Synthesis and Theoretical Study of Some Intermediates in the Projected Synthesis of Tetracyclic Xanthones

Badie A. Ahmed[1] , Walid Y. Yousif[2]

[1] *Dept. Of Chemistry, College of Science, University of Mosul , Mosul , Iraq*

[2] *Dept. of basic Science , College of Agriculture and Forestry, University of Mosul , Mosul , Iraq*

(**Received:** 27 / 11 / 2008 ---- **Accepted:** 13 / 12 / 2010)

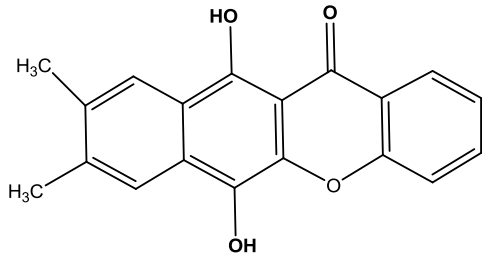
Abstract

The proposed chemical structure of some isolated intermediates **(1-5)** in the Diels-Alder reaction of substituted *p*-benzoquinone with cyclic and acyclic dienes was further confirmed by measuring some physico-parameters using semiempirical, quantum mechanins and molecular mechanics methods.

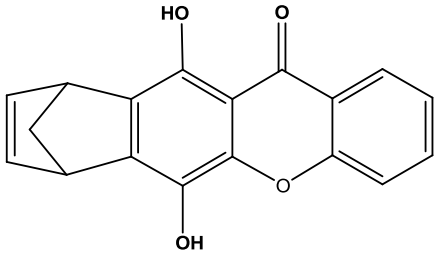
Introduction

The anthracycline antibiotics, constitute a class of natural products which is currently making a significant impact in the field of cancer chemotherapy[1-3]**.** Over the years, the synthesis of the anthracyclinones, theaglycones of anthracyclines, have been extensively investigated as a part of the ongoing search to derive analogues with higher therapeuticindex[4, 5]**.**Several approaches to the synthesis of certain xanthone containing anthracycline antibiotics in which the quinone ring is replaced byγ-pyrone were reported[6, 7]**.** Such structure is potentially less cardiotoxic than the parent antibiotics.

As part of our investigation in this field[8] synthesis of new tetracyclic xanthones **(A & B)** was of great interest.These molecules would be of great interest in the study of structure-activity-toxicity relationship of anthracyclines. With the aid of molecular modeling software[9], pharmaceutical scientist can modify the structural features of a potential drug candidate and make predictions about its physicochemical properties prior to laboratory synthesis.Recently, computational chemistry method is the method of choice because it deals with the use of theory and computer technology to calculate molecular properties which are used widely in academic and industry to gain insight into complex problems .



A



B

Experimental

Melting points were measured on Electrothermal 1A 9000 Digital series 1998 apparatus (uncorrected) ^{1}H-NMR spectra were determined (France) with Bruker Am 400 MHz using $CDCl_3$ as solvent, IR spectra were recorded on Perkin-Elmer 590 B spectrophotometer, U.V. spectra were obtained using SP 800 Pye-unicam. Thin layer chromatography technique was used to monitor the reaction progress. Theoretical calculation of H.F., S.E. and 3D-structures were obtained using Chem 3D Ultra Molecular Modeling and Analysis version 8.0.3.

2-(2`-Methoxybenzoyl)-1,4-benzoquinone (1)[8]

To a stirred suspension of silver (II) oxide (4.25g, 34.3 mmol) and trimethoxy benzophenone (3.13g, 11.4 mmol) in acetone (100 ml) was added nitric acid (6N, 16.6ml). The caurse of the reaction was monitored by T.L.C. The reaction mixture was diluted with chloroform (100ml), water (70 ml) and stirred. The organic layer was separated, washed with water (2×25ml) and dried ($MgSO_4$). Solvent removed under vacuum afforded (2.7g, 98%) of the title compound as orange solid, m.p. 130^{o}C.

