SYNTHESIS AND POLYBROMINATION OF AZULENO[6,5-*d*]-THIAZOLE AND IT'S 2-METHYL DERIVATIVES

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Abstract-Azuleno[6,5-*d*]thiazole (**5a**) and its 2-methyl derivative (**8**) were obtained by the deethoxycarbonylation of the corresponding diethyl azuleno[6,5-*d*]thiazole-5,7-dicarboxylate (**4a**) and 2-methyl derivative (**6b**) which were synthesized from diethyl 2-acetylamino-6-aminoazulene-1,3-dicarboxylate (**1**) in a few steps. Polybromination of **5a** and **8** in 10% aqueous THF led to the corresponding 5-bromo-7,9-azulenequinono[6,5-*d*]thiazole (**9a**) and 2-methyl derivative (**9b**), respectively.

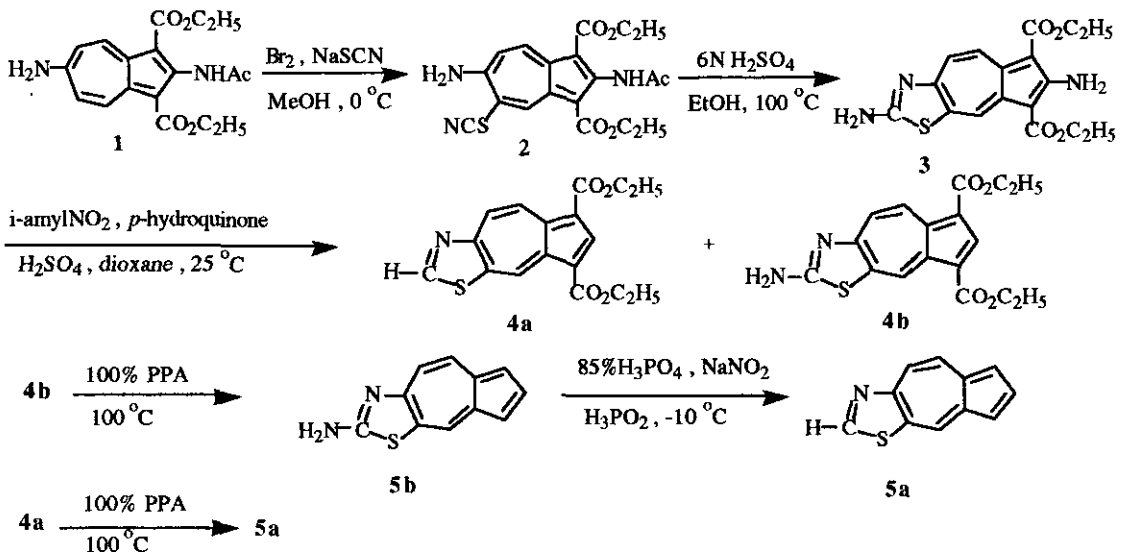
The azulenoid heterocyclic compounds which consist of an azulene ring condensed with heterocyclic aromatics are of interest not only in their physical properties[1,2] and chemical behaviors,[3] but also in their physiological activities. Heterocyclic compounds fused with the five-membered ring of azulene, such as furan,[4] thiophene,[5] pyrrole,[4] pyrazole,[6] imidazole,[7] thiazole,[8] pyridine,[9] pyridazine,[10] pyrimidine,[7] pyrazine,[11] thiapyran,[12] and quinoxaline[13] are known. However, no azuleno[6,5-*d*]thiazoles and its 2-methyl derivatives are known. We describe herein a facile method for the synthesis of these novel heterocyclic compounds, azuleno[6,5-*d*]thiazole (**5a**) and its 2-methyl derivative (**8**), in which a heterocycle was fused with the seven-membered ring of the azulene, and we report an application of azulenequinone synthesis[14] to prepare two azulenequinone derivatives (**9a**) and (**9b**) which have a fused-thiazole on the seven-membered moiety.

