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A TRIDENT SCHOLAR PROJECT REPORT

NO. 115

SYNTHESIS OF AZULOQUINONES AS AN
EXPERIMENTAL DETERMINATION FOR A
THEORETICAL PREDICTION



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Synthesis of Azuloquinones as an
Experimental Determination for a
Theoretical Prediction

A Trident Scholar Project Report

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ABSTRACT

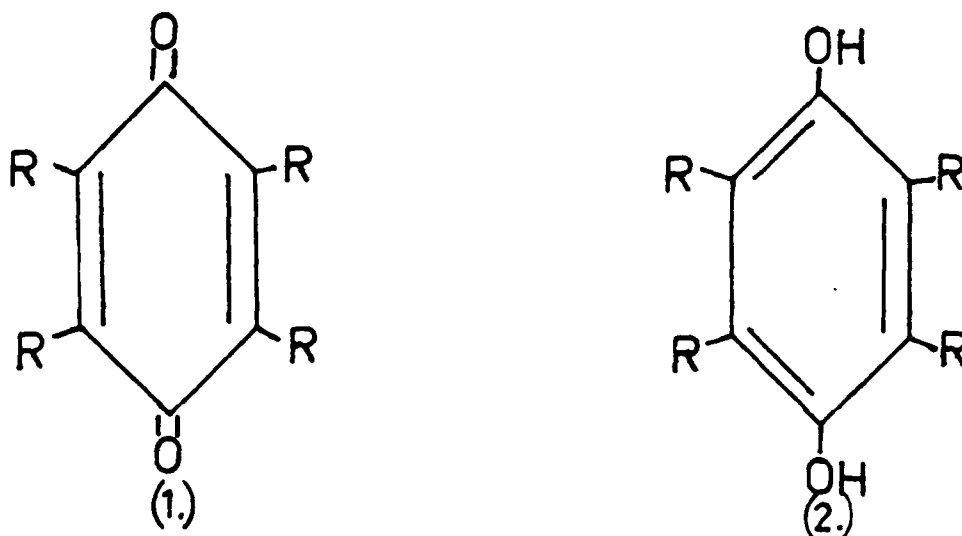
Quinones are chemical compounds utilized throughout naturally occurring biological systems in energy-transferring reduction/oxidation reactions. Quinones are also being tested in the area of anti-tumor agents. Azuloquinones are unknown quinones which may provide the specific energy that may match metabolic values.

Azuloquinone is a compound that has received a great deal of attention in theoretical chemistry recently. Quantum mechanical predictions on the relative energies and stabilities of the eleven possible isomers of azuloquinone have preceded the experimental determination of the measured energies for these compounds. The intent in this project was to synthesize several isomers of azuloquinone by simply varying the starting material conformation. Though the synthesis was not completed, there is extensive progress towards isolating isomeric azuloquinone and the route has been substantiated as a feasible way to synthesize azuloquinones. ↑

HISTORICAL

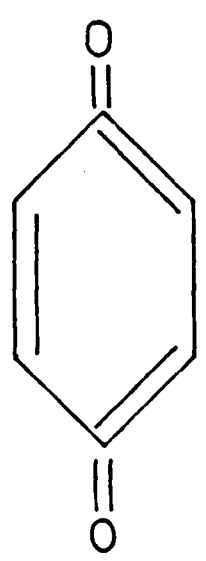
Background and Biochemistry

Quinones are one of the earliest and more fascinating families of compounds known. Virtually all of the quinones isolated and studied have the common structure (1) and an associated reduced form, hydroquinone (2).

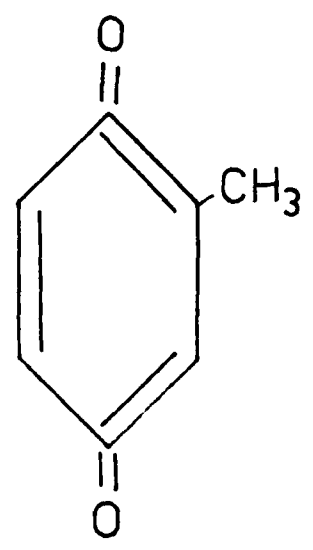


Quinones are generally named with the benzenoid aromatic structure as a root (Figure 1). Many different quinones have been associated from various naturally occurring biological systems. It appears that these systems provide an easily reversible oxidation/reduction energy-transferring reaction (Figure 2) used in intermediary metabolism and many chemical processes such as color photography.^{1,2}

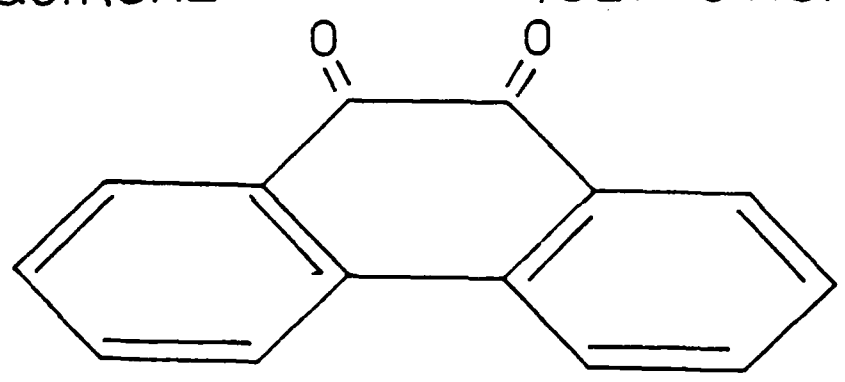
Natural quinones have been exploited by man for many centuries. The quinone alizarin was used in ancient Egypt, Persia and India as a brilliant red dye.³ As early as 2700 B.C.,



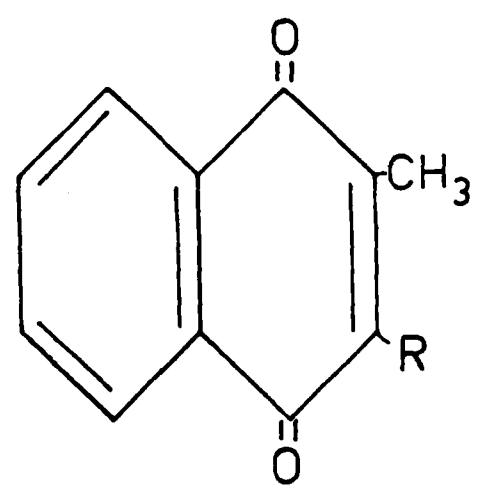
BENZOQUINONE



TOLUQUINONE



9,10 PHENATHRAQUINONE



VITAMIN K

Figure 1

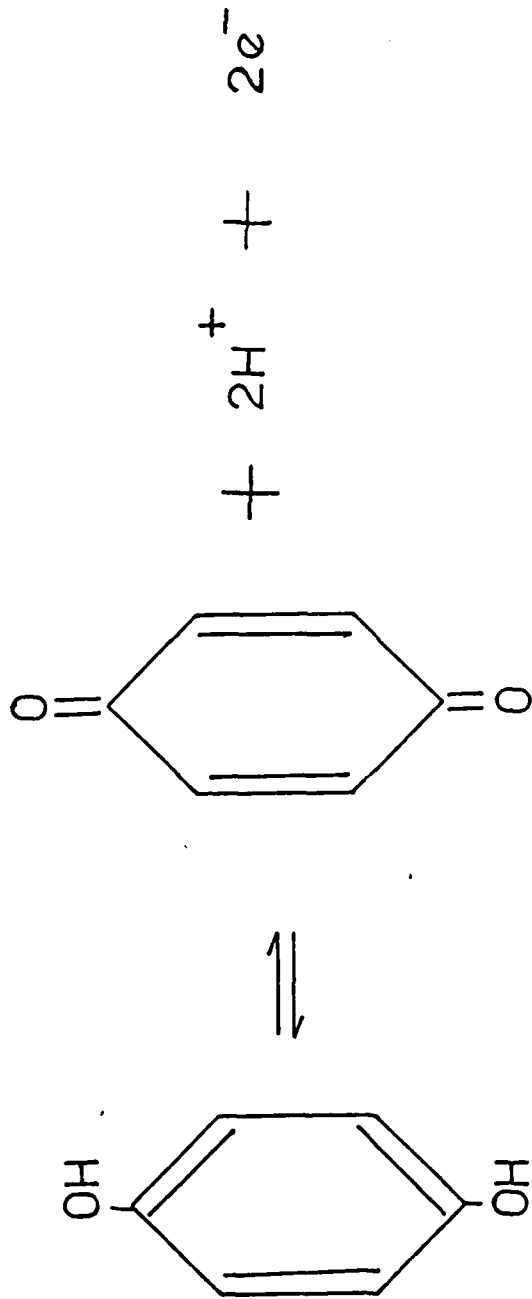
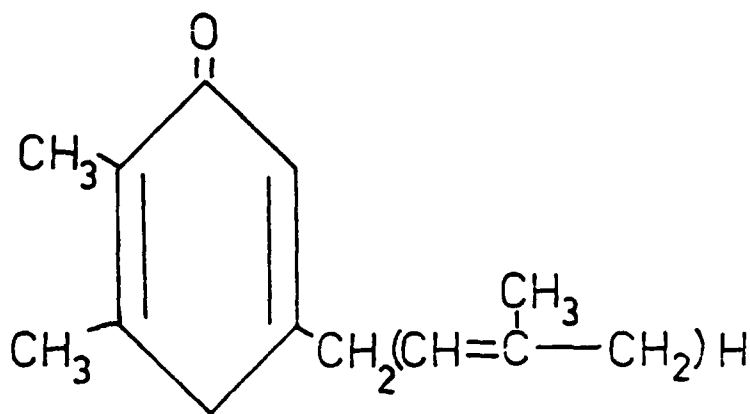


