SYNTHESIS OF THE PYRIDINO[4,3,2-*de*]QUINOLINE NUCLEUS: A DERIVATIVE OF THE DISCORHABDIN ALKALOIDS

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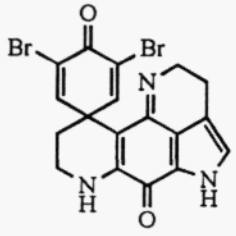
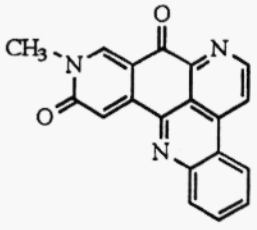
Abstract: A novel method of synthesis from catechol of the pyridino[4,3,2-*de*]quinoline nucleus structurally related to discorhabdin alkaloids is developed. Proof of the position of the chlorine substituent in the key chlorination step was obtained by x-ray diffraction analysis of an intermediate **8**.

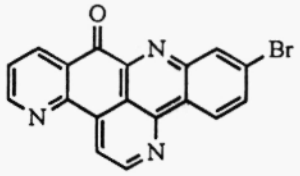
In a search for antiviral and antitumor compounds from marine sources, some highly cytotoxic extracts were found from heavily pigmented green and brown sponges of the genus *Latronlia du Bocage* (family Latronliidae, order Hadromerida) (1). Initial work on the New Zealand *Latronculia* extract showed that the cytotoxity was due to a polar pigment. Three pigments were identified and named as discorhabdins A, B, and C (2). Bioassay showed that these compounds were not only active against certain viruses but also against some cancer cells (active *in vitro* against P338 with ED50 0.03, 0.05 and 0.1 μg/ml, respectively) (3). Further investigation of this group of compounds resulted in the isolation of a series of cytotoxic compounds in sponges and other marine sources, such as makaluvamines (4), damirones A and B (5), batzellines (6) and isobatzellines (7). Recently some new cytotoxic compounds were found, such as tsitsikammamines (8) and veiutamine (9).