The reaction of diethyl 2-acetylamino-6-aminoazulene-1,3-dicarboxylate (**1**)[15] with thiocyanogen bromide

gave the 5-thiocyano compound (**2**) in 98% yield. Deacetylation of compound (**2**), on treatment with an aqueous 6N sulfuric acid solution in ethanol at 100 °C, formed the thiazole ring by annelation to give *diethyl 6-amino-2-aminoazuleno[6,5-d]thiazole-5,7-dicarboxylate* (**3**) in 98% yield. The structure of **3** was confirmed by its ir spectrum which revealed no absorption of thiocyano group. Reacton of **3** with isoamyl nitrite in the presence of concentrated sulfuric acid and *p*-hydroquinone in dioxane at 25 °C[16] produced diethyl azuleno[6,5-*d*]thiazole-5,7-dicarboxylate (**4a**) and diethyl 2-aminoazuleno[6,5-*d*]-thiazole-5,7-dicarboxylate (**4b**) in 62% and 25% yields, respectively. Heating of **4b** in 100% phosphoric acid at 100 °C resulted in deethoxycarbonylation to give 2-aminoazuleno[6,5-*d*]thiazole (**5b**) in 92% yield. *The spectral data (^{1}H Nmr and ir) have shown that* **5b** *exists in the amino form.*

The replacement of the 2-amino functionality of **5b** with hydrogen was achieved by use of the following procedure:[17] Compound **5b** was diazotized with a concentrated aqueous sodium nitrite solution in 85% phosphoric acid at -10 °C and followed by addition of hypophosphorous acid to give azuleno[6,5-*d*]thiazole (**5a**) in 23% yield. The same compound was also obtained by the treatment of **4a**, with 100% phosphoric acid at 100 °C in 90% yield (Scheme 1).

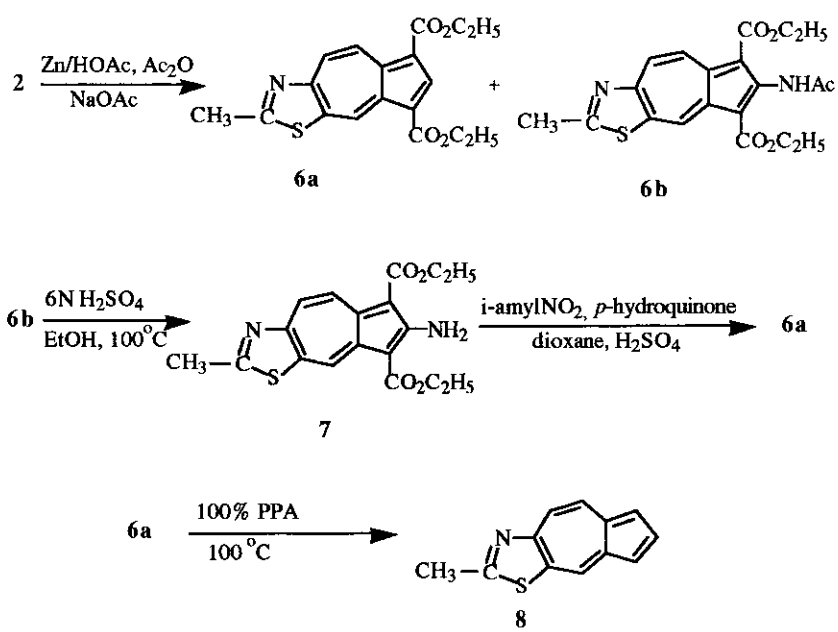
Scheme 1



Reductive acetylation of compound (**2**), on treatment with zinc dust in acetic acid and acetic anhydride at room temperature, underwent ring closure to give a mixture of diethyl 2-methylazuleno[6,5-*d*]thiazole-5,7-dicarboxylate (**6a**) and diethyl 6-acetylamino-2-methylazuleno[6,5-*d*]thiazole-5,7-dicarboxylate (**6b**) in

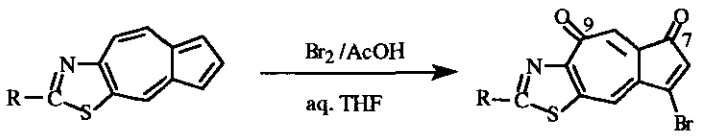
15% and 53% yields. ^{1}H-Nmr spectrum of **6a** revealed that there is a singlet at δ 8.80, which is corresponding to the H-6 proton on the five-membered ring. Hydrolysis of **6b**, on heating with the 6N H_2SO_4 in ethanol at 100 °C gave diethyl 6-amino-2-methylazuleno[6,5-*d*]thiazole-5,7-dicarboxylate (**7**) in 98% yield, followed by deamination to obtain **6a** in 86% yield. Furthermore, the deethoxycarbonylation of **6a** by heating with 100% phosphoric acid at 100 °C gave 2-methylazuleno[6,5-*d*]thiazole (**8**) in 95% yield (Scheme 2).

