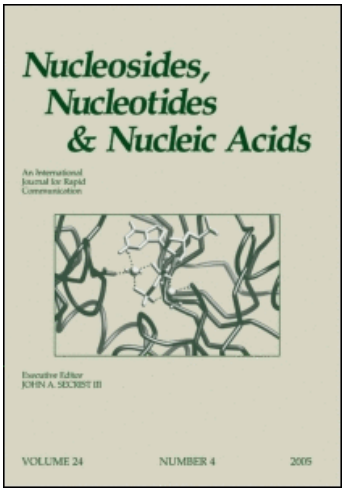

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Synthetic Studies on the Isomeric *N*-Methyl Derivatives of *C*-Ribavirin

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SYNTHETIC STUDIES ON THE ISOMERIC *N*-METHYL DERIVATIVES OF *C*-RIBAVIRIN

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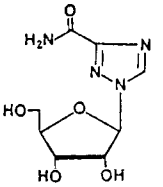
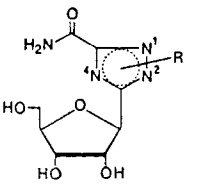
ABSTRACT: The syntheses of all three of the mono-*N*-methyl derivatives of *C*-ribavirin (3-β-*D*-ribofuranosyl-1,2,4-triazole-5-carboxamide, 2) have been accomplished. Reaction of 1-(β-*D*-ribofuranosyliminomethyl)-2-methylhydrazine (7) with ethyl oxamate (8) in boiling ethanol gave the N^1-methyl-*C*-ribavirin (3). A similar treatment of β-*D*-ribofuranosyl-1-carboximidic acid methyl ester (6) with N^1-methyloxamic hydrazide (10) furnished the N^2-methyl-*C*-ribavirin (4). Direct methylation of unprotected 2 with methyl iodide in the presence of potassium carbonate in dimethyl sulfoxide gave N^4-methyl isomer (5) as the major product. Structural assignments of 3, 4, and 5 were based on the unequivocal synthetic sequences, ^{1}H and ^{13}C NMR data and confirmed by single crystal X-ray diffraction analysis.

Ribavirin (1-β-*D*-ribofuranosyl-1,2,4-triazole-3-carboxamide, 1)[1], a synthetic nucleoside analogue of guanosine[2,3] synthesized and reported in 1972, is singular in its broad-spectrum of activity against both DNA and RNA viruses.[4,5] Ribavirin has been developed clinically[6] and approved for human use in an aerosol form for the treatment of lower respiratory disease caused by respiratory syncytial virus.[7-10] Ribavirin has also shown



Ribavirin

1



2, R = H, C-Ribavirin
3, R = N^1-CH_3
4, R = N^2-CH_3
5, R = N^4-CH_3

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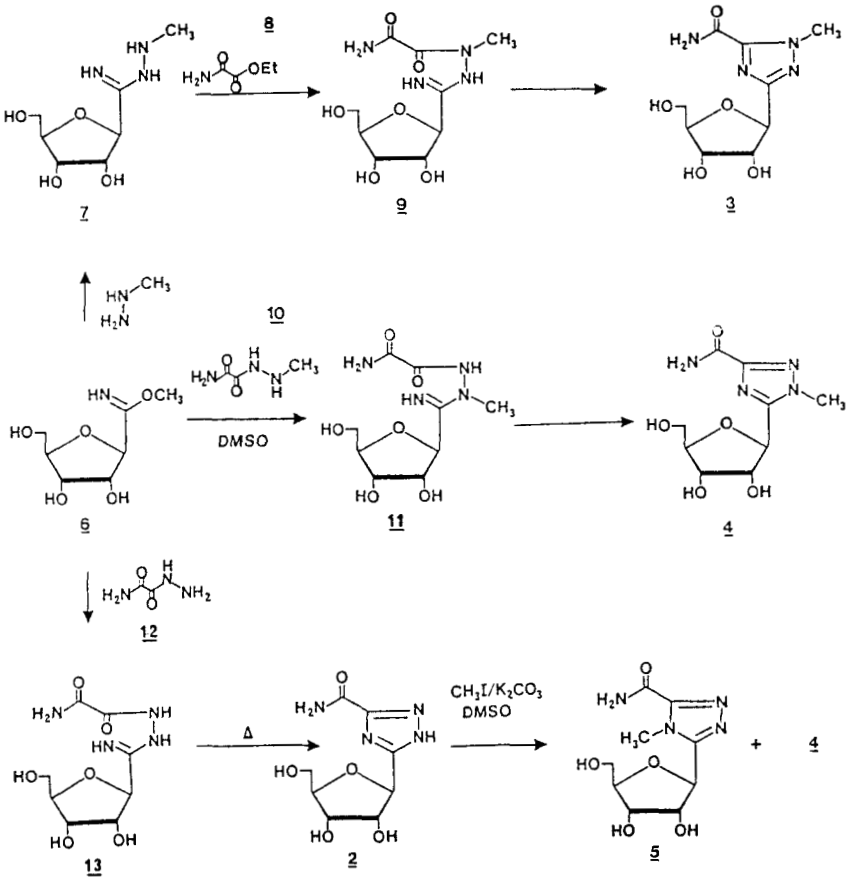
considerable efficacy in the treatment of influenza A and B by a small-particle aerosol route of administration.[11-15] Administered intravenously, ribavirin is effective in the treatment of Lassa fever[16,17] and epidemic hemorrhagic fever with renal syndrome caused by Hantaan virus.[18] Although a Sindbis viral mutant has recently been shown to be resistant to ribavirin,[19] its failure in general to induce viral resistance and its minimal drug-related toxicity are of particular interest.

