Nucleocyclitols. Synthesis of Substituted Purinyl-*muco*-inositol Derivatives

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Several carbocyclic nucleoside analogs possessing a 6-substituted purine linked to a mesylated *muco*-inositol were synthesized. The coupling of triethylamine-activated 6-chloropurine with 2,3-anhydro-1,5,6-tri-*O*-(methanesulfonyl)-*epi*-inositol gave a 6-chloro purinyl *muco*-inositol amenable to further synthetic transformations in the heterocyclic moiety by substitution of the chlorine atom by nitrogen nucleophiles such as methylamino, diethylamino, benzylamino, hydrazino, morpholino, hydroxylamino, piperidino, and glycyl groups.

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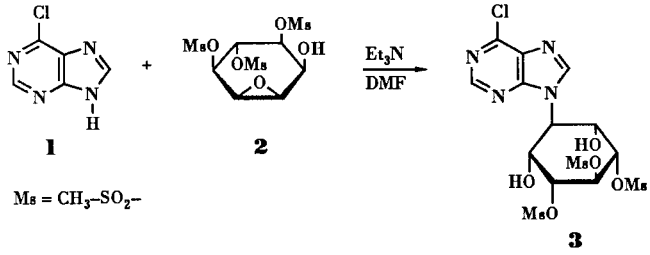
The reaction of 6-chloropurine (**1**), activated by triethylamine, with 2,3-anhydro-1,5,6-tri-*O*-(methanesulfonyl)-*epi*-inositol (**2**) in dimethylformamide at 80° gave regioselectively the 3′-(6-chloropurin-9-yl)-3′-deoxy-1′,5′,6′-tri-*O*-(methanesulfonyl)-*muco*-inositol (**3**) in 75% yield.



1 **2** **3**

Ms = CH_3–SO_2–

Previous studies [1,3] showed, in general, the ready interaction of an activated heterocycle with an adequately substituted inositol to give nucleocyclitols analogous to compound **3**. The activation of the purine molecule, already achieved through the formation of its sodium salt, was now obtained in an easier and cleaner way through the use of triethylamine. With respect to the oxirane ring, its reactivity seems to be conditioned by the presence of neighboring substituents, since epoxy hydrocarbons proved to be unreactive under our conditions.

The structure of compound **3** was readily established through its transformation into the 6-amino derivative by reaction with ammonia in a closed vessel. The structure of the resulting 3′-(adenin-9-yl)-3′-deoxy-1′,5′,6′-tri-*O*-(methanesulfonyl)-*muco*-inositol (**13**) was established in a previous paper [1], by ^{13}C-nmr data.

We intended to functionalize both moieties of this type of carbocyclic nucleoside analog in the search for new substances with diverse biological actions. Published [4] and current experiments in our laboratory showed interesting effects upon the vegetal cell and prompted us to develop the synthesis of a group of derivatives of compound **3** differently substituted in the purine ring.

Changes in the inositol portion proved to be very difficult owing to an unusual resistance of the mesyl groups to nucleophilic displacement. This resistance allowed us to perform many relatively drastic reactions on the heterocyclic moiety without changes in the inositol portion.

By a similar procedure to that followed for the synthesis of **3** and starting from 6-*N*-methylaminopurine, 3′-(6-methylaminopurin-9-yl)-*muco*-inositol (**4**) was obtained in 80% yield. This compound also resulted from the reaction of **3** with methylamine hydrochloride in the presence of triethylamine, although in lower yield (51%).

Scheme 1 shows several alternatives of substitution employing different nucleophiles.

The 6-diethylamino derivative **5** was obtained by two routes. One route (77%) was extremely mild and consisted in the reaction of compound **3** with diethylamine at room temperature for 12 hours. The other route was undertaken to determine the influence of the activating triethylamine upon the reactive groups of the molecule (chlorine and mesyl groups) and consisted in a long reflux (96 hours) of **3** with triethylamine in dimethylformamide to give **5** in 61% yield.

Other substitutions involved the use of cyclic, secondary nitrogen nucleophiles such as piperidine and morpholine to give compounds **7** and **11** respectively. The procedure required long reflux periods (40-50 hours) in ethanol, but the yields were high.

The use of primary amines as free bases shortened the time of reflux, which varied from 1.5 to 24 hours in methanol or ethanol, as occurred with benzylamine to give **6** and hydrazine hydrate to yield **8**.

