Synthesis and Structural Insights of Novel 2-Diethylamino-6-methyl-4(*3H*)-pyrimidinones

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Abstract: The synthesis of three previously unknown 2-diethylamino-6-methyl-4(*3H*)-pyrimidinones *via* the condensation reaction of ethyl 2-alkylacetoacetates with *N,N*-diethylguanidine is described. The reported compounds, 5-ethyl- 1, 5-*n*-propyl- 2, and 5-*n*-butyl-2-diethylamino-6-methyl-4(*3H*)-pyrimidinone 3, were characterized by ^{1}H and ^{13}C NMR, IR, UV and mass spectrometry, and their tautomerism is discussed and compared with literature data for similar compounds. The results of NOE experiments suggest that in solution 1, 2 and 3, exist predominantly as the 4(*3H*)-lactam tautomers (**N3**).

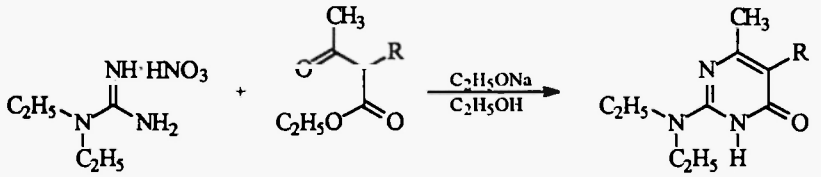
Introduction

Our interest in the synthesis of novel pyrimidinones is justified by their inherent biological activity which might render such compounds as valuable pharmaceuticals or agrochemicals [1]. Previous work from our laboratories led to the preparation of new aminopyrimidinone derivatives which exhibit high toxicity and tested as potential fungicides [2]. These results along with the importance of pyrimidinones in the chemistry of natural compounds [3], encouraged us to pursue this research by reexamining a simple but important principal synthesis of pyrimidinones: the condensation reaction of β-keto esters with guanidines. Most β-keto esters react quite easily with guanidines to form oxopyrimidines [4], but surprisingly, as the unexpected paucity of literature data shows, this facile synthesis has not been fully exploited. We therefore proceeded to use the reaction of various β-keto esters with substituted guanidines systematically, as a trivial but efficient way of preparing novel 4-pyrimidinones [5]. In this work we report the synthesis of three new tautomeric pyrimidinones, 5-ethyl- 1, 5-*n*-propyl- 2, and 5-*n*-butyl-2-diethylamino-6-methyl-4(*3H*)-pyrimidinone 3, by cyclization of ethyl 2-ethyl-, 2-*n*-propyl- and 2-*n*-butyl-acetoacetates with *N,N*-diethylguanidine. Compounds 1, 2, and 3, were characterized by ^{1}H and ^{13}C NMR, IR, UV, MS and elemental analysis, and their tautomerism is discussed and compared with literature data for similar compounds.

Results and Discussion

5-Ethyl- 1, 5-*n*-propyl- 2, and 5-*n*-butyl-2-diethylamino-6-methyl-4(*3H*)-pyrimidinone 3, were synthesized by condensation of the appropriate ethyl 2-alkyl-acetoacetate, 4, 5 or 6, with *N,N*-diethylguanidinium nitrate 7 (Scheme 1). The β-keto esters 4, 5 and 6 were readily available by the reaction of the corresponding alkyl halide with the Na

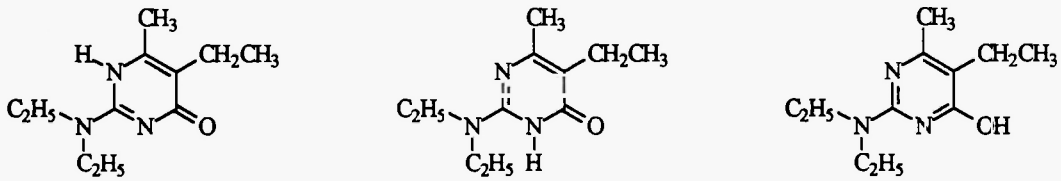
derivative of ethyl acetoacetate [6], and the *N,N*-diethylguanidinium nitrate 7 was prepared from dicthylammonium nitrate and calcium cyanamide [7].



7 4 R = C_2H_5 1 R = C_2H_5
5 R = *n*-C_3H_7 2 R = *n*-C_3H_7
6 R = *n*-C_4H_9 3 R = *n*-C_4H_9

Scheme 1. Synthesis of 2-Diethylamino-6-methyl-4(*3H*)-pyrimidinones.

