

SYNTHESIS OF MERIDINE, A PENTACYCLIC AZA-AROMATIC ALKALOID

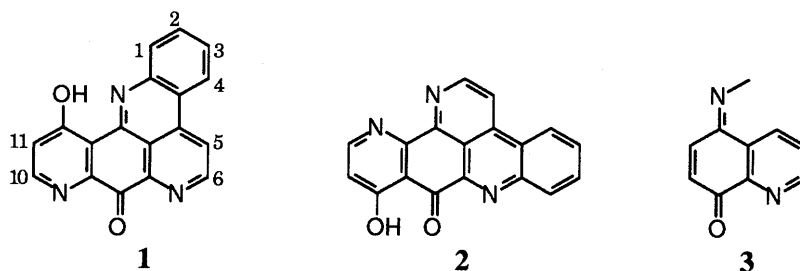
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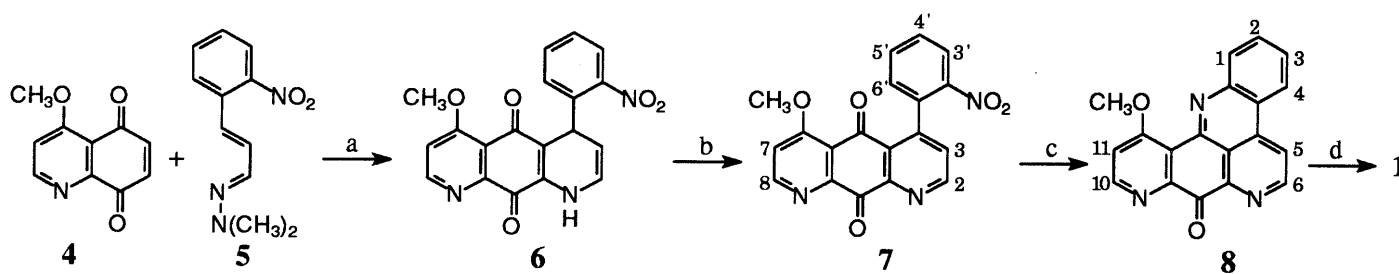
A pentacyclic aza-aromatic alkaloid, meridine (**1**), was synthesized from 4-methoxy-5,8-quinolinedione (**4**) and *o*-nitrocinnamaldehyde *N,N*-dimethylhydrazone (**5**) in four steps.

KEYWORDS meridine; aromatic alkaloid; hetero Diels-Alder reaction; synthesis

During the past ten years, a series of structurally related polycyclic aromatic alkaloids have been isolated from marine organisms.¹⁾ In 1991, Schmitz *et al.* reported the isolation and structural determination of new pentacyclic aromatic alkaloids, meridine (**1**) and 11-hydroxyascididemin (**2**), possessing an iminoquinolinequinone structure (**3**).²⁾ We report synthesis of **1** using hetero Diels-Alder reaction.



The hetero Diels-Alder reaction of 4-methoxy-5,8-quinolinedione (**4**)³⁾ and *o*-nitrocinnamaldehyde *N,N*-dimethylhydrazone (**5**) (prepared from *o*-nitrocinnamaldehyde and *N,N*-dimethylhydrazine) in refluxing dichloromethane containing acetic anhydride⁴⁾ regioselectively afforded **6**. The adduct (**6**) was refluxed with 10% palladium on carbon in toluene to furnish **7**⁵⁾ (6% yield from **4**).⁶⁾ The nitro compound (**7**) was hydrogenated in methanol using 10% palladium on carbon as a catalyst, followed by oxidation with air to afford a pentacyclic compound (**8**)⁷⁾ in 48% yield. Finally, **8** was treated with 48% hydrobromic acid to furnish meridine (**1**)⁸⁾ in 72% yield. The spectroscopic data obtained for **1** were identical to the values reported for the natural product, meridine.



a: $(\text{CH}_3\text{CO})_2\text{O}$, CH_2Cl_2 , reflux, 8 h; b: 10% Pd-C, toluene, reflux, 1 h; c: H_2 (1 atm), 10% Pd-C, methanol, 25°C, 30 min; d: 48% HBr, 60–70°C, 10 min.

