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Article

The Diels-Alder Reaction with *O*-2,3-Dimethylene-1,4-Naphthoquinone: A Useful Intermediate for the Synthesis of the B Ring of Anthracyclinones

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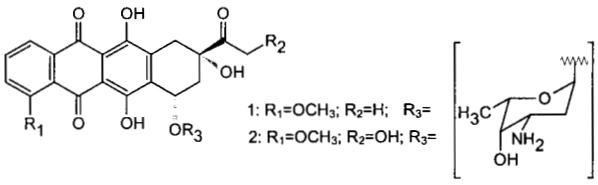
Neste trabalho são descritas as tentativas do uso do dieno *orto*-2,3-dimetileno-1,4-naftoquinona (**3**) na reação de Diels-Alder com dienófilos típicos. Este intermediário é útil na construção do anel B do esqueleto carbocíclico das antraciclinonas. O dieno **3** tem como característica preferencial sofrer dimerização levando a substância **9,** um esqueleto recém reconhecido na literatura como agente tripanocida. Entre os diversos subprodutos isolados e identificados, foi possível assinalar e caracterizar um novo heterociclo **13**.

This work describes the attempt to use the diene *ortho*-2,3-dimethylene-1,4-naphthoquinone (**3**) in a Diels-Alder reaction with typical dienophiles. The intermediate **3** is useful for the synthesis of the anthracyclinone skeleton by a convergent route to the B ring. The reactions failed to give the desired Diels-Alder adduct in a good yield, but instead led to a spiro-dimer **9** which was recently described as a trypanocide agent. Among the by-products generated in these reactions it was possible to isolate and characterize a new heterocyclic compound **13**.

Keywords: *anthracyclinone, dimethylenenaphthoquinone, Diels-Alder reaction*

Introduction

In recent years, many efforts have been directed towards the synthesis of anthracyclins, a group of natural antibiotics isolated from the cultures of several *Streptomyces* spp. The great interest came from the significant antineoplasic activities that a certain number of this class of naturally occurring anthraquinoid compounds such as daunomycin **1** and adriamycin **2**, possess[1,2]. Although these compounds have excellent therapeutic values for cancer chemotherapy[3], their utility is limited due to a number of toxic side effects[4].



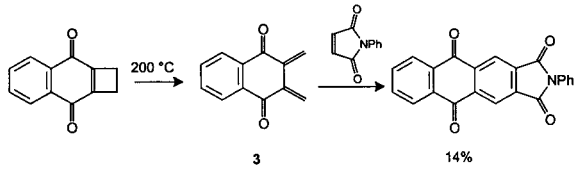
More recently, an improved pharmacological profile has been achieved for some synthetic analogs of this class of compounds. This has stimulated the development of total syntheses of these compounds and of their new analogs for biological screening tests[5]. Several synthetic strategies were developed for the production of these clinically useful compounds. The main problem in these syntheses lies in the preparation of the corresponding aglycones, the anthracyclinone moiety, the synthesis of which has been set as a challenging target for many research groups[6]. Many different anellation strategies for the tetracyclic aglycone

skeleton have been published in the last few years[7]. However, the construction of the B ring by convergent coupling of CD and A ring building blocks is one of the least studied approaches (Scheme 1)[8].

Results and Discussion

In an attempt to advance new developments in this area, we started exploring the approaches to the B ring *via* the intermediate *ortho*-2,3-dimethylene-1,4-naphthoquinone (**3**) as a CD quinoid building block which, in principle, would produce the tetracyclic aglicone skeleton by a Diels-Alder reaction.

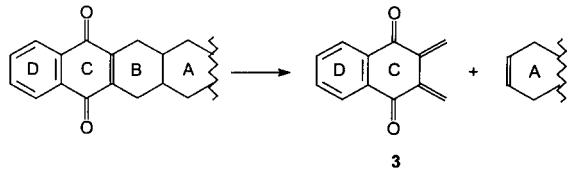
We present our results here on the *in situ* generation of **3** in the presence of trapping dienophiles in order to evaluate **3** as an adequate building block for our purposes. The literature survey revealed that one attempt to generate **3** and use it in the Diels-Alder reaction has already been conducted, employing dehydrocyclobutan[b]naphthalen-3,8-dione, by thermally opening the cyclobutan moiety[9]. The use of such a route by Cava *et al.* in the presence of trapping dienophiles produces very low yields of the Diels-Alder adduct, as shown below[9].



