Synthesis and Theoretical Calculations of Novel 5-Aryl Substituted 2,4,7-Trioxo and 4,7-Dioxo-2-thioxopyrido[2,3-*d*]pyrimidines

René Rodríguez, Margarita Suárez*, Estael Ochoa, Alhmed Morales, and Leandro González

Laboratorio de Síntesis Orgánica, Facultad de Química, Universidad de La Habana, Cuba

Nazario Martín, Margarita Quinteiro, Carlos Seoane*, and José L. Soto

Departamento de Química Organica, Facultad de Química, Universidad Complutense, 28040-Madrid, Spain

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New substituted pyrido[2,3-*d*]pyrimidines **5** and **6** have been prepared in one-step from the readily available 6-amino-2,4-dioxotetrahydropyrimidine (**1**) or 6-amino-4-oxo-2-thioxotetrahydropyrimidine (**2**) and the arylidene substituted Meldrum's acid. The substitution pattern of the ethylene moiety in compounds **5** and **6** results in a strong *push-pull* electronic effect. The semiempirical calculations using the AM1 method reveal two equally favoured conformations showing a distorted geometry. The calculated charge density values confirm the observed ^{13}C nmr chemical shifts.

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Pyrido[2,3-*d*]pyrimidine derivatives form a class of fused heterocyclic compounds which present interesting pharmacological and biological properties. Thus, they have been used as effective antitumor agents [1], as herbicide antidotes [2], antibacterians [3], diuretics [4] or antivirals [5].

The synthesis of these compounds is well documented in the literature and the pyrimidine or pyridine rings have been used as the former precursor on which the second heterocyclic system is constructed [6]. Pyrido[2,3-*d*]-pyrimidines have also been prepared by ring transformation of other heterocyclic fused systems such as amino-pyrimido[4,5-*d*]pyrimidine [7] and pyrano[2,3-*d*]-pyrimidines [8].

With regard to the synthesis of pyrido[2,3-*d*]pyrimidine-2,4,7-triones, some synthetic procedures from suitable pyrimidine-2,4-diones have been previously reported [9].

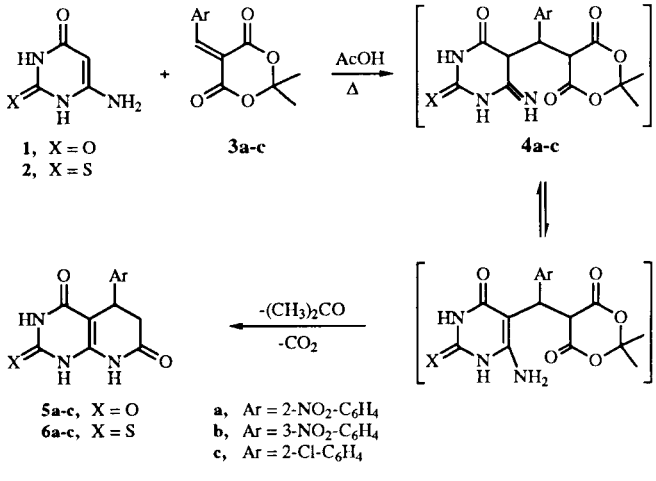
Recently we have described the synthesis and semiempirical calculations of various fused heterocyclic compounds containing the 1,4-dihydropyridine (1,4-DHP) moiety [10].

In this paper we describe a versatile synthesis of novel 5-aryl-2,4,7-trioxo-1,2,3,4,5,6,7,8-octahydropyrido-[2,3-*d*]pyrimidines (**5**) and 5-aryl-4,7-dioxo-2-thioxo-1,2,3,4,5,6,7,8-octahydropyrido[2,3-*d*]pyrimidines (**6**) as novel dihydropyridine containing ring systems.

The preparations of compounds **5** and **6** have been carried out by refluxing equimolecular amounts of 6-amino-2,4-dioxo-1,2,3,4-tetrahydropyrimidine (**1**) or 6-amino-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine (**2**) in acetic acid with the appropriate 5-arylidene substituted Meldrum's acid (**3**).

The novel compounds are obtained in moderate to good yields as stable crystalline solids which are easily purified by recrystallization from ethanol.

