Synthetic Nucleosides. LV.[1,2] Facile Displacement Reactions in the D-Mannitol Series. II. Synthesis of Some 3-Aminohexitols

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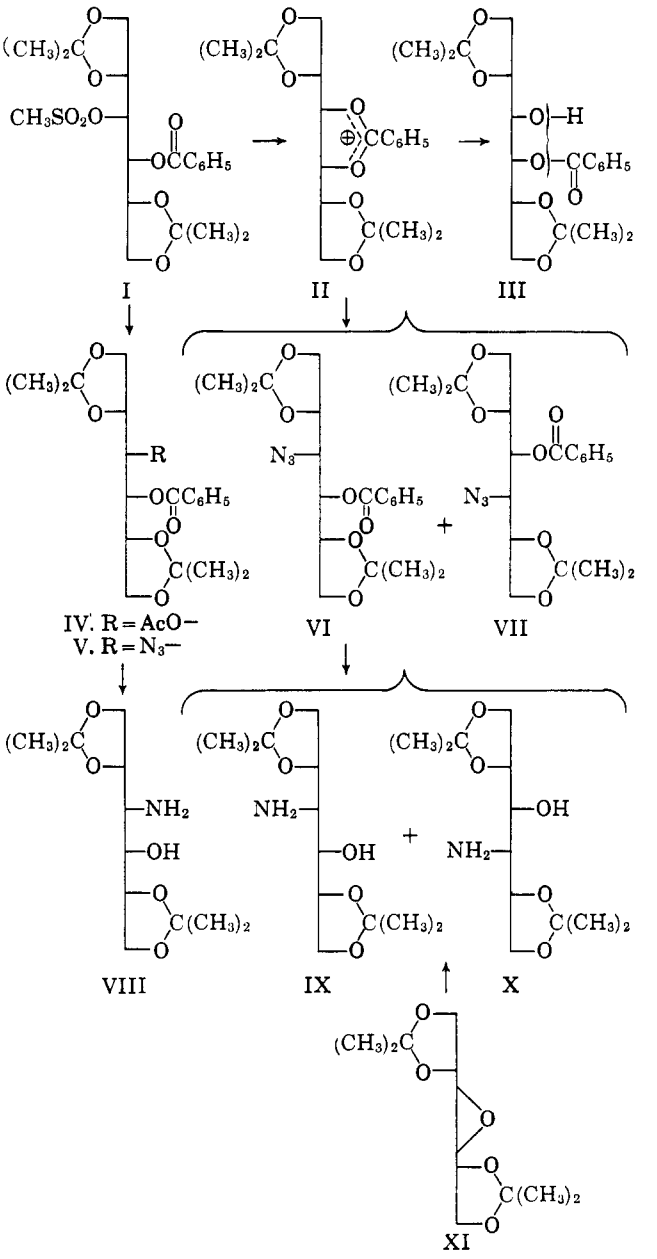
The mesylate group of 4-O-benzoyl-1,2:5,6-di-O-isopropylidene-3-O-mesyl-D-mannitol (I) undergoes SN2 reaction with azide ion; reduction of the product with lithium aluminum hydride gave 3-amino-3-deoxy-1,2:5,6-di-O-isopropylidene-D-altritol (VIII), m.p. 115–116°. Ring opening of 3,4-anhydro-1,2:5,6-di-O-isopropylidene-D-talitol (XI) gave two aminohexitols, namely, 3-amino-3-deoxy-1,2:5,6-di-O-isopropylidene-D-mannitol (IX) and 3-amino-3-deoxy-1,2:5,6-di-O-isopropylidene-D-iditol (X). The structures of the three amino hexitols were established unequivocally by inversion of the 4-hydroxyl group of VIII to the D-*ido*-configuration, then showing identity of the benzoyl derivatives (XVII and XVIII) prepared by the two routes.

In the previous paper of this series, evidence was presented that the mesylate group of 4-O-benzoyl-1,2:5,6-di-O-isopropylidene-3-O-mesyl-D-mannitol (I) could be ejected by both the direct SN2 displacement to the acetate, IV, and by anchimeric reaction to III, *via* the ortho ester ion II; the ratio of SN2 reaction to anchimeric reaction was qualitatively proportional to the strength of the nucleophilic entering group and inversely proportional to the nucleophilic strength of the anchimeric group. The direct SN2 displacement of the mesylate group of I by the highly nucleophilic azide ion to form V is the subject of this paper.

