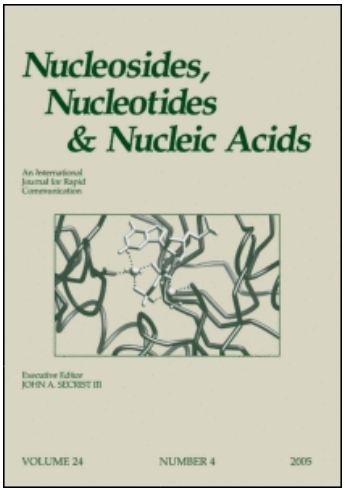

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Regiochemical Aspects in Reactions of 6-Azauridine Dialdehyde

Josef Nemec[ab]; Jerry M. Rhoades[ab]
[a] Division of Biochemical and Clinical Pharmacology, St. Jude Children's Research Hospital, Memphis, Tennessee [b] The Department of Medicinal Chemistry, University of Tennessee Center for the Health Sciences, Memphis, Tennessee

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REGIOCHEMICAL ASPECTS IN REACTIONS OF 6-AZAURIDINE DIALDEHYDE

Josef Nemec* and Jerry M. Rhoades

Division of Biochemical and Clinical Pharmacology
St. Jude Children's Research Hospital
and
The Department of Medicinal Chemistry
University of Tennessee Center for the Health Sciences
Memphis, Tennessee 38101

ABSTRACT: Conversions of 6-azauridine dialdehyde (1) have been investigated. The reaction of 1 with equimolecular amount of N,N'-diphenylethylenediamine (3) is highly regioselective, leading to the monoimidazolidine 4b (81%) and the bisimidazolidine 6 (10%). Two equivalents of 3 per one mole of 1 produced 6 in 90% yield, while the monoimidazolidine 5 was not found in either experiment. In contrast to 3, hydroxylamine reacted with 1 more rapidly and nonregioselectively with the formation of bisoxime 10a,b, isolated as a mixture of 90% E,E-isomer 10a and 10% of Z,Z-isomer 10b.

In the preceding communication of this series, we reported on studies of equilibrium mixtures of hemiacetals and hemialdals of 6-azauridine dialdehyde (1)[1,2], prepared from the known anti-neoplastic and anti-psoriatic agent 6-azauridine (2)[3] by an oxidative cleavage with sodium metaperiodate. The reactivity and transformations of 1 were examined, with a view to its possible chemical and biological utilities. In this paper we describe the reactions of N,N'-diphenylethylenediamine (3) and hydroxylamine with the dialdehyde 1 and present evidence for the structure of the products.

The diamine 3 was used by Wanzlick and Löchel to characterize aldehydes as crystalline 1,3-diphenylimidazolidines.[4] These derivatives, which can be conveniently used to protect aldehyde groups,[5] are stable in alkaline media but can be easily hydrolyzed under acidic conditions.

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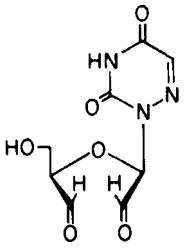
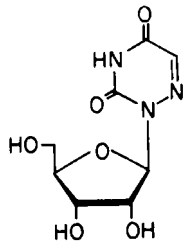
Since the two latent[2] aldehyde groups of 1 are not equivalent, treatment of 1 with 3 could lead to two monoimidazolidines, represented formally by the structures 4a and 5, as well as one bisimidazolidine 6. An examination of CPK space-filling molecular models suggested that the reaction of the aldehyde group of 1, derived from the C_3'-atom[6], which gives rise to 4a, would be stereochemically preferred to the product of a reaction with the C_2'-atom, the result of which would be derivative 5. Indeed, when the aldehyde 1 was treated with an equimolecular amount of diamine 3, a high degree of regioselectivity was observed in favor of the carbon atom 3'; thus, the monoimidazolidine 4a (4b) was obtained in 81% yield together with 10% of bisimidazolidine 6. Under more vigorous reaction conditions, including prolonged heating of 1 with two equivalents of 3, reaction with the second aldehyde group occurred, leading to the formation of derivative 6 in 90% yield. In neither experiment, however, was the second monoimidazolidine, i.e., 5, found among the products. Similar observations were reported[7] when dialdehydes of pyrimidine and purine nucleosides were reduced under slightly acidic conditions with sodium borohydride; thus, the aldehyde group distal to the nucleoside base reacted selectively.

