Synthesis of (−)-Hyosamine and (−)-4-Deoxystreptamine[1a]

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Abstract: (−)-Hyosamine and (−)-4-deoxystreptamine were synthesized starting from *N*-acetyl-D-glucosamine and their absolute configurations were unambiguously established. Accordingly, the absolute structures of hygromycin B and destomycin A have been confirmed by the present synthesis. The absolute configuration assigned earlier to streptomycin was also supported by the synthesis of (−)-4-deoxystreptamine, an enantiomer of the compound obtained by degradation of streptomycin.

Reinvestigation of Wolfrom's streptamine synthesis[2] has provided a convenient preparation of optically active inosadiamines from D-glucosamine.[3] In the present paper, we wish to report the synthesis of (−)-hyosamine and (−)-4-deoxystreptamine from (1*S*)-1-acetamido-3-amino-1,3-dideoxy-*myo*-inositol (**2**) and (1*R*)-1,5-diacetamido-1,5-dideoxy-*myo*-inositol (**12**), respectively, which were prepared from *N*-acetyl-D-glucosamine.

Although (+)- and (−)-hyosamine were obtained from hygromycin B and destomycin A, respectively, and their absolute configurations were proposed, the results reported by the two groups[4a,b] were incompatible with each other. In the present study the structure of (−)-hyosamine is assigned as (1*S*)-1-amino-1,2,3-trideoxy-3-methylamino-*scyllo*-inositol, in agreement with the results of the Kyoto group.[4b] The absolute configurations of the two stereoisomeric antibiotics, hygromycin B and destomycin A, are thus fully established.

The present synthesis of (−)-4-deoxystreptamine, which derives its absolute stereochemical assignment from the starting material, glucosamine, confirms the absolute configuration assigned to streptomycin on the basis of Reeves' cuprammonium method applied to active *N,N'*-diacetyl-4-deoxystreptamine (**15**)[5,6] or di-*O*-methylstreptamine[7] and the configuration assigned by X-ray spectroscopy.[8] The optical rotation of synthetic **15** and that of an authentic sample derived from streptomycin[4b] were shown to be equal in value but opposite in sign.

Results and Discussion

(−)-Hyosamine. (1*S*)-1-Acetamido-1,3-dideoxy-3-nitro-*myo*-inositol (**1**) was obtained as the predominant product on treatment of the hydrolysate of ethyl 2-acetamido-2,6-dideoxy-6-nitro-1-thio-β-L-iodofuranoside with a slight excess of sodium methoxide in methanol.[3] Hydrogenation of **1** (Figure 1) over Raney nickel T-4[9] gave in 86% yield (1*S*)-1-acetamido-3-amino-1,3-dideoxy-*myo*-inositol (**2**), which was identified as its pentaacetyl derivative, **3**.[10] N-Methylation of **2** was effected by hydrogenation over palladium on charcoal catalyst in aqueous formaldehyde to give a mixture of the 3-methylamino and 3-dimethylamino analogs of **2**. Without further purification the mixture was hydrolyzed at reflux in 6 *N* hydrochloric acid and the hydrochlorides obtained were fractionated by gradient elution (1.5–3.0 *N* hydrochloric acid) using an Amberlite CG-120 (H^+) column to afford crystalline (1*S*)-1-amino-1,3-dideoxy-3-methylamino-*myo*-inositol dihydrochloride (**4**) and (1*S*)-1-amino-1,3-dideoxy-3-dimethylamino-*myo*-inositol dihydrochloride (**5**) in 28 and 18% yields, respectively, together with a 37% yield of the known[10] 1,3-diamino-1,3-dideoxy-*myo*-inositol dihydrochloride (**6**). Acetylation of **4** and **5** gave the acetyl derivatives **7** and **8**. Characterization of **4** and **7** was performed by comparing their ir and nmr spectra with those of the racemic compounds.[11] Compounds **5** and **8** were identified by elemental analyses and their ir and nmr spectra.