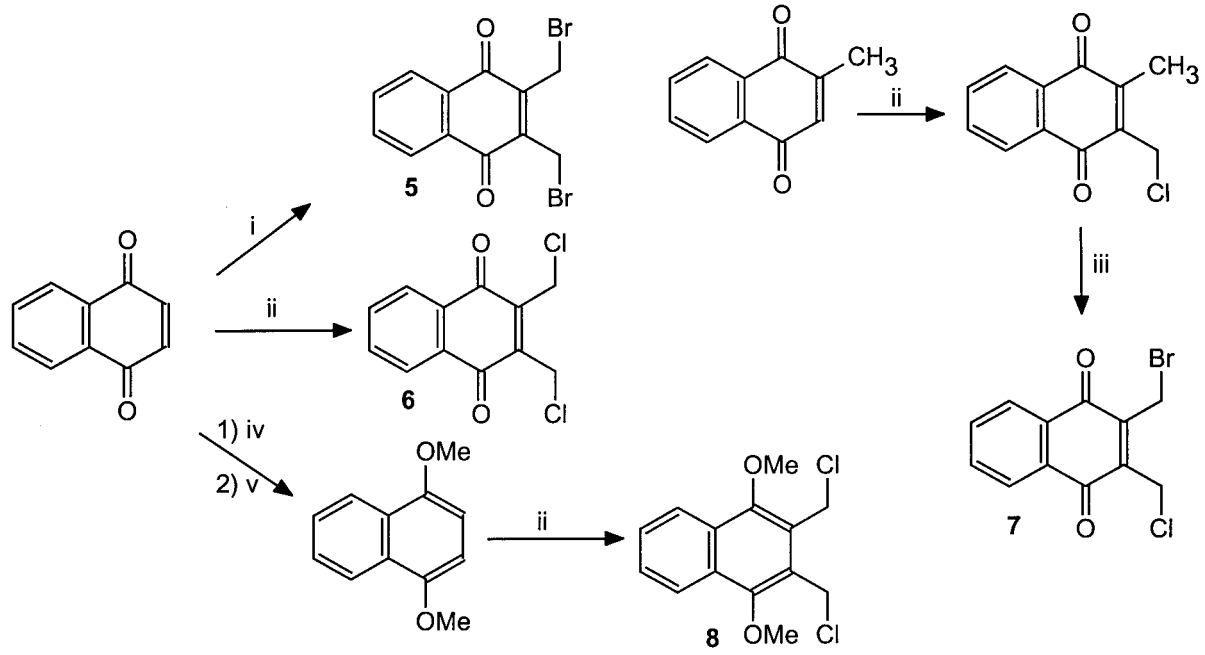
We decided to focus our attention on the generation of **3** by iodide-anion induced dehalogenation, a mild and efficient condition for the generation of *o*-quinodimethide intermediates[10,11].

Several dihalogenated quinone derivatives, such as **5**, **6** and **7**, that in principle would give **3** by dehalogenation methods, were synthesized from 1,4-naphthoquinone and 2-methyl-1,4-naphthoquinone, by straightforward procedures from the literature, as shown in Scheme 2[12-14]. Compounds **7** and **8** are new. The dimethyl ether **8** was synthesized on purpose for structural comparison between the generation of *o*-naphthoquinodimethide from **6**, and its reduced *o*-dichloromethylnaphthalene form, which can also furnish the dimethide intermediate, having its carbonyls protected.

Dehalogenation of the quinonoids **5**, **6**, **7** and **8** under several reaction conditions, in the presence of Diels-Alder dienophiles, is shown in Table 1. These results represent our best reactions after several trials for optimization of the conditions, such as solvents, reagent molar ratios, tempera-



Scheme 1. Retrosynthetic analysis of the anthracyclinone general structure based on the construction of the B ring.



