Synthesis of 3-(4-Oxo-4*H*-quinolizinyl-3) and 3-(4-Oxo-4*H*-pyridino[1,2-*a*]pyrimidinyl-3) Substituted Lactic Acid Derivatives

Marko Škof, Jurij Svete* and Branko Stanovnik*

Faculty of Chemistry and Chemical Technology, University of Ljubljana, Aškerčeva 5, 1000 Ljubljana, Slovenia

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Dedicated to the memory of the late Professor Raymond N. Castle

A one-step 'ring switching' transformation of (*S*)-3-[(dimethylamino)methylidene]-5-(methoxycarbonyl)tetrahydrofuran-2-one (**4**) with 2-pyridineacetic acid derivatives (**5-7**) and 2-aminopyridines (**8**, **9**) afforded the corresponding 3-(4-oxo-4*H*-quinolizinyl-3)- (**15-17**) and 3-(4-oxo-4*H*-pyridino[1,2-*a*]pyrimidinyl-3)-2-hydroxypropanoates (**18**, **19**), respectively.

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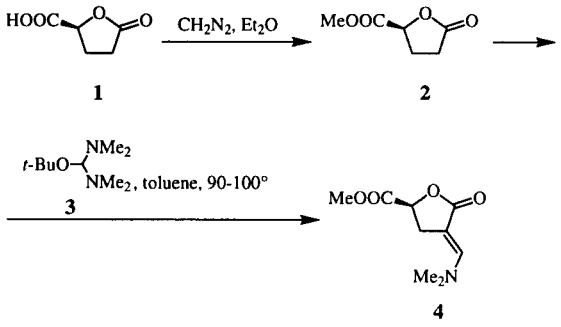
Quinolizines and their 1-aza analogs, pyridino[1,2-*a*]-pyrimidines are important classes of heterocyclic systems due to their occurrence in biologically active compounds, *e.g.*, as constituents of various naturally occurring and synthetic alkaloids [1,2]. An important synthetic route for the preparation of pyridino[1,2-*a*]pyrimidine derivatives is intramolecular cyclization of *N*-(pyridinyl-2) substituted aminomethylidenemalonates and related compounds, which leads to substituted 4-oxo-4*H*-pyridino-[1,2-*a*]pyrimidines [2-9].

3-Dimethylaminopropenoates proved to be versatile and effective reagents for the synthesis of a variety of mono-, bi-, and polycyclic heterocyclic systems and, among them, also for the preparation of 4-oxo-4*H*-quinolizine- and 4-oxo-4*H*-pyridino[1,2-*a*]pyrimidine derivatives [7-10]. Recently, chiral 3-dimethylaminopropenoate analogs derived from L-pyroglutamic acid proved to be a useful synthetic tool for the preparation of optically active 3-heteroarylalanine derivatives and heterocyclic systems with an α-amino acid structural element [11-14]. On the other hand, much less attention has been paid to the synthesis and utilization of heteroaryl substituted α-hydroxy acid derivatives, although chiral hydroxy acids, like lactic acid, malic acid, mandelic acid, tartaric acid, and their derivatives found a wide applicability in asymmetric synthesis, especially as chiral synthons, chiral auxiliaries, and resolving agents [15]. In continuation of our work in this field, we now report the 'ring switching' transformation of (*S*)-3-[(dimethylamino)methylidene]-5-(methoxycarbonyl)tetrahydrofuran-2-one (**4**) into 3-(4-oxo-4*H*-quinolizinyl-3)- (**15-17**) and 3-(4-oxo-4*H*-pyridino[1,2-*a*]-pyrimidinyl-3)-2-hydroxypropanoates (**18**, **19**).