We have already described the synthesis of racemic hyosamine[11] from racemic **4** and the present synthesis of (−)-hyosamine followed the reported procedure. Thoroughly dried **4** was treated with acetyl bromide and acetic anhydride (1:1) in a sealed tube at 145–150° for 6 hr and the reaction product was further acetylated to give the oily (1*R*)-penta-*N,O*-acetyl-1-amino-2-bromo-1,2,3-trideoxy-3-methylamino-*scyllo*-inositol (**9**). After being purified on a silica gel column, the oily **9** was hydrogenated in the presence of Raney nickel T-4 and Amberlite IR-4B (OH^-) to afford (1*S*)-penta-*N,O*-acetyl-1-amino-1,2,3-trideoxy-3-methylamino-*scyllo*-inositol [the pentaacetyl derivative (**10**) of (−)-hyosamine] in 6% yield based on **4**. Its specific rotation was +7.5° (methanol) and all its physical constants were in good agreement with those of an authentic sample derived from destomycin A.[4a] Consequently, the absolute configurations of the stereoisomeric antibiotics hygromycin B and destomycin A are

(1) (a) Presented at the 26th Annual Meeting of the Chemical Society of Japan, Hiratsuka, Apr 1972, Abstract Vol. III, p 1266. (b) Keio University. (c) University of Illinois.

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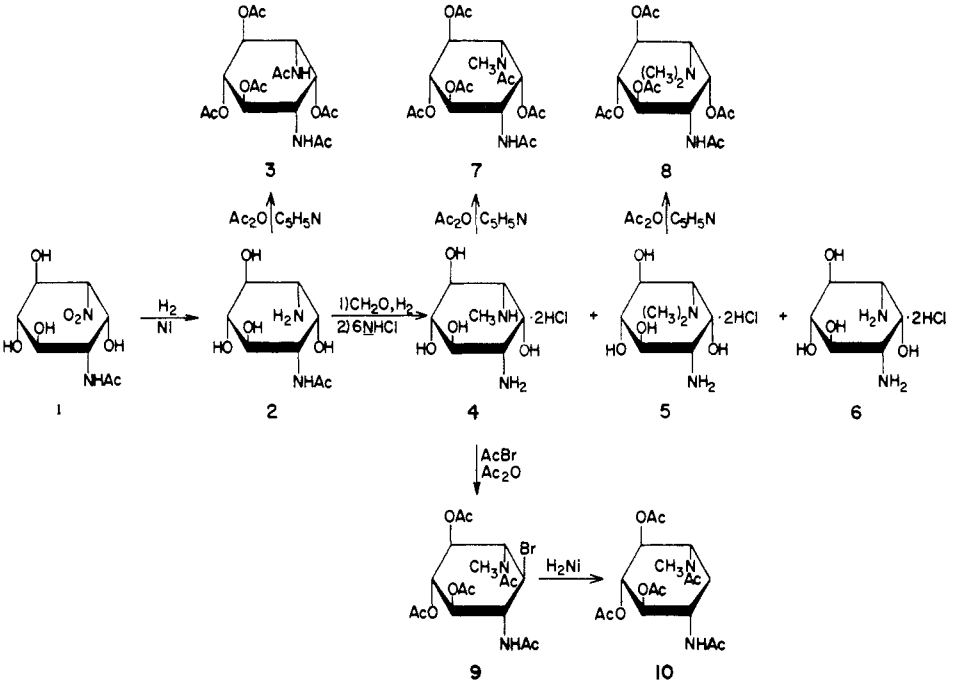

Figure 1. Synthetic route to penta-*N*,*O*-acetyl derivative (**10**) of (−)-hyosamine.

