REACTION OF 2-AMINOAZULENES WITH ALDEHYDES.
ONE POT SYNTHESIS OF DIAZULENO[2,1-b:1,2-e]PYRIDINES†

Tetsuo Okujima, Tomomi Terazono, Shunji Ito,* Noboru Morita,* and Toyonobu Asao

Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan

Abstract - Diazuleno[2,1-b:1,2-e]pyridines (2a and 2b) were prepared in one pot by the reaction of 2-aminoazulene (1a) with paraformaldehyde or benzaldehyde in moderate yields. Bis(2-amino-3-ethoxycarbonyl-1-azulenyl)methane (8a) was formed by the reaction of ethyl 2-aminoazulene-1-carboxylate (1b) with 1/2 molar amount of paraformaldehyde. Treatment of 8a with paraformaldehyde at room temperature afforded three heterocyclic compounds (9, 10, and 11). When 2-acetylaminoazulenes (1c and 1d) were used for this reaction, bis(2-acetylamino-1-azuleny)methanes (8b and 8c) were exclusively formed.

INTRODUCTION

The reaction of azulenes with aldehydes under acidic conditions leads to the formation of di(1-azulenyl)methane derivatives along with 1,3-bis(1-azulenylmethyl)azulene derivatives.1,2 The reaction have been applied to the substituted azulenes including 2-methoxy- and 2-hydroxyazulenes, and a variety of substituted bis(1-azulenyl)methane derivatives have been obtained in high yields.3 It has also been reported that the extremely stable carbocations with high pK_R^+ values were derived from di(1-azulenyl)phenylmethane and tri(1-azulenyl)methane derivatives.2b,4

A novel azulene analogue of calixarenes5 consisting of four molecules of 2-methoxyazulene, i.e., [1.1.1.1]-2-methoxyazulenophane, has been synthesized using 2-methoxyazulenes and paraformaldehyde under acidic conditions.3a Our studies to prepare the calixarene derivatives from azulenes have been focused on the reaction of 2-aminoazulene derivatives with aldehydes. To the best of our knowledge, no

† Dedicated to Prof. Shô Ito on the occasion of his 77th birthday.
reactions of 2-aminoazulenes with aldehydes to produce di(1-azulenyl)methane derivatives have been reported hitherto. We have investigated the reaction of several 2-aminoazulenes (1a–d) with aldehydes toward the synthesis of calixarene derivatives. In this paper, we will report the reaction of 2-aminoazulenes (1a–d) with aldehydes under acidic conditions.

RESULTS AND DISCUSSION

We have carried out the reaction of 2-aminoazulene (1a) with aldehydes in acetic acid to prepare the di(1-azulenyl)methane derivatives. However, the reaction afforded diazuleno[2,1-b:1,2-e]pyridine (2a) as the sole product in 47% yield (Scheme 1). Synthesis of 2a by a multi-step reaction starting from 1a has been reported by Morita et al. Likewise, 6-phenyldiazuleno[2,1-b:1,2-e]pyridine (2b) was obtained by the reaction of 1a with benzaldehyde in 51% yield.

Scheme 2 illustrates a possible mechanism for the formation of 2a and 2b by the reaction of 1a with aldehydes. Mixing of 1a with aldehydes initially leads to the formation of 5, because the reaction of azulenes with aldehydes has been known to give bis(1-azulenyl)methane derivatives.

Scheme 1

\[
\begin{align*}
1a & \quad \xrightarrow{\text{RCHO, MeCOOH}} \quad 2a: R = H \\
 & \quad \xrightarrow{\text{RCHO, MeCOOH}} \quad 2b: R = \text{Ph}
\end{align*}
\]

Scheme 2

\[
\begin{align*}
1a & \quad \xrightarrow{\text{RCHO, MeCOOH}} \quad 5 \\
5 & \quad \xrightarrow{[O]} \quad 6 \\
6 & \quad \xrightarrow{\text{NH}_3} \quad 7 \\
7 & \quad \xrightarrow{\text{H}^+} \quad 2a: R = H \\
 & \quad \xrightarrow{\text{H}^+} \quad 2b: R = \text{Ph}
\end{align*}
\]

\(^1\)H NMR chemical shift of H in 2a is observed at down field (δ 9.24) compared with that of pyridine (δ 7.64). Large upfield shifts of H₄,₈ and H₅,₇ (δ 6.77 and 7.21, respectively) in 2b compared with those of
2a (δ 7.21 and 8.33, respectively) are attributable to the anisotropic effect of the phenyl group at the 6 position. A remarkable difference of the vicinal coupling constants ($J_{1,2} = 10.8, J_{2,3} = 8.3, J_{3,4} = 10.8,$ and $J_{4,5} = 8.2$ Hz for 2a; $J_{1,2} = 10.8, J_{2,3} = 8.3, J_{3,4} = 10.9,$ and $J_{4,5} = 8.9$ Hz for 2b) in $^1$H NMR spectra suggests a large bond alternation in azulene moiety. Thus, the 22π-electron periferality seems to be less important for 2a and 2b.

