Synthesis and Biological Evaluation of Nucleosides Containing 8-Aminoimidazo[1,2-*a*]pyrazine as an Isosteric Replacement for Adenine [1]

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Dedicated to the memory of Dr. Roland K. Robins

A number of novel *C*-nucleosides related to purine derivatives are described in which the purine moiety has been replaced by the isosteric heterocycle, 8-aminoimidazo[1,2-*a*]pyrazine. The nucleosides prepared include the ribo, 3′-deoxy, 2′,3′-dideoxy, and 2′,3′-unsaturated derivatives. These *C*-nucleosides represent derivatives containing acid stable glycosyl bonds and they can be considered as analogs of adenine- or 3-deazaadenine-containing nucleosides. Preparation of the parent ribonucleoside was accomplished by reaction of the C-1 functionalized sugar, (2*S*)-1-amino-3,6-anhydro-1-deoxy-4,5-*O*-isopropylidene-7-*O*-trityl-D-*allo*-heptitol with 2,3-dichloropyrazine, followed by ring closure to the 8-chloroimidazo[1,2-*a*]pyrazine nucleoside, conversion to the 8-amino derivative and deblocking. A single crystal X-ray structure of the parent 8-amino-3-(β-D-ribofuranosyl)imidazo[1,2-*a*]pyrazine is described and the conformation compared to that of formycin. The sugar-modified analogs were prepared by subsequent functional group manipulations on the sugar moiety. Biological evaluation against HIV in H9 T-lymphoid cell culture showed the nucleosides to be devoid of significant antiviral activity compared to DDA. The 3-deazaadenosine analog also demonstrated weak suppression of mouse splenic NK activity toward YAC cells (mouse lymphoma cell targets). The imidazo[1,2-*a*]pyrazine analog of 3-deazaadenosine showed antiinflammatory activity *in vivo* in the rat pleurisy carrageenan model in the same range with 3-deazaadenosine.

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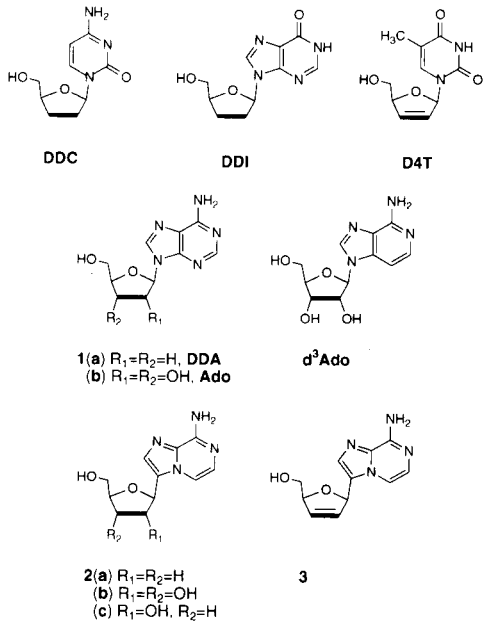
The nucleoside analogs, 2′,3′-dideoxyadenosine (DDA), 2′,3′-dideoxyinosine (DDI), 2′,3′-dideoxycytidine (DDC), and 2′,3′-dideoxy-2′,3′-didehydrothymidine (D4T) have been extensively examined as antiviral agents, particularly for the treatment of AIDS [1]. The mechanism of action of these agents involves the sequential phosphorylation in the cytoplasm of cells to give the nucleoside 5′-triphosphate which inhibits the viral reverse transcriptase (RT) by acting as a chain terminator [2]. In consideration of the preferred sugar conformations of certain anti-HIV-1 nucleosides, it has been postulated that the spatial relationship between the base and the 5′-hydroxyl group is critical for overall activity [3]. Structure-activity relationships have shown that the presence of a 2′,3′-dideoxy sugar (such as found in DDA, DDI or DDC) or a 2′,3′-double bond (such as found in D4T) provide for excellent activity when the sugar modification is matched with the appropriate nucleic acid base. In the case of the purine nucleosides, however, the deoxygenated nucleosides have a short half-life due to the acid lability of their glycosyl linkage. An attempt to circumvent this undesirable property utilized co-delivery of DDI with anti-acids and a second attempt utilized 2′-fluoro derivatives which electronically stabilize the glycosyl bond. This latter approach provided derivatives as potent as the parent compounds, but increased toxicity was also observed [4]. An alternative way of stabilizing the glycosyl bond in 2′,3′-dideoxynucleosides is to prepare *C*-nucleosides; this requires isosteric modification of the aglycone.

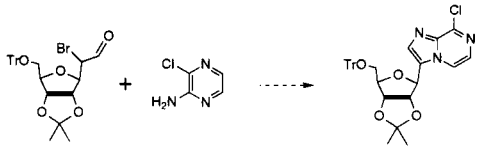
Chart 1



In this work we describe the preparation of nucleoside analogs bearing 8-aminoimidazo[1,2-*a*]pyrazine as a replacement for adenine. This heterocyclic substitution can also be considered an isosteric replacement for 3-deazaadenine, the heterocyclic component of nucleosides which have been studied as antiinflammatory and immunosuppressive agents [5,6]. 3-Deazaadenosine (d^3Ado) has also been suggested to inhibit methylation processes [7,8]. In addition, d^3Ado is reported to possess broad-spectrum antiviral activity [9,10], which may be mediated by *S*-adenosylhomocysteine hydrolase (SAH hydrolase) inhibitory activity [11-14] since phosphorylation *in vivo* does not occur [5]. Interesting close structural aza-analogs of these imidazo[1,2-*a*]pyrazine nucleosides are the 1,2,4-triazolo[4,3-*a*]-pyrazine nucleosides previously described by Schneller *et al* [15,16].

Two synthetic approaches to the 3-substituted imidazo-[1,2-*a*]pyrazine ring system were examined and these are shown in Schemes 1 and 2.