4a,5,8,8a-Tetrahydro-4a-(2`-methoxybenzoyl)-6,7-dimethyl-1,4-naphthaquinone (3)[8]

2,3-Dimethyl-1,3-butadiene (0.8ml, 7mmol) was added to a stirred solution of the quinone (1) (0.42g, 1.72mmol) in dry benzene (50ml). The progress of the reaction was monitored by T.L.C. which revealed after (5 days of continuous stirring the absence of the starting material. Removal of the solvent under vacuum gave a solid product (0.5/9qi%) as a yellow solid m.p. 117-118^{o}C.

5,-8-Dihydro-1,4-dihydroxy-2-(2`-methoxybenzoyl)-6.7-dimethyl naphthalene(4)[8]

Adduct (3) (0.83g, 2.56mmol) was dissolved in a mixture of distilled pyridine and methanol (1:1 v/v, 16.6ml). The mixture was stirred at 30°C (12h). A yellow precipitate was separated, washed with ether and dried. (0.58g, 70%) m.p. 223-225°C.

Endo-4a,5,8,8a-tetrahydro-5,8-methano-4a-(2`-methoxybenzoyl)-1,4-naphthaquinone (2)[8]

Freshly distilled cyclopentadiene (1ml, 12.5mmol) was added to a stirred solution of benzoquinone (1) (0.5g, 2mmol) in dry benzene (50ml), The progress of the reaction was monitored by T.L.C. After overnight stirring, the solvent was removed to give an oily residue which solidified after treating with cold petroleum ether (40-60 °C). Purification by column chromatography on silica gel (ethylacetate. n-hexane 1:2) gave the product (2) as yellow solid (50%) m.p. 125-126 °C.

Endo-5-8-dihydro-5,8-methano-1,4-dihydroxy-2-(2`-methoxy benzoyl) naphthalene (5)[8]

Adduct(2) (150mg, 0.46mmol) was dissolved in distilled pyridine (1ml). The mixture was stirred at 30 °C (for 3 days). Evaporation of the solvent afforded dark residue (semisolid 62%).