In view of ribavirin's proven potential for therapeutic use, many efforts had been directed into the synthesis of its analogues. Among them the *C*-nucleoside analogue, 3-β-*D*-ribofuranosyl-1,2,4-triazole-5-carboxamide (**2**) was synthesized by Poonian and Nowoswiat.[20] As part of a synthetic program directed toward the preparation of novel azole nucleosides as antiviral agents, we have now synthesized all three of the mono-*N*-methyl derivatives of **2**, namely the N^1-methyl- (**3**), N^2-methyl- (**4**) and N^4-methyl- (**5**) *C*-ribavirin. These *N*-methyl derivatives, especially the N^1-methyl isomer **3**, are expected to act as inhibitors of the guanine N^7-methyl transferase,[21] which transfers the methyl group from *S*-adenosylmethionine to the N^7-position of guanine in the viral messenger RNA cap and carry out the viral protein synthesis.

The synthesis of the *N*-methyl derivatives of the *C*-nucleoside analogue of ribavirin was carried out by direct methylation of **2**, as well as by the ring closure of the coupling product of the β-*D*-ribofuranosyl-1-carboximidic acid methyl ester[20] (**6**) with an appropriate methylhydrazine derivative (SCHEME I). Thus, reaction of **6** with methylhydrazine in anhydrous methanol at room temperature gave a 68% yield of 1-(β-*D*-ribofuranosyliminomethyl)-2-methylhydrazine (**7**). On heating intermediate **7** with ethyl oxamate (**8**) in ethanol for 24 h with the exclusion of moisture, a complex reaction mixture was obtained which, after column chromatography, purification and recrystallization from aqueous ethanol, gave a 14% yield of the desired N^1-methyl-*C*-ribavirin (**3**) as crystalline material with mp 191-192 °C.

In the preparation of the N^2-methyl-*C*-ribavirin (**4**) the coupling of the methyl imidate **6** with the corresponding N^1-methyloxamic hydrazide (**10**) was required. Preparation of **10** was first tried by direct methylation of oxamic hydrazide (**12**) with methyl iodide in the presence of a base, however, the reaction gave a complex mixture of products and failed to give the desired product. Reaction of methyl hydrazine with ethyl oxamate

SCHEME I



(8) in anhydrous ethanol at room temperature gave a mixture of two products in a ratio of 93:7. The products were easily separated to give 83% of a major product and 3% of a minor product. Assignment of the two products was achieved unambiguously from comparison of their ^{1}H NMR signals.[22] The major product was determined to be the desired N^1-methyloxamic hydrazide (10) and the minor product was the corresponding N^2-methyloxamic hydrazide. Thus, treatment of 6 with N^1-methyloxamic hydrazide (10) in boiling anhydrous ethanol gave a 40% yield of N^2-methyl-*C*-ribavirin (4), as white needles of mp 174-175 °C.

