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AN EFFICIENT ROUTE TO AMINOANTHRAQUINONES AND DERIVATIVES VIA A DIELS-ALDER REACTION.

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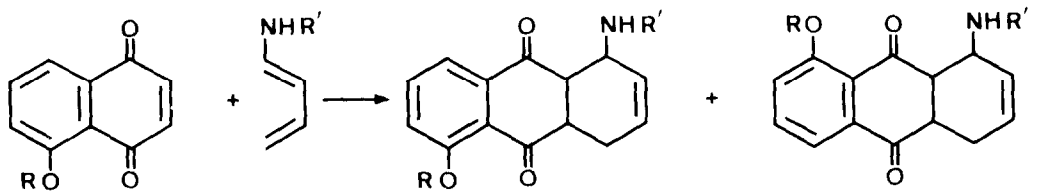
Summary : Cycloadditions of (E)-1-N-carbobenzoxyamino-1,3-butadiene to naphtoquinones followed by aromatization of the adducts and deprotection of the amino group afford regioselective syntheses of -5 and -8 substituted aminoanthraquinones.

The Diels-Alder reaction between naphtoquinones and appropriate dienes offers an attractive way to functionalized anthraquinones[1-6]. The regioselectivity of the reaction can be predicted by the frontier molecular orbital theory only when a good polarized donor diene is used[4]. Thus, cycloadditions of vinyl acrylic acid and its methyl ester to juglone 1a make an exception[6] to orientation rules in naphtoquinones[7]. In view to obtain -5 and -8 substituted aminoanthraquinones of special interest in cancer chemotherapy, we plan to carry out their synthesis by the Diels-Alder route and to investigate their regiochemistry.

So the readily available (E)-1-N-carbobenzoxyamino-1,3-butadiene 2[8] reacts with dienophiles 1a, 1b[9] and 1c[10] in toluene and gives the regioisomer adducts 3 and 4 (scheme). The orientation of the cycloaddition is indicated in table I.

Scheme



1 2 3 4

1a, 3a, 4a : R = H 1b, 3b, 4b : R = CH_3 1c, 4c : R = $COCH_3$ 2, 3, 4, R' = $COOCH_2C_6H_5$

Table I[m]

	R	Time[n]	Yield %[o]	Ratio of adducts 3 : 4
a	H	1h	56	1 : 3[p]
b	CH_3	5h	57	11 : 1[q]
c	$COCH_3$	1h30	64	0 : 1

(m) All reactions are carried out under nitrogen, in freshly distilled toluene at 110° using excess diene.

(n) The reactions are followed by TLC.

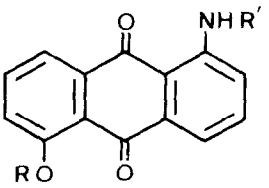
(o) Yields of isolated pure products 3 and 4 are based on 1.

(p) Evaluated by ^1H NMR spectra of the crude mixture[11].

(q) 3b and 4b (m.p. 176° and 180° respectively) are separated by column chromatography.

The reaction is more regioselective with 1b and 1c comparatively to 1a. Starting with methyljuglone, we observe an inversion of the regiochemistry[12] which is in agreement with Kelly's hypothesis[2]. But acetyljuglone gives the unexpected -1,8[13] regioisomer 4c (m.p. 154°). A similar opposite regiochemistry has already been reported by Boeckman et al.[14] with a lower regiospecificity. According to Boeckman's observations, it seems that the anomalous regiochemical behavior exhibited by the acetate derivative 1c toward the diene 2 is not only accomodated by the primary orbital effects, but by secondary orbital interactions in the concerted transition state as it has been pointed out by Alston[15, 16].

These adducts, when aromatized with manganese dioxide[17] give the corresponding anthraquinones 5a, 5b, 6a, 6c. Deprotection of the amino group in compounds 5a, 5b, 6a by hydrogen bromide in acetic acid[18] lead to the -5 and -8 substituted aminoanthraquinones 5d, 5e and 6d which are identified by their IR and ^1H NMR data (table II) and comparison with authentic samples.