Discorhabdin C



Amphimedine

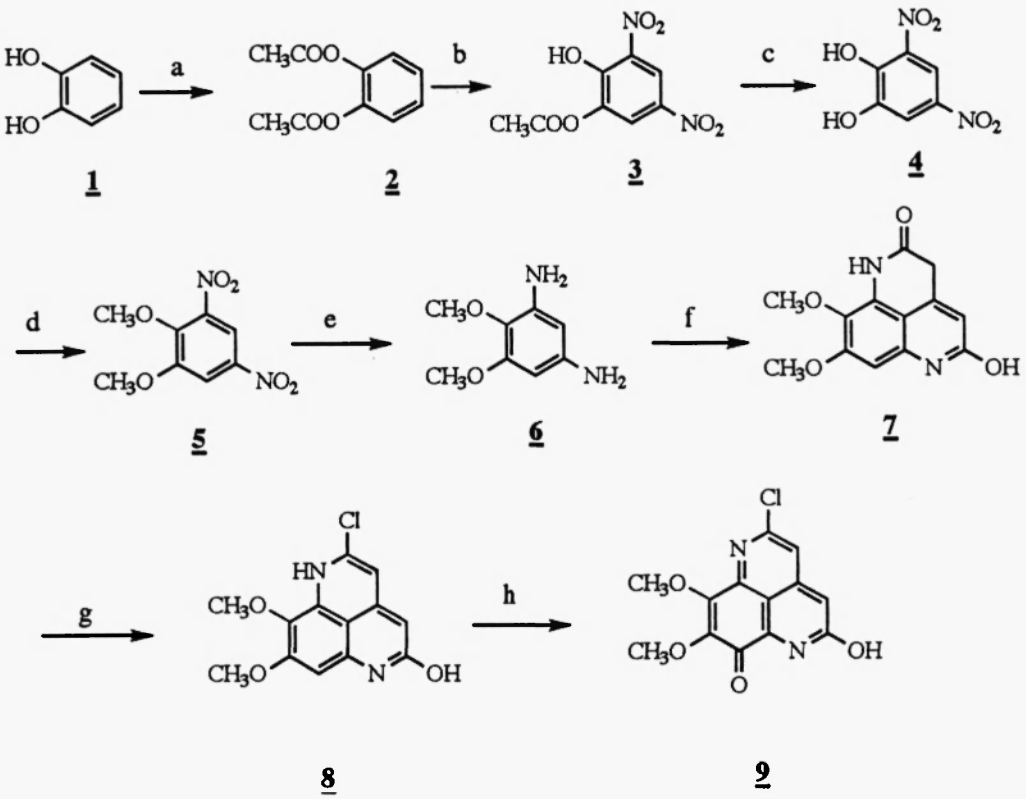


2-Bromoleptoclinidine

Most of these cytotoxic compounds contain the structurally novel pyrrolo[4,3,2-*de*]quinoline nucleus. Many research groups (10) were therefore interested in the synthetic chemistry and physiological properties of this pyrrolo[4,3,2-*de*]quinoline nucleus and its derivatives.

Some cytotoxic compounds containing the pyridino[4,3,2-de]quinoline nucleus were also found in sponges and other marine sources. Amphimedine (11), isolated from a sponge, was active against P338 cells *in vitro* (Ed50 2.8 μg/ml). 2-Bromoleptoclinidone (12), isolated from an ascidian, also active against p338 cells *in vitro* and with higher activity (ED50 0.4 μg/ml). Interestingly all of these compounds contain the pyridino[4,3,2-*de*]quinoline nucleus. However, the synthetic chemistry and physiological properties of this kind of pyridino[4,3,2-*de*]quinoline nucleus and its derivatives have not yet been studied .

In our previous paper (13), we described the synthesis of furano[4,3,2-*de*]quinoline. We describe herein an efficient synthesis of the novel pyridino[4,3,2-*de*]quinoline nucleus (scheme I).



Scheme I: (a) $(CH_3CO)_2O$, H_2SO_4; (b) HNO_3; (c) HCl , CH_3OH; (d) Me_2SO_4, K_2CO_3; (e)H_2/Pd/C; (f) $(EtOCOCH_2)CO$; (g) i. $POCl_3$, ii. H_2O; (h) H_2O_2, CH_3COOH

This methodology starts from the commercially available catechol. The catechol 1 was first treated with acetic anhydride to produce 1,2-diacetoxybenzene 2. Compound 2 was nitrated by fuming nitric acid to produce 6-acetoxy-2,4-dinitrophenol 3. Dinitrophenol 3 was deprotected by hydrochloric acid to produce 3,5-dinitro-1,2-dihydroxybenzene 4. Compound 4 was then methylated with dimethylsulfate to produce the key intermediate

1,2-dimethoxy-3,5-dinitrobenzene **5** (97% yield) (14). Compound **5** was reduced by catalytic hydrogenation then cyclized using diethyl 1,3-acetonedicarboxylate to produce the tricyclic intermediate 5-hydroxy-8,9-dimethoxy-1,2,3-trihydropyridino[4,3,2-*de*]quinolin-2-one **7** (62% yield) (15). Compound **7** was chlorinated with $POCl_3$ then hydrolyzed to produce the monochloro product 2-chloro-5-hydroxy-8,9-dimethoxy-1-hydropyridino[4,3,2-*de*]quinoline **8** (89% yield) (16). In order to identify the position of the chlorine atom in this monochloro product, we have carried out an x-ray crystallographic determination. The results of crystallography (see figure 1, table 1 and table 2) showed that this monochloro product is 2-chloro-5-hydroxy-8,9-dimethoxy-1-hydropyridino[4,3,2-*de*]quinoline **8**. Finally compound **8** was oxidized with hydroperoxide in acetic acid to afford the pyridino[4,3,2-*de*]quinoline nucleus **9** (17) as a violet crystalline product (72% yield).

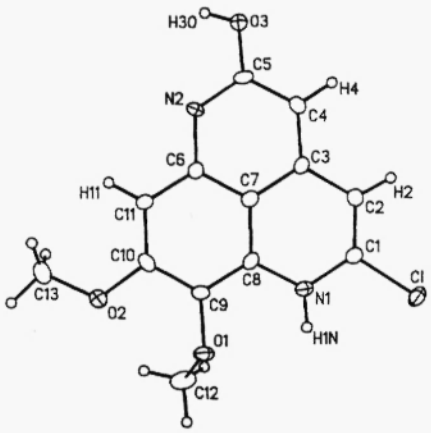


Figure 1. X-ray crystal structure (18) of 2-chloro-5-hydroxy-8,9-dimethoxy-1-hydropyridino[4,3,2-*de*]quinoline **8**

