THE DIELS-ALDER REACTION OF 1-CYCLOHEXENECARBALDEHYDE N,N-DIMETHYLHYDRAZONE WITH JUGLONE

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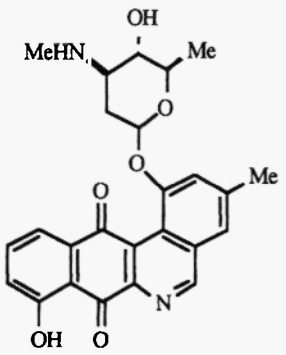
Abstract: The synthesis of 1-cyclohexenecarbaldehyde N,N-dimethylhydrazone 7 from cyclohexanecarbaldehyde by using a three step sequence is reported. The Diels-Alder reaction of juglone 5 with azadiene 7 provides hexahydrobenzo[*b*]phenantridine 14a in 55% yield along with tetrahydrobenzo[*b*]phenantridines 15a and 15b. Angular tetracyclic quinone 15a was formed in 47% yield by carring out the cycloaddition of 5 and 7 in the presence of oxygen. Under this oxidant condition compound 15a undergoes partial oxidation to tetracyclic quinone 17.

Introduction

Phenantroviridin 1 and its aglycone 2 isolated from *Streptomyces Viridiochromgenes* 3972 (1), are active against lung carcinoma MBA 9812 in mice. It is noteworthy that these compounds are the unique examples of naturally occurring quinones containing the benzo[*b*]phenantridine framework.



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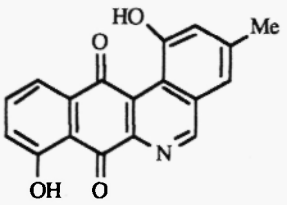

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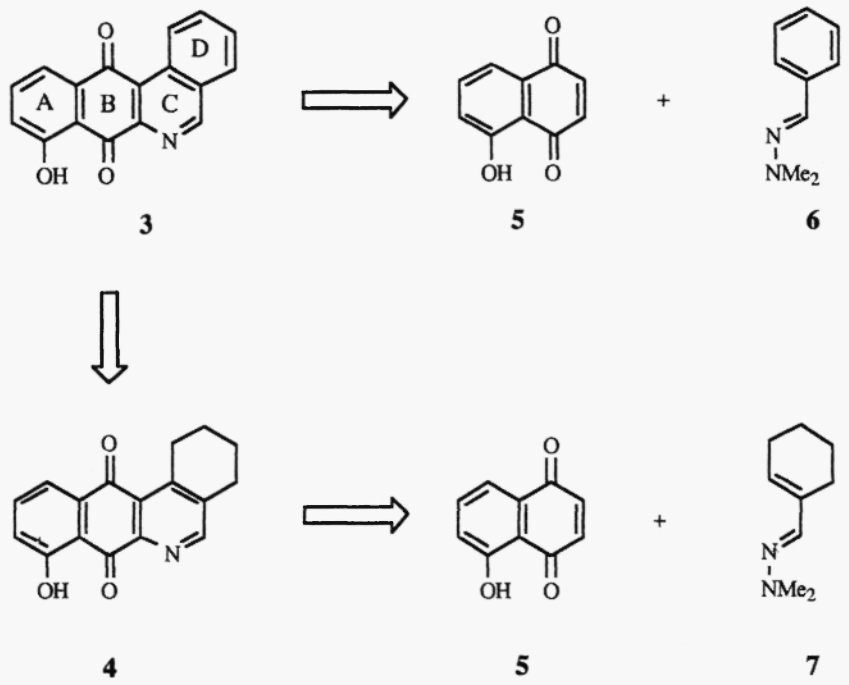
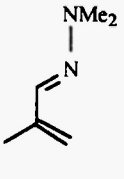
Gould *et al* have reported the regioselective synthesis of benzophenantridine 2 from 2,5-dimethylphenol employing the coupling of a cyanophthalide with an appropriate cinnamate as the key step (2,3). Following our interest to develop new synthetic methods of angular tetracyclic quinones through cycloaddition reactions (4-6) we envisioned that 8-hydroxybenzo[*b*]phenanthridine 3, a model compound containing the ring system of the natural occurring quinone 2, could be constructed *via* an AB + D = ABCD strategy based on the disconnection across the C ring of the aromatic tetracyclic system of 3 or its potential precursor 8-hydroxy-1,2,3,4-tetrahydrobenzo[*b*]phenanthridine 4.



