# HETERO DIELS-ALDER REACTION WITH INDOLOQUINONES

Roland BARRET,[a,c,*] Nathalie ROUE,[c,1)] and H. FILLION[b]

*Laboratoire de Chimie Thérapeutique,[a] Laboratoire de Chimie Organique,[b] Faculté de Pharmacie, 8 avenue Rockefeller F69373 Lyon Cedex08 France and UPRESA 6013,[c] Faculté de Pharmacie, 51 rue Cognacq-Jay, F51100 Reims, France.*

The hetero Diels-Alder reaction of 4,7-indoloquinones with crotonaldehyde dimethylhydrazone afforded 5-methyl-5,6-dihydropyrido[6,5-*b*]indole-4,9-dione ([1,8] isomer) and 5-methyl-5,6-dihydropyrido[5,6-*b*]indole-4,9-diones ([1,5] isomer). The 6,7,8,9-tetrahydrocarbazole-2,5-dione region-selectively afforded 4-methyl-1,4,6,7,8,9-hexahydropyrido[2,3-*b*]carbazole-5,11-dione. The regiochemistry of these reactions was controlled by the substitution of the nitrogen and the 2-C atom of the indole moiety: the unsubstituted quinones afforded the [1,8] regioisomer, whereas the [1,5] compounds were obtained with the quinones bearing an electron-withdrawing substituent on the nitrogen or the 2-C atom.

**KEYWORDS** Diels-Alder reaction; indoloquinone; heterocycle

Many indoloiminoquinone alkaloids have been isolated from several sponges and ascidians (isobatzellins,[2)] discorhabdins,[3)] makaluvamines,[4)] wakayin[5)] tsitsikammamines,[6)] veiutamine.[7)]). Some, such as discorhabdin C **1**, have cytotoxic and antitumor activities.[8)]

The structure of the latter compound is relatively complex and the pharmacophor group responsible for the antitumor activity is unknown. Thus we planned to synthesize the tetrahydropyridoindoloquinone moiety **2** using to hetero Diels-Alder strategy (Chart 1).

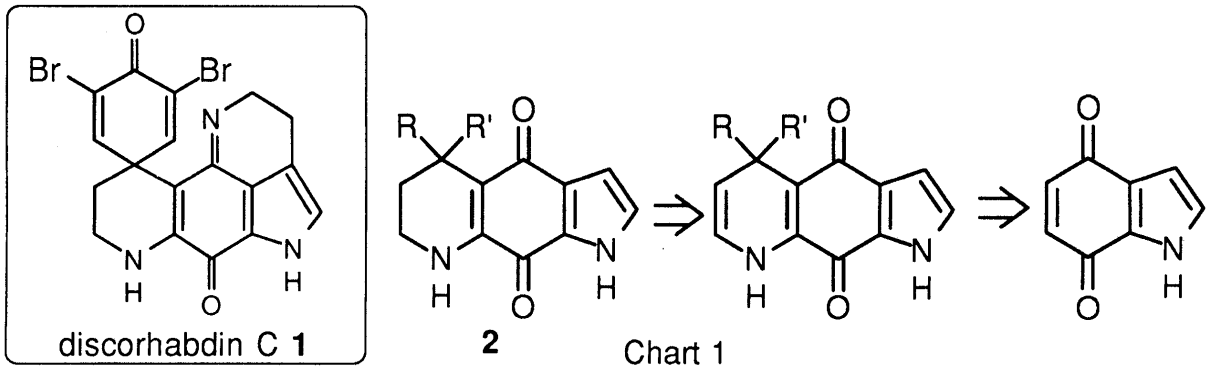


Chart 1

In this work, we studied the regiochemistry of this reaction in terms of the substitution of the indoloquinone.

The hetero Diels-Alder reactions were carried out at the solvent (acetonitrile) reflux temperature with a 1.5 equivalent of hetero-diene **3**[9)] with indoloquinones **4a-f**. The two regioisomers **5a-f** and **6a-f** were isolated by column chromatograpy and the regiochemistry was studied in 2D-NMR experiments (HMQC and HMBC) (Table 1 and Chart 2).

* To whom correspondence should be addressed.