Volatile or less stable primary amines were used as hydrochlorides in the presence of triethylamine or potassium carbonate to liberate the bases in the alcoholic media of the reaction. This procedure was employed with methylamine hydrochloride to give compound **4**, with hydroxylamine to afford **9**, and with glycine to provide **12**. In the

Scheme I

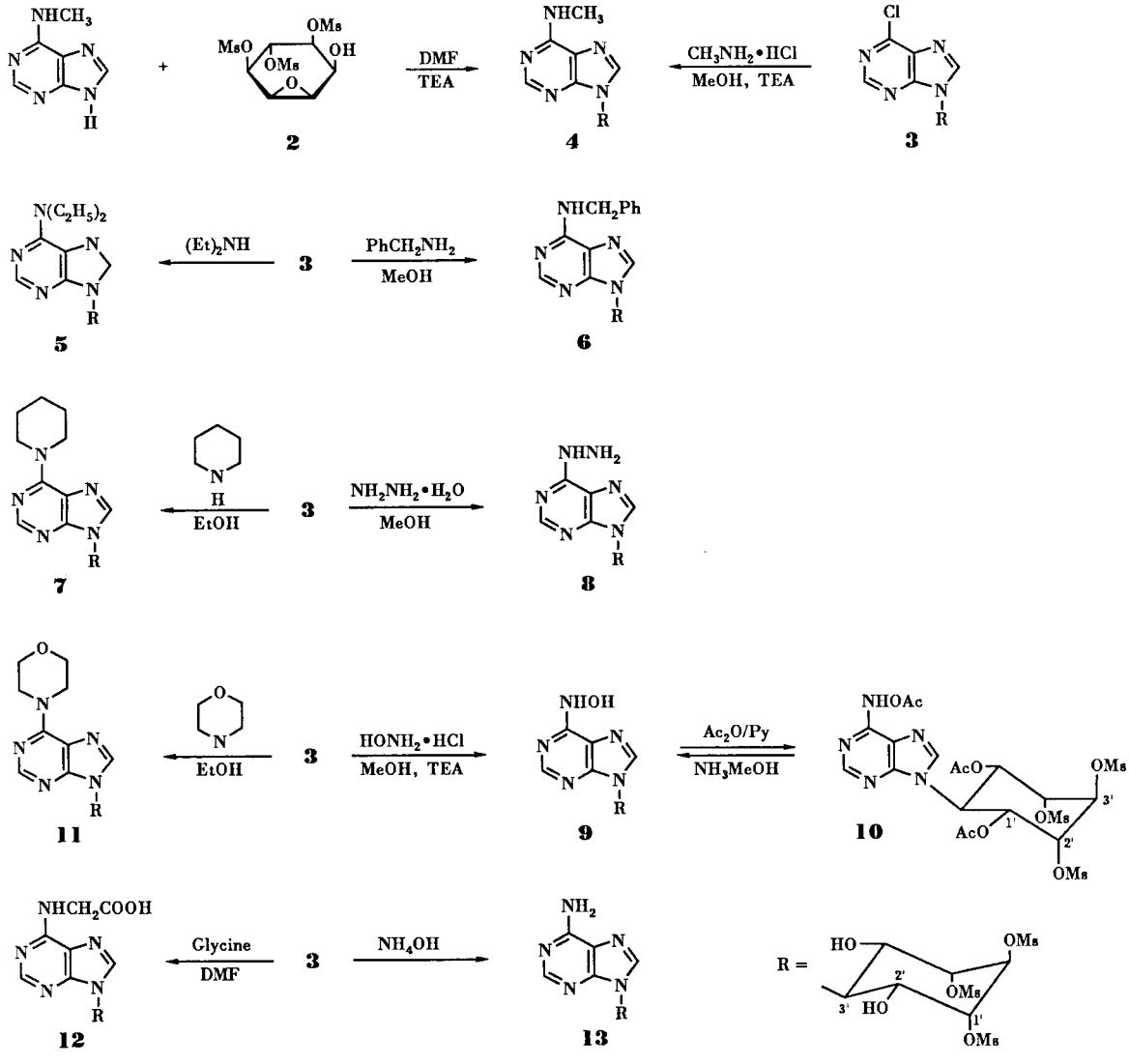


Table I

^{13}C-NMR Chemical-shifts for the 6-Chloropurine Anion and Compound **3**

	Chemical Shifts [a]										
Compound	C-2	C-4	C-5	C-6	C-8	C-1'	C-2'	C-3'	C-4'	C-5'	C-6'
Chloropurine anion I	146.6	163.4	132.7	144.0	157.2						
Compound **3**	150.8	148.7	131.4	152.2	148.2	77.2	64.3	58.3	64.3	77.2	73.6
Δδ**I**-**3**	-4.2	+14.7	+1.3	-8.2	+9.2						