The representation of both monoimidazolidines as 4a and 5 with free aldehyde groups was previously used for convenience; however, the IR spectrum of 4a, taken in a KBr disc, displayed no distinct bands attributable to the aldehydic proton at ≈2740 and 2855 cm^{-1}. The carbonyl region of 1720-1740 cm^{-1} was equivocal because the carbonyl group of the heterocyclic base also exhibited an absorption band in that area. On the other hand, the spectrum did not show a strong and broad band around 1120 cm^{-1}, which is characteristic for the C-O-C group in polymerized aldehydes and was found in the starting dialdehyde 1. Importantly, there was found no signal for a free aldehyde proton in the NMR spectrum of 4a at 9-10 ppm.[8-10] Acetylation of this compound by acetic anhydride in pyridine provided the monoacetate 4c, the NMR spectrum of which displayed a minor downfield shift (0.09 ppm) for the anomeric proton but a major downfield shift (0.96 ppm) for only one proton.[11] This observation was confirmed by the acetylation *in situ* of a sample of 4a in the NMR tube in a time-dependent manner; thus, these spectral data suggested that the monoimidazolidine actually existed in the hemiacetal form 4b, rather than having either a free aldehyde group, as in 4a, or a polymerized form.



1



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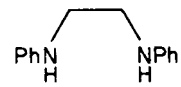

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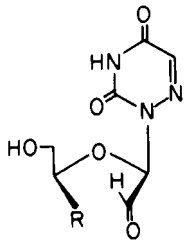
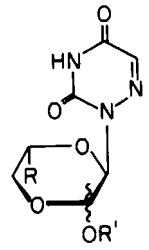
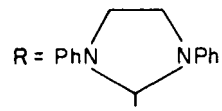
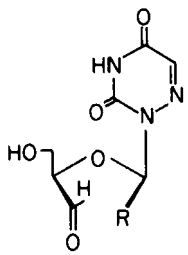


4a



4b : R' = H
4c : R' = Ac





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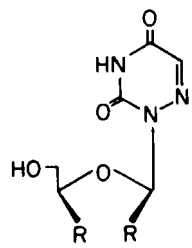

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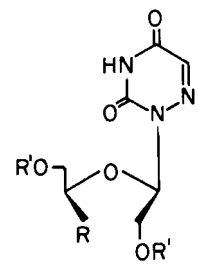
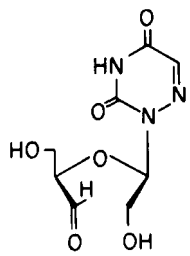
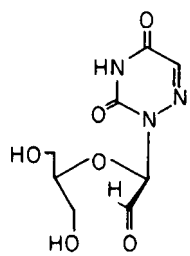


7a : R' = H
7b : R' = Ac



7c



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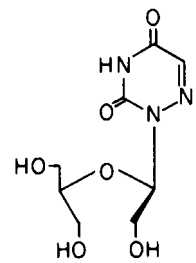
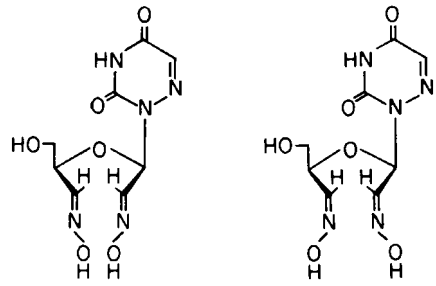


9

The position of the imidazolidine ring, however, remained to be established. Accordingly, 4b was reduced (vide infra) into the diol 7a, which, upon acetylation, gave the diacetate 7b. Comparison of the NMR spectra of this diol and its diacetate revealed a downfield shift ($\Delta\delta$ 0.29) for the anomeric proton in 7b versus 7a. A similar effect, even though less pronounced, was observed between 4b and its acetate 4c (vide supra). This indicated the proximity of the acetoxy group and the anomeric proton and suggested the structure 4b, rather than 5, for the parent monoimidazolidine. The unequivocal proof of the structure, however, was accomplished via the following reaction sequence. The aldehyde group of 4b was reduced by sodium borohydride in alkaline medium[4]; thus making certain that the integrity of the imidazolidine ring was preserved while the diol 7a was formed. Treatment of this diol with a cation exchange resin yielded the deprotected aldehyde 7c, which was subjected in situ to a strongly acid hydrolysis at an elevated temperature. Under these conditions, the nucleoside and ether bonds were cleaved and the three carbon atom fragment, corresponding to the C_3'-, C_4'-, and C_5'-atoms of the ribofuranosyl residue, was isolated and identified as the methylglyoxal bisphenylhydrazone. It is known that glyceraldehyde, being very reactive in solutions, is transformed into methylglyoxal when distilled from a strongly acidic milieu.[7] Hence, the isolation of methylglyoxal bisphenylhydrazone afforded unequivocal proof of the structure 7c and consequently of the monoimidazolidine 4a (4b). The alternative regioisomer 5, if subjected to the same procedure, would have led to the monoaldehyde 8; in turn, this would have yielded glycerol as the three carbon atom fragment. Indeed, in model experiments the triol 9 and the dialdehyde 1 led to glycerol and methylglyoxal, respectively.

