Pergamon

Tetrahedron Letters, Vol. 38, No. 25, pp. 4441-4442, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00926-X

Synthesis of Cystodamine, a Pentacyclic Aza-aromatic Alkaloid

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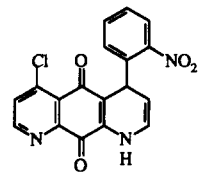
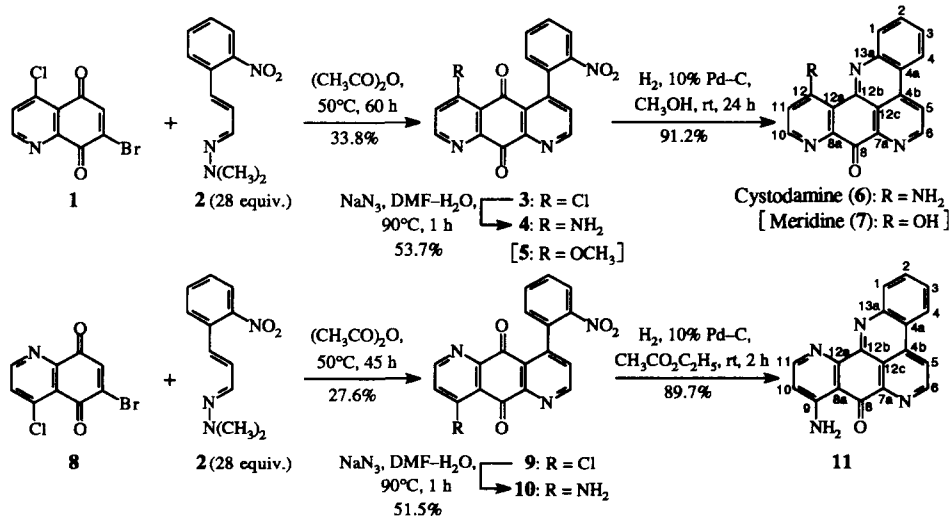
Abstract: A pentacyclic aza-aromatic alkaloid, cystodamine (**6**), and its isomer (**11**) were synthesized from 7-(or 6-)bromo-4-chloro-5,8-quinolinedione (**1**, **8**) and *o*-nitrocinnamaldehyde dimethylhydrazone (**2**) using hetero Diels-Alder reaction.

A number of biologically active polycyclic aromatic alkaloids including iminoquinolinequinone structure have been isolated from marine organisms in recent years.[1] Cystodamine (**6**) is a pentacyclic aromatic alkaloid isolated from a Mediterranean ascidian *Cystodytes delle chiajei* (Polycitoridae), and showed activity against human leukemic lymphoblasts.[2] We report here the synthesis of **6** and its isomer **11** using hetero Diels-Alder reaction.

The hetero Diels-Alder reaction[3] of 7-bromo-4-chloro-5,8-quinolinedione[4] (**1**) with *o*-nitrocinnamaldehyde dimethylhydrazone (**2**, prepared from *o*-nitrocinnamaldehyde and *N,N*-dimethylhydrazine) in a small amount of chloroform containing acetic anhydride[3a] proceeded regioselectively[3c] to afford 6-chloro-4-(2-nitrophenyl)pyrido-[3,2-*g*]quinoline-5,10-dione (**3**, 34% yield) and 6-chloro-4-(2-nitrophenyl)-1,4-dihydropyrido[3,2-*g*]quinoline-5,10-dione (**3'**, 21% yield). The chloro compound (**3**) was treated with sodium azide in aqueous *N,N*-dimethylformamide to give **4** in 54% yield. Finally, **4** was hydrogenated in methanol using 10% palladium on carbon as a catalyst to furnish cystodamine[5] (**6**) in 91% yield. The reaction of **3** with sodium methoxide in methanol at 25°C for 30 min afforded methoxyquinone (**5**, 75% yield), a synthetic intermediate[6] of meridine (**7**); the structure was determined by X-ray crystallographic analysis.[7] Similarly, an isomer[8] (**11**) of cystodamine (**6**) was prepared from 6-bromo-4-chloro-5,8-quinolinedione[9] (**8**) and **2**.



3'



Acknowledgements This work was partly supported by a Grant-in-Aid for Scientific Research (No. 03671018) from the Ministry of Education, Science and Culture, Japan. We thank Mr. N. Eguchi, Ms. T. Koseki and Ms. S. Yoshioka in the Analytical Center of our College for measurement of spectral data (MS and NMR).

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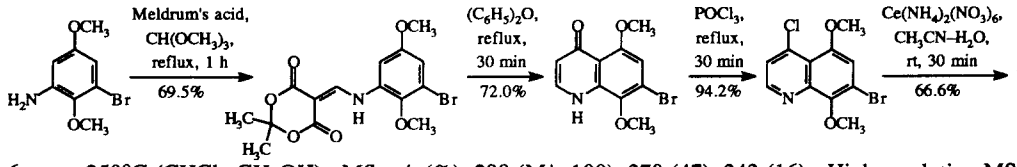
3. *a*) Nebois, P.; Barret, R.; Fillion, H. *Tetrahedron Lett.*, **1990**, *31*, 2569-2572; *b*) Villacampa, M.; Pérez, J. M.; Avendaño, C.; Menéndez, J. C. *Tetrahedron*, **1994**, *50*, 10047-10054; *c*) Lévesque, S.; Brassard, P. *Heterocycles*, **1994**, *38*, 2205-2218.
4. The quinone (**1**) was prepared from 3-bromo-2,5-dimethoxyaniline (Guay, V.; Brassard, P. *J. Heterocycl. Chem.*, **1987**, *24*, 1649-1652) *via* 7-bromo-5,8-dimethoxy-4(1*H*)-quinolinone using Cassis' method (Cassis, R.; Tapia, R.; Valderrama, J. A. *Synth. Commun.*, **1985**, *15*, 125-133) in four steps.