Scheme



1, X = O
2, X = S

3a-c

4a-c

5a-c, X = O
6a-c, X = S

a, Ar = 2-NO_2-C_6H_4
b, Ar = 3-NO_2-C_6H_4
c, Ar = 2-Cl-C_6H_4

The starting materials were prepared by following the literature procedures. Thus, pyrimidines **1** and **2** were prepared from ethyl cyanoacetate and urea or thiourea respectively, in the presence of sodium ethoxide by following the Traube procedure [11]. Compounds **3** were obtained from Meldrum's acid by reaction with the appropiate aldehyde in the presence of triethylamine as the basic catalyst [12].

It is worth mentioning that formation of **5** and **6** takes place in dilute solutions due to the low solubility of the starting pyrimidine **1** and **2** in acetic acid. Attempts to carry out the reaction in other solvents such as alcohols, dimethylformamide or dimethyl sulfoxide did not improve either solubility or yields.

Formation of pyrido[2,3-*d*]pyrimidines **5** and **6** takes place through a Hantzsch-like mechanism by conjugated addition of the enamine compound **1** or **2** to the α,β-unsaturated carbonyl compound **3** to form the intermediate

4 followed by iminoenamino tautomerism and subsequent 6-*exo-trig* cyclization [13]. The loss of acetone and carbon dioxide molecules yields the novel compounds **5** and **6**.

Pyrido[2,3-*d*]pyrimidines **5** and **6** show satisfactory analytical and spectroscopic data. Thus, in addition to the amino and carbonyl signals at 3200-3425 cm^{-1} (NH) and 1695-1720 cm^{-1} (C=O) and 1685-1695 cm^{-1} (C=O), the ir spectra of compounds **6** show the C=S signal at 1350-1355 cm^{-1}. The ^1H nmr spectra show the coupled pyridine protons on C-6 and C-5 as a double doublet centered at δ (C-6) 3.19-3.33 and δ (C-5) 4.32-4.52 ppm respectively (see Experimental). The ^{13}C nmr spectra of compounds **5** and **6** present the pyridine carbonyl group at δ 168.1-168.8. The carbonyl group at C-2 in compounds **5** and thiocarbonyl group in compounds **6** appear at δ 162.4-162.7 and 174.2 respectively. The presence of the oxygen or sulfur atoms on C-2 have an influence on the δ value of the other carbonyl group at C-4 which appear at *ca.* δ 150 for **5** and at lower field values (δ 160) for **6**. A *push-pull* effect is also observed in the olefinic carbons C-4a and C-8a due to the electronic behaviour of their substituents. Thus, C-4a appear at low δ values (88-93) and C-8a gives a peak at lower field value (δ 146-148.5). The assignment of C-5 and C-6 carbons was carried out by DEPT-135° experiments as it is shown in the Table 1.

The geometry for compounds **5b** and **6b** has been obtained by quantum chemical AM1 calculations and

Table 1

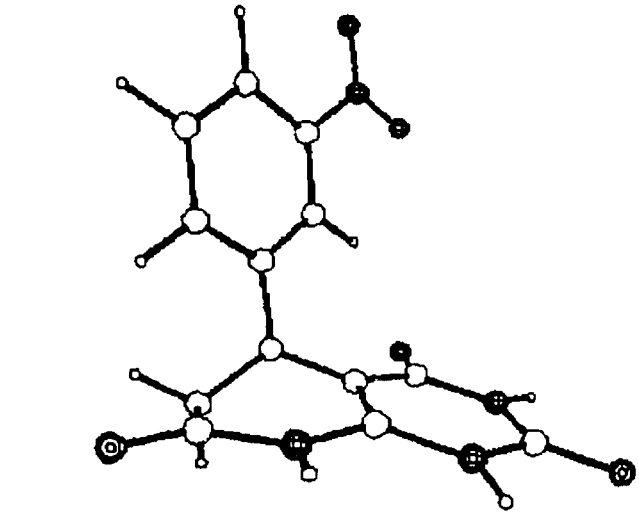
^{13}C NMR Data for the Novel Pyrido[2,3-*d*]pyrimidines **5a-c** and **6a-c**

