VIIc or VIIIc was shown to be unfeasible by a time study. A solution of 0.15 g. of VIc in 1.5 ml. of methanol and 1 ml. of 0.01 *N* aqueous hydrochloric acid was stored at 20°; 0.1-ml. aliquots were removed at time intervals and immediately neutralized with sodium bicarbonate. Paper chromatograms were run with 20 λ of each aliquot, using VIc (R_f 0.90) and IXc (R_f 0.52) as standards. After 9 hr., starting material VIc and monoisopropylidene derivatives VIIc and VIIIc (R_f 0.80) were present; before all the starting material had been consumed, the nonacetonated hexitol (IXc) at R_f 0.52 was present, thus showing that there was no selectivity in hydrolysis of the isopropylidene groups of VIc. All of VIc was consumed after 20 hr., but a strong spot of IXc was present; at no time was there an accumulation of monoacetone derivatives.

3-Benzamido-4-*O*-benzoyl-3-deoxy-D-altritol (IXb).—To a stirred solution of 6.3 g. of VIb[4] in 300 ml. of tetrahydrofuran was added 300 ml. of 1 *N* aqueous hydrochloric acid. Some VIb separated which gradually redissolved on stirring. After 18 hr., the solvent was concentrated by spin evaporation *in vacuo* until most of the tetrahydrofuran had been removed. The product was collected on a filter, washed with water, and dried, then leached with 100 ml. of chloroform to remove any intermediate hydrolysis products. Recrystallization from methanol gave 4.1 g. (79%) of white crystals, m.p. 189–192°. The melting point of IXb varied with each preparation within the range of 179–195°, although it was usually sharp. The infrared spectra of the materials with different melting points were indistinguishable. The analytical sample had m.p. 179–181°; $[\alpha]^{23}D$ + 13 ± 1° (1.08%); ν_{max} 3400 (broad OH and NH), 1690 (ester C=O), 1610 (amide C=O), 1510 (amide NH), and 718 cm.$^{-1}$ (CH of benzoate).

Anal. Calcd. for $C_{20}H_{23}NO_7$: C, 61.7; H, 5.97; N, 3.60. Found: C, 61.5; H, 5.60; N, 3.67.

This compound in 10% aqueous dimethylformamide consumed 1.0 moles of periodate in 15 min., 1.2 moles in 75 min., and 2.5 moles in 46 hr. In a preparative run, the reaction was stopped after 45 min. by addition of a slight excess of ethylene glycol and the products (X and XI) isolated by extraction with dichloromethane. Paper chromatography of the sirup showed only a single spot when detected by aniline hydrogen phthalate. That this was a mixture of X and XI was indicated by hydrolysis with boiling 1 *N* hydrochloric acid for 48 hr. Spin evaporation of the charcoal-clarified solution *in vacuo* at room temperature gave a glass that showed on paper chromatography a series of spots positive to ninhydrin; the major spots (XII and XIII) had R_f 0.09 and 0.01.

Reaction of IXc with 3 moles of benzaldehyde in boiling benzene in the presence of a trace of *p*-toluenesulfonic acid, after removal of water under a Dean–Stark trap, gave an oil which had characteristics of a dibenzylidene derivative rather than XIV; with 1 mole of benzaldehyde, starting material was recovered after water removal was complete, also indicating formation of a dibenzylidene derivative. With anhydrous copper sulfate as a catalyst, similar results were obtained.

