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Synthesis of 5-(Methylamino)-1-β-D-ribofuranosylimidazole-4-carboxamide, a Synthetic Intermediate for 3-Methyl-9-β-D-ribofuranosylpurines

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Treatment of 2′,3′,5′-tri-*O*-benzoyl-*N*,*N*-dimethyladenosine (**2c**) with methyl iodide in $AcNMe_2$ gave the 3-methyl derivative (**3c**) as a sole product. Alkaline hydrolysis of **3c** afforded the title imidazolecarboxamide (**4a**), whose hydroxy groups were acetylated selectively with Ac_2O–pyridine. Similar methylation of 2′,3′,5′-tri-*O*-benzyl-*N*,*N*-dimethyladenosine (**2d**) followed by alkaline hydrolysis provided 2′,3′,5′-tri-*O*-benzyl-**4a** (**4d**) in good yield.

Keywords——imidazole nucleoside; imidazolecarboxamide; (methylamino)imidazole; *N*-methylation; *N*,*N*-dimethyladenosine; ring-opening; trimethyladenosine iodide; glycosidic bond cleavage

No kind of 3-methyl-9-β-D-ribofuranosylpurine was known until the recent syntheses of 3-methylguanosine (**5**),[1] 3-methylinosine (**6**),[2] and 3-methyladenosine,[3] whereas the syntheses of all the other *N*-methyl isomers of these nucleosides had already been established.[4] The compounds **5** and **6** have been synthesized from a key intermediate, 5-(methylamino)-1-β-D-ribofuranosylimidazole-4-carboxamide (**4a**),[1,2] and compounds of this type are expected to be useful for syntheses of other new 3-methyl-9-β-D-ribofuranosylpurines. This paper presents a detailed account of the syntheses of the triacetyl ester (**4b**) and tribenzyl ether (**4d**) of **4a**, as well as **4a**.[5]