	C-2	C-4	C-4a	C-5	C-6	C-7	C-8a
5a	162.4	150.1	88.1	29.2	37.7	168.7	148.5
5b	162.7	150.2	88.6	32.7	37.9	169.2	114.8
5c	162.4	150.1	87.8	30.6	37.1	168.8	147.4
6a	174.3	159.9	92.9	29.3	34.7	168.1	148.5
6b	174.2	160.1	93.2	32.7	37.5	168.7	148.0
6c	174.3	159.9	92.6	30.5	36.8	168.3	146.9

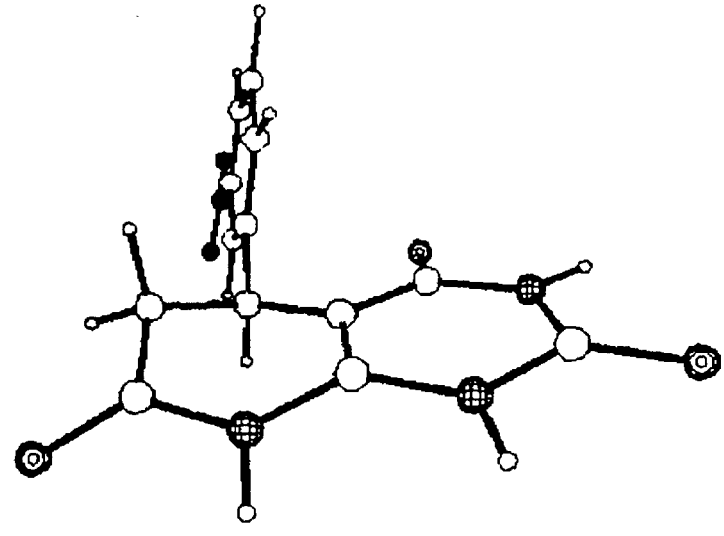
Table 2

Relevant Structural Parameters of the Favoured Conformations **A** and **B** for Compound **5b** and **6b**

	5b (A)	**5b (B)**	**6b (A)**	**6b (B)**
C7-N8-C8a	120.58	121.39	120.45	121.55
C6-C5-C4a	109.22	112.14	108.85	113.55
N8-C8a-C4a-C5	4.35	-1.46	4.66	-1.37
C7-N8-C8a-C4a	12.86	-9.01	13.22	-2.32
C6-C5-C4a-C8a	-34.68	26.26	-35.72	17.16
C2'-C1'-C5-C4a	65.41	126.53	63.01	131.74
Ha6-C6-C5-H5	-72.89	-163.20	-71.57	-151.05
Hb6-C6-C5-H5	45.71	-44.82	47.08	-33.45
O4-C4-C4a-C8a	175.51	173.05	175.90	174.06
C4a-C8a-N1-C2	-1.97	-0.35	-2.24	-2.08
C8a-C4a-C4-N3	-3.88	-6.22	-3.53	-5.02
N1-C2-N3-C4	1.30	-1.24	1.91	-0.72
N1-C8a-C4a-C4	4.38	4.12	4.50	4.56
X2-C2-N1-C8a	179.44	178.88	179.43	-179.89



Compound **5b (A)**



Compound **5b (B)**

Figure. Geometry for the minimun energy conformations **A** and **B** for compound **5b**.

shows two favoured conformations for the pyridone ring: in the conformation **A**, C-5 and C-6 atoms are out of the molecular plane, being located C-5 below and C-6 above this plane, with the phenyl group on C-5 in a pseudoaxial position. Conformation **B** is similar to **A**, C-5 and C-6 atoms lying above and below, the molecular plane respectively. Now the phenyl group appears in a pseudoequatorial position. in both favoured geometries, the pyridone system exhibits a twisted conformation with the phenyl ring bisecting the pyridone moiety as it is shown by the dihedral angles in Table 2 (Figure 1).

The charge density values for the more relevant atoms are collected in Table 3. The calculated values for the

olefinic carbons C-4a and C-8a confirm the observed electronic *push-pull* effect on the ^{13}C nmr data.