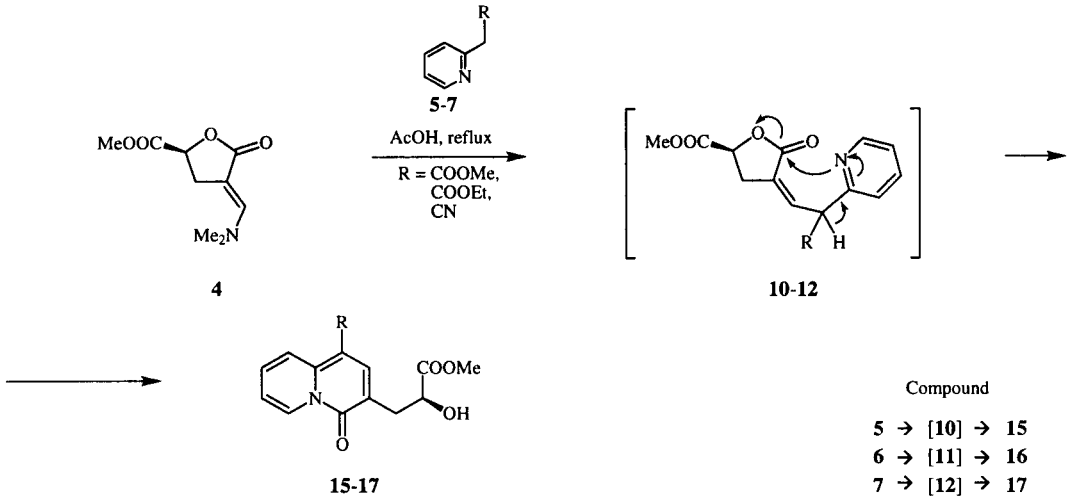
The starting compound, (*S*)-3-[(dimethylamino)methylidene]-5-(methoxycarbonyl)tetrahydrofuran-2-one (**4**), was prepared in two steps from commercially available (*S*)-5-oxotetrahydrofuran-2-carboxylic acid (**1**). Thus, **1** was first esterified to give the ester **2** followed by treatment with bis(dimethylamino)-*tert*-butoxymethane (**3**) at 90-100° to give (*S*)-3-[(dimethylamino)methylidene]-5-(methoxycarbonyl)tetrahydrofuran-2-one (**4**) in 58% yield (Scheme 1) [13,16].

Scheme 1



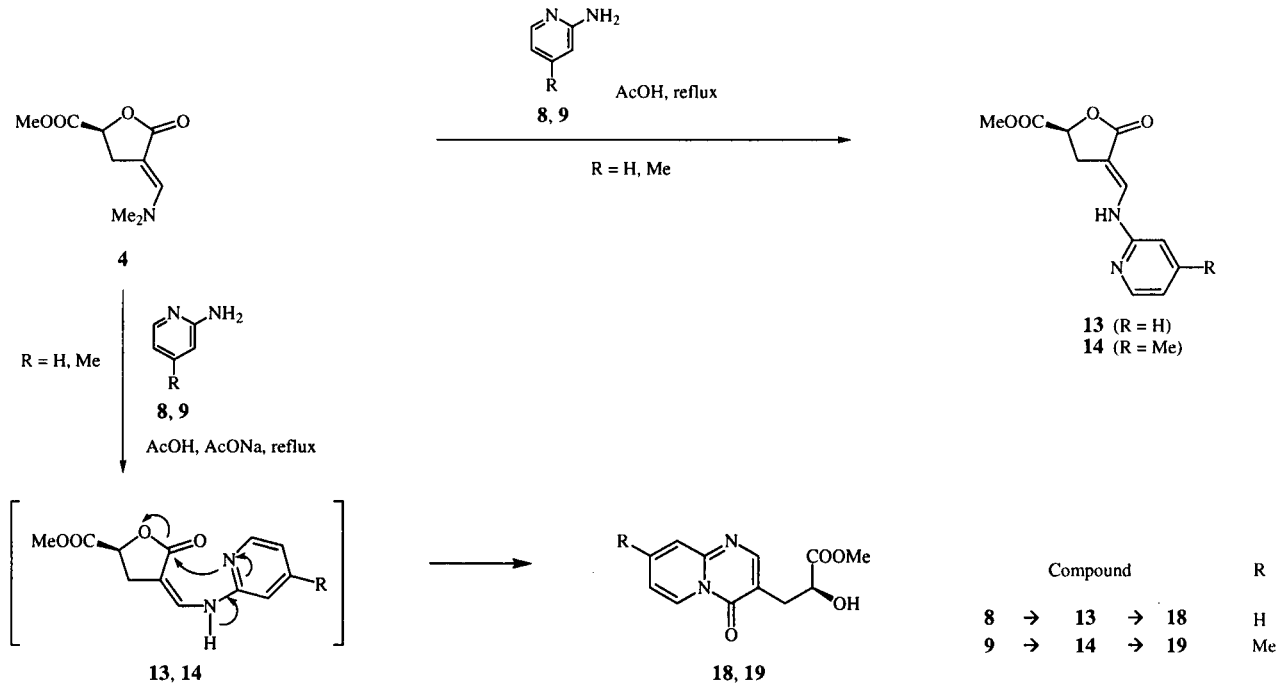
Compound **4** was then treated with two types of ambident nucleophilic compounds (1,3-dinucleophiles): pyridineacetic acid derivatives **5-7** as *C,N*-ambident nucleophiles and 2-aminopyridines **8**, **9** as *N,N*-ambident nucleophiles. Reactions of **4** with methyl 2-pyridineacetate (**5**), ethyl 2-pyridineacetate (**6**), and 2-pyridineacetonitrile (**7**) in refluxing acetic acid afforded methyl 3-(1-methoxycarbonyl-4-oxo-4*H*-quinolizinyl-3)-2-hydroxypropanoate (**15**), methyl 3-(1-ethoxycarbonyl-4-oxo-4*H*-quinolizinyl-3)-2-hydroxypropanoate (**16**), and methyl 3-(1-cyano-4-oxo-4*H*-quinolizinyl-3)-2-hydroxypropanoate (**17**), respectively (Scheme 2).

