Preparation of Azido Derivatives from Amino Acids and Peptides by Diazo Transfer

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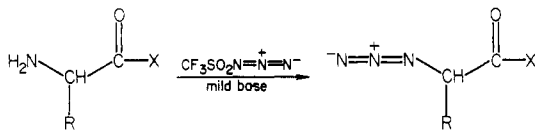
Mild and general methods for converting an amino group to an azido group, and their application to a series of amino acid and peptide derivatives, are described. For example, treatment of an aqueous solution of L-leucine with a solution of $CF_3SO_2N_3$ (I) in CH_2Cl_2, with the pH maintained at 9–9.5 overnight, afforded after workup 67% of optically pure 2-azido-4-methylpentanoic acid as its dicyclohexylamine salt. Azido compounds were similarly obtained from L-Phe, L-Glu, L-Asn, L-Trp, DL-Met, L-Tyr-Gly, and LL-Ala-Phe. Treatment of a CH_2Cl_2 solution of L-alanine ethyl ester and I with a catalytic amount of trioctylmethylammonium chloride afforded the optically pure azido ester in 62% yield; the method was also applied to esters of L-Leu and L-Phe. Results of studies on the optical and chemical stability of these compounds are also reported.

Analogues of amino acids in which the amino group is replaced by an azido group have been known for quite some time as synthetic precursors to amino acids.[1] The ease and mildness of the azido–amino reduction has led to their use as protected amino acids in the preparation of sensitive aminoacyl carbohydrate,[2] lipid,[3] and nucleotide[4] derivatives, but this use has hitherto been limited by the unavailability of azido analogues of many amino acids, especially those bearing reactive functional groups. Known examples were prepared via the appropriate α-bromo acids or esters, which are readily available, generally in partially or totally racemic form, only for the simpler aliphatic cases.

These limitations, as well as the potential of the azido group in peptide chemistry as a precursor of other functional groups and as a photoreactive functionality, prompted us to seek a general method for conversion of an amino group to an azido group, with retention of optical purity, under conditions compatible with the reactive functionality found in amino acids and peptides.

Preparation of azides from simple amines by diazo transfer using a sulfonyl azide had been reported previously in the literature;[5,6] these reactions, although too harsh as such to be applicable to amino acids and peptides, served as the basis for the methods reported here. In order to demonstrate their effectiveness, we applied them to the synthesis of a series of amino acid and peptide-derived azido compounds (eq 1), many of which are described here for the first time. Some details of their chemistry, which were revealed during these studies, are reported as well.



(1)

X = OH, OR', NHR'

Results and Discussion

Cavender and Shiner's work strongly suggested that trifluoromethanesulfonyl azide (triflyl azide) should be more potent than other sulfonyl azides as a diazo-transfer reagent,[5] and it was deemed the reagent of choice.

Aqueous conditions were employed, allowing the diazo transfer to be applied to water-soluble amino acids and peptides, and pH values near the pK_a of the target amino group were expected to suffice. Yields were only slightly improved via the use of a phase-transfer catalyst in the case of some of the amino acids; catalysis would not be expected to be effective if transfer of two components (substrate anion and base catalyst) was required.

In the case of amino acid esters under the same conditions, substantial yield improvement was observed if a phase-transfer agent was used (this has been reported previously for diazo transfer[6]); in this case, only a base need be transferred to the organic phase. The resulting azido esters were, however, found to be substantially racemized; with acetate or even *p*-nitrobenzoate as the base, excellent yields of diazo transfer were obtained, but racemization persisted. It was found by using GC monitoring that the reaction of the amino ester and triflyl azide in CH_2Cl_2 proceeds uncatalyzed to a slight degree but goes readily to completion within 24 h in the presence of a catalytic amount of trioctylmethylammonium chloride, which apparently functions as a base catalyst. The resulting one-phase procedure produced optically pure azido esters in all cases.

Lower yields of azide had been obtained by Cavender and Shiner[5] when the triflyl azide reagent was prepared beforehand, rather than being generated in situ by treating a mixture of amine and azide ion with triflic anhydride. Since we found the latter conditions more conducive to undesired side reactions involving amino acids and peptide functionality (e.g., the amide group of asparagine being dehydrated to a nitrile group) it seemed more prudent to use the preformed reagent consistently in the present work.