The UV–VIS spectra of 2a and 2b in acetonitrile are shown in Figure 1. When a drop of concentrated hydrochloric acid was added into the solutions, the color of the solutions changed from brown to deep red, which exhibited a strong absorption at 436 (log ε 5.13) and 438 (5.14) nm, respectively (Figure 2). These results indicate the formation of diazuleno[2,1-b:1,2-e]pyridiniums (3a and 3b) by the protonation of 2a and 2b. Conjugate acids (3a and 3b) are stabilized by the canonical structures 4 as shown in Chart 1.

![Figure 1. UV–VIS spectra of 2a (solid line) and 2b (dotted line) in acetonitrile.](image1)

![Figure 2. UV–VIS spectra of 3a (solid line) and 3b (dotted line) in acetonitrile.](image2)

**Chart 1**

![Chart 1](chart1)

The p$K_a$ values of the conjugate acids (3a and 3b) were determined spectrophotometrically at 25 °C in a buffer solution prepared in 50% aqueous acetonitrile. The p$K_a$ values of 3a (7.0 ± 0.1) and 3b (6.5 ± 0.1) are relatively high for pyridine derivatives. The larger p$K_a$ values of 3a and 3b compared with that of pyridine (p$K_a$ 5.17) provide a criterion of the relatively high basicity of 2a and 2b. They are as large as
that of 2,6-dimethylpyridine (pKₐ 6.75). The protonation and the neutralization of 2a and 2b are completely reversible. Neutralization of the acidic solutions of 3a and 3b with NaOH regenerated the absorption of 2a and 2b in the UV–VIS region quantitatively.

We have then attempted the reaction of ethyl 2-aminoazulene-1-carboxylate (1b) with paraformaldehyde to examine the effect of 1-ethoxycarbonyl substituent on azulene ring as shown in Scheme 3. Table 1 summarizes the results under several conditions. In contrast to the formation of 2a and 2b, bis(2-amino-3-ethoxycarbonyl-1-azulenyl)methane (8a) was formed in 87% yield using 1/2 molar amount of paraformaldehyde (entry 1). The product (8a) did not afford diazuleno[2,1-b:1,2-e]pyridine derivative even in refluxing acetic acid.

**Scheme 3**

![Scheme 3](image)

**Table 1. Reaction of Ethyl 2-Amino-1-carboxylate (1b) with Paraformaldehyde at Room Temperature**

<table>
<thead>
<tr>
<th>entry</th>
<th>1b : HCHO</th>
<th>conditions</th>
<th>8a</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 : 1</td>
<td>20 h</td>
<td>87%</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>1 : 1.2</td>
<td>20 h</td>
<td>0%</td>
<td>85%</td>
</tr>
<tr>
<td>3</td>
<td>1 : 1</td>
<td>4 h</td>
<td>73%</td>
<td>25%</td>
</tr>
</tbody>
</table>

Use of 1.2 molar amounts of paraformaldehyde afforded 1-aza-10-ethoxycarbonyl-1,2,3,4-tetrahydrobenz[a]azulene-3-spiro-1’-(3’-ethoxycarbonyl-1’,2’-dihydroazulene)-2’-imine (9) in 85% yield instead of 8a (entry 2). When the reaction of 1b with the equimolar amount of paraformaldehyde was stopped at an early stage, 8a and 9 were obtained in 73 and 25% yields, respectively (entry 3). Formation of 9 could be attributable to the further reaction from 8a with paraformaldehyde under the conditions.

We have found that the reaction of 8a with paraformaldehyde in acetic acid gives three heterocyclic compounds (9, 10, and 11) (Scheme 4). Table 2 summarizes the results under various conditions. The products ratio depends on the reaction conditions. Treatment of 8a with 5-molar amount of paraformaldehyde gave 9 in 43% yield along with 10 and 11 in 21 and 26% yields, respectively (entry 2). When the reaction was stopped at an early stage (5 h), the ratio of the products (9 and 10) increased to 4:1.
(entry 1) in comparison with that of entry 2 (9:10 = 2:1). Thus, it is considered that the first step of the reaction is the formation of 9. The yield (26%, entry 2) of 11 is increased by a prolonged reaction time (55%, entry 3) or by the addition of a large excess of paraformaldehyde (35%, entry 4). The yield (43%, entry 2) of 9 is significantly decreased by the prolonged reaction time (4%, entry 3). Thus, it is thought that only 9 reacts with another paraformaldehyde to afford 11. Compound (10) could be formed from the isomerization of 9. Thus, 10 is the major product when a less amount of paraformaldehyde was used (entry 5).