Scheme 2



On the other hand, treatment of **4** with 2-aminopyridine (**8**) or 2-amino-4-methylpyridine (**9**) in refluxing acetic acid gave only the substitution products **13** and **14** [17]. The presence of sodium acetate was required in order to achieve the transformation into the corresponding methyl 3-(4-oxo-4*H*-pyridino[1,2-*a*]pyrimidinyl-3)-2-hydroxypropanoate (**18**) and methyl 3-(8-methyl-4-oxo-4*H*-pyridino[1,2-*a*]pyrimidinyl-3)-2-hydroxypropanoate (**19**). Attempts to cyclize compounds **13** and **14** independently into 3-(4-oxo-4*H*-pyridino[1,2-*a*]pyrimidinyl-3)-2-hydroxypropanoates **18**, **19** resulted in decomposition of starting materials and formation of inseparable mixtures of products. Nevertheless, the isolation of intermediates **13** and **14** offers an additional proof for the reaction pathway of these 'ring switching' transformations which proceed *via* intermediates **10-14**, followed by opening of the furanone ring of **10-14** thus, enabling the formation of the fused pyridine system in products **15-19**. This reaction mechanism is also in accordance with previous results in the preparation and cyclization of analogous 2-pyridinylaminomethylidene compounds (Scheme 3) [3-10,17].

Scheme 3



EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The ^{1}H nmr spectra and ^{13}C nmr spectra were obtained on a Bruker Avance DPX 300 (300 MHz) spectrometer with deuteriochloroform and dimethyl-d_6 sulfoxide as solvents and tetramethylsilane as internal standard. The microanalyses for C, H, and N were obtained on a Perkin-Elmer CHN Analyser 2400. The optical rotations were measured on a Perkin-Elmer 241 MC Polarimeter.

(*S*)-5-(Methoxycarbonyl)tetrahydrofuran-2-one (**2**), (*S*)-3-(dimethylaminomethylidene)-5-(methoxycarbonyl)tetrahydrofuran-2-one (**4**), and (*S*)-5-methoxycarbonyl-3-[(4-methylpyridinyl-2)aminomethylidene]-2-oxotetrahydrofuran (**14**) were prepared according to the procedures described in the literature [13,16,17].

The Synthesis of (*S*)-5-Methoxycarbonyl-3-[(pyridinyl-2)aminomethylidene]-2-oxotetrahydrofuran (**13**).

