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SYNTHESIS OF HETEROCYCLE-ANNULATED AZULENEQUINONE DERIVATIVES

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Abstract - Treatment of 2-methoxyazulene (**2**) with 4.2 equiv. of bromine in aqueous THF at 0℃ for 1 h afforded 3-bromo-2-methoxy-1,5- (**1a**) and -1,7-azulenequinone (**1b**) in a 16:1 ratio. Reaction of 1a with o-aminobenzenethiols gave 12H-azuleno[1,2-b]benzo[*e*][1,4]thiazine-7,11-dione derivatives (**6a,b**).

Azulenequinones have attracted much attention from the viewpoint of their physicochemical properties and pharmacological activities.[1] Recently, we have reported the preparation of 1,5- and 1,7-azulenequinones and their derivatives in high yields by the one-pot procedure using 4.0-4.5 equiv. of bromine in aqueous THF on azulene.[2] In these syntheses, 1,5- and 1,7- azulenequinones were obtained in a 3:1 ratio. We have also reported the utility of 3-bromo-1,5- and -1,7-azulenequinones as very useful synthons.[3]

Azulenequinone derivatives annulated with thiophene, furan, or pyrazole ring have been reported[4,5] by

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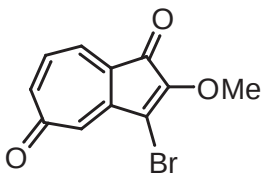
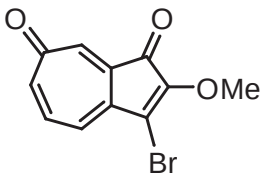
[†]Dedicated to Professor James P. Kutney on the occasion of his 70th birthday.

several groups, however, azulenequinones annulated with benzothiazine ring is still unknown. We wish to report here the synthesis and properties of 12*H*-azuleno[1,2-*b*]benzo[*e*][1,4]thiazine-7,11-dione and related compounds by the reaction of 3-bromo-2-methoxy-1,5-azulenequinone (**1a**) with *o*-disubstituted benzenes such as *o*-aminobenzenethiol.

3-Bromo-2-methoxy-1,5-azulenequinone (**1a**) having leaving groups on the C-2 and C-3 positions was prepared by our method of bromine-oxidation of 2-methoxyazulene[6] (**2**). Namely, to a stirred solution of **2** in aqueous THF was added 4.2 equiv. of bromine in acetic acid during 1 h at 0°C. To this solution was added water, and the mixture was kept at room temperature for two days. The solution was extracted with dichloromethane. The combined organic layers were evaporated in vacuo, and the residue was separated by chromatography on alumina to give **1a**[7] (yellow needles; mp 168-170°C, 63% yield), **1b**[8] (yellow needles; mp 143-145°C, 4% yield), and a small amount of dimer (**3**,[9] reddish violet needles; mp > 300°C). The structures of products were determined as follows. Both the MS spectrum of **1a**,**b**



1a



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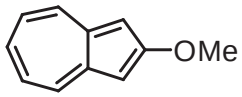
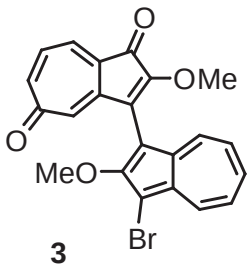


2



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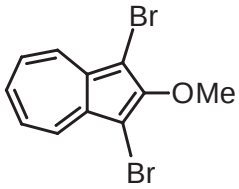

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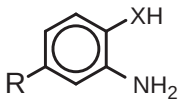
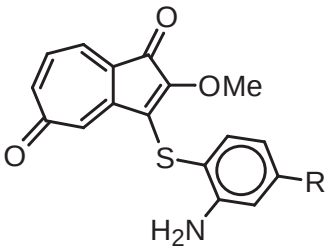
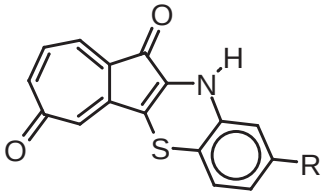