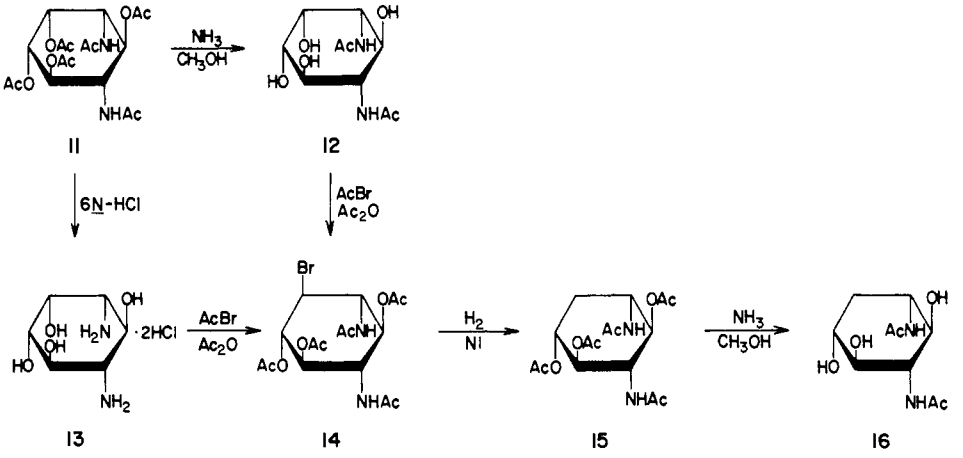

Figure 2. Synthetic route to derivatives (**15** and **16**) of (−)-4-deoxystreptamine.

established by correlation to that of *N*-acetyl-D-glucosamine.

(−)-4-Deoxystreptamine. (1*R*)-Hexa-*N*,*O*-acetyl-1,5-diamino-1,5-dideoxy-*myo*-inositol (**11**) was obtained in 28% yield from 2-acetamido-2,6-dideoxy-6-nitro-D-glucose *via* (1*R*)-5-acetamido-1,5-dideoxy-1-nitro-*myo*-inositol.[3] O-Deacetylation of **11** (Figure 2) with ammoniacal methanol afforded the *N*,*N*′-diacetyl derivative (**12**) in 97% yield. Hydrolysis of **11** with boiling 6 *N* hydrochloric acid afforded the dihydrochloride **13**. Hydroxyl groups vicinal and cis to amino or acetamido groups in aminocyclitols are preferentially displaced by halogen in a mixture of acetyl halide and acetic anhydride.[11-13] Since the hydroxyl group on C-2 is cis to a vicinal amino group in **12** and **13**, the hydroxyl group should be displaced by bromide ion in a mixture of acetyl bromide and acetic anhydride with inversion of the configuration at C-2. Treatment of **12** or **13** in a sealed tube with acetyl bromide and acetic anhydride (2:1) at 145–150° for 8 hr gave (1*S*)-penta-*N*,*O*-acetyl-1,3-diamino-4-bromo-1,3,4-trideoxy-*scyllo*-inositol (**14**) in 26 or 23% yield, respectively.

The nmr spectrum of **14** in dimethyl-d_6 sulfoxide showed four singlets in the acetyl methyl region, at δ 1.70, 1.75, 1.88 (2), and 1.97, which were attributed to two equatorial acetamido and three equatorial acetoxyl groups, respectively.[14] Lack of the signal due to an axial acetoxyl group in **14** indicated that the axial hydroxyl group on C-2 of **12** and **13** had been displaced by bromine. Catalytic hydrogenolysis of **14** by the usual procedure afforded an 85% yield of (1*S*)-penta-*N*,*O*-acetyl-1,3-diamino-1,3,4-trideoxy-*scyllo*-inositol [the pentaacetyl derivative (**15**) of (−)-4-deoxystreptamine], whose nmr spectrum in dimethyl-d_6 sulfoxide contained five singlets, δ 1.71, 1.75, 1.87, 1.93, and 1.94, which were assigned to two equatorial acet-

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amido and three equatorial acetoxyl groups, respectively. Among three 1,3-diaminocyclohexanetriols having all-trans configurations, only 4-deoxystreptamine can be optically active. Therefore, owing to the reaction sequences and spectral data, structure **15** was readily assigned. O-Deacetylation of **15** afforded the *N,N'*-diacetyl derivative (**16**) in 75% yield. Its optical rotation and that of an authentic sample derived from streptomycin[6a] were equal and opposite. Consequently, the absolute configuration of (+)-4-deoxystreptamine assigned by Dyer and Todd[5] from application of Reeves' cuprammonium method has been fully supported by the present synthesis.