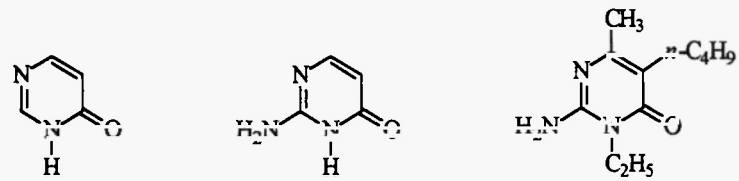
In principle, for each compound three tautomeric forms are possible corresponding to different protonation sites: at the ring nitrogen atoms (the cycloamidic or lactam tautomers, **N1** and **N3**), and at the exocyclic oxygen atom (the enol tautomer, **OH**), (Scheme 2) [8]. The physico-chemical properties of 1, 2 and 3 clearly indicate their existence



N1 **N3** **OH**

Scheme 2. Monomeric Structures for the Enol and Keto Tautomers of 1.

as lactam tautomers (**N1** and/or **N3**) both in solid state and in solution; however, the distinction between the two possible lactam forms (**N1** and/or **N3**) is a difficult task. Comparison of the spectral characteristics of 1, 2 and 3 (^{1}H NMR, UV, IR, vide infra) with those of model compounds such as 4(*3H*)-pyrimidinone 8 and 2-amino-4(*3H*)-pyrimidinone 9 (isocytosine), whose tautomerism has been investigated in detail in various media [9], or with 2-amino-3-ethyl-5-*n*-butyl-



8 9 10

-6-methyl-4(*3H*)-pyrimidinone 10, whose X-ray crystal structure, solved recently by us, shows its existence in solid state in the amino-oxo form [10], suggests but does not necessarily prove, the prevalence of the 4(*3H*)-tautomer (**N3**) in the solid state and in solution. Nevertheless, on the basis of the following data and arguments we conclude that derivatization of the 4-pyrimidinone in 1, 2 and 3 did not lead to higher concentrations of **N1** over **N3**, i.e. **N3** in all cases is the predominant tautomer [11].

The relatively high melting points of the synthesized compounds (123 °C, 121 °C and 107 °C for 1, 2 and 3) as compared to that of pyrimidine (22 °C), suggest their existence in the solid state as cyclic amides (**N1** and/or **N3**). This

conclusion is upheld by strong C=O stretching bands in the 1600-1700 cm^{-1} region of their IR spectra in KBr pellets and in solution. The UV spectra of 1, 2 and 3, display the same general pattern: two absorption bands centered at 230 and 300 nm, in good agreement with the UV spectrum of 9 in aqueous solution where the presence of the cycloamidic forms has been established unambiguously [12,13].

The alkyl substituents at ring positions *5* and *6*, and on the exocyclic N, increased remarkably the solubility of 1, 2 and 3 in organic solvents, and thus, in comparison with 8 and 9, they are not soluble in water. We may conclude that their H-bonding ability is reduced as compared with 8 and 9. Consequently, the low frequency of the C=O absorption band in the IR spectra of 1, 2 and 3, at about 1640 cm^{-1}, can be attributed mostly to resonance interaction with the lone pair of the vicinal nitrogen in the **N3** tautomer, and less to H-bonding by intermolecular association [14]. The C=O group of a ketone absorbs around 1700 cm^{-1}, whereas conjugation in an amide decreases the C=O force constant and lowers the highly coupled (with C-N) C=O absorption to the 1650 cm^{-1} region [15]. The shift of the C=O stretching frequency to lower wavenumbers with intermolecular H-bonding is concentration-dependent and usually disappears at concentrations < 0.01 M (in nonpolar solvents) [14], however, the IR spectra of dilute CCl_4 solutions of 1, 2 and 3, with concentrations varying from 0.1 to 0.001 M, exhibited the same low frequency C=O absorption which did not change considerably upon dilution. The similarity of the IR spectra of 1, 2 and 3 in KBr matrix and in CCl_4 solution, suggests their existence in solid state and in solution in the same tautomeric form, respectively as cycloamides of **N3** type. Accordingly, the other strong band present in the IR spectra of 1, **2** and **3**, at *ca.* 1580 cm^{-1}, can be assigned tentatively to NH bending and deformation, known as "amide II band" [16].