A mixture of (*S*)-3-[(dimethylamino)methylidene]-5-(methoxycarbonyl)tetrahydrofuran-2-one (**4**) (199 mg, 0.001 mole), 2-aminopyridine (**8**) (94 mg, 0.001 mole), and glacial acetic acid (4 ml) was heated at reflux temperature for 2 hours. Volatile components were evaporated *in vacuo*, the solid residue crystallized from ethyl acetate, and the precipitate collected by filtration to give compound **13** in 94% yield, mp 192-194°; $[\alpha]_D^{23}$ = -4.0° (*c* = 0.72, DMF); ^{1}H nmr (300 MHz, dimethyl-d_6 sulfoxide): δ 2.94 (1H, ddd, H_{4a}), 3.25 (1H, ddd, H_{4b}), 3.73 (3H, s, OMe), 5.15 (1H, dd, H_5), 6.94-6.99 (2H, m, $H_{5'}$ and $H_{3'}$), 7.69 (1H, ddd, $H_{4'}$), 8.23-8.25 (1H, m, $H_{6'}$), 8.29 (1H, br d, *CH*NH), 9.76 (1H, d, CH*NH*), J_{H4a-CH} = 2.1 Hz, J_{H4b-CH} = 2.3 Hz, J_{H4a-H5} = 4.6 Hz, J_{H4b-H5} = 10.2 Hz, $J_{H4a-H4b}$ = 16.5 Hz, $J_{H4'-H6'}$ = 1.9 Hz, $J_{H4'-H5'}$ = 8.3 Hz, $J_{H3'-H4'}$ = 7.1 Hz, J_{NH-CH} = 11.5 Hz; ^{13}C nmr (75.5 MHz, dimethyl-d_6 sulfoxide): δ 28.5, 52.3, 72.0, 95.1, 110.8, 117.5, 133.5, 138.4, 148.0, 152.3, 170.9, 171.6.

Anal. Calcd. for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.28. Found: C, 58.34; H, 5.10; N, 11.07.

The Synthesis of (*S*)-5-Methoxycarbonyl-3-[(4-methylpyridinyl-2)-aminomethylidene]-2-oxotetrahydrofuran (**14**) [17].

This compound was prepared in 70% yield from (*S*)-3-[(dimethylamino)methylidene]-5-(methoxycarbonyl)tetrahydrofuran-2-one (**4**) and 2-amino-4-methylpyridine (**9**) according to the procedure described previously [17]. Additional characterization available: ^{13}C nmr (75.5 MHz, dimethyl-d_6 sulfoxide): δ 21.5, 29.5, 53.2, 73.0, 95.7, 111.8, 119.8, 134.7, 148.6, 150.1, 153.4, 171.9, 172.5.

The Synthesis of Methyl (*S*)-3-(4-Oxo-4*H*-quinolizinyl-3)-2-hydroxypropanoates (**15-17**).

General Procedure.

A mixture of (*S*)-3-[(dimethylamino)methylidene]-5-(methoxycarbonyl)tetrahydro-furan-2-one (**4**) (0.001 mole), 2-pyridineacetic acid derivative (**5-7**) (0.001 mole), and glacial acetic acid (4 ml) was heated at reflux temperature for 3 hours. Volatile components were evaporated *in vacuo*, the solid residue crystallized from ethyl acetate, and the precipitate collected by filtration to give substituted 2-hydroxypropanoates (**15-17**). The following compounds were prepared in this manner:

Methyl (*S*)-3-(1-Methoxycarbonyl-4-oxo-4*H*-quinolizinyl-3)-2-hydroxypropanoate (**15**).

This compound was prepared from methyl 2-pyridineacetate (**5**), 3 hours of reflux, the crude product was purified by column chromatography using diethyl ether as solvent to give **15** in 43% yield, mp 101-103° (from ethyl acetate); $[\alpha]_D^{23}$ = -52.9° (*c* = 0.68, CH_2Cl_2); ^{1}H nmr (300 MHz, dimethyl-d_6 sulfoxide): δ 2.81 (1H, dd, H_{3a}), 3.08 (1H, dd, H_{3b}), 3.63 (3H, s, OMe), 3.85 (3H, s, OMe), 4.38 (1H, ddd, H_2), 5.52 (1H, d, OH), 7.38-7.43 (1H, m, $H_{7'}$), 7.84-7.89 (1H, m, $H_{8'}$), 8.29 (1H, s, $H_{2'}$), 9.06-9.09 (1H, m, $H_{9'}$), 9.18 (1H, br d, $H_{6'}$), J_{H2-H3a} = 8.3 Hz, J_{H2-H3b} = 4.9 Hz, $J_{H3a-H3b}$ = 13.6 Hz, J_{OH-CH} = 6.4 Hz, $J_{H6'-H7'}$ = 6.8 Hz; ^{13}C nmr (75.5 MHz, dimethyl-d_6 sulfoxide): δ 36.9, 52.3, 52.6, 69.4, 101.1, 115.6, 117.8, 123.9, 128.8, 134.9, 141.1, 144.2, 158.5, 166.0, 174.8.

Anal. Calcd. for $C_{15}H_{15}NO_6$: C, 59.01; H, 4.95; N, 4.59. Found: C, 59.06; H, 4.90; N, 4.43.