Experimental Section[15]

(1*S*)-1-Acetamido-3-amino-1,3-dideoxy-*myo*-inositol (2). A solution of (1*S*)-1-acetamido-1,3-dideoxy-3-nitro-*myo*-inositol[3] (**1**, 434 mg) in water (40 ml) was hydrogenated overnight at room temperature in a Parr shaker in the presence of Raney nickel T-4 (20 mg) under 30 psi of hydrogen pressure. After the catalyst had been filtered, the filtrate was evaporated to give an oily product which became a white powder upon trituration with water and ethanol: yield 329 mg (86%); mp 249–253° dec, $[\alpha]^{19}D$ +50° (*c* 1.0, water); λ_{max}^{KBr} 2.96 (OH, NH_2), 6.14, and 6.42 μ (NHAc). Paper chromatography, of **2** showed a single ninhydrin positive spot (R_f 0.25) in solvent A. Recrystallization from water–methanol afforded an analytical sample.[16] Compound **2** was characterized by converting it to its pentaacetyl derivative **3**, mp 284–287° (lit.[10] mp 283.5–285°).

N-Methylation of 2. Preparation of (1*S*)-1-Acetamido-1,3-dideoxy-3-methylamino-*myo*-inositol (4) and (1*S*)-1-Acetamido-1,3-dideoxy-3-dimethylamino-*myo*-inositol (5). A solution of **2** (354 mg) in formalin (13 ml; prepared by dissolving paraformaldehyde in water, concentration determined as 3.8 mg/ml using dimedone) was hydrogenated in the presence of prehydrogenated 5% palladium on charcoal (335 mg) under atmospheric pressure at room temperature for 18 hr. About 100 ml of hydrogen was absorbed. After the catalyst was filtered, the filtrate was evaporated and the residue was heated with 6 *N* hydrochloric acid (20 ml) on a steam bath for 3 hr. The mixture was evaporated and the oily residue was dissolved in a small amount of water and placed on top of a column [Amberlite CG-120 (H^+), 80 ml, 1.0 × 40 cm] packed in 1.5 *N* hydrochloric acid. The column was eluted gradiently with hydrochloric acid (1.5–3.0 *N*). The eluates were analyzed by paper chromatography at room temperature using solvent B and divided into three fractions. The first fraction eluted was evaporated and the residue was crystallized from water and ethanol to give **5** as colorless needles:[16] yield 81 mg (18%); mp 231.5–232.5°; $[\alpha]^{17}D$ −7° (*c* 1.0, water); λ_{max}^{KBr} 6.10 μ (NH_2); R_f 1.6 (solvent B) relative to R_f 1.0 for compound **6**.

The second fraction eluted (R_f 1.3 relative to compound **6**) was evaporated and crystallized from water and ethanol to afford **4** as colorless needles; yield 125 mg (28%); mp 272° dec; $[\alpha]^{16}D$ −10° (*c* 1.0, water). Compound **4** was identified by comparing its ir and nmr (D_2O) spectra with those of racemic **4**.[11]

The slower moving fraction (R_f 1.0 by definition) gave 1,3-diamino-1,3-dideoxy-*myo*-inositol dihydrochloride (**6**) as colorless needles, yield 126 mg (37%). Compound **6** was identified with an authentic sample[19] by ir and paper chromatography.