© 1998 Pharmaceutical Society of Japan

NII-Electronic Library Service

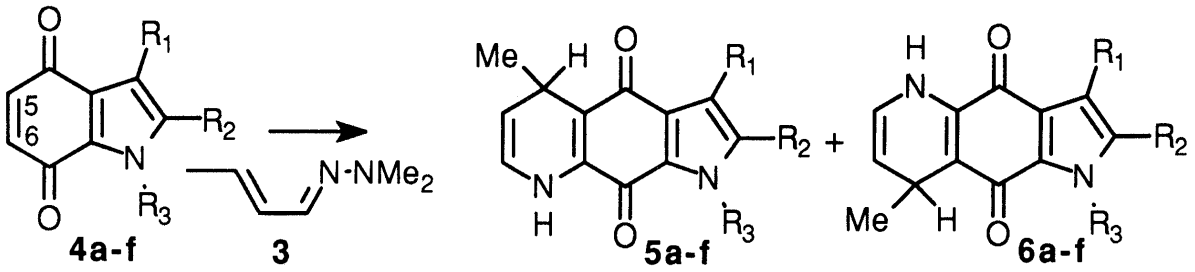


Chart 2

Table 1. Hetero Diels-Alder Reactions of Indoloquinones with **3**

| Quinone | $R_1$ | $R_2$ | $R_3$ | Yield (%) | 5a-f/5'a-f |
|---|---|---|---|---|---|
| **4a** | H | H | $SO_2Ph$ | 40 | 15/85 |
| **4b** | H | H | $SO_2C_6H_4Me$-p | 50 | 15/85 |
| **4c** | H | $CO_2Et$ | H | 54 | 30/70 |
| **4d** | H | H | $CO_2Me$ | 42 | 30/70 |
| **4e** | H | H | H | 26 | 65/35 |
| **4f** | | $-(CH_2)_4-$ | H | 25 | 100/0 |

In the 2D-NMR experiments (HMBC) with the major product of the reaction with **4e** showed correlations betwen the 3-H proton ($\delta$ = 7.25 ppm, d, $J$ = 4.0 Hz) and the carbon atom of the carbonyl group at $\delta$ = 182.2 ppm. Thus this carbon atom was 4-C. This carbon correlated with a quintet signal ($\delta$ = 3.5 ppm, q, $J$ = 6.5 Hz). The proton near the nitrogen atom of the dihydropyridine nucleus ($\delta$ = 6.1 ppm, dd, $J$ = 4.2 Hz and $J$ = 8.0 Hz) correlated with 8a-C ($\delta$ = 171.8 ppm) (Chart 3). All these facts show that the major compound was the [1,8] isomer **5e**.

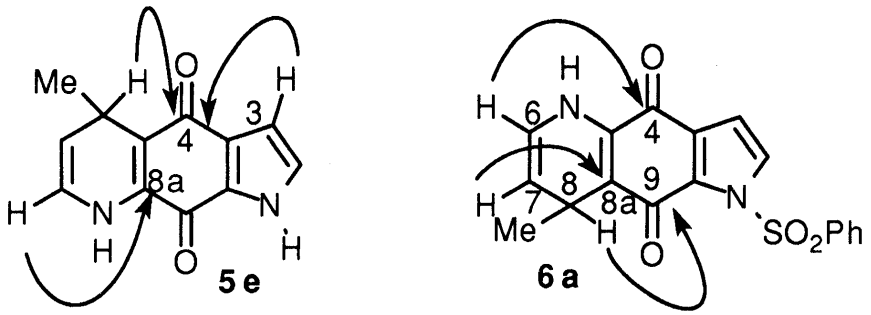


Chart 3

The same study showed that the major isomer with the electron-withdrawing-substituted quinones **4a-d** were the [1,5]-isomers **6a-d**. For example, with the major Diels-Alder adduct obtained with **4a**, the HMBC experiment showed a correlation between the quintet of 8-H ($\delta$ = 3.5 ppm, q, $J$ = 6.5 Hz) and the carbonyl at 174 ppm (9-C). This study was performed with all the major isomeric compounds of the different reactions.
Recently, the same result was observed with the carbazole-1,5-quinone **7a** which reacted with the metacrolein dimethylhydrazone **8** to give only one regioisomer **9a**.
The *N*-ethylcarbazolequinone **7** gave the major product with the same regiochemistry (**9b/10b** = 93/7) (Chart 4).[10]