Figure 2

quinones were used for medicinal purposes in China.⁴

Of even greater interest and importance, quinones have proven central in biochemical, molecular biological and medicinal research in recent years. Various quinones are known to be essential to certain prominent biological systems and reactions. For instance, the quinone called plastoquinone is found abundantly in the chloroplasts of



all plants. Plastoquinone functions in the electron-transfer system in the form of a plastoquinone-hydroplastoquinone "pool" that has the capability of moving the ten electrons necessary for photosynthetic phosphorylation. Plastoquinone is also a very necessary molecule in the electron transport chain found in the mitochondria of eucaryotic cells. Rhoquinone and ubiquinone (Figure 3) (known as coenzyme Q) are also found in mitochondria.⁶ The process that all three quinones mediate is known as oxidative phosphorylation in which the compound

THE ELECTRON TRANSPORT SYSTEM 201

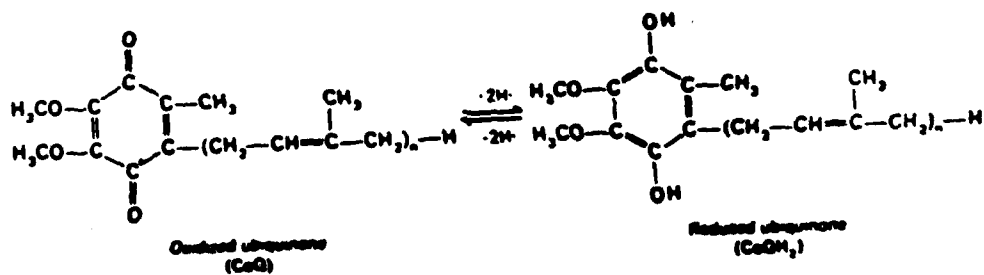
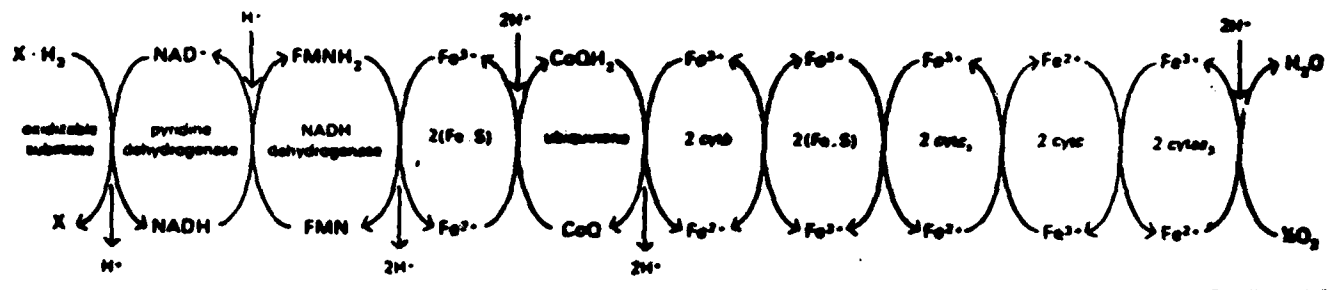


Figure 3

Adenosine Triphosphate (ATP) is formed from Adenosine Diphosphate (ADP). ATP is the chemical which provides the energy to drive the energetically unfavorable but vital reactions that occur in living matter. Inside the mitochondria a reduction/oxidation gradient is created in which the quinone/hydroquinone reaction transfers electrons and provides the energy needed to form ATP.⁷

Phylloquinone, better known as Vitamin K (Figure 1) is a quinone synthesized by bacteria in the small intestine. One of Vitamin K's functions is in the biosynthesis of proteins that are essential for blood coagulating or blood clotting. It is hypothesized that phylloquinone reacts at the genetic level and stimulates the synthesis of messenger-RNA for producing these specialized proteins.⁸

Quinones often act as precursors and catalysts to many needed compounds in the body. For instance, in the natural production of tetracycline, the quinone preteramid is believed to be the product in the manufacturing of this well known antibiotic.⁹ Quinones also are essential to the biosynthesis of aflatoxins, chemicals produced by fungi associated with the destruction of domestic fowl such as turkeys and chickens.¹⁰

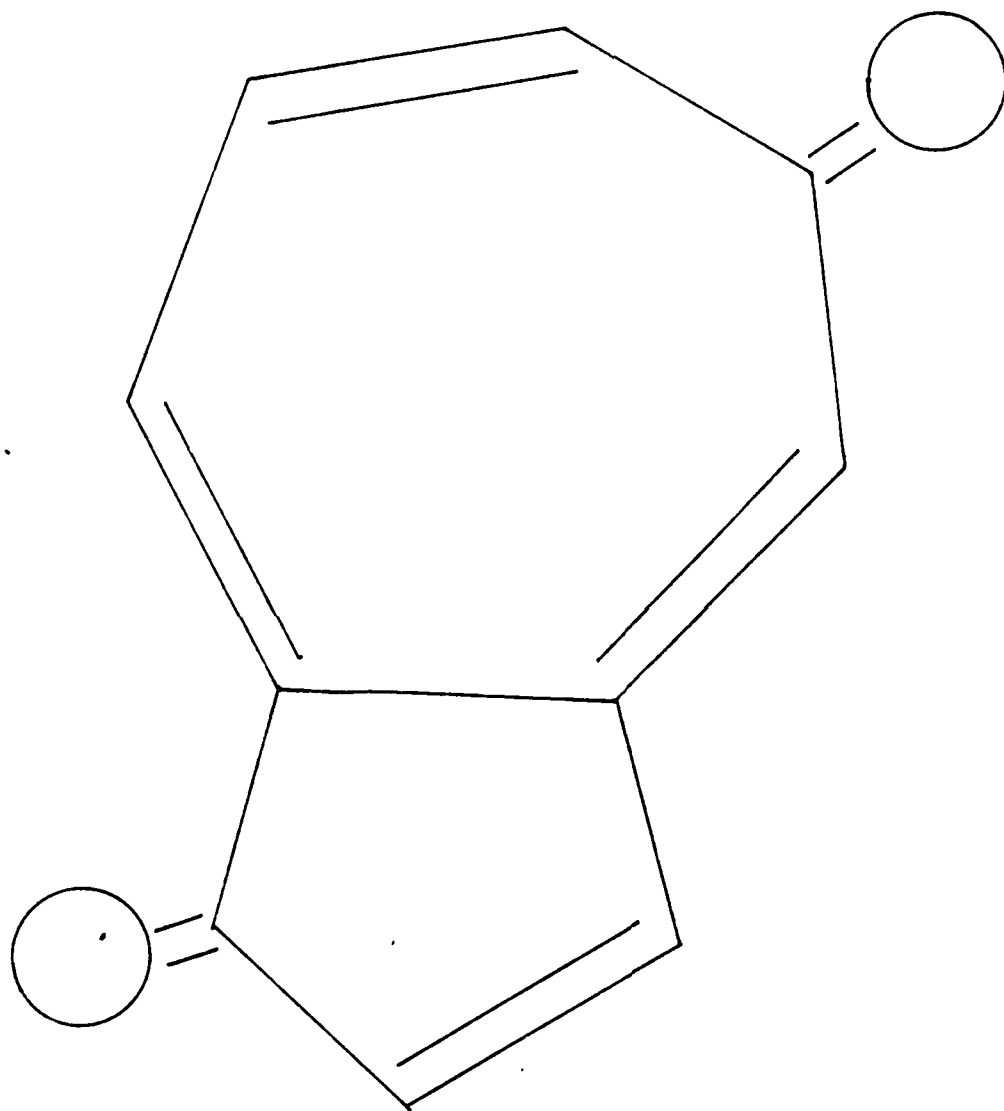
A species of insect, known as the bombardier beetle, uses a mixture of hydrogen peroxide and benzoquinones in a very unique defense mechanism. When attacked, the bombardier beetle shoots a jet of this mixture at its adversary and the violent reaction that occurs literally dissolves the attacker.¹¹ It

has been found that treatment of living mammalian cells with tocopherolquinone (closely related to Vitamin E) seems to retard the aging processes of the cell.¹²