Treatment of I with sodium azide in boiling dimethylformamide for two hours led to an oil which showed strong azide absorption at 2110 cm.$^{-1}$ and diminished mesylate absorption at 1170 cm.$^{-1}$.[3] Reduction of this oil with lithium aluminum hydride gave an amino hexitol, m.p. 115–116°, in 45% yield from I. This aminohexitol could have structure VIII if azide ion attacked by an SN2 mechanism *via* V; if the ortho ester mechanism operated then the aminohexitol could have structure IX or X, formed *via* the azides VI or VII, respectively. The fact that no other ninhydrin positive material could be detected with thin-layer chromatography indicated that this aminohexitol probably had the altritol configuration (VIII), since the introduction of azido through the anchimeric assistance of the benzoyl group should have given two isomers *via* the ortho ester ion, II.

These isomeric aminohexitols, IX and X, were readily synthesized by treatment of the anhydrotalitol (XI)[4] with methanolic ammonia at 100° for fourteen hours. Although the mixed isomers crystallized, they were not readily separable by crystallization. However, chromatographic separation on alumina was achieved by use of chloroform as an eluent. The first aminohexitol eluted had m.p. 94–96° and was called isomer A; the second isomer (B) eluted had m.p. 83–85°. These two



aminohexitols, A and B, were clearly separable on thin-layer chromatography. In addition, A and B were clearly stereoisomeric to the aminohexitol obtained by the azide pathway[6] which gave strong presumptive

(1) This work has been generously supported by grant no. CY-5845 from the National Cancer Institute, U. S. Public Health Service.

(2) For a previous paper of this series see B. R. Baker and A. H. Haines, *J. Org. Chem.*, **28**, 438 (1963).

(3) The crude azide also showed some hydroxyl absorption at 3500 cm.$^{-1}$, indicating the presence of some III formed *via* the ortho ester ion, II.

(4) The anhydro talitol (XI) has been prepared by partial tosylation of 1,2:5,6-di-O-isopropylidene-D-mannitol, followed by treatment with methanolic sodium methoxide.[5] Although this procedure did work in this laboratory, the product (XI) was difficult to isolate and purify due to contamination with the ditosylate, thus limiting the availability of this material. An alternate route has now been developed; treatment of the mesyl mannitol, I, with methanolic sodium methoxide gave XI which was readily purified by one crystallization in 59% yield. In addition, this route from I was readily scaled up to 100 g. of product (XI).

(5) P. Bladon and N. Owen, *J. Chem. Soc.*, 604 (1950).

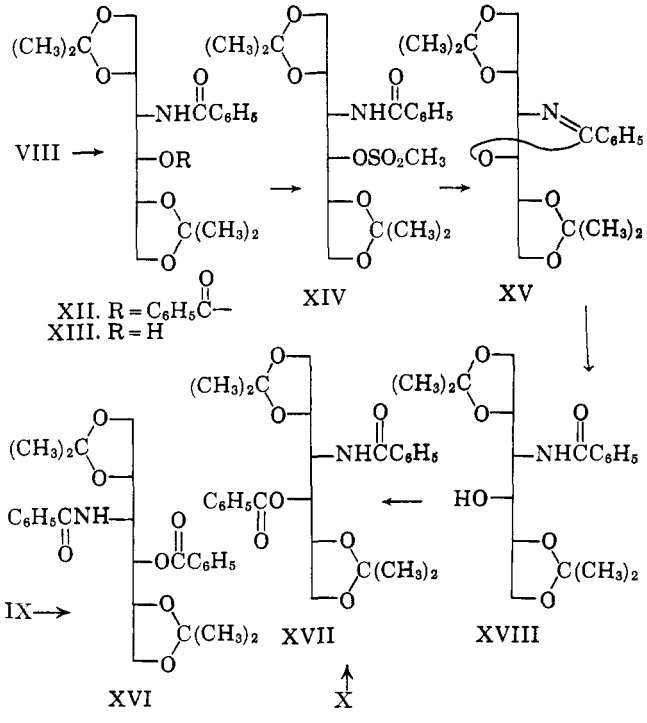
(6) In addition, the N,O-dibenzoyl derivatives, XII, XVI, and XVII were clearly isomeric.

evidence that the azidohexitol has structure V and the aminohexitol derived thereform has the amino-altritol structure, VIII.