Workup was straightforward except in a few cases. Azido acids were conveniently purified by recrystallization of their dicyclohexylamine salts if the acid itself was noncrystalline. Azido esters were purified by distillation. Removal of the byproduct triflamide with mercuric ion[7] (see Experimental Section) was troublesome in the tryptophan and asparagine cases, apparently due to formation of mercury complexes of the side-chain functionalities, and was obviated by using a modified extractive workup in these cases.

The reactivity of the azides prepared in this way fell into several well-defined patterns. Azido acids were found to be exceptionally base stable;[8] the leucine derivative, for

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(2) Bertho, A.; Strecker, E. *Justus Liebigs Ann. Chem.* **1957**, *607*, 194–201 and references therein.

(3) Huber, W. F. *J. Am. Chem. Soc.* **1955**, *77*, 112–6.

(4) Wieland, T.; Jaenicke, F. *Justus Liebigs Ann. Chem.* **1958**, *613*, 95–102.

(5) Cavender, C. J.; Shiner, V. J., Jr. *J. Org. Chem.* **1972**, *37*, 3567–9.

(6) Nakajima, M.; Anselme, J.-P. *Tetrahedron Lett.* **1976**, 4421–2.

(7) Behrend, E.; Haas, A. *J. Fluorine Chem.* **1974**, *4*, 99–106.

0022-3263/81/1946-5173$01.25/0

example, was recovered quantitatively from a solution in 1 N NaOH kept at room temperature for 4 days, during which time it had lost ~7% of its original optical activity. Overnight reflux in 1 N NaOH caused complete racemization, but no destruction of the azido group or formation of ketonic species was detected. The azido acids obtained were therefore assumed to be optically pure; this was confirmed in the leucine case by catalytic hydrogenation of the azido acid back to L-leucine having a rotation essentially equal [$[\alpha]^{25}_D$ +15.5° (*c* 4, 6 N HCl)] to that of the L-leucine from which it was prepared ($[\alpha]^{25}_D$ +15.9°, same conditions).

Similar results (<5% loss of optical activity) were obtained for reduction of compounds **6** and **10** (see Table I) back to their amino precursors, after storage at −10 °C for periods of 4 and 8 months, respectively. The optical purity of the peptide azide derivatives was confirmed for compound **6** by lack of deuterium incorporation when the reaction was run in a D_2O-based system, as evidenced by IR and NMR spectroscopy. The stability of these substances toward alkaline conditions was found to be considerably lower, however, than that of the azido acids; treatment of the azido dipeptide derived from Ala-Phe with 1 M NaOD in D_2O at room temperature resulted in ~30% epimerization in 5 min, as measured by NMR. Similarly, ethyl L-2-azidopropionate was observed to racemize at pH 9.7 (aqueous CH_3OH) with a half-time of about 1 h.

Base-catalyzed decomposition to give imines (and thence carbonyl compounds) via loss of nitrogen, as reported for species such as α-(azidoaryl)acetic esters,[1,17,20] α-azido ketones,[18] and α-azido nitriles,[19] was not observed by us under these conditions. All of these azido compounds, however, are sensitive to highly acidic conditions (pH <2), decomposing rapidly in aqueous solution to afford carbonyl-containing compounds with evolution of nitrogen.[20]

Experimental Section

General Methods. Infrared and NMR spectra were recorded on Perkin-Elmer 727B and Varian T60 spectrometers, respectively. Optical rotation measurements were performed on a Perkin-Elmer 141 polarimeter with a 1-dm cell. All yields reported are isolated yields and in many cases were not optimized. Melting points are uncorrected. Elemental analyses were performed by Galbraith Laboratories.

Trifluoromethanesulfonyl azide (triflyl azide) was freshly prepared as an approximately 1 M solution in CH_2Cl_2, as needed for each reaction from triflic anhydride, by the method of Cavender and Shiner.[5] It was washed once with 1 equiv of 1 N NaOH to remove all traces of acid. The yield was taken to be 50% for the purposes of determining the amounts of triflyl azide used in subsequent reactions reported here. (Base titration of triflic acid formed during reaction indicated that about 50% of the anhydride had hydrolyzed during the reaction.)

Caution: Explosions may be expected to result in situations involving neat triflyl azide,[5] and, although we experienced no problems handling CH_2Cl_2 solutions of the azide, we feel that for safety's sake the solutions should under no circumstances be allowed to evaporate or be stored for any length of time.

