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SYNTHESIS, TAUTOMERISM AND DIELS-ALDER REACTIONS OF 1,4-DIHYDROXY-9,10-ANTHRAQUINON-9-IMINES

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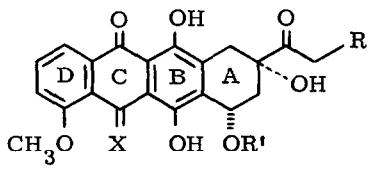
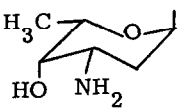
Summary: The ammonolysis of quinizarin and simple derivatives thereof affords 9-imino-derivatives, the tautomeric forms of which act as dienophiles in Diels-Alder reactions to yield tetracyclic compounds of potential value as anthracyclinone precursors.

During the past few years there has been much interest in the synthesis of anthracycline antibiotics because of the antitumor activity which they possess and compounds as daunomycin (1) and adriamycin (2) have been introduced in the treatment of several types of human cancer. However the cardiotoxic side effects associated with these drugs have stimulated the search for analogues with lower cardiotoxicity and improved antitumor activity[1].



1,	R = H	X = O	daunomycin
2,	R = OH	X = O	adriamycin
3,	R = H	X = NH	5-iminodaunomycin
4,	R = OH	X = NH	5-iminoadriamycin



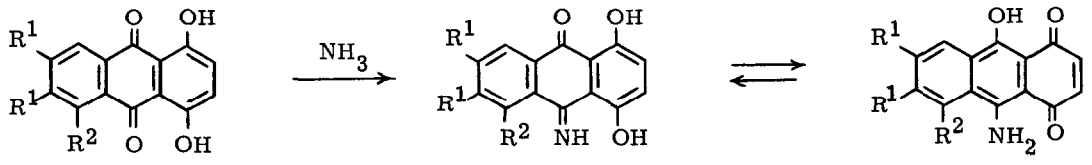
Recently, Acton et al. reported[2] that the 5-imino derivatives of daunomycin and adriamycin (3, 4), obtained by derivatization of the natural anthracyclines, retain the antitumor activity and are significantly less toxic than the clinically important 1 and 2.

As a part of a general development of new approaches to compounds related to anthracyclinones, we have been exploring the synthesis of BCD synthons which allow the construction of the tetracyclic system of 3 and 4 in a subsequent Diels-Alder reaction.

We report herein a novel route to the tetracyclic skeleton of 5-imino anthracyclinones starting from the commercially available 1,4-dihydroxy-9,10-anthraquinone (quinizarin, 5) or from simple derivatives thereof.

It has now been found that 5, by treatment with aqueous ammonia in methanol at

room temperature for a period of 6 days, can be efficiently converted into the quinone monoimine 8 (75%)[3], as violet crystals, m.p. 278° (sub.). The structure 8 was evidenced by



a b

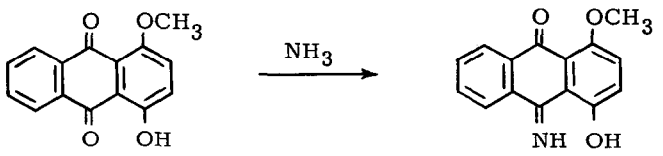
5, R^1 = H R^2 = H
6, R^1 = CH_3 R^2 = H
7, R^1 = H R^2 = OCH_3

8, R^1 = H R^2 = H
9, R^1 = CH_3 R^2 = H
10, R^1 = H R^2 = OCH_3

the presence of one N atom (elemental analysis and mass spectrum) and from the ^{1}H-n.m.r. spectrum (DMSO-d_6) which indicated the presence of a strongly chelated OH group (sharp singlet at δ 15.20) and showed two broad singlets at δ 13.30 and 9.70[4]. The existence of tautomerism in quinone monoimines of type 8 will be discussed below.

Simple quinizarin derivatives, such as 6, react similarly giving the respective quinone monoimine 9, m.p. 275° (sub.). We have also studied the reaction in O-substituted derivatives of quinizarin. Thus, quinizarin diacetate reacts readily under the above ammonolysis conditions yielding 8, the first step of the reaction presumably being the hydrolysis of the OAc groups.

The ammonolysis of quinizarin monomethyl ether 11 occurs readily under similar conditions and yields only a regioisomeric quinone monoimine 12 in 75% yield. The structure 12 was supported by the i.r. spectrum in $CHCl_3$, which shows a non chelated carbonyl band at 1665 cm^{-1}. The ^{1}H-n.m.r. spectrum shows a sharp singlet at δ 16.14 attributable to a OH group chelated with the peri =NH group (broader singlet at δ 11.05). It is to be noted



11 12

that quinizarin dimethyl ether does not react with ammonia under the mild conditions described above[5]. These results appear to indicate that the presence of peri OH groups favours the reaction presumably by intramolecular hydrogen bonding with the imino group[6].

Moreover, ammonolysis of 5-methoxyquinizarin (7) is also effected readily to give the quinone monoimine 10 in 85% yield. The formation of a single regioisomeric imine, in accord with the results of Acton et al.[2] in daunomycin (1) and adriamycin (2) indicates that

the presence of the peri OCH_3 group also favours the formation of the quinone monoimine.