[a] Shifts given in ppm downfield from TMS, for solutions in DMSO-d_6

case of compound **9** the insertion through the nitrogen atom of the nucleophile was ascertained by acetylation to give **10**; subsequent *O*-deacetylation at room temperature with sodium methoxide in methanol afforded the starting compound **9**.

The action of ammonia was a special case which required the use of a 25% solution of aqueous ammonia in a sealed tube at 110° for 15 hours to give the previously described [1] 6-amino derivative **13**.

Compounds **3**, **6**, and **10** showed ^{1}H-nmr spectra amen-

able of first order analysis which allowed the determination of the preferred conformation of these compounds. The purinyl moiety preferred the equatorial position and the mesyl group is in the axial position.

Thus, the coupling constants for H-2′-H-3′ and H-3′-H-4′ in compound **3** were 8 Hz, which support a *trans*-diaxial relationship for these pairs of protons. Likewise, these protons in compound **6** showed couplings of 10 Hz. The acetate **10** also showed for the corresponding protons (see numbering in Scheme 1) coupling constants of 11 Hz.

It is reasonable to postulate an analogous conformation for the remaining derivatives on the basis of the strong limitations imposed by the substituted purinyl portion to the conformational mobility of the inositol ring.

Analysis of ^{13}C-nmr data of **3** provides an independent confirmation of the structure, which was established through its transformation into compound **13** [1]. In **3** there are two principal problems to clarify, which are the points of attachment of the heterocyclic and the inositol moieties.

In the ^{13}C-nmr spectrum of **3** in deuterated dimethyl sulfoxide the inositol moiety showed four peaks for the six carbon atoms of the ring, two of these peaks being of double intensity. A higher-field, single-intensity resonance (δ 58.3) can be attributed to the point of insertion (C-3′) of the base. The symmetrical pattern of ^{13}C-resonances for the inositol moiety support the postulated insertion of the purine at C-3′ (see Table 1), and not at C-2′. The other ^{13}C-resonances can be assigned by considering that the axial substituents on C-1′ and C-5′ would exert a strong α-effect upon both carbon atoms giving rise to a doubly intense, downfield peak at δ 77.2. Other doubly intense peak at δ 64.3 can be ascribed to the other two magnetically equivalent carbon atoms, C-2′ and C-4′. The resonance of these carbons at higher field can be speculatively attributed to the influence of the neighboring mesyl groups (β-effect) and to the vicinal purine ring. The last signal at δ 73.6 was assigned to C-6′.

With reference to the point of attachment of C-3′ of the inositol moiety to N^9 of the chloropurine ring, substitution at N^7 of the purine ring is usually identified with a uv maxima of 272-276 nm [5], coupling at N^9 exhibits [5] maxima of 260-262 nm. The uv spectrum of compound **3** in ethanol exhibits a maxima at 260-262 nm, which supports the N^9 structure.

This structure is confirmed by the ^{13}C-nmr data, which are also useful in cases in which the uv maxima are ambiguous [3]. The ^{13}C-nmr parameters can be used for assignment of the site of glycosylation of nitrogen heterocycles [6]. This method is based upon the fact that, when the free pair of electrons on the nitrogen atom in the anion is glycosylated, an upfield shift for the carbon α to the glycosylated nitrogen atom, and a downfield shift for the β- and γ-carbon atoms were observed [6], when compared with their base anion. On this basis, the ^{13}C-chemical shifts of **3** were compared with those of the 6-chloropurine anion formed by treatment of 6-chloropurine with lithium hydroxide in deuterated dimethyl sulfoxide. Thus, large upfield shifts (see Table 1) for C_4 and C_8, which are α to the substituted nitrogen atom (N^9), were observed. The bridgehead nature of C-5 explains the reverse behavior shown by this carbon atom [6]. A substitution at N^7 should afford a different pattern of displacement. Thus, this case adds another method establishing the previously described [1,3] procedures to establish the site of attachment of the purine.