3-*O*-Benzoyl-4-*O*-carbomethoxy-1,2:5,6-di-*O*-isopropylidene-D-mannitol (XVI).—To a stirred solution of 3.0 g. of XV[3,12] in 10 ml. of chloroform and 20 ml. of pyridine cooled in an ice bath and protected from moisture was added dropwise a solution of 3 ml. of methyl chloroformate in 10 ml. of chloroform over a period of 15 min. After being heated in a bath at 65° for 2 days, the mixture was cooled and poured into 200 ml. of ice–water with good stirring. The separated aqueous layer was extracted with additional chloroform (two 20-ml. portions). The combined chloroform extracts were washed with two 30-ml. portions of water, dried with magnesium sulfate, then spin evaporated to residue *in vacuo*. Traces of pyridine were removed from the residue by spin evaporation of toluene (two 30-ml. portions). Crystallization of the residue from methanol gave 1.4 g. (40%) of white crystals, m.p. 86–87°; $[\alpha]^{24}D$ + 21.9 ± 0.7° (0.46%); ν_{max} 1740 (carbonate C=O), 1710 (benzoate C=O), and 705 cm.$^{-1}$ (benzoate CH).

Anal. Calcd. for $C_{21}H_{28}O_9$ C, 59.4; H, 6.60. Found: C, 59.4; H, 6.42.

The mother liquor was spin evaporated *in vacuo* and the residue recrystallized from ethyl acetate–petroleum ether (b.p. 30–60°) to give 1.0 g. (33%) of unchanged XV. An additional 0.2 g. (total 46%) of product XVI could be obtained by evaporation of the filtrate and crystallization from methanol.

Although the carbomethoxylation of XV was explored in depth, no conditions could be found that converted more of XV to the product. However, 5 days at room temperature gave the same yield as 2 days at 65°.

3-*O*-Benzoyl-D-mannitol (XX).—This compound was isolated as a by-product in the acid hydrolysis of XVI, as described subsequently. Recrystallization from ethanol gave white crystals, m.p. 173–174°; $[\alpha]^{24}D$ + 5.7 ± 0.6° (0.76%); ν_{max} 3450, 3300, (OH), 1690 (hydrogen-bonded C=O of benzoate), and 715 cm.$^{-1}$ (CH of benzoate).

Anal. Calcd. for $C_{13}H_{18}O_7$: C, 54.5; H, 6.29. Found: C, 54.7; H, 6.13.

Sugihara and Yuen[12] have prepared this compound by ion-exchange-catalyzed hydrolysis of XV and have recorded m.p. 177–178° and $[\alpha]^{22}D$ +6.35° (2.9% in acetone). Although they believed the structure to be the 3-benzoate (XX) because of the mild conditions used, there was a possibility for our more severe conditions to cause rearrangement of the 3-benzoate to the 1-benzoate, particularly since 1-*O*-benzoyl-D-mannitol 4,5-carbonate (XVIII) also was isolated in our hydrolysis. However, XX is clearly isomeric to 1-*O*-benzoyl-D-mannitol,[16c] m.p. 121–122°, $[\alpha]^{15}D$ +9° (5.22% in ethanol).

The following preparative method was developed. A solution of 500 mg. of XV in 22 ml. of methanol and 20 ml. of 1 *N* aqueous hydrochloric acid was allowed to stand at room temperature for about 18 hr. The solution was neutralized by stirring with Dowex 21K (carbonate form), then spin evaporated *in vacuo*. The solid residue (0.34 g.) was recrystallized from ethanol to yield 0.25 g. (64%) with m.p. 173–174° that was identical with the preparation isolated from hydrolysis of XVII.

1-(and 3)-*O*-Benzoyl-D-mannitol 4,5-Carbonate (XVIII and XIX).

A. Kinetic Study of Hydrolysis.—A solution of 100 mg. of XVI in 10 ml. of tetrahydrofuran and 8 ml. of 1 *N* hydrochloric acid was stirred at 23°. Aliquots were removed at intervals and neutralized with Dowex 21K (carbonate form). Each aliquot was analyzed by t.l.c. using as standards XVI (R_f 0.92) and XX (R_f 0.16). At the end of 2 hr., a spot at R_f 0.7 was detectable (monoisopropylidene derivative of XVII) and starting material was still present. At the end of 7–9 hr., all the starting material was consumed and the major spot was at R_f 0.27 (a mixture of XVII and XIX). After 9 hr., XX (R_f 0.16) began to appear and, at the end of 52 hr., was one of the two major spots along with R_f 0.30. It appears that XX is formed by the hydrolysis of XVII competing with ring closure to XIX.