It is possible to predict that isomer B has the D-*manno* configuration (IX) because of its greater retention on alumina. If the assumption is made that the most favored conformation of the carbon skeleton is a planar zig-zag,[7] then the amino and hydroxyl groups are more sterically available for binding on alumina with the D-*manno* configuration (IX) than with the D-*ido* configuration (X) (see Fig. 1). That this configurational assignment was correct was shown in the following way.

Benzoylation of the amino-altritol (VIII)—obtained by the azide route—gave the di-O,N-benzoyl derivative (XII), m.p. 202–203°, in 82% yield. Removal of the O-benzoyl group with methanolic sodium methoxide afforded the crystalline N-benzoyl derivative (XIIII) in 90% yield. The crystalline O-mesyl derivative (XIV) was obtained from XIII in 68% yield by reaction with mesyl chloride in pyridine.

When a system containing *vicinal* mesyloxy and acylamido groups with a *trans* relationship is treated with sodium acetate in 2-methoxyethanol, expulsion of the mesoyloxy group with inversion of the configuration of the carbon atom carrying the leaving group takes place, the reaction proceeding through an oxazoline.[8]



The examples quoted[8] were with systems containing a furanose or pyranose ring, thus proceeding through a bicyclic oxazoline; such reactions are then limited to a *trans* relationship of anchimeric and leaving groups.[9, 10] In contrast, this inversion reaction in open chain compounds can proceed with either the

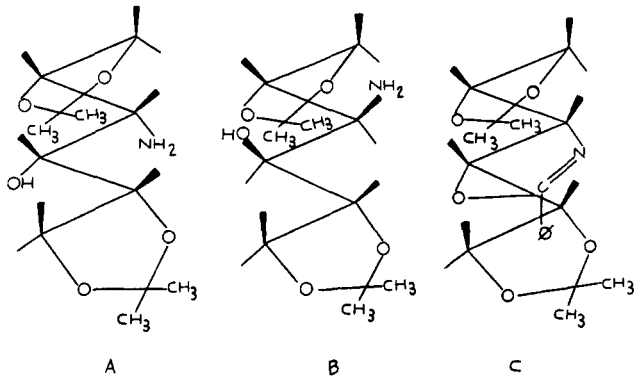


Fig. 1.—"Zig-zag" conformation of aminohexitols: A, D-*ido*-configuration of X; B, D-*manno*-configuration of IX; C, D-*ido*-configuration of oxazoline (XV).

cis or *trans* configuration (Fischer convention), since an oxazoline with either *cis* or *trans* groups can then be obtained when not limited by a bicyclic system.[10, 11] Therefore it could be anticipated that treatment of the altritol mesylate (XIV) with sodium acetate in boiling 95% 2-metl oxyethanol should give the benzamido iditol, with inversion *via* an oxazoline. In previous cases,[8] the intermediate oxazoline was deliberately hydrolyzed by having water present. Surprisingly, when the altritol mesylate (XIV) was heated with this reagent under the usual conditions,[8b] both the benzamido iditol (XVIII)[12] and the intermediate oxazolino iditol (XV) were obtained in crystalline form in a ratio of 1:2.

The presence of the oxazoline (XV) as a reaction product can be rationalized in two ways. Either XV and XVIII were readily interconverted and a work-up through chloroform extraction converted some XVIII back to XV, or the oxazoline (XV) was far more stable than the previous bicyclo oxazolines.[8–10] That the benzamido alcohol (XVIII) was not readily converted to XV by boiling its solution in benzene, or in the presence of a mild dehydrating agent such as anhydrous copper sulfate, was shown experimentally. That the oxazoline was extremely stable to hydrolysis was shown by increasing the reaction time from 19 to 160 hours; again both XV and XVIII were obtained, but in a ratio of 1.3:1. That the oxazoline (XV) would slowly hydrolyze to XVIII was further shown by refluxing a solution of pure XV in 50% aqueous 2-methoxyethanol for twenty-four hours, after when 3% of XVIII was isolated and 58% of XV was recovered unchanged, a ratio of 19:1. In fact, the difficulty of hydrolysis of XV

(7) S. A. Barker, E. J. Bourne, and D. H. Whiffen, *J. Chem. Soc.*, 905 (1952).