Table 1. Selected interatomic distances (Å) of 2-chloro-5-hydroxy-8,9-dimethoxy-1-hydropyridino[4,3,2-*de*]quinoline **8**

Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance
Cl	C1	1.729(6)	C2	C3	1.432(8)
O1	C9	1.380(7)	C3	C4	1.377(8)
O1	C12	1.408(7)	C3	C7	1.423(9)
O2	C10	1.367(7)	C4	C5	1.416(8)
O2	C13	1.422(7)	C6	C7	1.416(8)
O3	C5	1.281(7)	C6	C11	1.376(8)
N1	C1	1.368(8)	C7	C8	1.423(8)
N1	C8	1.387(7)	C8	C9	1.368(9)
N2	C5	1.353(8)	C9	C10	1.413(8)
N2	C6	1.386(7)	C10	C11	1.388(8)
C1	C2	1.336(8)			

Table 2. Selected interatomic angles (deg) of 2-chloro-5-hydroxy-8,9-dimethoxy-1-hydropyridino[4,3,2-*de*]quinoline **8**

Atom 1	Atom 2	Atom 3	Angle	Atom 1	Atom 2	Atom 3	Angle
C9	O1	C12	115.4(5)	N2	C6	C11	120.6(6)
C10	O2	C13	117.8(5)	C7	C6	C11	121.5(6)
C1	N1	C8	119.7(5)	C3	C7	C8	121.7(6)
C5	N2	C6	122.7(5)	C6	C7	C8	117.7(6)
Cl	C1	N1	114.0(5)	N1	C8	C7	117.6(6)
Cl	C1	C2	121.1(6)	N1	C8	C9	121.2(6)
N1	C1	C2	124.9(6)	C7	C8	C9	121.1(6)
C1	C2	C3	119.0(6)	O1	C9	C8	118.8(6)
C2	C3	C4	124.3(6)	O1	C9	C10	121.9(6)
C2	C3	C7	117.0(6)	C8	C9	C10	119.2(6)
C4	C3	C7	118.7(6)	O2	C10	C9	114.2(6)
C3	C4	C5	120.6(6)	O2	C10	C11	124.6(6)
O3	C5	N2	118.7(6)	C9	C10	C11	121.2(6)
O3	C5	C4	121.7(6)	C6	C11	C10	119.2(6)
N2	C5	C4	119.7(6)	C3	C7	C6	120.5(6)
N2	C6	C7	117.9(6)				

Details of the antitumor properties of **9** and its lexitropsin conjugates will be reported in due course.

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14. Compound **5**: Calcd for $C_8H_8N_2O_6$ 228.0382, found 228.0381 (M^+, 100%); ^1H NMR ($CDCl_3$): δ 8.25 (d, *J* = 2 Hz, 1 H, Ar-H), 7.95 (d, *J* = 2 Hz, 1 H, Ar-H), 4.11 (s, 3 H, OCH_3), 4.01 (s, 3 H, OCH_3).
15. Compound **7**: Calcd for $C_{13}H_{12}N_2O_4$ 260.0797, found 260.0783 (M^+, 77%); ^1H NMR (dmso-d_6): δ 11.44 (s, 1 H, OH), 10.00 (s, 1 H, NH), 6.48 (s, 1 H, Ar-H), 6.04 (t, 1 H, Py-H), 3.86 (d, 2 H, CH_2), 3.82 (s, 3 H, OCH_3), 3.65 (s, 3 H, OCH_3).
16. Compound **8**: Calcd for $C_{13}H_{11}N_2O_3Cl$ 278.0458, found 278.0439 (M^+, 100%); ^1H NMR (dmso-d_6): δ 10.58 (s, 1 H, OH), 10.50 (s, 1 H, NH), 6.32 (s, 1 H, Ar-H), 5.83 (s, 1 H, Ar-H), 5.28 (s, 1 H, Ar-H), 3.78 (s, 3 H, OCH_3), 3.62 (s, 3 H, OCH_3).
17. Compound **9**: Calcd for $C_{13}H_9N_2O_4Cl$ 292.0251, found 292.0264 (M^+, 54%); ^1H NMR (dmso-d_6): δ 11.69 (s, 1 H, OH), 7.88 (s, 1 H, Py-H), 7.71 (s, 1 H, ClPy-H), 3.97 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3).
18. The crystal structure was solved using the program SHELXL93: Sheldrick, G. M. SHELXL93, University of Göttingen, 1993.

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