Even though imidazolidines 4b and 6 were quite stable on regular and two-dimensional TLC on silica gel, a high degree of decomposition was encountered during column chromatography on the same adsorbent. In order to circumvent this problem, a modified flash chromatography[12] was employed (vide infra).

In contrast to the reactivity of diamine 3, hydroxylamine reacted with 1 much more rapidly and nonregioselectively, with the formation of the bisoxime 10a,b in 90% yield. Since aldoximes can form cis-trans-isomers, it was not surprising to find that the crude product consisted



10a 10b

of a mixture of such isomers. Attempts to isolate the pure isomers of 10a and 10b met only with limited success. The highest isomeric purity was achieved through a quick, temperature controlled fractional crystallization from dioxane-benzene. The crystalline product thus obtained was a solvate (mp 105-107°C, displaying one well defined spot on TLC); this contained one molecule of dioxane that could not be removed without appreciable decomposition of the compound. The NMR spectrum taken in Me_2SO-d_6 exhibited low-field sharp signals between 11.55-11.16 ppm, integrating for two protons that disappeared on the addition of deuterium oxide; these signals were assigned to the hydroxyimino hydrogens. Close examination revealed that the signals were composed of two major singlets at 11.16 and 11.39 ppm, each integrating for approximately 0.9 H, and two minor singlets (2 x ≈0.1 H) that were shifted downfield from the parent ones, each by 0.16 ppm. The hydrogen atoms of the oxime trigonal carbons at C_2' and C_3' were observed as two doublets at δ7.50 (J = 6 Hz) and 7.29 (J = 7 Hz), each integrating for ≈0.9 H, and an upfield multiplet at 6.5-7.0 ppm (totally ≈0.2 H). Based on these data and the chemical shift correlations, the following assignment was made. It was reported[13-17] that the hydrogen atom of the aldoxime trigonal carbon is more deshielded in the E-isomer [this proton is cis-(syn-) to the oxime OH group] than in the Z-isomer, and that the proton of the oxime hydroxyl group is more deshielded in the Z-form [i.e., NOH is trans-(anti-) to the proton of the aldoxime trigonal carbon atom] than in the E-form. Thus, the application of these correlations on our example suggested that the bisoxime 10a,b was composed of approximately 90% E,E-isomer 10a and 10% of Z,Z-isomer, 10b.

Attempts to reduce 10a,b to the corresponding diaminonucleoside with hydrogen on palladium or platinum [18,19] led only to a complex mixture of compounds.