B. Cyclization of XVII.—The infrared spectrum of the hydrolysis products after a 12-hr. hydrolysis showed carbonyl absorption of benzoate at 1710, linear carbonate (of XVII) at 1740, and cyclic carbonate (of XIX) at 1780 cm.$^{-1}$. After longer reaction time or warmer temperature, the 1740-cm.$^{-1}$ band gradually decreased and the 1780-cm.$^{-1}$ band increased showing acid-catalyzed cyclization of XVII to XIX; however, these more strenuous conditions also led to a greater proportion of the rearranged product (XVIII) and the overhydrolyzed product (XX). Thus, the ratio of XVII, XIX, and XX will vary somewhat depending upon the reaction conditions. The XX present was readily removed by crystallization and the linear carbonate (XVII) could be cyclized to XIX in boiling pyridine. A kinetic study showed that cyclization was complete after 5-hr. reflux in pyridine.

C. Preparative Method.—A solution of 4.0 g. of XVI in 160 ml. of tetrahydrofuran and 120 ml. of 1 *N* aqueous hydrochloric acid was stirred for 12 hr. at 30–35°. The solution was neutralized with Dowex 21K (carbonate form), then spin evaporated *in vacuo*. Crystallization of the residue from methanol gave 0.50 g. (17%) of XVIII, m.p. 163–165°. Recrystallization from ethanol gave white prisms, m.p. 164–166°; $[\alpha]^{24}D$ 0.5 ± 0.8° (0.65%); ν_{max} 3400, 3250, (OH), 1810 (cyclic carbonate C=O), 1690 (benzoate C=O), and 715 cm.$^{-1}$ (benzoate CH).

Anal. Calcd. for $C_{14}H_{16}O_8$: C, 53.8; H, 5.13. Found: C, 54.0; H, 5.21.

The filtrate from the 0.50 g. was spin evaporated *in vacuo*. Crystallization from ethyl acetate containing ethanol gave 0.3 g. (11%) of XX. Spin evaporation of the filtrate *in vacuo* gave a residue which was dissolved in 30 ml. of reagent pyridine and the solution refluxed for 5 hr. The residue remaining after spin evaporation *in vacuo* was partitioned between 20 ml. of benzene and 20 ml. of water. The separated aqueous layer was washed once more with 20 ml. of benzene; the benzene washings containing by-products were rejected. The aqueous solution was spin evaporated *in vacuo* leaving a sirup of crude XIX that could not be crystallized, but was used for periodate oxidation; yield 1.6 g. (54%); ν_{max}^{film} 1790 (cyclic carbonate C=O), 1710 (benzoate C=O), and no 1740-cm.$^{-1}$ linear carbonate carbonyl. Thin layer chromatography showed one major spot at R_f 0.45 in 4:1 benzene–methanol.

Conversion of XIX to D-Arabinose (XXIII).—A solution of the above 1.6 g. of XIX in 110 ml. of water containing 4.4 g. of sodium periodate was allowed to stand. After 30 min. the solution was extracted with benzene to remove by-products resulting from oxidation of mannitol monobenzoates; infrared examination showed no carbonate carbonyl absorption. After 8 hr., the periodate solution was extracted with five 50-ml. portions of ethyl acetate. The combined extracts were dried with magnesium sulfate, then spin evaporated *in vacuo*. The residue was dissolved in ethanol and stirred with Dowex 21K (carbonate form), until neutral when spotted on moist indicator paper which removed traces of acetic acid that interfered with the next step; yield 0.85 g. (59%) of crude XXII; ν_{max}^{film} 1780 (cyclic carbonate C=O), and 1710 cm.$^{-1}$ (benzoate C=O); t.l.c. in 10:1 benzene–methanol showed a single spot at R_f 0.30.