Scheme 2



Polybrominations of **5a** and **8** were carried out in accordance with the procedure described in the paper.[14] Reaction of **5a** and **8** in 10% aqueous THF with bromine in acetic acid at 5-10 °C gave 5-bromo-7,9-azulenequinono[6,5-*d*]thiazole (**9a**) and 2-methyl-5-bromo-7,9-azulenequinono[6,5-*d*]thiazole (**9b**) in 83% and 87% yield, respectively (Scheme 3).

Scheme 3



5a: R=H
8: R=CH_3

9a: R=H
9b: R=CH_3

EXPERIMENTAL

All melting points are uncorrected. The instruments to record spectra were, for ultraviolet-visible Shimadzu UV-202 and UV-160, for infrared Perkin-Elmer IR-983G spectrophotometers, for mass spectra Finnigan TSQ-46C, for high-resolution mass spectra JEOL JMS-HX110, for nuclear magnetic resonance (^{1}H nmr) Bruker AC-300. Chemical shifts (δ) and coupling constants (Hz) were measured with respect to TMS.

Diethyl 2-acetylamino-5-thiocyano-6-aminoazulene-1,3-dicarboxylate (2)

To a solution of **1** (500 mg, 1.45 mmol) and NaSCN (235 mg, 2.9 mmol) in 25 ml of MeOH, a solution of bromine (348 mg, 2.2 mmol) in 5 ml of MeOH which was saturated with NaBr was added at 0 °C. After the reaction mixture was stirred for 3 h, the mixture was concentrated under reduce pressure, diluted with water, extracted with EtOAc, and dried over anhydrous Na_2SO_4. Removal of EtOAc in *vacuo* gave the residue which was purifed by column chromatography (silica gel, EtOAc:n-hexane = 5:1) to obtain a yellow solid. It was crystallized from EtOAc and CH_2Cl_2 (1: 2) to afford **2** (570 mg, 98%) as a yellow prisms; mp 282 °C (decomp.).

2: ^{1}H-Nmr (300 MHz, DMSO-d_6) δ 1.33 (6H, t, J=7.0 Hz, $CO_2CH_2C\underline{H}_3$ x 2), 2.13 (3H, s, NHCO-$C\underline{H}_3$), 4.27 (4H, q, J=7.0 Hz, $CO_2C\underline{H}_2CH_3$ x 2), 7.84 (1H, d, J=11.3 Hz, H-7), 8.63 (2H, br s, NH_2), 9.04 (1H, d, J=11.3 Hz, H-8), 9.56 (1H, s, H-4), 9.89 (1H, s, $N\underline{H}COCH_3$); ir (KBr) 3402, 3394, 3300, 2159, 1685 cm^{-1}; ms (40 ev) m/z 401 (M^+), 359, 313, 241; HRms m/z Calcd for $C_{19}H_{19}N_3O_5S$ 401.1045, Found 401.1031.

Diethyl 2-amino-6-aminoazuleno[6,5-*d*]thiazole-5,7-dicarboxylate (3)

A solution of **2** (450 mg, 1.1 mmol) in 30 ml of EtOH was added 6N H_2SO_4 (5 ml), the mixture was stirred at reflux for 3 h. After cooling, neutralization with 6M NaOH, the yellow precipitate was collected, washed with water and dissolved in EtOAc. After drying over anhydrous Na_2SO_4, the solvent was removed in *vacuo* , 387 mg of pure **3** was obtained as yellow solid (98%); mp 298 °C (decomp.).

3: ^{1}H-Nmr (300 MHz, DMSO-d_6) δ 1.37 (6H, t, J=7.0 Hz, $CO_2CH_2C\underline{H}_3$ x 2), 4.35 (4H, q, J=7.0 Hz, $CO_2C\underline{H}_2CH_3$ x 2), 7.45 (2H, br s, NH_2), 7.78 (1H, d, J=11.4 Hz, H-9), 8.23 (2H, br s, NH_2), 9.03 (1H, d, J=11.4 Hz, H-8), 9.45 (1H, s, H-4); ^{13}C-nmr (75.0 MHz, DMSO-d_6) 14.51, 59.11, 59.34, 95.45, 99.84, 122.85, 123.83, 128.38, 137.86, 140.78, 157.96, 158.99, 165.50, 165.67, 168.61; ir (KBr) 3490, 3338, 2980, 1652, 1589 cm^{-1}; ms (40 ev) m/z 359 (M^+), 313, 268, 241; HRms m/z Calcd for $C_{17}H_{17}N_3O_4S$ 359.0939, Found 359.0925.