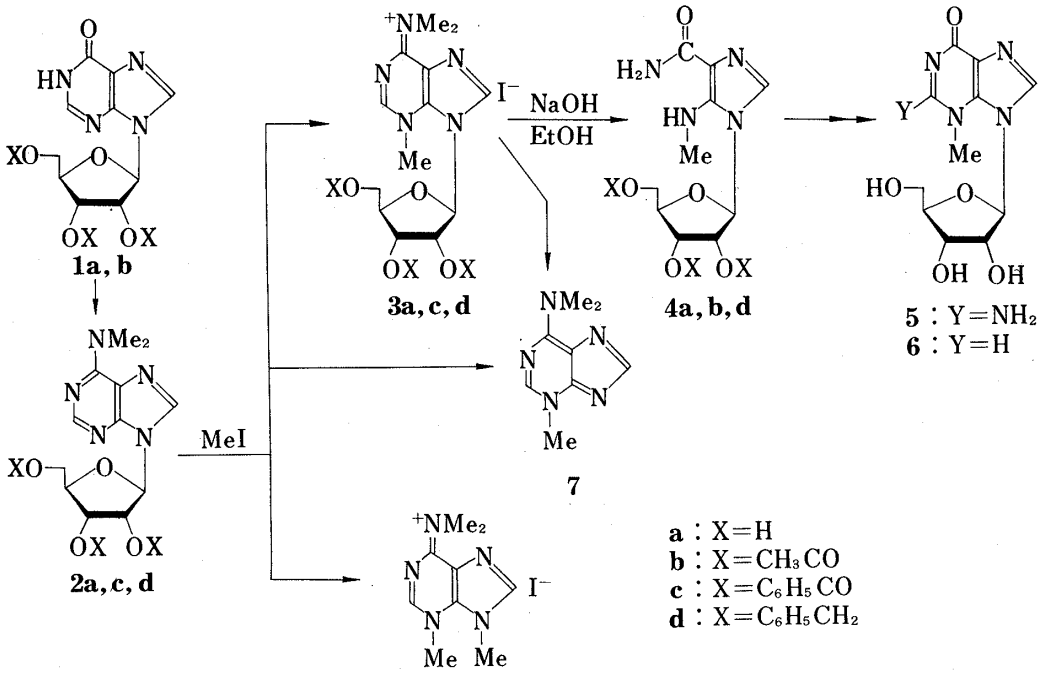

Chart 1

Since we had established the synthesis of 1-alkyl analogs of **4** from *N*,*N*-dimethyl-9-alkyladenines[6] as a model for the synthesis of **4**, *N*,*N*-dimethyladenosine (**2a**) appeared to be a good starting material for our purpose. Compound **2a** was prepared from 2′,3′,5′-tri-*O*-acetylinosine (**1b**)[7,8b] in 85% yield by our modification of the method of Žemlička and Šorm.[8] Contrary to expectation, reaction of **2a** with methyl iodide in $AcNMe_2$ at 40°C took place sluggishly and the products isolated were *N*,*N*,3-trimethyladenine (**7**)[9] and *N*,*N*,3,9-tetramethyladeninium iodide (**8**).[6a] We considered that **7** had resulted from glycosidic bond cleavage of the initially formed *N*,*N*,3-trimethyladenosine iodide (**3a**), and methylation of **7** then produced **8**.[6a] If the glycosidic bond cleavage of **3a** is a unimolecular process, introduction of an electron-withdrawing group at the 2′-position should slow down the cleavage as a result of destabilization of the intermediate ribosyl cation. Assuming that the reaction takes place by displacement by I^- at the 1′-position, modification of the 2′-hydroxy group with a bulky group would block the backside of the leaving group. Whichever mechanism operates, benzoylation of the 2′-hydroxy group of **3a** should stabilize the glycosidic bond. 2′,3′,5′-Tri-*O*-benzoyl-*N*,*N*-dimethyladenosine (**2c**) was, in fact, successfully methylated with a large excess of methyl iodide to give 2′,3′,5′-tri-*O*-benzoyl-3-methyladenosine iodide (**3c**), mp 189–190°C (dec.), in 83% overall yield based on **2a**. The structure of **3c** was assignable on the basis of comparison of the ultraviolet (UV) and nuclear magnetic resonance (NMR) spectra with those of *N*,*N*,3,9-tetraalkyladeninium salts.[6a] The site of methylation was confirmed by the formation of **7** on treatment of **3c** with hot AcOH.

Compound **3c** was heated in a mixture of 2 N aq. NaOH and EtOH (2: 1, v/v) and the product was purified on cation-exchange resin to give **4a**, mp 182—184°C, in 70% yield. The correctness of the structure of **4a** was supported by its UV spectra (similar to those[6b] of the 1-alkyl analogs) and by its NMR spectrum (see "Experimental"), which exhibited a methylamino group and an amido group. Alternatively, isolation of **4a** was achieved through its acetate. Treatment of crude **4a** with Ac_2O–pyridine at room temperature followed by chromatographic separation on silica gel provided 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-5-(methylamino)imidazole-4-carboxamide (**4b**) as a heavy oil in 75% yield based on **3c**. The NMR spectrum of **4b** (see "Experimental") showed that three acetyl groups had been incorporated and that the methylamino group remained intact, indicating that the acetylation had occurred at the sugar moiety selectively. Treatment of **4b** with NH_3–MeOH gave **4a** in 72% yield.

In view of the usefulness of the benzyl group as a protecting group we next tried to synthesize 1-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)-5-(methylamino)imidazole-4-carboxamide (**4d**). Treatment of **2a** with benzyl chloride in the presence of base gave 2′,3′,5′-tri-*O*-benzyl-*N*,*N*-dimethyladenosine (**2d**), mp 88—89°C, in 89—91% yield. 2′,3′,5′-Tri-*O*-benzyl-*N*,*N*,3-trimethyladenosine iodide (**3d**), mp 143—144°C (dec.), was obtained in 81% yield by methylation of **2d** in the manner employed for the synthesis of **3c**. The glycosidic bond of **3d** was so weak that brief treatment of **3d** with hot AcOH gave **7**. However, heating **3d** in a mixture of 1 N aq. NaOH and EtOH (1: 1, v/v) afforded 1-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)-5-(methylamino)imidazole-4-carboxamide (**4d**) as a glass in almost quantitative yield. The structure of **4d** was assigned on the basis of its NMR spectrum.