To a solution of 0.80 g. of crude XXII in 10 ml. of methanol was added 0.3 ml. of 1 *N* methanolic sodium methoxide. After standing for 18 hr. at room temperature in a closed flask, the solution was neutralized with Dowex 50W-X8 (H^+ form). The filtrate was evaporated to a sirup *in vacuo* and the residue crystallized from a small amount of methanol to yield 0.10 g. (23%) of D-arabinose (XXIII), m.p. 154–155°. Recrystallization from methanol gave white crystals of D-arabinose, m.p. 159–160°, $[\alpha]^{24}D$ −42.1 ± 0.6° (0.92%). A mixture with authentic D-arabinose (m.p. 159–160°) gave no depression in melting point and the infrared spectra of the two samples were identical.

In some runs the D-arabinose was isolated as the tosylhydrazone, m.p. 153°, that was identical with a sample, m.p. 156°, prepared from authentic D-arabinose.

3-Benzamido-4-*O*-carbomethoxy-3-deoxy-1,2:5,6-di-*O*-isopropylidene-D-altritol (XXV). A.—Treatment of 3-benzamido-3-deoxy-1,2:5,6-di-*O*-isopropylidene-D-altritol[4] with methyl chloroformate in chloroform–pyridine, as described for the preparation of XVI, after crystallization from ethanol, gave 34% of crude XXV, m.p. 138–142°. Recrystallization from methanol–water afforded white crystals, m.p. 155–157°; $[\alpha]^{24}D$ + 8.9 ± 0.5° (0.72%); ν_{max} 3500 (NH), 1740 (linear carbonate C=O), and 1640, 1610 cm.$^{-1}$ (amide I and II).

Anal. Calcd. for $C_{21}H_{29}NO_8$: C, 59.6; H, 6.86; N, 3.31. Found: C, 59.5; H, 6.63; N, 3.32.

B.—Preparation by the sodium salt method as described for the corresponding carboisobutoxy derivative gave, after crystallization from ethyl acetate–petroleum ether (b.p. 30–60°), 30 mg. (26%) of product, m.p. 155–157°, that was identical with preparation A.

3-Benzamido-4-*O*-carboisobutoxy-3-deoxy-1,2:5,6-di-*O*-isopropylidene-D-altritol.—A stirred mixture of 100 mg. of 3-benzamido-3-deoxy-1,2:5,6-di-*O*-isopropylidene-D-altritol,[4] 5 ml. of toluene, and 12 mg. of a 55% suspension of sodium hydride, protected from moisture, was stirred for 15 min. at 30–35° when hydrogen evolution was complete. After the addition of 1.1 equiv. of isobutyl chloroformate, the mixture was stirred in a bath at 50° for 18 hr. The toluene solution was washed with water, dried with magnesium sulfate, and spin evaporated. The crystalline residue was recrystallized from ethyl acetate–petroleum ether (b.p. 30–60°) to give 60 mg. (47%) of product, m.p. 158–160°; no attempt was made to get a second crop. Recrystallization again from the same solvents gave white crystals, m.p. 160–161°; $[\alpha]^{24}D$ + 5.1 ± 0.9° (0.39%); ν_{max} 3400 (NH), 1740 (carbonate C=O), and 1640, 1510 cm.$^{-1}$ (amide I and II).

Anal. Calcd. for $C_{24}H_{35}NO_8$: C, 61.9; H, 7.53; N, 3.01. Found: C, 62.0; H, 7.72; N, 2.82.