8a-c

a: X=S, R=H
b: X=S, R=CF_3
c: X=NH, R=H

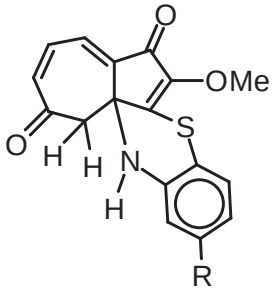


5a,b



6a,b

a: R=H
b: R=CF_3



7a,b

showed their molecular ion peaks at m/z 268 and 266 (rel int. 1:1). In the ^{1}H NMR spectrum of **1a**, the signal at δ 4.35 can be assigned for the methoxy protons and each signal at 6.84, 6.87, 7.02, and 7.13 can be assigned for H-4, H-6, H-7, and H-8 on the seven-membered ring, respectively. The ^{13}C NMR spectrum of **1a** showed two carbonyl carbon at δc 184 and 187. Characteristic carbonyl absorptions of azulenequinone in IR spectrum of **1a** were observed at 1703 and 1589 cm^{-1}. On the basis of all of these spectral data, the structure of **1a** was assigned as a 1,5-azulenequinone derivative as shown in Scheme. Similarly, structures of **1b** and **3** were established as shown in the Scheme. Interestingly, 1,5-azulenequinone (**1a**) was obtained more selectively (ratio **1a:1b**=16:1) than 3-bromo-1,5-azulenequinone and 3-bromo-1,7-azulenequinone (3:1).[2]

2 underwent bromination with NBS to give 1,3-dibromo-2-methoxyazulene (**4**) which was considered as one of the intermediates in above reaction. Indeed, a solution of **4** in aqueous THF was treated with bromine in acetic acid under the same condition of **2** to give **1a** and **1b**, similarly.

3-Bromo-1,5-azulenequinone generally undergoes nucleophilic substitution. In case of butylthiol, this quinone further undergos nucleophilic addition and oxidation.[3] Accordingly, if 1,5-azulenequinone has good leaving group at 2 and 3 position like **1a**, double nucleophilic substitution will be expected. Consequently, reaction of **1a** with several kind of *o*-disubstituted benzenes was examined to give results as shown in Table 1. When we monitored this reaction by TLC, **5a** (orange needles; mp 69-71°C, 33% yield) occurred immediately, and starting material **1a** disappeared within 60 min, while **6a** (green needles; mp > 300°C, 52% yield) and **7a** (orange oil, 5% yield) gradually increased.

Isolated **5a** in benzene were converted into **6a** and **7a**.

In these reaction, at first nucleophilic substitution took place generally to give products (**5a-c**). **5a** and **5b** underwent further nucleophilic substitution to give a main products (**6a**) and (**6b**) as expected products and nucleophilic addition to give minor products (**7a**) and (**7b**).

The IR spectrum of **5a** shows the characteristic absorption bands at 3344, 3308, and 3282 cm^{-1} assigned for the amino group. Characteristic carbonyl absorption of 1,5-azulenequinone appeared at 1680 and 1597 cm^{-1}. The ^{1}H-NMR spectrum of **5a** shows that signals observed at δ 3.92 and 4.23 are assigned for

the methoxy protons and the amino protons, respectively. Also, the signals at δ 6.72, 6.74, 7.19, and 7.41 are assigned for benzene ring protons. On the basis of these spectral data, the structure of **5a** was established. Analogously, the structure of **6a** was determined as follows. The IR spectrum of **6a** shows two carbonyl absorption bands of 1,5-azulenequinone at 1680 and 1597 cm^{-1}. In the ^{1}H-NMR spectrum of **6a**, there are signals at δ 5.75, 6.57, 6.91, and 7.04 and at δ 6.81, 6.83, 6.95, and 6.99 due to two sets of four protons on the seven-membered ring and benzene ring, respectively.

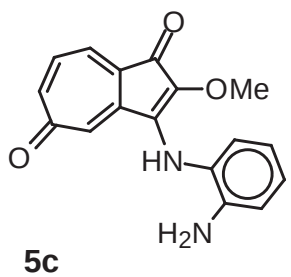
The ^{1}H-NMR spectrum of **7a** shows that signals at δ 4.21, 2.52, and 2.70 can be assigned for methoxy protons and non-equivalent methylene protons, respectively. These data suggested that **5a** underwent second nucleophilic attack at 3a-position.

The results of the similar reactions of **1a** with 2-amino-4-trifluoromethylbenzene (**8b**) and *o*-phenylene-diamine (**8c**) are summarized in Table 1.