EXPERIMENTAL

Melting points (Kofler hot-stage) are uncorrected. The tlc were conducted on silica gel G (Merck) plates (0.25 mm layer thickness) with the following solvents: A) 1:4 (v/v) absolute ethanol-benzene, B) 9:1 (v/v) chloroform-methanol, and C) 1:1 (v/v) ethyl acetate-methanol. The spots were detected with 1) iodine vapor, 2) sodium iodide-1-butanol for epoxides. The ir spectra were recorded in Nujol mulls with a Perkin-Elmer 710 B spectrophotometer. The uv were recorded with a Hewlett Packard 8451A spectrophotometer. The ^{1}H- and ^{13}C-nmr spectra were recorded at 20-25° with a Varian XL-100 spectrophotometer at 100 (^{1}H) and 25.2 (^{13}C) MHz with TMS as the internal reference standard.

3′-(6-Chloropurin-9-yl)-3′-deoxy-1′,5′,6′-tri-*O*-(methanesulfonyl)-*muco*-inositol (**3**).

6-Chloropurine (**1**, 600 mg, 3.8 mmoles) was dissolved by refluxing in anhydrous DMF (40 ml). The solution was cooled to 70° and triethylamine (10 ml) was added. The solution was magnetically stirred at that temperature for 1 hour and then 2,3-anhydro-1,5,6-tri-*O*-(methanesulfonyl)-*epi*-inositol [2] (**2**, 1.5 g, 3.8 mmoles) was added. After 24 hours at 80° with magnetic stirring, the solution was evaporated to dryness, dried in a vacuum dessicator for 24 hours and the residue was macerated with methanol (20 ml). The precipitate **3** obtained (1.56 g, 75% yield) had mp 272° dec; tlc (solvent A, reagent 1) R_f 0.36; uv (methanol): λ max 261 (ϵ 7.8); ir (Nujol): ν max 3215 (OH), 1600 (C=N), 1160 cm^{-1} (sulfonyl group); ^{1}H-nmr (DMSO-d_6): δ 3.33 (6H, CH_3SO_2), 3.43 (3H, CH_3SO_2), 4.00 (t, H-3′, $J_{2',3'} = J_{3',4'} = 8$ Hz), 5.13 (m, H-5′, H-6′), 5.85 (m, H-2′, H-4′), 8.80 and 8.85 (H-2, H-8 purine ring); ^{13}C-nmr (DMSO-d_6): δ 150.8 (C-2), 148.7 (C-4), 131.4 (C-5), 152.2 (C-6), 148.2 (C-8), 77.2 (C-1′, C-5′), 73.6 (C-6′), 64.3 (C-2′, C-4′), 58.3 (C-3′).

Anal. Calcd. for $C_{14}H_{19}ClN_4O_{11}S_3$: C, 30.52; H, 3.48; Cl, 6.43; N, 10.17; S, 17.46. Found: C, 30.84; H, 3.77; Cl, 6.18; N, 9.88; S, 17.72.

3′-(6-Methylaminopurin-9-yl)-3′-deoxy-1′,5′,6′-tri-*O*-(methanesulfonyl)-*muco*-inositol (**4**).

Procedure (a).

6-*N*-Methylaminopurine (113 mg, 0.75 mmole) was dissolved in boiling DMF (20 ml). The solution was cooled to 70° and triethylamine (6 ml) was added. After 1 hour of stirring at that temperature compound **2** (300 mg, 0.75 mmole) was added and the solution was stirred at 80° for 40 hours and then evaporated to dryness. The residue was macerated with methanol and thus af-

forded a solid which recrystallized from acetone gave **4** (330 mg, 80% yield), mp 219-220°, tlc R_f 0.19 (solvent A, reagent 1).

Procedure (b).

Compound **3** (100 mg, 0.18 mmole) was dissolved in a mixture of methanol (7 ml) and triethylamine (3 ml), and after a short reflux methylamine hydrochloride (15 mg, 0.22 mmole) was added. The solution was refluxed for 20 hours then evaporated to dryness and the residue, recrystallized from methanol, gave compound **4** (50 mg, 51% yield); uv (methanol): λ max 262 nm (ε 13.49); ir: 1600 (C=N), 1130 cm^{-1} (sulfonyl group); ^{1}H-nmr (perdeuteriopyridine): δ 2.98 (d, CH_3), 3.30 (3H, CH_3SO_2), 3.32 (6H, CH_3SO_2), 5.12 (H-3'), 5.74 (m, 5H, inositol ring), 8.05 and 8.17 (2H, H-2, H-8, purine).