In a recent cancer research symposium funded by the National Institute of Health, a project was presented in which quinones were used in the interference of cancerous metabolism in living cells.¹³

Thus, it can be seen that quinones have found application in many diverse and essential functions. This again can be accounted for in virtually all cases by the unique property that characterizes all quinones, that is, the energy producing/electron transferring and reversible oxidation/reduction reaction of quinones, semiquinones, and hydroquinones. The specific use of any quinone by a biological system is due to the specific reduction potential produced in the reduction/oxidation reaction unique to that particular quinone and which is a function of the substituents and structures of that quinone. For this reason, azuloquinones (Figure 4) present a good opportunity for a medicinal use in which some "fine tuning" of the energy needed by the particular system can be enhanced - especially since there are eleven different isomers, each of which should have a different reduction potential or energy.

There is a possibility in the practical application of these azuloquinones once they have been synthesized. Over



1,5 AZULOQUINONE

Figure 4

1500 other quinones have been tested by the National Cancer Institute and some have shown significant anti-tumor activity. However, these have all been benzenoid quinones.¹⁴ "The wide range of redox potentials and alkylating abilities expected for the azuloquinones and their derivatives qualifies them as promising candidates for anti-tumor testing."¹⁵

The Aromatic Backbone

The non-benzenoid aromatic structure of the azuloquinone is known as azulene (Figure 5). Azulene is a unique molecule, distinguished by its very deep purple color. The five-membered ring with a coincident side to a seven-membered ring provides an unusual system for aromaticity. Azulene, largely from synthetic sources, is known to have chemical properties very different from normal benzenoid aromatics. For instance, the dipole moment for azulene is 1 Debye.¹⁶

This unusually high dipole for a hydrocarbon without heteroatoms is indicative of other electronic properties that characterize the extensive delocalization of electrons in this carbon molecule. As an illustration, if one were to draw all the possible resonant structures for azulene (Figure 5) one can see why azulene is characterized by a peculiar reactivity to electrophilic attack on the five-membered ring in contrast to no reactivity on the seven-membered ring.¹⁷

Azuloquinone is simply the quinone form of azulene. If

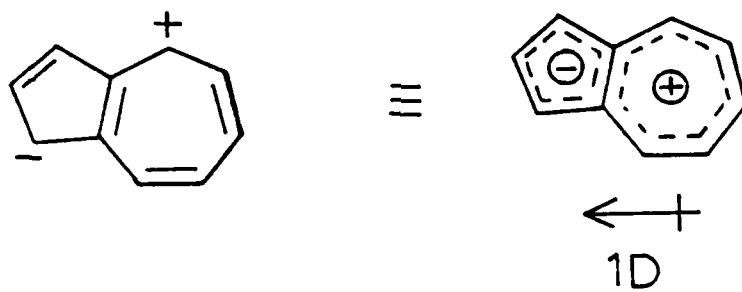
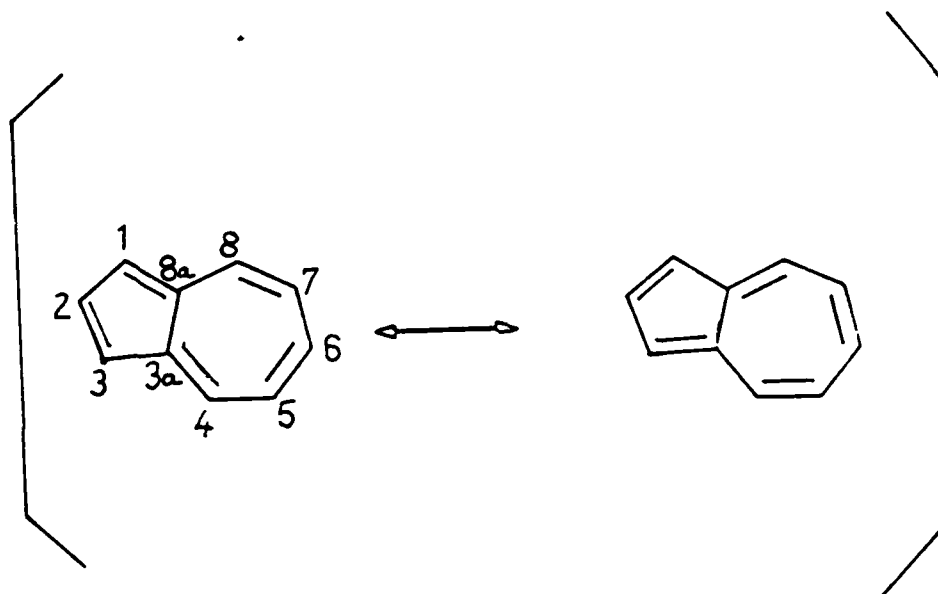


Figure 5

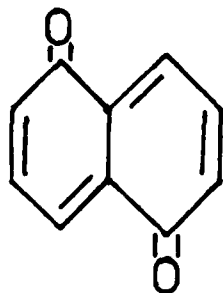
one were to draw all of the possible forms, or isomers, of azuloquinone, 11 different structures are possible (Figure 6). Azuloquinone provides a unique challenge to the synthetic organic chemist since only one of the isomers, 1,2 azuloquinone, has ever been made and characterized.¹⁸

Theoretical Predictions

A group of workers from the University of Nevada, Reno, Louisiana State University, and DuPont Company recently presented an extensive set of theoretical predictions concerning the stabilities and reactivities of the possible isomers of azuloquinone.¹⁹ The attractiveness of azuloquinone as a testing ground for theories in structure, bonding, and reactivity in unsaturated carbonyl compounds is due to several factors:²⁰ 1) The abundance of isomers provides a means to make extensive comparisons - mainly because

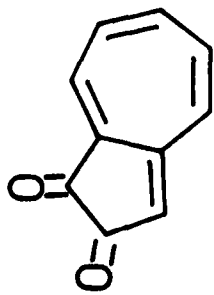
"Theoretical calculations on the electronic nature of molecules generally prove more successful in predicting differences between similar substances than in predicting absolute quantities - thus no group of compounds could be more valuable than a set of isomers.²¹

2) The molecule contains only 18 atoms, which is within a "manageable" range for sophisticated molecular orbital treatments and 3) A family of compounds known as naphthoquinones

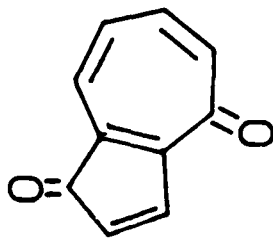


1,5 NQ

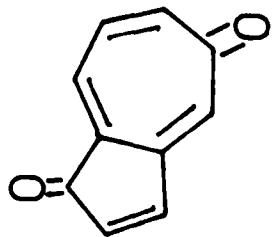
.AQ



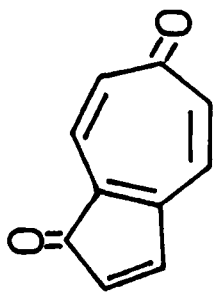
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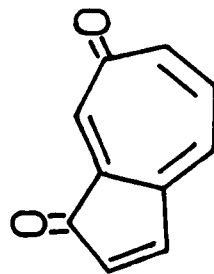
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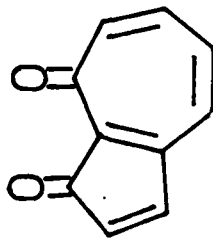
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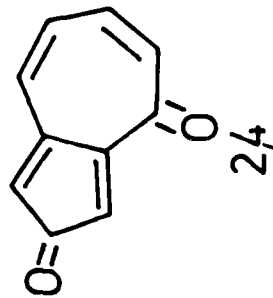
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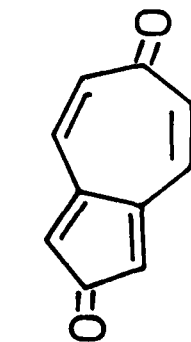
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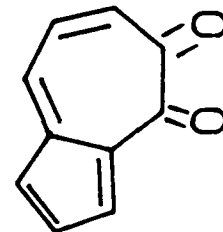
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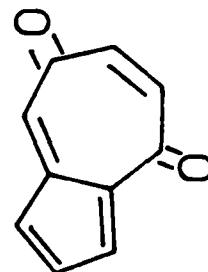
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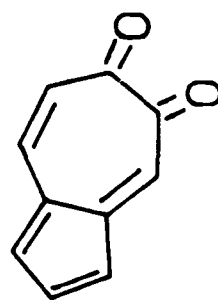
2,6