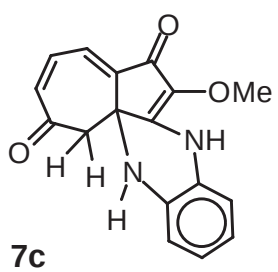
Table 1. Reactions of **1a** with *o*-aminobenzenethiols (**8a-c**).

Substrate Reagent	Products (yield %)		
8a	**5a**[10] (33)	**6a**[11] (52)	**7a**[12] (5)
8b	**5b** (12)	**6b**[13] (60)	**7b** (trace)
8c	**5c**[14] (15)	-	**7c**[15] (15)

The reaction of **1a** with **8b** afford **5b**, **6b**, and **7b**. However, **8c** did not give annulated type compound (**6c**).



5c



7c

The electronic spectra of 1,5-azulenequinones showed the absorption maximum of the longest

wavelength band centered at 450 nm, while those in the **6a** and **6b** are shown bathochromic shift and similar to those of 1,2-azulenequinone.[16] In order to clarify the origin of this bathochromic shift, we next synthesized azulenequinone derivatives having an amino group at the C-2 position and compared with their electronic spectra. The reaction of **1a** with ethylamine afforded **9**[17] (reddish violet needles; mp 70-72°C, 30% yield) and **10**[18] (reddish orange needles; mp 111-113°C, 45% yield).

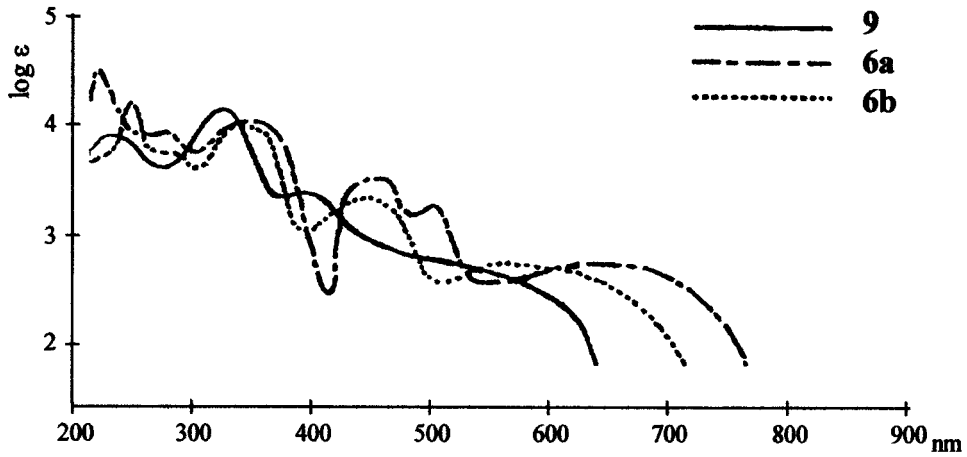
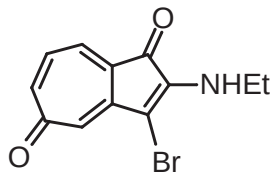
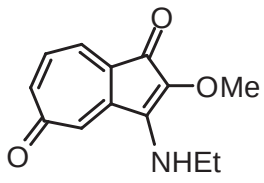


Figure 1. Electronic spectra (in MeOH) of azulenequinones (**6a**, **6b**, and **9**).

As shown in Figure 1, the electronic spectrum of **9** was shown bathochromic shift and similar to that of 1,2-azulenequinone. Therefore, compounds (**6a**, **6b**, and **9**) must be considered a little contribution of 1,2-azulenequinone form such as the structure (**11**).