Direct *N*-methylation of the *C*-ribavirin (2), prepared from β-*D*-ribofuranosyl-1-carboximidic acid methyl ester (6) and oxamic hydrazide (12) according to the procedure of Poonian and Nowoswiat,[20] was carried out by using CH_3I in the presence of anhydrous K_2CO_3 in DMSO. Formation of

two products was indicated in the crude reaction mixture (by ^{1}H NMR). The isomeric mixture was separated on a silica gel column using a gradient solvent of EtOAc and EtOAc:H_2O:*n*-PrOH (4:2:1, upper phase) to afford, according to the elusion order, the N^4-methyl isomer 5 as the major product (44%)[23] and the N^2-methyl isomer 4 as the minor product (19%). The minor product 4 was found to be identical in all aspects with the one prepared by the ring closure method.

The structural assignments of the three *N*-methyl *C*-nucleoside analogues of ribavirin, 3, 4 and 5, were based on their individual spectroscopic properties and confirmed by single X-ray diffraction analysis on one of them. Some of the most pertinent data for the three isomers, 3, 4, and 5, as well as the parent compound 2 are summarized in TABLE 1. The ^{1}H NMR resonance of $C_{1'}$-H in the parent compound 2 appears as a doublet centered at δ 4.94 with a coupling constant of 4 Hz.[20] In comparison, the N^1-methyl isomer 3 has a similar resonance for the $C_{1'}$-H as a doublet centered at δ 5.01 with a coupling constant of 4.3 Hz, while the resonance of $C_{1'}$-H in the other two *N*-methyl isomers (N^2-methyl 4 and N^4-methyl 5), which both have a methyl group in closer proximity to position of the $C_{1'}$-H than that of the N^1-methyl isomer 3, appear similarly shielded at δ 4.87 (4, d, J = 5.9 Hz) and δ 4.61 (5, d, J = 5.9 Hz), respectively. Also, the methyl signals of the N^1-isomer 3 and N^4-isomer 5, which both have a carboxamide group at the neighboring position, appear as a singlet at δ 4.08 and δ 4.09, respectively, are different from the methyl signal of the N^2-isomer 4 (δ 3.92, s).

The ^{13}C resonances of carbons 3 and 5 in the *N*-methyl compounds were compared with the corresponding resonances in the *C*-nucleoside analogue of ribavirin 2. As shown in TABLE 1, ^{13}C resonances of carbons 3 and 5 in the N^1-methyl 3 undergo a small downfield shift of 0.1 ppm and an upfield shift of 8.4 ppm, respectively, as compared to the corresponding resonances in compound 2. The ^{13}C resonances of carbons 3 and 5 in the N^2-methyl isomer 4 undergo an upfield shift of 4.4 ppm and a small downfield shift of 0.1 ppm, respectively, as compared to the corresponding resonances in 2. In the N^4-methyl isomer 5, an upfield shift in the ^{13}C resonance of both carbons 3 and 5 (0.3 ppm and 8.1 ppm, respectively) was observed. These shifting patterns of the ^{13}C resonances in the three *N*-methyl isomers have a strong resemblance to the previous observations made on *N*-substituted triazoles both in the shifting direction and the magnitude.[24]

TABLE 1. Pertinent ^{1}H- and ^{13}C-NMR Data of the *N*-Substituted *C*-Nucleoside Analogues of Ribavirin, 2, 3, 4, and 5

	2 R=H	3 R=CH_3 (N^1)	4 R=CH_3 (N^2)	5 R=CH_3 (N^4)
^{1}H NMR[a]				
$C_{1'}$-H	4.94 (d, 4Hz)[b]	5.01 (d, 4.3Hz)	4.87 (d, 5.9Hz)	4.61 (d, 5.9Hz)
N-CH_3	---	4.08	3.92	4.09
^{13}C NMR[a]				
C-3	159.1	159.2 (+0.1)[c]	154.7 (-4.4)	158.8 (-0.3)
C-5	155.0	146.6 (-8.4)	155.1 (+0.1)	146.9 (-8.1)

[a]In DMSO-d_6, δ. [b]Coupling constants are given in parentheses. [c]Difference of chemical shift when compared with 2, (+) stands for downfield shift, (-) stands for upfield shift.

