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PREPARATION OF 5-AMINO-7(6H)-FURAZANO[3,4-d]PYRIMIDINONE AN ANALOG OF PTERIN[1]

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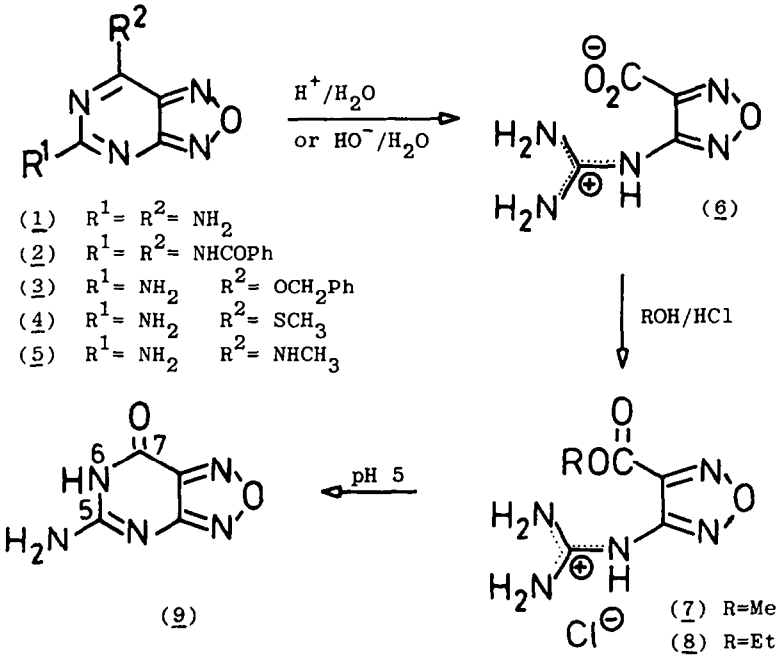
ABSTRACT - 5-Aminofurazano[3,4-d]pyrimidines carrying a variety of substituents at position 7 suffer ring cleavage by either acid or base to give 4-guanidino-3-furazancarboxylic acid (6), the esters of which can be recyclised to give the pterin analog 5-amino-7(6H)-furazano[3,4-d]pyrimidinone (9). The pyrimidine ring of (9) is cleaved by hydrolysis, and the furazan ring by hydrogenolysis.

The simple furazan, or 1,2,5-oxadiazole, ring system has been known for a long time, as have benzene fused derivatives of it. Furazans fused to other heterocyclic ring systems are less common, however, and furazano [3,4-d]pyrimidines remained largely unstudied until quite recently, when Taylor *et al*. developed a new general method for their preparation,[2] and recognised their great potential for the synthesis of other heterocycles.[2,3,4] Furazano[3,4-d]pyrimidines are isoelectronic with pteridines, and can also be considered as pteridine analogs in which the pteridine 6 and 7 carbon atoms have been replaced by an oxygen atom. Practically all the furazano[3,4-d]pyrimidines which have been reported in the literature, however, carry a nitrogen substituent at position 7, and we know of only three examples of 7-oxo compounds.[2,5,6] The 7-oxo compound, 5-amino-7(6H)-furazano[3,4-d]pyrimidinone (9) has never been described, although it should be of particular interest, since it corresponds in substitution pattern to the very common naturally occurring pterin system, as found, for example, in the folates.

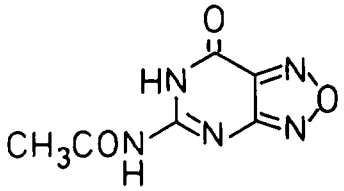
Furazanopyrimidines (1) and (2) have already been described[2,4] and we prepared furazanopyrimidines (3) and (4) by lead tetraacetate oxidation[2] of 2,4-diamino-6-benzyloxy-5-nitrosopyrimidine and 2,4-diamino-6-methylthio-5-nitrosopyrimidine, respectively. In a search for the 5-amino-7-oxo compound (9) we subjected the four furazanopyrimidines, (1) - (4), to various hydrolytic conditions, both acidic and basic. In no case could any 5-amino-7(6H)-furazano[3,4-d]pyrimidinone (9)