NII-Electronic Library Service

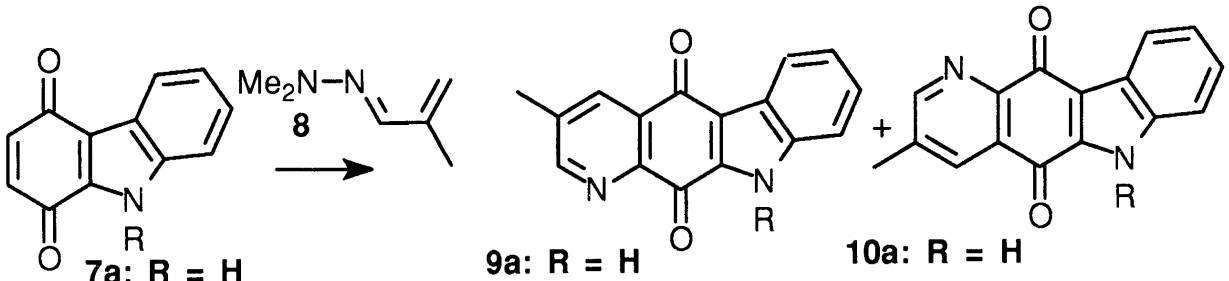


Chart 4

We calculated the HOMO and LUMO energies using the semiempirical AM1 method with **4a**, **4e**, and the diene **3**.

The calculations of the orbital coefficients of the quinones showed that larger values were located on the 5-C atom for **4e** (-0.095, but -0.075 for 6-C) and the 6-C atom for **4a** (-0.095, but -0.075 for 5-C). With the hetero diene **3**, the most important value was on the 4-C atom (-0.070 for 4-C and -0.126 for 1-N) . The regiochemistry observed in the cycloaddition agreed with that predicted from the orbital coefficient values: the major isomer with **4e** was [1,8]-compound **5e**, whereas with **4a** the major isomer was the [1,5]-compound **6a**.

These results suggest that the regiochemistry of the hetero Diels-Alder reaction was oriented upon the substitution of the indole moiety: with the electron-withdrawing-substituted compounds **4a-d** the [1,5]-regioisomers were favored whereas with the -un-substituted compounds **4e-f**, the [1,8]-isomers were obtained. The application of this reaction to the synthesis of pyrroloquinoline alkaloids is in progress in our laboratory.

## References and Notes

1) Present adress: *CNT Novum, Karolinska Institute S-141 52 Huddinge, Sweden.*
2) Sun H. H., Sakemi S., Burres N., McCarthy P., *J. Org. Chem.*, **55**, 4964-4966 (1990).
3) Perry N. B., Brunt J. W., McCombs J. D., Munro M. H. G., *J. Org. Chem.*, **51**, 5476-5478 (1988); Kita Y., Tohma H., Inagaki M., Hatanaka K., Yakura T., *J. Am. Chem. Soc.*, **114**, 2175-2180 (1992); Tao X. L., Cheng J. F., Nishiyama S., Yamamura S., *Tetrahedron*, **50**, 2017-2028 (1994).
4) Radisky D. C., Radisky E. S., Barrows L. R., Copp B. R., Kramer R. A., Ireland C. M., *J. Am. Chem. Soc.*, **115**, 1632-1638 (1993).
5) Copp B. R., Ireland C. M., Barrows L. R., *J. Org. Chem.*, **56**, 4596-4597 (1991).
6) Hooper G. J., Davis-Coleman M. T., Kelly-Borges M., Coetzee P. S., *Tetrahedron Lett.*, **37**, 7135-7138 (1996).
7) Venables D. A., Barrows L. R., Lassota P., Ireland C. M., *Tetrahedron Lett.* , **38**, 721-722 (1997).
8) Perry N. B., Blunt J. W., Munro M. H. G., *Tetrahedron*, **44**, 1727-1734 (1988).
9) Ghosez L., Serckx-Poncin B., Rivera M., Bayard P., Sainte F., Dumoulin A., Frisque-Hestain A. M., Mockel A., Munoz L., Bernard-Henriet C., *Lect. Heterocycl. Chem.*, **8**, 69-78 (1985); Chigr M., Fillion H., Rougny A., *Tetrahedron Lett.*, **29**, 5913-5916 (1988); Nebois P., Fillion H., *Tetrahedron Lett.*, **32**, 1307-1310 (1991); Zjawiony J. K., Srivastata A. R., Hufford C. D., Clark A. M., *Heterocycles*, **39**, 779-880 (1994).
10) Poumaroux A., Bouaziz Z., Dommard M., Fillion H., *Heterocycles*, **45**, 585-596 (1997).

(Received December 26, 1997; accepted February 3, 1998)

NII-Electronic Library Service