Table 3

Charge Density Values for the Pyrido[2,3-*d*]pyrimidine Atoms

	5b (A)	5b (B)	6b (A)	6b (B)
N-8	-0.334	-0.347	-0.342	-0.342
C-7	0.319	0.322	0.319	0.322
C-6	-0.177	-0.180	-0.177	-0.180
C-5	0.012	0.021	0.011	0.020
C-4a	-0.323	-0.316	-0.312	-0.305
C-8a	0.268	0.263	0.253	0.248
O (C-4)	-0.339	-0.326	-0.330	-0.316
O (C-7)	-0.317	-0.310	-0.314	-0.310
N-1	-0.332	-0.335	-0.290	-0.294
C-2	0.409	0.400	0.135	0.136
N-3	-0.358	-0.364	-0.316	-0.321
C-4	0.376	0.375	0.364	0.361
X	-0.347	-0.350	-0.175	-0.184

Finally, the calculated heats of formation and dipole moments are collected in Table 4, as corresponding to the two energetically favoured conformations for compounds **5b** and **6b**.

Table 4

Heats of Formation and Dipole Moments for the Favoured Conformations **A** and **B** for Compounds **5b** and **6b**

Molecule	5b (A)	5b (B)	6b (A)	6b (B)
Heat of Formation (Kcal/mol)	-55.32	-52.54	-55.70	-53.32
Dipole Moment (Debye)	6.704	6.513	6.771	5.897

In conclusion, we describe a new fictionalization procedure of pyrido[2,3-*d*]pyrimidines **5** and **6** from the readily available 6-amino-2,4-dioxotetrahydropyrimidine (**1**) or 6-amino-4-oxo-2-thioxotetrahydropyrimidine (**2**) and the arylidene substituted Meldrum's acid. Theoretical calculations show a distorted geometry with two favoured conformations and confirm the electronic *push-pull* effect observed in the ^{13}C nmr spectra. The compounds now reported, **5** and **6** can be considered as promising candidates for further functionalization leading to other fused heterocyclic systems containing the 1,4-DHP moiety.

EXPERIMENTAL

Melting points were determinated in capillary tubes in a Gallenkamp apparatus and are uncorrected. The nmr spectra were recorded at 250 MHz on a Bruker AC-250F spectrometer in dimethyl sulfoxide-d_6 solution. Chemical shifts are given as δ values against tetramethylsilane as internal standard. The ir spectra were measured with a Bruker IRS48 instrument as potassium bromide pellets. Microanalyses were performed by the Servicio de Microanáisis of the Universidad Complutense of Madrid. The reaction was monitored by tlc performed on silica-gel plates (Merck 60-F) and using benzene:methanol (7:3) as the eluent. The geometry optimization was carried out with the semiempirical AM1 method by using the MOPAC molecular orbitals set. Previously, the molecular geometry was optimized by using Allinger's Molecular Mechanics with PCMODEL program. Calculations were performed on a PC 486/33 computer. Meldrum's acid, *o*-nitrobenzaldehyde, *m*-nitrobenzaldehyde, *o*-chlorobenzaldehyde, triethylamine, ethyl cyanoacetate, urea and thiourea were obtained from commercial sources.

6-Amino-2,4-dioxo-1,2,3,4-tetrahydro-1,3(2*H*)pyrimidine (**1**) and 6-amino-4-oxo-2-thyoxo-1,2,3,4-tetrahydro-1,3(2*H*)-pyrimidine (**2**) were obtained by following the method previously reported in the literature [11]. 5-Arylidene-2,2-dimethyl-1,3-dioxan-4,6-diones **3a-c** were obtained by the standard procedure [12].

5-Aryl-2,4,7-trioxo-1,2,3,4,5,6,7,8-octahydropyrido[2,3-*d*]-pyrimidines **5a-c** and 5-Aryl-4,7-dioxo-2-thioxo-1,2,3,4,5,6,7,8-octahydropyrido[2,3-*d*]pyrimidines **6a-c**.

General Procedure.

A mixture of the corresponding 6-amino-1,2,3,4-tetrahydro-1,3(2*H*)-pyrimidine **1** or **2** and the respective arylidene-2,2-dimethyl-1,3-dioxane-4,6-diones **3a-c** in glacial acetic acid (250 ml) was refluxed for a variable length of time (22-30 hours, monitored by tlc). The solution was concentrated *in vacuo* to 20 ml and then poured into ice water. The solid that precipitated was collected by filtration and washed with water until neutral *p*H. Further purification was accomplished by recrystallization from ethanol.