4,5



4,7



5,6

13

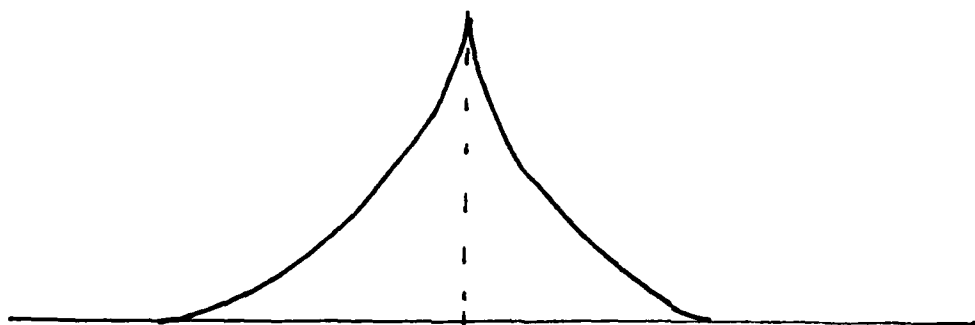
Figure 6

can be linked experimentally with the prediction data on the azuloquinones. Prior calculations on this benzenoid quinone, and other similar quinones, gave good comparisons with experimental data for these compounds - therefore, the predictions concerning azuloquinones are also expected to be similar to the experimental results obtained.

The theoretical studies used several sophisticated techniques in predicting the stabilities and reactivities of the isomers of azuloquinone. There are basically two ways in which to approach the molecule. The first is to use a method known as Slater-Type Atomic Orbitals (STO-3G) in which ab initio (from the beginning) type calculations are used (Figure 7). Essentially the molecule is broken into individual atoms, each electron orbital in each atom is formulated and then the molecule is reconstructed utilizing huge banks of computers in order to calculate all of the interactions between all (of the electrons in all) of the orbitals within the molecule. For economic reasons this fundamental method is usually avoided and a different technique is used, namely a Modified Intermediate Neglect of Differential Overlap (MINDO/3). MINDO/3 (Figure 8) is not quite as accurate as STO-3G, but it provides many calculations with satisfactory results. If one were to compare the wave equations of electron probability for adjacent atoms, the plots of electron density resemble the illustration in Figure 7. What MINDO/3 does while calculating molecular

STO-3G

15

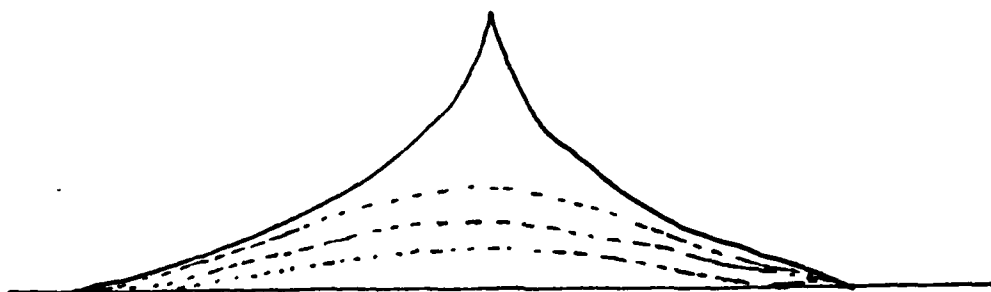


s - STO

SLATER TYPE ATOMIC ORBITAL

- AB INITIO -

$$e^{-ar} = \sum_i c_i e^{-br^2}$$



3 GAUSSIAN ORBITALS

$$\int e^{-a_1 r} e^{-a_2 r} \Rightarrow \sum_i \sum_j c_i c_j \int e^{-b_1 r^2} e^{-b_2 r^2}$$

- Overall more accurate than

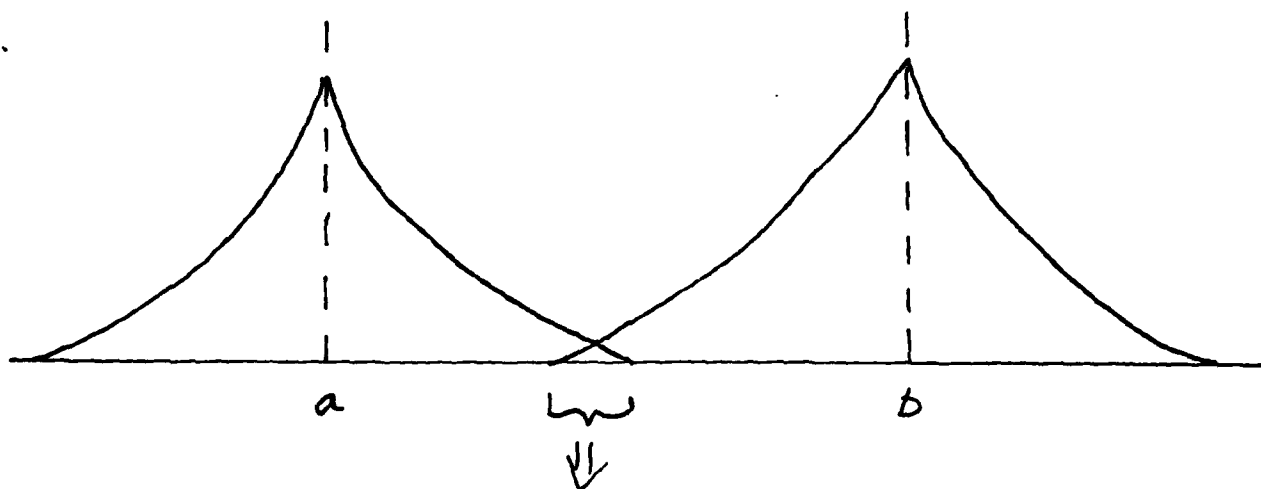
MINDO / 3

Figure 7

MINDO / 3

16

MODIFIED INTERMEDIATE NEGLECT OF DIFFERENTIAL OVERLAP



(overlap region for constructing
molecular orbitals)

- APPROXIMATE INTEGRALS OVERLAP
- MANY INTEGRALS TRIED IN ORDER TO
DETERMINE MOST PROBABLE

Figure 8

energies is to neglect the overlap (X-area) or the interaction between all of the orbitals in each atom in the molecule. The results are no less desirable (although more approximate) and it is economically much more acceptable since the computer time is cut substantially. Using MINDO/3, parameters can be calculated - then, once the compound is made, the experimentalist can measure the calculated physical properties (in this case, the reduction potential of the quinone/hydroquinone reaction) of the real molecule and then compare the theoretical predictions and the experimental results.

For instance, by using MINDO/3 programs, the theorists came up with a list of heats of formation for the eleven isomers of azuloquinone (Figure 9). The -6.4 kcal/mole value for the 1,5-azuloquinone predicts that this is the most energetically favorable structure for azuloquinone, while +9.5 kcal/mole for the 5,6 AQ isomer calculates this to be the most unfavorable isomer.

