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Synthesis of a Wakayin Model Compound: Oxidative Formation of a New Pyrrole Ring in the Indol-3-yl-indoloquinone System

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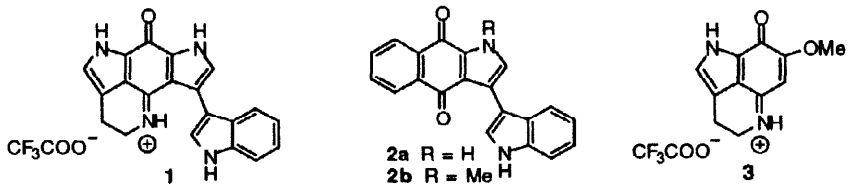
Abstract: The oxidative formation of a new pyrrole ring in the indol-3-yl-indoloquinone system afforded a simple synthesis of the wakayin model compound **2b**.

Wakayin **1**, first isolated and characterized as its trifluoroaceate salt by C. M. Ireland and co-workers in 1991, is a novel cytotoxic pyrroloiminoquinone alkaloid from Ascidian *clavelina* species.[1] It shows various biological activities, one of which is inhibition of topoisomerase[2] I and II. Its unique indole-substituted bispyrroloiminoquinone structure provides an interesting challenge for organic synthesis.



Scheme 1

Retrosynthetic analysis of wakayin, which may well follow its biogenesis, suggests tryptamine and the tricyclic quinonimine **3** as precursors, with the middle pyrrole ring being generated by an oxidative cyclization process (Scheme 1). Compound **3**, which has been reported by several groups,[3-8] has been used as a precursor of discorhabdin C[3] and makaluvamine D,[4,7] which are, as well as wakayin, alkaloids containing the pyrrolo[4,3,2-de] quinoline nucleus.

In searching for a method applicable to the construction of the critical pyrrole ring D from tryptamine, compounds **2**, which are indol-3-ylbenzo[f]indole-4,9-diones, were chosen as target models because of their simplicity. In this communication, we report a method for the oxidative formation of such a new pyrrole ring in the model compound **2b**.

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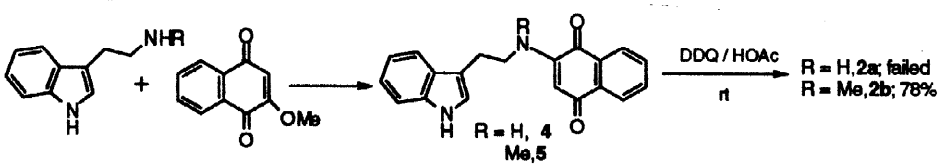

Scheme 2

As shown in Scheme 2, tryptamine was reacted with 2-methoxynaphthoquinone in refluxing ethanol to afford 2-(indol-3-ylethylamino)-naphthoquinone **4**[9] in high yield (68.3%), but various attempts to oxidatively cyclize compound **4** to **2a** failed. Similarly, N-methyltryptamine yielded aminonaphthoquinone **5**[10] in excellent yield (91%). Surprisingly, reaction of **5** with the oxidant DDQ in HOAc gave the desired model compound **2b**[11] in good yield (78%); the structure of **2b** was confirmed by X-ray crystallography.[12]

The failure of **4** to give any of the cyclization product **2a** under similar DDQ treatment indicates that a successful synthesis of **2a** must start with an N-alkyltryptamine containing a readily removable N-alkyl blocking group. Studies in this direction, as well as those employing the tricyclic imine **3** are under investigation.

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9. Compound **4**: Dark red solid, mp 181-183°C. Anal. Calcd for $C_{20}H_{16}N_2O_2$: C.75.95; H, 5.06; N, 8.86. Found: C, 75.83; H, 5.04; N, 8.72.
10. Compound **5**: Dark red solid, mp 176-177°C. Anal. Calcd for $C_{21}H_{18}N_2O_2$: C, 76.36; H, 5.45; N, 8.48. Found: C, 76.24; H, 5.47; N, 8.38.
11. Compound **2b**: Dark purple solid, mp 300-303°C. ^{1}H NMR (360 MHz, DMSO-d_6), δ 11.33 (s, 1H), 8.37 (s, 1H), 8.06 (m, 2H), 7.88 (s, 1H), 7.82 (d, *J*=7.8 Hz, 1H), 7.76 (m, 2H), 7.43 (d, *J*=8.0 Hz, 1H), 7.13 (dd, *J*=7.2, 8.0 Hz, 1H), 7.07 (dd, *J*=7.8, 7.2 Hz, 1H), 4.11 (s, 3H). ^{13}C NMR (90 MHz, DMSO-d_6), δ 179.68, 174.95, 135.94, 134.14, 133.06, 132.78, 130.80, 130.12, 126.89, 126.73, 126.05, 125.64, 125.42, 122.41, 121.12, 119.54, 119.40, 119.24, 111.57, 106.41. MS m/z (rel. intensity), 137 (22.7), 163 (15.0), 200 (9.6), 227 (12.5), 269 (10.5), 297 (13.3), 326 (100). HRMS required 326.105528, found 326.104370.
12. Crystal data for **2b**: $C_{21}H_{14}N_2O_2$, *M*=326.34, monoclinic, space group $P2_1/c$, *a*=14.2202(8)Å, *b*=7.1871(4)Å, *c*=15.5625(8)Å, α=90°, β=109.949(1)°, γ=90°, V=1495.08(14)Å^3, Z=4, ρ_{calcd}=1.450 Mg/m^3, F(000)=680, crystal dimensions 0.22 x 0.40 x 0.55 mm. Tables of atom positions, thermal parameters and a complete listing of bond distances and angles have been deposited at Cambridge Crystallographic Data Center.