5. **6**: mp >250°C ($CHCl_3$-CH_3OH). MS *m/z* (%): 298 (M^+, 100), 270 (47), 243 (16). High-resolution MS Calcd for $C_{18}H_{10}N_4O$: 298.0855. Found: 298.0856. IR (KBr): 3336, 1686, 1610, 1330, 1294 cm^{-1}. ^{1}H-NMR (270 MHz, DMSO-d_6 + 1 drop of HCl) δ: 7.541 (1H, d, *J* = 7.3 Hz, C_{11}-H), 7.987 (1H, ddd, *J* = 8.3, 6.9, 1.0 Hz, C_3-H), 8.089 (1H, td, *J* = 6.9, 1.0 Hz, C_2-H), 8.342 (1H, d, *J* = 7.3 Hz, C_{10}-H), 8.699 (1H, dd, *J* = 6.9, 1.0 Hz, C_1-H), 9.031 (1H, dd, *J* = 8.3, 1.0 Hz, C_4-H), 9.245 (1H, d, *J* = 5.6 Hz, C_5-H), 9.393 (1H, d, *J* = 5.6 Hz, C_6-H). ^{1}H-NMR (500 MHz, CD_2Cl_2 + 2 drops of CF_3CO_2D) δ: 7.375 (1H, d, *J* = 7.0 Hz, C_{11}-H), 7.967 (1H, ddd, *J* = 8.2, 7.3, 1.2 Hz, C_3-H), 8.055 (1H, ddd, *J* = 8.2, 7.3, 1.2 Hz, C_2-H), 8.242 (1H, d, *J* = 7.0 Hz, C_{10}-H), 8.372 (1H, dd, *J* = 8.2, 1.2 Hz, C_1-H), 8.696 (1H, dd, *J* = 8.2, 1.2 Hz, C_4-H), 8.968 (1H, d, *J* = 5.5 Hz, C_5-H). 9.426 (1H, d, *J* = 5.5 Hz, C_6-H). ^{13}C-NMR (125 MHz, CD_2Cl_2 + 2 drops of CF_3CO_2D) δ: 113.90 (C_{12a}), 114.93 (C_{11}), 118.58 (C_{12c}), 121.40 (C_{4a}), 124.18 (C_4), 124.18 (C_5), 131.64 (C_1), 132.17 (C_3), 134.23 (C_2), 138.97 (C_{8a}), 139.44 (C_{10}), 139.48 (C_{4b} or C_{7a}), 139.68 (C_{4b} or C_{7a}), 143.38 (C_{12b}), 144.32 (C_{13a}), 150.39 (C_6), 160.37 (C_{12}), 175.42 (C_8).
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7. Schmitz, F. J.; DeGuzman, F. S.; Hossain, M. B.; van der Helm, D. *J. Org. Chem.*, **1991**, *56*, 804-808.
8. **11**: mp >250°C ($CHCl_3$-ether). MS *m/z* (%): 298 (M^+, 100), 270 (53), 243 (14). High-resolution MS Calcd for $C_{18}H_{10}N_4O$: 298.0855. Found: 298.0854. IR (KBr): 3388, 3276, 1640, 1620, 1598, 1288 cm^{-1}. ^{1}H-NMR (500 MHz, CD_2Cl_2 + 2 drops of CF_3CO_2D) δ: 7.289 (1H, d, *J* = 7.0 Hz, C_{10}-H), 8.140 (1H, ddd, *J* = 7.9, 7.0, 1.2 Hz, C_3-H), 8.215 (1H, ddd, *J* = 8.2, 7.0, 1.2 Hz, C_2-H), 8.460 (1H, d, *J* = 7.0 Hz, C_{11}-H), 8.527 (1H, dd, *J* = 8.2, 1.2 Hz, C_1-H), 8.831 (1H, dd, *J* = 7.9, 1.2 Hz, C_4-H), 9.036 (1H, d, *J* = 5.8 Hz, C_5-H), 9.511 (1H, d, *J* = 5.8 Hz, C_6-H). ^{13}C-NMR (125 MHz, CD_2Cl_2 + 2 drops of CF_3CO_2D) δ: 110.94 (C_{8a}), 114.46 (C_{10}), 117.65 (C_{12c}), 123.02 (C_{4a}), 123.32 (C_5), 124.68 (C_4), 132.98 (C_1), 133.46 (C_3), 134.84 (C_2), 140.06 (C_{4b}), 140.45 (C_{12b}), 141.41 (C_{11}), 143.90 (C_{7a}), 145.53 (C_{13a}), 146.87 (C_{12a}), 149.00 (C_6), 159.90 (C_9), 186.07 (C_8).
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(*Received in Japan* 10 *April* 1997; *revised* 6 *May* 1997; *accepted* 9 *May* 1997)