Acetylation of **4** with acetic anhydride and pyridine at room temperature gave the hexaacetyl derivative **7**, which did not crystallize. It was identified by comparison of its nmr spectrum ($CDCl_3$) with that of authentic racemic crystalline **7**.

Acetylation of **5** gave crystalline (1*S*)-penta-*N,O*-acetyl-1-amino-1,3-dideoxy-3-dimethylamino-*myo*-inositol (**8**):[16] mp 218°, $[\alpha]^{23}D$ +22° (*c* 1.0, chloroform); λ_{max}^{KBr} 5.73 (OAc), 5.92, and 6.49 μ (NHAc); nmr (60 MHz, $CDCl_3$) δ 2.33 [6-proton singlet, $N(CH_3)_2$], 2.13 (3-proton singlet, axial OAc), 2.07, 2.05, 2.03 (3-proton singlets, equatorial OAc), and 1.90 (3-proton singlet, equatorial NHAc).

(1*S*)-Penta-*N,O*-acetyl-1-amino-1,2,3-trideoxy-3-methylamino-*scyllo*-inositol [Pentaacetyl Derivative of (−)-Hyosamine] (10). A mixture of finely powdered dry **4** (157 mg), acetyl bromide (1.3 ml), and acetic anhydride (1.3 ml) was heated in a sealed tube at 145–150° for 6 hr. After it had cooled, the mixture was poured into ethanol (10 ml) and evaporated to dryness. The residue was acetylated with acetic anhydride and pyridine overnight at room temperature. The mixture was evaporated to dryness and the residue was chromatographed on aluminum oxide and eluted with chloroform containing 3% methanol. Tlc of the products using chloroform–methanol (9:1) showed two close spots which were identified as (1*R*)-penta-*N,O*-acetyl-1-amino-2-bromo-1,2,3-trideoxy-3-methylamino-*scyllo*-inositol (**9**) and **7**. Without further purification, the mixture was dissolved in 50% aqueous ethanol (10 ml) and hydrogenated in the presence of Raney nickel T-4 and Amberlite IR-4B (OH^-) in a Parr shaker at room temperature for 19 hr. The solution was filtered and evaporated to afford a colorless oil whose tlc showed two components corresponding to **7** and **10**. The product was chromatographed on a silica gel column (15 g) and eluted with chloroform containing 3% methanol. The crude **10** isolated was recrystallized from chloroform and ether to furnish colorless needles: yield 13 mg (6%); mp 156.5–157°; $[\alpha]^{27}D$ +7.5° (*c* 1.0, methanol). This compound proved to be identical with an authentic sample of **10**[4a] derived from destomycin A by comparison of tlc behavior, melting points, specific rotations, and ir spectra.

(1*R*)-1,5-Diacetamido-1,5-dideoxy-*myo*-inositol (12). Compound **11**[3] (1.13 g) was O-deacetylated by allowing it to stand overnight at room temperature in ammoniacal methanol (140 ml), then evaporating the solution. The crude product was recrystallized from water and ethanol to give **12** as colorless needles:[16] yield 0.67 g (97%); mp 285–286°; $[\alpha]^{26}D$ +30° (*c* 1.0, water); λ_{max}^{KBr} 2.85 (OH), 3.00 (NH), 6.11, and 6.41 μ (NHAc).

(1*R*)-1,5-Diamino-1,5-dideoxy-*myo*-inositol Dihydrochloride (13). A mixture of **11**[3] (456 mg) and 6 *N* hydrochloric acid (20 ml) refluxed for 90 min. The mixture was then evaporated to dryness and the residue was crystallized from ethanol–water to afford **13** as colorless plates:[16] yield 241 mg (91%); mp 240° dec; $[\alpha]^{20}D$ +11° (*c* 1.0, water); λ_{max}^{KBr} 6.26 and 6.67 μ (NH_3^+). The crystals lose water of crystallization on drying over phosphorus pentoxide *in vacuo* at 100°.

