Synthetic and tautomeric studies of 5-amino-2,3-dihydro-1,2,4-oxadiazol-3-one

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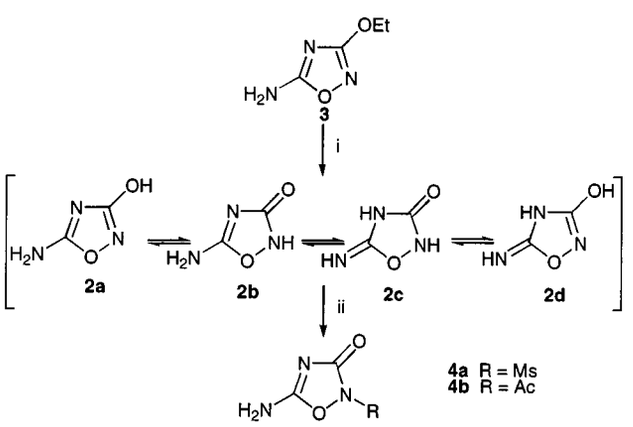
5-Amino-2,3-dihydro-1,2,4-oxadiazol-3-one **2** was synthesized as an analogue of cytosine. Among the possible four tautomers it was established by spectroscopic methods and *ab initio* calculations that it exists as a lactam form **2b** like cytosine. The NH is more acidic than NH_2, thus it could be regioselectively mesylated and acetylated under basic conditions.

Introduction

Comparison between –CH=CH– of benzenoid hydrocarbons and either the divalent –S– or –O– in their sulfur and oxygen containing counterparts is a well-known subject within benzenoid hydrocarbon and heterocyclic chemistry. New analogues of pyrimidine bases are of interest as potential biologically active agents. On this basis, we have previously studied 5-amino-2,3-dihydro-1,2,4-thiadiazol-3-one **1**[1–5] as an analogue of cytosine. As an extension of our work, we report our synthetic and tautomeric results on 5-amino-2,3-dihydro-1,2,4-oxadiazol-3-one **2,** which is the oxygen counterpart of **1**. Tautomeric structures of pyrimidine bases are of great importance and significance in view of the relationship between structure and reactivity.[6]

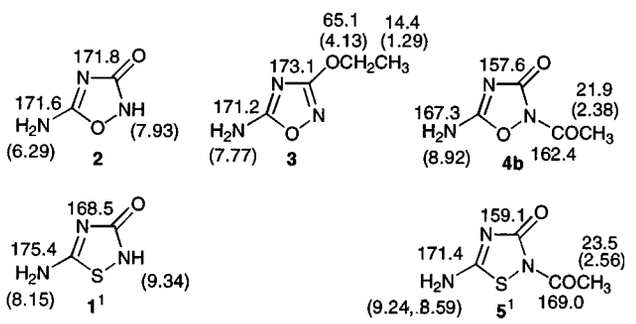
Results and discussion

Target compound **2** was synthesized *via* cleavage of the ethyl group in 5-amino-3-ethoxy-1,2,4-oxadiazole **3** by boron tribromide[7] in 70% yield (Scheme 1). The preparation of



Scheme 1 *Reagents and conditions*: i, BBr_3, CH_2Cl_2, −15 °C, 6 h; ii, RCOCl, base.

5-amino-3-ethoxy-1,2,4-oxadiazole **3** was accomplished following a literature procedure,[8] the melting point of **3** being identical with that reported. However, the same dealkylation method (HCl–dioxane),[9–11] which was applied to the formation of 2,3-dihydro-1,3,4-thiadiazol-2-ones from alkoxy-1,3,4-thiadiazoles failed for **3**. The heteronuclear multiple bond correlation (HMBC) experiment[12] was performed for **3** to determine the chemical shifts of the two ring carbons. The experiment was optimized for a long-range ^1H–^{13}C coupling of 7 Hz. These traces show that the CH_2 interacts with the carbon absorbing at 173.1 ppm (C(3)). Thus, the ^{13}C chemical shifts of C(3) and C(5) could be assigned as 173.1 and 171.2 ppm, respectively (Scheme 2).



Scheme 2 δ_H (400 MHz; DMSO-d_6; Me_4Si), δ_C (100 MHz; DMSO-d_6; Me_4Si).