Scheme 1

The retrosynthetic analysis of the target compounds 3 and 4 requires regiocontrolled Diels-Alder reaction between 5-hydroxy-1,4-naphthoquinone 5 (juglone) as an AB synthon and the corresponding N,N-dimethylhydrazones 6 or 7 (Scheme 1). The possibility to construct the tetracyclic skeleton by using hydrazones type 6 was reported in a previous work (7). This study demonstrated that benzaldehyde N,N-dimethylhydrazone 6 and *p*-methoxybezaldehyde N.N-dimethyhydrazone were unreactive to the cycloaddition with juglone 5 and other dienophiles. The reluctance of these hydrazones was ascribed to the low polarization of the 1-azadiene system and also to the low energy of their corresponding HOMO.

By considering that the Diels-Alder reaction of α,β-unsaturated dimethylhydrazones with quinones is now recognized as a powerful method to obtain quinones fused to nitrogen six membered rings (8-16), we decided to explore the construction of the tetracyclic quinone 4 through cycloaddition of 5-hydroxy-1,4-naphthoquinone 5 (juglone) and N,N-dimethylhydrazone 7. The regiochemistry of the cycloaddition of juglone 5 with methacrolein N,N-dimethylhydrazone 8 and crotonaldehyde N,N-dimethylhydrazone 9 has been established by Potts (9) and Fillion (12). The high regiocontrol observed in these cycloadditions has been ascribed to the high polarization of the azadienes and to the directing effect of the 5-hydroxy group of the dienophile. We have recently reported molecular orbitals calculations of hydrazones 8 and 9 which indicate that the C-4 atom possesses the larger HOMO coefficient than the N-1 atom confirming the relative high polarization of this 1-azabuta-1,3-diene system (7).



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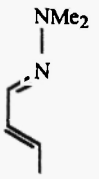

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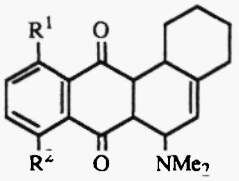
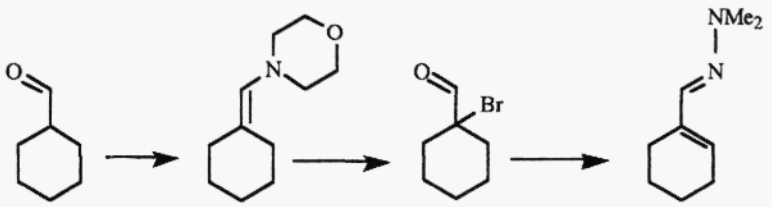


10a. $R^1 = H$, $R^2 = OH$
b. $R^1 = OH$, $R^2 = H$

Results and Discussion

There are some reported methods to obtain 2-cyclohexenecarbaldehyde (17-20), a suitable precursor of N,N-dimethylhydrazone 7 however we decided to attemp the synthesis of this azadiene from cyclohexanecarbaldehyde as shows Scheme 2. This route is based on the well established reaction of enamines with halogens that form α-haloimmonium salts, which on hydrolysis yield the corresponding halocarbonyl compounds (21).



11 **12** **13** **7**

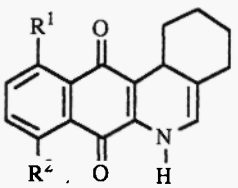
Scheme 2

Enamine 12 was prepared in nearly quantitatively yield by condensation of cyclohexanecarbaldehyde 11 with morpholine. Reaction of enamine 12 with bromine at low temperature followed by hydrolysis furnished bromoaldehyde 13 in 70% yield. Aldehyde 13 was reacted with excess N,N-dimethylhydrazine at reflux in dichloromethane to provide 7 in 79% yield. Hydrazone 7 was purified by column chromatography on silica gel and was storaged at low temperature (-10°C) to avoid decomposition.

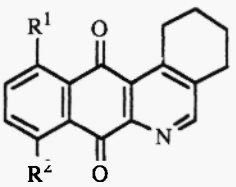
The reaction of azadiene 7 with juglone 5 in excess was carried out in acetonitrile with admission of air. The cycloaddition occurred slowly (5 days) at room temperature to afford a complex reaction mixture. The main product, that precipitated into the mixture reaction as a green solid, was isolated by filtration. The ^1H and ^{13}C NMR spectra display signals in agreement with heterocyclic angular quinone 14a (55% yield). Silica gel chromatography of the filtrate allowed the isolation of tetracyclic quinones 15a and 15b in 27 and 2% yield

respectively along with a mixture of regioisomers 16a and 16b . No attempts were made in order to separate isomers 16a and 16b which were reported by Fillion *et al* as secondary products from the reaction of juglone 5 and 1-dimethylamino-4-methyl-1-azabuta-1,3-diene 9 (12).