(1*S*)-Penta-*N,O*-acetyl-1,3-diamino-4-bromo-1,3,4-trideoxy-*scyllo*-inositol (14). A. A mixture of **12** (200 mg), acetyl bromide (4 ml), and acetic anhydride (2 ml) was heated in a sealed tube at 145–150° for 8 hr, then cooled. The reaction mixture was poured into ethanol (20 ml) and the solution was evaporated to dryness. The residue was treated with acetic anhydride (5 ml) and pyridine (5 ml) overnight at room temperature, then the mixture was evaporated to give a crystalline product, which was recrystallized from ethanol to afford **14** as colorless needles: yield 89 mg (26%); mp 275–276°; $[\alpha]^{25}D$ −7° (*c* 1.0, pyridine); λ_{max}^{KBr} 3.05 (NH), 6.02, and 6.41 μ (NHAc).

B. A mixture of **13** (200 mg), acetyl bromide (4 ml), and acetic anhydride (2 ml) was treated as described in part A of this section to give **14** (81 mg, 23%).

(1*S*)-Penta-*N,O*-acetyl-1,3-diamino-1,3,4-trideoxy-*scyllo*-inositol (15). A solution of **14** (103 mg) in 50% aqueous ethanol (20 ml) was hydrogenated as described in the preparation of **10**. The crude product was recrystallized from ethanol to afford **15** as colorless needles:[16] yield 72 mg (85%); mp 309–310°; $[\alpha]^{20}D$ −13° (*c* 1.0, pyridine); λ_{max}^{KBr} 3.02 (NH), 5.71 (OAc), 6.01, and 6.37 μ (NHAc).

(1*S*)-1,3-Diacetamido-1,3,4-trideoxy-*scyllo*-inositol (16). Compound **15** (53 mg) was O-deacetylated as described in the preparation of **12** to give a white powder, which was recrystallized from water and ethanol to afford **16** as colorless needles:[16] yield 26 mg (75%); mp 288–289°; $[\alpha]^{22}D$ −5° (*c* 1.0, water); λ_{max}^{KBr} 6.11 and 6.31 μ (NHAc) [lit.[5] mp 291–292°; $[\alpha]^{29}D$ +5° (*c* 0.97, water)].

Supplementary Material Available. A listing of microanalytical data will appear following these pages in the microfilm edition of this

(15) Evaporations were performed below 50° under diminished pressure. Melting points were determined on a Mitamura Riken micro hot-stage and are uncorrected. Specific rotations were determined with a Jasco automatic polarimeter DIP-SL. Nmr spectra were measured with a Varian A-60D spectrometer employing tetramethylsilane as an internal standard, and peak positions are given in δ values. Infrared spectra were recorded on potassium bromide disks with a Jasco IR-E infrared spectrophotometer. Tlc was performed on silica gel (Wako gel B-10, Wako Pure Chemical Industries, Ltd.) plates and compounds were detected by iodine vapor or by heating with 30% sulfuric acid. Paper chromatography (descending) used Toyo Roshi No. 52 paper with the solvent systems A [1-butanol–pyridine–water (6:4:3, v/v)] and B [1-butanol–pyridine–water–acetic acid (6:4:3:1, v/v)].

(16) Microanalyses within acceptable limits have been obtained for these compounds. See paragraph at end of paper regarding supplementary material.

volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 20× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JACS-73-8734.