Another prediction presented by the theoreticians in their work with MINDO/3 was a relative list of the predicted energy gaps (Figure 10) between the π -LUMO (Lowest Unoccupied Molecular Orbital) and π -HOMO (Highest Occupied Molecular Orbital) for each isomer. This parameter is a measure of how quickly each molecule will tend to dimerize or recombine with itself (Figure 11). One of the isomers with a relatively

<u>CPD</u>	ΔH MINDO/3 (kcal/mole)	π HOMO/LUMO GAP MINDO/3
1,2 AQ	-0.4	7.72
1,4 AQ	-0.8	7.77
1,5 AQ	-6.4	8.64
1,6 AQ	-0.6	7.70
1,7 AQ	-5.3	8.35
2,4 AQ	+4.7	7.78
2,6 AQ	4.7	7.91
4,5 AQ	+7.0	7.86
4,7 AQ	+7.2	8.23
5,6 AQ	+9.6	7.78

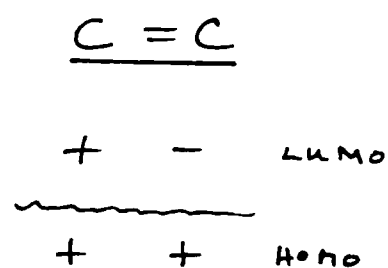
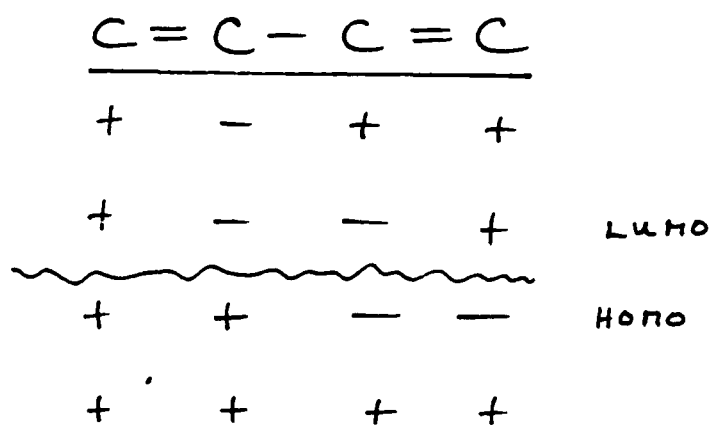
Figure 9

HOMO / LUMO

- HIGHEST OCCUPIED

- LOWEST UNOCCUPIED

MOLECULAR ORBITALS



DIELS - ALDER

REACTION

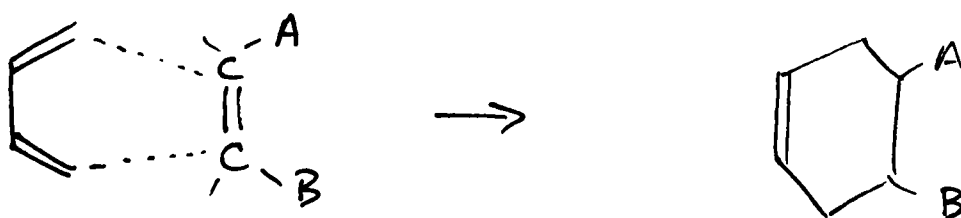


Figure 10

DIELS-ALDER DIMERIZATION
OF
AZULOQUINONE

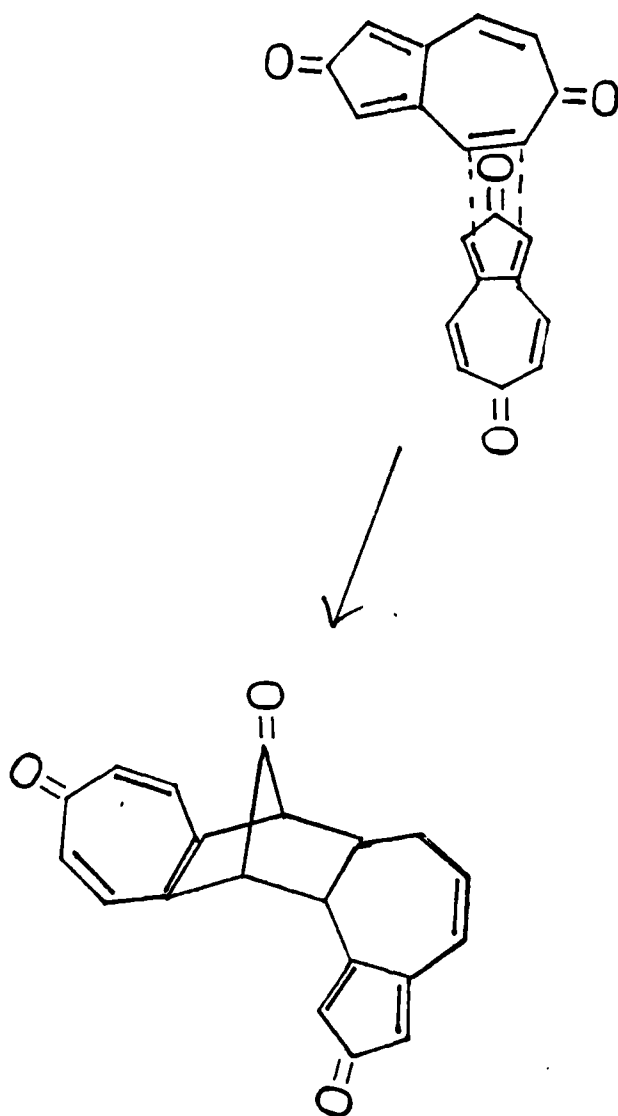


Figure 11

low π -LUMO/ π -HOMO energy spacing is 2,6 AQ. Workers in Japan in an attempt to isolate the 1,3-bis(carboethoxy) - 2,6 azuloquinone qualitatively substantiated this prediction since they were unable to isolate and characterize the monomer of this particular molecule (Figure 12), but the predicted dimeric product was found. The isomer with the greatest π -LUMO/ π -HOMO gap should be the least likely to dimerize - thus, it is apparent that the 1,5 and 1,7 azuloquinones would be the most desirable to use to attempt synthesis and isolation.

The theorists predicted other stabilization and reactivity parameters, but the aforementioned are the most critical to the synthetic chemist trying to isolate and determine the reduction potential for a particular azuloquinone.

Synthetic Background

In synthesizing the general azulene nucleus, there were several different routes that had been worked out by other synthetic studies. For instance, some Japanese workers used a synthetic route utilizing a fulvene as starting material (Figure 13). The biggest problem with this route is lack of control. The five-membered ring would have definite steric and inductive limitations on possible substitution.²³