Anal. Calcd. for $C_{15}H_{23}N_5O_{11}S_3$: C, 33.01; H, 4.22; N, 12.83; S, 17.50. Found: C, 32.85; H, 4.13; N, 13.00; S, 17.14.

3'-(6-Diethylaminopurin-9-yl)-3'-deoxy-1',5',6'-tri-*O*-(methanesulfonyl)-*muco*-inositol (**5**).

Compound **3** (100 mg, 0.18 mmole) was dissolved in diethylamine (2 ml) and the solution was kept at room temperature for 12 hours. The solution was then evaporated to dryness and the residue, recrystallized from a 1:1 mixture of 2-propyl alcohol-petroleum ether (bp 60-80°), gave compound **5** (82 mg, 77% yield), mp 203-204°, tlc R_f 0.38 (solvent A, reagent 1); uv (methanol): λ max 279 nm (ε 18.6); ir: 1580 (C=N), 1120 cm^{-1} (sulfonyl group); ^{1}H-nmr (perdeuteriopyridine): δ 1.20 (6H, CH_3), 3.43 (3H, CH_3-SO_2), 3.46 (6H, CH_3-SO_2), 3.78 (4H, CH_2), 5.95 (m, 6H, inositol ring), 8.18 and 8.23 (H-2 and H-8 purine).

Anal. Calcd. for $C_{18}H_{29}N_5O_{11}S_3$: C, 36.79; H, 4.97; N, 11.92; S, 16.36. Found: C, 37.09; H, 5.20; N, 11.91; S, 15.98.

Reaction with Triethylamine.

Compound **3** (100 mg, 0.18 mmole) was dissolved in a mixture of DMF (10 ml) and triethylamine (5 ml, 0.035 mmole) and the solution was stirred at 70-80° for 96 hours. After evaporation to dryness and maceration of the solid with cold water an insoluble product was removed by filtration (65 mg, 61% yield), tlc R_f 0.40 (solvent A, reagent 1). Recrystallization of this crude product from ethanol gave a product with mp consistent with compound **5**, mp 203-204°. Their identity was further confirmed by their ^{1}H-nmr spectra.

3'-(6-Benzylaminopurin-9-yl)-3'-deoxy-1',5',6'-tri-*O*-(methanesulfonyl)-*muco*-inositol (**6**).

Compound **3** (600 mg, 1.09 mmoles) and benzylamine (0.25 ml, 2.3 mmoles) were refluxed for 6 hours in methanol (60 ml). Upon cooling the solution compound **6** crystallized (500 mg, 73% yield). Recrystallization from 2-propyl alcohol-acetone (3:1) gave a compound with mp 169-171°; tlc R_f 0.43 (solvent A, reagent 1); uv (methanol): λ max 252 nm (ε 13.7); ir: 1610 (C=N), 1120 cm^{-1} (sulfonyl group); ^{1}H-nmr (DMSO-d_6): δ 3.48 (6H, CH_3-SO_2), 3.63 (3H, CH_3SO_2), 4.66 (t, H-3', $J_{2',3'} = J_{3',4'} = 10$ Hz), 4.96 (m, 4H, OH, CH_2), 5.28 (m, 3H, inositol ring), 5.95 (2H, H-2', H-4' inositol ring), 7.48 (m, 5H, phenyl group), 8.40 (s, 3H, H-2, H-8, NH).

Anal. Calcd. for $C_{21}H_{27}N_5O_{11}S_3$: C, 40.57; H, 4.38; N, 11.26; S, 15.47. Found: C, 40.19; H, 4.63; N, 10.96; S, 15.17.

Compound **6** Hydrochloride.

Compound **6** was suspended in warm water and the suspension was acidified with concentrated hydrochloric acid until dissolution of the precipitate. The solution was evaporated to dryness and the residue, recrystallized from 2-propyl alcohol-xylene (1:1) gave mp 168-169°, tlc R_f 0.12 (solvent A, reagent 1).

3'-[6-(piperidin-1-yl)-purin-9-yl]-3'-deoxy-1',5',6'-tri-*O*-(methanesulfonyl)-*muco*-inositol (**7**).