3-Amino-*N*-carbophenoxy-3-deoxy-1,2:5,6-di-*O*-isopropylidene-D-altritol (XXVII).—To a stirred solution of 2.0 g. of XXIV[4] in 80 ml. of methylene chloride and 2 ml. of triethylamine, protected from moisture and cooled in an ice bath, was added 1.1 ml. of phenyl chloroformate. The mixture was stirred at ambient temperature for 75 min. after the addition, then washed with water, 100 ml. of ice-cold 0.2 *N* hydrochloric acid, and again with water (two 50-ml. portions). Dried with magnesium sulfate, the solution was spin evaporated *in vacuo*. Crystallization from ethyl acetate–petroleum ether (b.p. 30–60°) gave 2.6 g. (94%) of white crystals as a mixture of fine needles and heavy prisms. The needles were readily separated by swirling the mixed crystals with petroleum ether (b.p. 30–60°) and decanting the suspension of needles from the heavy prisms; in this way 2.5 g. of prisms, m.p. 54–65°, and 0.10 g. of needles, m.p. 62–65°, were obtained. A mixture of the two melted at 54–65°; they are apparently dimorphs since both give proper combustion analyses for XXVII. The needles had ν_{max} 3450, 3300 (NH, OH), 1720 (urethane C=O), and 1510 cm.$^{-1}$ (amide NH). The prisms had $[\alpha]^{24}D$ + 5.4 ± 0.3° (1.15%) and ν_{max} 3450, 3300 (NH, OH), 1720 (urethane C=O), and 1590 cm.$^{-1}$ (amide NH).

Anal. Calcd. for $C_{19}H_{27}O_7N$: C, 59.8; H, 7.09; N, 3.67. Found (prisms): C, 60.0; H, 7.26; N, 3.39. Found (needles): C, 60.0; H, 7.16.

Recrystallization of the prisms from ethyl acetate–petroleum ether (b.p. 30–60°) again gave a few needles, but mostly the prismatic dimorph of unchanged melting point range.

3-Amino-*N*-carbomethoxy-3-deoxy-1,2:5,6-di-*O*-isopropylidene-D-altritol (XXVIII).—XXVIII was prepared with methyl chloroformate as described for the preparation of XXVII. Recrystallization from ethyl acetate–petroleum ether (b.p. 30–60°) afforded 0.40 g. (66%) of white needles, m.p. 97–98°; $[\alpha]^{24}D$ + 19.0 ± 0.5° (0.86%); ν_{max} 3500 (NH, OH), 1710 (urethane C=O), and 1510 cm.$^{-1}$ (amide NH).

Anal. Calcd. for $C_{14}H_{25}NO_7$: C, 52.7; H, 7.84; N, 4.39. Found: C, 52.7; H, 7.61; N, 4.38.

3-Amino-4-*O*-benzoyl-*N*-carbophenoxy-3-deoxy-1,2:5,6-di-*O*-isopropylidene-D-altritol (XXIX).—To a stirred and ice-cooled solution of 2.6 g. of XXVII in 50 ml. of reagent pyridine, protected from moisture, was added 3.0 ml. of benzoyl chloride dropwise over a period of about 10 min. After an additional 18 hr. at ambient temperature, the mixture was poured into 500 ml. of ice-cold 1% aqueous sodium bicarbonate. The product was collected on a filter, washed with water, and dried. Recrystallization from ethyl acetate–petroleum ether (b.p. 30–60°) gave 3.1 g. (94%) of white needles, m.p. 167–168°; $[\alpha]^{24}D$ + 5.9 ± 0.5° (0.65%); ν_{max} 3450 (NH), 1720 (benzoate and urethane C=O), 1510 (amide NH), and 710 cm.$^{-1}$ (benzoate CH).

Anal. Calcd. for $C_{26}H_{31}NO_8$: C, 64.3; H, 6.39; N, 2.89. Found: C, 64.5; H, 6.57; N, 2.69.

Similarly, **3-amino-4-*O*-benzoyl-*N*-carbomethoxy-3-deoxy-1,2:5,6-di-*O*-isopropylidene-D-altritol (XXX)** was prepared and, after recrystallization from ethanol–water, 0.27 g. (68%) was obtained as white crystals, m.p. 138–139°; $[\alpha]^{24}D$ + 8.3 ± 1.2° (0.40%); ν_{max} 3500 (NH), 1700 (benzoyl and urethane C=O), 1510 (amide NH), and 710 cm.$^{-1}$ (benzoate CH).

Anal. Calcd. for $C_{21}H_{29}NO_8$: C, 59.6; H, 6.86; N, 3.31. Found: C, 59.7; H, 6.91; N, 3.46.