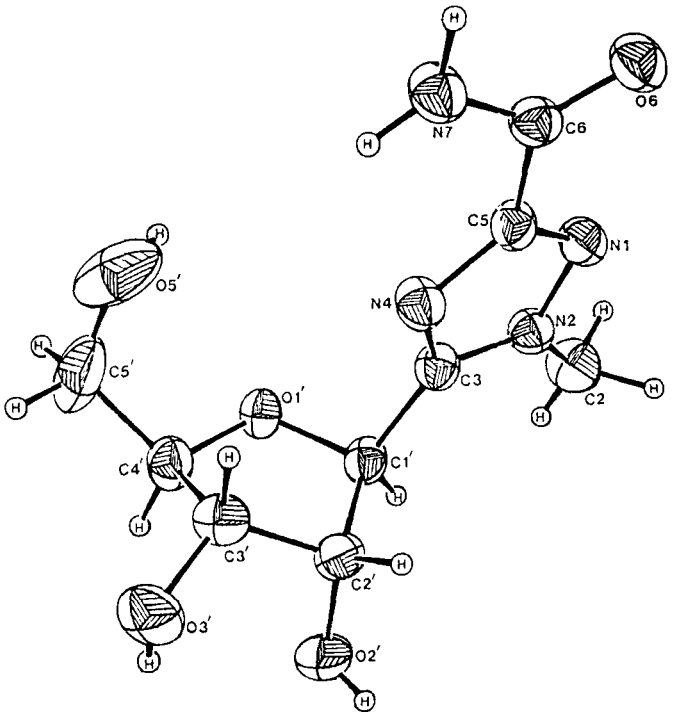


FIGURE 1. ORTEPII drawing of compound 4.

In addition to the spectroscopic properties discussed above, a single crystal X-ray diffraction analysis was performed on one of the isomers, the N^2-methyl isomer 4. FIGURE 1 (produced with ORTEPII)[25] illustrates the molecular conformation of the N^2-methyl-*C*-ribavirin (4).[26]

All compounds prepared in this study have been evaluated *in vitro* for their ability to inhibit the growth of L1210-leukemia, WI-L2 and CCRF-CEM (for antitumor effects), as well as against HSV-2, Adeno-2, Para-3, Rhino 1-A, influenza A viruses (for antiviral effects). These compounds are devoid of any significant biological effects in these systems.

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR, 300 MHz and 75 MHz, respectively) were recorded on an IBM NR/300 FT-NMR spectrometer. Chemical shifts are reported in parts per million values (δ) relative to tetramethylsilane (TMS) as an internal standard. Infrared spectra (IR) were recorded with a Perkin-Elmer 1420 spectrophotometer and Ultraviolet spectra (UV) were recorded on a Beckman DU-50 spectrophotometer. Mass spectra-exact mass analysis (MS-exact) were recorded at $\geq$ 20 eV on a VG-ZAB or a VG-7070 spectrometer performed at Department of Chemistry, University of California, Riverside, California. Elemental analyses were performed by Robertson Laboratory, Florham Park, New Jersey. Thin-layer chromatography (TLC) was run on silica gel 60 F-254 plates (EM Reagents). Silica gel (E. Merck, 230-400 mesh) was used for flash chromatography. All solvents used were reagent grade. Detection of nucleoside components on TLC was by UV light and with 10% sulfuric acid in MeOH spray followed by heating.

1-Methyl-3-(β-*D*-ribofuranosyl)-1,2,4-triazole-5-carboxamide (3). A solution of the hydrazine (7, 1.41 g, 6.87 mmol) and ethyl oxamate (8, 885 mg, 7.56 mmol) in anhydrous ethanol (50 mL) was allowed to reflux for 24 h with the exclusion of moisture. After removal of solvent under reduced pressure, the residual product was subjected to flash column chromatography using MeOH:CH_2Cl_2 gradient (0% - 10%) to afford a homogeneous product which, after crystallization from aqueous ethanol, gave 3 as white needles, 0.25 g (14%); mp 191-192 °C; IR (KBr): 1690 (C=O, m) cm^{-1}; UV (H_2O): 220 nm (sh, ϵ 10,900), no maxima observed above 220 nm;

^{1}H NMR (DMSO-d_6): δ 3.4-3.6 (2H, $2H_{5'}$, two m), 3.91 (1H, $H_{4'}$, m), 4.02 (1H, $H_{3'}$, m), 4.08 (3H, N_1-CH_3, s), 4.17 (1H, $H_{2'}$, m), 4.69 (1H, $C_{3'}$-OH, d, J=4.7 Hz), 4.71 (1H, $C_{5'}$-OH, t, J=6.0 Hz), 4.87 (1H, $C_{2'}$-OH, d, J=8.0 Hz), 5.01 (1H, $H_{1'}$, d, J=4.3 Hz), 7.89 and 8.15 (2H, $CONH_2$, two s); ^{13}C NMR (DMSO-d_6): δ 38.0, 61.7, 72.2, 72.7, 76.9, 83.4, 146.6, 159.2, 159.7; MS-exact: m/z 258.0945 (calcd. for $C_9H_{14}N_4O_5$, 258.0964).

