Synthesis of a Novel Ring-Expanded Nucleoside Analogue Containing the Imidazo[4,5-*e*][1,3]diazepine Ring System With a Guanidinocarbamoyl-Substituted Cyclopropylidene Group in Place of a Sugar Moiety

Huan-Ming Chen and Ramachandra S. Hosmane*

Laboratory for Drug Design and Synthesis, Department of Chemistry & Biochemistry, University of Maryland, Baltimore County, 1000 Hilltop Circle, Baltimore, Maryland 21250

Donna M. Baldisseri

Department of Biochemistry, University of Maryland School of Medicine, Baltimore, Maryland 21201

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The synthesis of a novel ring-expanded nucleoside analogue, (*Z*)-1-((2-Guanidinocarbamoyl-cyclopropylidene)methyl)-4,5,7,8-tetrahydro-6*H*-6-iminoimidazo[4,5-*e*][1,3]diazepine-4,8-dione (**1**) has been reported. It was prepared starting from methyl imidazole-4,5-dicarboxylate by sequential condensations with 2-bromo-2-bromomethylcyclopropane-1-carboxylate and guanidine. The overall yield for the two-step synthesis is 46%.

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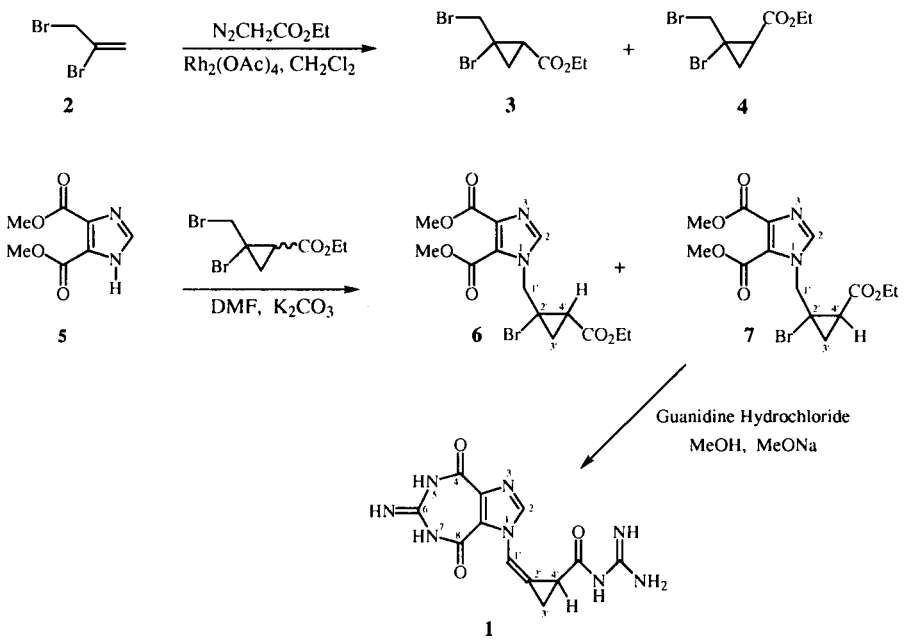
In view of recent reports [1-7] that nucleoside analogues containing substituted cyclopropylidene groups in place of the sugar moiety display broad-spectrum antiviral activities, we present here the synthesis of a novel ring-expanded nucleoside analogue **1**. It was synthesized starting from methyl imidazole-4,5-dicarboxylate in two steps in 46% overall yield.

The necessary ethyl 2-bromo-2-bromomethylcyclopropane-1-carboxylate was synthesized (Scheme 1) in >97% yield, as a mixture of *Z*- and *E*-isomers (**3** and **4**) in a 1:1.5 ratio, by a slightly modified literature procedure [7] by addition of ethyl diazoacetate to a solution of 2,3-dibromopropene (**2**) in dichloromethane in the presence of rhodium (II) acetate dimer ($Rh_2(OAc)_4$) as a catalyst. Alkylation of methyl imidazole-4,5-dicarboxylate (**5**) [8] with a mixture of **3** and **4** using sodium carbonate in dimethylformamide at 100° for 48 hours afforded a mixture of *Z*-isomer **6** and *E*-isomer **7** in a 1:1.5 ratio. It is to be noted that analogous reactions with adenine with a mixture of **3** and **4** have been reported to form the corresponding alkenes resulting from elimination of hydrogen bromide from the initially formed alkyl halide intermediates [7]. The two isomers **6** and **7** were separated by silica gel flash chromatography, eluting with chloroform. Both were colorless liquids, and were isolated in 26% (**6**) and 39% (**7**) yields. The ^{1}H nmr chemical shift of the H-4' (the proton adjacent to the ethoxycarbonyl group on the cyclopropyl ring) served as the diagnostic tool in distinguishing the two isomers. In the *E* isomer **7**, the H-4', which is on the same side as the bromo group on the cyclopropyl ring, absorbed relatively downfield (δ 2.48) as compared to that in the *Z*-isomer **6** (δ 2.19). A similar pattern of chemical shifts was observed for the H-1 proton in the isomeric precursors *(Z)*- and (*E*)-2-bromo-2-bromomethylcyclopropane-1-carboxylate (**3**, δ 2.12; **4**, δ 2.49). The structures **6** and **7** were conclusively established by two-dimensional ^{1}H NOESY. The *Z*-isomer **6** exhibited distinct NOE coupling between H-2 and H-4', whereas no such coupling was present in the *E*-isomer **7**.