Diethyl azuleno[6,5-*d*]thiazole-5,7-dicarboxylate (4a) and its 2-amino derivative (4b)

To a stirred solution of **3** (500 mg, 1.4 mmol), hydroquinone (2.31 g, 21 mmol) and conc. H_2SO_4 (137 mg, 1.4 mmol) in dioxane (125 ml) at 25 °C was added isopentyl nitrite (2.45 g, 21 mmol) in dioxane (10 ml) during 20 min. After stirring for 3 h, the reaction mixture was quenched by adding 1M Na_2SO_3 (100 ml) and extracted with EtOAc, the organic layer was washed with saturated $NaHSO_3$, dried over anhydrous Na_2SO_4 and concentrated under reduce pressure. The crude residue was subjected to column chromatography (silica gel, EtOAc:n-hexane = 1:1) to give **4a** (285 mg, 62%) as a pink needles (from acetone), mp 148-150 °C, and **4b** (120 mg, 25%) as a dark red needles (from EtOAC), mp > 300 °C, respectively.

4a: ^{1}H-Nmr (300 MHz, $CDCl_3$) δ 1.45 (6H, t, J=7.2 Hz, $CO_2CH_2C\underline{H}_3$ x 2), 4.46 (4H, q, J=7.1 Hz, $CO_2C\underline{H}_2CH_3$ x 2), 8.50 (1H, d, J=11.1 Hz, H-9), 8.79 (1H, s, H-6), 9.33 (1H, s, H-2), 9.78 (1H, d, J=11.1 Hz, H-8), 10.46 (1H, s, H-4); ^{13}C-nmr (75.0 MHz, $CDCl_3$) δ 14.54, 60.18, 60.25, 115.63, 117.97, 127.01, 132.97, 133.21, 137.02, 138.73, 141.54, 142.76, 159.08, 159.36, 164.99, 165.05; ir (KBr) 2988, 1675, 1426, 1384 cm^{-1}; ms (40 ev) m/z 329 (M^+), 299, 271, 241, 200; HRMS m/z Calcd for $C_{17}H_{15}NO_4S$ 329.0827, Found 329.0831.

4b: ^{1}H-Nmr (300 MHz, DMSO-d_6) δ 1.35 (6H, t, J=7.1 Hz, $CO_2CH_2C\underline{H}_3$ x 2), 4.31 (4H, q, J=7.1 Hz , $CO_2C\underline{H}_2CH_3$ x 2), 7.92 (1H, d, J=11.1 Hz, H-9), 8.28 (1H, s, H-6), 8.87 (2H, br s, NH_2), 9.47 (1H, d, J=11.0 Hz, H-8), 9.91 (1H, s, H-4); ^{13}C-nmr (75.0 MHz, DMSO-d_6) δ 14.43, 59.38, 113.07, 114.51, 128.50, 130.35, 134.73, 135.30, 135.77, 136.73, 137.92, 163.64, 164.42, 172.62; ir (KBr) 3330, 3328 , 2986, 1660, 1515 cm^{-1}; ms (40 ev) m/z 344 (M^+), 299, 271, 241, 200; HRms m/z Calcd for $C_{17}H_{16}N_2O_4S$ 344.0827, Found 344.0831.

Azuleno[6,5-*d*]thiazole (5a) and its 2-amino derivative (5b)

To a vigorously stirred hot 100% phosphoric acid (5 ml) was quickly added **4a** or **4b** (100 mg) at 100 °C. After only 15 min stirring, crushed ice (50 g) was added. The mixture was extracted with CH_2Cl_2. The organic extract was washed with saturated $NaHCO_3$ and brine, then dried over anhydrous Na_2SO_4. After the solvent was removed, the residue was chromatographed on silica gel with CH_2Cl_2 to give **5a** (56 mg,

90%) as blue prisms (from EtOAc), mp 128-130 °C, and **5b** (58 mg, 92%) as purplish blue prisms (from EtOAc), mp 232 °C (decomp.), respectively.