(8) (a) B. R. Baker and R. E. Schaub, *J. Org. Chem.*, **19**, 646 (1954); (b) B. R. Baker, R. E. Schaub, and J. H. Williams, *J. Am. Chem. Soc.*, **77**, 7 (1955); (c) R. W. Jeanloz, *ibid.*, **79**, 2591 (1957).

(9) G. E. McCasland, R. K. Clark, Jr., and H. E. Carter, *ibid.*, **71**, 637 (1949).

(10) S. Winstein and R. Boschan, *ibid.*, **72**, 4669 (1950).

(11) J. Attenburrow, D. F. Elliot, and G. F. Penny, *J. Chem. Soc.*, 310 (1948).

(12) In initial runs, XVIII was obtained as cubic crystals, m.p. 109–111°. In later runs a new dimorph was isolated as needles, m.p. 122–124°. After isolation of the higher melting form, the lower melting form was not isolated again. Although the two dimorphs had different spectra in Nujol mull, the lower melting dimorph gave the same spectrum as the high melting dimorph when heated at 100° for a short time. The low melting dimorph melted at 122° when the melting point was slowly taken. After ordinary melting at 109–111°, the cooled and resolidified material then remelted at 122° when taken rapidly. Both dimorphs gave the same dibenzoyl derivative (XVII). The high melting dimorph was unusual in that it showed two carbonyls in the infrared at 1650 (medium) and 1620 (strong) cm.$^{-1}$, whereas the low melting dimorph showed only one band at 1625 cm.$^{-1}$; that the high melting dimorph was not a mixture of mono-O- and mono-N-benzoyl derivatives or a fortuitous mixture of mono-, di-, and no-benzoyl derivatives of proper analytical values was shown by a negative ninhydrin test. The only other explanation currently available is that some type of peculiar intra- or intermolecular bonding in the crystal structure takes place to give the second, but weak, carbonyl band.

to XVIII suggests that some of the benzamido alcohol (XVIII) may well have arisen by SN2 displacement of the mesylate of XIV by acetate, followed by hydrolysis of the acetate group.

The unusual stability of XV can probably be attributed to the steric effects of the two adjacent isopropylidene groups, with additional stability conferred to the molecule by the "sandwich" structure of the favored conformation (see Fig. 1, XV).

Further benzoylation of the benzamido iditol (XVIII), obtained from the mesylate (XIV), gave a dibenzoyl derivative (XVII), m.p. 162–164°. Benzoylation of the isomer B (IX) gave a dibenzoyl derivative, m.p. 138–139°, that was clearly isomeric with XVII. However, benzoylation of isomer A (X) gave a dibenzoyl derivative, m.p. 162–164°, that was identical in all respects with the dibenzoyl derivative (XVII) obtained via the altritol mesylate (XIV); furthermore, O-debenzoylation of XVII obtained from X gave the N-benzoyl derivative (XVIII), m.p. 122–124°, identical with the same compound obtained *via* the altritol mesylate (XIV).

The identity of XVII and XVIII from the two routes confirms unequivocally the tentative configurational assignments made earlier; *i.e.*, the sodium azide reaction on the D-mannitol derivative, I, leads to an aminohexitol of the D-*altro*-configuration, and ring-opening of the anhydro-talitol (XI) with ammonia leads to the less retained isomer A of D-*ido*-configuration (IX) and the more-retained isomer B of D-*manno*-configuration.

In conclusion, open chain sugar derivatives offer greater flexibility in synthetic transformations since formation of a ring such as oxirane or oxazoline is not limited to *trans* configuration, as is the case with furanoses or pyranoses. Further work on conversion of these aminohexitols to amino-pentoses and hexoses is worthy of pursuit.