A group of French workers prepared an azulene nucleus

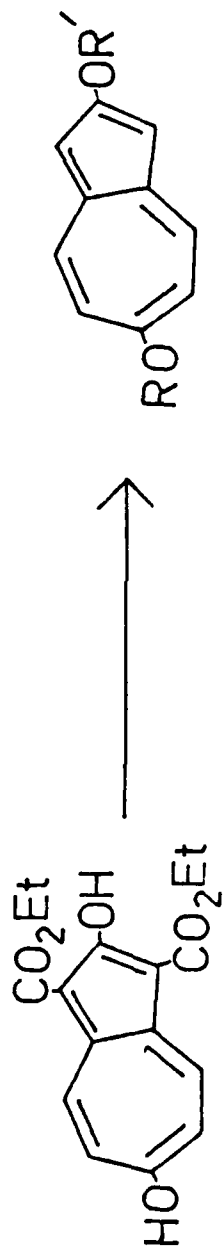


Figure 12

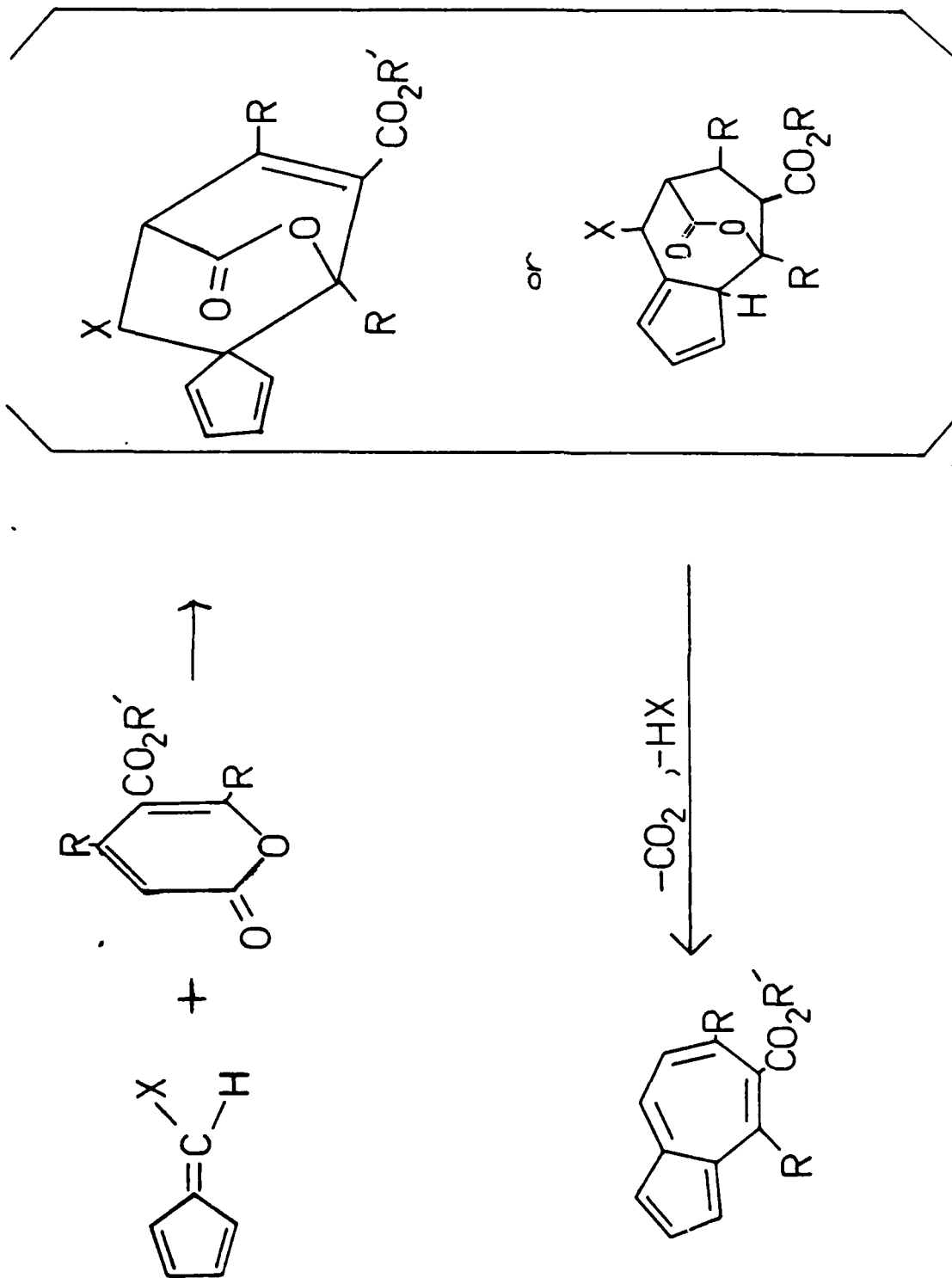


Figure 13

by preparing a diazoketone from phenylpropranic acid.²⁴ By reacting this diazo compound with catalytic Cu, they generated a carbene intermediate which added intramolecularly to the phenyl ring. The French encountered many problems with dimerization, by-products and serious side reactions (Figure 14). There are two things to note about their synthesis: 1) The best results were achieved in reactions carried out at very high dilutions and, 2) there were no substituents on the phenyl ring, a factor which would affect the reactions done in this Trident project.

Scott, et al.,²⁵ modified the French approach somewhat by 1) using CuCl instead of Cu as a ring closure catalyst, 2) varying the solvents used and, 3) adding a methyl group substituent to the phenyl ring. They reported results that were encouraging enough so that their ring closure technique was used in this project to complete the critical ring closure reaction.

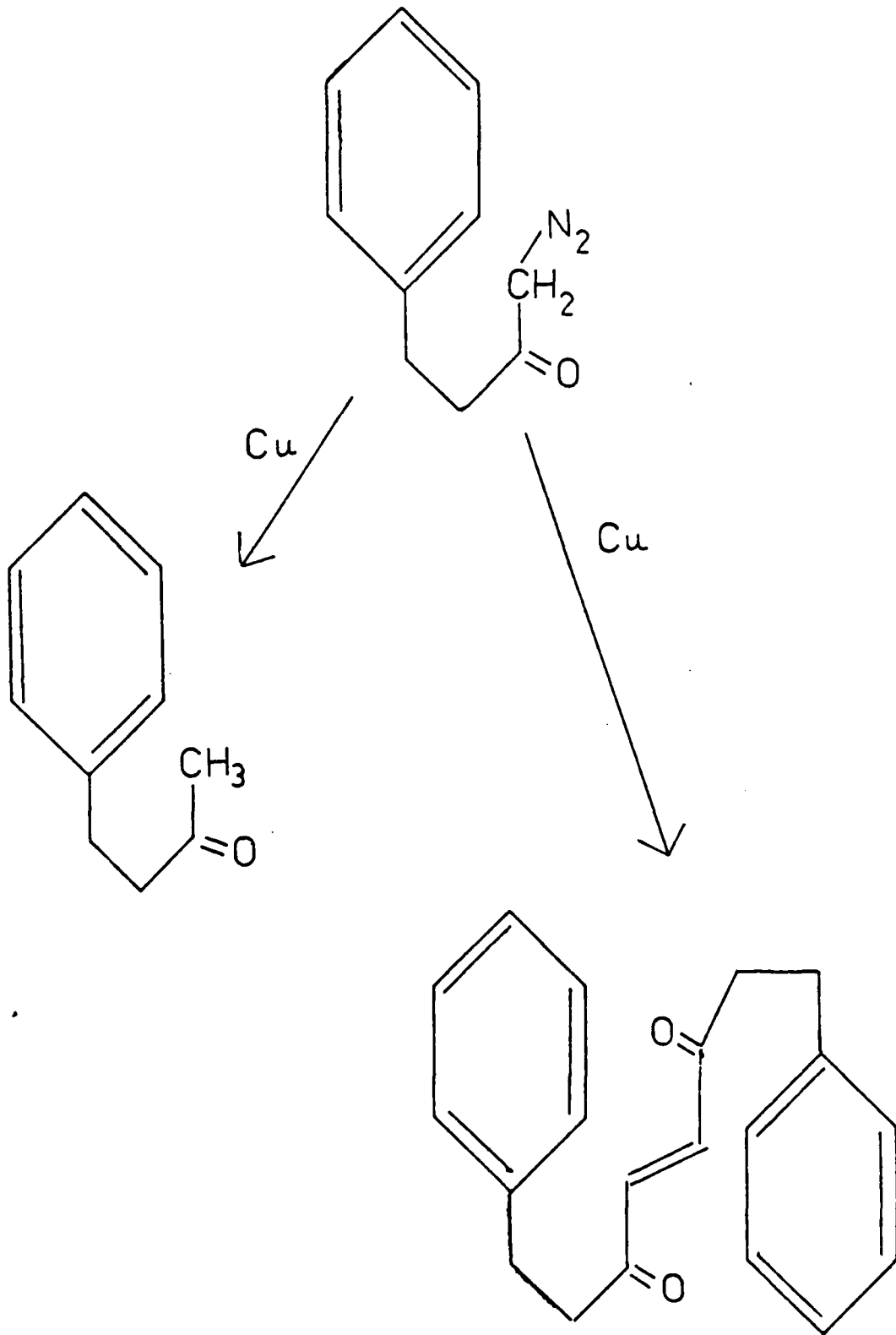
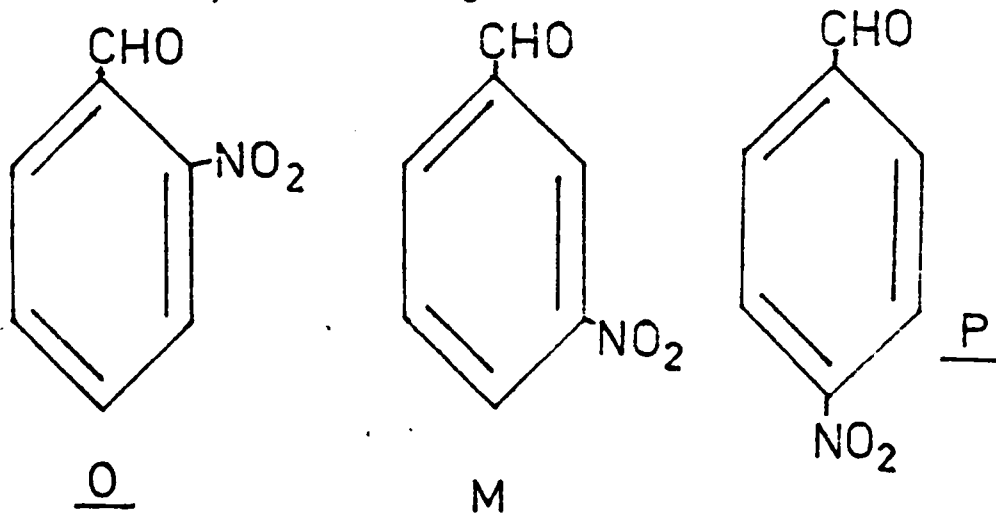


Figure 14

DISCUSSION

The synthetic route to azuliquinone utilized in this project was chosen because of the ease in keeping a substituent on the original phenyl ring, while still achieving an azulene conformation. The key ring-closure reaction is one in which an intramolecular ring reaction is accomplished by incorporating Scott's²⁶ carbene addition to the phenyl ring.