EXPERIMENTAL SECTION

All chemicals were of A.C.S. certified grade and were used without further treatment, unless stated otherwise. Petroleum ether refers to the fraction of bp 38-46°C. The hexane used contained a mixture of isomers; the boiling range was 65.2-67.4°C. Almost all evaporations were conducted on a rotary evaporator in vacuo (12-20 mm Hg) and at bath temperatures of 30-40°C. Analytical thin-layer chromatography (TLC) was performed on silica gel with fluorescent indicator (Macherey-Nagel Polygram Sil G/UV_{254}, 0.25 mm layer). Preparative layer chromatographic separations were carried out on layers of silica gel either 1.0 or 2.0 mm of the same provenience. The plates were treated in a stream of dry nitrogen for 24 h prior to use. Modified flash chromatography[12] was carried out using silica gel 60 (E. Merck), particle size 0.040-0.063 mm (230-400 mesh ASTM). The modification consisted of the use of a mixture of dyes (e.g., pHydrion, 1-11 pH, concentrated pH indicator from American Scientific Products No. P1123-5) as an internal standard to facilitate the detection of products. This technique conveniently required the collection of only a few fractions. The column was reused several times without having the separation capacity significantly altered; for this purpose the column was deactivated by a polar system (e.g., MeOH) and reactivated by abs. EtOH, $CHCl_3$, and hexane (in that order). Unless stated otherwise, analytical samples were dried at room temperature in vacuo (0.10-0.01 mm Hg) for 10 h. Elemental analyses were performed by Midwest Microlab Ltd., Indianapolis, IN. Melting points were determined with a Fisher digital melting point analyzer Model 355 and were not corrected. Infrared spectra were recorded on a Beckman IR-spectrophotometer 4230 with polystyrene as the standard; in the IR spectra: s = strong, m = medium, w = weak, sp = sharp, sr = shoulder. Ultraviolet spectra were measured with a Perkin-Elmer UV-spectrophotometer 575. Nuclear magnetic resonance spectra were obtained at ambient temperature on a JEOL spectrometer Model JNM-MH-100. Tetramethylsilane was used as an internal standard. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; m, multiplet. Coupling constants are given in hertz. Optical rotations were determined with a Rudolph Autopol III Automatic Polarimeter at 589 nm, using a 1.00 dm microcell.

3(R)-(3,5(2H,4H)-dioxo-1,2,4-triazin-2-yl)-5(S)-(1,3-diphenylimidazolidin-2-yl)-2(R,S)-hydroxy-1,4-dioxane (4b). A solution of dialdehyde 1 (486 mg, 2.00 mmol) and N,N'-diphenylethylenediamine (3) (425 mg, 2.00 mmol) in anhydrous tetrahydrofuran (10 mL) was stirred at room temperature under a nitrogen atmosphere. After 51 h the solvent was removed in vacuo and the THF was substituted by abs. EtOH. This solution, after having been stirred for 23 h at room temperature, was subjected to a slow azeotropic distillation (≈3 h), as EtOH was gradually replaced by toluene. The toluene solution was cooled, providing 81.5% (713 mg) of a crude 4b. Mother liquors deposited 10.8% (137 mg) of 6. An analytical sample of 4b was obtained by the combination of flash chromatography (see at 6) and recrystallization from THF-petroleum ether 4:1 and THF-cyclohexane 3:2, mp 181.9-182.9°C (dec.); TLC (silica gel), R_f 0.90 ($CHCl_3$-95% EtOH 7:2); $[\alpha]_D^{23}$ -43.3° ± 0.3° (c 0.99, 95% EtOH); NMR (Me_2SO-d_6) δ 3.3-4.0 (m, 7H, H-5', NCH_2, OH), 4.40 (s, broad, 1H, H-4'), 5.00 (t, J = 2 Hz, 1H, H-2'; +D_2O: d, J = 2 Hz), 5.54 (d, J = 1 Hz, 1H, H-3'), 5.65 (d, J = 2 Hz, 1H, H-1'), 6.5-6.95 (m, 6H, Ph), 7.0-7.4 (m, 5H, H-5, Ph), 12.2 (s, broad, 1H, N_3H, exchangeable with D_2O); IR (KBr) ν (cm^{-1}) 3520 (m, sp), 3440 (w, sr), 3190 (m), 1735 (s), 1700 (s), 1600 (s), 1500 (s), 1265 (w), 1110 (m), 1090 (m), 750 (s); UV (95% EtOH) λ (nm) (ε) 206 (29400), 220 (9190), 252 (38720); UV (0.1 N HCl) λ (nm) (ε) 203 (22900), 218 (5800), 242 (9950); UV (0.1 N NaOH) λ (nm) (ε) 221 (12340), 246 (29500).

Anal. Calc'd for $C_{22}H_{23}N_5O_5$ (437.5): C, 60.40; H, 5.30; N, 16.01. Found: C, 60.60; H, 5.38; N, 15.85.