be isolated, however, and every reaction was found to give the same ring cleaved product, 4-guanidino-3-furazancarboxylic acid (6), sometimes in over 90% yield. Beardsley[7] had earlier obtained the same product by acid hydrolysis of (1) and (5). Compound (6) is a very high melting solid, insoluble in organic solvents and in water, but soluble in aqueous acid or base. We write it in its zwitterionic form. Its u.v. spectrum shows only two maxima in aqueous sodium hydroxide, at 235 and 273 nm, and this pattern is different from that expected for either a furazano[3,4-d]pyrimidine[2] or a 7(6H)-furazano[3,4-d]pyrimidinone, both of which would show a strong absorption band above 300 nm.
Compound (6) could be converted readily into both a sodium and a hydrochloric acid salt, each of which regenerated (6) when its aqueous solution was neutralised. Compound (6) was also converted easily into its corresponding methyl (7) or ethyl (8) ester by refluxing it in methanolic or ethanolic hydrogen chloride respectively. Both esters were isolated as their mono hydrochlorides, which dissolved in water to give acidic solutions. These solutions were stable at room temperature but if heated they decomposed to regenerate (6). The same solutions rapidly decomposed if the pH was brought up to about 9. We found however, that careful neutralisation of aqueous solutions of esters (7) and (8) to pH 5 and boiling for a few minutes promoted a clean intramolecular cyclisation to afford the desired 5-amino-7-oxo compound (9) in good yield.

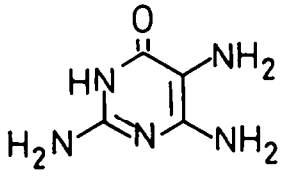
The u.v. spectrum of 5-amino-7(6H)-furazano[3,4-d]pyrimidinone (9) showed a strong high wavelength absorption band at 325 nm, as well as bands at 221 and 273 nm, and this pattern speaks for the presence of a fused ring furazanopyrimidine system, rather than a simple unfused furazan ring. The proton n.m.r. spectrum of (9) in dimethylsulphoxide showed only a single broad exchangeable peak at 7.13 p.p.m. The carbon-13 n.m.r. spectrum measured in the same solvent was more informative,

however, and showed the presence of four distinguishable carbon atoms Compound (9) was very susceptible to cleavage of the pyrimidine ring. Treatment of it with 5% aqueous hydrochloric acid regenerated the guanidinofurazan carboxylic acid (6), while heating it in solutions of dry hydrochloric acid in the appropriate alcohol gave esters (7) and (8). These reactions demonstrate the presence of the furazan ring in (9). Treatment of (9) with acetic anhydride converted it into its acetate (10), which could also be obtained directly from (6) by boiling the latter in acetic anhydride. Acetate (10) was also very susceptible to cleavage of the pyrimidine ring, and all attempts to convert it back into (9) yielded only the ring cleaved product (6).



(10)

The presence of an intact pyrimidine ring in compounds (9) and (10) was proved by hydrogenolysis experiments, which cleaved the furazan ring. Thus, hydrogenation of (9) in 0.1 M sodium hydroxide with palladised charcoal gave 2,4,5-triamino-6(1H)-pyrimidinone (11). isolated as its sulphuric acid salt. Hydrogenation of (9) in glacial acetic acid, followed by heating the reaction mixture, gave the known[8] 5-acetamido-2,4-diamino-6(1H)-pyrimidinone (12) in almost quantitative yield. This product was hydrolysed to (11) with sulphuric acid. Finally, hydrogenation in acetic acid of (10), the acetate derivative of (9), afforded 2,5-diacetamido-4-amino-6(1H)-pyrimidinone (13). This diacetyl derivative of (11) has not so far been reported. The disposition of the two acetamido groups in it is assigned on the basis of the known greater nucleophilicity of a 5-amino group as compared with a 4-amino group on a pyrimidine nucleus, and also by analogy with the formation of monoacetate (12) from (9). Hydrolysis of diacetate (13) in 20% sulphuric acid afforded 2,4,5-triamino-6(1H)-pyrimidinone (11).