Results and Discussion

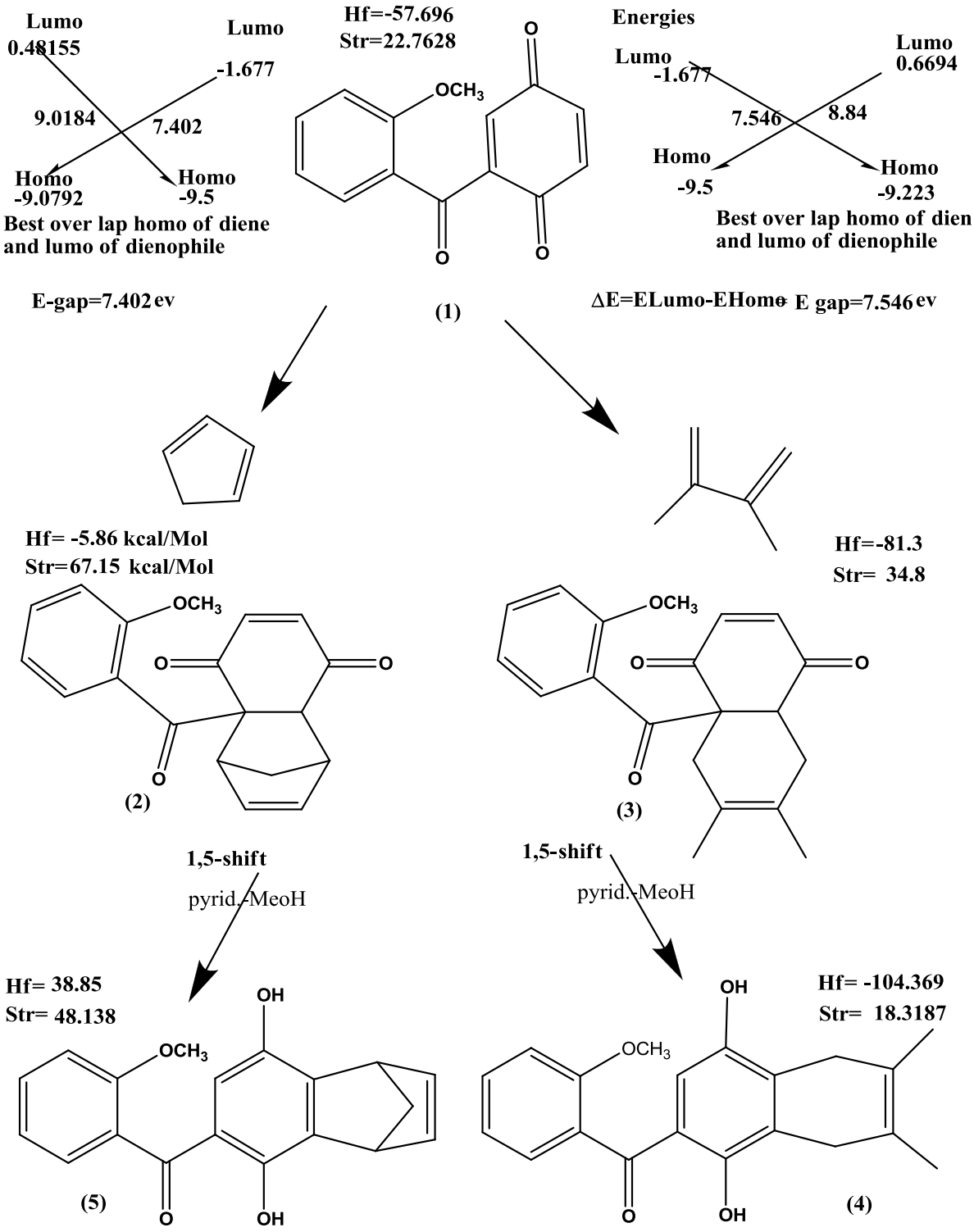
Putting in mind the requirements of γ-pyrone ring generation, the synthetical benzoqinonone (1) have been choiced to serve as precursor for the construction of the desired xanthones (A&B). The rational was that demethylation of the 2`-OMe group will afford OH group necessary for γ-pyrone ring closer.

In connection with scheme I, Diels-Alder reaction of quinine (1) with 2,3-dimethyl-1,3-butadiene and cyclopentadiene furnished the adducts (3) and (2) respectively, with angular aroyl substituents. [1,5]-Aroyl migration of the adducts with methanol-pyridine gave the desired aroyl hydroquinones (4) and (5). Oxidation of (4) and (5) (Ag_2O/benzene/□), followed by demethylation of quinones ($AlCl_3/CH_2Cl_2/0°C$) and finally intramolecular cyclization (MeOH/□□) afforded the final xanthone products A&B in good overall yield.

The structures of all the synthesized intermediates (1-5) were confirmed by spectroscopic methods (i.r., u,v, and NMR),(see table 1) and because of their importance as close synthone towards the target xanthones, further data namely physico-parameters which are vital for pharmaceutical study and drug design was obtained from computational chemistry. We suggested an explanation for these results in terms of frontier molecular orbital[10] [FMO] theory which has been used extensively to explain and predict reactivity in 2,4-cycloaddition reactions. This theory states that the Gibbs Free energy of activation is related to the energy gap between the (dominant) interaction Homo and Lumo which can be experimentally assessed ionization potential and electron affinity respectively. See scheme (1).The theoretical calculations of scheme(1) are tabulated in table(2).

