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SYNTHESIS OF DIAZA-ANTHRAQUINONES BY HETERO DIELS-ALDER CYCLOADDITION REACTIONS

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Abstract- Using 3-methyl-1-dimethylamino-1-azabuta-1,3-diene and 3(tert-butyl dimethylsilyl)oxy-1-dimethylamino-1-azabuta-1,3-diene as 1-azadienes and quinoline-5,8-dione and carbostyrilquinone as dienophiles, several diaza-anthraquinones have been obtained. Structure assignments were mainly based on IR spectroscopic data. The accessibility of N-oxidation products has been also investigated.

Diazaquinomicin A (DQM, fig.1) has been isolated and characterized by Omura et al.[1-3], as a new neutral antifolate antibiotic, active against Gram-positive bacteria. The site of action of DQM was studied and compared with other known synthetic antibacterial and antitumor drugs such as trimethoprim, methotrexate and 5-fluorouracil. It was described as a thymidilate synthase inhibitor competitively with 5,10-methylene tetrahydrofolate[4]. Preparation of derivatives with higher solubility was claimed to be of interest in creating new antitumor drugs. This paper deals with a synthetic approach to DQM analogues by hetero Diels-Alder cycloaddition reactions.

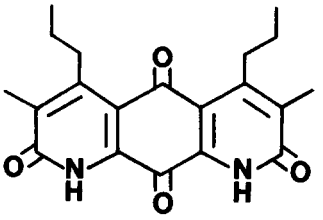
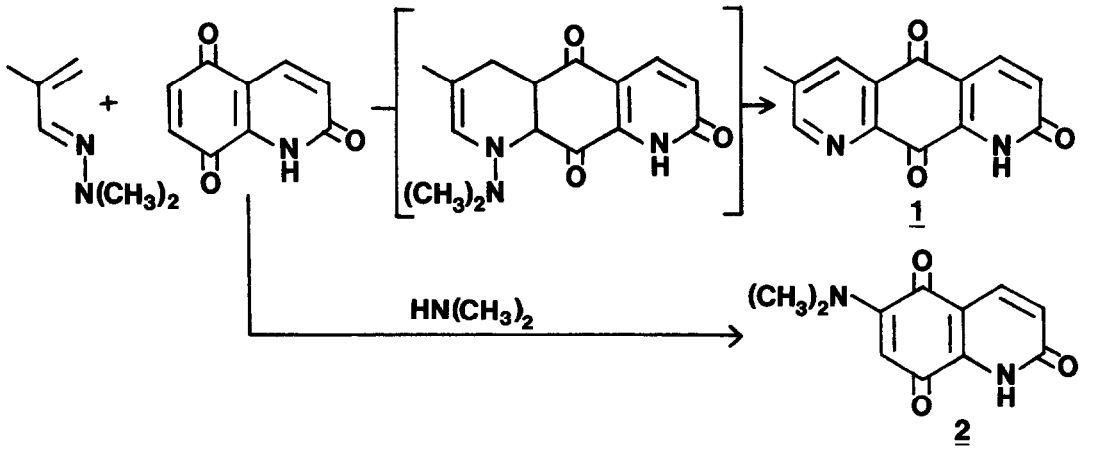


Figure 1

Cycloadditions between azanaphthoquinones and appropriate dienes are efficient and regioselective methods of synthesis of aza-anthraquinones[5,6]. Regioselective (or regiospecific) cycloadditions of an electron-rich diene with an azanaphthoquinone are controlled by the relative electron deficiencies of the carbonyl groups[6]. As carbostyrilquinone is readily available from 8-hydroxyquinoline[7], we investigated the reactions of such quinone with 1-aza-dienes, compounds extensively studied by Ghosez and coworkers[8,9]. In this context, only one example of cycloaddition between carbostyrilquinone and 1,2-dimethylenecyclohexane has been previously reported to give anthracyclin

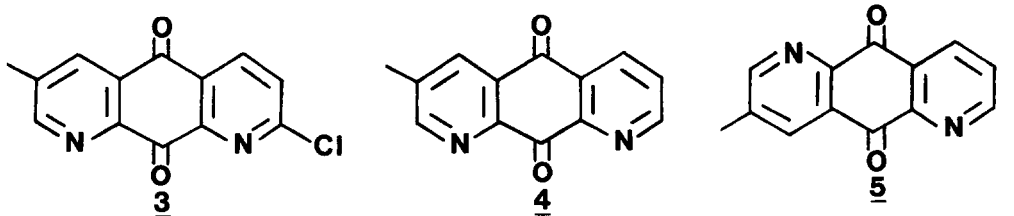
analogues[10].