Compound **3** (100 mg, 0.18 mmole) was dissolved in a mixture of ethanol (20 ml) and piperidine (1 ml, 10.1 mmoles). The solution was refluxed for 50 hours and then evaporated to dryness. The residue, macerated with methanol cooled and filtered gave compound **7** (80 mg, 74% yield). Recrystallization from ethanol gave a compound with mp 203°, tlc R_f 0.67 (solvent A, reagent 1); uv (methanol): λ max 248 nm (ε 14.7); ^{1}H-nmr (DMSO-d_6): δ 1.63 (m, 6H, CH_2), 3.28 (s, 6H, CH_3SO_2), 3.40 (s, 3H, CH_3SO_2), 4.18 (m, 4H, CH_2), 4.76 (H-3'), 5.03 (m, H-1', H-5', H-6'), 5.68 (H-2', H-4'), 8.15 (s, H-2, H-8, purine).

Anal. Calcd. for $C_{19}H_{29}N_5O_{11}S_3$: C, 38.06; H, 4.87; N, 11.68; S, 16.04. Found: C, 38.23; H, 5.03; N, 11.75; S, 15.84.

3'-(6-Hydrazinopurin-9-yl)-3'-deoxy-1',5',6'-tri-*O*-(methanesulfonyl)-*muco*-inositol (**8**).

Compound **3** (100 mg, 0.18 mmole) was dissolved in ethanol (8 ml) and 85% hydrazine hydrate (0.2 ml, 3.4 mmoles) was added. The solution was refluxed for 90 minutes and, on cooling, a solid was collected (80 mg). By evaporation of the mother liquors a second crop (16.5 mg) was obtained (total yield 70%). Recrystallization of the product from ethanol gave compound **8**, mp 218-220° dec, tlc R_f 0.15 (solvent A, reagent 1); uv (methanol): λ max 260 nm (ε 18.00), 286 (ε 17.00); ^{1}H-nmr (DMSO-d_6): δ 3.31 (6H, CH_3-SO_2), 3.45 (3H, CH_3-SO_2), 4.80 (H-3'), 5.07 (m, H-1', H-5', H-6'), 5.73 (m, H-2', H-4'), 7.1 (NH), 8.15 and 8.22 (2H, purine ring).

Anal. Calcd. for $C_{14}H_{22}N_6O_{11}S_3 \cdot 2C_2H_5OH$: C, 33.85; H, 5.36; N, 13.16; S, 15.06. Found: C, 33.90; H, 5.16; N, 12.94; S, 15.01.

3'-(6-Hydroxylaminopurin-9-yl)-3'-deoxy-1',5',6'-tri-*O*-(methanesulfonyl)-*muco*-inositol (**9**).

Compound **3** (1 g, 1.82 mmoles) was dissolved in a 95:5 mixture of methanol-water (120 ml), then triethylamine (10 ml) and hydroxylamine hydrochloride (190 mg, 2.73 mmoles) were added. The solution was refluxed for 24 hours and then evaporated to dryness. The residue was triturated with ethanol to afford compound **9** (683 mg, 69% yield) which was recrystallized from ethanol to give a product with mp 219-221°, tlc R_f 0.17 (solvent A, reagent 1); uv (methanol): λ max 250 nm (ε 16.93); ir: 1600 (C=N), 1150 cm^{-1} (sulfonyl group); ^{1}H-nmr (perdeuteriopyridine): δ 3.52 (6H, CH_3SO_2), 3.56 (3H, CH_3SO_2), 5.36 (H-3'), 5.96 (m, 5H, inositol ring), 8.26 and 8.38 (H-2 and H-8 purine ring).

Anal. Calcd. for $C_{14}H_{21}N_5O_{12}S_3 \cdot C_2H_5OH$: C, 32.37; H, 4.58; N, 11.80; S, 16.20. Found: C, 32.66; H, 4.32; N, 11.86; S, 16.60.

6'-(6-Acetoxylaminopurin-9-yl)-1',5',6'-di-*O*-acetyl-6'-deoxy-2',3',4'-tri-*O*-(methanesulfonyl)-*muco*-inositol (**10**).