**Scheme 4**

**Table 2. Reaction of Bis(2-amino-1-azulenyl)methane (8a) with Paraformaldehyde at Room Temperature**

<table>
<thead>
<tr>
<th>entry</th>
<th>8a : HCHO</th>
<th>time</th>
<th>9a)</th>
<th>10</th>
<th>11a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 b)</td>
<td>1 : 5</td>
<td>5 h</td>
<td>17%</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>1 : 5</td>
<td>20 h</td>
<td>43%</td>
<td>21%</td>
<td>26%</td>
</tr>
<tr>
<td>3</td>
<td>1 : 5</td>
<td>42 h</td>
<td>4%</td>
<td>18%</td>
<td>55%</td>
</tr>
<tr>
<td>4</td>
<td>1 : 10</td>
<td>21 h</td>
<td>29%</td>
<td>14%</td>
<td>35%</td>
</tr>
<tr>
<td>5</td>
<td>1 : 2</td>
<td>20 h</td>
<td>28%</td>
<td>43%</td>
<td>17%</td>
</tr>
</tbody>
</table>

a) The yields of the compounds (9 and 11) were determined by 1H NMR, since 9 and 11 were decomposed significantly on repeated column chromatography. b) Starting compound (8a) was recovered in 54% yield.

To prove the pathway of the reaction of 8a with paraformaldehyde, we have studied the reaction of each product (9, 10, and 11) under similar conditions. Warming a solution of 9 in benzene at 50 °C in the presence of acetic acid for 2 h afforded 10 in 50% yield. Compound (10) was also obtained by the prolonged warming (94 h) of a solution of 11 under similar conditions in 62% yield. Compound (9) readily reacted with paraformaldehyde in dichloromethane in the presence of acetic acid at room temperature to give 11 in 83% yield. No reaction of 10 took place with paraformaldehyde under similar conditions. On the basis of these results, a possible pathway can be illustrated as shown in Scheme 5.
Bis(2-amino-1-azulenyl)methane (8a) reacted with benzaldehyde to give 6,10-diethoxycarbonyl-7,9-diaza-7,8,9,16-tetrahydro-8-phenyldiazuleno[2,3-d:3,2-g]cyclooctene (12) as the sole product, although the reactivity of 8a with benzaldehyde was relatively low (Scheme 6). Prolonged refluxing for 6 days of a mixture of 8a and benzaldehyde in benzene in the presence of acetic acid afforded 12 in 66% yield.

To examine the reactivity of azulene bearing an amino group protected with acetyl function, we have carried out the reactions of 2-acetylaminoazulenes (1c and 1d) with paraformaldehyde (Scheme 7). The reaction in acetic acid at room temperature for 1 day exclusively gave bis(2-acetylamino-1-
azulenyl)methanes (8b and 8c) in 77 and 79% yields, respectively. The product (8c) remained toward the reaction with paraformaldehyde under similar conditions.

We have demonstrated that the reaction of 1a with paraformaldehyde or benzaldehyde in acetic acid affords diazuleno[2,1-b:1,2-e]pyridines (2a and 2b) in one pot. The reaction of 1b with paraformaldehyde resulted in the formation of bis(2-amino-1-azulenyl)methane derivative (8a). When 1c and 1d were used, the reaction leads to an exclusive formation of bis(2-acetylamino-1-azulenyl)methanes (8b and 8c). The reaction using 2-aminoazulenes with amino protecting group is potentially useful for the preparation of bis(2-amino-1-azulenyl)methane derivatives. Extending this methodology to produce calixarene like compounds will be a focus of future work.

**EXPERIMENTAL**

**General.** Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. MS spectra were obtained with a JEOL HX-110 or a Hitachi M-2500 instrument usually at 70 eV. IR spectra were recorded on a Shimadzu FTIR-8100M or a Hitachi 270-30 spectrophotometer and UV–VIS spectra were measured on a Hitachi U-3410 or a Hitachi 340 spectrophotometer. NMR spectra (1H and 13C NMR) were recorded on a JEOL JNM A500 at 500 MHz (125 MHz) or a Bruker AM 600 spectrometer at 600 MHz (150 MHz). Elemental analyses were performed at the Instrumental Analysis Center of Chemistry, Faculty of Science, Tohoku University.

**Diazuleno[2,1-b:1,2-e]pyridine (2a).** A solution of 2-aminoazulene (1a) (106 mg, 0.740 mmol) and paraformaldehyde (21 mg, 0.70 mmol) in acetic acid (3 mL) was stirred at rt for 30 h. The reaction mixture was poured into water and extracted with CH2Cl2. The organic layer was washed with aqueous NaHCO3 solution, dried with MgSO4, and concentrated under reduced pressure. The residue was purified by column chromatography (Al2O3, ethyl acetate) to give 2a (49 mg, 47%). brown needles; mp 225–227 °C (decomp) (lit., 8 153–155 °C); MS (70 eV) m/z (rel intensity) 279 (M+, 100); IR (KBr disk) νmax 1590, 1572, 1398, 1314, 1266, 1200, 810, and 690 cm−1; UV–VIS (MeCN) λmax, nm (log ε) 228 (4.24), 261 (4.38), 360 (4.64), 381 (4.64), 396 (4.68), 415 (4.70), and 436 (4.57); 1H NMR (600 MHz, CDCl3) δ = 9.24 (s, 1H, H6), 8.33 (d, J = 8.2 Hz, 2H, H5,7), 8.05 (d, J = 10.8 Hz, 2H, H1,11), 7.53 (s, 2H, H12,14), 7.27 (dd, J = 10.8, 8.3 Hz, 2H, H3,9), 7.21 (dd, J = 10.8, 8.2 Hz, 2H, H4,8), and 7.06 (dd, J = 10.8, 8.3 Hz, 2H, H2,10); 13C NMR (150 MHz, CDCl3) δ = 161.21 (C12a,13a), 144.79 (C11a,14a), 139.27 (C5a,6b), 134.84 (C1,11), 133.65 (C3,9), 126.98 (C4,8), 126.53 (C2,10), 126.51 (C5,7), 121.16 (C5b,6a), 120.67 (C6), and 116.93 (C12,14). Anal. Calcd for C21H13N·1/3H2O: C, 88.39; H, 4.83; N 4.91. Found: C, 88.41; H, 5.67; N, 4.77.