NMR is a "slow" method for observation of individual tautomers which interconvert with low energy barriers; usually those which involve cleavage and formation of H-heteroatom bonds give time-averaged signals [17]. The broad, low field signals in the ^1H NMR spectra of compounds 1, 2 and 3, are concentration dependent, and disappear upon adding D_2O (see Experimental). They are NH peaks and their broadening is attributed to the nuclear quadrupole moment effect of the adjacent nitrogen and/or proton exchange between tautomeric forms in equilibrium. Recent NMR data show chemical shifts of 12.54 ppm for the NH proton of 8 [18] and 11.11 ppm for the NH proton of 9 [19] in DMSO-d_6 as solvent, a medium in which both compounds are known to exist primarily as the **N3** form. Similarly, the NMR signals of the NH protons of 1, 2 and 3 appear around 11.3 ppm, suggesting by analogy the prevalence of the **N3** form, in which the deshielding effect experienced by NH is attributed to charged resonance cycloamidic forms as well as to hydrogen bonding with the carbonyl group. The tautomerism of pyrimidinones 1, 2 and 3 in solution was addressed also by NOE experiments [20]. A positive NOE enhancement (2-3 % in $CDCl_3$ and in DMSO-*d6*) of the NH signal is observed on irradiation of the NCH_2 peak in the ^1H NMR spectra of 1, 2 and 3. This result firmly confirms the presence of keto forms in solution. Irradiation of the 6-methyl (in DMSO-*d6*) did not show any effect at the NH, which indicates a tautomeric preference in solution for the **N3** lactam form [21].

Comparison of the ^{13}C NMR spectra of 1, 2 and 3 with data reported in the literature for other 4-pyrimidinones [22] is not suited, except maybe regarding the presence of keto *vs.* enol forms, since the exocyclic nitrogen in 1, 2 and 3 can change significantly the chemical shifts of the ring carbons. Reports on the ^{13}C NMR of isocytosine 9 and derivatives are old enough to have needed high concentration solutions for analysis, which could be attained only in strongly acidic or basic media [23], and therefore are not suitable for comparison. In general, ^{13}C NMR spectra of fixed (nontautomeric) 4-pyrimidinones of **N1** type as compared with fixed **N3** type show considerable downfield shift of the

carbonyl signal C4 (*ca.* 170 ppm for **N1** type nontautomeric 4-pyrimidinones) [23,24]. In comparison with a variety of natural compounds which contain the isocytosine moiety in fixed **N3** type keto form (chemical shift for the pyrimidinonic carbonyl group between 162 and 164 ppm) [25], compounds 1, 2 and 3 exhibit similar features in their ^{13}C NMR spectra, which seems to be consistent with a **N3** type structure.

Keto-enol tautomerism in appropriate pyrimidinones is well known and a large amount of work has been carried out, both experimentally and theoretically, to elucidate the qualitative and quantitative aspects of pyrimidine tautomerism and to determine the physico-chemical properties of individual tautomers [26]. It has been shown that the tautomeric form adopted depends on molecular environment [26b], and this influence on pyrimidine tautomerism is directly relevant to the role of these heterocyclic compounds on the structure and function of nucleic acids. In this context the presented synthesis of the novel pyrimidinones 1, 2 and 3, along with elucidation of their structure, besides exploiting a facile and productive route to new compounds with potential biological activity, may bring insights to the phenomenon of tautomerism. The biological testing of such new compounds might lead to the discovery of valuable pharmaceuticals and agrochemicals.

Experimental

Solvents were distilled and/or stored over 4 Å molecular sieves prior to use. All other reagents were used as obtained from commercial sources or purified according to standard procedures. Melting points were measured on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The IR spectra were recorded using a Mattson-Galaxy FT-IR 3000 spectrometer. ^1H and ^{13}C NMR spectra were recorded at ambient temperature on a Gemini 300 MHz spectrometer and were referenced to solvent signals. Data were reported as follows: chemical shift in ppm on the δ scale, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hertz. Mass spectra were obtained using a VG Trio-1 GC-MS spectrometer. The UV spectra were recorded on a Shimadzu UV-VIS Spectrophotometer UV-160, in 1 cm cuvettes using 2 ml of 5×10^{-3} M solutions of each of the three compounds in ethanol:water (1:1). Elemental analyses were performed by The Center for Fundamental Materials Research, MSU, East Lansing, MI. Compounds 4, 5, 6, and 7, were prepared according to literature procedures [7-8] and characterized by ^1H NMR.