2(R,S)-Acetoxy-3(R)-(3,5(2H,4H)-dioxo-1,2,4-triazin-2-yl)-5(S)-1,3-diphenylimidazolidin-2-yl)-1,4-dioxane (4c). To the monoimidazolidine 4b (150 mg, 0.343 mmol) in anhydrous pyridine (3.5 mL) was added acetic anhydride (2.0 mL) and the reaction mixture was set aside at room temperature with occasional swirling for 30 min. After this period TLC (ether) revealed no starting material left; the solution was evaporated in a nitrogen stream, and the residue was coevaporated in vacuo with toluene-pyridine 1:1 (5 x 5 mL). The off-white mass was suspended in cyclohexane and filtered off to deposit 153 mg (93%) of the crude product. An analytical sample of 4c was obtained by recrystallization

from CH_2Cl_2-hexane 1:1 and CH_2Cl_2-pentane 2:1; mp 118-120°C, TLC (silica gel), R 0.6 (Et_2O), 0.45 (Et_2O-hexane 5:1); $[\alpha]^{21}$-85.2°$_D$± 1.8° (c 1.07, 95% EtOH); NMR (Me_2SO-d_6) δ 2.00 (s, 3H, CH_3CO), 3.3-4.1 (m, 6H, H-5', NCH_2), 4.55 (m, 1H, H-4'), 5.59 (s, 1H, H-3'), 5.74 (s, 1H, H-1'), 5.96 (s, 1H, H-2'), 6.6-7.0 (m, 6H, Ph), 7.1-7.4 (m, 5H, H-5, Ph), 12.2 (s, broad, 1H, N_3H, exchangeable with D_2O); IR (KBr) ν (cm^{-1}) 3200 (w), 1740 (sr), 1730 (s), 1700 (s), 1600 (s), 1500 (s), 1230 (m), 1155 (m), 1110 (w), 750 (s); UV (95% EtOH) λ (nm) (ε) 209 (23700), 222 (8000), 252 (25950): UV (0.1 N HCl) λ (nm) (ε) 205 (18560), 221 (6470), 243 (9260); UV (0.1 N NaOH) λ (nm) (ε) 224 (12200), 247 (25100).

Anal. Calc'd for $C_{24}H_{25}N_5O_6$ (479.5): C, 60.12; H, 5.26; N, 14.61. Found: C, 59.94; H, 5.34; N, 14.57.

1(S)-O-[(R)-(3,5(2H,4H)-dioxo-1,2,4-triazin-2-yl)-(1,3-diphenylimidazolidin-2-yl)methyl]-1-(1,3-diphenylmidazolidin-2-yl)ethylene glycol (6). The dialdehyde 1 (486 mg, 2.00 mmol) was dissolved in abs. ethanol (15 mL) and N,N'-diphenylethylenediamine (3) (849 mg, 4.00 mmol) was added. This solution was heated to 75°C under a nitrogen atmosphere with magnetic stirring. After having been heated for 55 h, the reaction solution was concentrated in vacuo to a small volume and coevaporated with a mixture of abs. ethanol-toluene (1:1) (5 x 10 mL). The residue was dissolved in toluene (20 mL) and heated to 105°C under nitrogen. The reaction was terminated after 27 h; the solvent was removed in vacuo, and an off-brown solid was extracted with hexane (4 x 4 mL). These extracts, containing mostly unreacted 3, were discarded. The yield of the crude product was 90.2% (1.14 g). [TLC (silica gel, $CHCl_3$ - 95% EtOH 15:1) revealed that the crude product contained a small amount of monoimidazolidine 4b and a minute amount of the diamine 3.] Flash chromatography of this material (silica gel, column 20 x 130 mm, eluent $CHCl_3$ - abs. EtOH 30:1) followed by recrystallization from methylene chloride - cyclohexane, and ether-petroleum ether, led to an analytical sample, mp 196.8-197.9°C; TLC (silica gel), R_f 0.96 ($CHCl_3$ - 95% EtOH 7:2); $[\alpha]^{23}_D$ + 153.1° ± 0.3° (c 0.98, 95% EtOH); NMR (Me_2SO-d_6) δ 3.0-4.2 (m, 11H, H-4', H-5', NCH_2), 5.02 (s, broad, 1H, OH, exchangeable with D_2O), 5.60 (s, 1H, H-3'), 5.89 (s, broad, 1H, H-2' or H-1'), 6.00 (s, broad, 1H, H-1' or H-2'), 6.5-7.0 (m, 12H, Ph), 7.1-7.4 (m, 8H, Ph), 7.60 (s, 1H, H-5'); IR (KBr) ν (cm^{-1}) 3460 (m, broad), 1720 (sr), 1700 (s), 1600 (s),

1500 (s), 1260 (w), 1100 (m), 750 (s); UV (95% EtOH) λ (nm) (ε) 206 (55200), 220 (16160), 250 (54600); UV (0.1 N HCl) λ (nm) (ε) 205 (28200), 217 (7570), 240 (14680); UV (0.1 N NaOH) λ (nm) (ε) 220 (17700), 249 (47000).