**6-Phenyldiazuleno[2,1-b:1,2-e]pyridine (2b).** The same procedure was followed, using 1a (1.01 g, 7.05
mmol), benzaldehyde (386 mg, 3.64 mmol), and acetic acid (40 mL) at rt for 52 h afforded 2b (645 mg, 51%). Brown needles; mp 276–281 °C (decomp); MS (70 eV) m/z (rel intensity) 355 (M^+, 100); IR (KBr disk) \( \nu_{\text{max}} \) 1584, 1534, 1518, 1498, 1400, 1258, 1218, 710, and 696 cm\(^{-1}\); UV–VIS (MeCN) \( \lambda_{\text{max}} \) 261 (4.23), 359 (4.66), 379 (4.67), 396 (4.70), 415 (4.73), and 435 (4.56); \(^1\)H NMR (600 MHz, CDCl\(_3\)) \( \delta = 8.08 \) (d, \( J = 10.8 \) Hz, 2H, H\(_{1,11}\)), 7.74–7.69 (m, 3H, H\(_{3',4',5'}\)), 7.63 (s, 2H, H\(_{12,14}\)), 7.54–7.53 (m, 2H, H\(_{2',6'}\)), 7.21 (d, \( J = 8.9 \) Hz, 2H, H\(_{5,7}\)), 7.11 (dd, \( J = 10.9, 8.3 \) Hz, 2H, H\(_{3,9}\)), 7.00 (dd, \( J = 10.8, 8.3 \) Hz, 2H, H\(_{2,10}\)), and 6.77 (dd, \( J = 10.9, 8.9 \) Hz, 2H, H\(_{4,8}\)); \(^13\)C NMR (150 MHz, CDCl\(_3\)) \( \delta = 161.19 \) (C\(_{12a,13a}\)), 145.56 (C\(_{11a,14a}\)), 142.88 (C\(_6\)), 139.97 (C\(_{5a,6b}\)), 138.18 (C\(_1\)), 134.92 (C\(_{11}\)), 133.34 (C\(_3,9\)), 130.54 (C\(_5,7\)), 130.08 (C\(_3',5'\)), 128.76 (C\(_4\)), 127.90 (C\(_2',6'\)), 127.24 (C\(_4,8\)), 126.31 (C\(_2,10\)), 119.03 (C\(_{5b,6a}\)), and 117.26 (C\(_{12,14}\)). Anal. Calcd for C\(_{27}\)H\(_{17}\)N·1/3H\(_2\)O: C, 89.72; H, 4.93; N, 3.88. Found: C, 89.98; H, 4.93; N, 3.88.

**Bis(2-amino-3-ethoxycarbonyl-1-azulenyl)methane (8a).** A solution of ethyl 2-aminoazulene-1-carboxylate (1b) (2.33 g, 10.4 mmol) and paraformaldehyde (181 mg, 6.03 mmol) in acetic acid (55 mL) was stirred at rt for 24 h. The precipitated crystals were collected by filtration, washed with water, and dried in vacuo. The filtrate was diluted with CH\(_2\)Cl\(_2\). The organic layer was worked up and combined with the precipitated crystals. The mixture was purified by column chromatography (SiO\(_2\), 5% ethyl acetate/CH\(_2\)Cl\(_2\)) to afford 8a (2.08 g, 87%). Orange plates; mp 205–210 °C (decomp); MS (70 eV) m/z (rel intensity) 442 (M^+, 65); IR (KBr disk) \( \nu_{\text{max}} \) 3460, 3416, 3348, 3320, 1666, 1642, 1618, 1604, 1520, 1434, 1256, 1238, and 1110 cm\(^{-1}\); UV–VIS (CH\(_2\)Cl\(_2\)) \( \lambda_{\text{max}} \), nm (log \( \varepsilon \)) 311 (5.01); \(^1\)H NMR (600 MHz, CDCl\(_3\)) \( \delta = 8.94 \) (d, \( J = 9.6 \) Hz, 2H, H\(_4\)), 8.06 (d, \( J = 10.7 \) Hz, 2H, H\(_8\)), 7.35 (dd, \( J = 10.0, 9.6 \) Hz, 2H, H\(_5\)), 7.29 (dd, \( J = 10.0, 9.7 \) Hz, 2H, H\(_6\)), 7.27 (dd, \( J = 10.7, 9.7 \) Hz, 2H, H\(_7\)), 6.01 (br, 4H, 2-NH\(_2\)), 4.40 (q, \( J = 7.1 \) Hz, 4H, 3-COOEt), 4.35 (s, 2H, CH\(_2\)), and 1.42 (t, \( J = 7.1 \) Hz, 6H, 3-COOEt); \(^13\)C NMR (150 MHz, CDCl\(_3\)) \( \delta = 166.73 \) (3-COOEt), 159.31 (C\(_2\)), 142.54 (C\(_3a\)), 140.54 (C\(_8a\)), 130.93 (C\(_6\)), 129.37 (C\(_5\)), 128.55 (C\(_4\)), 127.81 (C\(_7\)), 126.60 (C\(_8\)), 110.02 (C\(_1\)), 98.12 (C\(_3\)), 59.53 (3-COOEt), 19.38 (CH\(_2\)), and 14.66 (3-COOEt). Anal. Calcd for C\(_{27}\)H\(_{26}\)N\(_2\)O\(_4\)·1/3H\(_2\)O: C, 72.30; H, 6.18; N, 6.25. Found: C, 72.43; H, 6.18; N, 6.04.