2-Methyl-3-(β-*D*-ribofuranosyl)-1,2,4-triazole-5-carboxamide (4). A solution of the methyl imidate (6, 3.00 g, 15.7 mmol) and the hydrazine (10, 1.84 g, 15.7 mmol) in anhydrous ethanol (120 mL) was allowed to reflux for 24 h with the exclusion of moisture. After removal of solvent under reduced pressure, the residual product was subjected to flash column chromatography using MeOH:CH_2Cl_2 gradient (2% - 15%) to afford a homogeneous product which, after crystallization from aqueous ethanol, gave 4 as white needles, 1.73 g (40%); mp 174-175 °C; IR (KBr): 1675 (C=O, s) cm^{-1}; UV (H_2O): 220 nm (sh, ϵ 7,000), no maxima observed above 220 nm; ^{1}H NMR (DMSO-d_6): δ 3.3-3.6 (2H, $2H_{5'}$, two m), 3.85 (1H, $H_{4'}$, m), 3.92 (3H, N_2-CH_3, s), 3.97 (1H, $H_{3'}$, m), 4.37 (1H, $H_{2'}$, m), 4.78 (1H, $C_{5'}$-OH, t, J=5.5 Hz), 4.87 (1H, $H_{1'}$, d, J=5.9 Hz), 5.06 (1H, $C_{3'}$-OH, d, J=5.2 Hz), 5.25 (1H, $C_{2'}$-OH, d, J=6.0 Hz), 7.53 and 7.70 (2H, $CONH_2$, two s); ^{13}C NMR (DMSO-d_6): δ 36.1, 61.6, 71.0, 74.0, 75.3, 85.6, 154.7, 155.1, 160.5; MS-exact: m/z 258.0950 (calcd. for $C_9H_{14}N_4O_5$, 258.0964). Anal. calcd. for $C_9H_{14}N_4O_5$: C, 41.86; H, 5.46; N, 21.70. Found: C, 41.96; H, 5.33; N, 21.41.

Preparation of 2-Methyl-3-(β-*D*-ribofuranosyl)-1,2,4-triazole-5-carboxamide (4) and 4-Methyl-3-(β-*D*-ribofuranosyl)-1,2,4-triazole-5-carboxamide (5). To a solution of the *C*-nucleoside analogue of ribavirin 2[20] (450 mg, 1.84 mmol) and potassium carbonate (255 mg, 1.84 mmol) in DMSO (9 mL) was added dropwise methyl iodide (120 μL, 1.9 mmol) via syringe. The resultant mixture was allowed to stir at room temperature overnight. After removal of solvent *in vacuo* at 50 °C the residual product was dissolved in MeOH (10 mL) and the solid was filtered off. To the filtrate was added neutral aluminum oxide and concentrated to dryness. The mixture was subjected to column chromatography (silica gel) using a gradient of EtOAc:H_2O:*n*-PrOH (4:2:1, upper phase) and EtOAc (0% to 50%) to afford, according to the elusion order, the N^4 isomer 5 (210 mg, 44%) and the N^2 isomer 4 (89 mg, 19%). The two products were crystallized from aqueous

ethanol individually to give analytical samples. The N^2 isomer product 4 was found to be identical with the one obtained by a different route described above. The N^4 isomer 5 exhibits physical and spectral properties as follows: mp 142-144 °C; IR (KBr): 1690 (C=O, m) cm^{-1}; UV (H_2O): λ_{max} 220 nm (ϵ 9,300); UV (pH 1): λ_{max} 221 nm (ϵ 8,800); UV (pH 11): λ_{max} 220 nm (ϵ 9,200); ^1H NMR (DMSO-d_6): δ 3.3-3.6 (2H, $2H_{5'}$, two m), 3.78 (1H, $H_{4'}$, m), 3.96 (1H, $H_{3'}$, m), 4.09 (3H, N_4-CH_3, s), 4.21 (1H, $H_{2'}$, m), 4.61 (1H, $H_{1'}$, d, J=5.9 Hz), 4.66 (1H, $C_{5'}$-OH, t, J=5.7 Hz), 4.95 (1H, $C_{3'}$-OH, d, J=4.8 Hz), 5.07 (1H, $C_{2'}$-OH, d, J=5.8 Hz), 7.94 and 8.11 (2H, $CONH_2$, two s); ^{13}C NMR (DMSO-d_6): δ 37.8, 62.2, 71.3, 74.3, 77.8, 85.1, 146.9, 158.8, 160.2; MS-exact: m/z 258.0943 (calcd. for $C_9H_{14}N_4O_5$, 258.0964).