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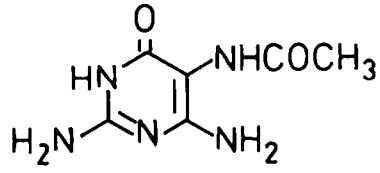

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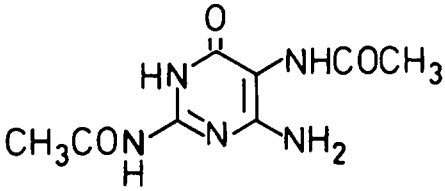

(13)

The susceptibility to hydrolytic cleavage of the pyrimidinone ring in the 7-oxofurazanopyrimidines depends markedly on the nature of the substituent at position 5, and this correlates with their observed lactam carbonyl stretching frequency (Table). The very high frequency for 5-acetamido-7(6H)-furazano[3,4-d]pyrimidinone (10), and to a lesser extent for 5-amino-7(6H)-furazano[3,4-d]pyrimidinone (9), shows that the carbon oxygen bond in these compounds must have a very high degree of double bond character, with a corresponding low degree of double bond character for the N^6-C^7 bond.

This is directly reflected in the great ease with which both of these compounds suffer cleavage at the N^6-C^7 bond under acidic conditions, and probably explains why they have not been isolated before. 5-Phenyl-7(6)-furazano[3,4-d]pyrimidinone, on the other hand, has a lower lactam carbonyl stretching frequency, and is reported to be relatively stable towards ring cleavage in acid solution.[2,9]

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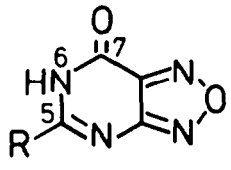
TABLE

Lactam carbonyl stretching frequencies



R	cm^{-1}	Ref.
H	1698	6
Ph	1710	9
NH_2	1725	
$NHCOCH_3$	1745	

EXPERIMENTAL

^{13}C n.m.r. spectra were measured on a Bruker WP-80 instrument, and ^1H n.m.r. spectra either on this instrument or on a JEOL PMX-60. Chemical shifts were determined relative to tetramethylsilane. U.v. spectra were recorded using a Pye Unicam SP8-200 spectrophotometer, and i.r. spectra using a Perkin-Elmer 298 spectrophotometer.

5-Amino-7-benzyloxyfurazano[3,4-d] pyrimidine (3). 2,4-Diamino-6-benzyloxy-5-nitrosopyrimidine[10] (1.56 g, 6.36 mmol) was suspended in acetic acid (25 ml) under an atmosphere of nitrogen, and lead tetraacetate (3.13 g, 7.06 mmol) added over a period of 0.5 h. The resulting suspension was stirred under nitrogen for 12 h, by which time the colour had changed from purple to yellow. The suspended solid product was filtered off. Evaporation of the filtrate to dryness and trituration of the residue with water (25 ml) gave more product. Crystallisation from acetone/ethanol afforded yellow prisms of 5-amino-7-benzyloxyfurazano[3,4-d] pyrimidine (3) (1.47 g, 95%), m.p. 214°C (decomp.) (Found: C, 54.10 H, 3.97; N, 28.96. $C_{11}H_9N_5O_2$ requires C, 54.32; H, 3.73; N, 28.80%); $\nu_{max.}$ (nujol) 3400, 3330, 3160, 1655, and 1630 cm^{-1}; $\lambda_{max.}$ (EtOH) 218, 256, and 340 nm (log ε 4.15, 3.74, and 3.52); δ_H (80 MHz; d_6-dmso) 5.64 (2H, s, CH_2), 7.47 (5H, m, Ph), 7.88 (2H, br s); δ_C (20 MHz; d_6-dmso) 69.6, 128.8, 128.9, 129.2, 135.0, 135.2, 160.4, 162.9, and 163.1.

5-Amino-7-methylthiofurazano[3,4-d] pyrimidine (4). - 2,4-Diamino-6-methyl thio-5-nitrosopyrimidine[11] (16.6 g, 0.76 mol) was suspended in acetic acid (150 ml) under an atmosphere of nitrogen, and lead tetraacetate (43.02 g) 0.077 mol) added over a period of 0.5 h The resulting suspension was stirred