Anal. Calc'd for $C_{36}H_{37}N_7O_4$ (631.7): C, 68.45; H, 5.90; N, 15.52. Found: C, 68.25; H, 6.16; N, 15.39.

1(S)-O-[1(R)-(3,5(2H,4H)-dioxo-1,2,4-triazin-2-yl)-2-hydroxyethyl]-1-(1,3-diphenylimidazolidin-2-yl)ethylene glycol (7a). To a magnetically stirred solution of imidazolidine 4b (875 mg, 2.00 mmol) in methanol (60 mL) and water (0.7 mL) was added an aqueous solution (5.0 mL) of sodium borohydride (1.514 g, 40.0 mmol) in four portions during 45 min. The temperature was maintained at 0-5°C. After 1 h TLC (ether) did not detect the presence of the starting material. The reaction was quenched with CO_2; the solution was saturated with ammonium sulfate and extracted with methylene chloride (4 x 10 mL). The extract was dried ($MgSO_4$) and evaporated to dryness. Plate chromatography on silica gel (2 x 200 x 200 mm, Et_2O-MeOH 10:1, extraction with CH_2Cl_2-abs. EtOH 10:1) of the crude product led to the diol (7a) (804 mg, 91.5%) as a yellowish foam; TLC (silica gel), R_f 0.72 ($CHCl_3$-95% EtOH 7:2), 0.78 (Et_2O-MeOH 10:1); $[\alpha]_D^{21}$ - 14.8° ± 0.4° (c 0.98, 95% EtOH); NMR ($CDCl_3$) δ 3.2-4.1 (m, 11H, H-2', H-4', H-5', NCH_2, OH), 5.39 (d, J = 6 Hz, 1H, H-3'), 5.92 (t, J = 5 Hz, 1H, H-1'), 6.4-7.6 (m, 11H, H-5, Ph); IR (KBr) ν (cm^{-1}) 3440 (m, broad), 1725 (sr), 1702 (sr), 1695 (s), 1600 (s), 1500 (s), 1270 (w), 1110 (m), 755 (s); UV (95% EtOH) λ (nm) (ε) 208 (25000), 222 (8370), 254 (26000); UV (0.1 N HCl) λ (nm) (ε) 205 (19110), 220 (5990), 243 (9700); UV (0.1 N NaOH) λ (nm) (ε) 223 (11590), 252 (25500).

Anal. Calc'd for $C_{22}H_{25}N_5O_5$ (439.5): C, 60.13; H, 5.73; N, 15.94. Found: C, 59.88; H, 6.01; N, 15.64.

2-O-Acetyl-1(S)-O-[2-acetoxy-1(R)-(3,5(2H,4H)-dioxo-1,2,4-triazin-2-yl)ethyl]-1-(1,3-diphenylimidazolidin-2-yl)ethylene glycol (7b). A solution of diol 7a (150 mg, 0.341 mmol) in anhydrous pyridine (3.5 mL) and acetic anhydride (2.0 mL) was kept at room temperature for 45 min. The reaction mixture, showing no starting diol (TLC-Et_2O), was evaporated to dryness with nitrogen. The residue was codistilled with pyridine-toluene 1:1 (5 x 5 mL) and the crude product was purified by thick layer

chromatography (silica gel, 2 x 200 x 200 mm, Et_2O, extraction with CH_2Cl_2-abs. EtOH 10:1). The diacetate 7b was obtained in 79.5% yield (142 mg) as a chromatographically homogeneous yellowish foam; TLC (silica gel), R_f 0.6 (Et_2O); 0.45 (Et_2O-hexane 5:1); $[\alpha]_D^{21}$-18.5° ± 0.2° (c 1.03, 95% EtOH); NMR ($CDCl_3$) δ 1.92 (s, 6H, CH_3CO), 3.5-3.9 (m, 4H, NCH_2), 4.0-4.4 (m, 5H, H-2', H-4', H-5'), 5.50 (d, J = 3 Hz, 1H, H-3'), 6.21 (t, J = 6 Hz, 1H, H-1'), 6.6-7.0 (m, 6H, Ph), 7.1-7.4 (m, 4H, Ph), 7.46 (s, 1H, H-5); IR (KBr) ν (cm^{-1}) 1735 (s), 1700 (s), 1600 (s), 1500 (s), 1230 (s), 1100 (w), 750 (s); UV (95% EtOH) λ (nm) (ε) 207 (25000), 222 (9000), 254 (26240); UV (0.1 N HCl) λ (nm) (ε) 205 (18500), 220 (5610), 243 (8780); UV (0.1 N NaOH) λ (nm) (ε) 223 (11800), 252 (25470).