The structure of **2** was verified to be 5-amino-2,3-dihydro-1,2,4-oxadiazol-3-one by ^1H and ^{13}C NMR and IR spectroscopy. In the ^1H NMR, the disappearance of the ethyl group of **3** and appearance of the NH (7.93 ppm) signal of **2** served as supporting evidence for the deethylation of **3** to give **2**. The ^{13}C NMR contains signals for the two ring carbons at 171.8 and 171.6 ppm respectively.

Compound **2** can theoretically exist in four tautomeric forms, **2a–d** (Scheme 1). The ^1H NMR spectrum presents evidence that **2** exists as either a lactam or a lactim because only two peaks appear in the ratio 2:1. However, structure **2c** containing three different hydrogens cannot be entirely excluded because the two amide NHs might have very similar chemical shifts and therefore appear as one signal. ^{13}C NMR spectroscopy is a sensitive technique for the investigation of tautomerism. It has been demonstrated in purine and pyrimidine that the ^{13}C chemical shift for a lactam carbonyl lies upfield from those of a lactim.[13] In the same way, the ^{13}C chemical shift of C(3) in **2** shows a lower chemical shift than that of **3**. It indicates that **2** exists as a stable lactam form, either **2b** or **2c**. A conjugated enamine with a carbonyl group is a more stable lactam structure than an unconjugated imine. Consequently, **2** exists as a stable lactam form **2b** like cytosine and **1**.

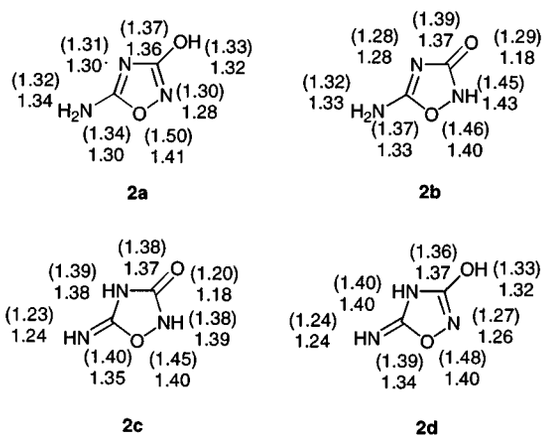
We conducted *ab initio* calculations on the tautomers of 5-amino-2,3-dihydro-1,2,4-oxadiazol-3-one **2a–d** with the GAUSSIAN94 package[14] on a Cray Y-MP C916 supercomputer. Standard 3-21G* and 6-31G* basis sets[15] were used to optimize geometries at the Hartree–Fock (HF) level.

Table 1 Relative energies (in Kcal mol^{-1}) and total energies (in arbitrary units) for **2a–d** tautomers

	2a	2b	2c	2d
MP4//HF/6-31G*[a]	1.00	0.00	7.13	24.68
	(−391.652904)[b]	(−391.654505)[b]	(−391.643146)[b]	(−391.615169)[b]
MP2//HF/6-31G*[a]	0.55	0.00	7.45	25.08
	(−391.586657)[b]	(−391.587527)[b]	(−391.575650)[b]	(−391.547565)[b]
MP2//HF/3-31G*[a]	5.81	0.00	5.10	19.63
	(−389.035249)[b]	(−389.044507)[b]	(−389.036382)[b]	(−389.013218)[b]

[a] MP4//HF/6-31G* and MP2//HF/6-31G* (3-21G*) represent an MP4 and an MP2 single point calculation at the HF optimized geometry with 6-31G* (3-21G*) basis set respectively. [b] The values in parentheses are total energies.

Second-order (MP2) and fourth-order Möller–Pleset perturbation (MP4) calculations were carried out at the HF optimized geometries to obtain improved energy comparisons. The calculated total energies and relative energies of the tautomers studied at the MP2 and the MP4 levels are given in Table 1. The changes in molecular geometry associated with lactam–lactim tautomerism are similar in both basis sets (Scheme 3). The ring



Scheme 3 Optimized bond distances (in Å) at the HF/6-31G* and HF/3-21G* (the values in parentheses) levels.

structure is almost planar. The significant changes are in the C–O bond distance and C–N bond distance. The optimized C(3)–O(7) distance of 1.32 Å at 6-31G* in **2a** is shortened to 1.18 Å in **2b** on account of the double bond. The N(2)–C(3) bond distance of 1.28 Å in **2a** increases by 0.15 Å in the C–N single bond distance of 1.43 Å in the **2b** tautomer. These results are in good agreement with other *ab initio* studies on the tautomerism of the pyrimidine bases.[2,10,11,16] The most stable tautomer is **2b** at both the 3-21G* and 6-31G* levels, in good agreement with spectroscopic results.