1-(β-*D*-Ribofuranosyliminomethyl)-2-methylhydrazine (7). To a solution of methyl imidate 6 (5.00 g, 26.2 mmol) in anhydrous MeOH (75 mL) was added dropwise methylhydrazine (1.5 mL, 29 mmol) via syringe under argon. The resultant solution was allowed to stir at room temperature for 4 days. After removal of solvent under reduced pressure the residual solid was triturated with acetone and collected. After washing with cold MeOH and acetone there was obtained 3.66 g (68%) of 7: mp 164-165 °C (dec); IR (KBr): 3360 (s), 3200 (s), 1655 (s), 1618 (m) cm^{-1}; UV (H_2O): λ_{sh} 220 nm (ϵ 2,900); UV (pH 1): λ_{max} 233 nm (ϵ 2,200); UV (pH 11): λ_{max} 223 nm (ϵ 5,000); ^1H NMR (DMSO-d_6): δ 2.55 (3H, N_2-CH_3, br s), 3.4-3.6 (2H, $2H_{5'}$, two m), 3.70 (1H, $H_{4'}$, m), 3.90 (1H, $H_{3'}$, m), 3.96 (1H, $H_{2'}$, m), 4.00 (1H, $H_{1'}$, d, J=3.5 Hz), 4.21 (1H, N_2-H, br s), 4.79 (1H, $C_{3'}$-OH, br s), 4.95 (1H, $C_{5'}$-OH, br s), 5.33 (3H, $C_{2'}$-OH and NH_2, br s); ^{13}C NMR (DMSO-d_6): δ 37.8, 60.6, 70.2, 74.8, 82.9, 83.3, 148.2. Anal. calcd. for $C_7H_{15}N_3O_4$: C, 40.97; H, 7.37; N, 20.48. Found: C, 40.93; H, 7.20; N, 20.34.

N^1-Methyloxamic Hydrazide (10). To a solution of ethyl oxamate 8 (10.0 g, 85.4 mmol) in anhydrous ethanol (500 mL) was added dropwise methyl hydrazine (4.7 mL, 89 mmol) at room temperature with the exclusion of moisture. The resultant solution was allowed to stir at room temperature and the reaction was followed by TLC until 8 was completely consumed (about 28 h). After removal of solvent under reduced pressure the white solid was collected and washed with ethyl ether. The ^1H NMR spectrum of the crude product shows a mixture of two products 10 and its corresponding N^2-methyl isomer in a ratio of 93:7 (determined by

integrating the corresponding methyl signals). The crude product was suspended in MeOH (100 mL), and the solid was isolated by filtration to afford pure 10 and the filtrate was concentrated to about 30 mL and again the solid was collected. Combination of the two crops of product afforded 8.3 g of 10 (83%). The remaining filtrate was concentrated and subjected to column chromatography purification to afford 250 mg (3%) of the N^2-methyl isomer. 10: mp 182-183 °C; IR (KBr): 3380 and 3260 (N-H, s), 1655 (C=O, s), 1590 (C=O, Fermi resonance band, m) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.45 (3H, N_1-CH_3, d, J=5.9 Hz), 4.96 (1H, N_1-H, m), 7.76 and 8.04 (2H, $CONH_2$, two s), 10.17 (1H, N_2-H, s); ^{13}C NMR (DMSO-d_6): δ 38.2, 158.3, 162.3; MS-exact: m/z 117.0543 (calcd. for $C_3H_7N_3O_2$, 117.0538). N^2-Methyl isomer: ^1H NMR (DMSO-d_6): δ 2.97 (3H, N_2-CH_3, s), 4.78 (2H, NH_2, s), 7.25 and 7.58 (2H, $CONH_2$, two s).

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26. Details of the crystal and molecular structure will be reported elsewhere.

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