General Procedure. To a stirred solution of sodium ethoxide (11 mmoles) in dry ethanol (100 ml) was added 1.96 g of *N,N*-diethylguanidinium 7 nitrate (11 mmoles) and the mixture was refluxed for 30 minutes, cooled in an ice bath and filtered. To the filtrate were added dropwise 11 mmoles of ethyl 2-alkylacetoacetate (vacuum distilled) 4, 5 or 6, under stirring, and the reaction mixture was refluxed for 12 hours. After cooling, 50 ml of water were added and the yellow solution was carefully acidified with glacial acetic acid until neutral to litmus paper. The mixture was worked up either by column chromatography over silica gel with hexane/ether (10:1, v/v), or by continuous extraction with CH_2Cl_2 for 24 hours. Removal of solvent on a rotary evaporator gave a crystalline residue of 1, 2 or 3, which was purified further by recrystallization from CH_3NO_2 (yield after recrystallization: 56%, 54% and 44% for 1, 2 and 3).

2-Diethylamino-5-ethyl-6-methyl-4(*3H*)-pyrimidinone 1 was obtained as white needle crystals, mp 123 °C; UV λ_{max} ($\varepsilon_{max} \times 10^{-3}$): 230 nm (25), 280 nm (20); IR (KBr): 3209 (NH), 1637 (C=O), 1593 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 11.2 (s, 0.8H, exchangeable), 3.53 (q, *J* = 7.1 Hz, 4H), 2.39 (q, *J* = 7.4 Hz, 2H), 2.16 (s, 3H), 1.16 (t, *J* = 7.1 Hz, 6H), 1.01 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 165.56, 162.49, 150.53, 111.96, 41.73, 21.83, 18.39, 13.45, 13.18; MS (EI) m/z for $C_{11}H_{19}N_3O$ 209 (49), 194 (91), 180 (100), 166 (52), 137 (24), 96 (12). *Anal.* Calcd. for $C_{11}H_{19}N_3O$: C, 63.15; H, 9.09; N, 20.09. Found: C, 62.94; H, 8.94; N, 20.06.

2-Diethylamino-6-methyl-5-*n*-propyl-4(*3H*)-pyrimidinone 2 was obtained as white needle crystals, mp 121 °C; UV λ_{max} ($\varepsilon_{max} \times 10^{-3}$): 232 nm (34), 310 nm (12); IR (KBr): 3242 (NH), 1649 (C=O), 1581 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 11.35 (s, 0.82 H, exchangeable), 3.53 (q, *J* = 7.1 Hz, 4H), 2.34 (t, J = 7.7 Hz, 2H), 2.16 (s, 3H), 1.44 (m, J_1 = 7.7 Hz and J_2 = 7.4 Hz, 2H), 1.16 (t, *J* = 7.1 Hz, 6H), 0.91 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 165.89, 162.80, 150.57, 110.45, 41.67, 27.25, 22.23, 22.06, 14.20, 13.16; MS (EI) m/z for $C_{12}H_{21}N_3O$ 223 (20), 208 (19), 195 (11), 194 (100), 180 (15), 151 (8), 96 (13). *Anal.* Calcd. for $C_{12}H_{21}N_3O$: C, 64.57; H, 9.41; N, 18.83. Found: C, 64.30; H, 9.15; N, 18.92.

5-*n*-Butyl-2-diethylamino-6-methyl-4(*3H*)-pyrimidinone 3 was obtained as white needle crystals, mp 107 °C; UV λ_{max} ($\varepsilon_{max} \times 10^{-3}$): 230 nm (27), 300 nm (10); IR (KBr): 3211 (NH), 1642 (C=O), 1577 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 11.3 (s, 0.64H, exchangeable), 3.54 (q, *J* = 7.1 Hz, 4H), 2.35 (t, J = 7.7 Hz, 2H), 2.15 (s, 3H), 1.25-1.45 (m,

4H), 1.16 (t, J = 7.1 Hz, 6H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 165.61, 162.74, 150.44, 110.76, 41.70, 31.31, 24.98, 22.87, 22.03, 14.06, 13.17; MS (EI) m/z for $C_{13}H_{23}N_3O$ 237 (56), 222 (49), 209 (12), 208 (84), 195 (28), 194 (1001), 166 (18), 165 (13), 164 (12), 96 (21). *Anal.* Calcd. for $C_{13}H_{23}N_3O$: C, 65.82; H, 9.70; N, 17.72. Found: C, 65.64; H, 9.53; N, 17.59.

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