Nakatsuka *et al.*[1a] reported the five-step synthesis of **4b** from 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-5-aminoimidazole-4-carbonitrile *via* **4a**. Recently, Bridson and Reese[10] reported the conversion of 5-amino-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)imidazole-4-carboxamide into the corresponding 5-methylamino derivative (type **4**) by sequential treatment with *p*-thiocresol–formaldehyde and $NaBH_4$. The common starting material utilized by these groups is 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide, whereas our starting material is the more readily available inosine (**1a**). In conclusion, the present work provides an easy route to **4a**, **b**, **d** on a large scale, and the use of these compounds as starting materials should permit syntheses of various kinds of 9-β-D-ribofuranosylpurines methylated at the 3-position.

Experimental

Melting points are corrected. UV spectra were measured with a Hitachi 323 spectrophotometer using solutions in 95% aq. EtOH, 0.1 N aq. HCl (pH 1), 0.005 M phosphate buffer (pH 7), and 0.1 N aq. NaOH (pH 13). Unless otherwise stated, NMR spectra were recorded on a JEOL JNM-PS-100 spectrometer as 0.25 M solutions at 23—25°C using Me_4Si as an internal standard. The following abbreviations are used: b=broad, d=doublet, m=multiplet, q=quartet, s=singlet, t=triplet. Optical rotations were measured with a JASCO DIP-SL polarimeter. We are indebted to Mr. Y. Itatani and Miss Y. Arano at Kanazawa University for microanalyses and NMR spectroscopy.

***N*,*N*-Dimethyladenosine (2a)**——A solution of **1b** (120 g, 0.304 mol)[7,8b] in $CHCl_3$ (1.5 l) was treated with a 2 M solution (300 ml) of (chloromethylene)dimethylammonium chloride[11] in $CHCl_3$, and the mixture was refluxed for 2 h. It was cooled with ice-water and a suspension of $NaHCO_3$ (153 g) in H_2O (1.5 l) was added slowly with vigorous stirring. Stirring was continued for a further 1 h after complete addition of aq. $NaHCO_3$. The organic layer was dried over Na_2SO_4 and then evaporated to dryness *in vacuo* to leave a viscous oil. This was added slowly to ice-cooled 50% aq. $HNMe_2$ (920 ml) and the mixture was stirred at room temperature for 3 h. The mixture was then evaporated to dryness *in vacuo* and the resulting solid was recrystallized from MeOH to give **2a** (76.6 g, 85% yield) as colorless needles, mp 185—186°C (lit.[8] mp 182—184°C).[12] UV $\lambda_{max}^{95\%EtOH}$ 277 nm (ε 19500); $\lambda_{max}^{H_2O\,(pH1)}$ 269 (19000); $\lambda_{max}^{H_2O\,(pH7)}$ 276 (19100); $\lambda_{max}^{H_2O\,(pH13)}$ 277 (19300).

2′,3′,5′-Tri-*O*-benzoyl-*N*,*N*-dimethyladenosine (2c)——A mixture of **2a** (12.40 g, 0.042 mol), benzoyl chloride (18.4 g, 0.158 mol), and pyridine (300 ml) was stirred at 55—60°C for 22 h, concentrated to half the initial volume, then poured onto crushed ice (150 ml). The mixture was stirred for 2 h and benzene (200 ml) was added. The whole was stirred vigorously for a further 1.5 h. The organic layer was then stirred vigorously and 10% aq. HCl was added until the aqueous layer reached pH 2. The benzene solution was washed successively with H_2O, sat. aq. $NaHCO_3$ and H_2O, dried over $MgSO_4$, then evaporated to dryness *in vacuo* to leave a slightly yellow caramel. This was used in the next step without further purification. NMR (CCl_4) δ: 3.39 (6H, b, Me_2), 4.68 (3H, b, $H_{(5')}$'s) and $H_{(4')}$), 6.1—6.4 (3H, m, $H_{(1')}$, $H_{(2')}$, and $H_{(3')}$), 7.1—7.5 (9H, m, phenyl protons), 7.7—8.1 (8H, m, phenyl and purine protons).