9



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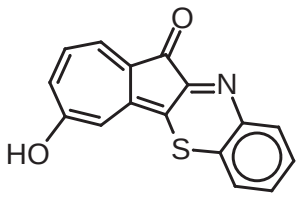

11

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7. **1a**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.35 (3H, s, OCH_3), 6.84 (1H, dd, *J* =2.5, 0.5 Hz, H-4), 6.87 (1H, ddd, *J* =12.2, 2.5, 1.0 Hz, H-6), 7.02 (1H, dd, *J* =12.2, 8.0 Hz, H-7), 7.13 (1H, ddd, *J* =8.0, 1.0, 0.5 Hz, H-8); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 59.48 (OCH_3), 126.56, 126.85 (CH), 129.20 (CH), 133.39 (CH), 134.13, 142.50, 143.35 (CH), 155.87, 184.36 (C=O), 186.66 (C=O); MS (EI, 70 eV): m/z (rel int.) 268 (M^+, 10), 266 (M^+, 10), 240 (38), 238 (39), 159 (100).
8. **1b**: IR (KBr) 1701 (C=O) and 1587 cm^{-1} (C=O); ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.33 (3H, s, OCH_3), 6.69 (1H, dd, *J*=8.4, 1.0 Hz, H-4), 6.70 (1H, ddd, *J*=12.3, 2.7, 1.0 Hz, H-6), 7.06 (1H, dd, *J*=12.3, 8.4 Hz, H-5), 7.10 (1H, d, *J* =2.7 Hz, H-8); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 59.47 (OCH_3), 122.36 (CH), 129.48, 132.26 (CH), 134.99, 135.83 (CH), 137.37 (CH), 140.12, 154.56, 185.14 (C=O), 188.03 (C=O); MS (EI, 70 eV): m/z (rel int.) 268 (M^+, 24), 266 (M^+, 24), 240 (28), 238 (29), 159 (100).
9. **3**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.88 (3H, s, OCH_3-Az), 4.25 (3H, s, OCH_3-AQ), 6.27 (1H, d, J=2.5 Hz, H-4), 6.84 (1H, ddd, *J* =12.0, 2.5, 1.0 Hz, H-6), 7.06 (1H, dd, *J* =12.0, 8.0 Hz, H-7), 7.30 (1H, t, *J* =9.8 Hz, H-7'), 7.31 (1H, d, *J*=8.0 Hz, H-8), 7.43 (1H, t, *J* =9.8 Hz, H-5'), 7.60 (1H, tt, *J* =9.8, 0.5 Hz, H-6'), 7.79 (1H, dd, *J* =9.8, 0.5 Hz, H-8'), 8.33 (1H, dd, *J* =9.8, 0.5 Hz, H-4');
10. **5a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.92 (3H, s, OCH_3), 4.23 (2H, br, NH_2), 6.72 (1H, td, *J* =8.0, 1.0 Hz, H-5'), 6.74 (1H, dd, *J* =8.0, 1.0 Hz, H-3'), 6.82 (1H, ddd, *J* =11.6, 2.4, 0.5 Hz, H-6), 6.92 (1H, d, *J* =2.4 Hz, H-4), 7.00 (1H, dd, *J* =11.6, 7.9 Hz, H-7), 7.08 (1H, dd, *J* =7.9, 1.0 Hz, H-8), 7.19 (1H, td, *J* =8.0, 1.0 Hz, H-4'), 7.41 (1H, dd, *J* =8.0, 1.0 Hz, H-6'); ^{13}C NMR (125.65 MHz, $CDCl_3$) δ 59.12 (OCH_3), 110.87, 115.27 (C-3'), 118.79 (C-5'), 126.07 (C-8), 128.32 (C-4), 131.26 (C-4'), 133.88 (C-7), 134.59, 135.93 (C-6'), 139.27, 142.62 (C-6), 144.11, 148.45, 156.61, 185.08 (C=O), 187.19

(C=O).