3-Amino-3-deoxy-1,2:5,6-di-*O*-isopropylidene-D-altritol 3,4-Carbonate (XXXIII). A.—A solution of 0.75 g. of XXVII in 50 ml. of reagent pyridine was refluxed for 18 hr., then spin evaporated *in vacuo*. Traces of pyridine were removed by spin evaporation of toluene (two 10-ml. portions) *in vacuo*. Recrystallization of the residue from ethyl acetate–petroleum ether (b.p. 30–60°) gave 0.35 g. (56%) long, white needles, m.p. 202–203°; $[\alpha]^{24}D$ − 36.3 ± 0.9° (0.57%); ν_{max} 3300 (NH), and 1750, 1730 (d) cm.$^{-1}$ (cyclic carbonate C=O).

Anal. Calcd. for $C_{13}H_{21}NO_6$: C, 54.4; H, 7.32; N, 4.88. Found: C, 54.5; H, 7.26; N, 5.03.

No attempt was made to obtain a second crop.

B.—A mixture of 100 mg. of XXIV and 82 mg. of diphenyl carbonate were fused on a steam bath for 2.5 hr. The semicrystalline mass was recrystallized from methanol to give 30 mg. (27%) of product, m.p. 201–202°, that was identical with preparation A. The yield could probably be improved by using a larger excess of diphenyl carbonate and either a longer reaction time or higher fusion temperature.

3-Amino-3-deoxy-D-altritol 3,4-Carbonate (XXXVI).—A mixture of 150 mg. of XXXIII, 10 ml. of tetrahydrofuran, and 7 ml. of 1 *N* aqueous hydrochloric acid was stirred at room temperature for 18 hr., then neutralized with Dowex 1-X8 (carbonate form). Spin evaporation *in vacuo* gave a residue that was recrystallized from methanol to yield 90 mg. (83%) of white needles, m.p. 180–

181°; $[\alpha]^{24}D$ − 79 ± 2° (0.38%); ν_{max} 3300 (NH, OH), and 1750, 1730 (d) cm.$^{-1}$ (cyclic carbonate C=O).

Anal. Calcd. for $C_7H_{13}NO_6$: C, 40.6; H, 6.28; N, 6.76. Found: C, 40.8; H, 6.15; N, 7.04.

3-Amino-4-*O*-benzoyl-*N*-carbophenoxy-3-deoxy-D-altritol (XXXI).—A preliminary kinetic study on the hydrolysis of XXIX with 3:2 tetrahydrofuran–aqueous hydrochloric acid (1 *N*) showed that hydrolysis was complete in 18 hr. at 23°; at that time, t.l.c. in 5:1 benzene–methanol showed that the starting material (R_f 0.95) had disappeared and only a single spot with R_f 0.30 remained.

A mixture of 3.0 g. of XXIX, 180 ml. of tetrahydrofuran, and 120 ml. of 1 *N* aqueous hydrochloric acid was stirred at room temperature for 18 hr., then neutralized with Dowex 1-X8 (carbonate form). The residue remaining after spin evaporation *in vacuo* was further dried by spin evaporation *in vacuo* of an ethanol solution. Crystallization from 1:1 ethyl acetate–benzene gave 1.75 g. (70%) of white crystals, m.p. 127–129°; $[\alpha]^{24}D$ − 11 ± 1° (0.33%); ν_{max} 3500, 3350 (NH, OH), 1700 (benzoate and urethane C=O), and 715 cm.$^{-1}$ (benzoate CH).

Anal. Calcd. for $C_{20}H_{23}NO_8$: C, 59.2; H, 5.68; N, 3.46. Found: C, 59.1; H, 5.73; N, 3.39.

Similarly, hydrolysis of XXX gave XXXII as a glass that gave a single spot (R_f 0.36) on t.l.c.; however, the infrared spectrum indicated a mixture of XXXII and the cyclized urethane (XXXV) since the carbonyl absorption was broadened to 1700–1730 cm.$^{-1}$.