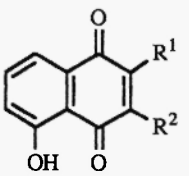
Assignment of structure 14a is in accord with the directing effect of the 5-hydroxy group in juglone 5 and related 1,4-naphthoquinones in cycloaddition reactions with azadienes 8 and 9 (8, 12), and other electron rich dienes (4, 22) where the cycloadditions are highly regioselective. Furthermore, FMO calculations of azadiene 7 showed that the primary orbital of the C-4 atom posses a higher HOMO coefficient (0.3593) than the primary orbital of the N-1 atom (-0.1962) thus indicating a high polarization of the 1-azabuta-1,3-diene system (23).



14a. R^1=H, R^2=OH
b. R^1=OH, R^2=H



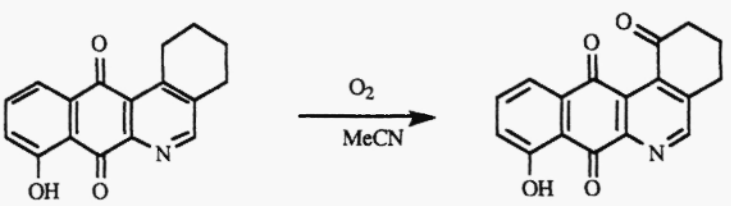
15a. R^1=H, R^2=OH
b. R^1=OH, R^2=H



16a. R^1 = NMe_2, R^2=H
b .R^1 = H, R^2=NMe_2

These results could be explained by considering that the Diels-Alder adducts 11a,b generated by cycloaddition between compounds 5 and 7 are unstable and undergo 1,2 elimination followed by double bond rearrangement to give quinones 14a,b and dimethylamine. The released triethylamine adds to juglone 5 and a subsequent aerial oxidation of the corresponding addition products yield quinones 15a,b. The aromatization of the heterocyclic ring of quinones 14a,b to the angular quinone 15a,b occurs by aerial oxidation during the reaction and/or the isolation procedure. This transformation was confirmed through purity control by tlc of compound 14a which showed its convertion to compound 15a on the chromatographic support. Oxidation attemps of quinone 14a directed to prepare quinone 15a with silver (I) oxide and active manganese dioxide were unsuccessful.

In view of the above results we attempted to improve the formation of angular quinone 15a from 14a by carring out the cycloaddition under oxygen atmosphere. After 10 days a complex mixture reaction was obtained at room temperature. From this mixture compound 14a. 15a and 17 (24) were isolated by column chromathography on silica gel in 18, 47 and 2.1% yield respectively. Compounds 16a,b were detected by tlc in the mixture reaction and were not isolated. The structural assignement of compound 17 is tentatively proposed on the basis of the carbonyl absorption at the C-1 position (1710 cm-1)(4) and by comparison of the aromatic proton chemical shifts with those of regioisomers 15a and 15b (25). The formation of 17 by oxidation of 15a is under study in order to confirm its structure.



15a **17**

Conclusions

In summary, azadiene 7 is easily prepared in a three step sequence from cyclohexanecarbaldehyde in 55% overall yield. Cycloaddition of diene 7 with juglone 5 is highly regiocontrolled to provide two valuable benzophenantridines 14a and 15a structurally related with the skeleton of phenantrovidinon aglycon. The formation of angular tetracyclic quinone 17 which exhibite an oxygenation level similar to aglycon 2 will stimulate studies with 7 and structurally related azadienes directed towards the synthesis of analogues of the naturally occurring antibiotic 2.

Acknowledgements

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(23) The HOMO coefficients calculations of N,N-dimethylhydrazone **7** were performed by using the AM1 semiempirical method: N-1 = -0.1962, C-2 = -0.3186, C-3 = 0.2782 and C-4 = 0.3593.
(24) For a similar benzylic oxidation of benz[*a*]anthraquinones under aerobic basic conditions see reference 4.
(25) ^{1}H NMR spectra of compound **15a**: δ ppm (200 MHz, $CDCl_3$), 1.89 (m, 4H, 2- and 3-H), 2.94 (m, 2H, 4-H), 3.41 (m, 2H, 1-H), 7.32 (dd, 1H, J = 1.8, 7.8 Hz, 9-H), 7.69 (t, 1H, J = 7.8 Hz, 10-H), 7.76 (dd, 1H, J = 1.8, 7.8 Hz, 11-H), 8.74 (s, 1H, 5-H), 12.47 (s, 1H, OH). Compound **15b**: 1.91 (m, 4H, 2- and 3-H), 2.95 (m, 2H, 4-H), 3.46 (m, 2H, 1-H), 7.46 (dd, 1H, J = 1.2, 7.8 Hz, 9-H), 7.67 (t, 1H, J = 7.8 Hz, 9-H), 7.89 (dd, 1H, J = 1.2, 7.8 Hz), 8.76 (s, 1H, 5-H), 12.60 (s, 1H, OH).

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