2′,3′,5′-Tri-*O*-benzyl-*N*,*N*-dimethyladenosine (2d)——i) A mixture of **2a** (7.38 g, 0.025 mol), benzyl chloride (25 ml), powdered KOH (53 g), dioxane (50 ml), and benzene (100 ml) was stirred under reflux for 1.5 h. The mixture was evaporated to dryness and H_2O (100 ml) was added to the residue. The resulting solution was extracted with benzene (3×50 ml). The combined benzene extracts were washed successively with 0.1 N aq. HCl (4×50 ml), 10% aq. NaOH, and H_2O, dried over $MgSO_4$, and evaporated to dryness to leave a sirup. Treatment of this substance with hot hexane (150 ml) gave crystalline **2d** (12.80 g, 91% yield), mp 85—88°C. Recrystallizations from hexane gave colorless needles, mp 88—89°C. *Anal.* Calcd for $C_{33}H_{35}N_5O_4$: C, 70.07; H, 6.24; N, 12.38. Found: C, 70.18; H, 6.07; N, 12.58. UV $\lambda_{max}^{95\%EtOH}$ 276 nm (ε 19100). NMR (CCl_4) δ: 3.46 (6H, b, Me_2), 3.57 and 3.81 (1H each, ABX type q's, $J_{AB}=11$ Hz, $J_{AX}=J_{BX}=3$ Hz, $H_{(5')}$'s), 4.06—4.40 (3H, m, $H_{(4')}$, $H_{(3')}$, and $H_{(2')}$), 4.25 and 4.35 (1H each, AB type d's, $J=11$ Hz, $PhC\underline{H}_2$), 4.45 and 4.55 (1H each, AB type d's, $J=12$ Hz, $PhC\underline{H}_2$), 4.72 (2H, s, $PhC\underline{H}_2$), 6.10 (1H d, $J=2.5$ Hz, $H_{(1')}$), 7.17 and 7.22 (a total of 15H, s, Ph's), 7.93 and 8.14 (1H each, s, purine protons). $[\alpha]_D^{22}-32.3\pm0.1°$ ($c=0.319$, MeOH).

ii) A mixture of **2a** (19.79 g, 0.067 mol), 50% NaH (12.86 g, 0.268 mol), and $HCONMe_2$ (300 ml) was stirred at room temperature for 1.5 h. Benzyl chloride (33.93 g, 0.268 mol) was added to the stirred mixture over a period of 20 min, and stirring was continued for a further 2 h. After addition of EtOH, the mixture was evaporated to dryness *in vacuo*. The residue was worked up in a manner similar to that described under method (i) to give **2d** (33.57 g, 89% yield), mp 87—88°C, identical [infrared (IR) spectrum and mixed melting-point test] with the product obtained by method (i).

2′,3′,5′-Tri-*O*-benzoyl-*N*,*N*,3-trimethyladenosine Iodide (3c)——The whole amount of **2c** described above was treated with methyl iodide (42 ml) in $AcNMe_2$ (85 ml) at 40°C for 240 h. The resulting precipitate was filtered off, washed successively with $AcNMe_2$ (40 ml), EtOH (15 ml) and hot H_2O (60 ml), and dried to give **3c** (13.8 g) as slightly yellow prisms, mp 186—188°C (dec.). The combined $AcNMe_2$ and EtOH washings were evaporated to dryness and the residual semisolid was recrystallized from EtOH to afford a second crop (12.4 g, total yield 83% based on **2a**). Recrystallizations from MeOH gave colorless plates, mp 189—190°C (dec.). *Anal.* Calcd for $C_{34}H_{32}IN_5O_7$: C, 54.48; H, 4.30; N, 9.34. Found: C, 54.51; H, 4.24; N, 9.30. UV $\lambda_{max}^{95\%EtOH}$ 285 nm (ε 19900). NMR [$(CD_3)_2SO$] δ: 3.43 and 3.82 (3H each, s, NMe_2), 4.35 (3H, s, $N_{(3)}Me$), 4.68 (1H, m, $H_{(4')}$), 5.03 (2H, m, $H_{(5')}$'s), 6.18 (1H, b, $H_{(3')}$), 6.63 (1H, b, $H_{(2')}$), 7.03 (1H, d, $J=3$ Hz, $H_{(1')}$), 7.4—8.2 (15H, m, Ph's), 8.82 and 9.00 (1H each s, purine protons). $[\alpha]_D^{25}-51.1\pm1.1°$ ($c=0.335$, MeOH).