Methyl (*S*)-3-(1-Ethoxycarbonyl-4-oxo-4*H*-quinolizinyl-3)-2-hydroxypropanoate (**16**).

This compound was prepared from ethyl 2-pyridineacetate (**6**), 3 hours of reflux, the crude product was purified by column chromatography using diethyl ether as solvent to give **16** in 35% yield, mp 78-80° (from ethyl acetate); $[\alpha]_D^{23}$ = -3.0° (*c* = 0.63, CH_2Cl_2); ^{1}H nmr (300 MHz, dimethyl-d_6 sulfoxide): δ 1.35 (3H, t, CH_2CH_3), 2.81 (1H, dd, H_{3a}), 3.09 (1H, dd, H_{3b}), 3.63 (3H, s, OMe), 4.33 (2H, q, CH_2CH_3), 4.38 (1H, ddd, H_2), 5.53 (1H, d, OH), 7.40 (1H, dt, $H_{7'}$), 7.86 (1H, ddd, $H_{8'}$), 8.28 (1H, s, $H_{2'}$), 9.08 (1H, br s, $H_{9'}$), 9.18 (1H, br d, $H_{6'}$), $J_{CH3-CH2}$ = 7.2 Hz, J_{H2-H3a} = 8.3 Hz, J_{H2-H3b} = 4.9 Hz, $J_{H3a-H3b}$ = 13.6 Hz, J_{OH-CH} = 6.4 Hz, $J_{H7'-H6'}$ = 7.1 Hz, $J_{H7'-H9'}$ = 1.3 Hz, $J_{H8'-H9'}$ = 9.2 Hz, $J_{H8'-H7'}$ = 6.8 Hz, $J_{H8'-H6'}$ = 1.5 Hz. ^{13}C nmr (75.5 MHz, dimethyl-d_6 sulfoxide): δ 15.1, 36.9, 52.3, 61.2, 69.4, 101.3, 115.5, 117.7, 123.9, 128.7, 134.7, 141.1, 144.1, 158.4, 165.5, 174.8.

Anal. Calcd. for $C_{16}H_{17}NO_6$: C, 60.18; H, 5.37; N, 4.39. Found: C, 60.09; H, 5.24; N, 4.36.

Methyl (*S*)-3-(1-Cyano-4-oxo-4*H*-quinolizinyl-3)-2-hydroxypropanoate (**17**).

This compound was prepared from 2-pyridineacetonitrile (**7**), 3 hours of reflux, in 45% yield, mp 111-113° (from ethyl acetate); $[\alpha]_D^{23}$ = -33.8° (*c* = 0.48, CH_2Cl_2); ^{1}H nmr (300 MHz, dimethyl-d_6 sulfoxide): 2.80 (1H, dd, H_{3a}), 3.06 (1H, dd, H_{3b}), 3.64 (3H, s, OMe), 4.39 (1H, br dd, H_2), 5.53 (1H, d, OH), 7.42-7.47 (1H, m, $H_{7'}$), 7.91-7.93 (2H, m, $H_{8'}$ and $H_{9'}$), 8.07 (1H, s, $H_{2'}$), 9.11-9.14 (1H, m, $H_{6'}$), J_{H2-H3a} = 8.4 Hz, J_{H2-H3b} = 4.5 Hz, $J_{H3a-H3b}$ = 13.6 Hz, J_{OH-CH} = 5.6 Hz; ^{13}C nmr (75.5 MHz, dimethyl-d_6 sulfoxide): δ 36.5, 52.4, 69.0, 83.6, 115.6, 117.5, 118.2, 123.4, 128.9, 135.8, 140.8, 145.2, 157.8, 174.7.

Anal. Calcd. for $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.44; N, 10.29. Found: C, 62.08; H, 4.17; N, 10.29.

The Synthesis of Methyl (*S*)-3-(4-Oxo-4*H*-pyridino[1,2-*a*]-pyrimidinyl-3)-2-hydroxypropanoates (**18**, **19**).

General Procedure.