Compound **9** (100 mg, 0.17 mmole) was dissolved in a 1:1 mixture of pyridine-acetic anhydride (4 ml), kept 24 hours at room temperature, and then the solution was refluxed for 40 minutes. The solution was evaporated to dryness and the residue, macerated with cold water, gave the triacetate **10** which was recrystallized from ethanol (109 mg, 96% yield), mp 211-212°, tlc R_f 0.53 (solvent B, reagent 1). Deacylation of a sample with methanolic ammonia afforded the starting compound **9**, mp and mixed mp

219-221°; uv (methanol): λ max 250 nm (ε 14.56); ^{1}H-nmr (perdeuteriopyridine): δ 1.86 (6H, CH_3-CO), 2.34 (3H, CH_3CO), 3.56 (6H, CH_3SO_2), 3.69 (3H, CH_3SO_2), 5.98 (H-6'), 6.16 (m, H-2', H-3', H-4'), 6.97 (t, H-1', H-5', $J_{1',6'} = J_{5',6'} = 11$ Hz, $J_{1',2'} = J_{4',5'} = 2$ Hz), 8.83 and 9.13 (H-2, H-8, purine ring).

Anal. Calcd. for $C_{20}H_{27}N_5O_{15}S_3$: C, 35.66; H, 4.04; N, 10.39; S, 14.28. Found: C, 35.42; H, 4.15; N, 10.40; S, 14.61.

3'-[6-(Morpholin-1-yl)purin-9-yl]-3'-deoxy-1',5',6'-tri-*O*-(methanesulfonyl)-*muco*-inositol (**11**).

Compound **3** (400 mg, 0.72 mmole) was dissolved in boiling ethanol (40 ml) and morpholine (1 ml, 11.5 mmoles) was added. The solution was refluxed for 40, hours then evaporated to dryness and the residue was macerated with ethanol. The solid obtained (364.6 mg, 84% yield) had mp 230-232°, tlc R_f 0.57 (solvent A, reagent 1); uv (methanol): λ max 282 nm (ε 13.99); ir: 1580 (C=N), 1120 cm^{-1} (sulfonyl group); ^{1}H-nmr (DMSO-d_6): δ 3.30 (6H, CH_3SO_2), 3.45 (3H, CH_3SO_2), 3.76 (4H, CH_2morpholinyl), 4.23 (4H, CH_2 morpholinyl), 4.80 (H-3'), 5.10 (m, H-1', H-5', H-6'), 5.73 (m, H-2', H-4'), 8.26 (s, H-2, H-8, purine ring).

Anal. Calcd. for $C_{18}H_{27}N_5O_{12}S_3$: C, 35.94; H, 4.49; N, 11.65; S, 15.97. Found: C, 36.20; H, 4.65; N, 11.91; S, 15.70.

3'-[6-(2-Aminoacetic)purin-9-yl]-3'-deoxy-1',5',6'-tri-*O*-(methanesulfonyl)-*muco*-inositol (**12**).

A mixture of compound **3** (300 mg, 0.54 mmole), glycine hydrochloride (120 mg, 1.0 mmole) and potassium carbonate (150 mg), suspended in DMF-water (1:1; 15 ml), was refluxed 24 hours at 120°. The solution was then evaporated to dryness, the residue was dissolved in boiling water and the solution was acidified to approximately *p*H 4 with formic acid-water (1:1). By cooling the solution compound **12** was obtained (205 mg, 64% yield), mp 190° dec; tlc R_f 0.15 (solvent C, reagent 1); uv (methanol): λ max 252 nm (ε 15.43); ^{1}H-nmr (perdeuteriopyridine): δ 3.30 (3H, CH_3SO_2), 3.35 (6H, CH_3SO_2), 4.58 (CH_2), 5.16 (t, H-3'), 5.80 (m, 5H, inositol ring), 8.14 (s, H-2, H-8, purine ring).

Anal. Calcd. for $C_{16}H_{23}N_5O_{13}S_3$: C, 32.59; H, 3.93; N, 11.88; S, 16.31. Found: C, 32.34; H, 4.23; N, 11.80; S, 15.92.

3'-(adenin-9-yl)-3'-deoxy-1',5',6'-tri-*O*-(methanesulfonyl)-*muco*-inositol (**13**).

Compound **3** (60 mg, 0.1 mmole) was suspended in 25% ammonium hydroxide (3 ml) and heated in a closed ampoule at 110° for 15 hours. After cooling, the dark solution was filtered and evaporated to dryness. The residue was chromatographed preparatively on a silica gel plate (1 mm layer thickness) by double developing with solvent B. Compound **13** was isolated (30 mg, 52% yield), mp and mixed mp 248-250°, lit [1] mp 248-250°.

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