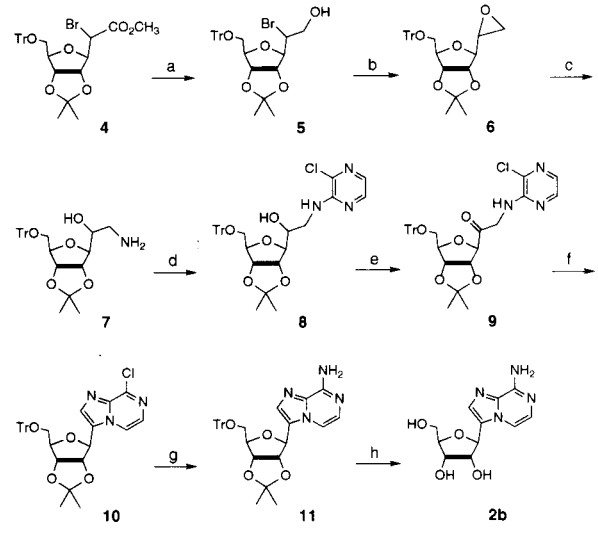
Scheme 1



1. K_2CO_3, isoamylOH, 100°C; *2.* isoamylOH, 100°C; 3. 2-PrOH, 80°C; *4.* $(CH_3O)_2CH_2CH_3$, 80 °C; *5.* $(CH_3O)_2CH_2CH_3$, AgOAc, 50°C; *6.* H_2O,2-PrOH, NaOAc, 50°C

The first approach, shown in Scheme 1, involved the condensation of the appropriate α-bromoaldehyde, (2ξ)-3,6-anhydro-2-deoxy-2-bromo-4,5-*O*-isopropylidene-7-*O*-trityl-*aldehydo*-D-*allo*-heptose, (prepared from D-ribose in 4 steps by the method of Clingerman and Secrist [17]) with 2-amino-3-chloropyrazine to form the imidazo[1,2-*a*]pyra-

Scheme 2



a. $LiBH_4$, THF ; *b.* NaH, DMF ; *c.* NH_3, MeOH ; *d.* Et_3N, dioxane, 2,3-dichloropyrazine; *e.* pyridine/SO_3,DMSO or TFAA, Et_3N, DMSO ; *f.* TFA, TFAA, pyridine, $PhCH_3$; *g.* NH_3, iPrOH, 100 °C,18 h ; *h.* 90% aq. TFA

Table I. Positional and Thermal Parameters and Their Estimated Standard Deviations.

Atom	*x*	*y*	*z*	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
N1	1157(1)	614.8(6)	1052.0(3)	45(4)	56(4)	53(3)	-7(3)	-2(3)	2(3)
C2	1129(1)	638.6(8)	991.3(3)	40(4)	66(4)	51(4)	7(4)	-4(4)	-3(4)
C3	932(1)	562.7(8)	966.5(3)	39(4)	61(4)	47(4)	-5(4)	7(4)	4(4)
N4	835(1)	486.7(6)	1013.4(2)	41(3)	60(3)	50(3)	6(4)	4(3)	0(3)
C5	650(2)	388.3(7)	1015.0(4)	50(5)	57(4)	64(5)	-10(4)	3(4)	1(4)
C6	614(2)	327.4(9)	1068.3(3)	69(6)	71(5)	53(4)	-8(6)	-3(5)	-1(4)
N7	749(1)	356.3(6)	1120.2(3)	58(4)	62(4)	60(4)	-8(4)	1(4)	7(4)
C8	926(2)	452.1(8)	1118.7(3)	54(5)	68(4)	45(4)	9(4)	9(4)	5(4)
N8	1058(1)	485.9(7)	1168.4(3)	58(4)	76(4)	53(3)	-2(4)	-7(3)	3(4)
C9	980(2)	521.9(8)	1063.5(3)	44(4)	66(5)	48(4)	0(5)	0(4)	0(4)
C1'	809(1)	564.1(8)	906.1(3)	40(4)	50(4)	64(4)	-5(4)	7(4)	6(4)
O1'	792(1)	433.1(5)	883.5(2)	62(3)	51(2)	51(2)	-1(3)	-4(3)	1(2)
C2'	971(2)	634.2(7)	858.1(3)	39(4)	63(4)	45(4)	-3(4)	4(4)	6(4)
O2'	968(1)	771.4(5)	860.7(2)	75(4)	48(3)	65(3)	-7(3)	13(3)	2(3)
C3'	846(1)	578.7(8)	799.9(3)	33(4)	65(4)	53(4)	5(4)	-10(3)	1(4)
O3'	616(1)	653.2(5)	782.0(2)	42(3)	62(3)	68(3)	5(3)	-7(3)	9(3)
C4'	737(2)	444.8(7)	819.3(3)	40(4)	51(4)	51(4)	-1(4)	-5(4)	-3(4)
C5'	862(2)	329.9(8)	788.6(3)	52(5)	50(4)	62(4)	9(4)	-12(4)	-2(4)
O5'	1144(1)	329.7(5)	792.7(2)	41(3)	67(3)	61(3)	2(3)	0(3)	-4(3)

All atomic parameters have been multiplied by 10^3.
The form of the anisotropic thermal parameter is $\exp[-2\pi^2(h^2a^{*2}U_{11}+k^2b^{*2}U_{22}+l^2c^{*2}U_{33}+2hka^*b^*U_{12}+2hla^*c^*U_{13}+2klb^*c^*U_{23})]$
Estimated standard deviations in the least significant digits are shown in parentheses.

zine ring. This condensation failed under a variety of conditions, mainly due to the instability of the protected sugar α-bromoaldehyde under the reaction conditions. The reaction of simple alkyl α-bromoaldehydes with 2-amino-3-chloropyrazine to generate 3-alkyl-8-chloroimidazo-[1,2-*a*]pyrazines has been previously demonstrated by ourselves and others [18-22].

Table II. Positional and Thermal Parameters for Hydrogen Atoms.

Atom	*x*	*y*	*z*	*U*, Å^2
HC2	123	70	97	6
HC5	55	36	98	7
HC6	49	26	107	8
H1N8	114(2)	54.5(9)	117.1(3)	6
H2N8	98(2)	45.5(9)	120.9(3)	6
HC1'	61(2)	58.6(8)	90.5(3)	5
HC2'	115	62	86	6
HO2'	82(2)	81.6(8)	89.5(4)	6
HC3'	97	58	77	6
HO3'	68(2)	73.1(8)	77.4(3)	6
HC4'	55	44	81	5
H1C5'	81	33	75	7
H2C5'	80	25	81	7

All atomic parameters have been multiplied by 10^2.