**1-Aza-10-ethoxycarbonyl-1,2,3,4-tetrahydrobenz[a]azulene-3-spiro-1’-(3’-ethoxycarbonyl-1’,2’-dihydroazulene)-2’-imine (9).** A solution of ethyl 2-aminoazulene-1-carboxylate (1b) (600 mg, 2.79 mmol) and paraformaldehyde (100 mg, 3.33 mmol) in acetic acid (9 mL) was stirred at rt for 20 h. Workup followed by recrystallization from benzene/hexane gave 9 (536 mg, 85%). Red needles; mp 218–223 °C (decomp); MS (70 eV) m/z (rel intensity) 454 (M^+, 100); IR (KBr disk) \( \nu_{\text{max}} \) 3440, 3388,
3312, 3290, 2980, 1686, 1586, 1562, 1458, 1436, 1376, 1258, 1220, 1208, and 1142 cm⁻¹; UV–VIS (CH₂Cl₂) \( \lambda_{\text{max}} \), nm (log \( \varepsilon \)) 248 (4.43), 327 (4.78), and 402 (4.35); \(^1\)H NMR (600 MHz, CDCl₃) \( \delta = 10.06 \) (br, 1H, 2'-NH), 8.87 (d, \( J = 9.7 \) Hz, 1H, H₉), 8.23 (d, \( J = 12.0 \) Hz, 1H, H₃'), 7.70 (d, \( J = 9.9 \) Hz, 1H, H₅), 7.47 (br, 1H, H₁), 7.34 (dd, \( J = 10.0 \), 9.7 Hz, 1H, H₈). 7.25 (dd, \( J = 10.0 \), 9.3 Hz, 1H, H₇), 7.20 (dd, \( J = 9.9 \), 9.3 Hz, 1H, H₆), 6.78 (ddd, \( J = 12.0 \), 8.0, 1.0 Hz, 1H, H₅'), 6.46 (ddddd, \( J = 11.0 \), 8.0, 0.9, 0.8 Hz, 1H, H₆'), 6.37 (ddddd, \( J = 11.0 \), 8.5, 0.9 Hz, 1H, H₇'), 6.22 (d, \( J = 8.5 \), 0.9 Hz, 1H, H₈'), 4.47 (q, \( J = 7.1 \) Hz, 2H, COOEt), 4.39 (q, \( J = 7.1 \) Hz, 2H, COOEt), 3.69 (d, \( J = 12.7 \) Hz, 1H, H₂), 3.43 (ddd, \( J = 12.7 \), 4.4, 1.9 Hz, 1H, H₂'), 2.98 (dd, \( J = 16.5 \), 1.9 Hz, 1H, H₁), 1.49 (t, \( J = 7.1 \) Hz, 3H, COOEt), and 1.43 (t, \( J = 7.1 \) Hz, 3H, COOEt); \(^1\)C NMR (150 MHz, CDCl₃) \( \delta = 180.05 \) (C₂'), 166.95 (COOEt), 165.25 (COOEt), 161.35 (C₃ₐ'), 158.58 (C₈ₐ'), 156.19 (C₁₀), 143.24 (C₉ₐ), 140.22 (C₄b), 138.12 (C₅'), 135.86 (C₇'), 132.95 (C₆'), 132.04 (C₄'), 130.50 (C₇'), 129.72 (C₈'), 129.19 (C₈'), 129.00 (C₉), 127.50 (C₆), 127.11 (C₅), 112.60 (C₃'), 109.27 (C₄a), 96.44 (C₁₀), 60.23 (COOEt), 59.54 (COOEt), 50.16 (C₂), 46.15 (C₃), 30.43 (C₄), 14.78 (COOEt), and 14.40 (COOEt). Anal. Calcd for C₂₈H₂₆N₂O₄·1/₃H₂O: C, 73.03; H, 5.84; N, 6.08. Found: C, 73.40; H, 5.89; N, 5.88.