ACKNOWLEDGEMENT

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REFERENCES AND NOTES

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- 2) F. J. Schmitz, F. S. DeGuzman, M. B. Hossain, D. van der Helm, *J. Org. Chem.*, **56**, 804 (1991).
- 3) P. Withopf, H. Lackner, *Tetrahedron*, **43**, 4549 (1987).
- 4) P. Nebois, R. Barret, H. Fillion, *Tetrahedron Lett.*, **31**, 2569 (1990).
- 5) **7**: mp 262–266°C (dec.) (yellow needles from CH₂Cl₂–ether). MS *m/z* (%): 361 (M⁺, 0.3), 316 (33), 315 (100). High-resolution MS Calcd for C₁₉H₁₁N₃O₅: 361.0699. Found: 361.0696. Ir (KBr): 1700, 1676, 1584, 1516, 1472, 1350, 1302, 1268, 1224, 1058, 980 cm⁻¹. ¹H-NMR (270 MHz, CDCl₃) δ: 3.99 (3H, s, OCH₃), 7.17 (1H, d, *J* = 5.9 Hz, C₇-H), 7.28 (1H, dd, *J* = 7.6, 1.3 Hz, C₆-H), 7.44 (1H, d, *J* = 5.0 Hz, C₃-H), 7.67 (1H, ddd, *J* = 7.6, 7.6, 1.3 Hz, C₄-H), 7.77 (1H, ddd, *J* = 7.6, 7.6, 1.3 Hz, C₅-H), 8.35 (1H, dd, *J* = 7.6, 1.3 Hz, C₃-H), 8.92 (1H, d, *J* = 5.9 Hz, C₈-H), 9.12 (1H, d, *J* = 5.0 Hz, C₂-H).
- 6) The low yield of **7** is primarily due to the gradual decomposition of the quinone (**4**) during the hetero Diels-Alder reaction.
- 7) **8**: mp 250–255°C (dec.) (yellow needles from CH₂Cl₂–ether). MS *m/z* (%): 313 (M⁺, 100), 312 (45), 284 (26), 283 (24), 255 (32). High-resolution MS Calcd for C₁₉H₁₁N₃O₂: 313.0851. Found: 313.0852. Ir (KBr): 1686, 1598, 1572, 1330, 1304, 1066, 984, 758 cm⁻¹. ¹H-NMR (270 MHz, CDCl₃) δ: 4.25 (3H, s, OCH₃), 7.30 (1H, d, *J* = 5.6 Hz, C₁₁-H), 7.84 (1H, ddd, *J* = 8.3, 8.3, 1.0 Hz, C₃-H), 7.96 (1H, ddd, *J* = 8.3, 8.3, 1.0 Hz, C₂-H), 8.36 (1H, dd, *J* = 8.3, 1.0 Hz, C₁-H), 8.62 (1H, dd, *J* = 8.3, 1.0 Hz, C₄-H), 8.69 (1H, d, *J* = 5.6 Hz, C₅-H), 8.91 (1H, d, *J* = 5.6 Hz, C₁₀-H), 9.34 (1H, d, *J* = 5.6 Hz, C₆-H).
- 8) **1**: mp >250°C (yellow powder from CH₂Cl₂–ether) [lit.,²) mp >250°C]. MS *m/z* (%): 299 (M⁺, 100), 271 (20), 243 (43). High-resolution MS Calcd for C₁₈H₉N₃O₂: 299.0695. Found: 299.0695. Ir (KBr): 1690, 1606, 1478, 1468, 1336, 1322, 1296, 1216, 1106, 866, 772 cm⁻¹. ¹H-NMR (270 MHz, CDCl₃) δ: 7.28 (1H, d, *J* = 5.6 Hz, C₁₁-H), 7.89 (1H, ddd, *J* = 7.9, 7.9, 1.3 Hz, C₃-H), 8.00 (1H, ddd, *J* = 8.3, 7.9, 1.3 Hz, C₂-H), 8.27 (1H, dd, *J* = 8.3, 1.3 Hz, C₁-H), 8.67 (1H, dd, *J* = 7.9, 1.3 Hz, C₄-H), 8.70 (1H, d, *J* = 5.6 Hz, C₅-H), 8.82 (1H, d, *J* = 5.6 Hz, C₁₀-H), 9.42 (1H, d, *J* = 5.6 Hz, C₆-H), 15.33 (1H, s, OH). ¹³C-NMR (67.8 MHz, CDCl₃-CF₃CO₂D) δ: 115.24s, 117.30s, 120.07d, 122.26s, 123.43d, 124.58d, 128.61d, 132.79d, 135.00d, 139.76s, 139.89s, 139.94s, 143.99d, 144.26s, 148.01s, 151.10d, 174.00s, 175.70s.

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