α-Azido Acids. General Procedure. Details omitted here appear in Table I. In a typical reaction, 0.012 mol of the amino acid was dissolved in sufficient aqueous 1 N NaOH to bring the pH to 9.5, 1 equiv of triflyl azide in CH_2Cl_2 (~1 M) was added, and the mixture was stirred magnetically at room temperature, with occasional addition of sufficient 1 N NaOH to maintain the pH between 9 and 9.5. (This may be conveniently accomplished by using a pH stat/autoburet, or, alternatively, the reaction may be buffered with an excess of 0.25 M $Na_2B_4O_7$, with no reduction in yield.)

After the mixture was stirred overnight, the phases were separated, and the organic phase was discarded. The aqueous phase was treated with 1 equiv of 1 M aqueous mercuric acetate, and the resulting heavy, white precipitate, a mercuric salt of triflamide,[7] was removed by suction filtration and washed with 50 mL of water.[10] The pH of the combined filtrates was adjusted to 3.5 with 2 N H_2SO_4, and the mixture was extracted four times with 25 mL of ether. The united ethereal extracts were dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. Traces of solvent and acetic acid were removed by evacuation with a mechanical pump for 1 h.

Inasmuch as oils were frequently obtained at this stage, the highly crystalline dicyclohexylamine (DCHA) salts were prepared by treating a concentrated ethereal solution of the crude product with freshly distilled dicyclohexylamine (Aldrich) until a pH of 9 was indicated by using moist Hydrion papers. Cooling and scratching with a stirring rod was occasionally necessary to bring about crystallization, and the solid was recrystallized once from acetone or acetonitrile. Spectral data showed no significant impurities at this stage; however, analyses were performed on samples which had been repeatedly recrystallized.

Ethyl L-Azidopropanoate. Freshly distilled L-alanine ethyl ester (5.73 g, 0.049 mol) was dissolved in 10 mL of CH_2Cl_2, 1 equiv of triflyl azide in CH_2Cl_2 (~1 M) was added along with a catalytic amount (~0.1 mmol) of trioctylmethylammonium chloride, and the solution was stirred magnetically at room temperature. The reaction was monitored by using gas chromatography (6 ft, SE-30/Chromosorb W). When the reaction was complete (typically 10–15 h), the reaction mixture was washed twice with 30-mL portions of 0.5 N citric acid. The CH_2Cl_2 layer was dried over anhydrous Na_2SO_4 and filtered, the solvent evaporated, and the azido ester distilled at reduced pressure, affording 4.32 g (62%) of the pure product, bp 70–74 °C (aspirator pressure).

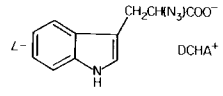
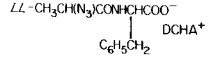
Ethyl 2-azido-5-methylpentanoate and methyl 2-azido-3-phenylpropanoate were prepared similarly. Details appear in Table I.

***N*-[L-2-Azido-3-(4-hydroxyphenyl)propionyl]glycine.** L-Tyrosylglycine (1.0 g, 4.4 mmol) was dissolved in sufficient 1 N NaOH to bring the pH to 9.05. The solution was treated with ~2 equiv of triflyl azide solution and stirred magnetically for 24 h, with periodic readjustment of the pH with 1 N NaOH for the first few hours as necessary. The organic phase was separated, and an equal volume of ethyl acetate was added to the aqueous layer. The mixture was stirred vigorously while being acidified to pH with 2 N H_2SO_4. The aqueous layer was removed and extracted twice with 20-mL portions of ethyl acetate. The united organic extracts were dried over Na_2SO_4, gravity filtered, and evaporated in vacuo. The residue crystallized upon removal of traces of solvent with a mechanical vacuum pump. The solid was extracted overnight with $CHCl_3$ in a Soxhlet apparatus to remove traces of triflamide and then recrystallized from water, affording 0.38 g (33%) of white crystals, mp 139–140 °C.

Dicyclohexylammonium *N*-(L-2-azidopropionyl)-L-phenylalaninate was prepared by using a similar procedure and starting with 500 mg (2.1 mmol) of L-alanyl-L-phenylalanine. In this case, 0.20 g (0.5 mmol) of trioctylmethylammonium chloride was added to the initial aqueous solution. A solution of the crude product and 1 equiv of dicyclohexylamine was treated with sufficient anhydrous ether to cause crystallization of the salt: yield