2′,3′,5′-Tri-*O*-benzyl-*N*,*N*,3-trimethyladenosine Iodide (3d)——A mixture of **2d** (2.83 g, 5 mmol), methyl iodide (5 ml), and $AcNMe_2$ (10 ml) was kept at 40°C for 144 h. A small amount of precipitate that separated was removed by decantation and the solution was shaken well after addition of benzene (100 ml) and H_2O (100 ml). The resulting oily precipitate was collected by decantation and treated with AcOEt (50 ml) to give **3d** (2.88 g, 81% yield) as a slightly yellow solid, mp 140—141°C (dec.). Recrystallizations from EtOH gave colorless plates, mp 143—144°C (dec.). *Anal.* Calcd for $C_{34}H_{38}IN_5O_4$: C, 57.71; H, 5.41; N, 9.90. Found:

C, 57.71; H, 5.30; N, 9.93. UV $\lambda_{max}^{95\%\,EtOH}$ 291 nm (ε 18500). NMR [$(CD_3)_2SO$] δ: 3.43 and 3.85 (3H each, s, NMe_2), 3.73 (2H, b, $H_{(5')}$'s), 4.23 (3H, s, $N_{(3)}Me$), 4.50 (a total of 4H, s, $PhCH_2$, overlapped with broad signals due to $H_{(3')}$ and $H_{(4')}$), 4.76 (4H, s, $PhCH_2$'s), 4.95 (1H, b, $H_{(2')}$), 6.43 (1H, d, J=4.5 Hz, $H_{(1')}$), 7.33 (15H, m, Ph's), 8.58 and 8.75 (1H each, s, purine protons). $[\alpha]_D^{24}$ −73.2±0.1° (c=0.360, MeOH).

5-(Methylamino)-1-β-D-ribofuranosylimidazole-4-carboxamide (**4a**)——i) A solution of **3c** (45.0 g, 0.06 mol) in 2 N aq. NaOH–EtOH (600 ml: 300 ml) was refluxed for 2 h and concentrated to half the initial volume. EtOH (300 ml) was added to the mixture and ion-exchange resin [Biorad AG 50W-X8 (H^+), 510 ml] was added in small portions to the ice-cooled mixture. The mixture was then transferred to a column packed with the ion exchanger (300 ml). The column was washed successively with H_2O–EtOH (2: 1, v/v, 4 l) and H_2O (2 l). Sequential elution of the column with cold 5% aq. NH_3 (600 ml), 10% aq. NH_3 (2.5 l), and 15% aq. NH_3 (3.8 l) and concentration of the combined ammoniac eluate gave a slightly yellow oil. This was dissolved in MeOH (400 ml) and insoluble materials were removed by filtration. The solution was evaporated to dryness and the residue was treated with hot EtOH (240 ml). After cooling, the resulting precipitate was collected by filtration and dried to give **4a** (10.24 g), mp 176—178°C. Silica gel (20 g) was added to the filtrate and the mixture was evaporated to dryness. The residual solid was placed on top of a silica gel (10 g) column and the column was eluted with AcOEt–EtOH (4: 1, v/v, 1.2 l). The eluate was evaporated to dryness to afford a second crop (1.22 g, total yield 70%), mp 167—169°C. Recrystallizations from EtOH gave colorless prisms, mp 182—184°C. *Anal.* Calcd for $C_{10}H_{16}N_4O_5$: C, 44.11; H, 5.92; N, 20.58. Found: C, 44.14; H, 6.10; N, 20.39. UV $\lambda_{max}^{95\%\,EtOH}$ 270 nm (ε 9000); $\lambda_{max}^{H_2O\,(pH1)}$ 259 (7600); $\lambda_{max}^{H_2O\,(pH7)}$ 267 (8300); $\lambda_{max}^{H_2O\,(pH13)}$ 268 (8500). NMR [$(CD_3)_2SO$] δ: 2.82 (3H, d, J=5 Hz, Me), 3.56 (2H, b, $H_{(5')}$'s), 3.88 (1H, m, $H_{(4')}$), 4.04 (1H, m, $H_{(3')}$), 4.28 (1H, m, $H_{(2')}$), 5.02 (1H, t, J=5 Hz, CH_2OH), 5.15 and 5.42 (1H each, d, J=5 Hz, OH's), 5.48 (1H, d, J=5 Hz, $H_{(1')}$), 5.64 (1H, bq, MeNH), 6.85 and 6.98 (1H each, b, NH_2), 7.55 (1H, s, $H_{(2)}$). $[\alpha]_D^{26}$ −62.6±1.3° (c=0.637, H_2O).