Like **1**[1,2] and 5-amino-2,3-dihydro-1,3,4-thiadiazol-2-one[10,17] the hydrogen at the 2-position in **2** is more acidic than the amino group. Compound **2** was mesylated and acetylated under basic conditions to form 5-amino-2-mesyl-2,3-dihydro-1,2,4-oxadiazol-3-one **4a** and 2-acetyl-5-amino-2,3-dihydro-1,2,4-oxadiazol-3-one **4b**, respectively. The structure of **4a** was determined by X-ray crystallography. A drawing of the structure **4a**, showing the atom numbering scheme, is given in Fig. 1.

The amide carbonyl group of **4b** (162.4 ppm) was identified with the HMBC experiment, through its interaction with the methyl group. Compound **4b** was confirmed by comparison of the ^{13}C chemical shifts of 2-acetyl-5-amino-2,3-dihydro-1,2,4-thiadiazol-3-one **5**[1] (Scheme 2).

Experimental

All melting points were obtained using an electrically heated Thomas–Hoover capillary melting point apparatus and were uncorrected. The ^{1}H and ^{13}C NMR spectra were obtained using a Bruker ARX-400 spectrometer at 400 MHz and 100 MHz

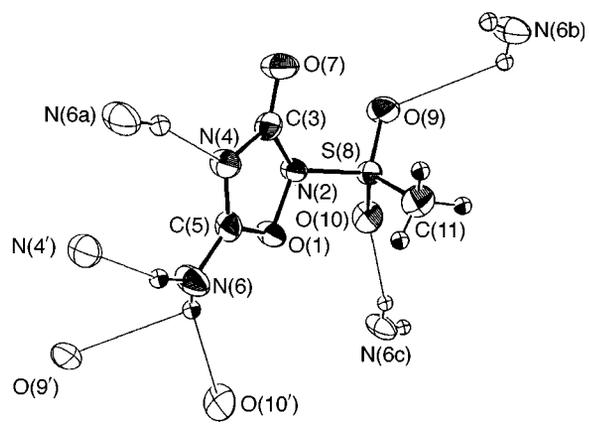


Fig. 1 ORTEP drawing of 5-amino-2-mesyl-2,3-dihydro-1,2,4-oxadiazol-3-one **4a**, showing the atomic numbering used for the crystallographic analysis.

respectively with tetramethylsilane as reference. IR spectra were recorded on a Jasco Report-100 infrared spectrophotometer. Elemental analyses were carried out on an Elementar Analysensysteme GmbH Vario EL at the Korea Basic Science Institute, Seoul, Korea. Most of the commercially available starting materials and solvents were purchased from Aldrich Chemical Company.

5-Amino-3-ethoxy-2,3-dihydro-1,2,4-oxadiazol-3-one 3

Compound **3** was obtained by the procedure described in the literature[8] as a white precipitate (61% from H_2O), mp: 115–116 °C (lit.[8] 114–114.5 °C) (Found: C, 36.5; H, 5.6; N, 32.3. $C_4H_7N_3O_2$ requires C, 37.2; H, 5.5; N, 32.5%); ν_{max} KBr/cm^{-1} 3250, 3175 (NH), 3025, 2975 (CH), 1710, 1680 (NH), 1580 (C=N), 1040 (C–O); δ_H (400 MHz; DMSO-d_6; Me_4Si) 7.77 (br, 2H, NH_2), 4.13 (q, 2H, CH_2, J = 7.0), 1.29 (t, 3H, CH_3, J = 7.1); δ_C (100 MHz; DMSO-d_6; Me_4Si) 173.1 (*C*–OEt), 171.2 (C=N), 65.1 (CH_2), 14.4 (Me).