**Reaction of Bis(2-amino-3-ethoxycarbonyl-1-azulenyl)methane (8a) with Paraformaldehyde.** A solution of 8a (443 mg, 1.00 mmol) and paraformaldehyde (300 mg, 10.0 mmol) in acetic acid (24 mL) was stirred at rt for 21 h. Workup followed by column chromatography (Al₂O₃, CH₂Cl₂ and ethyl acetate) gave 6,10-diethoxycarbonyl-7,9-diaza-7,8,9,16-tetrahydrodiazuleno[2,3-d:]3,2-g]cyclooctene (10) (63 mg, 14%), and a mixture of 1-aza-10-ethoxycarbonyl-1,2,3,4-tetrahydrobenz[a]azulene-3-spiro-1'-(3'-ethoxycarbonyl-1',2'-dihydroazulene)-2'-amine (9) and 6,10-diethoxycarbonyl-7,9-diaza-7,8,9,16-tetrahydro-7,15b-methanodiazuleno[2,3-d:]3,2-g]cyclooctene (11) (293 mg) with a ratio of 45 (29%) : 55 (35%). These compounds (9 and 11) were separable by repeated column chromatography (Al₂O₃, 10 to 70% ethyl acetate/CH₂Cl₂).

10: orange needles; mp 269–271 °C (decomp); MS (70 eV) m/z (rel intensity) 454 (M⁺, 100); IR (KBr disk) \( \nu_{\text{max}} \) 3328, 1660, 1644, 1580, 1558, 1540, 1524, 1432, 1366, 1228, 1158, and 1128 cm⁻¹; UV–VIS (CH₂Cl₂) \( \lambda_{\text{max}} \), nm (log \( \varepsilon \)) 244 (4.47), 306 (5.12), and 368 (4.27); \(^1\)H NMR (600 MHz, CDCl₃) \( \delta = 8.91 \) (br dd, \( J = 8.6 \), 7.0 Hz, 2H, H₇₉), 8.77 (d, \( J = 9.7 \) Hz, 2H, H₅₁₁), 8.20 (d, \( J = 10.4 \) Hz, 2H, H₁₁₃), 7.27 (dd, \( J = 10.4 \), 8.8 Hz, 2H, H₂₁₄), 7.26 (dd, \( J = 9.9 \), 9.7 Hz, 2H, H₄₁₂), 7.20 (dd, \( J = 9.9 \), 8.8 Hz, 2H, H₃₁₃), 6.24 (dt, \( J = 15.6 \), 8.6 Hz, 1H, H₈), 4.94 (d, \( J = 16.7 \) Hz, 1H, H₁₆), 4.76 (dt, \( J = 15.6 \), 7.0 Hz, 1H, H₈), 4.70 (d, \( J = 16.7 \) Hz, 1H, H₁₆), 4.43 (q, \( J = 7.1 \) Hz, 4H, 6,10-COOEt), and 1.45 (t, \( J = 7.1 \) Hz, 6H, 6,10-COOEt); \(^1\)C NMR (150 MHz, CDCl₃) \( \delta = 167.45 \) (6,10-COOEt), 159.56 (C₆ₐ₉ₐ), 142.18 (C₅ₐ₁₀ₐ).
140.84 (C_{15a,16b}), 130.80 (C_{3,13}), 129.26 (C_{4,12}), 128.60 (C_{5,11}), 127.65 (C_{2,14}), 127.00 (C_{1,15}), 113.83 (C_{15b,16a}), 98.49 (C_{6,10}), 59.69 (6.10-COOEt), 52.64 (C_{8}), 21.84 (C_{16}), and 14.70 (6.10-COOEt). Anal. Calcd for C_{28}H_{26}N_{2}O_{4}: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.71; H, 5.85; N, 6.11.