In the second approach [18,19], shown in Scheme 2, the saccharidic α-bromoester **4** was reduced with lithium borohydride and converted to the epoxide **6** in the presence of strong base. Opening of the epoxide with ammonia analogous to the method of Baker [23] gave a key intermediate, (2ξ)-1-amino-3,6-anhydro-1-deoxy-4,5-*O*-isopropylidene-7-*O*-trityl-D-*allo*-heptitol (**7**). Displacement of chloride from 2,3-dichloropyrazine by the amino group of **7** produced the vicinal (3-chloropyrazin-2-ylamino) alcohol **8**. This alcohol was then oxidized to the ketone **9** using either trimethylamine sulfur trioxide complex/dimethyl sulfoxide or trifluoroacetic anhydride/dimethyl sulfoxide. The imidazo[1,2-*a*]pyrazine ring closure was then accomplished using trifluoroacetic anhydride/trifluoroacetic acid in toluene/pyridine to furnish the desired 8-chloro-4,5-isopropylidene-7-*O*-trityl-3-(β-D-ribofuranosyl)imidazo[1,2-*a*]pyrazine **10**. It should be noted that if pyridine was left out of the reaction, the acid labile protecting groups were removed and a complex mixture of products was obtained. The 8-chloro group was then readily displaced with ammonia in isopropanol at 100° and the blocking groups were removed with 90% aqueous trifluoroacetic acid to give the desired **2b**.

A sample of **2b** was crystallized from ethanol with a trace of water and a single crystal X-ray diffraction experiment undertaken. A diagram of the solved structure is shown in Figure 1 and verifies the proposed structure of **2b** (see Tables I-IV). Of particular note is the glycosyl torsion angle C2-C3-C1'-O1' of 134.1° which places it in the *syn* conformation, closer to the 109.8° angle seen for the *C*-nucleoside antibiotic formycin monohydrate [24] than to the *anti* conformation (9.9°) found in adenosine [25]. Furthermore, the ribose ring of **2b** exists in a C1' *exo* conformation (C1' is 0.63 Å out of the plane of the other four atoms) with a phase angle [26] of 126.7° which is closer to the C2' *endo* conformation (phase angle of 148.0°) of formycin than the C3' *endo* conformation (phase angle of 7.1°) of adenosine. It is interesting to note that the exocyclic bond C4'-C5' exhibits a *gauche*$^+$ conformation (C3'-C4'-C5'-O5' = 52.9°) compared to the *trans* conformations seen for both formycin (175.8°) and adenosine (176.9°). As expected, all the atoms of the imidazo[1,2-*a*]pyrazine ring system were coplanar within 0.02 Å. No crystallographic evidence exists for the presence of the imino form in the crystalline state.

Table III. Selected Interatomic Distances[a]

Atom1	Atom2	Distance	Atom1	Atom2	Distance
N1	C2	1.38 (1)	C8	C9	1.45 (1)
N1	C9	1.33 (1)	C1'	O1'	1.44 (1)
C2	C3	1.38 (1)	C1'	C2'	1.52 (1)
C3	N4	1.39 (1)	O1'	C4'	1.46 (1)
C3	C1'	1.48 (1)	C2'	O2'	1.41 (1)
N4	C5	1.37 (1)	C2'	C3'	1.55 (1)
N4	C9	1.38 (1)	C3'	O3'	1.44 (1)
C5	C6	1.35 (1)	C3'	C4'	1.54 (1)
C6	N7	1.37 (1)	C4'	C5'	1.50 (1)
N7	C8	1.33 (1)	C5'	O5'	1.42 (1)
C8	N8	1.34 (1)			

[a]In angstroms. Numbers in parentheses are estimated standard deviations in the least significant digits.

The synthetic route used to prepare the 2',3'-dideoxy-, the 2',3'-dideoxy-2',3-didehydro-, and the 3'-deoxy-nucleosides, **2a**, **3**, and **2c**, respectivley, is shown in Scheme 3

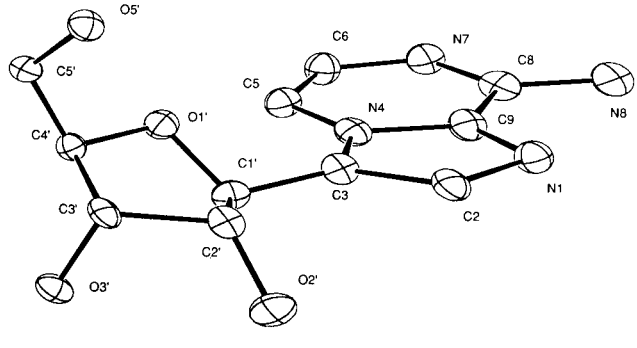


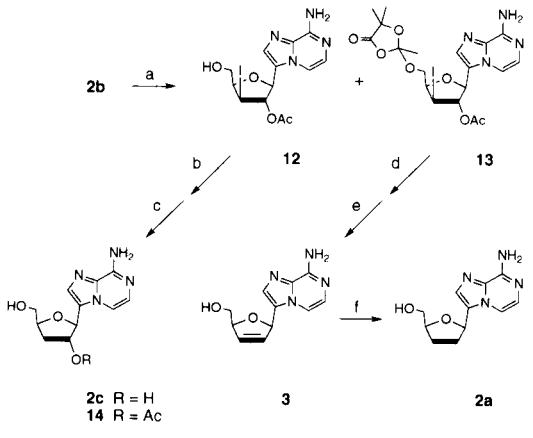
Figure 1

Table IV. Selected Interatomic Angles[a]

Atom1	Atom2	Atom3	Angle	Atom1	Atom2	Atom3	Angle	Atom1	Atom2	Atom3	Angle
C2	N1	C9	104.2 (7)	N7	C8	N8	120.5 (8)	C1'	C2'	C3'	101.3 (7)
N1	C2	C3	111.6 (8)	N7	C8	C9	121.0 (8)	O2'	C2'	C3'	113.5 (7)
C2	C3	N4	105.6 (7)	N8	C8	C9	118.6 (9)	C2'	C3'	O3'	111.1 (7)
C2	C3	C1'	131.3 (8)	N1	C9	N4	112.7 (7)	C2'	C3'	C4'	103.8 (6)
N4	C3	C1'	122.7 (8)	N1	C9	C8	130.2 (8)	O3'	C3'	C4'	105.4 (7)
C3	N4	C5	132.0 (8)	N4	C9	C8	117.1 (8)	O1'	C4'	C3'	106.2 (7)
C3	N4	C9	105.9 (7)	C3	C1'	O1'	109.5 (7)	O1'	C4'	C5'	107.5 (7)
C5	N4	C9	122.0 (7)	C3	C1'	C2'	114.8 (8)	C3'	C4'	C5'	115.2 (7)
N4	C5	C6	116.9 (9)	O1'	C1'	C2'	103.2 (7)	C4'	C5'	O5'	113.0 (8)
C5	C6	N7	124.9 (9)	C1'	O1'	C4'	106.1 (7)				
C6	N7	C8	118.1 (8)	C1'	C2'	O2'	116.0 (7)				

[a]In degrees. Numbers in parentheses are estimated standard deviations in the least significant digits.