The synthetic route (Figure 15, a&b) proposed by Professor C. F. Rowell of the U.S.N.A. Chemistry Department utilizes the various isomers (ortho, meta, and para) of nitrobenzaldehyde as starting materials.



By simply varying the location of the nitro (NO_2) group on nitrobenzaldehyde, we could synthesize the 1,4 and 1,8, by using ortho-benzaldehyde; 1,5 and 1,7, from meta-benzaldehyde; 1,6, from para-nitrobenzaldehyde, azuliquinones. Referring to Figure 9, one will observe that these five isomers represent

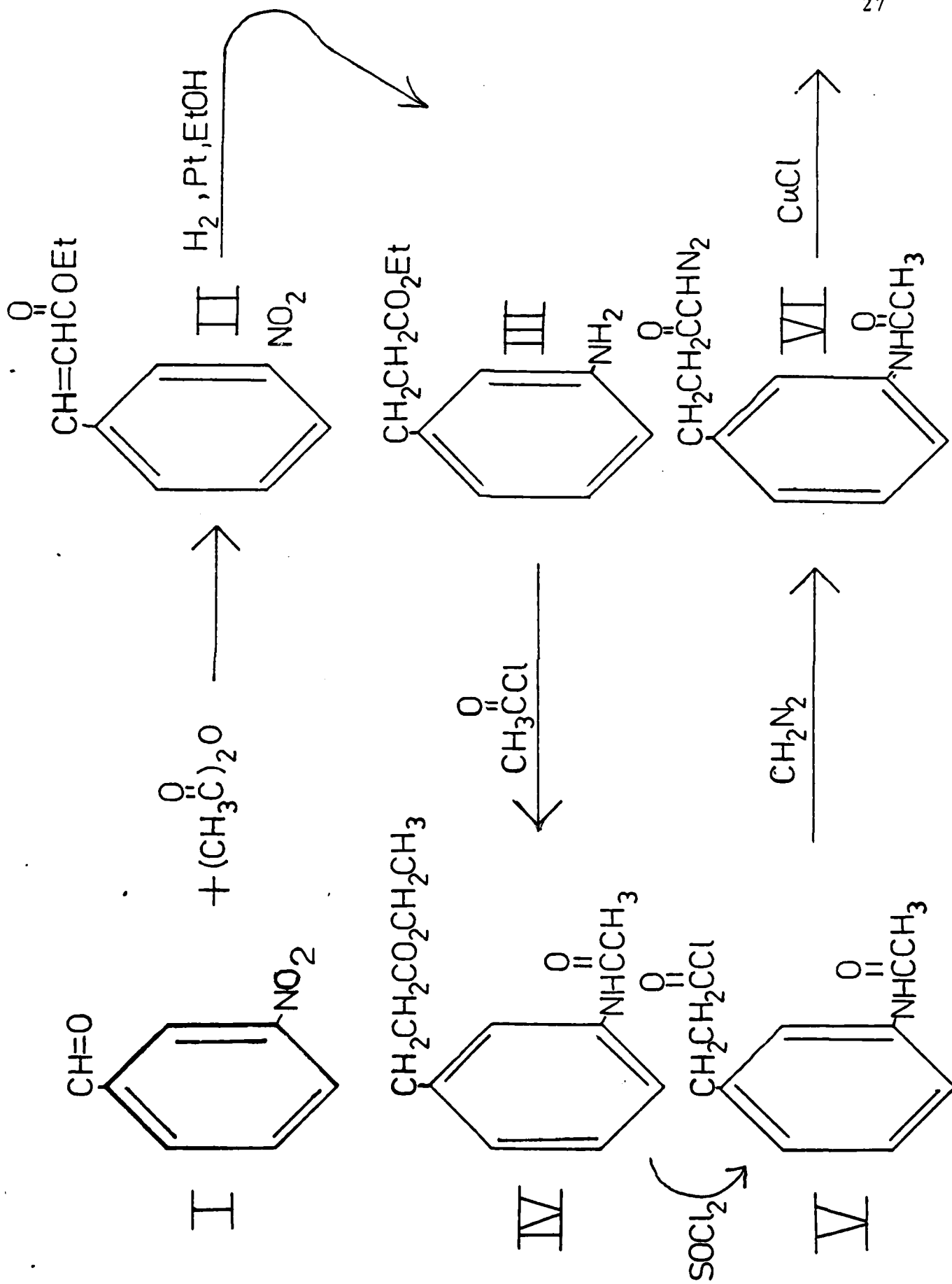


Figure 15a

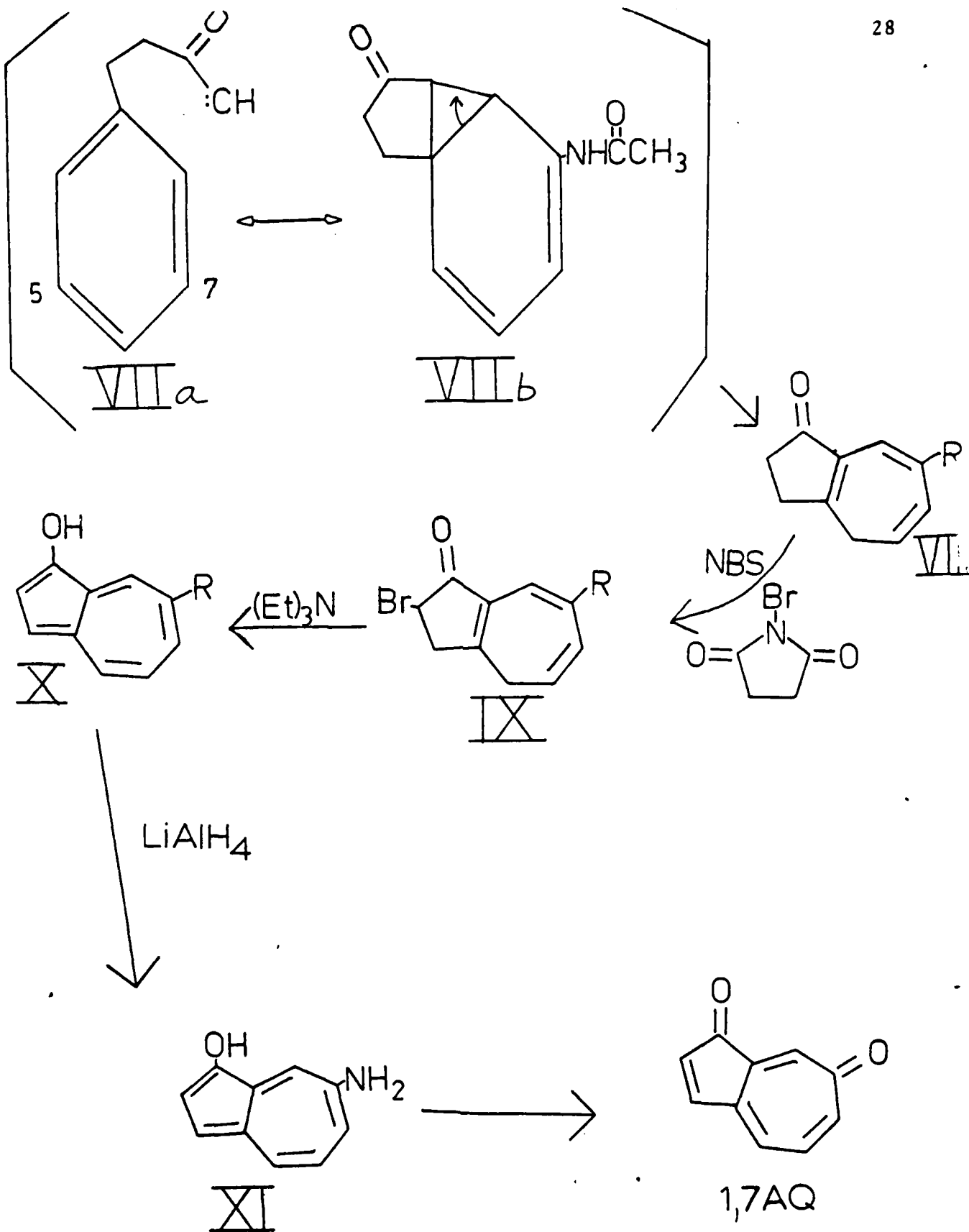


Figure 15b

a good range from the most stable isomer (1,5) to a lesser stable (1,6) one, thus providing a means by which to observe the experimental behavior and compare the theoretical predictions for both stable and unstable conformations of azuloquinone.