Finally, condensation of **7** with excess guanidine in the presence of sodium methoxide in absolute methanol gave the target (*Z*)-1-((2-guanidinocarbamoylcyclopropylidene)methyl)-4,5,7,8-tetrahydro-6*H*-6-iminoimidazo[4,5-*e*][1,3]diazepine-4,8-dione (**1**) as yellowish crystals in 71% yield. The proton and carbon-13 nmr spectral data, elemental microanalyses, and low and high resolution mass spectral data are consistent with structure **1**. The *Z* isomeric structure of **1** was corroborated by 2D ^{1}H NOESY coupled with molecular modeling. The NOESY of **1** indicated strong NOE couplings between H-2 and the two cyclopropyl H-3' protons, and no coupling was present between H-2 and H-4'. While it was easy to rationalize the absence of coupling between H-2 and H-4' in the *Z*-isomer **1** as shown, the observed strong couplings between H-2 and H-3' was more difficult to discern from a planar model. In the absence of the corresponding *E*-isomer for comparison, we had to resort to molecular modeling for a possible explanation. The molecular modeling of both **1** and its *E*-isomer counterpart was performed using Insight^{TM}/Discover^{TM} [9]. The energy-minimized structures revealed that the two H-3' protons in **1** are indeed quite close to H-2, and the measured distances between H-2 and H-3'a or between H-2 and H-3'b are 2.61 Å and 3.22 Å, respectively. On the other hand, the same distances in the *E*-isomer are 4.89 Å and 4.51 Å, respectively. Furthermore, the measured distances between H-2 and H-4' in the *Z*- and *E*-isomers are 4.40

Scheme I



Å and 3.34 Å, respectively. These molecular modeling data are consistent with the observed NOESY results, and attest to the accuracy of the *Z* isomeric structure of **1** as assigned. It is, however, to be noted that **1** can exist in several tautomeric forms in solution. No attempts were made to establish the predominent tautomeric form in either the solid state or solution.

EXPERIMENTAL

The ^1H and ^{13}C nmr spectra were recorded on a General Electric QE-300 NMR spectrometer operating at 300 MHz for ^1H and 75 MHz for ^{13}C. The data are reported in the following format: chemical shift (all relative to tetramethylsilane), multiplicity (s=singlet, d=doublet, dt=double triplet, dd=double doublet, t=triplet, q=quartet, m=multiplet, b=broad, coupling constants, integration and assignment). Elemental microanalyses were performed by Atlantic Microlab, Inc., Norcross, Georgia. Evaporations were done under reduced pressure on a rotary evaporator. Thin layer chromatography was performed on Merck Kieselgel 60 F_{254} (0.2 mm thickness). Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Dry solvents were prepared as follows: methanol was distilled from calcium hydride and was stored over molecular sieves (type 3Å); methylene chloride was distilled from calcium hydride and was stored over molecular sieves (type 3Å); dimethylformamide was dried over calcium oxide and then distilled under reduced pressure from calcium hydride, and was subsequently stored over molecular sieves (type 3Å). All starting materials were purchased from Aldrich Chemical Co. All solvents were reagent grade and were purchased from VWR Scientific. All yields reported are for dry compounds that require no further purification for use in other reactions.

Methyl (*Z*)-1-((1-Bromo-2-carbethoxycyclopropyl)methyl)-imidazole-4,5-dicarboxylate (**6**) and Methyl (*E*)-1-((1-Bromo-2-carbethoxycyclopropyl)methyl)imidazole-4,5-dicarboxylate (**7**).

A mixture of methyl imidazole-4,5-dicarboxylate (**5**) (0.45g, 2.5 mmoles) and potassium carbonate (0.35g, 2.5 mmoles) in 20 ml of anhydrous dimethylformamide was stirred at 100° for 3 hours, then a mixture of ethyl *Z*- and *E*-2-bromo-2-bromomethylcyclopropane-1-carboxylate (**3** and **4**) (1.07g, 3.75 mmoles) was added in portions to the above mixture. It was allowed to stir for another 48 hours at 100°. The reaction mixture was evaporated *in vacuo*. The residue was dissolved in water, the solution was neutralized with 2 *M* hydrochloric acid, and extracted with chloroform. The combined extract, after drying over anhydrous magnesium sulfate, was evaporated to dryness *in vacuo*. The resulting residue was purified by silica gel column chromatography, eluting with chloroform, to give **6** (0.25 g, 26%) and **7** (0.38 g, 39%) as colorless liquids. The following are the spectroscopic and analytical data of the two isomers.