The reaction with 3-methyl-1-dimethylamino-1-azabuta-1,3-diene was regioselective and yielded 1, which isomeric purity was corroborated by its 200 MHz ^{1}H-NMR spectrum (Tables 1 and 2). The secondary product 2 is formed by addition of dimethylamine to the starting quinone according to previously proposed reaction mechanisms for such 1-azadiene[9]. Structure 2 was confirmed by carrying out the direct addition. In both reactions no addition on the 3,4-double bond of carbostyrilquinone was detected.



The best results (68% of 1) were obtained under N_2 atmosphere and equimolecular proportion of reactants. When the reaction was performed in air and/or 2 equivalents of the starting quinone were used, the yield of 2 was increased while that of 1 decreased.

To confirm structure 1, it was transformed into 3 by treatment with phosphorus oxychloride and this derivative was compared with the two cycloaddition products 4 and 5, obtained from quinoline-5,8-dione and 3-methyl-1-dimethylamino-1-azabuta-1,3-diene.

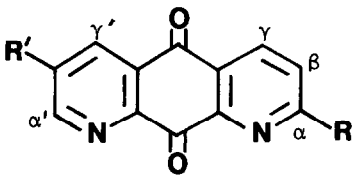


The last mentioned reaction has been studied by Potts to give the diazaanthraquinone 4[6,11] as the only obtained isomer, but by modifying the reaction conditions, the regioselectivity drops to give up to 12% of 5 (see experimental).

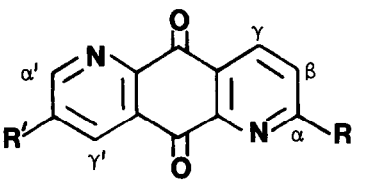
^{1}H-NMR spectra of isomers 4 and 5 (Tables 1 and 2) are practically identical but while compound 5 only shows a carbonyl stretching IR band, according to its greater symmetry, compounds 3 and 4[6,11] show two carbonyl bands in agreement with their assigned structures (Table 3).

The electronic effect of the pyridine nitrogen atom increases the frequency of the neighbour carbonyl group as it is known to occur, for instance, in 1-aza-5,10-anthraquinone[5] in which the C5-carbonyl band appears at 1671 cm^{-1} while the C10-carbonyl band occurs at 1686 cm^{-1}. In compounds 3 and 4 the additional pyridine nitrogen atom augments the difference between the two carbonyl bands.

TABLE 1.- ^{1}H-NMR data (δ values relative TMS).



General structure for compounds 1,3,4 and 6



5 (R=H, R'=CH_3)

Compound	Solvent	R	R'	Hα(R=H)	Hβ	Hγ	Hα'	Hγ'	R'	NH
1	$DMSO_{d-6}$	OH[a]	CH_3	--	6.98	8.15	8.90	8.37	2.59	b
2	Cl_3CD	OH[a]	---	--	6.68	7.89[c]	--	--	--	d
3	Cl_3CD	Cl	CH_3	--	7.77	8.58	8.99	8.41	2.59	-
4[e]	Cl_3CD	H	CH_3	9.18	7.79	8.66	9.00	8.44	2.60	-
5	Cl_3CD	H	CH_3	9.16	7.81	8.75	8.98	8.54	2.61	-
6	$DMSO_{d-6}$	H	OH	9.08	7.88	8.52	8.62	7.75	11.53	-

a: As carbonyl tautomer.
b: Only observed in $CDCl_3$ at 9.80 ppm.
c: δH7=5.71; $\delta N(CH_3)_2$=3.33.
d: Not observed.
e: According with ref. 11.

Due to the presence of a third carbonyl group, the possibility of hydrogen bonding and the different electronic effects of both nitrogen atoms in 1, the study of the stretching carbonyl IR region is more difficult but structure 1 is confirmed from that of compound 3. Said structure is consistent with an addition reaction controlled by the greater electron-deficience of carbostyrilquinone 8-carbonyl group.