Experimental[13]

3-Amino-3-deoxy-1,2:5,6-di-O-isopropylidene-D-altritol (VIII).—A mixture of 8.8 g. (20 mmoles) of 3-O-benzoyl-1,2:5,6-di-O-isopropylidene-4-O-mesyl-D-mannitol (X),[2] 4.0 g. (61 mmoles) of sodium azide, and 80 ml. of dimethylformamide was heated under reflux for 2 hr., during which time considerable darkening occurred. The reaction mixture was diluted with 300 ml. of chloroform and washed with 100 ml. of water. The aqueous layer was extracted with chloroform (2 × 60 ml.), and the combined organic solutions washed with 60 ml. of water. Concentration of the dried (magnesium sulfate) solution *in vacuo*, yielded a sirup which was dissolved in benzene and treated with charcoal; reconcentration gave 6.2 g. (83%) of a sirup consisting mainly of the azido compound V; ν_{max}^{film} 3500 (OH),[3] 2110 (N_3), 1710 cm.$^{-1}$ (ester C=O).

To a stirred suspension of 1.1 g. of lithium aluminum hydride in 30 ml. of dry ether was added a solution of 5.7 g. of the sirupy azido compound V in 30 ml. of dry ether at such a rate that a gentle reflux was obtained. After the reaction mixture had been heated under reflux for 1 hr., 2.8 ml. of ethyl acetate was added followed by a further 60 ml. of ether, and then 2.1 ml. of water. The suspension was refluxed for a further 10 min., and then filtered, with the aid of more ether. Treatment of the filtrate with charcoal, concentration of residue *in vacuo*, and crystallization from petroleum ether gave 1.48 g. (39%) of VIII, m.p. 113–115°. A further 0.22 g. of VIII was obtained on extracting the precipitated inorganic hydroxides with hot chloroform increasing the overall yield to 45%. The analytical sample obtained from ethyl acetate–petroleum ether had m.p. 115–116°; $[\alpha]^{26}D$ 2.5 ± 0.7; ν_{max}^{Nujol} 3400, 3300, 3150 (NH_2, OH); 1600 (NH_2); and no azide absorption near 2110 cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{23}NO_5$: C, 55.1; H, 8.89; N, 5.31. Found: C, 55.3; H, 8.81; N, 5.30.

Thin-layer chromatography[14] of the mother liquor from the crystallizations revealed only one detectable ninhydrin positive spot, identical with the crystalline product.

3,4-Anhydro-1,2:5,6-di-O-isopropylidene-D-talitol(XI).—A solution of 2.88 g. (6.5 mmoles) of I and 0.37 g. (6.85 mmoles) of sodium methoxide in 40 ml. of anhydrous methanol was heated under reflux for 2 hr., with protection from moisture. After filtration, the reaction mixture was diluted with 200 ml. of chloroform and washed with 30 ml. of water. The aqueous solution was extracted with chloroform (2 × 15 ml.). The combined organic solutions were dried with magnesium sulfate, then concentrated to a sirup *in vacuo*. Methyl benzoate was removed from the residue by the addition and spin-evaporation of 15 ml. of water *in vacuo*. The residue was crystallized at −15° from methanol–water to yield 0.91 g. (59%) of XI, m.p. 53–55°. Bladon and Owen[5] record m.p. 54–56° for the same compound prepared *via* 1,2-5,6-di-O-isopropylidene-3-O-tosyl-D-mannitol.

3-Amino-3-deoxy-1,2:5,6-di-O-isopropylidene-D-iditol (X) and 3-Amino-3-deoxy-1,2:5,6-di-O-isopropylidene-D-mannitol (IX).—A solution of 0.845 g. (3.5 mmoles) of 3,4-anhydro-1,2:5,6-di-O-isopropylidene-D-talitol (XI) in 10 ml. of methanol previously saturated with ammonia at 0°, was heated in a steel pressure vessel at 100° for 14 hr.; the reaction mixture was then concentrated *in vacuo* to give 0.87 g. of a sirup,[15] which partially crystallized on standing. A solution of the sirup in 3 ml. of chloroform was introduced onto a 35 × 2 cm. column of alumina.[16] The column was eluted with chloroform and 30-ml. fractions were collected. Fractions 2–4 were combined and concentrated *in vacuo* to give 0.3 g. of a residue which was crystallized from ethyl acetate–petroleum ether to yield 0.158 g. of X, m.p. 94–96°, $[\alpha]^{24}D$ −3.9 ± 0.3; ν_{max}^{Nujol} 3400, 3300, 3200 (OH and NH_2); 1590 (NH_2); 890, 870, 850 cm.$^{-1}$ (unassigned).