A mixture of (*S*)-3-[(dimethylamino)methylidene]-5-(methoxycarbonyl)tetrahydrofuran-2-one (**4**) (0.001 mole), aminopyridine (**8**, **9**) (0.001 mole), anhydrous sodium acetate (0.001 mole), and glacial acetic acid (4 ml) was heated at reflux temperature for

3 hours. Volatile components were evaporated *in vacuo*, the oily residue dissolved in water (25 ml), and the product extracted with chloroform (3 times, 30 ml each time). Organic phases were collected, dried over anhyhrous sodium sulphate, and filtered. Volatile components evaporated *in vacuo* and the residue purified by column chromatography using ethyl acetate as solvent. Fractions containing the product were combined and volatile components evaporated *in vacuo*. The residue was crystallized from ethyl acetate and the precipitate collected by filtration to give substituted 2-hydroxypropanoates (**18**, **19**). The following compounds were prepared in this manner:

Methyl (*S*)-3-(4-Oxo-4*H*-pyridino[1,2-*a*]pyrimidinyl-3)-2-hydroxypropanoate (**18**).

This compound was prepared from 2-aminopyridine (**8**), reflux for 3 hours, in 19% yield, mp 133-135° (from ethyl acetate); $[\alpha]_D^{23}$ = -9.0° (*c* = 0.52, CH_2Cl_2); ^{1}H nmr (300 MHz, dimethyl-d_6 sulfoxide): δ 2.76 (1H, dd, H_{3a}), 3.00 (1H, dd, H_{3b}), 3.63 (3H, s, OMe), 4.38 (1H, ddd, H_2), 5.54 (1H, d, OH), 7.35 (1H, dt, $H_{7'}$), 7.63 (1H, td, $H_{9'}$), 7.91 (1H, ddd, $H_{8'}$) 8.23 (1H, s, $H_{2'}$), 8.96 (1H, ddd, $H_{6'}$), $J_{H2\text{-}H3a}$ = 8.3 Hz, $J_{H2\text{-}H3b}$ = 4.9 Hz, $J_{H3a\text{-}H3b}$ = 13.6 Hz, $J_{OH\text{-}CH}$ = 6.6 Hz, $J_{H7'\text{-}H9'}$ = 1.3 Hz, $J_{H7'\text{-}H6'}$ = 7.1 Hz, $J_{H7'\text{-}H8'}$ = 6.8 Hz, $J_{H9'\text{-}H6'}$ = 0.9 Hz, $J_{H9'\text{-}H8'}$ = 8.7 Hz, $J_{H8'\text{-}H6'}$ = 1.5 Hz; ^{13}C nmr (75.5 MHz, dimethyl-d_6 sulfoxide): δ 34.1, 52.4, 69.2, 113.4, 117.2, 126.8, 127.5, 137.2, 151.0, 154.9, 158.1, 174.8.

Anal. Calcd. for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.28. Found: C, 58.21; H, 4.98; N, 10.92.

Methyl (*S*)-3-(8-Methyl-4-oxo-4*H*-pyridino[1,2-*a*]pyrimidinyl-3)-2-hydroxypropanoate (**19**).

This compound was prepared from 4-methyl-2-aminopyridine (**9**), reflux for 3 hours, yield 15%, mp 135-137° (from ethyl acetate); $[\alpha]_D^{23}$ = -25.9° (*c* = 0.96, CH_2Cl_2); ^{1}H nmr (300 MHz, dimethyl-d_6 sulfoxide): δ 2.45 (3H, s, 8-Me), 2.73 (1H, dd, H_{3a}), 2.97 (1H, dd, H_{3b}), 3.62 (3H, s, OMe), 4.36 (1H, ddd, H_2), 5.52 (1H, d, OH), 7.21 (1H, dd, , $H_{7'}$), 7.48 (1H, br s, $H_{9'}$), 8.17 (1H, s, $H_{2'}$), 8.86 (1H, d, $H_{6'}$), $J_{H2\text{-}H3a}$ = 8.3 Hz, $J_{H2\text{-}H3b}$ = 5.1 Hz, $J_{H3a\text{-}H3b}$ = 13.8 Hz, $J_{OH\text{-}CH}$ = 6.4 Hz, $J_{H7'\text{-}H9'}$ = 1.7 Hz, $J_{H7'\text{-}H6'}$ = 7.3 Hz; ^{13}C nmr (75.5 MHz, dimethyl-d_6 sulfoxide): δ 21.5, 34.1, 52.3, 69.3, 112.3, 119.6, 124.7, 126.8, 148.7, 150.9, 155.2, 158.1, 174.8.

Anal. Calcd. for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68. Found: C, 59.63; H, 5.30; N, 10.36.

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