Z-isomer **6** : R_f 0.16 (chloroform:methanol (30:1)); ^1H nmr (deuteriochloroform): δ 7.84 (s, 1H, imidazole), 4.68 (d, J = 15.0 Hz, 1H, H-1'), 4.55 (d, J = 15.0 Hz, 1H, H-1'), 4.21 (q, J = 6.9 Hz, 2H, OCH_2), 3.95 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 2.19 (dd, J_{cis} = 9.3 Hz, J_{trans} = 7.2 Hz, 1H, H-4'), 1.83 (t, $^2J = {}^3J_{trans}$ = 6.9 Hz, 1H, H-3'), 1.57 (dd, ^2J = 6.9 Hz, J_{cis} = 9.3 Hz, 1H, H-3'), 1.29 (t, J = 6.9 Hz, 3H, CH_3); ^{13}C nmr (deuteriochloroform): δ 14.20 (CH_3), 20.08 (C-3'), 27.43 (C-4'), 36.35 (C-2'), 52.27 (OCH_3), 52.63 (OCH_3), 55.61 (C-1'), 61.66 (OCH_2), 140.10, 140.20 and 140.20 (imidazole carbons), 160.96 and 162.59 (COOMe), 167.65 (COOEt); ms: (FAB) m/z 389, 391 (MH^+); hrms (FAB) m/z Calcd. for $C_{14}H_{18}{}^{79}BrN_2O_6$: 389.0348; Found: 389.0364; Calcd. for $C_{14}H_{18}{}^{81}BrN_2O_6$: 391.0330; Found: 391.0344.

E-isomer **7** : R_f 0.23 (chloroform:methanol (30:1)); ^1H nmr (deuteriochloroform): δ 7.65 (s, 1H, imidazole), 5.09 (d, J = 15.3

Hz, 1H, H-1'), 4.70 (d, J = 15.3 Hz, 1H, H-1'), 4.22 (q, J = 7.2 Hz, 2H, OCH_2), 3.95 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 2.48 (dd, J_{cis} = 9.3Hz, J_{trans} = 7.2 Hz, 1H, H-4'), 1.78 (m, 2H, H-3'), 1.32 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C nmr (deuteriochloroform): δ 14.10 (CH_3), 23.71 (C-3'), 29.65 (C-4'), 35.05 (C-2'), 50.11 (C-1'), 52.21 (OCH_3), 52.63 (OCH_3), 62.04 (OCH_2), 139.21, 139.30 and 139.30 (imidazole carbons), 160.76 and 162.57 (COOMe), 169.88 (COOEt); ms: (FAB) m/z 389, 391 (MH^+); hrms (FAB) m/z Calcd. for $C_{14}H_{18}{}^{79}BrN_2O_6$: 389.0348; Found: 389.0355; Calcd. for $C_{14}H_{18}{}^{81}BrN_2O_6$: 391.0330; Found: 391.0337.

(*Z*)-1-((2-Guanidinocarbamoylcyclopropylidene)methyl)-4,5,7,8-tetrahydro-6*H*-6-iminoimidazo[4,5-*e*][1,3]diazepine-4,8-dione (**1**).

Guanidine hydrochloride (0.33g, 3.5 mmoles) was added to a solution of a mixture of methyl (*E*)-1-((1-bromo-2-carbethoxycyclopropyl)methyl)imidazole-4,5-dicarboxylate (**7**) (0.35 g, 0.89 mmole) and 1 ml of 25% sodium methoxide solution (4.6 mmoles) in 30 ml of absolute methanol. The mixture was stirred at room temperature for 48 hours, filtered if necessary, and the clear filtrate was purified by rotating disk chromatography on a Chromatotron™ (silica gel plate, 2 mm thickness), eluting with methanol. Appropriate uv-absorbing fractions were collected and evaporated to yield **1** as yellowish crystals (200 mg, 71%); R_f 0.53 (silica gel, chloroform:methanol:30% ammonium hydroxide (2:2:1)); mp >250 °C; ^1H nmr (deuteriodimethylsulfoxide): δ 8.44 (s, 1H, imidazole), 7.87 (br s, 1H, H-1'), 7.55 (br s, 5H, NH, exchangeable with D_2O), 7.28 (br s, 1H, NH, exchangeable with D_2O), 7.01 (br s, 1H, NH, exchangeable with D_2O), 2.30 (m, J = 6.0 and 2.4 Hz, 1H, H-4'), 1.65 (m, 1H, H-3'), 1.54 (m, 1H, H-3'); ^{13}C nmr (deteriodimethylsulfoxide): δ 8.48 (C-3'), 22.94 (C-4'), 111.61 (C-1'), 118.26 (C-2'), 138.53, 138.61, 139.27, 139.37, 139.37 (C-2, 3a, 4, 8, 8a), 151.92 (C-6), 158.51 (C-7'), 172.64 (C-5'); ms: (FAB) m/z 317 (MH^+); hrms (FAB): Calcd. for $C_{12}H_{13}N_8O_3$: 317.1111; Found: 317.1118.

Anal. Calcd. for $C_{12}H_{12}N_8O_3$: C, 45.57; H, 3.82; N, 35.43. Found: C, 45.63; H, 4.03; N, 35.67.

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