Anal. Calcd. for $C_{12}H_{23}NO_5$: C, 55.1; H, 8.89; N, 5.36. Found: C, 55.1; H, 9.14; N, 5.60.

Fractions 6–12 were combined and concentrated to yield 0.27 g. of a residue which crystallized from ethyl acetate–petroleum ether to give 0.148 g. of IX, m.p. 83–85°, $[\alpha]^{24}D$ +22.9 ± 0.3; ν_{max}^{Nujol} 3400, 3100 (broad OH and NH_2); 1580 (NH_2); 860, 845 cm.$^{-1}$ (unassigned).

Anal. Calcd. for $C_{12}H_{23}NO_5$: C, 55.1; H, 8.89; N, 5.36. Found: C, 55.0; H, 8.63; N, 5.47.

The absorptions between 800–900 cm.$^{-1}$ were useful for following the chromatographic separation by means of infrared spectra.

3-Benzamido-3-deoxy-4-O-benzoyl-1,2:5,6-di-O-isopropylidene-D-altritol (XII).—To a solution of 1.37 g. (5.25 mmoles) of VIII in 7 ml. of reagent pyridine was added 2.5 ml. (22 mmoles) of benzoyl chloride. After 5 hr. at room temperature protected from moisture, the mixture was poured into 100 ml. of ice–water saturated with sodium bicarbonate. The precipitate was collected, washed with water, and recrystallized from methanol–ethyl acetate to yield 2.03 g. (82%) of XII, m.p. 202–203, $[\alpha]^{26}D$ 0.5 ± 0.6; ν_{max}^{Nujol} 3400 (amide NH); 1710 (ester C=O), 1640 (amide C=O); 1510 (amide NH), 708 cm.$^{-1}$ (C—H of benzoate).

Anal. Calcd. for $C_{26}H_{31}NO_7$: C, 66.5; H, 6.67; N, 2.98. Found: C, 66.7, H, 6.43; N, 3.07.

3-Benzamido-3-deoxy-1,2:5,6-di-O-isopropylidene-D-altritol (XIII).—To a suspension of 1.78 g. (3.8 mmoles) of XII in 50 ml. of methanol was added about 0.05 g. of metallic sodium, and the mixture was heated under reflux for 2 hr., solution taking place in about 5 min. Water (0.1 ml.) was added followed by excess solid carbon dioxide. Concentration yielded a residue which was extracted with 1:1 ethyl acetate–chloroform. The filtered extract was taken to dryness and the residue crystallized from ethyl acetate–petroleum ether to give 1.24 g. (90%) of XIII,

(13) Routine identifications were by means of infrared and mixed melting points; the latter were taken by the capillary tube method in a Mel-Temp apparatus and are uncorrected. Petroleum ether refers to that fraction of b.p. 30–60°. Rotations were measured in a 1-dm. microtube in a 1% chloroform solution.

(14) The apparatus used for thin-layer chromatography was that supplied by Brinkmann Instruments Inc. Silica Gel G was used as the adsorbent, and the chromatograms were developed with acetone–chloroform (1/4 by volume); spots were detected with a ninhydrin spray.

(15) Thin-layer chromatography of the crude reaction product revealed two components; their R_f values were approximately 0.52 and 0.42.

(16) The alumina used for chromatography was Bio-Rad chromatographic aluminum oxide (neutral alumina AG-7, 100–200 mesh) to which 6% water had been added yielding a Brockmann activity of III. See H. Brockmann and H. Schodder, *Ber.*, **74**, 73 (1941).

m.p. 95–96°, $[\alpha]^{26}D$ +37.8 ± 0.7; ν_{max}^{Nujol} 3500 (OH); 3400 (amide NH); 1640 (amide C=O); 1520 (amide N); 720 (C—H of benzoate); and no ester C=O near 1710 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{27}NO_6$: C, 62.4; H, 7.46; N, 3.83. Found: C, 62.6; H, 7.64; N, 3.89.