Anal. Calc'd for $C_{26}H_{29}N_5O_7$ (523.6): C, 59.65; H, 5.58; N, 13.38. Found: C, 59.48; H, 5.63; N, 13.24.

Methylglyoxal Bisphenylhydrazone from 1(S)-O-[1(R)-(3,5(2H,4H)-dioxo-1,2,4-triazin-2-yl)2-hydroxyethyl]-1-(1,3-diphenylimidazolidin-2-yl)-ethylene glycol (7a). A solution of 7a (108 mg, 0.246 mmol) in ethanol-water 1:1 (10 mL) was magnetically stirred at room temperature with cation exchange resin (Bio-Rad AG 50W-X8/100-200 mesh/H^+, 800 mg). After 30 min the resin was removed by filtration, washed (EtOH-H_2O 1:1, 15 mL), and the combined filtrates were evaporated to dryness. The residue was codistilled with water (3 x 3 mL), dried in vacuo, and dissolved in 20% H_2SO_4 (11 mL). This solution was refluxed for 1 h and subsequently distilled at atmospheric pressure to receive 8.0 mL of a distillate. The use of a cold finger reflux condenser protruding into the reaction flask during the reflux period and employing a distillation collar adapter significantly increased the yield of methylglyoxal. The distillate was allowed to react at room temperature with phenylhydrazine (0.60 mL) in the presence of 50% acetic acid (0.60 mL). After 1 h a precipitate was collected and washed with 1 N acetic acid (2 x 0.5 mL) and with water (2 x 0.5 mL). The crude methylglyoxal bisphenylhydrazone was obtained in 54.3% yield (33.1 mg). Recrystallization of this product from benzene-petroleum ether 1:1 afforded an analytical sample, mp 144.0-144.8°C, which was identical (mp, mixed mp, R_f, IR spectrum) with an authentic sample of methylglyoxal bisphenylhydrazone.

Methylglyoxal Bisphenylhydrazone from 2(R)-O-[1(R)-(3,5(2H,4H)-dioxo-1,2,4-triazin-2-yl)-2-oxoethyl]glyceraldehyde (6-Azauridine Dialdehyde), (1). A solution of 1 (150 mg, 0.617 mmol) in 20% H_2SO_4 (12 mL) was refluxed for 1 h and then distilled in the same manner as was described in a similar experiment with 7a. Treatment of the distillate (7.0 mL) with phenylhydrazine (1.0 mL) and glacial acetic acid (0.15 mL) yielded a crude methylglyoxal bisphenylhydrazone (94 mg, 60.4%), the crystallization of which, from benzene-carbon tetrachloride, gave an analytical sample (mp 144.0-145.0°C, which was identical [mixed mp, IR spectrum, TLC (ether-cyclohexane 1:1)] with an authentic specimen of methylglyoxal bisphenylhydrazone.

Acid Hydrolysis of 2-O-[1(R)-(3,5(2H,4H)-dioxo-1,2,4-triazin-2-yl)-2-hydroxyethyl]glycerol (9).

(a) A solution of 9 (150 mg, 0.607 mmol) in 20% H_2SO_4 (12 mL) was treated in the same manner as described in the experiment with the dialdehyde 1. No methylglyoxal bisphenylhydrazone was isolated in this case.

(b) A solution of 9 in H_2SO_4 [the same quantity as in sub(a)] was refluxed for 30 min, cooled to 0°C, mixed with Et_2O (15 mL), and neutralized with $KHCO_3$. The emulsion was evaporated to dryness and extracted with abs. EtOH-Me_2CO 10:1 (5 x 10 mL). The solvents were removed and the semi-solid was re-extracted with abs. EtOH (3 x 5 mL). Ethanol was evaporated and the residue was dried at 1 mm Hg at room temperature for 1 h, and then dissolved in anhydrous pyridine (5 mL). The solution was cooled to 0°C and benzoyl chloride (0.5 mL) was added in one portion to the reaction mixture which was stirred at 25°C. After 90 min the mixture was concentrated in a stream of nitrogen, dissolved in CH_2Cl_2 (20 mL) and treated successively with H_2O, aqueous solution of $KHCO_3$, H_2O, and dried with $MgSO_4$. Evaporation of the solvent yielded 97 mg (39.5%) of a crude product that, after recrystallization from MeOH, gave glycerol tribenzoate (mp 73-74°C), which was identical with the authentic sample of the compound [mixed mp, IR spectrum and TLC (Et_2O-hexane 1:2 and Et_2O-MeOH 5:1)].