11. **6a**: UV λ max (MeOH) 230 (log ε 3.91, sh), 240 (3.96), 242 (3.96), 270 (3.96), 338 (3.85), 354 (3.86), 375 (3.83), 377 (3.74, sh), 388 (3.46, sh), 470 (3.39), 500 (3.35, sh), 660 nm (2.66); IR (KBr) 3278 (NH), 1680 (C=O), and 1597 cm^{-1} (C=O); ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.75 (1H, d, *J* =2.4 Hz, H-6), 6.57 (1H, ddd, *J* =12.2, 2.4, 1.0 Hz, H-8), 6.81 (1H, td, *J* =7.8, 1.0 Hz, H-3), 6.83 (1H, dd, *J* =7.8, 1.0 Hz, H-1), 6.91 (1H, dd, *J* =8.0, 1.0 Hz, H-10), 6.95 (1H, dd, *J* =7.8, 1.0 Hz, H-4), 6.99 (1H, td, *J* =7.8, 1.0 Hz, H-2), 7.04 (1H, dd, *J* =12.2, 8.0 Hz, H-9), 9.52 (1H, br, NH); ^{13}C NMR (125.65 MHz, DMSO-d_6) δ 113.59, 117.44 (C-1), 121.41 (C-6), 123.78 (C-10), 124.41 (C-3), 127.88 (C-4), 128.72, 129.22 (C-2), 134.34 (C-9), 135.30, 136.32, 140.03 (C-8), 140.78, 142.94, 180.08 (C=O, C-11), 186.00 (C=O, C-7).
12. **7a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.52 (1H, d, *J* =15.8 Hz, CHH), 2.70 (1H, dd, *J* =15.8, 1.5 Hz, CHH), 4.21 (3H, s, OMe), 6.60 (1H, dd, *J* =12.2, 1.5 Hz, H-6), 6.97 (1H, dd, *J* =12.2, 7.0 Hz, H-7), 7.04 (1H, d, *J* =7.0 Hz, H-8), 7.07 (1H, td, *J* =8.0, 1.0 Hz, H-4'), 7.09 (1H, dd, *J* =8.0, 1.0 Hz, H-6'), 7.26 (1H, td, *J* =8.0, 1.0 Hz, H-5'), 7.30 (1H, dd, *J* =8.0, 1.0 Hz, H-3'), 7.67 (1H, br, NH).
13. **6b**: Dark green needles; mp 213-215 °C; UV λ max ($CDCl_3$) 240 (log ε 4.43, sh), 260 (4.04), 272 (4.03), 334 (4.22), 354 (4.25), 375 (4.16), 425 (3.45, sh), 450 (3.58), 480 (3.53, sh), 615 (3.04), 667 (2.94, sh), 724 nm (2.63, sh); IR (KBr) 3296 (NH), 1681 (C=O), and 1593 cm^{-1} (C=O); ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.76 (1H, d, *J* =2.4 Hz, H-6), 6.58 (1H, ddd, *J* =12.2, 2.4, 1.0 Hz, H-8), 6.92 (1H, dd, *J* =7.8, 1.0 Hz, H-10), 7.02 (1H, d, *J* =2.0 Hz, H-1), 7.03 (1H, dd, *J* =12.2, 7.8 Hz, H-9), 7.07 (1H, dd, *J* =8.2, 2.0 Hz, H-3), 7.12 (1H, d, *J* =8.2 Hz, H-4), 9.68 (1H, br, NH); ^{13}C NMR (125.65 MHz, DMSO-d_6) δ 112.94 (CH), 119.53, 120.66 (CH), 122.18 (CH), 123.36 (CF_3, J_{C-F}=270 Hz), 124.54 (CH), 128.35, 128.64 (CH), 129.58 (C-CF_3, J_{C-CF}=32 Hz), 134.34 (CH), 135.02, 137.85, 140.40 (CH), 142.49, 179.99 (C=O), 185.92 (C=O).
14. **5c**: Orange needles; mp 165-170 °C; IR (KBr) 3330 (m), 3270 (m), 3230 (m), 1676 (m), 1630 (m), 1580 cm^{-1} (s); ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.58 (3H, s, OCH_3), 5.11 (2H, br, NH_2), 6.52 (1H, td, *J* =8.0, 1.0 Hz, H-5'), 6.66 (1H, ddd, *J* =12.2, 2.4, 1.0 Hz, H-6), 6.71 (1H, dd, *J* =8.0, 1.0 Hz, H-3'), 6.92 (1H, dd, *J* =8.0, 1.0 Hz, H-6'), 6.93 (1H, dd, *J* =7.9, 1.0 Hz, H-8), 6.97 (1H, td, *J* =8.0, 1.0 Hz, H-4'), 7.15 (1H, d, *J* =2.4 Hz, H-4), 7.17 (1H, dd, *J* =12.2, 7.9 Hz, H-7), 8.97 (1H, br, NH); ^{13}C NMR (125.65 MHz, DMSO-d_6) δ 58.50 (OCH_3), 114.80 (C-3'), 115.24 (C-5'), 121.76 (C-8), 123.25 (C-2), 126.53 (C-4), 126.89 (C-6'), 127.28 (C-4'), 136.13 (C-7), 137.58 (C-8a), 137.71 (C-1'), 139.36 (C-6), 140.56 (C-2'), 143.80 (C-3a), 149.11 (C-3), 181.24 (C=O, C-1), 186.82 (C=O, C-5); MS (EI, 70 eV): m/z (rel int.) 294 (M^+, 30), 279 (20), and 263 (100).
15. **7c**: Orange needles; mp 71-72 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.54 (1H, d, *J* =16.2 Hz, CHH),