TABLE 2.- J Values in Hz.

Compound	αβ	βγ	αγ	α'γ'
1	--	9.5	--	2.1
2	--	9.0	--	--
3	--	8.2	--	2.1
4	4.6	7.9	1.7	2.1
5	4.6	7.9	1.7	2.1
6	4.6	7.9	1.7	2.8
7	--	9.5	--	--
8	4.6	7.9	1.6	1.0
9	6.6	7.8	1.1	a
10	4.5	8.0	1.7	a
11	6.6	7.8	1.2	a

a: Not determined.

TABLE 3.- IR carbonyl frequencies of diaza-anthraquinones (KBr; cm^{-1}).

Compound	cm^{-1}	
1	1650	1675
3	1670 (C5=O)	1695 (C10=O)
4	1670 (C5=O)	1695 (C10=O)
5	1685 (C5=O and C10=O)	
6*	1670 (C5=O)	1680 (C10=O)
7	1650-1680	
8+9	1680	
10+11	1660	1680

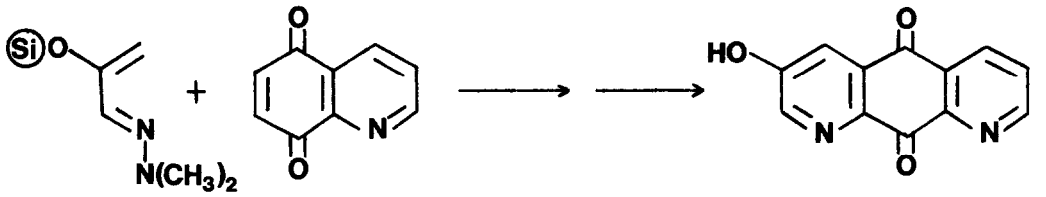
* Two maxima of one broad band

Hetero Diels-Alder cycloaddition reaction between quinoline 5,8-dione and 3(tert-butyldimethylsilyl)oxy-1-dimethylamino-1-azabuta-1,3-diene was also regioselective giving 6 after treatment of the adduct with hot methanol.

Once again the IR frequency values of the quinone carbonyl bands (Table 3) are in agreement with the proposed structure. By comparing such values with those of compound 4 we can clearly see the shift of the C10-carbonyl band to lower frequency in compound 6 due to the electron releasing effect of the 3-hydroxyl group.

Assignation of ^{1}H-NMR signals of compounds 1-6 (Tables 1 and 2) was based on literature data. The main difference between isomers 4[11] and 5 was found in their γ'-protons chemical shift. The δ and J values of β and γ-protons in

compounds 1 and 2 are similar to those described for carbostyrilquinone[7]. The electronic effect of the 2-chloro-substituent in 3 explains the assignation of its β and γ-protons. In 6, the 3-hydroxyl-group is responsible of the upfield chemical shift of its α' and γ'-protons.



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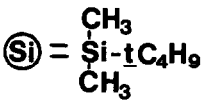
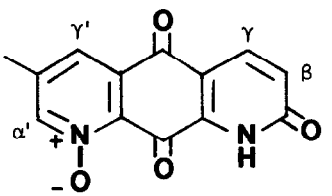


Taking into account the biological interest and reactivity of the possible diaza-anthraquinone N-oxide derivatives, we study their accessibility. Thus, N-oxidation of 1 with MCPBA gave 7. Similarly, mixtures of N-oxides 8 and 9 (6:4) and 10 and 11 (7:3), according to the greater oxidation of the more electron-rich methyl substituted pyridine-ring, were obtained from 4 and 5 respectively.



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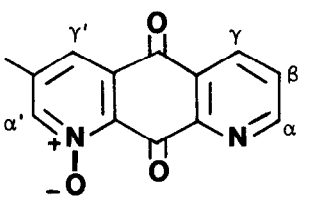

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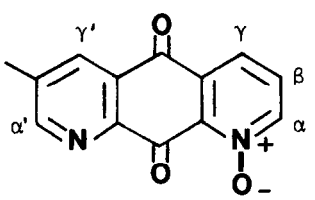

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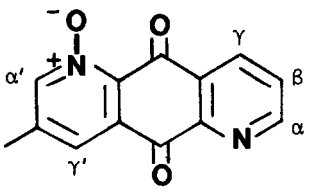