(8) A notable exception is the asparagine case, where base rapidly decomposes the azido acid to a substance tentatively identified as fumaramidic acid; similar reactivity has been observed for 2-azidobutanedioic acid (see ref 9).
(9) Curtius, T.; Hartmann, F. *Chem. Ber.* **1912**, *45*, 1050–56.
(10) If byproduct triflamide is not removed at this point, it will form salts with dicyclohexylamine which are not easily removed from the final product.
(11) Freudenberg, K.; Keller, R. *Chem. Ber.* **1938**, *71*, 329–34.
(12) Telesnina, T. R.; Antonov, V. K.; Shemyakin, M. M. *Zh. Obshch. Khim.* **1968**, *38*, 1691–6.
(13) Darapsky, A.; Berger, H. *J. Prakt. Chem.* **1917**, [2] *96*, 301–27.
(14) Diethyl ester described: Bertho, A.; Schmidt, I.; Strecker, E. *Justus Liebigs Ann. Chem.* **1962**, *651*, 185–94.
(15) Forster, M. O.; Fierz, H. E. *J. Chem. Soc.* **1908**, 1862.
(16) Freudenberg, K.; Kuhn, W.; Bumann, I. *Chem. Ber.* **1930**, *63*, 2380–90.
(17) Raap, R. *Tetrahedron Lett.* **1969**, 3493–4.
(18) Edwards, O. E.; Purushothaman, K. K. *Can. J. Chem.* **1964**, *42*, 712–6.
(19) Jarris, B. B.; Nicholas, P. E. *J. Org. Chem.* **1979**, *44*, 2951–2.
(20) Curtius, T. *Chem. Ber.* **1912**, *45*, 1057–93 and references therein.

Table I. Azido Compounds Prepared by Diazo Transfer from Amino Precursors[a]

product	structure	recryst solv	yield, g (%)	mp or bp (pressure), °C	$[\alpha]^{25}_D$, deg	IR, cm^{-1}	NMR, δ [solvent]	ref
1	*L*-$(CH_3)_2CHCH_2CH(N_3)COO^-$ $DCHA^+$	acetone	2.7 (66.7)[b]	123–125	−8.6 (*c* 4, MeOH)	2850–3000, 2090, 1625 (KBr pellet)	1.2–2.2 (br, 25 H), 1.15 (d, 7 H), 3.00 (br, 2 H), 3.80 (t, 1 H) [$CDCl_3$]	2, 11
2	*L*-$C_6H_5CH_2CH(N_3)COO^-$ $DCHA^+$	acetone	1.0 (22.4)[b]	138–140 dec	−41.3 (*c* 4, MeOH)	2850–3050, 2100, 1625 (KBr pellet)	1.0–2.2 (br, 22 H), 2.7–3.5 (complex m, 5 H), 4.00 (d d, 1 H), 7.30 (s, 5 H), [$CDCl_3$]	13
3	*L*-$^-OOCCH_2CH_2CH(N_3)COO^-$ $(DCHA^+)_2$	acetone	1.5 (23.4)	145–147	−15.0 (c 4, MeOH)	2800–2950, 2090, 1590 (KBr pellet)	1.0–2.2 (br, 46 H), 2.95 (br, 4 H), 3.60 (t, 1 H), [$CDCl_3$]	14
4	*DL*-$CH_3SCH_2CH_2CH(N_3)COO^-$ $DCHA^+$	CH_3CN	1.3 (31.0)	104–106		2850–2940, 2090, 1622 (KBr pellet)	1.2–210 (br, 22 H), 2.20 (s, 3 H), 2.2–3.3 (complex m, 6 H), 3.90 (d d, 1 H) [$CDCl_3$]	
5[d]		CH_3CN	1.20 (24.3)	149–150 dec	−20.9 (c 4, MeOH)	3240, 2940, 2840, 2100, 1640, 760 (KBr pellet)	1.0–2.4 (br, 22 H), 2.85–3.50 (br, 4 H), 4.1 (d d, 1 H), 7.00–8.00 (m, 5 H) [$CDCl_3$]	
6		acetone	0.35 (36.8)[c]	167–168	+63.9 (c 4, MeOH)	3350, 2930–2850, 2100, 1660, 1625 (KBr pellet)	1.41 (d, 3 H), 3.10 (t, 2 H), 4.05 (q, 1 H), 4.90 (q, 1 H), 7.20 (s, 5 H) [$CDCl_3$; free acid]	
7	*L*-$N_3C(CH_2$-*p*-$C_6H_4OH)$-$HCONHCH_2COOH$	H_2O	0.38 (33)	139–140	+15.9 (*c* 4, EtOH)	3350, 3000, 2110, 1715, 1660 (KBr pellet)	2.90 (d, 2 H), 3.90 (s, 2 H), 4.20 (d d, 1 H), 7.00 (d d, 4 H) [D_2O]	
8	*L*-$C_6H_5CH_2CH(N_3)COOC_2H_5$		1.09 (44.3)[c]	84–86 (0.2 mm)	−44.9 (neat)	2950–3050, 2110, 1740, 1190–1290, 705–780 (neat)	1.20 (t, 3 H), 3.10 (d d, 2 H), 4.20 (m, 3 H), 7.20 (s, 5 H) [neat]	13
9	*L*-$CH_3CH(N_3)COOC_2H_5$		4.32 (62)[c]	70–74 (aspirator pressure)	−16.4 (neat)[f]	2850–2950, 2140, 1740, 1200–1300 (neat)	1.40 (t, 3 H), 1.60 (d, 3 H), 4.05 (q, 1 H), 4.40 (q, 2 H) [neat]	15, 16
10	*L*-$(CH_3)_2CHCH_2CH(N_3)COOC_2H_5$		1.40 (40)[c]	95 (aspirator pressure)	−7.4 (*c* 4, benzene; 20 °C)[g]	2950–2850, 2100, 1730, 1260–1190 (neat)	1.00 (d, 6 H), 1.40 (t, 3 H), 1.80 (m, 3 H), 3.90 (d d, 1 H), 4.40 (q, 2 H) [neat]	2, 11, 12
11	*L*-$H_2NCOCH_2CH(N_3)COO^-$ $DCHA^+$	*e*	0.74 (19)	96–100	−50.9 (*c* 4, H_2O)	2950–2800, 2120, 1610 (KBr pellet)	1.2–2.2 (br, 22 H), 2.50 (d, 1 H), 2.70 (d, 1 H), 3.20 (br, 2 H), 4.20 (d d, 1 H), [D_2O]	