under nitrogen for 12 h, by which time the colour had changed from blue to yellow. The suspended solid product was filtered off and the filtrate evaporated to dryness and the residue triturated with water to afford more product. Crystallisation from acetone and water using charcoal gave greenish yellow needles of 5-amino-7-methylthio furazano[3,4-d]pyrimidine (4) (12.8 g, 78%), m.p. 228-29°C (Found: C, 32.81 H, 2.75; N, 37.80; S, 17.32. $C_5H_5H_5S$ requires C, 32.78; H, 2.75; N, 38.23; S, 17.50%); $\nu_{max.}$ (nujol) 3450, 3290, 3150, 1630, and 1595 cm^{-1}; $\lambda_{max.}$ (EtOH) 210, 304, and 360 nm (log ε 4.31, 3.91, and 3.70); δ_H (60 MHz; d_6-dmso) 2.72 (3H, s, CH_3), 7.83 (2H, br s, NH_2); δ_C (20 MHz; d_6-dmso) 11.9, 138.6, 160.2 161.1, and 167.1.

4-Guanidino-3-furazancarboxylic acid (6)

(a) 5,7-Diaminofurazano[3,4-d]pyrimidine (1)[2] (6.07 g, 39.9 mmol) was added to a mixture of water (30 ml) and conc. hydrochloric acid (20 ml) and the suspension refluxed for 2 h. The reaction mixture was cooled and the precipitated solid collected, washed with water and dried to give pure 4-guanidino-3-furazancarboxylic acid (6) (6.47 g, 95%), m.p. 300°C (decomp.) (Found: C, 28.42; H, 3.19; N, 41.36. $C_4H_5N_5O_3$ requires C, 28.07; H, 2.94; N, 40.92%); $\nu_{max.}$ (nujol) 3380, 3350, 3180, 3080, 1690, and 1670 cm^{-1}; $\lambda_{max.}$ (0.1M NaOH) 235 and 273 nm (log ε 3.88 and 3.58).

(b) 5,7-Dibenzamidofurazano[3,4-d] pyrimidine (2)[4] (2.86 g, 7.94 mmol) was suspended in water and aqueous sodium hydroxide (5 M) added dropwise until all solid material had dissolved. The solution was refluxed for 1 h, cooled, and neutralised with dilute hydrochloric acid. The precipitated solid was collected and washed with water and acetone to give pure (6) (1.07 g, 88%).

(c) 5-Amino-7-benzyloxyfurazano[3,4-d] pyrimidine (3) (0.34 g, 1.40 mmol) was suspended in a solution of sodium hydroxide (0.81 g, 20.2 mmol) in water (40 ml) and the mixture refluxed for 1.5 h. The solution was cooled and neutralised with dilute hydrochloric acid. The precipitated solid was collected, washed with water, and dried, to give (6) (0.31 g, 54%).

(d) 5-Amino-7-methylthiofurazano[3,4-d] pyrimidine (4) (0.50 g, 3 mmol) was warmed in concentrated aqueous hydrochloric acid (10 ml) for 4 hr. After cooling, the precipitate was collected, washed with water, and dried, to give (6) (0.45 g, 95%).

The sodium salt of (6) was prepared by dissolving the latter in the minimum volume of warm 0.4M aqueous sodium hydroxide and then allowing the solution to cool. The precipitated solid was collected, washed with water, and dried. m.p. >300°C (decomp.); $\nu_{max.}$ (nujol) 3580, 3490, 3450, 3360, 3220, and 1650 cm^{-1}; $\lambda_{max.}$ (0.1M NaOH) 234 and 274; (0.1M HCl) 244.

The hydrochloric acid salt of (6) was prepared by bubbling dry hydrogen chloride gas through a finely divided suspension of (6) in diethyl ether at 0°C, or by allowing a hot solution of (6) in concentrated hydrochloric acid to cool slowly. The hydrochloride of (6) was obtained as colorless prisms m.p. >300°C (decomp.); $\nu_{max.}$ (nujol) 3360, 3260, 3170, 3130, 2560, 2480, and 1675 cm^{-1}; $\lambda_{max.}$ (0.1M NaOH) 232 and 274 nm.

Methyl and Ethyl esters of 4-guanidino-3-furazancarboxylic acid (7) and (8).

The appropriate alcohol (150 ml) was saturated with dry hydrogen chloride gas at room temperature, and 4-guanidino-3-furazancarboxylic acid (6) (6.00 g, 35.06 mmol) added. The suspension was refluxed for 15 h, and any unreacted

starting material filtered off while the solution was still hot. After cooling, the filtrate was diluted with ether and chilled. The resulting precipitate was collected and washed with ether to give the ester hydrochloride of (6) in yields of 75-80% based on reacted starting material.

