Chem. Pharm. Bull. **42**(6) 1363—1364 (1994)

SYNTHESIS OF MERIDINE, A PENTACYCLIC AZA-AROMATIC ALKALOID

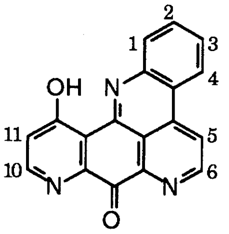
Yoshiyasu KITAHARA, Fumiyasu TAMURA, and Akinori KUBO*

Meiji College of Pharmacy, 1-35-23, Nozawa, Setagaya-ku, Tokyo 154, Japan

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.



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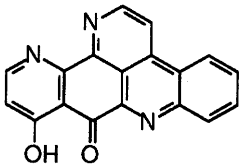

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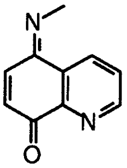

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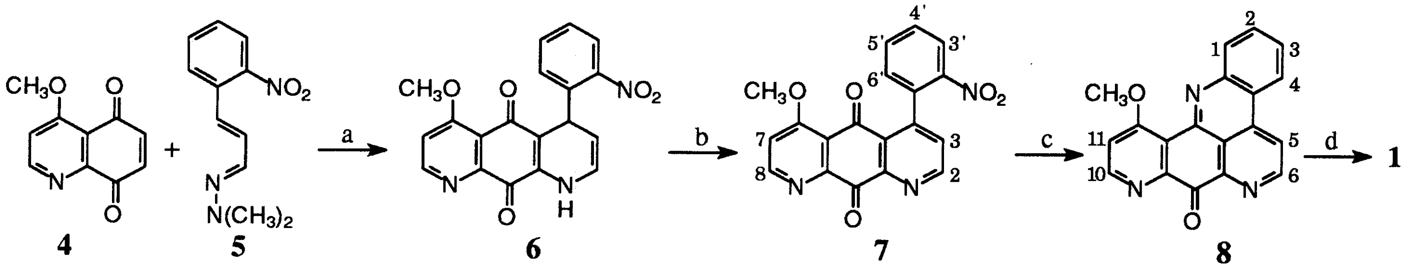
The hetero Diels-Alder reaction of 4-methoxy-5,8-quinolinedione (**4**)[3] and *o*-nitrocinnamaldehyde *N*,*N*-dimethylhydrazone (**5**) (prepared from *o*-nitrocinnamaldehyde and *N*,*N*-dimethylhydrazine) in refluxing dichloromethane containing acetic anhydride[4] regioselectively afforded **6**. The 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: $(CH_3CO)_2O$, 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 This work was partly supported by a Grant-in-Aid for Scientific Research (No. 03671018) from the Ministry of Education, Science, and Culture, Japan.

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2) F. J. Schmitz, F. S. DeGuzman, M. B. Hossain, D. van der Helm, *J. Org. Chem.*, **56**, 804 (1991).

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5) **7**: mp 262–266°C (dec.) (yellow needles from CH_2Cl_2–ether). MS *m/z* (%): 361 (M^+, 0.3), 316 (33), 315 (100). High-resolution MS Calcd for $C_{19}H_{11}N_3O_5$: 361.0699. Found: 361.0696. Ir (KBr): 1700, 1676, 1584, 1516, 1472, 1350, 1302, 1268, 1224, 1058, 980 cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 3.99 (3H, s, OCH_3), 7.17 (1H, d, J = 5.9 Hz, C_7-H), 7.28 (1H, dd, J = 7.6, 1.3 Hz, $C_{6'}$-H), 7.44 (1H, d, J = 5.0 Hz, C_3-H), 7.67 (1H, ddd, J = 7.6, 7.6, 1.3 Hz, $C_{4'}$-H), 7.77 (1H, ddd, J = 7.6, 7.6, 1.3 Hz, $C_{5'}$-H), 8.35 (1H, dd, J = 7.6, 1.3 Hz, $C_{3'}$-H), 8.92 (1H, d, J = 5.9 Hz, C_8-H), 9.12 (1H, d, J = 5.0 Hz, C_2-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 CH_2Cl_2–ether). MS *m/z* (%): 313 (M^+, 100), 312 (45), 284 (26), 283 (24), 255 (32). High-resolution MS Calcd for $C_{19}H_{11}N_3O_2$: 313.0851. Found: 313.0852. Ir (KBr): 1686, 1598, 1572, 1330, 1304, 1066, 984, 758 cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 4.25 (3H, s, OCH_3), 7.30 (1H, d, J = 5.6 Hz, C_{11}-H), 7.84 (1H, ddd, J = 8.3, 8.3, 1.0 Hz, C_3-H), 7.96 (1H, ddd, J = 8.3, 8.3, 1.0 Hz, C_2-H), 8.36 (1H, dd, J = 8.3, 1.0 Hz, C_1-H), 8.62 (1H, dd, J = 8.3, 1.0 Hz, C_4-H), 8.69 (1H, d, J = 5.6 Hz, C_5-H), 8.91 (1H, d, J = 5.6 Hz, C_{10}-H), 9.34 (1H, d, J = 5.6 Hz, C_6-H).

8) **1**: mp >250°C (yellow powder from CH_2Cl_2–ether) [lit.,[2] mp >250°C]. MS *m/z* (%): 299 (M^+, 100), 271 (20), 243 (43). High-resolution MS Calcd for $C_{18}H_9N_3O_2$: 299.0695. Found: 299.0695. Ir (KBr): 1690, 1606, 1478, 1468, 1336, 1322, 1296, 1216, 1106, 866, 772 cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.28 (1H, d, J = 5.6 Hz, C_{11}-H), 7.89 (1H, ddd, J = 7.9, 7.9, 1.3 Hz, C_3-H), 8.00 (1H, ddd, J = 8.3, 7.9, 1.3 Hz, C_2-H), 8.27 (1H, dd, J = 8.3, 1.3 Hz, C_1-H), 8.67 (1H, dd, J = 7.9, 1.3 Hz, C_4-H), 8.70 (1H, d, J = 5.6 Hz, C_5-H), 8.82 (1H, d, J = 5.6 Hz, C_{10}-H), 9.42 (1H, d, J = 5.6 Hz, C_6-H), 15.33 (1H, s, OH). ^{13}C-NMR (67.8 MHz, $CDCl_3$-CF_3CO_2D) 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.

(Received March 28, 1994; accepted May 6, 1994)