3-Amino-6-(and 4)-*O*-benzoyl-3-deoxy-D-altritol 2,3-Carbonate (XXXIV and XXXV). **A.**—A kinetic study on ring closure of XXXI was necessary since it soon became apparent that benzoyl migration in XXXV to give XXXIV was taking place. A solution of XXXI in pyridine was refluxed and aliquots at time intervals were examined by t.l.c. with 4:1 benzene–methanol and by the disappearance of the amide NH of XXXI at 1510 cm.$^{-1}$. After 10 min., starting material XXXI with R_f 0.43 was still present and a new spot appeared at R_f 0.35. At the end of 30 min. starting material was absent by t.l.c. and the product showed no NH band at 1510 cm.$^{-1}$; at this point, a major spot at R_f 0.35 was present and minor spot at R_f 0.40. By 90 min., both spots at R_f 0.35 and 0.40 were about equal intensity, but after 3 hr. only a trace of the spot at R_f 0.35 was present. As shown subsequently, the crystalline, rearranged benzoate (XXXIV) isolated at the end of 3 hr. had R_f 0.40.

B.—A solution of 400 mg. of XXXI in 25 ml. of pyridine was refluxed for 3 hr., then spin evaporated *in vacuo*. Traces of pyridine were removed by spin evaporation of toluene (two 10-ml. portions). Crystallization of the residue as rosettes from ethyl acetate in an open flask occurred slowly as the hydrate of the 6-benzoate (XXXIV) formed; yield 200 mg. (62%), m.p. 82–85°. Repeated recrystallization from ethyl acetate was still slow, indicating that water vapor was necessary for crystallization. The melting point remained at 82–85°; $[\alpha]^{24}D$ + 52.2 ± 0.5° (0.75%); ν_{max} 3500, 3300 (NH, OH), 1740 (cyclic carbonate C=O), 1710 (benzoate C=O), 1650 (weak, water), 705 (benzoate CH), and no amide NH near 1510 cm.$^{-1}$.

Anal. Calcd. for $C_{14}H_{17}NO_7 \cdot H_2O$: C, 51.1; H, 5.78; N, 4.26; O, 38.9. Found: C, 51.5; H, 5.87; N, 4.43; O, 38.9.

This compound consumed 1/2 mole of periodate in 5 hr., 1 mole in 18 hr., and no additional periodate in 24 hr.; the slow uptake was compatible with the nonterminal *vic*-glycol structure of XXXIV.

C.—A reaction run as in B, but for 30-min. reflux, gave a glass that was mainly XXXV, but could not be crystallized.

2-*O*-Benzoylglycolaldehyde (XXI) 2,4-Dinitrophenylhydrazone. **A.**—A solution of 0.75 g. of XXXIV in 200 ml. of water containing 1.0 g. of sodium metaperiodate was allowed to stand at room temperature for 24 hr., then extracted with methylene chloride. Evaporation of the combined extracts *in vacuo* gave 310 mg. of crude XXI. Conversion to the 2,4-dinitrophenylhydrazone in the usual manner gave 450 mg. (44% based on XXXIV) of orange crystals, m.p. 183–185°; ν_{max} 3300 (NH), 1710 (benzoate C=O), 1500 (NO_2), and 710 cm.$^{-1}$ (benzoate CH).

Anal. Calcd. for $C_{14}H_{12}N_4O_5$: C, 52.3; H, 3.49; N, 16.3. Found: C, 52.4; H, 3.69; N, 16.2.

Ohle and Melkonian[18] have recorded m.p. 185° for this compound prepared by a different route.

The other fragment (XXXVIII) was isolated as a glass by spin evaporation of the aqueous periodate solution *in vacuo* and extraction with absolute ethanol. This glass had ν_{max} 3300 (broad NH, OH), and 1750–1710 (broad, cyclic urethane C=O and aldehyde C=O); since a band near 710 cm.$^{-1}$ was absent, no benzoate was present. This glass could not be crystallized and was resistant to boiling with 2.5 *N* hydrochloric acid for 18 hr. Further studies on the preparation of XXXVIII (*via* XXXVII) and its conversion to the free tetrose will be pursued.