Methyl 4-guanidino-3-furazancarboxylate (7). - m.p. 159-60°C (decomp.) (Found: C, 27.47; H, 3.90; N, 31.50. $C_5H_8ClN_5O_3$ requires C, 27.09; H, 3.64; N, 31.60%); $\nu_{max.}$(nujol) 3380, 3070 br, 1740, and 1690 cm^{-1}; $\lambda_{max.}$(EtOH) 245 nm (log ε 4.07); δ_H (60 MHz; d_6-dmso) 4.00 (3H, s, OCH_3) and 8.57 (5H, br s, NH); δ_C (20 MHz; d_6-dmso) 53.6, 142.2, 150.2, 155.4, and 157.4; m/z 154 (M^+-OCH_3HCl 3%), 70 (42), and 32 (100).

Ethyl 4-guanidino-3-furazancarboxylate (8). - m.p. 173-79°C (decomp.) (Found: C, 30.33; H, 4.46; N, 29.33. $C_6H_{10}ClN_5O_3$ requires C, 30.58; H, 4.28; N, 29.72%); $\nu_{max.}$(nujol) 3400, 3080 br, 1730, and 1680 cm^{-1}; $\lambda_{max.}$(EtOH) 247 nm (log ε 3.80); δ_H (60 MHz; d_6-dmso) 1.40 (3H, t, J=7Hz, $CH_2\underline{CH_3}$), 4.51 (2H, q, J= 7Hz $\underline{CH_2}CH_3$), and 8.52 (5H, br s NH); δ_C (20 MHz; d_6-dmso) 13.8, 63.1, 142.6, 150.1, 155.5, and 157.1; m/z 199 (M^+-HCl, 13%), 155 (6), and 70 (100).

5-Amino-7(6H)-furazano[3,4-d]pyrimidinone (9). - Ethyl 4-guanidino-3-furazan 3-carboxylate monohydrochloride (8.HCl) (1.00 g, 4.24 mmol) was added to water (50 ml) and the pH of the mixture adjusted to 5 with dilute sodium hydroxide. The mixture was boiled to dissolve all solid material and while still hot the pH was again adjusted to 5. After boiling for a further 2 min. and then cooling, the solution deposited a crystalline product which was collected, washed with water, and then recrystallised from water to give 5-amino-7(6H)-furazano[3,4-d]pyrimidinone (9) (0.53 g 81%) m.p. 277-78°C (decomp.) Found: C, 31.05; H, 2.23; N, 45.49. $C_4H_3N_5O_2$ requires C, 31.38; H, 1.98; N, 45.75%); $\nu_{max.}$(nujol) 3360, 3210, and 1725 cm^{-1}; $\lambda_{max.}$(EtOH) 221, 273, and 325 nm (log ε 4.05, 3.68, and 3.60); δ_H(60 MHz; d_6-dmso) 7.13 (br s); δ_C(20 MHz; d_6-acetone) 140.4, 154.5, 155.7, and 161.4.

Solvolysis of 5-Amino-7(6H)-furazano[3,4-d]pyrimidinone (9).

(a) (9) (100 mg, 0.65 mmol) was refluxed for two hours in 6M hydrochloric acid (10 ml). The solution was cooled, when crystals of the hydrochloride salt of 4-guanidino-3-furazan carboxylic acid (6) separated out (98 mg 72%)

(b) (9) (500 mg, 3.26 mmol) was dissolved in a solution (10 ml) of hydrogen chloride gas in either methanol or ethanol. After refluxing the solution for 3 h. and cooling, the hydrochloride salt of the corresponding ester (7) or (8) crystallised out. Yield 65%

5-Acetamido-7(6H)-furazano[3,4-d]pyrimidinone (10).