**11:** orange crystals; mp 150–153 °C; MS (70 eV) m/z (rel intensity) 466 (M^{+}, 42); IR (KBr disk) ν_{max} 1680, 1478, 1454, 1430, 1208, and 1200 cm^{-1}; UV–VIS (CH_{2}Cl_{2}) λ_{max}, nm (log ε) 229 (4.54), 251 (4.46), 275 (4.32), 335 (4.59), and 383 (4.34); ^{1}H NMR (600 MHz, CDCl_{3}) δ = 9.48 (d, J = 10.1 Hz, 1H, H_{5}), 8.01 (d, J = 9.8 Hz, 1H, H_{1}), 7.83 (d, J = 12.1 Hz, 1H, H_{11}), 7.62 (dd, J = 9.9, 9.5 Hz, 1H, H_{2}), 7.48 (dd, J = 10.1, 9.9 Hz, 1H, H_{4}), 7.34 (dd, J = 9.8, 9.5 Hz, 1H, H_{2}), 6.56 (ddd, J = 12.1, 8.0, 1.0 Hz, 1H, H_{12}), 6.44 (dddd, J = 11.2, 7.9, 1.0, 0.8 Hz, 1H, H_{14}), 6.35 (ddd, J = 11.2, 8.0, 0.9, 0.7 Hz, 1H, H_{13}), 6.15 (ddd, J = 7.9, 0.9 Hz, 1H, H_{15}), 5.44 (d, J = 18.1 Hz, 1H, H_{8}), 5.15 (d, J = 18.1 Hz, 1H, H_{8}), 4.60 (dq, J = 10.8, 7.1 Hz, 1H, COOEt), 4.40 (dq, J = 10.8, 7.1 Hz, 1H, COOEt), 4.29 (dq, J = 11.0, 7.1 Hz, 1H, COOEt), 4.23 (dq, J = 11.0, 7.1 Hz, 1H, COOEt), 3.56 (d, J = 12.3 Hz, 1H, H_{17}), 3.48 (d, J = 12.3 Hz, 1H, H_{17}), 3.33 (dd, J = 16.5, 1.5 Hz, 1H, H_{16}), 3.04 (d, J = 16.5 Hz, 1H, H_{16}), 1.49 (t, J = 7.1 Hz, 3H, COOEt), and 1.27 (t, J = 7.1 Hz, 3H, COOEt); ^{13}C NMR (150 MHz, CDCl_{3}) δ = 168.76 (C_{9a}), 164.72 (COOEt), 164.59 (COOEt), 159.61 (C_{6a}), 159.25 (C_{15a}), 158.99 (C_{10a}), 141.95 (C_{5a}), 139.03 (C_{16b}), 136.32 (C_{3}), 136.02 (C_{12}), 135.54 (C_{5}), 133.75 (C_{14}), 132.19 (C_{13}), 131.83 (C_{11}), 131.42 (C_{1}), 128.37 (C_{4}), 126.81 (C_{2}), 124.91 (C_{15}), 119.17 (C_{10}), 116.44 (C_{16a}), 107.52 (C_{6}), 73.86 (C_{8}), 60.35 (COOEt), 59.83 (COOEt), 50.70 (C_{17}), 42.84 (C_{15b}), 34.09 (C_{16}), 14.54 (COOEt), and 14.34 (COOEt). Anal. Calcd for C_{29}H_{26}N_{2}O_{4}·1/3H_{2}O: C, 73.71; H, 5.69; N, 5.93. Found: C, 73.89; H, 5.83; N, 5.80.

**Reaction of 8a with Benzaldehyde.** A solution of 8a (103 mg, 0.233 mmol) and benzaldehyde (265 mg, 2.50 mmol) in acetic acid (3 mL) and benzene (20 mL) was refluxed for 6 days. Workup followed by column chromatography (Al_{2}O_{3}, CH_{2}Cl_{2}) gave 6,10-diethoxycarbonyl-7,9-diaza-7,8,9,16-tetrahydro-8-phenyldiazuleno[2,3-d:3,2-g]cyclooctene (12) (82 mg, 66%). orange crystals; mp 190–191 °C; MS (70 eV) m/z (rel intensity) 530 (M^{+}, 100); IR (KBr disk) ν_{max} 3295, 1655, 1557, 1538, 1524, 1497, 1154, and 1125 cm^{-1}; UV–VIS (CH_{2}Cl_{2}) λ_{max}, nm (log ε) 248 (4.53), 309 (5.17), and 372 (4.34); ^{1}H NMR (500 MHz, CDCl_{3}) δ = 9.00 (br d, J = 8.2 Hz, 2H, H_{7,9}), 8.83 (d, J = 9.6 Hz, 2H, H_{5,11}), 8.22 (d, J = 10.2 Hz, 2H, H_{1,15}), 7.80 (d, J = 7.3 Hz, 2H, H_{2,6}), 7.55 (dd, J = 7.4, 7.3 Hz, 2H, H_{3,5}), 7.52 (t, J = 8.2 Hz, 1H, H_{8}), 7.46 (t, J = 7.4 Hz, 1H, H_{4}), 7.29 (dd, J = 10.2, 9.9 Hz, 2H, H_{2,14}), 7.27 (dd, J = 9.9, 9.6 Hz, 2H, H_{4,12}), 7.22 (dd, J = 9.9, 9.9 Hz, 2H, H_{3,13}), 5.03 (d, J = 16.7 Hz, 1H, H_{16}), 4.81 (d, J = 16.7 Hz, 1H, H_{16}), 4.42–4.35 (m, 4H, 6,10-COOEt), and 1.38 (t, J = 7.2 Hz, 6H, 6,10-COOEt); ^{13}C NMR (125 MHz, CDCl_{3}) δ = 167.22 (6,10-COOEt), 158.75 (C_{6a,9a}), 142.34 (C_{5a,10a}), 140.97 (C_{15a,16b}), 139.57 (C_{1})
130.95 (C_{3,13}), 129.68 (C_{3',5'}), 129.35 (C_{4,12}), 129.08 (C_{5,11}), 127.72 (C_{2,14}), 127.15 (C_{1,15}), 125.84 (C_{2',6'}), 113.85 (C_{15b,16a}), 98.73 (C_{6,10}), 66.126 (C_8), 59.66 (6,10-COOEt), 22.28 (C_{16}), and 14.58 (6,10-COOEt). Anal. Calcd for C_{34}H_{30}N_2O_4: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.84; H, 5.72; N, 5.20.