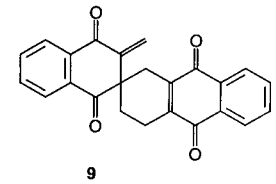
i) HBr/CH_2O, AcOH, H_2SO_4; ii) HCl/CH_2O, AcOH, H_2SO_4;
iii) NBS/CCl_4, benzoyl peroxide; iv) $Na_2S_2O_4$; v) Me_2SO_4

Scheme 2. Syntheses of the compounds **5**, **6**, **7** and **8**.

Table 1. Experimental details of reaction conditions and products.

Substrates	Conditions	Dienophile	Product (%)*
5	a***	Dimethyl fumarate	9(33); 10(5); Polymers**
5	b#	Maleic anhydride	9(82); Polymers
5	c	Dimethyl fumarate	9(18); 10(6); 11(1); 12(2); Polymers
6	d	Dimethyl fumarate	9(42); 10(8); Polymers
7	e	Dimethyl fumarate	9(26); 10(17); Polymers
8	f	Maleic anhydride	13(12); Polymers

Product (structures)



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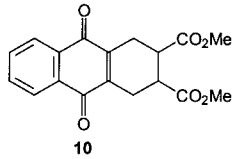

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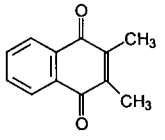

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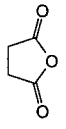

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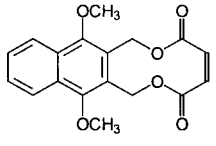

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*Isolated by silica gel column chromatography from the reaction residue after vacuum evaporation of the solvent. Eluant: hexane/ethyl acetate (increasing polarity).

**Highly insoluble polar tar obtained from the reaction mixture after vacuum evaporation of the solvent.

***Conditions: dry nitrogen atmosphere and dry solvents.

#The same yield of **9** is obtained in the absence of any dienophile.

a) 1.5 mmol of **5**/29 mL acetone was slowly added over NaI (21 mmol)/dienophile (3.5 mmol)/ acetone (60 mL), followed by reflux (1 h).

b) 0.7 mmol of **5**/5 mL DMF was slowly added over NaI (14 mmol/dienophile (4.0 mmol)/DMF (30 mL). The reaction was maintained at 70 °C for 30 min.

c) 1.5 mmol of **5**/benzene (25 mL)/methanol (5 mL) was slowly added (25 °C) over Mg (83 mmol)/benzene (25 mL)/methanol (15 mL)/dienophile (1.5 mmol), followed by heating (30 min) at 70 °C.

d) 3.5 mmol of **6**/acetone (40 mL) was slowly added (2 h) over NaI (40 mmol)/acetone (80 mL)/ dienophile (6.0 mmol), followed by reflux (30 min).

e) 1.6 mmol of **7**/acetone (30 mL) was added (1 h) over NaI (21 mmol)/acetone (60 mL)/ dienophile (3.5 mmol), followed by reflux (1 h).

f) 1.8 mmol of **8**/DMF (15 mL) was added over NaI (22 mmol)/DMF (30 mL)/dienophile (3.8 mmol), followed by heating (70 °C) for 30 min.

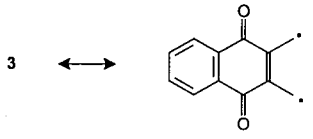
ture, and order of reagent mixing. As can be seen, the results are not very encouraging as a route to the B ring of anthracyclinones, since the major product is the spiroquinone **9**, also a Diels-Alder type product, which was isolated from almost all quinonoid substrates under various conditions (a-e). The dimethyl ether **8** is very unreactive toward the Diels-Alder type reaction, but gives a very complex reaction mixture from which it was possible to isolate the cyclic diester **13** (1,8-dihydro-9,14-dimetoxynaphtho[2,3-c][1,6]dioxecin-3,6-dione of maleic acid), a new ten-membered maleic acid obtained in a very low yield (condition f). After evaporation of the solvent all of the reactions furnished insoluble tar, which we supposed to be polymers. Typical Diels-Alder products were only detected in the presence of dimethylfumarate as dienophile, but in a very low yield. Maleic anhydride did not react at all by this pathway.