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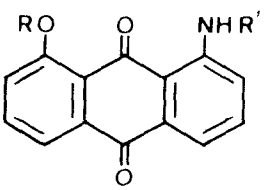

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5a : R = H , R' = $COOCH_2C_6H_5$
5b : R = CH_3, R' = $COOCH_2C_6H_5$
5d : R = H , R' = H
5e : R = CH_3, R' = H

6a : R = H , R' = $COOCH_2C_6H_5$
6c : R = $COCH_3$, R' = $COOCH_2C_6H_5$
6d : R = H , R' = H

Table II

	Yield %	m.p. [°C]	IR** (KBr), ν cm^{-1}	^{1}H NMR (80 MHz, $CDCl_3$) δ ppm
5a	95*	218	3440, 3200, 1730, 1670, 1635, 820, 715	12.59 (s, peri-OH), 11.98 (NH), 8.93 to 7.68 (m, 11H), 5.34 (s,2H)
5b	60	221	3205, 1730, 1670, 1640, 810, 705	11.77 (NH), 8.74 to 7.25 (m, 11H), 5.26 (s, 2H), 4.04 (s, 3H)
5d	78	216 (214^{20})	3440, 3320, 1620, 1600, 800, 710	12.62 (s, peri-OH), 7.8 to 6.7 (m, 8H)
5e	74	229	3450, 3330, 1665, 1615, 810, 715	8.2 to 6.85 (m, 8H), 4.03 (s, 3H)
6a	95*	211	3440, 3250, 1740, 1670, 1625, 845, 747	12.46 (s, peri-OH), 11.66 (NH), 9.02 to 7.3 (m, 11H), 5.3 (s, 2H)
6c	57	204	3250, 1760, 1730, 1670, 1645, 850, 745	11.64 (NH), 8.93 to 7.25 (m, 11H), 5.27 (s, 2H), 2.46 (s, 3H)
6d	77	234 ($230\text{-}1.4^{20}$)	3450, 3340, 1670, 1620, 845, 750	12.85 (s, peri-OH), 7.75 to 6.75 (m, 6H), 6.72 (NH_2)

* Oxidation of a mixture of 3a and 4a yields 95 % of 5a and 6a which are separated by preparative TLC.

** The IR spectra of -1,5 disubstituted anthraquinones show caracteristic absorptions at 820-800 and 715-705 cm^{-1} . Those are shifted near 845 and 745 cm^{-1} for the -1,8 regioisomers. These values are in good agreement with those of Sakata et al.[19]

Reaction of 2 with benzoquinone and naphtoquinone proceeds similarly. Thus, cycloaddition of 1-N-carbobenzoxyamino-1,3-butadiene to appropriate quinones followed by aromatization of the adducts and hydrogenolysis of the carbamate group affords a facile and regioselective procedure for the syntheses of -5 or -8 substituted aminoanthraquinones.

Satisfactory analytical and spectral data have been obtained for all new compounds reported in this work.

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11 - The 80 MHz NMR spectra of 3a and 4a are very similar, but the two compounds can be differentiated by the position of the resonance due to the peri-OH protons (sharp singlets in CD Cl_3) at δ 11.85 ppm for 3a and δ 11.72 ppm for 4a).

12 - Methylation of anthraquinone 5a (minor product) by CH_3I/Ag_2O according to procedure described in reference[9] gives a compound which is identified as the major product 5b.

13 - Acetylation of 6a (100 mg) with 10 ml of acetic anhydride at 140° yields a compound identical with 6c. On the other hand, the hydrolysis of 6c (KOH 10 %, Et OH) gives only the -1,8 regioisomer 6a.

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17 - Compounds 3 or 4 are stirred at room temperature during 30 hours with 5 equivalents of activated manganese dioxide in $CHCl_3$. After filtration and evaporation of the solvent, the corresponding residue is chromatographied on silicagel.

18 - Deprotection of the amino group is carried out at room temperature by HBr (33 % in acetic acid). After the usual work-up, the corresponding aminoanthraquinone is purified by recristallization from ethanol.

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