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for products 1–7. [b] Tetraheptylammonium bromide (0.1 mmol) was added initially to the reaction mixture in these cases. [c] Trioctylmethylammonium chloride was added (as described in the Experimental Section) in these cases. [d] Triflyl amide was removed from the reaction mixture at pH 6.0 by successive extractions with ether. [e] After removal of the triflamide, the pH of the aqueous phase was adjusted to 3.5, and it was evaporated to dryness in vacuo. The azido acid was extracted out of the residue by stirring with anhydrous methanol. After being filtered, the methanol solution was neutralized with dicyclohexylamine and the salt of the azido acid precipitated by addition of ether. [f] Lit. −18.1°; $[\alpha]^{25}_{578}$ −20.1°. [g] Lit. −7.8° (*c* 4, benzene; 20 °C).

0.35 g (36.8% yield, as calculated for the hemihydrate); mp 167-168 °C.

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Registry No. 1, 79410-34-7; 2, 79410-36-9; 3, 79410-38-1; 4, 79410-40-5; 5, 79410-42-7; 6, 79410-44-9; 7, 79410-45-0; 8, 79410-46-1; 9, 79410-47-2; 10, 79464-63-4; 11, 79410-49-4; L-Leu, 61-90-5; L-Phe, 63-91-2; L-Glu, 56-86-0; DL-Met, 59-51-8; L-Trp, 73-22-3; LL-Ala-Phe, 3061-90-3; L-Tyr-Gly, 673-08-5; L-Phe-Oet, 3081-24-1; L-Ala-Oet, 3082-75-5; L-Leu-Oet, 2743-60-4; L-Asn, 70-47-3; triflyl azide, 3855-45-6.

Long-Bridged Cyclonucleosides. 1. Synthesis and Reactions of Some Purine 8,2′-(N^{α}-Methylhydrazino) and 8,2′-(N^{α}-Methyloxamido) Cyclonucleosides