B.—Oxidation of crystalline XVIII, as described in A, gave an oil which was converted to the 2,4-dinitrophenylhydrazone, m.p. 183–185°, that was identical with preparation A.

3-Amino-3-deoxy-D-altritol 2,3-Carbonate (XXXVII). **A.**—A solution of 50 mg. of XXXIV in 3 ml. of 0.3 *N* methanolic sodium methoxide was allowed to stand at room temperature for 18 hr. in a stoppered flask. The solution was neutralized with Dowex 50W-X8 (H^+ form), then evaporated to residue *in vacuo*. Crystallization from ethanol–ethyl acetate gave 21 mg. (63%) of white plates, m.p. 166–167°; $[\alpha]^{24}D$ + 68 ± 1° (0.30%); ν_{max} 3300 (NH, OH), 1740 (cyclic urethane C=O), and no benzoate CH near 710 cm.$^{-1}$.

Anal. Calcd. for $C_7H_{13}NO_6$: : 40.8; H, 6.17; N, 6.76. Found: C, 40.8; H, 6.17; N, 7.00.

This compound was recovered unchanged under the acid conditions used for hydrolysis of XXXIII to XXXVI.

B.—A solution of 70 mg. of XXXVI in 3 ml. of reagent methanol containing a drop of 1 *N* methanolic sodium methoxide was allowed to stand 18 hr., then processed as in A to yield 50 mg. (71%), m.p. 166–167°, that was identical with preparation A.

3-Amino-3-deoxy-1,2:5,6-di-*O*-isopropylidene-D-altritol (VIa) and -D-mannitol.—The availability of 4-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-D-arabo-3-hexulose[12] suggested that it be investigated as a source of VIa by oximation and reduction. This route was much less effective for preparation of VIa than the azide displacement route (II → I) described earlier,[4] since both VIa and the corresponding mannitol isomer were obtained; separation by crystallization gave large losses.

A solution of 1.8 g. of the keto sugar[12] in 50 ml. of ethanol was added to a solution of 1.05 g. of hydroxylamine and 2.0 g. of anhydrous sodium acetate in 10 ml. of water. After being refluxed for 2 hr., the mixture was poured into 500 ml. of water and extracted with five 100-ml. portions of chloroform. The combined extracts were washed with 50 ml. of water, dried with magnesium sulfate, and spin evaporated *in vacuo;* the residue was dissolved in ether, clarified with charcoal, and again spin evaporated. The residual oxime (1.3 g., 70%), which failed to crystallize, had ν^{film} 3400 (OH), 1725 (benzoate C=O), 1700 (sh) (C=N), and 710 cm.$^{-1}$ (benzoate CH).

A solution of 1.3 g. of the oxime in 20 ml. of reagent ether was added to a stirred mixture of 1.3 g. of lithium aluminum hydride in 40 ml. of reagent ether. After being refluxed for 2 hr., the reaction mixture was processed as previously described for preparation of VIa.[4] Spin evaporation *in vacuo* of the combined chloroform–ether solutions gave 0.74 g. (83%) of mixed isomers as a semicrystalline mass.

For crystallization, 0.42 g. was dissolved in ethyl acetate, petroleum ether (b.p. 30–60°) was added to turbidity, and the solution was seeded with VIa to yield 0.10 g. (24% recovery, 14% based on ketone) of VIa, m.p. 111–114°. 3-Amino-3-deoxy-1,2:5,6-di-*O*-isopropylidene-D-mannitol could be isolated by chromatography on neutral alumina as previously described.[4] Elution with chloroform containing 1% methanol gave VIa in the early fractions and later fractions eluted the mannitol isomer, m.p. 80–83°, with 14% recovery.

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(18) H. Ohle and G. A. Melkonian, *Ber.*, **74B**, 291 (1941).