ii) A solution of **4b** (386 mg, 0.97 mmol) in NH_3-saturated MeOH (60 ml) was allowed to stand at 0°C overnight. The mixture was then evaporated to dryness *in vacuo* and the residual oil was crystallized by treating it with EtOH (5 ml) to give **4a** (190 mg, 72% yield), mp 172—177°C. Recrystallizations from EtOH gave colorless prisms whose IR spectrum and melting point were identical with those of a sample from (i).

1-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-5-(methylamino) imidazole-4-carboxamide (**4b**)——Alkaline hydrolysis of **3c** (3.00 g, 4 mmol) was conducted in the same way as described under method (i) for the preparation of **4a**. The resulting mixture was concentrated to half the initial volume then brought to pH 2 with conc. aq. HCl. The resulting precipitate was removed by filtration. The filtrate was washed with benzene (3×15 ml) and then brought to pH 8 with 10% aq. NaOH. It was evaporated to dryness *in vacuo* and the residue was extracted with hot EtOH (3×20 ml). The combined EtOH extracts were concentrated and the residue was extracted again with hot EtOH (15 ml). Removal of the solvent by evaporation gave a caramel (1.55 g). This was dissolved in pyridine (80 ml). Ac_2O (12 ml) was added to the solution and the mixture was allowed to stand at room temperature for 2 h. After addition of EtOH (80 ml), the mixture was left to stand at room temperature overnight. It was then evaporated to dryness and the residue was extracted with hot benzene (20 ml). Insoluble material was washed with benzene (4×10 ml). The combined benzene extracts were evaporated to dryness to leave a dark caramel. This was purified on a silica gel (100 g) column. Elution with $CHCl_3$–EtOH (15: 1, v/v) gave **4b** (1.19 g, 75% yield) as a slightly brown oil. NMR [$(CD_3)_2SO$] δ: 2.09 (6H, s, MeCO's), 2.13 (3H, s, MeCO), 2.81 (3H, d, J=5.5 Hz, HNMe), 4.33 (3H, b, $H_{(4')}$ and $H_{(5')}$'s), 5.38 (1H, b, $H_{(3')}$), 5.5—5.9 (3H, m, $H_{(1')}$, $H_{(2')}$, and MeNH), 6.97 and 7.12 (1H each, b, NH_2), 7.68 (1H, s, $H_{(2)}$).

The picrate of **4b** was prepared by dissolving **4b** (349 mg) in EtOH (1 ml) and adding a saturated solution (5 ml) of picric acid in EtOH. The yellow solid (469 mg, 85% yield), mp 170—178°C (dec.), thus obtained was recrystallized from MeOH to give yellow needles, mp 177—178°C (dec.). *Anal.* Calcd for $C_{22}H_{25}N_7O_{15}$: C, 42.11; H, 4.02; N, 15.63. Found: C, 42.12; H, 4.00; N, 15.54.