Scheme 3



a. $CH_3CO_2C(CH_3)_2COCl$, NaI, CH_3CN *b.* H_2, 10% Pd/C, NaOAc, EtOH *c.* NH_3/MeOH *d.* Zn, AcOH, EtOH *e.* NH_3, MeOH, 100 °C, 18 h *f.* H_2, 10% Pd/C, EtOH.

Thus, **2b** was treated with the Mattocks reagent [27] α-acetoxyisobutyryl chloride and sodium iodide, essentially as described earlier for the nucleosides adenosine, tubercidin and formycin. In this instance, however, the only identifiable products, obtained after opening of the initially formed 2',3'-acetoxonium ion, were the *trans* (D-*xylo*) iodoacetates **12** and **13**. The 5'-deblocked derivative **12** was generated from **13** by removal of the 5'-trimethyldioxolanone moiety during silica gel purification of the products. This led to varying ratios of **12** and **13** being obtained from different preparations, depending on the type of silica gel used and the column contact time in the chromatographic purification. However, it is important to note that the only detectable group at the 5'-position in the reaction products was the trimethyldioxolanone moiety; no evidence (nmr) was seen for the α-acetoxyisobutyryl group at this position. Also, only the xylofuranosyl isomers appeared to be formed as none of the isomeric arabinofuranosyl 2'-iodo-3'-acetate derivatives were detected. It is interesting to compare this product distribution with that seen by others in the reactions of adenosine, the *C*-nucleoside formycin, and 7-deazaadenosine (tubercidin) with α-acetoxyisobutyryl halides under similar conditions. Adenosine, when treated with α-acetoxyisobutyryl bromide at room temperature gives only the trimethyldioxolanone at the 5'-position, and an ~9:1 mixture of 3'-bromo-2'-acetate-*xylo* to 2'-bromo-3'-acetate-*arabino* isomers [28-30]; with formycin, only the α-acetoxyisobutyryl group is observed at the 5'-position and the 3'-bromo-2'-acetate-*xylo*:2'-bromo-3'-acetate-*arabino* ratio is ~3:1 [31]; with tubercidin only the trimethyldioxolanone at the 5'-position is seen and only the 3'-bromo-2'-acetate-*xylo* isomer [31]. Thus, the *C*-nucleoside imidazo[1,2-*a*]pyrazine of this study closely parallels tubercidin in reactivity and regioselectivity of products and appears to differ distinctly from formycin, with which it has greater conformational similarity by X-ray studies. It appears that the presence of the trimethyldioxolanone at C5' may shift the regioselectivity of the 2',3'-acetoxonium ion opening by halide ion toward the 3'-position (adenosine, tubercidin and this study) whereas the presence of the α-acetoxyisobutyryl group at C5' allows for more opening of the acetoxonium ion at C2'. However, the electronic and steric effects of the aglycone cannot be ruled out as having some effect on the opening. It is not clear this time what determines the nature of the substituent formed at C5' in this reaction (*i.e.* whether a trimethyldioxolanone group or a α-acetoxyisobutyryl group is obtained).

Reductive elimination of the vicinal haloacetate intermediate **13** with zinc powder [32] was readily achieved and deblocking with methanolic ammonia gave the 2',3'-unsaturated derivative **3**. Hydrogenation of **3** with 10% palladium on carbon gave the 2',3'-dideoxy analog **2a**.

The preparation of the 8-amino-3-(β-D-3'-deoxyribofuranosyl)imidazo[1,2-*a*]pyrazine nucleoside **2c** was car-

ried out in a straightforward manner shown in Scheme 3. Thus, catalytic hydrogenation of the intermediate **12**, followed by deblocking with methanolic ammonia gave **2c**.

Biological Evaluation.

Compound **2a, 2b** and **3** were tested in an HIV inhibition assay in cell culture. Uninfected H9 T-lymphoid cells were treated with half log dilutions of drug (highest concentration 12 μM). After 24 hours the cultures were infected with 1.0 infectious unit/100 cells of HIV (strain IIIB) and sampled on alternate days beginning with day 3 (50% of the culture volume was replaced with each sampling). Cells were assayed for productive virus infection by fixed-cell immunofluorescence using anti-HIV-1 human serum. Of the product nucleosides, only **2a** exhibited slight inhibition at the highest levels in experiments where DDA showed strong inhibition of virus growth at concentration levels as low as 1.5 μM.

3-Deazaadenosine has been reported to suppress T cell and natural killer (NK) cell activity (5). Suppression of NK cell activity by d^{3}Ado and **2b** were examined in parallel *in vitro* (33). NK activity in mice as stimulated with polyinosinc and polycytidylic acids (100 μg/mouse) a day before the assay. Spleen cells were then tested for their lytic activity to YAC cells (mouse lymphoma targets) over a four hour time period in the presence of the test substances. Lytic activity of NK cells was assessed by the release of ^{51}Cr, used to label the YAC target cells. Both compounds weakly inhibited NK activity in a dose-dependent manner (d^{3}Ado IC_{50} 100 μM and **2b** >200 μM) compared to a vehicle control (dimethyl sulfoxide). The compounds were not toxic to YAC cells at these concentrations; **2b** also inhibited lytic activity of purified mouse NK cells suggesting that the inhibition was directly on NK cells and not through other mediators. In summary, both compounds are weak inhibitors of NK activity.

The 3-deazaadenosine analog **2b** was examined for anti-inflammatory activity as a potential inhibitor of inflammatory cell migration in the rat pleural cavity following carrageenan injection (the standard rat pleurisy carrageenan model). Similar studies measuring PMN's per pleural cavity have been reported with a variety of other deazapurine nucleosides [5]. In a parallel experiment with 3-deazaadenosine, **2b** (at 5 mg/kg i.v.) showed inhibition of the inflammatory effect equal to or better than 3-deazaadenosine (at 6 mg/kg i.v.). The 3-deazaadenosine isostere **2b** was shown in other studies (data not presented) not to be a substrate for mammalian adenosine deaminase and neither a substrate nor an inhibitor of *S*-adenosylhomocysteine hydrolase at meaningful concentrations.