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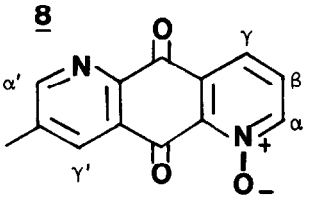

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Structure assignment of N-oxides 7-11 was based on ^{1}H-NMR and IR spectroscopic data (Tables 2,4 and 3 respectively). ^{1}H-NMR spectra of compounds 7-11 show significative upfield chemical shifts for pyridine N-oxidated ring protons. As both nitrogen atoms in compounds 8-11 have opposite electronic effects, the observed IR spectrum for 8 and 9 (as a mixture) has only one carbonyl band while that of 10 and 11 (as a mixture) has two carbonyl bands.

The found low yields in the N-oxidation reactions can be explained because they are subject to steric hindrance as well as electron-attracting carbonyl groups interference[12].

TABLE 4.- ^{1}H-NMR data for N-oxides (δ values relative TMS)

Compound	Solvent	Hα	Hβ	Hγ	Hα'	Hγ'	CH_3
7	$DMSO_{d-6}$	--	6.72[a]	7.98[a]	7.78	8.50	2.38
8	Cl_3CD	9.18	7.75	8.58	7.95	8.45[b]	2.49
9	Cl_3CD	8.58	7.61	8.11	9.00	8.36	2.58
10	Cl_3CD	9.12	7.81	8.73	8.06[b]	8.44[b]	2.49
11	Cl_3CD	8.57	7.63	8.22	8.94	8.48	2.60

a: These signals appear as dd. The observed extracoupling of 1.3 Hz besides the β-γ coupling may be attributed to a phenolic tautomeric structure for this compound. The NH ⇄ OH proton is not clearly observed in the spectrum.

b: Not resolved, wide singlet.

EXPERIMENTAL

Melting points are uncorrected and were measured with a Buchi capillary melting point apparatus. IR spectra were recorded on a Perkin-Elmer 577 spectrophotometer and ^{1}H-NMR spectra with a Brucker (200 MHz) spectrometer.

6-Methyl-2-oxo-1,8-diaza-9,10-anthraquinone (1) To a stirred solution of carbostyrilquinone[7] (1 g,5.7 mmol) in anhydrous tetrahydrofuran (200 ml) under N_2 atmosphere 3-methyl-1-dimethylamino-1-azabuta-1,3-diene[13] (0.72 g, 6 mmol) was added. The reaction was stirred at room temperature in the dark for 4 days. The precipitate thus obtained was filtered under N_2 atmosphere and refluxed in ethanol for 0.5 hr. After cooling, compound 1 crystallized as yellow plates (0.9 g, 68%); mp> 300°C. Found: C 65.07; H 3.59; N 11.34. Calc. for $C_{13}H_8N_2O_3$: C 64.98; H 3.35; N 11.66%.

6-Dimethylamino-carbostyrilquinone (2) a) It was obtained from the mother liquors of the above reaction after filtration of compound 1. b) A solution of dimethylamine (2.56 ml, 20 mmol) and carbostyrilquinone (1.05 g, 6 mmol) in tetrahydrofuran (150 ml) was stirred for 6.5 hr. The black precipitate formed was removed by filtration and the solvent was evaporated in vacuo. The residue was extracted with chloroform and the extract was poured into an excess of petroleum ether. Compound 2 precipitated as crystals (0.76 g, 58%); mp 226-228°C. Found: C 60.88; H 4.86; N 13.08. Calc. for $C_{11}H_{10}N_2O_3$: C 60.52; H 4.60; N 12.80%.

2-Chloro-6-methyl-1,8-diaza-9,10-anthraquinone (3) Compound 1 (0.46 g, 1.9 mmol) was solved in phosphorus oxychloride (10 ml) and the solution was heated at 130°C for 0.5 hr. The reaction mixture was poured into ice and neutralized with aqueous ammonia. The resulting solution was extracted with chloroform and the organic solution was dried over anhydrous sodium sulfate and concentrated in vacuo yielding compound 3 (0.37 g, 75%), mp>300°C (acetone). Found: C 60.50; H 3.00; N 11.10. Calc. for $C_{13}H_7ClN_2O_2$: C 60.33; H 2.72; N 10.82%.