These results are unexpected in the sense that the generation of *o*-naphthoquinodimethide intermediates in the presence of dienophiles provides cycloadducts in good yields, as has already been reported in *o*-naphthoquinodimethide chemistry[15]. The use of Mg as a dehalogenation agent[16] (condition c) did not improve the yield of **10**, but it was possible to isolate the by-products **11** and **12** in very low yields (see Table 1), which were probably produced by a reduction pathway.

Conclusions

It is interesting to point out that our results and those of Cava[9,10], were intended to generate the intermediate *ortho*-2,3-dimethylene-1,4-naphthoquinone (**3**), in the presence of dienophiles, gave the Diels-Alder type product **10** in a low yield, either by dehalogenation or by thermal reaction conditions.

We can speculate that such results may indicate that the reactive form from the dehalogenation reaction is distributed between **3** and the bi-radical stabilized intermediate, resembling the canonical form **4**, which suffer preferential typical radical coupling reactions, leading to dimers and to polymers by radical-induced polymerization, and not to Diels-Alder type products as expected. Step by step elimination of the halogens via radical pathways can also be a starting point for the explanation of our results.



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From a chemical point of view, although our strategy to synthesize the B ring failed, on the other hand it opened a new route to spirodione quinonoid derivatives of **9**, a structural type recently reported in the literature as a promising trypanocide[17].

All compounds described in this work have been analyzed by ^{1}H-NMR, ^{13}C-NMR, MS, IR and UV spectra, and are in agreement with the assigned structures. Table 2 show the physical and spectral data for the new compounds.

Table 2. Physical and spectral data for new compounds*.

Compound	m.p. °C (solvent)	I.R.** (KBr, cm^{-1})	^{1}H-NMR*** ($CDCl_3$, TMS, ppm)	M.S. (M/Z, %)
7	126-128 (Hexane)	1670, 1595, 1290, 730	4.60 (s, -CH_2Br, 2H); 4.70 (s, -CH_2Cl, 2H); 7.7-8.30 (m, Ar-H, 4H).	298 (M^+, 4); 262 (10); 264 (10); 218 (100); 220 (30); 183 (90); 155 (30).
8	95-97 (Hexane)	2990, 2940, 1585, 1450, 1350, 1280, 765	3.95 (s, -OCH_3, 6H); 5.00 (s, -CH_2-, 4H); 7.30-7.55 (m, Ar-H, 2H); 7.80-8.10 (m, Ar-H, 2H).	284 (M^+, 11); 262 (11); 220 (35); 218 (100); 183 (93); 80 (10).
9	190-192 °C (Hexane / Ethyl-acetate)	1700, 1660, 1600, 1590, 1380, 1290	1.90-2.10 (m, -CH_2-, 2H); 2.50-2.70 (m, -CH_2CH_2-, 2H); 2.97 (d, J = 20 Hz, -CH-, 1H); 3.58 (d, J = 20 Hz, -CH-, 1H); 5.4 (s, -CH=, 1H); 6.18 (s, -CH=, 1H); 7.68-8.26 (m, Ar-H, 8H)	368 (M^+, 100); 350 (10); 340 (14); 321 (10); 333 (4); 209 (22); 197 (26).
13	98.5-99.5 (Hexane/Ethyl-acetate)	3060, 2840, 1720, 1610, 1590, 1440, 1360, 1065	4.02 (s, -OCH_3, 6H); 5.58 (s, -CH_2-CH_2-, 4H); 6.40 (s, -CH=, 2H); 7.48-7.62 (m, Ar-H, 2H); 8.04-8.16 (m, Ar-H, 2H)	328 (M^+, 87); 229 (100); 216 (16)

* The known compounds **5, 6, 10, 11, 12** have physical and spectral data in agreement with the published literature[12-14]; **Perkin Elmer-281B; ***Varian XL-100/12; Low resolution M.S. obtained on a VG Micromass 12 Spectrometer and Exact mass Finnigan 4000 GC-MS instrument: **7**: 298.9404 (calcd. for $C_{12}H_8O_2BrCl$: 298.9396); **8**: 284.0369 (calcd. for $C_{14}H_{14}O_2Cl_2$: 284.0370); **9**: 368.1035 (calcd. for $C_{24}H_{16}O_4$: 368.1048); **13**: 328.0958 (calcd. for $C_{18}H_{16}O_6$: 328.0946).

Acknowledgment

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