Isosteric replacement of 3-deazaadenine in d^{3}Ado with 8-aminoimidazo[1,2-*a*]pyrazine abolished or diminished antiviral and immunosuppressive activity while retaining or enhancing the antiinflammatory activity of the parent.

EXPERIMENTAL

Proton nmr spectra were recorded on Varian XL-200 or SC-300 spectrometers in the solvents specified in the text. Chemical shifts are reported in ppm (δ) and signals are described as s (singlet), d (doublet), t (triplet), m (multiplet), dd (doublet of doublets), dt (doublet of triplets) and brs (broad singlet). Mass spectra were obtained with a Varian MAT 731 instrument. Ultraviolet spectra were obtained with a Perkin-Elmer UV spectrophotometer. Column chromatography was performed on E. Merck silica gel 60 (70-230 mesh) or grade 62 (60-200 mesh). X-ray data were collected with a Rigaku AFC5R diffractometer controlled by software supplied by Rigaku and Molecular Structure Corporation.

(2ξ)-3,6-Anhydro-2-bromo-2-deoxy-4,5-*O*-isopropylidene-7-*O*-trityl-D-*allo*-heptitol (**5**).

Methyl 3,6-anhydro-2-deoxy-2-bromo-4,5-*O*-isopropylidene-7-*O*-trityl-D-*allo*-heptonate **4** [18], (5.11 g, 9.03 mmoles) was added to 260 mg (11.9 mmoles) of lithium borohydride in 20 ml of tetrahydrofuran while stirring in an ice bath. After 30 minutes the reaction was warmed to room temperature and quenched with water. The tetrahydrofuran was evaporated and the aqueous phase was extracted twice with ether. The ethereal layer was dried (magnesium sulfate), filtered and concentrated to give 4.24 g (87%) of **5** as an opaque oil. A small portion of **5** was purified on silica gel prep plates (2 x 1000 μ, 4:1 hexane:ethyl acetate) to give 59 mg of **5** as a white solid; ^{1}H nmr (deuteriochloroform): δ 1.36, 1.53 (2s, 6H, $C(CH_3)_2$), 2.32 (m, 1H, OH), 3.26 (m, 2H, H_5, $H_{5'}$), 3.89-4.04 (m, 2H, H_1, H_4), 4.18 (m, 2H, CH_2), 4.21-4.29 (m, 1H, CH), 4.60-4.84 (m, 2H, H_2, H_3), 7.18-7.54 (m, 15H, trityl); ms: (FAB, Li) m/z 545, 547 ($M^+ + 7$).

Anal. Calcd. for $C_{29}H_{31}BrO_5$: C, 64.56; H, 5.79. Found: C, 64.21; H, 5.80.

(2ξ)-1,2-Anhydro-3,6-anhydro-4,5-*O*-isopropylidene-7-*O*-trityl-D-*allo*-heptitol (**6**).

To a solution of 4.11 g (7.63 mmoles) of **5** in 70 ml of dry dimethylformamide was added 336 mg (8.4 mmoles) of sodium hydride (60% in oil) and the mixture was stirred at room temperature overnight. Addition of 5 ml of water destroyed excess sodium hydride. The reaction was evaporated to a residual oil which was partitioned between ether and 10% sodium carbonate. The etheral solution was washed with 3 x 100 ml of water, dried (magnesium sulfate) and concentrated to give 3.36 g (96%) of **6** as a light yellow oil; ^{1}H nmr (deuteriochloroform): δ 1.33, 1.53 (2s, 6H, $C(CH_3)_2$), 2.68-2.88 (m, 2H, CH_2), 3.09-3.34 (m, 3H, CH, H_5, $H_{5'}$), 3.97 (dt, 1H, H_4), 4.18 (m, 1H, H_3), 4.52 (m, 1H, H_2), 4.66 (dd, 1H, H_1), 7.18-7.52 (m, 15H, Tr); ms: (FAB, Li) m/z 465 ($M^+ + 7$).

(2ξ)-1-Amino-3,6-anhydro-1-deoxy-4,5-*O*-isopropylidene-7-*O*-trityl-D-*allo*-heptitol (**7**).

A solution of 2.6 g (5.67 mmoles) of **6** in 30 ml of methanol was treated with 80 ml of methanol saturated with ammonia and heated in a bomb at 100° for 2 hours. Concentration gave a light amber liquid which was taken up in dichloromethane and filtered with charcoal over Celite. Evaporation provide 2.21 g (82%) of **7** as an oil; ^{1}H nmr (deuteriochloroform): δ 1.34, 1.52 (2s, 6H,

$C(CH_3)_2$, 1.36-1.76 (brs, 3H, OH, NH_2), 2.87 (d, 2H, CH_2), 3.18-3.41 (m, 2H, H_5, $H_{5'}$), 3.56-3.70 (m, 1H, CH), 3.86 (dt, 1H, H_4), 4.14 (m, 1H, H_1), 4.54-4.82 (m, 2H, H_2, H_3), 7.16-7.56 (m, 15H, Tr); ms: (FAB, Li) m/z 482 ($M^+ + 7$).

(2*S*)-3,6-Anhydro-1-deoxy-1-(3-chloropyrazin-2-ylamino)-4,5-*O*-isopropylidene-7-*O*-trityl-D-*allo*-heptitol (**8**).

A solution of 760 mg (5.03 mmoles) of 2,3-dichloropyrazine, 0.89 ml (646 mg, 6.38 mmoles) of triethylamine and 2.22 g of crude **7** in 10 ml of dioxane was heated at reflux overnight. The reaction was evaporated and then partitioned between dichloromethane and water. The organic layer was dried (magnesium sulfate) and concentrated to an amber oil. Purification on a silica gel columln (gradient elution 20 to 40% ethyl acetate in hexanes) gave 1.0 g (40%) of **8** as a white solid; ^{1}H nmr (deuteriochloroform): δ 1.34, 1.52 (2s, 6H, $C(CH_3)_2$), 3.04 (d, 1H, OH), 3.18-3.62 (m, 3H, H_5, $H_{5'}$, CH), 3.71-4.19 (m, 4H, CH_2, H_4, H_1), 4.79-4.82 (m, 2H, H_2, H_3), 6.62 (t, 1H, NH), 7.18-7.49 (m, 15H, Tr), 7.58 (dd, 1H), 7.84 (dd, 1H); ms: (FAB, Li) m/z 594, 596 ($M^+ + 7$).