3-Methyl-1,5-diaza-9,10-anthraquinone (5) To a stirred solution of quinoline 5,8-dione[14] (2 g, 12 mmol) in anhydrous benzene (150 ml) under nitrogen atmosphere, 3-methyl-1-dimethylamino-1-azabuta-1,3-diene (1.34 g, 12 mmol) was added. After 12 hr. at room temperature the solvent was removed in vacuo. The residue was solved and refluxed in ethanol for 2 hr. After evaporation under diminished pressure compound 5 was separated from 4 and purified by column chromatography on silicagel using chloroform/ethanol 95:5 (0.4 g, 12%), mp 289-290°C (ethanol). Found: C 69.75; H 3.67; N 12.60. Calc. for $C_{13}H_8N_2O_2$: C 69.62; H 3.59; N 12.49%.

3(Tertbutyldimethylsilyl)oxy-1-dimethylamino-1-azabuta-1,3-diene[8]. To a cold solution of 2-oxopropyliden-N,N-dimethylhydrazine (2 g, 17.4 mmol) in anhydrous methylene chloride (100 ml) under nitrogen atmosphere, anhydrous trietylamine (2.2 g, 21 mmol) and tertbutyldimethylsilyl trifluoromethanesulfonate (5.3 g, 20 mmol) were added and stirred for 1 hr. After evaporation in vacuo at room temperature, cold n-pentane (100 ml) was added and the solution was allowed to stand for 2 hr. at 0°C. After filtration the solution was evaporated under diminished pressure at room temperature to give the diene (4.2 g, 91%) as a yellow oil. ^{1}H-NMR δ(60 MHz, Cl_3CD; TMS as external reference) 0.02 (6H, s), 0.81 (9H, s), 2.70 (6H, s), 4.30 (2H, d), 6.58 (1H, ws).

3-Hydroxy-1,8-diaza-9,10-anthraquinone (6) To a stirred solution of quinoline 5,8-dione (2 g, 12 mmol) in anhydrous methylene chloride (75 ml) under N_2 atmosphere 3(tertbutyldimethylsilyl)oxy-1-dimethylamino-1-azabuta-1,3-diene (3 g, 13 mmol) recently prepared was added. The reaction was stirred at room temperature overnight. The precipitate thus obtained was filtered and refluxed in methanol for 0.5 hr. After cooling compound 6 was filtered and recrystallized (1.2 g, 43%); mp>300°C(methanol-water). Found: C 63.39; H 2.88; N 12.27. Calc. for $C_{12}H_6N_2O_3$: C 63.70; H 2.77; N 12.38%.

N-oxidation reactions. General procedure: An excess of m-chloroperbenzoic acid (MCPBA) was added to a solution of anthraquinones in chloroform. The reaction was stirred at room temperature and was followed by thin-layer chromatography. During this time additional MCPBA was added twice. The resulting reaction mixture was washed with 10% aqueous potassium carbonate

and extracted with chloroform. The organic solution was dried under anhydrous sodium sulfate and evaporated. The residue was purified by column chromatography (silicagel, chloroform: ethanol, 95:5).

3-Methyl-7-oxo-1,8-diaza-8H-9,10-anthraquinone-1-oxide (7) Reaction time: 30 days, 10% yield; mp>300°C. Found: C 60.75; H 3.08; N 10.78. Calc. for $C_{13}H_8N_2O_4$: C 60.93; H 3.14; N 10.93%.

3-Methyl-1,8-diaza-9,10-anthraquinone-1-oxide and 6-methyl-1,8-diaza-9,10-anthraquinone-1-oxide (8 and 9) Reaction time: 10 days, 6% yield. Found: C 65.09; H 3.48; N 11.89. Calc. for $C_{13}H_8N_2O_3$: C 64.98; H 3.35; N 11.66%.

3-Methyl-1,5-diaza-9,10-anthraquinone-1-oxide and 7-methyl-1,5-diaza-9,10-anthraquinone-1-oxide (10 and 11) Reaction time: 10 days, 5% yield. Found: C 65.64; H 3.18; N 11.42. Calc. for $C_{13}H_8N_2O_3$: C 64.98; H 3.35; N 11.66%.

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