3.01 (1H, dd, *J* =16.2, 1.0 Hz, CHH), 4.16 (3H, s, OCH_3), 6.46 (1H, dd, *J* =12.2, 1.0 Hz, H-6), 6.72 (1H, dd, *J* =8.0, 1.0 Hz, H-6'), 6.90 (1H, td, *J* =8.0, 1.0 Hz, H-4'), 6.92 (1H, d, *J* =6.7 Hz, H-8), 6.95 (1H, td, *J* =8.0, 1.0 Hz, H-5'), 6.96 (1H, dd, *J* =8.0, 1.0 Hz, H-3'), 7.05 (1H, dd, *J* =12.2, 6.7 Hz, H-7), 7.64 (2H, br, NH).

16. T. Morita, M. Karasawa, and K. Takase, *Chem. Lett.*, 1980, 197.
17. **9**: UV λ max (MeOH) 220 (log ε 4.12), 311 (4.28, sh), 323 (4.41), 335 (4.37, sh), 370 (3.66), 388 (3.65), 411 (3.56, sh), 470 (3.15, sh), 525 (3.07, sh), 580 nm (2.91, sh); IR (KBr) 3323 (NH), 1708 (C=O), and 1580 cm^{-1} (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.29 (3H, t, *J* =7.3 Hz, CH_3), 3.76 (2H, qd, *J* =7.3, 6.5 Hz, CH_2), 4.99 (1H, brt, *J* = 6.5 Hz, NH), 6.66 (1H, dd, *J* =2.4, 0.5 Hz, H-4), 6.76 (1H, ddd, *J* =12.2, 2.4, 1.2 Hz, H-6), 6.86 (1H, dd, *J* =12.2, 7.9 Hz, H-7), 6.99 (1H, ddd, *J* =7.9, 1.2, 0.5 Hz, H-8); ^{13}C NMR (125.65 MHz, $CDCl_3$) δ 16.30 (CH_3), 37.88 (CH_2), 114.63 (C-4), 125.67 (C-8), 132.75 (C-7), 134.92 (C-8a), 143.20 (C-6), 143.31 (C-3), 144.30 (C-2), 146.98 (C-3a), 185.65 (C-1), 186.76 (C-5); MS (EI, 70 eV): m/z (rel int.) 281 (M^+, 30), 279 (M^+, 30), 253 (76), 251 (77), 238 (97), 236 (100).
18. **10**: UV λ max (MeOH) 229 (log ε 4.22), 254 (4.16, sh), 318 (4.08, sh), 332 (4.11), 424 (3.51), 482 nm (3.34, sh); IR (KBr) 3314 (NH), 1672 (C=O), and 1589 cm^{-1} (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34 (3H, t, *J* =7 Hz, CH_3), 3.80 (2H, quintet, *J* =7 Hz, CH_2), 4.11 (3H, s, OCH_3), 6.20 (1H, brt, *J* = 7 Hz, NH), 6.73 (1H, ddd, *J* =11.9, 2.1, 1.0 Hz, H-6), 6.96 (1H, d, *J* =2.1 Hz, H-4), 7.02 (1H, dd, *J* =8.2, 1.0 Hz, H-8), 7.08 (1H, dd, *J* =11.9, 8.2 Hz, H-7); ^{13}C NMR (125.65 MHz, $CDCl_3$) δ 16.05 (CH_3), 39.55 (CH_2), 59.55 (OCH_3), 121.85 (C-8), 124.35 (C-4), 136.88 (C-7), 137.38 (C-2), 138.59 (C-8a), 139.33 (C-6), 141.55 (C-3a), 149.47 (C-3), 181.34 (C-5), 187.86 (C-1); MS (EI, 70 eV): m/z (rel int.) 231 (M^+, 77), 203 (29), 188 (100).