Anal. Calcd. for $C_{33}H_{34}ClN_3O_5$: C, 67.39; H, 5.83; N, 7.15. Found: C, 67.10; H, 5.97; N, 6.74.

3,6-Anhydro-1-deoxy-1-(3-chloropyrazin-2-ylamino)-4,5-*O*-isopropylidene-7-*O*-trityl-D-*allo*-hept-2-ulositol (**9**).

Method 1.

A solution of 117 mg (0.2 mmole) of **8**, 0.5 ml of triethylamine and 0.5 ml of dimethyl sulfoxide was treated with 83.7 mg (0.60 mmole) of trimethylamine-sulfur trioxide complex, stirred overnight at room temperature, and then heated at 40° for 2.5 hours. The reaction was partitioned between chloroform and water. The organic layer was washed again with water, then dried (magnesium sulfate) and concentrated to 123.2 mg of an amber oil. Purification on a 20 ml silica gel column (1:4 ethyl acetate:hexanes) gave 52 mg (44%) of **9** as a viscous oil.

Method 2.

Trifluoroacetic anhydride (0.32 ml, 476 mg, 2.26 mmoles) in 1.5 ml of dichloromethane was added dropwise to 0.21 ml (250 mg, 3.0 mmoles) of dry dimethyl sulfoxide and 1.5 ml of dichloromethane while stirring at −78°. After 10 minutes, 889 mg (1.51 mmoles) of **8** in 2.5 ml of dichloromethane was added dropwise, and stirring was continued for 10 minutes. The reaction was then warmed to room temperature and stirred for 50 minutes. Triethylamine (0.6 ml) was added dropwise, and stirring was continued for 30 minutes. The reaction was diluted with ether, washed several times with water, dried (magnesium sulfate) and concentrated to 849 mg of a yellow solid. Purification on a 100 ml silica gel column (gradient elution 10 to 20% ethyl acetate in hexanes) gave 490.4 mg (55%) of **9** as a white solid; ^{1}H nmr (deuteriochloroform): δ 1.36, 1.54 (2s, 6H, $C(CH_3)_2$), 3.21-3.39 (m, 2H, H_5, $H_{5'}$), 4.36 (m, 1H, H_4), 4.48 (d, 1H, H_1), 4.56 (m, 2H, CH_2), 4.62 (dd, 1H, H_3 or H_2), 5.01 (dd, 1H, H_2 or H_3), 5.76 (m, 1H, NH), 7.15-7.46 (m, 15H, Tr), 7.57 (d, 1H), 7.80 (d, 1H); ms: (FAB, Li) m/z 592, 594 ($M^+ + 7$).

Anal. Calcd. for $C_{33}H_{32}ClN_3O_5$: C, 67.63; H, 5.50; N, 7.17. Found: C, 67.87; H, 5.74; N, 7.06.

8-Chloro-3-(5-*O*-trityl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)-imidazo[1,2-*a*]pyrazine (**10**).

To 392 mg (0.67 mmole) of **9** in 5 ml of toluene was added 0.65 ml (634 mg, 8.0 mmoles) of pyridine. The resulting solution was cooled in an ice bath and 0.15 ml (4.67 mmoles) of trifluoroacetic acid was added. After 30 minutes 0.66 ml (4.67 mmoles) of trifluoroacetic anhydride was added and stirring was continued at 0° for 30 minutes, and then at room temperature overnight. The reaction was diluted with toluene, washed with 10% sodium carbonate, dried (magnesium sulfate), and concentrated to 412 mg of a residual oil. Purification on a silica gel column (gradient elution 20 to 30% ethyl acetate in hexanes) gave 242.6 mg (64%) of **10** as a white solid; ^{1}H nmr (deuteriochloroform): δ 1.34, 1.55 (2s, 6H, $C(CH_3)_2$), 3.15-3.30 (m, 2H, $H_{5'}$, $H_{5''}$), 4.31 (dt, 1H, $J_{3'4'}$ = 3.5 Hz, $J_{4'5'}$ = 7.2 Hz, $H_{4'}$) 4.82 (dd, 1H, $J_{3'4'}$ = 3.5 Hz, $J_{2'3'}$ = 6.7 Hz, $H_{3'}$), 4.90 (dd, 1H, $J_{2'3'}$ = 6.7 Hz, $J_{1'2'}$ = 5.2 Hz, $H_{2'}$), 5.14 (d, 1H, $J_{1'2'}$ = 5.2 Hz, $H_{1'}$), 7.13-7.30 (m, 16H, Tr, H_5 or H_6), 7.68 (s, 1H, H_2), 8.33 (d, H_5 or H_6); ms: (FAB) m/z 568, 570 ($M^+ + 1$).

Anal. Calcd. for $C_{33}H_{30}ClN_3O_4$: C, 69.77; H, 5.32; N, 7.46. Found: C, 69.52; H, 5.62; N, 7.26.

8-Amino-3-(5-*O*-trityl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)-imidazo[1,2-*a*]pyrazine (**11**).

To a solution of 5.05 g (8.9 mmoles) of **10** in 200 ml of 2-propanol was added 200 ml of ammonia. The reaction was heated at 100° for 16 hours, purged with nitrogen and evaporated. The residue was dissolved in dichloromethane, washed with 10% sodium carbonate, dried (magnesium sulfate) and concentrated to provide 4.22 g (85%) of **11** as a white solid; ^{1}H nmr (deuteriochloroform): δ 1.38, 1.62 (2s, 6H, $C(CH_3)_2$), 3.30 (m, 2H, $H_{5'}$, $H_{5''}$), 4.33 (dt, 1H, $J_{3'4'}$ = 3.5 Hz, $H_{4'}$), 4.84 (dd, 1H, $J_{3'4'}$ = 3.5 Hz, $J_{2'3'}$ = 6.7 Hz, $H_{3'}$), 4.96 (dd, 1H, $J_{2'3'}$ = 6.7 Hz, $J_{1'2'}$ = 5.2 Hz, $H_{2'}$), 5.17 (d, 1H, $J_{1'2'}$ = 5.2 Hz, $H_{1'}$), 5.43 (s, 2H, NH_2), 7.03 (d, 1H, J = 4.7 Hz, H_5 or H_6), 7.20-7.40 (m, 15H, Tr), 7.50 (s, 1H, H_2), 7.79 (d, 1H, J = 4.7 Hz, H_5 or H_6); ms: (FAB, Li) m/z 555 ($M^+ + 7$).

