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The Oxidative Amination of Diethyl 2-Hydroxyazulene-1,3-dicarboxylate and Cycloheptimidazol-2(1*H*)-one

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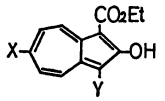
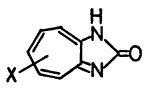
Synopsis. The reaction of diethyl 2-hydroxyazulene-1,3-dicarboxylate with morpholine, pyrrolidine, piperidine, and dimethylamine in the presence of copper(II) acetate gave the respective 6-aminoazulene derivatives. Similarly, the reaction of cycloheptimidazol-2(1*H*)-one with morpholine gave the 6-aminocycloheptimidazole derivative, while the reaction with pyrrolidine gave the 4-(or 5-)aminocycloheptimidazole derivative.

Azulene derivatives carrying amino groups on a seven-membered ring have usually been obtained by the nucleophilic substitution reaction,[1-3] by the Schmidt reaction on acetylazulene derivatives,[4] or by the reaction of acetamidotropolone with ethyl cyanoacetate.[5] Similarly, 4-, 5-, and 6-aminocycloheptimidazole derivatives have also been obtained by the nucleophilic substitution reaction,[6,7] Schmidt reaction,[8] or reduction of nitro group.[6] In the preceding paper,[9] we have reported that the reaction of tropone and tropolone with several kinds of amines in the presence of copper(II) salt afforded 2-aminotropones and 3- and 5-aminotropolones. In the course of the investigation of the oxidative amination of seven-membered aromatics, it was found that the title compounds were also aminated on treatment with amines, and these results will be reported in this paper.

When diethyl 2-hydroxyazulene-1,3-dicarboxylate (**1**) was heated with a solution of copper(II) acetate and morpholine in ethanol, a yellow crystalline product (**2a**), $C_{20}H_{23}O_6N$, was obtained in about 20% yield. The UV spectrum exhibited maxima at 234, 265, 348, 405, and 430 nm (sh), suggesting that **2a** is an azulenic compound. The NMR spectrum exhibited signals at 7.14 (C_5– and C_7–H, d, J=12 Hz) and 9.10 ppm (C_4– and C_8–H, d, J=12 Hz) besides the signals due to the hydroxyl, morpholino methylene, and ester ethyl groups. The elemental analysis and these spectral data indicate that **2a** is diethyl 2-hydroxy-6-morpholinoazulene-1,3-dicarboxylate. The treatment of **1** with pyrrolidine, piperidine, and dimethylamine under similar conditions gave 6-(1-pyrrolidinyl) (**2b**), 6-piperidino (**2c**), and 6-dimethylamino (**2d**) derivatives, respectively. The alkaline hydrolysis and decarboxylation of **2a** to obtain 2-hydroxy-6-morpholinoazulene failed, and the product obtained was ethyl 2-hydroxy-6-morpholinoazulene-1-carboxylate (**3a**). Similarly, monomethyl esters (**3b** and **3c**) were also obtained from **2b** and **2c**.

When cycloheptimidazol-2(1*H*)-one (**4**) was heated with a solution of copper(II) acetate and morpholine in methanol, a yellowish-orange crystalline product (**5a**), $C_{12}H_{13}O_2N_3$, mp 310 °C (dec) was obtained in about 15% yield. The UV spectrum of **5a** showed maxima at 255, 292, and 420 nm. The NMR spectrum (in trifluoroacetic acid) exhibited signals at 7.76 (C_5– and C_7–H, d, J=13.2 Hz) and 8.23 ppm (C_4– and C_8–H, d, J=13.2 Hz), indicating that **5a** is 6-morpholinocycloheptimidazol-2(1*H*)-one. On the other hand, when **4** was treated with pyrrolidine under similar conditions, yellow crystals (**5b**) $C_{12}H_{13}ON_3$, mp 297 °C (dec) were obtained. The NMR spectrum (in trifluoroacetic acid) exhibited signals due to aromatic protons at 7.3—8.1 ppm (4H) as a complex multiplet; the splitting pattern is quite different from that of **5a**. The UV spectrum, which shows maxima at 245, 279, 367, and 457 nm is also quite different from that of **5a**. Therefore, **5b** must be 4-(or 5-)(1-pyrrolidinyl)cycloheptimidazol-2(1*H*)-one.