(a) 5-Amino-7(6H)-furazano[3,4-d]pyrimidinone (9) (0.42 g, 2.7 mmol) was added to freshly distilled acetic anhydride (10 ml) and the mixture refluxed for 2 h. The solution was evaporated and the residue chromatographed on a column of silica gel, eluting with ethyl acetate/hexane (3:2), to give 5-acetamido-7(6H)-furazano[3,4-d]pyrimidinone (10) (0.40 g, 75%). After crystallisation from acetone/hexane this had m.p. 186-87°C (Found: C, 37.21; H, 2.55; N, 35.95. $C_6H_5N_5O_3$ requires C, 36.93; H, 2.58; N, 35.89%); $\nu_{max.}$ (nujol) 3600, 3560, 3430, 1745, 1700, and 1625 cm^{-1}; $\lambda_{max.}$(EtOH) 235, 260 sh, and 319 nm (log ε 4.05, 3.81, and 3.60); δ_H (60 MHz; d_6-acetone) 2.36 (3H, s, $CO\underline{CH_3}$) and 11.57 (2H, br s, 2xNH).

(b) 4-Guanidino-3-furazancarboxylic acid (6) (3.21 g, 18.7 mmol) was added to

freshly distilled acetic anhydride (40 ml) and the suspension refluxed until all solid material had dissolved (2 h). The solution was evaporated and the brown residue chromatographed on a column of silica gel, eluting with ethyl acetate/hexane (3:2), to afford (10) (2.62 g, 72%).

Solvolysis of 5-Acetamido-7(6H)-furazano[3.4-d]pyrimidinone (10).

(a) (10) (200 mg, 1.02 mmol) was refluxed for 20 min. in concentrated hydrochloric acid (20 ml) and the solution then neutralised with concentrated aqueous ammonia. The precipitate was collected, washed with water, and dried, to give 4 guanidino-3-furazancarboxylic acid (6) (150 mg, 86%).

(b) (10) (1.00 g, 5.12 mmol) was dissolved in a solution (20 ml) of hydrogen chloride gas in either methanol or ethanol. After refluxing the solution for 2.5 h and cooling, the corresponding ester of 4-guanidino-3-furazancarboxylic acid, (7) or (8), crystallised out as its hydrochloride salt. Yield 65%.

Hydrogenation of 5-Amino-7(6H)-furazano[3,4-d]pyrimidinone (9)

(a) A solution of (9) (103 mg, 0.67 mmol) in deaerated 0.1M sodium hydroxid (10 ml) was hydrogenated at room temperature and pressure over 10% palladised charcoal(70 mg) until uptake of hydrogen ceased. The catalyst was removed by filtration and concentrated sulphuric acid (5 ml) added to the filtrate. On cooling, colorless needles of the sulphate of 2,4,5-triamino-6(1H)-pyrimidinone [8] (11) were obtained (100 mg, 61%).

(b) A solution of (9) (100 mg, 0.65 mmol) in acetic acid (15 ml) was hydrogenated at room temperature and pressure over 10% palladised charcoal (50 mg) until uptake of hydrogen ceased. The reaction mixture was warmed on a steam bath for 1 h and then filtered to remove the catalyst. Evaporation of the acetic acid and trituration of the residue with water afforded a solid product, which was recrystallised from water to give 5-acetamido-2,4-diamino-6(1H)-pyrimidinone [12] (12) (70 mg, 56%).

2,5-Diacetamido-4-amino-6(1H)-pyrimidinone (13). - A solution of 5-acetamido-7(6H)-furazano[3,4-d] pyrimidinone (10) (1.01 g, 5.18 mmol) in acetic acid (25 ml) was hydrogenated at room temperature and pressure over 10% palladised charcoal until uptake of hydrogen ceased. The reaction mixture was warmed on a steam bath for 1 h, filtered to remove the catalyst, and evaporated. Trituration of the residue with water afforded a solid product which was crystallised from water to give (13) (0.78 g, 67%) m.p. >300°C (decomp.) (Found: C,39.59; H, 4.97; N, 28.90. $C_8H_{11}N_5O_3 \cdot H_2O$ requires C, 39.51; H, 5.38; N, 28.79%); $\nu_{max.}$ (nujol) 3350, 3200, and 1625br cm^{-1} $\lambda_{max.}$ (0.1M NaOH) 220, 238sh, and 262 nm (log ε 4.32, 3.84 and 3.91); (0.1M HCl) 265 nm (log ε 3.93); δ_H (60 MHz; d_6-dmso) 1.94 (3H, s, CH_3), 2.14 (3H, s, CH_3), 6.09 (2H, br s, NH_2), 8.36 (1H, br s, NH), and 11.11 (2H, br s, 2xNH).

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