5a: ^{1}H-Nmr (300 MHz, $CDCl_3$) δ 7.35 (1H, d, J=3.7 Hz, H-7), 7.42 (1H, d, J=3.7 Hz, H-5), 7.81 (1H, t, J=3.7 Hz, H-6), 7.90 (1H, d, J=10.9 Hz, H-9), 8.27 (1H, d, J=10.9 Hz, H-8), 8.80 (1H, s, H-4), 9.10 (1H, s, H-2); ^{13}C-nmr (75.0 MHz, $CDCl_3$) δ 118.29, 119.11, 121.17, 125.02, 128.67, 132.01, 134.32, 136.04, 154.86, 155.66, 160.10; ir (KBr) 2958, 2920, 1656, 1560, 1384 cm^{-1}; ms (40 ev) m/z 185 (M^+), 158, 149; HRms m/z Calcd for $C_{11}H_7NS$ 185.0299, Found 185.0312.

5b: ^{1}H-Nmr (300 MHz, Acetone-d_6) δ 7.17 (1H, d, J=3.7 Hz, H-7), 7.24 (1H, d, J=3.7 Hz, H-5), 7.33 (2H, br s, NH_2), 7.38 (1H, d, J=10.6 Hz, H-9), 7.53 (1H, t, J=3.7 Hz, H-6), 8.19 (1H, d, J=10.7 Hz, H-8), 8.64 (1H, s, H-4); ^{13}C-nmr (75.0 MHz, Acetone-d_6) δ 116.35, 117.37, 119.30, 127.67, 129.47, 133.14, 134.02, 135.42, 136.21, 160.28, 170.30 ; ir (KBr) 3389, 3280, 1633, 1590, 1496 cm^{-1}; ms (40 ev) m/z 200 (M^+), 173, 158, 146 ; HRms m/z Calcd for $C_{11}H_8N_2S$ 200.0410, Found 200.0408.

Diethyl 2-methylazuleno[6,5-*d*]thiazole-5,7-dicarboxylate (6a) and its 6-acetylamino derivative (6b)

To a stirred solution of 2 (500 mg, 1.24 mmol) and NaOAc (580 mg, 4.3 mmol) in glacial acetic acid (10 ml) and acetic anhydride (10 ml) at 25 °C was added zinc dust (1.5 g, 23 mmol) over a period of 10 min. The color of the solution changed to brown as the zinc was added. After stirring for 5 h the suspension was poured into water and the whole extracted with CH_2Cl_2. The organic extract was washed with saturated $NaHCO_3$ and brine, then dried over anhydrous Na_2SO_4. After the solvent was removed, the residue was chromatographed on silica gel with EtOAc and n-hexane (1:1) to give two eluates. The first eluate afforded **6a** (64 mg, 15%) as pink prisms (from CH_2Cl_2); mp 146-148 °C. The second eluate gave **6b** (263 mg, 53%) as brownish yellow prisms (from EtOAc); mp 175-177 °C.

6a:^{1}H-nmr (300 MHz, $CDCl_3$) δ 1.47 (6H, t, J=7.0 Hz, $CO_2CH_2C\underline{H}_3$ x 2), 2.97 (3H, s), 4.45 (4H, q, J=7.0 Hz, $CO_2C\underline{H}_2CH_3$ x 2), 8.40 (1H, d, J=11.3 Hz, H-9), 8.80 (1H, s, H-6), 9.80 (1H, d, J=11.3 Hz, H-8), 10.40 (1H, s, H-4); ir (KBr) 2935, 1701, 1686 ,1471 cm^{-1}; ms (40 ev) m/z 343 (M^+), 298, 270, 199; HRms m/z Calcd for $C_{18}H_{17}NO_4S$ 343.3973, Found 343.3975.