**Bis(2-acetylamino-1-azulenyl)methane (8b).** The same procedure was followed, using 2-acetylaminoazulene (1c) (495 mg, 2.67 mmol), paraformaldehyde (42 mg, 1.40 mmol), and acetic acid (16 mL) at rt for 25 h afforded 8b (396 mg, 77%). blue prisms; mp 261–263 °C (decomp); MS (70 eV) m/z (rel intensity) 382 (M^+, 44); IR (KBr disk) ν\text{max} 3400, 1706, 1574, 1530, 1500, and 1238 cm\(^{-1}\); UV–VIS (CH\_2Cl\_2) λ\text{max}, nm (log ε) 242 (4.50), 306 (5.05), 354 (4.06), 370 (4.14), 387 (4.07), and 554 (2.68); \(^1\)H NMR (600 MHz, DMSO-\text{d}_6) δ = 10.03 (s, 2H, 2-NHCOMe), 8.28 (d, J = 9.5 Hz, 2H, H_4), 8.06 (d, J = 9.9 Hz, 2H, H_8), 7.97 (s, 2H, H_3), 7.48 (dd, J = 9.8, 9.8 Hz, 2H, H_6), 7.21 (dd, J = 9.8, 9.5 Hz, 2H, H_5), 7.04 (dd, J = 9.9, 9.8 Hz, 2H, H_7), 4.97 (s, 2H, CH\_2), and 2.25 (s, 6H, 2-NHCOMe); \(^1^3\)C NMR (150 MHz, DMSO-\text{d}_6) δ = 168.70 (2-NHCOMe), 144.79 (C_2), 139.51 (C_{3a}), 134.62 (C_{8a}), 134.33 (C_6), 133.53 (C_4), 131.05 (C_8), 123.57 (C_5), 122.57 (C_7), 115.85 (C_1), 107.85 (C_3), 23.82 (2-NHCOMe), and 19.87 (CH\_2). Anal. Calcd for C_{25}H_{22}N_2O_2: C, 78.51; H, 5.80; N, 7.32. Found: C, 78.28; H, 5.86; N; 7.25.

**Bis(2-acetylamino-3-ethoxycarbonyl-1-azulenyl)methane (8c).** The same procedure was followed, using ethyl 2-acetylaminoazulene-1-carboxylate (1d) (723 mg, 2.81 mmol), paraformaldehyde (53 mg, 1.77 mmol), and acetic acid (21 mL) at rt for 24 h afforded 8c (581 mg, 79%). purple crystals; mp 248–249 °C; MS (70 eV) m/z (rel intensity) 526 (M^+, 27); IR (KBr disk) ν\text{max} 3305, 1690, 1676, 1489, 1456, 1428, and 1130 cm\(^{-1}\); UV–VIS (CH\_2Cl\_2) λ\text{max}, nm (log ε) 248 (4.51), 312 (4.95), and 539 (2.96); \(^1\)H NMR (600 MHz, CDCl\_3) δ = 9.30 (d, J = 9.9 Hz, 2H, H_4), 9.30 (br, 2H, 2-NHCOMe), 8.43 (d, J = 10.1 Hz, 2H, H_8), 7.65 (dd, J = 10.0, 9.5 Hz, 2H, H_6), 7.46 (dd, J = 10.0, 9.9 Hz, 2H, H_5), 7.35 (dd, J = 10.1, 9.5 Hz, 2H, H_7), 4.87 (s, 2H, CH\_2), 4.42 (q, J = 7.1 Hz, 4H, 3-COOEt), 1.64 (s, 6H, 2-NHCOMe), and 1.45 (t, J = 7.1 Hz, 6H, 3-COOEt); \(^1^3\)C NMR (150 MHz, CDCl\_3) δ = 168.09 (2-NHCOMe), 166.28 (3-COOEt), 146.42 (C_2), 139.92 (C_{8a}), 139.52 (C_{3a}), 137.10 (C_6), 135.24 (C_4), 134.33 (C_8), 127.89 (C_5), 126.90 (C_7), 120.75 (C_1), 106.31 (C_3), 60.17 (3-COOEt), 24.00 (CH\_2), 23.64 (2-NHCOMe), and 14.52 (3-COOEt). Anal. Calcd for C_{31}H_{30}N_2O_6·1/3H_2O: C, 69.91; H, 5.80; N, 5.26. Found: C, 69.97; H, 5.82; N, 5.23.

REFERENCES


