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LETTERS

Synthesis of a Bis-pyrrolo-quinone Structure Analogue to Wakayin

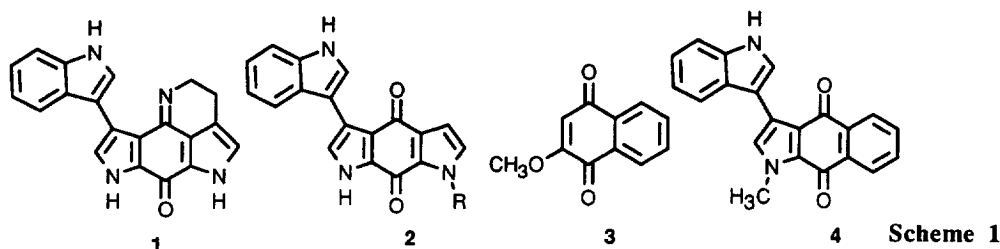
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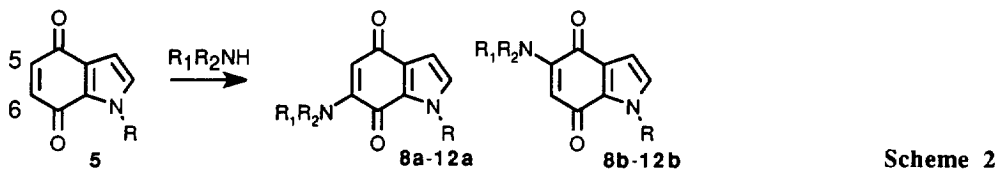
Abstract : The addition of different amines to indole-4,7-quinone is studied. The application of this reaction with indolyl-2-oxoethylamine lead to the preparation of an analogue of wakayin **2**. © 1999 Elsevier Science Ltd. All rights reserved.

Wakayin **1** isolated from *Ascidian clavelina*¹, shows biological activities such as inhibition of topoisomerases I and II². Until now no synthesis of this structure is reported and we planned to obtain the bispyrroloquinone structure **2** substituted with an indole moiety in position 3. Zhang³ described an approach of structure **4** by the reaction of methoxyquinoline-dione **3** with N-methyltryptamine and subsequent cyclisation by using DDQ in acetic acid (scheme 1).



In this work, we wanted first to study the regiochemistry of the addition of different amines to indole-4,7-quinone **5** and then the cyclisation to obtain the bis-indolequinone structure **2**.

In a previous study⁴, we have shown that the regiochemistry of the hetero-Diels-Alder reaction with crotonaldehyde dimethylhydrazone and **5**⁵ was dependent upon the substitution of the nitrogen atom. With an electron-withdrawing substituent on the nitrogen atom of the indole-4,7-quinone (R = SO₂-Ph-Me), the addition of benzylamine gave the 6-isomer⁶ whereas with a hydrogen⁶ or a methyl group⁷, the 5-isomer was the major product (scheme 2).



In our hands, with these conditions (quinone/amine : 1/1, solvent : benzene, room temperature or reflux⁶), the amines were formed in low yields.

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We observed that the yields were improved if the the ratio quinone/nucleophile was 1/5 and if an alcoholic solution of the quinone was added slowly (10 ml/h) to the amine in ethanol at room temperature (Table).

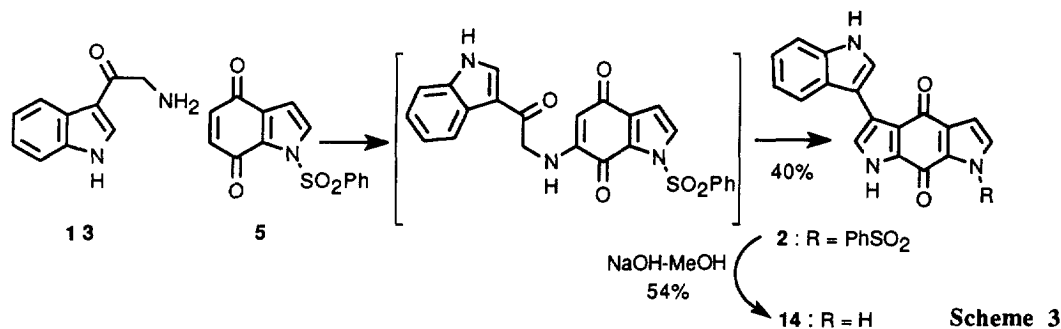
Table

| aminoquinones 8-12 | nucleophile | yield (%) | 8a-12a/8b-12b* |
|---|--------------------|-----------|-----------------|
| 8: R ₁ = R ₂ = H | NaN ₃ | 58 | 8a/8b = 75/25 |
| 9: R ₁ =PhCH ₂ CH ₂ -, R ₂ =H | phenylethylamine | 85 | 9a/9b= 70/30 |
| 10: R ₁ =R ₂ =benzyle | dibenzylamine | 77 | 10a/10b = 70/30 |
| 11: R ₁ =indol-3-yl-ethyl, R ₂ = H | tryptamine | 59 | 11a/11b = 90/10 |
| 12: R ₁ =indol-3-yl-ethyl, R ₂ =benzyl | N-benzyltryptamine | 63 | 12a/12b = 85/15 |

* : with **8**, **11** and **12** the ratio of regioisomers was calculated after chromatographic purification (silica gel); **9** and **10** were submitted to hydrolysis (MeOH-NaOH) and then the ratio of the deprotected regioisomers was calculated after separation by column chromatography.

The cyclisation of the tryptamine derivatives **11** and **12** with DDQ³ did not give the expected products. However, we succeeded by using the oxo-tryptamine **13**. This product was prepared from the N-Boc-tryptamine which was oxidized by the Yonemitsu procedure⁸ and deprotected with trifluoroacetic acid.

Very slow addition of indole-quinone **5** to the alcoholic solution of **13** (5 equivalents) gave **2** (only one isomer), which was purified by column chromatography and obtained as yellow crystals. This compound was hydrolyzed into **14**. The regiochemistry was determined by ¹H-¹³C NMR-correlations (HSQC and HMBC).



The application of this reaction to the total synthesis of wakayin is in progress.

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- 5** was synthesized from 4,7-dimethoxyindole (see: Showalter, H. D. H.; Pohlmann, G. *Org. Proc. Intern.*, **1992**, *24*, 484); 4,7-dimethoxyindole was sulfonylated and then oxidized by using CAN.
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- Compound **5** : Mp : 266-267°C; IR : ν (cm⁻¹): 3310, 3221, 2925, 1650, 1641, 1425. ¹H-NMR (500 MHz, CD₃OD) δ (ppm): 8.25 (1H, m, CH), 7.97 (1H, s, CH), 7.95 (1H, s, CH), 7.40 (1H, m, CH), 7.20 (2H, m, CH), 6.90 (1H, d, J=3 Hz, CH), 6.60 (1H, d, J=3Hz, CH). ¹³C-NMR (125 MHz, CD₃OD) δ (ppm): 179.7, 173.4, 138.0, 137.6, 134.8, 134.7, 129.3, 126.1, 126.0, 125.9, 124.0, 123.1, 122.3, 121.3, 117.1, 112.4, 108.3.