6b: ^{1}H-nmr (300 MHz, $CDCl_3$) δ 1.46 (6H, t, J=7.0 Hz, $CO_2CH_2C\underline{H}_3$ x 2), 2.30 (3H, s, $NHCOC\underline{H}_3$), 2.93 (3H, s), 4.46 (4H, q, J=7.0 Hz, $CO_2C\underline{H}_2CH_3$ x 2), 8.29 (1H, d, J=11.3 Hz, H-9), 9.22 (1H, d, J= 11.3 Hz, H-8), 9.87 (1H, s, H-4), 10.45 (1H, br s, $N\underline{H}COCH_3$); ir (KBr) 3259, 2979, 2909, 1711, 1693, 1652 cm^{-1}; ms (40 ev) m/z 400 (M^+), 358, 314, 240; HRms m/z Calcd for $C_{20}H_{20}N_2O_5S$ 400. 4492, Found 400.4489.

Diethyl 6-amino-2-methylazuleno[6,5-*d*]thiazole-5,7-dicarboxylate (7)

Compound **(7)** was synthesized from **6b** using the same procedure as that described for **3** (98%); mp 268 °C (decomp.).

7: ^{1}H-Nmr (300 MHz, $CDCl_3$) δ 1.48 (6H, t, J=7.0 Hz, $CO_2CH_2C\underline{H}_3$ x 2), 2.87 (3H, s), 4.49 (4H, q, J= 7.0 Hz, $CO_2C\underline{H}_2CH_3$ x 2), 7.70 (2H, br s, $N\underline{H}_2$), 8.20 (1H, d, J=11.4 Hz, H-9), 9.21 (1H, d, J=11.4 Hz, H-8), 9.73 (1H, s, H-4); ir (KBr) 3490, 2935, 1683, 1475 cm^{-1}; ms (40 ev) m/z 358 (M^+), 313; HRms m/z Calcd for $C_{18}H_{18}N_2O_4S$ 358.4119, Found 358.4114.

2-Methylazuleno[6,5-*d*]thiazole (8)

Compound **(8)** was synthesized from **6a** using the same procedure as that described for **5a-b** (95%); mp 92-94 °C.

8: ^{1}H-Nmr (300 MHz, $CDCl_3$) δ 2.90 (3H, s), 7.34 (1H, d , J=3.45 Hz, H-7), 7.40 (1H, d, J=3.45 Hz, H-5), 7.81 (1H, t, J=3.45 Hz, H-6), 7.80 (1H, d, J=10.9 Hz, H-9), 8.29 (1H, d, J=10.9 Hz, H-8), 8.72 (1H, s, H-4); ^{13}C-nmr (75.0 MHz , $CDCl_3$) δ 20.25, 117.83, 118.29, 120.47, 128.03, 128.60, 131. 52, 132.34, 134.82, 135.53, 155.66, 169.40; ir (KBr) 2948, 2915, 1653, 1545, 1378 cm^{-1}; ms (40 ev) m/z 199 (M^+), 158, 117; HRms m/z Calcd for $C_{12}H_9NS$ 199.2701, Found 199.2706.

5-Bromo-7,9-azulenequinono[6,5-*d*]thiazole (9a) and its 2-methyl derivative (9b)

To a stirred solution of **5a** or **8** (100 mg) in 10 % aqueous THF (20 ml) was added 4.3 equiv. of bromine (0.37 g) in acetic acid (4 ml) during 3 min at 5-10 °C. After stirring for 1 h water (20 ml) was added, the solution was kept at room temperature overnight and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, evaporated in *vacuo*, and the residue was purified by column chromatography (silica gel, CH_2Cl_2) to give **9a** (83%) as pale yellow needles (from CH_2Cl_2); mp 162 °C (decomp.), **9b** (87%) as a pale yellow needles (from CH_2Cl_2); mp 176 °C (decomp.).

9a: ^{1}H-Nmr (300 MHz, $CDCl_3$) δ 6.92 (1H, s, H-6), 7.34 (1H, s, H-4), 7.95 (1H, s, H-8), 9.15 (1H, s, H-2); ir (KBr) 2958, 2854, 1730, 1701, 1636, 1465 cm^{-1}; ms (40 ev) m/z 295 (M^++ 2), 293 (M^+), 267, 265, 186, 158.

9b: ^{1}H-Nmr (300 MHz, $CDCl_3$) δ 2.90 (3H, s), 6.89 (1H, s, H-6), 7.33 (1H, s, H-4), 7.85 (1H, s, H-8); ir (KBr) 2922, 2854, 1724, 1702, 1639, 1471 cm^{-1}; ms (40 ev) m/z 309 (M^++ 2), 307 (M^+), 295, 293, 229, 200.

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