The Total Synthesis of the Alkaloid Casimiroedine, an Imidazole Nucleoside[1a]

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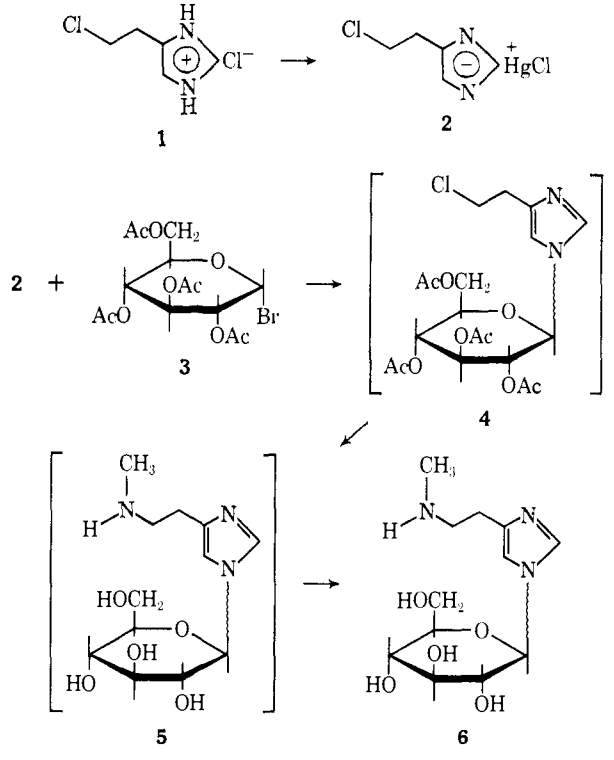
Abstract: The syntheses of the imidazole alkaloid casimiroedine (**7**), a natural product isolated from the seeds of the Mexican fruit "Zapote blanco," and its hydrolysis product casimidine (**6**) have been accomplished. The key step in the synthesis of casimiroedine (**7**) involves the formation of the peptide linkage between *trans*-cinnamic acid and casimidine. The unambiguous synthesis of **7** established the stereochemistry of the cinnamoyl moiety as trans. This assignment was corroborated by the synthesis of *cis*-casimiroedine (**8**) and spectral evidence.

Chemical investigations conducted on the seeds of the fruit of the tree *Casimiroa edulis* La Llave et Lejarza have shown them to contain a variety of constituents.[2-4] The principal constituent, the alkaloid casimiroedine (**7**), was found to be the cinnamic acid amide of casimidine (**6**).[5] Degradation studies[6] on casimidine confirmed the presence of *N*-methylhistamine and a carbohydrate fragment. An X-ray analysis[7,8] firmly established the structure of the carbohydrate as β-D-glucose and of casimidine as 4-[2-(methylamino)-ethyl]-1-(β-D-glucopyranosyl)imidazole. These studies provided the basic structure of casimiroedine (**7**) and left one question unanswered, whether casimiroedine was the *cis*- or *trans*-cinnamic acid amide of **6**. This final question has now been resolved by the total synthesis of casimiroedine.[1b]

Results and Discussion

Chemical Synthesis. The chloromercury derivative[9] (**2**) of 4-(2-chloroethyl)imidazole hydrochloride[10,11] (**1**) (Scheme I) was glycosylated with 2,3,4,6-tetra-*O*-acetyl-α-D-glucosyl bromide[12] (**3**) to provide **4** as a thick syrup. Rather than isolate nucleoside material at this point, the syrup was treated with methanolic methylamine in a steel reaction vessel at 100°. The purpose of this step was twofold: deacetylation of the glucose moiety and nucleophilic displacement of the chloro group. After removal of the excess methanolic methylamine, the

Scheme I



syrup (**5**) was purified on a Dowex 50W-X2 (NH_4^+) resin column which provided a single product (tlc). This crystalline solid was tentatively identified on the basis of pmr spectroscopy and elemental analysis as 4-[2-(methylamino)ethyl]-1-(β-D-glucopyranosyl)imidazole (**6**, casimidine). This assignment was confirmed by a comparison of the ir and mass spectra (EI) of this

(1) (a) This investigation was supported in part by Research Contract No. C72-3710 with the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Public Health Service. (b) R. P. Panzica and L. B. Townsend, presented in part before the Organic Chemistry Division, 24th Annual Northwest Regional Meeting of the American Chemical Society, University of Utah, Salt Lake City, Utah, June 1969, No. 149.

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