3-Benzamido-3-deoxy-1,2:5,6-di-O-isopropylidene-4-O-mesyl-D-altritol (XIV).—To a solution of 1.12 g. (3.1 mmoles) of XIII in 8 ml. of reagent pyridine was added 0.5 ml. (6.6 mmoles) of mesyl chloride. After 24 hr. at room temperature protected from moisture, the mixture was poured into 100 ml. of ice–water saturated with sodium bicarbonate; the precipitate was collected, washed with water, and crystallized from methanol–ethyl acetate to yield 0.71 g. (52%) of XIV, m.p. 138–139°, and 0.22 g. (16%), m.p. 133–135°. The analytical sample had m.p. 134–136°; $[\alpha]^{26}D$ +24.7 ± 0.6; ν_{max}^{Nujol} 3450 (amide NH); 1645 (amide C=O); 1510 (amide NH); 1335, 1175 cm^{-1} (sulfonate).

Anal. Calcd. for $C_{20}H_{29}NO_8S$: C, 54.2: H, 6.60; N, 3.16; S, 7.21. Found: C, 54.4; H, 6.45; N, 3.32; S, 7.29.

In a repeat preparation starting with 2.2 g. of XIV, 0.015 g. of the oxazoline (XV) was isolated from the mother liquor.

3-Amino-3-N,4-O-benzo-3-deoxy-1,2:5,6-di-O-isopropylidene-D-iditol (XV).—A mixture of 0.443 g. (1 mmole) of XIV, 0.33 g. (4 mmoles) of sodium acetate, and 3.3 ml. of 95% 2-methoxyethanol was heated under reflux for 19 hr. The mixture was diluted with 5 ml. of methylene dichloride and washed with water (2 × 10 ml.). The combined aqueous layers were back-extracted with 20 ml. of methylene dichloride and the combined organic extracts were then washed with 10 ml. of water. Dried over magnesium sulfate, the organic solution was evaporated to dryness *in vacuo* and the residue crystallized from methanol–water to yield 0.17 g. (49%) of XV, m.p. 86–88°; from the mother liquor was isolated XVIII, as described in the succeeding experiment.

Recrystallization of a similar preparation from methanol–water gave white crystals, m.p. 87–88°; $[\alpha]^{24}D$ −46.5 ± 0.4; ν_{max}^{Nujol} 1645 (C=N); 695 (benzoyl CH); and no OH—NH absorption at 3000–4000 cm.$^{-1}$

Anal. Calcd. for $C_{19}H_{25}NO_5$: C, 65.7; H, 7.27; N, 4.03. Found: C, 65.8; H, 7.21; N, 4.00.

When a solution of 100 mg. of pure XV in 4 ml. of 50% aqueous 2-methoxyethanol was refluxed for 24 hr., 3 mg. of XVIII could be isolated and 58 mg. of XV was recovered unchanged.

3-Benzamido-3-deoxy-1,2:5,6-di-O-isopropylidene-D-iditol (XVIII). **(A) From XIV.**—The mother liquor from the 0.17 g. of the preceding preparation was diluted with 50 ml. of water and extracted with methylene dichloride (4 × 20 ml.). Dried with magnesium sulfate, the combined extracts were concentrated and the residue crystallized from petroleum ether–ethyl acetate to yield 0.090 g. (25%) of the benzamido iditol,[12] XVIII, m.p. 121–123°, $[\alpha]^{24}D$ +22.9 ± 0.3; ν_{max}^{Nujol} 3450 (shoulder), 3350, 3200 (OH, NH); 1650 (m), 1620 (s) (amide I); 1540 (s) (amide II); 715, 695 cm.$^{-1}$ (shoulder) (benzoyl CH).

Anal. Calcd. for $C_{19}H_{27}NO_6$: C, 62.6; H, 7.64; N, 3.89. Found: C, 62.5; H, 7.32; N, 3.94.

This compound was recovered unchanged when its solution in benzene was refluxed 3 hr., then evaporated on a steam bath. It was also recovered unchanged when its benzene solution was stirred with anhydrous cupric sulfate for 3 days.

An earlier preparation of XVIII melted at 109–111° and showed ν_{max}^{Nujol} 3500 (OH); 3300 (NH); 1625 (amide I); 1540 (amide II); 720, 695 cm.$^{-1}$ (benzoate CH). This form was not isolated again.[12]

(B) By O-Debenzoylation of XVII Obtained from X.—Debenzoylation of 0.045 g. (0.096 mmole) of XVII as described for the preparation of XIII, gave, after recrystallization from ethyl acetate–petroleum ether, 0.023 g. (65%) of pure product, m.p. 122–124°. The material was identical with preparation A as shown by mixed melting point and identical infrared spectra.