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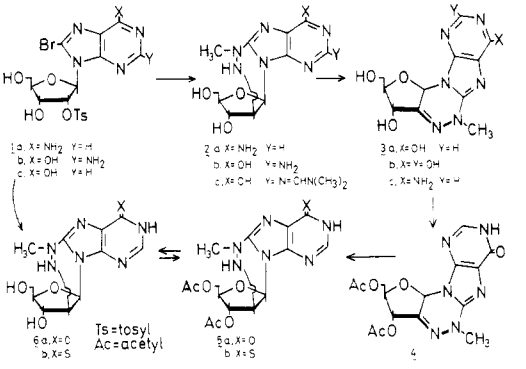
For expansion of the range of the model conformations of cyclonucleosides, synthesis of some long-bridged purine cyclonucleosides has been achieved. Thus, 8-bromo-2′-*O*-tosyladenosine (**1a**) and its guanine analogue (**1b**) with methylhydrazine gave the corresponding 8,2′-(N^{α}-methylhydrazino) cyclonucleosides **2a,b**. Treatment of **2a** and **2b** with nitrous acid yielded another type of long-bridged cyclonucleoside, 2′,N^{β}-didehydro-8,2′-(N^{α}-methylhydrazino)cycloinosine (**3a**) and its xanthine analogue (**3b**), respectively. Oxidation of **2a** with $NaIO_4$ or MCPBA gave the analogous cycloadenosine **3c**. Acetylation of **3a** followed by $NaBH_4$ reduction gave 3′,5′-di-*O*-acetyl-8,2′-(N^{α}-methylhydrazino)cycloinosine (**5a**), which was thiated to its thioinosine analogue **5b**. Deacetylation of **5a,b** afforded the corresponding parent 8,2′-(N^{α}-methylhydrazino) cyclonucleosides **6a,b**. Acidic hydrolysis of **2a** gave a new cyclonucleoside having the glycosidic bond to N_7. Catalytic hydrogenolysis of **2a** yielded the amino sugar nucleoside **8**. Compound **1a** with *N*-methylhydroxylamine gave 8-[(methylamino)-oxy]-9-(2′-*O*-tosyl-β-D-ribofuranosyl)adenine (**9**), 8,2′-(N^{α}-methyloxamido) cyclonucleoside **10**, and 8-(methylamino)-9-(β-D-arabinofuranosyl)adenine (**11**). Reduction of **10** with Zn/AcOH yielded 8-(methylamino)adenine which was isolated as hydrochloride **12**.

Among the hitherto known, large number of pyrimidine and purine cyclonucleosides,[1] notably missing members are those having a base–sugar bridge constructed by multiple atoms. In view of the numerous theoretically possible base–sugar conformations in natural nucleosidic or nucleotidic materials, it seems to be important to try to expand the presently limited bounds of the model conformations by bonding the base and sugar moieties with a reasonably longer chain. This type of cyclonucleoside might also be useful as a new type of synthetic intermediate for bifunctionalization at the base and sugar moieties, depending upon the chemical property of the bridge. We herein describe the syntheses and reactions of some purine 8,2′-cyclonucleosides containing an $N(CH_3)NH$, $N(CH_3)$-$N=$, or $N(CH_3)O$ bridge using bifunctional methylhydrazine and *N*-methylhydroxylamine as powerful synthetic tools.

Heating 8-bromo-2′-*O*-tosyladenosine (**1a**)[2] with excess methylhydrazine in methanol gave 8,2′-(N^{α}-methylhydrazino)-9-(2′-deoxy-β-D-arabinofuranosyl)adenine (**2a**) in 85% isolated yield (Scheme I). Similarly, **1b** with methylhydrazine provided 8,2′-(N^{α}-methylhydrazino)-9-(2′-deoxy-β-D-arabinofuranosyl)guanine (**2b**). Compound **2b** was sparingly soluble in most organic solvents and hence was converted to the N_2-[(dimethylamino)-methylene] derivative **2c** by treatment with DMF dimethyl acetal for spectroscopic measurements.[3] The UV and ^1H NMR spectra of these compounds are given in Tables I and II.

Scheme I



As the first step of base transformations, **2a** was treated with excess sodium nitrite in 80% acetic acid at 0 °C to afford another type of cyclonucleoside, 2′,N^{β}-didehydro-8,2′-(N^{α}-methylhydrazino)-9-(2′-deoxy-β-D-arabinofuranosyl)hypoxanthine (**3a**), in excellent yield. Similar treatment of **2b** with nitrous acid gave the corresponding xanthine analogue **3b** in a moderate yield.[4] The structures

(1) For reviews see: Ts'o, P. O. P., Ed. "Basic Principles in Nucleic Acid Chemistry"; Academic Press: New York, 1974; Vol. 1, p 170. (b) Ikehara, M. *Acc. Chem. Res.* **1969**, *2*, 47.

(2) Ikehara, M.; Maruyama, T. *Tetrahedron* **1975**, *31*, 1369.

(3) For compounds **2**, alternative structures in which the 1-nitrogen atom of methylhydrazine is attached to the $C_{2'}$ or its 2-nitrogen is attached to both $C_{2'}$ and C_8 were eliminated by conversion of **2** to **3** and also by X-ray analysis of **2a**.

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