2a: X=morpholino Y=CO_2Et
2b: X=1-pyrrolidinyl Y=CO_2Et
2c: X=piperidino Y=CO_2Et
2d: X=dimethylamino Y=CO_2Et
3a: X=morpholino Y=H
3b: X=1-pyrrolidinyl Y=H
3c: X=piperidino Y=H

4: X=H
5a: X=6-morpholino
5b: X=4-(or 5-)-(1-pyrrolidinyl)

Experimental

All the melting points were uncorrected. The NMR spectra were determined on a Hitachi H-60 instrument (Me_4Si), the UV spectra were recorded on a Hitachi EPS-3T spectrometer, and the IR spectra were taken on a Hitachi EPI-S spectrometer.

The Reaction of Diethyl 2-Hydroxyazulene-1,3-dicarboxylate (1) with Morpholine, Pyrrolidine, Piperidine, and Dimethylamine. To a solution obtained by dissolving copper(II) acetate (1.00 g) in ethanol (3 ml) and morpholine (3 ml), **1** (0.72 g) was added, and the mixture was heated at 70—75 °C for 48 h. The reaction mixture was diluted with water. The precipitate was collected, washed with water, and dried. Then it was dissolved in chloroform, hydrogen sulfide was passed through, and copper(II) sulfide was removed. After the solvent was evaporated, the residue was dissolved in benzene and passed through a silica gel column. The fraction eluted with benzene gave 380 mg of starting material, and the fraction eluted with a mixture of chloroform and ethanol (99: 1) gave 185 mg (20%) of diethyl 2-hydroxy-6-morpholinoazulene-1,3-dicarboxylate (**2a**) as yellow needles (from ethanol), mp 169.5—170.5 °C. UV (methanol) max: 234 (log ε 4.35), 265 (4.43), 348 (4.74), 405 (4.23), and 430 nm (sh, 4.10). Found: C, 64.07; H, 6.08; N, 3.71%. Calcd for $C_{20}H_{23}NO_6$: C, 64.33; H, 6.21; N, 3.75%.

The reaction of **1** with pyrrolidine, piperidine, and dimethylamine was carried out similarly.

Diethyl 2-hydroxy-6-(1-pyrrolidinyl)azulene-1,3-dicarboxy-

late (**2b**). Orange yellow prisms (from dioxane), mp 205—208 °C (dec). Yield, 23%. UV (methanol) max: 266 (log ε 4.44), 348 (4.77), 402 (4.25), and 431 nm (4.22). NMR ($CDCl_3$): δ, 6.60 (C_5– and C_7–H, d, J=12 Hz), and 8.90 (C_4– and C_8–H, d, J=12 Hz). Found: C, 67.51; H, 6.55; N, 3.56%. Calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92%.

Diethyl 2-hydroxy-6-piperidinoazulene-1,3-dicarboxylate (**2c**). Orange yellow prisms (from ethanol), mp 128—129 °C. Yield, 26%. UV (methanol) max: 232 (log ε 4.35), 266 (4.48), 351 (4.77), 402 (4.32), and 431 nm (4.25). NMR ($CDCl_3$): δ, 7.13 (C_5– and C_7–H, d, J=12 Hz), and 9.09 (C_4– and C_8–H, d, J=12 Hz). Found: C, 67.74; H, 6.68; N, 3.62%. Calcd for $C_{21}H_{25}NO_5$: C, 67.90; H, 6.78; N, 3.77%.

Diethyl 2-hydroxy-6-dimethylaminoazulene-1,3-dicarboxylate (**2d**). Orange prisms (from dioxane), mp 187—188 °C. UV (methanol) max: 230 (log ε 4.31), 265 (4.48), 347 (4.79), 402 (4.23), and 430 nm (4.17). NMR ($CDCl_3$): δ, 6.72 (C_5– and C_7–H, d, J=13 Hz), and 8.95 (C_4– and C_8–H, d, J=13 Hz). Found: C, 65.60; H, 6.50; N, 4.14%. Calcd for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23%.