5-Amino-2,3-dihydro-1,2,4-oxadiazol-3-one 2

Under N_2 atmosphere, compound **3** (1 g, 7.7 mmol) was suspended in CH_2Cl_2 (25 cm^3). A solution of BBr_3 (8.4 cm^3, 8.4 mmol, 1 M hexane solution) was added dropwise at −15 °C. The resulting mixture was stirred for 2 h at the same temperature then for 6 h at room temperature. The mixture was poured into ice–water and the resulting solid filtered and dissolved in 2 M NaOH. The solution was acidified with dilute hydrochloric acid to precipitate **2** (0.55 g, 70%); mp: 205–206 °C (Found: C, 23.3; H, 3.1; N, 41.1. $C_2H_3N_3O_2$ requires C, 23.8; H, 3.0; N, 41.6%); ν_{max} KBr/cm^{-1} 3250 (NH), 2750, 1660 (C=O), 1590 (C=N); δ_H (400 MHz; DMSO-d_6; Me_4Si) 7.93 (br, 1H, NH), 6.29 (br, 2H, NH_2); δ_C (100 MHz; DMSO-d_6; Me_4Si) 171.8 (C=O), 171.6 (C=N).

5-Amino-2-mesyl-2,3-dihydro-1,2,4-oxadiazol-3-one 4a

Compound **2** (0.5 g, 5 mmol) was dissolved in 2 M NaOH solution (10 cm^3) and mesyl chloride (0.45 cm^3, 5.9 mmol) was

added. After stirring for 18 h, the precipitate was filtered and recrystallized from water to give **4a** (0.22 g, 25%); mp: 182 °C (Found: C, 19.8; H, 2.7; N, 23.1; S, 17.9. $C_3H_5N_3O_4S$ requires C, 20.1; H, 2.8; N, 23.5; S, 17.9%); ν_{max} KBr/cm^{-1} 3350, 3180 (NH), 3030, 2945 (CH), 1769 (NH), 1673 (C=O), 1576 (C=N); δ_H (400 MHz; DMSO-d_6; Me_4Si) 9.29 (br, 2H, NH_2), 3.38 (s, 3H, Me); δ_C (100 MHz; DMSO-d_6; Me_4Si) 170.7 (C=N), 162.2 (C=O), 36.9 (Me).

2-Acetyl-5-amino-2,3-dihydro-1,2,4-oxadiazol-3-one 4b

Compound **2** (0.3 g, 3 mmol) was suspended in anhydrous pyridine (10 cm^3) at −5–0 °C. Acetyl chloride (0.21 cm^3, 3 mmol) was added dropwise to the stirred mixture over 6 h. The mixture was then poured into ice–water. The resulting solid was filtered and recrystallized from pyridine to give **4b** (0.27 g, 65%); mp: 198 °C (Found: C, 33.4; H, 3.55; N, 29.3. $C_2H_3N_3O_2$ requires C, 33.6; H, 3.5; N, 29.4%); ν_{max} KBr/cm^{-1} 3265 (NH), 3101 (CH), 1735 (NH), 1664 (C=O), 1589 (C=N); δ_H (400 MHz; DMSO-d_6; Me_4Si) 8.92 (br, 2H, NH_2), 2.38 (s, 3H, CH_3); δ_C (100 MHz; DMSO-d_6; Me_4Si) 167.3 (C=N), 162.4 (amide C=O), 157.6 (C=O), 21.9 (CH_3).

X-Ray crystal structure of 4a †

The structure was determined by the application of the direct method SHELXS 86[18] (all non-H atoms) and refined by full matrix least-squares (SHELXL 97[19]). Hydrogen atoms were located from ΔF synthesis and positionally refined. Final R_1 [$F \geq 4\sigma(F)$] and wR_2 [all data] were 0.0354 and 0.0848 for 120 refined parameters, $S[F^2]$ 0.986. And $(\Delta/\sigma)_{max}$ was 0.000. Maximum and minimum features in ΔF synthesis are 0.250 and −0.409 e Å^{-3}, respectively.

Acknowledgements

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† Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc.*, *Perkin Trans. 2*, available *via* the RSC web page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 188/149. See http://www.rsc.org/suppdata/perkin2/1999/81/ for crystallographic files in .cif format.

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