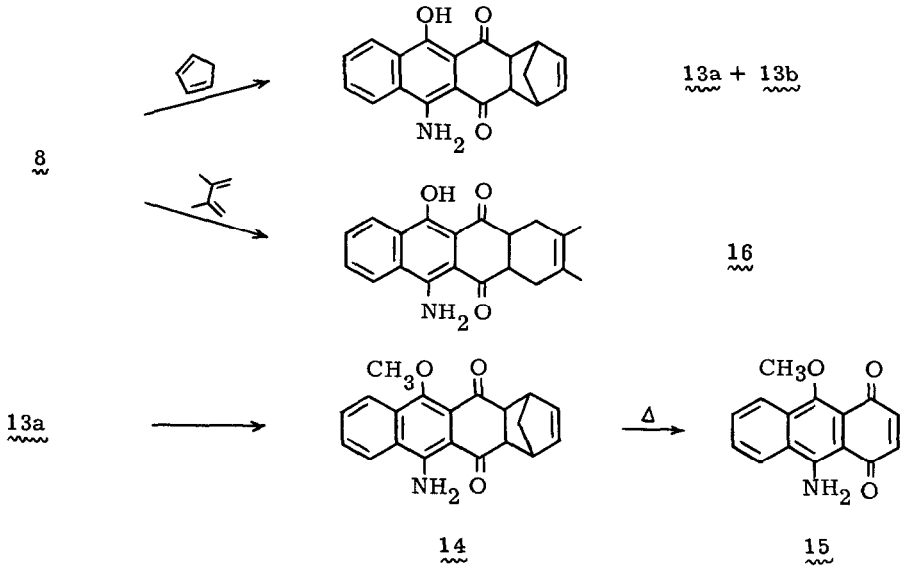
Quinizarin and its simple derivatives exhibit only one principal tautomer in solution, represented by the 9,10-anthraquinone structure 5-7. In contrast, the existence of an equilibrium in quinone monoimines 8-10 between the two main tautomers[7] a ⇌ b is evidenced from the ^{1}H-n.m.r. data summarized in the Table. In fact, the H-2 and H-3 protons resonate about midway compared to the values expected for aromatic and quinonoid protons, thus indicating the presence of 1,4-anthraquinone tautomers of the type b. Monomethyl

Table. Chemical shifts of the H-2 and H-3 protons in anthraquinone monoimines

Compound	in $CDCl_3$	in $(CD_3)_2SO$
8	7.12	7.09, 7.24 (J = 9.8)*
9	7.11	7.02, 7.17 (J = 9.8)*
10	-	7.12, 7.24 (J = 9.8)*
12	7.28	7.17, 7.50 (J = 9.6)*
15	6.83, 6.94*	6.82, 6.96 (J = 10.2)*

*AB system

ethers 12 and 15 are included in the Table as fixed derivatives of the 9,10- and 1,4-anthraquinonoid structures (a and b), respectively.



The presence of 1,4-anthraquinonoid tautomers favours the cycloaddition reactions, which are difficult to attain in quinizarin[8]. Thus, we have found that 8 reacts with cyclopentadiene at room temperature, in toluene as solvent, to yield the expected adduct 13 in 70% yield. The cycloadduct was found to be an endo/exo mixture (13a + 13b) in a 8:1 ratio,

as deduced from the ^{1}H-n.m.r. spectrum of the crude reaction mixture[9].

Methylation of the endo adduct 13a (ICH_3, K_2CO_3 in acetone) gives its methyl ether 14, which by refluxing in toluene undergoes a retro Diels-Alder reaction to afford 15, m.p. 175-178°, prepared as a model of 1,4-anthraquinonoid structure.

Cycloaddition of quinone imine 8 with 2,3-dimethylbutadiene also occurs readily by refluxing in toluene to yield the tetracyclic adduct 16, m.p. 175-176° C (85%)[10].

The novel anthraquinone monoimines reported herein, readily available from quinizarin (5) and derivatives, allow the annelation through Diels-Alder reactions with suitable dienes. This method provides a direct entry to 5-imino anthracyclinones, in which the presence of the imino group can facilitate the preparation of new analogues through elimination of this group or substitution by other groups.

Studies are in progress on the regioselectivity of Diels-Alder reactions of quinone monoimines 8 - 10 with asimmetrically substituted dienes which allow the functionalization of the A-ring.

Acknowledgment. We thank the Comisión Asesora de Investigación Científica y Técnica for financial support.

REFERENCES AND NOTES

1. For a recent review, see "Anthracycline Antibiotics", H.S. El Khadem Ed., Academic Press, New York, 1982.
2. a) G.L. Tong, D.W. Henry and E.M. Acton, J. Med. Chem., 22, 36 (1979); b) E.M. Acton and G.L. Tong, J. Med. Chem., 24, 669 (1981).
3. A 5% of a by-product, presumably the 9,10-diimine was isolated by chromatography.
4. The physical and spectral data of 8 were different from those of commercial 1-amino-4-hydroxy-9,10-anthraquinone.
5. However, formation of the 9-imino derivative under the more drastic Müller conditions[6] was not explored.
6. A. Müller, K. Körmendy and F. Ruff, Acta Chim. Acad. Sci. Hung., 58, 453 (1968).
7. The presence of 1,10- or 4,9-anthraquinonoid tautomers is not excluded.
8. Quinizarin and derivatives act only as dienophiles in Diels-Alder reaction with simple dienes at 200° in sealed tube (J.C. Vega, Sc. D. Thesis, Facultad de Ciencias, Madrid, 1973) to yield the fully aromatized adducts.
9. The mixture was separated by preparative t.l.c. on silica gel (benzene-ethyl acetate 3:1). The n.m.r. spectrum of the major endo isomer shows the exo protons at δ 3.37 while the endo protons of the minor exo isomer resonate at higher field (δ 2.68).
10. All new compounds gave satisfactory combustion analysis.

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