5-(2-Nitrophenyl)-2,4,7-trioxo-1,2,3,4,5,6,7,8-octahydropyrido-[2,3-*d*]pyrimidine (**5a**).

This compound was obtained by following the above general procedure, by refluxing **1** and **3a** for 29 hours in 54% yield, mp 309-311°, ir (potassium bromide): 3435, 3320, 3215 (NH), 1715, 1690 (C=O), 1530 (NO_2), 1460-1560 (Ph), 1345 (NO_2) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 10.97 (s, 1H, NH), 10.42 (s, 1H, NH), 9.77 (s, 1H, NH), 7.95-7.31 (m, 4H, Ph), 4.52 (d, 1H, H-5, $J_{5,6}$ 8.3), 3.30 (dd, 1H, H-6, $J_{6,6'}$ 16.2, $J_{6,5}$ 8.9), 2.49 (d, 1H, H-6', $J_{6',6}$ 16.2); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 168.7 (C7), 162.4 (C2), 150.1 (C4), 148.5 (C8a), 147.3, 136.8, 133.9, 128.3, 128.1, 124.8 (aryl), 88.1 (C4a), 37.7 (C6), 29.2 (C5).

Anal. Calcd. for $C_{13}H_{10}N_4O_5$ (302.23): C, 51.66; H, 3.33; N, 18.54. Found: C, 51.72; H, 3.41; N, 18.63.

5-(3-Nitrophenyl)-2,4,7-trioxo-1,2,3,4,5,6,7,8-octahydropyrido-[2,3-*d*]pyrimidine (**5b**).

This compound was obtained by following the above general procedure, by refluxing **1** and **3b** for 30 hours in 50% yield, mp 305-306°; ir (potassium bromide): 3435, 3320, 3215 (NH), 1715, 1690 (C=O), 1530 (NO_2), 1460-1560 (Ph), 1345 (NO_2) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 10.97 (s, 1H, NH), 10.42 (s, 1H, NH), 9.77 (s, 1H, NH), 7.95-7.31 (m, 4H, Ph), 4.52 (d, 1H, H-5, $J_{5,6}$ 8.3), 3.30 (dd, 1H, H-6, $J_{6,6}$ 16.2, $J_{6,5}$ 8.9), 2.49 (d, 1H, H-6', $J_{6,6}$ 16.2); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 169.2 (C7), 162.7 (C2), 150.2 (C4), 148.0 (C8a), 146.8, 145.0, 133.3, 130.2, 121.9, 121.3 (aryl), 88.6 (C4a), 37.9 (C6), 32.7 (C5).

Anal. Calcd. for $C_{13}H_{10}N_4O_5$ (302.23): C, 51.66; H, 3.33; N, 18.54. Found: C, 51.73; H, 3.51; N, 18.71.

5-(2-Chlorophenyl)-2,4,7-trioxo-1,2,3,4,5,6,7,8-octahydropyrido-[2,3-*d*]pyrimidine (**5c**).

This compound was obtained by following the above general procedure, by refluxing **1** and **3c** for 28 hours in 60% yield, mp 323-325°; ir (potassium bromide): 3420, 3310, 3220 (NH), 1700, 1690 (C=O), 1450-1565 (Ph) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 10.97 (s, 1H, NH), 10.39 (s, 1H, NH), 9.70 (s, 1H, NH), 7.48-7.14 (m, 4H, Ph), 4.45 (d, 1H, H-5, $J_{5,6}$ 8.34), 3.18 (dd, 1H, H-6, $J_{6,6'}$ 16.2, $J_{6,5}$ 8.2), 2.41 (d, 1H, H-6', $J_{6',6}$ 16.2); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 168.8 (C7), 162.4 (C2), 150.1 (C4), 147.4 (C8a), 138.8, 132.3, 129.9, 128.8, 127.6, 127.3, (aryl), 87.8 (C4a), 37.1 (C6), 30.6 (C5).

Anal. Calcd. for $C_{13}H_{10}ClN_3O_3$ (291.69): C, 53.53; H, 3.46; N, 14.41. Found: C, 53.67; H, 3.55; N, 14.62.