FMO theory accounts for stereo- and regioselective reaction take place in the direction of maximam Homo and Lumo overlap. Heat of formation (Hf) was calculated for the isolated intermediates (1-5) using quantum mechanics, semi-empirical method involving optimizing the electron-distribution and calculating the lowest energy of these stable conformations compounds. Steric energy (Str.) of products were calculated with the aid of molecular mechanic program (MM_2) which included total steric energy of product which attributed to stretching, bending, bonded and non-bonded interaction, vanderwall interaction, dipole-dipole and cross term interaction, using classical mechanics to minimal electrostatic repulsion of product which used to describe the force that holding the molecules together refer to MM_2, MM_3 and PM_3 theories.HF and Str, Homo,Lumo of compounds (1-5) were shown in scheme I.The energy minimization routine perform a local minimization only, therefore the result of minimization may vary depending on starting conformation in the mode. Gibbs energy of activation correlates with the energy gap between the dominat interaction Homo and Lumo, the gap between H-L and L-H become smaller and the rate will be higher. Energy of activation low and steric Energy also low, therefore, H.F. low. The more active reaction that have less change in energy.

The data obtained from theoretical calculation of Hf and Str. are strongly support the established structure of the intermediates and come in a good agreement with the spectroscopic evidences.Figure (1) and (2) illustrate the 3D-structure of (A) and (B) and reflect the planarity of the molecules. Furthermore, the theoretical calculations(Hf.andStr,Homo,Lumo)confirmthestabilityofthefollow-up intermediates (1-5) towards the target xanthones as shown in the scheme (1)and table (2).



Hf=heat of formation
Str=steric energy
Homo=Hight occupied molecular orbital
Lumo=Low unoccupied molecular orbital
Egap=ΔE=L-H
ev= electron volt

Scheme 1

Table (1):Spectroscopic data of compounds (1-4)

Compd. No.	U.V. λmax (nm)	I.R., ν(cm^{-1}),KBr.			1H-NMR δ(ppm),CDCl3
		C=O	C=C	O-H	
1	263 318	1647 1635	1622 1585	-	3.73(S,3H,OMe); 6.75(S,1H,H-3); 6.8-6.88(m,2H,H-5+H-6); 6.92(d,1H,H-3\); 7.11(t,1H,H-5\); 7.58(t,1H,H-4\); 7.92(d,1h,h-6\).
2	258 303	1672 1682	1633 1592	-	-
3	257 303	1645 1633	1625 1570	-	1.58(S,3H,Me-6 or Me-7); 1.61(S,3H,Me-6or Me-7); 1.8(d,1H,H-5d); 2.3(dd,2H,2H-8); 3.76(S,3H,OMe); 6.71(S,2H,H-2+H-3); 6.92(d,1H,H-3\); 7.05(t,1H,H-5\); 7.47(t,1H,H-4\); 7.55(d,1H,H-6\).
4	252 375	1631	1615 1595	3337-3450	1.79(S,3H,Me-6 or Me-7); 1.81(S,3H,Me-6 or Me-7); 3.25-3.31(m,4H,2H-5+2H-8); 3.79(s,3h,OMe); 4.67(S,1H,OH-4); 6.55(S,1H,H-3); 7.0-7.1(m,2H,H-3\+H-5\); 7.43-7.5(m,2H,H-4\+H-6\); 8.62(b,1H,OH-1).

Table (2):Physical properties of the compounds

Compounds	Hf kcal/Mole	Steric ,E kcal/Mole	Homo ev	Lumo ev
1	-57.696	22.7628	-9.5	-1.677
2	-5.86	67.15	-9.38205	-0.58515
3	-81.3	34.8	-9.25046	-0.77456
4	-104.369	18.3187	-8.74216	-0.3848
5	38.85	48.138	-6.98577	-1.1470
A	-79.62	2.554	-8.42557	-0.94216
B	-33.24	32.3	-8.67756	-0.64561
2,3-Dimethyl-1,3-butadiene	-5.64904	2.1277	-9.223	0.6694
Cyclopentadiene	46.87622	6.3918	-9.0792	0.48155