Anal. Calcd. for $C_{33}H_{32}N_4O_4 \cdot 0.5H_2O$: C, 71.08; H, 5.96; N, 10.05. Found: C, 70.98; H, 5.98; N, 9.83.

8-Amino-3-(β-D-ribofuranosyl)imidazo[1,2-*a*]pyrazine (**2b**).

A solution of 406 mg (0.74 mmole) of **11** in 12 ml of 90% aqueous trifluoroacetic acid was stirred at room temperature for 2.5 hours. Absolute ethanol (20 ml) was added to form trityl ethanol. Concentration gave a yellow semi-solid which was partitioned between ether and water. The aqueous phase was evaporated to a smaller volume and passed through a 50 ml anion exchange (AG 1 x X2 200-400 mesh) acetate column to give 111.2 mg (56%) of **2b** as a white solid. Recrystallization from ethanol containing a trace of water gave analytically pure material; uv (methanol): λ max 235.5 (29000), λ min 285 (6500); ^{1}H nmr (deuterium oxide): δ 3.79 (m, 2H, $H_{5'}$, $H_{5''}$), 4.15 (dt, 1H, $J_{3'4'}$ = 4.2 Hz, $H_{4'}$), 4.29 (dd, 1H, $J_{3'4'}$ = 4.2 Hz, $J_{2'3'}$ = 5.5 Hz, $H_{3'}$), 4.57 (dd, 1H, $J_{2'3'}$ = 5.5 Hz, $J_{1'2'}$ = 7.2 Hz, $H_{2'}$), 5.19 (d, 1H, $J_{1'2'}$ = 7.2 Hz, $H_{1'}$), 7.26 (d, 1H, J = 4.5 Hz, H_5 or H_6), 7.66 (s, 1H, H_2), 7.79 (d, 1H, J = 4.5 Hz, H_5 or H_6); ms: m/e (FAB) 267 ($M^+ + 1$).

Anal. Calcd. for $C_{11}H_{14}N_4O_4$: C, 49.62; H, 5.30; N, 21.04. Found: C, 49.63; H, 5.35; N, 20.91.

8-Amino-3-(2-*O*-acetyl-3-deoxy-3-iodo-β-D-*xylo*-pentofuranosyl)-imidazo[1,2-*a*]pyrazine (**12**) and 8-Amino-3-(2-*O*-acetyl-3-deoxy-3-iodo-5-(trimethyldioxolan-4-on-2-yl)-β-D-*xylo*-pentofuranosyl)-imidazo[1,2-*a*]pyrazine (**13**).

α-Acetoxyisobutyryl chloride (1.3 ml, 1.48 g, 9.0 mmoles) was added to a solution of 2.03 g (13.5 mmoles) of sodium iodide

(dried at 85° overnight) in 15 ml of acetonitrile. After 20 minutes 600 mg (2.25 mmoles) of **2b** was added and stirring was continued an additional 1.5 hours. The reaction was concentrated *in vacuo* and then partitioned between ethyl acetate and aqueous sodium bicarbonate containing sodium thiosulfate. The organic phase was dried (magnesium sulfate) and concentrated to provide 841 mg of a yellow brown solid. Purification on a silica gel column (E. Merck silica gel 60-70, 230 mesh, gradient elution 0 to 5% methanol in dichloromethane) gave 136 mg (11%) of **13** as a white solid and 482.6 mg (51%) of **12** as a whilte solid. Repeating the above procedure using different silica gel (E. Merck grade 62, 60-200 mesh) gave a 75% yield of **13**; for **12**, ^{1}H nmr (deuteriochloroform): δ 1.75 (s, 1H, OH), 2.14 (s, 3H, OAc), 3.79 (m, 2H, $H_{5'}$, $H_{5''}$), 3.92 (dt, 1H, $H_{4'}$), 4.45 (dd, 1H, $J_{2'3'}$ = 2.5 Hz, $H_{3'}$), 5.11 (d, 1H, $J_{1'2'}$ = 4 Hz, $H_{1'}$), 5.59 (s, 2H, NH_2), 5.94 (dd, 1H, $J_{1'2'}$ = 4 Hz, $J_{2'3'}$ = 2.5 Hz, $H_{2'}$), 7.32 (d, 1H, J = 4.7 Hz, H_5 or H_6), 7.62 (d, 1H, J = 4.7 Hz, H_5 or H_6), 7.68 (s, 1H, H_2); ms: (FAB) m/z 418 (M^+ + 1); for **13**, ^{1}H nmr (deuteriochloroform): δ 1.50, 1.57 (2s, 6H, $C(CH_3)_2$), 1.75 (s, 3H, OAc), 2.14 (s, 3H, CH_3), 3.58-3.94 (m, 3H, $H_{5'}$, $H_{5''}$, $H_{4'}$), 4.43 (dd, 1H, $H_{3'}$), 5.12 (d, 1H, $H_{1'}$), 5.53 (s, 2H, NH_2), 5.90 (m, 1H, $H_{2'}$), 7.36 (d, 1H, H_5 or H_6), 7.64 (m, 1H, H_5 or H_6), 7.69 (s, 1H, H_2); ms: (FAB) m/z 547 (M^+ + 1).

Anal. Calcd. for $C_{19}H_{23}N_4O_7I \cdot H_2O$: C, 40.44; H, 4.47; N, 9.93. Found: C, 40.78; H, 4.27; N, 9.93.

8-Amino-3-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)imidazo-[1,2-*a*]pyrazine (**3**).