1-(2,3,5-Tri-*O*-benzyl-β-D-ribofuranosyl)-5-(methylamino) imidazole-4-carboxamide (**4d**)——A mixture of **3d** (1.415 g, 2 mmol), 1 N aq. NaOH (50 ml), and EtOH (50 ml) was refluxed for 3 h. The mixture was then concentrated to *ca.* 30 ml and extracted with benzene (4×50 ml). The combined benzene extracts were dried over $MgSO_4$ then evaporated to dryness to leave an oily residue. This was purified on a silica gel (10 g) column. Elution with $CHCl_3$–EtOH (10: 1, v/v) and concentration of the eluate gave **4d** (1.07 g, 98% yield) as a slightly yellow heavy oil. NMR [0.13 M solution in $(CD_3)_2SO$] δ: 2.81 (3H, d, J=4 Hz, Me), 3.70 (2H, b, $H_{(5')}$'s), 4.33 (2H, b, $H_{(3')}$ and $H_{(4')}$), 4.58 (s, $PhCH_2$'s) and 4.67 (s, $PhCH_2$) (a total of 7H, overlapped with a broad signal due to $H_{(2')}$), 5.56 (1H, b, MeNH), 5.72 (1H, d, J=7 Hz, $H_{(1')}$), 6.95 and 7.05 (1H each, b, NH_2), 7.37 (16H, m, Ph's and $H_{(2)}$).

Glycosidic Bond Cleavage of 3c,d——A solution of **3d** (141 mg, 0.2 mmol) in AcOH (1 ml) was refluxed for 30 min. The mixture was evaporated to dryness and the residue was partitioned between 1 N aq. HCl and benzene. The aqueous layer was saturated with K_2CO_3 and extracted with benzene. The benzene extracts were dried over $MgSO_4$ and removal of the solvent by evaporation gave **7** (31 mg, 89% yield), mp 172—173°C, identical with an authentic sample[9b] as judged from the IR spectra.

In a separate run, a solution of **3d** (71 mg, 0.1 mmol) in AcOH (1 ml) was kept on a boiling water bath for 30 min. The mixture was evaporated to dryness *in vacuo* and the residue was dissolved in EtOH (1 ml).

Saturated picric acid (1 ml) in EtOH was added to the solution to give the picrate of **7** (37 mg, 90% yield), mp 189—190°C. Recrystallizations from EtOH gave yellow pillars, mp 196—197°C (sinter at 189°C). *Anal.* Calcd for $C_{14}H_{14}N_8O_7$: C, 41.38; H, 3.47; N, 27.58. Found: C, 41.37; H, 3.52; N, 27.33. This sample was identical (IR spectrum and mixed melting-point test) with a sample prepared from authentic **7**.[9b]

A suspension of **3c** (75 mg, 0.1 mmol) in AcOH (1 ml) was stirred on a boiling water bath for 3 h and the resulting mixture was treated in a manner similar to that described above to give the picrate of **7** (15 mg, 37% yield).

Reaction of 2a with Methyl Iodide——A solution of **2a** (1.48 g, 5 mmol) and methyl iodide (1.56 ml) in $AcNMe_2$ (10 ml) was kept at 40°C for 7 d. The precipitate that separated was recrystallized from H_2O to give colorless needles (100 mg, 6% yield), mp >300°C.[12] This product was identical with **8**[6a] as judged from the IR, UV, and NMR spectra. Et_2O (40 ml) was added to the $AcNMe_2$ solution and the resulting precipitate was collected by filtration. An aqueous solution of this material was neutralized by passing it through a column packed with Amberlite IRA-402 (HCO_3^-). The eluate was evaporated to dryness and the residual sirup was purified on a silica gel column using $CHCl_3$–EtOH (5: 1, v/v) as an eluent. Further purification on an alumina column (eluted with $CHCl_3$) gave **7** (410 mg, 29% yield), mp 172—173°C. Recrystallization from benzene gave colorless prisms, mp 173—174°C,[12] which were identical with an authentic sample[9b] (mixed melting-point test and IR, UV, and NMR spectroscopy).

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