(E- and Z-)-2(S)-[1(R)-(3,5(2H,4H)-dioxo-1,2,4-triazin-2-yl)-2-(hydroxyimino)ethyloxy]-3-hydroxy-propylidenehydroxylamine (10a,b). The dialdehyde 1 (243 mg, 1.00 mmol) was dissolved in water (5.0 mL) and hydroxylamine hydrochloride (139 mg, 2.00 mmol) and sodium carbonate (106 mg, 1.00 mmol) were added and the reaction mixture was stirred at room temperature. TLC revealed that the reaction was over in 30 min. The reaction mixture was evaporated to dryness in vacuo and the residue was extracted by THF-benzene 1:3. The yield of a white amorphous mass was 90.4% (247 mg), mp 97-101°C. Recrystallization of this material from dioxane-benzene 1:5, 9x, temperature <55°C gave an analytical sample: mp 105-107°C (dried at room temperature in vacuo 0.02 mm Hg for 12 h and for 1.5 h at 55°C); TLC (silica gel), R_f 0.60 ($CHCl_3$ - 95% EtOH 7:2); $[\alpha]_D^{23}$ + 88.2° ± 0.3° (c 1.03, 95% EtOH); NMR (Me_2SO-d_6) 3.2-3.9 (m, 2H, H-5' partly buried under 8H, CH_2, dioxane), 4.0-4.3 (m, 1H, H-4'), 4.83 (s, broad, 1H, C_5'-OH, exchangeable with D_2O), 6.23 (d, J = 6 Hz, 1H, H-1'), 6.5-7.0 (m, ≈0.2H, H-2', H-3'), 7.29 (d, J = 7 Hz, ≈0.9H, H-3'), 7.50 (d, J = 6 Hz, ≈0.9H, H-2'), 7.59 (s, 1H, H-5), 11.16 (s, ≈0.9H, NOH exch. D_2O), 11.32 (s, ≈0.1H, NOH, exch. D_2O), 11.39 (s, ≈0.9H, NOH, exch. D_2O), 11.55 (s, ≈0.1H, NOH, exch. D_2O), 12.25 (s, broad, 1H, H-3, exch. D_2O); IR (KBr) ν (cm^{-1}) 3520 (sp), 3400 (s, broad), 3220 (s, broad), 1720 (sr), 1700 (s), 1265 (m), 1115 (m), 1080 (m); UV (95% EtOH) λ (nm) (ε) 202 (16460), 232 (4030), 261 (6620); UV (0.1 N HCl) λ (nm) (ε) 201 (10330), 231 (4130), 258 (6520); UV (0.1 N NaOH); λ (nm) (ε) 221 (21450).

Anal. Calc'd for $C_8H_{11}N_5O_6 \cdot C_4H_8O_2$ (361.3): C, 39.89; H, 5.30; N, 19.39. Found: C, 40.04; H, 5.53; N, 19.18.

Attempted reductions of 10a,b with hydrogen and palladium on alumina or platinum on powdered charcoal in water or acetic acid, led to a complex mixture of compounds.

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REFERENCES AND NOTES

(1) (a) This paper is dedicated to the memory of Professor F. Šorm for his many contributions to organic chemistry and biochemistry.

(b) Nemec, J.; Avery, T.L.; Rhoades, J.M. Submitted for publication.

(c) This work was presented in part before the Division of Carbohydrate Chemistry at the 182nd National Meeting of the American Chemical Society, New York, N.Y., August1981 (CARB 33).

(d) The periodate oxidation products of carbohydrate derivatives are generally referred to as dialdehydes.[2] Even though these compounds actually exist as equilibrium mixtures of various cyclic and acyclic forms, they react very often as typical aldehydes. The structural representation as dialdehydes and the term dialdehyde are, therefore, a matter of convenience.

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