Zinc dust (335 mg, 5.1 mmoles) and 59 ml (1.0 mmole) of glacial acetic acid were added with stirring to a solution of 280 mg (0.51 mmole) of **13** in 15 ml of absolute ethanol. After 20 minutes, the suspension was filtered through Celite, evaporated to a smaller volume, diluted with ethyl acetate and washed with 10% sodium carbonate. The organic layer was dried (magnesium sulfate) and concentrated 179.5 mg of an oil. The oil was dissolved in 10 ml of methanol saturated with ammonia and stirred 4 hours in a pressure tube at room temperature. Evaporation under nitrogen gave 148.3 mg of white solid. Purification on an 80 ml silica gel column (gradient elution 0 to 20% methanol in dichloromethane) provided 49.5 mg (41%) of **3** as a white solid; uv (methanol): λ max 235 (30410), λ min 285 (6850); ^{1}H nmr (dimethyl sulfoxide): δ 3.32 (m, 1H, OH), 3.43 (m, 2H, $H_{5'}$, $H_{5''}$), 4.79 (m, 1H, $H_{4'}$), 6.12 (m, 1H, $H_{1'}$), 6.22 (m, 2H, $H_{2'}$, $H_{3'}$), 6.87 (s, 2H, NH_2), 7.22 (d, 1H, J = 4.5 Hz, H_5 or H_6), 7.39 (s, 1H, H_2), 7.81 (d, 1H, J = 4.5 Hz, H_5 or H_6); ms: (EI) m/z 232.

Anal. Calcd. for $C_{11}H_{12}N_4O_2 \cdot 0.3H_2O$: C, 55.59; H, 5.34; N, 23.58. Found: C, 55.54; H, 5.20; N, 23.25.

8-Amino-3-(2,3-dideoxy-β-D-*glycero*-pentofuranosyl)imidazo[1,2-*a*]pyrazine (**2a**).

A solution of 28 mg (0.12 mmole) of **3** in 10 ml of ethanol containing 30 mg of 10% palladium on carbon was hydrogenated overnight. The suspension was filtered over Celite and concentrated to 23.8 mg. Purification on a silica gel column (gradient elution 0 to 8% methanol in dichloromethane) gave 15.1 mg (54%) of **2a** as a white solid; uv (methanol): λ max 235 (29010), λ min 295 (7410); ^{1}H nmr (dimethyl sulfoxide): δ 1.81-2.29 (m, 4H, $CH_{2's}$), 3.40 (m, 2H, $H_{5'}$, $H_{5''}$), 4.02 (m, 1H, $H_{4'}$), 4.73 (t, 1H, OH), 5.14 (t, 1H, $H_{1'}$), 6.82 (s, 2H, NH_2), 7.20 (d, 1H, J = 4.5 Hz, H_5 or H_6), 7.48 (s, 1H, H_2), 7.70 (d, 1H, J = 4.5 Hz, H_5 or H_6); ms: (EI) m/z 234.

Anal. Calcd. for $C_{11}H_{14}N_4O_2 \cdot 0.55H_2O$: C, 54.11; H, 6.23; N, 22.95. Found: C, 54.02; H, 5.80; N, 22.57.

8-Amino-3-(2-*O*-acetyl-3-deoxy-β-D-*glycero*-pentofuranosyl)imidazo[1,2-*a*]pyrazine (**14**).

To 83.6 mg (0.20 mmole) of **12** in 5 ml of absolute ethanol containing 25 mg of palladium on carbon was added 20 mg (0.24 mmole) of sodium acetate in 1.0 ml of water and the reaction was hydrogenated overnight. The catalyst was filtered off over Celite and the filtrate was concentrated to give 109 mg of **14** as a yellow oil; ^{1}H nmr (deuteriochloroform): δ 2.14 (s, 3H, OAc), 2.27-2.45 (m, 2H, $H_{3'}$, $H_{3''}$), 3.66 (m, 1H, $H_{5'}$ or $H_{5''}$), 3.92 (m, 1H, $H_{5'}$ or $H_{5''}$), 4.48 (m, 1H, OH), 5.25 (d, 1H, $H_{1'}$), 5.57 (brs, 3H, NH_2, $H_{2'}$), 7.31 (d, 1H, J = 4.5 Hz, H_5 or H_6), 7.52 (s, 1H, H_2), 7.72 (d, 1H, J = 4.5 Hz, H_5 or H_6); ms: (FAB) m/z 293 (M^+ + 1).

8-Amino-3-(3-deoxy-β-D-*glycero*-pentofuranosyl)imidazo[1,2-*a*]-pyrazine (**2c**).

Compound **14** (40 mg, 0.137 mmole) was dissolved in 2 ml of methanol saturated with ammonia, stoppered and stirred at room temperature overnight. The solution was evaporated to an oil which was purified on a silica gel column (5% methanol in dichloromethane) to give 22 mg (64%) of **2c** as a light yellow solid; ^{1}H nmr (dimethyl sulfoxide): δ 1.84-2.10 (m, 2H, $H_{3'}$, $H_{3''}$), 3.26-3.52 (m, 2H, $H_{5'}$, $H_{5''}$), 4.22 (m, 1H, $H_{4'}$), 4.43 (m, 1H, $H_{2'}$), 4.81 (t, 1H, OH), 4.86 (d, 1H, OH), 5.41 (d, 1H, $H_{1'}$), 6.87 (s, 2H, NH_2), 7.25 (d, 1H, J = 4.5 Hz, H_5 or H_6), 7.51 (s, 1H, H_2), 7.76 (s, 1H, J = 4.5 Hz, H_5 or H_6); hrms: m/z Found: 250.1030 (M^+ Calcd. 250.1066).

X-ray Diffraction Study.

Crystals of **2b** ($C_{11}H_{14}N_4O_4$) formed from ethanol with a trace of water in space group $P2_12_12_1$ with a = 5.037(1)Å, b = 10.271(4)Å, and c = 22.267(6)Å for Z = 4 and a calculated density of 1.535 g/cm^3 and a calculated absorption coefficient of 9.62 cm^{-1}. An automatic four circle diffractometer equipped with CuKα radiation (λ = 1.5418Å) was used to measure 1059 potential diffraction peaks to 2θ = 120° of which 816 were observed ($I \geq 3\sigma$). The data were corrected Lorentz, polarization and background effects. Application of a multi-solution tangent formula approach to phase solution gave an initial model for the structure [34] which was subsequently refined with anisotropic temperature factors for the nonhydrogen atoms by least squares and Fourier methods. The positions for all hydrogen atoms bonded to carbon atoms were calculated and the positions for hydrogens bonded to heteroatoms were obtained from difference Fourier maps and refined with fixed temperature factors. The function $\Sigma\omega(|F_o| - |F_c|)^2$ with $\omega = 1/(\sigma F_o)^2$ was minimized with full matrix least squares to give an unweighted residual of 0.074.

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