5-(2-Nitrophenyl)-4,7-dioxo-2-thioxo-1,2,3,4,5,6,7,8-octahydro-pyrido[2,3-*d*]pyrimidine (**6a**).

This compound was obtained by following the above general procedure, by refluxing **2** and **3a** for 22 hours in 52% yield, mp 297-299°; ir (potassium bromide): 3430, 3315, 3215 (NH), 1705, 1690 (C=O), 1525 (NO_2), 1455-1560 (Ph), 1355 (C=S), 1345 (NO_2) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 12.40 (s, 1H, NH), 11.83 (s, 1H, NH), 9.44 (s, 1H, NH), 7.95-7.36 (m, 4H, Ph), 4.54 (d, 1H, H-5, $J_{5,6}$ 8.5), 3.33 (dd, 1H, H-6, $J_{6,6'}$ 16.4, $J_{6,5}$ 8.4), 2.52 (d, 1H, H-6', $J_{6',6}$ 16.4); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 174.3 (C2), 168.1 (C7), 159.9 (C4), 148.5 (C8a), 146.8, 136.2, 134.0, 128.6, 128.3, 124.8 (aryl), 92.9 (C4a), 37.4 (C6), 29.3 (C5).

Anal. Calcd. for $C_{13}H_{10}N_4O_4S$ (318.31): C, 49.05; H, 3.17; N, 17.60. Found: C, 49.22; H, 3.27; N, 17.70.

5-(3-Nitrophenyl)-4,7-dioxo-2-thioxo-1,2,3,4,5,6,7,8-octahydro-pyrido[2,3-*d*]pyrimidine (**6b**).

This compound was obtained by following the above general procedure, by refluxing **2** and **3b** for 22 hours in 48% yield, mp 266-268°; ir (potassium bromide): 3430, 3310, 3220 (NH), 1705, 1690 (C=O), 1525 (NO_2), 1455-1560 (Ph), 1350 (C=S), 1345 (NO_2) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 12.43 (s, 1H, NH), 11.80 (s, 1H, NH), 9.38 (s, 1H, NH), 8.09-7.59 (m, 4H, Ph), 4.35 (d, 1H, H-5, $J_{5,6}$ 7.5), 3.19 (dd, 1H, H-6, $J_{6,6'}$ 16.6, $J_{6,5}$ 8.1), 2.52 (d, 1H, H-6', $J_{6',6}$ 16.5); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 174.2 (C2), 168.7 (C7), 160.1 (C4), 148.0 (C8a), 146.2, 144.3, 133.2, 130.3, 122.0, 121.5 (aryl), 93.2 (C4a), 37.5 (C6), 32.7 (C5).

Anal. Calcd. for $C_{13}H_{10}N_4O_4S$ (318.31): C, 49.05; H, 3.17; N, 17.60. Found: C, 49.18; H, 3.28; N, 17.77.

5-(2-Chlorophenyl)-4,7-dioxo-2-thioxo-1,2,3,4,5,6,7,8-octahydro-pyrido[2,3-*d*]pyrimidine (**6c**).

This compound was obtained by following the above general procedure, by refluxing **2** and **3c** for 26 hours in 54% yield, mp 303-305°; ir (potassium bromide): 3425, 3350, 3200 (NH), 1695, 1685 (C=O), 1450-1555 (Ph), 1355 (C=S) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 12.41 (s, 1H, NH), 11.90 (s, 1H, NH), 9.37 (s, 1H, NH), 7.48-7.12 (m, 4H, Ph), 4.48 (d, 1H, H-5, $J_{5,6}$ 7.4), 3.21 (dd, 1H, H-6, $J_{6,6'}$ 16.4, $J_{6,5}$ 8.2), 2.42 (d, 1H, H-6', $J_{6',6}$ 16.4); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 174.3 (C2), 168.3 (C7), 159.9 (C4), 146.9 (C8a), 138.3, 132.3, 129.0, 127.7, 127.5, 124.8 (aryl), 92.6 (C4a), 36.8 (C6), 30.5 (C5).

Anal. Calcd. for $C_{13}H_{10}ClN_3O_2S$ (307.75): C, 50.74; H, 3.28; N, 13.65. Found: C, 50.81; H, 3.38; N, 13.72.

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