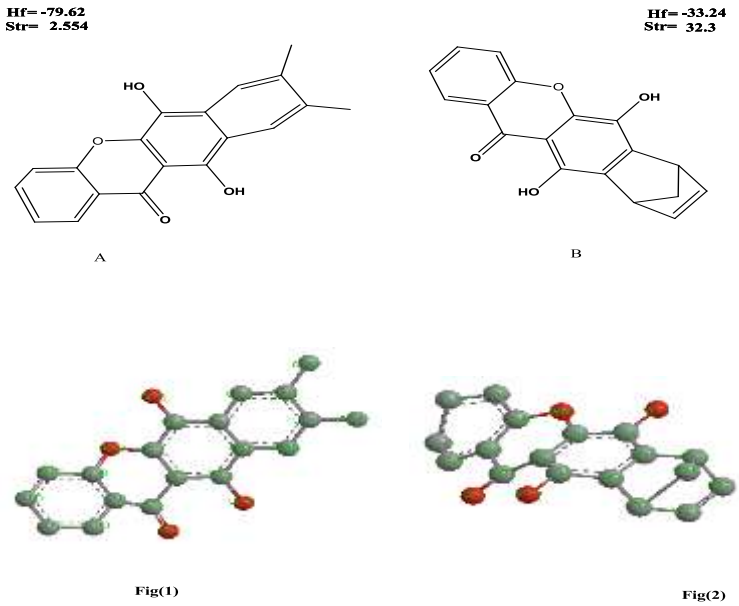


Figure (1) 3D-structure of (A) , Figure (2) 3D-structure of (B)

Reference

1. P.F. Wiley, Anthracycline antibiotics,H.S. El-Khadem, Ed.; academic press, New York, 1982,pp.159-173.
2. W.Prieb,Anthracyclineantibiotics,E.D.American Chem. Soc.; Washington DC, 1995,pp.183-203.
3. Y.S. Rho, W.J. Kim,S. Park. D.J. Yoo, H.S. Kong and S.R. Chung, Bull, Korean Soc.; 2001, 22, 6, 287.
4. P. Vogel, Current organic chemistry, 1998, 2, 255.
5. W.D. Wuiff, S.J.Tang ,P.C. and .X.U, Y.C. Synthesis, 1999, 3, 415.
6. C.M. Wong; W. Haque, H.Y. Larn; K .Marat, and E. Bock, J. Can. Chem., 61, 1788 (1983).
7. J.W ,Lown, and. S.M. Soudhi,J.Org.Chem, 1984, 49, 2844.
8. M.A.Abdulhakeem.Approaches to the synthesis of tetra cyclic Quinone,xanthone and anthrone systems Related to Anthracyclinone'',Ph.D thesis,2004,Mosul University.
9. J.H., Block and J.M., Beale ''Wilson and Gisvold's: Textbook of Organic Medicinal and PharmaceuticalChemistry'';11th ed.;NewYork; Lippncott Williansand Wilkins, April 2004,pp.919-945.
10. K. Fuku. Anegw. Chem. Int. Ed. Engl. 1982, 21, 801.

تحضير ودراسة نظرية لبعض المركبات الوسطية في تحضير الزانثونات ذات الحلقات الأربعة

بديع على احمد[١] ، وليد يعقوب يوسف[٢]

[١] *قسم الكيمياء ، كلية العلوم ، جامعة الموصل ، الموصل ، العراق*

[٢] *قسم العلوم الأساسية ، كلية الزراعة والغابات ، جامعة الموصل ، الموصل ، العراق*

(تاريخ الاستلام: ٢٧ / ١١ / ٢٠٠٨ ---- **تاريخ القبول:** ١٣ / ١٢ / ٢٠١٠)

الملخص

لقد تم دعم إثبات الصيغة التركيبية المفترضة لبعض المركبات الوسطيةالمعزولة(١-٥) فى تفاعل ديلز –الدير لمعوضات البارا- بنزوكوينون مع داينات حلقية وغير حلقية من خلال قياسات حسابية للخواص الفيزياوية باستخدام برنامج ميكانيكية الكم - CS-MOPAC وطريقة النظرية الميكانيكية الجزيئية .