The Alkaline Hydrolysis and Decarboxylation of 2a, 2b, and 2c. A solution of sodium hydroxide (150 mg) in water (1.5 ml) and ethanol (3 ml) was refluxed with **2a** (280 mg) for 5 h on a water bath. The mixture was diluted with water and acidified. The crystalline precipitate was washed with water and dried. The chromatographic separation on preparative TLC using Merck Silica Gel PF_{254} gave 80 mg of **2a** and 95 mg of ethyl 2-hydroxy-6-morpholinoazulene-1-carboxylate (**3a**), orange prisms (from dioxane), mp 166—168 °C. UV (methanol) max: 221 (log ε 4.45), 338 (4.76), and 400 nm (4.08). NMR ($CDCl_3$): δ, 6.57 (C_3–H, s), 7.0 (C_5– and C_7–H, m), 7.91 (C_4–H, d, J=12 Hz), and 8.77 (C_8–H, d, J=11 Hz). Found: C, 67.88; H, 6.50%. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36%.

Ethyl 2-hydroxy-6-(1-pyrrolidinyl) azulene-1-carboxylate (**3b**). Orange yellow scales (from dioxane), mp 185—186 °C. UV (methanol) max: 219 (log ε 4.39), 241 (4.03), 345 (4.83), 406 (4.12), and 438 (3.98). NMR ($CDCl_3$): δ, 6.5 (C_3–, C_5–, and C_7–H, m), 7.77 (C_4–H, d, J=12 Hz), and 8.61 (C_8–H, d, J=12 Hz). Found: C, 71.79; H, 6.93%. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71%.

Ethyl 2-hydroxy-6-piperidinoazulene-1-carboxylate (**3c**). Orange crystals (from ethanol), mp 114—115 °C. UV (methanol) max: 221 (log ε 4.41), 345 (4.73), and 409 nm (4.14). NMR ($CDCl_3$): δ, 6.45 (C_3–H, s), 6.9 (C_5– and C_7–H, m), 7.82 (C_4–H, d, J=12 Hz), 8.67 (C_8–H, d, J=11 Hz). Found: C, 72.57; H, 7.26%. Calcd for $C_{18}H_{21}NO_3$: C, 72.21; H, 7.07%.

The Reaction of Cycloheptimidazol-2(1H)-one (4) with Morpholine and Pyrrolidine. To a solution obtained by dissolving copper(II) acetate (2.00 g) in methanol (4 ml) and morpholine (4 ml), **4** (0.73 g) was added under stirring, and the mixture was heated at 70—75 °C for 48 h. Water was added to the reaction mixture and the precipitate was collected by filtration. The precipitate was dissolved in dilute hydrochloric acid, hydrogen sulfide was passed through the solution, and copper(II) sulfide was filtered off. The filtrate was neutralized with sodium hydrogencarbonate and the resulting crystalline precipitate was collected. Recrystallization from water gave 6-morpholinocycloheptimidazol-2(1*H*)-one (**5a**) as yellow needles, mp 310 °C (dec). Yield, 150 mg (15%). UV (methanol) max: 255 (log ε 4.37), 292 (sh, 3.78), and 420 nm (4.42). IR (KBr): 3300 and 1630 cm^{-1}. NMR (CF_3CO_2H): δ, 4.15 (morpholine CH_2, s, 8H), 7.76 (C_5– and C_7–H, d, J=13.2 Hz), and 8.23 (C_4– and C_8–H, d, J=13.2 Hz). Found: C, 62.33; H, 5.65; N, 18.07%. Calcd for $C_{12}H_{13}N_3O_2$: C, 62.32; H, 5.67; N, 18.07%.

A similar treatment of **4** with pyrrolidine (neutralization of the filtrate with sodium hydrogencarbonate, however, did not afford any precipitate and repeated extraction with chloroform was necessary) gave 4-(or 5-)(1-pyrrolidinyl)cycloheptimidazol-2(1*H*)-one (**5b**) as orange crystals, mp 297 °C (dec). Yield, 14%. UV (methanol) max: 245 (log ε 4.24), 279 (4.38), 367 (4.15), and 457 nm (4.09). IR (KBr): 3450 and 1625 cm^{-1}. NMR (CF_3CO_2H): δ, 2.1—2.6 (pyrrolidine CH_2, m, 4H), 3.9—4.4 (pyrrolidine CH_2, m, 4H), and 7.3—8.1 (aromatic H, m, 4H). Found: C, 67.09; H, 5.92; N, 19.04%. Calcd for $C_{12}H_{13}N_3O$: C, 66.95; H, 6.09; N, 19.52%.

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