3-Benzamido-4-O-benzoyl-3-deoxy-1,2:5,6-di-O-isopropylidene-D-iditol (XVII). **(A) From X.**—Benzoylation of 100 mg. (0.38 mmole) of X as described for the preparation of XII gave, after recrystallization from ethyl acetate–petroleum ether, 0.13 g. (72%) of white crystals, m.p. 162–164°, $[\alpha]^{24}D$ +63.1 ± 0.4; ν_{max}^{Nujol} 3300 (NH); 1710 (ester C=O); 1640 (amide I); 1545 (amide II); 715, 695 cm.$^{-1}$ (benzoyl CH).

Anal. Calcd. for $C_{26}H_{31}NO_7$: C, 66.5; H, 6.67; N, 2.98. Found: C, 66.4; H, 6.86; N, 3.11.

(B) By Benzoylation of XVIII Obtained from XIV.—To a solution of 25 mg. (0.068 mmoles) of XVIII (m.p. 121–123°) in 1 ml. of reagent pyridine was added 0.05 ml. (0.44 mmoles) of benzoyl chloride. After 24 hr. at room temperature in a stoppered flask, the mixture was processed as described for XII. Two recrystallizations from ethyl acetate–petroleum ether gave 12 mg. (31%) of white crystals, m.p. 163–164°, that were identical with preparation A as shown by mixed melting point and infrared spectra.

Similarly, benzoylation of the low melting dimorph (109–111°) of XVIII gave the same dibenzoate, XVII.

3-Benzamido-3-deoxy-4-O-benzoyl-1,2:5,6-di-O-isopropylidene-D-mannitol (XVI).—Treatment of a solution of 0.1 g. (0.38 mmole) of IX in 3 ml. of pyridine with 0.18 ml. (1.55 mmoles) of benzoyl chloride for 24 hr. at room temperature yielded, after recrystallization from ethyl acetate–petroleum ether, 0.125 g. (69%) of XVI, m.p. 133–135°. Further recrystallization gave the analytical sample, m.p. 138–139°; $[\alpha]^{24}D$ +45.8 ± 0.3; ν_{max}^{Nujol} 3390 (NH); 1710 (ester C=O); 1645 (amide I); 1525 (amide II); 730, 705 cm.$^{-1}$ (benzoyl CH).

Anal. Calcd. for $C_{26}H_{31}NO_7$: C, 66.5; H, 6.67; N, 2.98. Found: C, 66.7; H, 6.84; N, 3.07.

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Vasicinone. A Bronchodilator Principle from *Adhatoda Vasica* Nees (N. O. Acanthaceae)

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A Bronchodilator principle "Vasicinone" has been isolated from *Adhatoda vasica* Nees (N. O. Acanthaceae) and its identity established with 2,3(α-hydroxytrimethylene)-4-quinazolone obtained by the oxidation of Vasicine. Vasicinone has also been found to be identical with an alkaloid recently isolated from *Peganum harmala* Linn. It is shown that Vasicine can be converted to Vasicinone by autoöxidation.

Adhatoda vasica Nees is an evergreen subherbaceous bush and is used in the indigenous medicine as a remedy for cold, cough, bronchitis, asthma, etc.

Hooper,[1] found in it, "a nonvolatile body" of the nature of an alkaloid, an organic acid "Adhatodic acid" and a steam volatile "odorous principle." Sen and Ghose[2] obtained an alkaloid "Vasicine" from its leaves. Chopra and Ghosh[3,4] found that Vasicine possesses a slight but persistent bronchodilator effect. Mithal

(1) D. Hooper, *Pharm. J.*, **18**, 841 (1888).

(2) J. N. Sen and T. P. Ghose, *J. Indian Chem. Soc.*, **1**, 315 (1924).

(3) R. N. Chopra and S. Ghosh, *Indian J. Med. Res.*, **13**, 205 (1925).

(4) R. N. Chopra and S. Ghosh, *Indian Med. Gaz.*, **60**, 354 (1925).