The relative stability of each particular isomer of azuloquinone (1,4 through 1,8) was to be determined by the use of the electrochemical technique, cyclic voltametry. A known quantity of the azuloquinone would be put in solution and a current would run through the solution. By measuring the voltage at the maximum change in current as the hydroquinone is oxidized to the quinone (Figure 16A), a relative measure of the reduction potential of the azuloquinone may be calculated. If the polarity of the system were now reversed and the azuloquinone showed a return to its original monomeric reduced form (following a hysteretic loop), then it would be known that the azuloquinone in its monomeric form was stable to further reaction (Figure 16B). If there were some other effect observed, such as no return to the original point, then the azuloquinone was unstable and went on to other products, most probably the dimer (Figure 16C). Such a study was reported by a German research group where work showed several steps of oxidation and reduction could be found for their more complicated system when studied in this way.²⁸

The first reaction shown (Figure 15A) gives ethyl ester

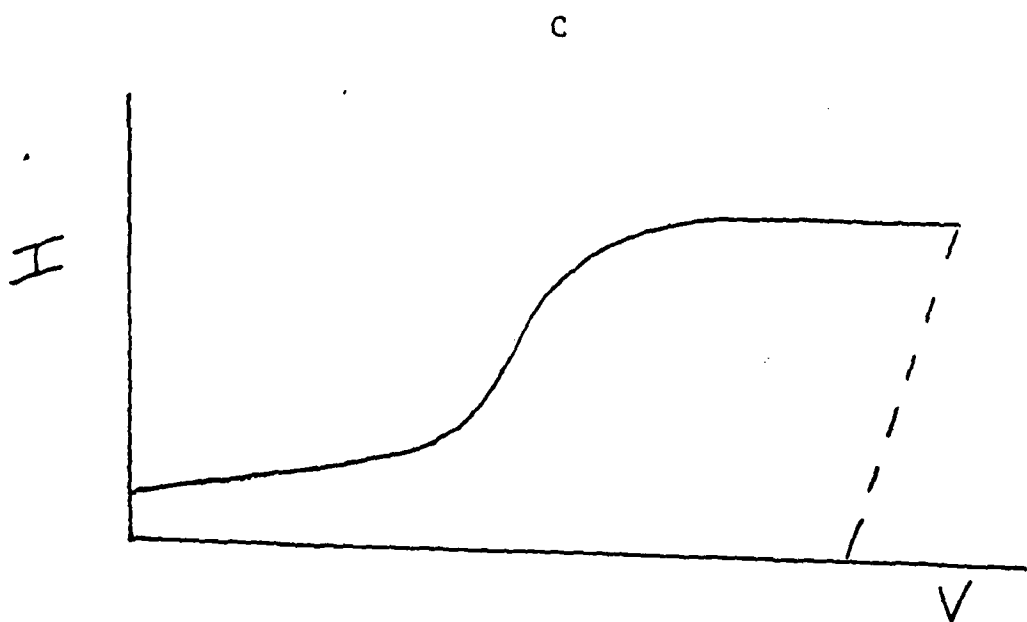
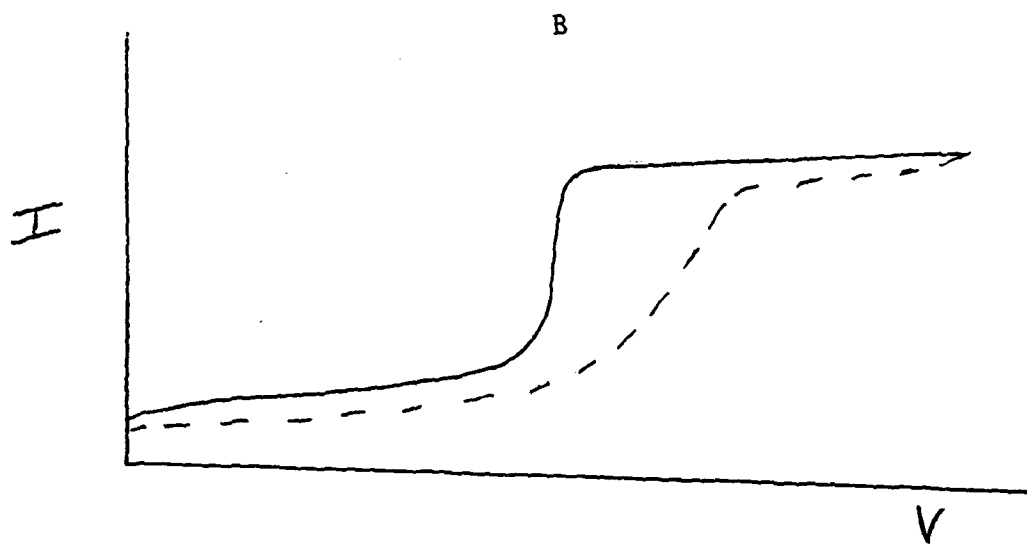
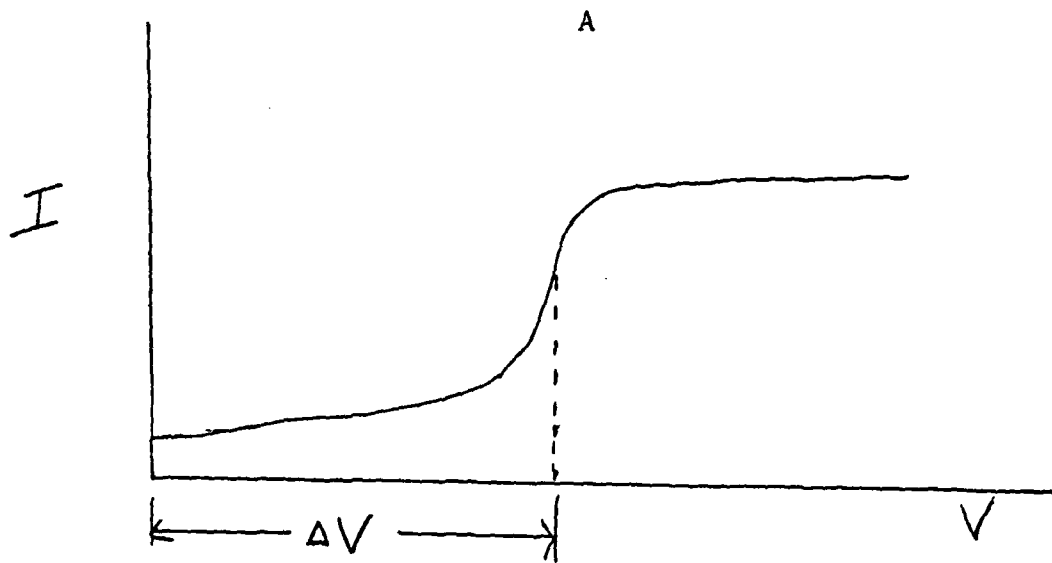


Figure 16

after the nitrocinnamic acid (I) is treated with SOCl_2 , followed by reaction with methanol and pyridine. Before this series of reactions was utilized, an attempt to isolate the amino hydrocinnamic acid (XII) without esterifying the carboxylic group failed due to an equilibrium problem encountered with the various species of the Zwitter ion (Figure 17). It was found that the only way to avoid this problem was to eliminate one of the ionic locations on the molecule. Thus the acid was first esterified before the reduction of the nitro group to the amine.

It was soon discovered that the first hydrogenation step using platinum (Pt) on carbon, H_2 gas at atmospheric pressure, and ethanol as a solvent was not saturating the double bond (Figure 18). The pressure of H_2 was then raised to 50 psig and the solution was shaken vigorously in a special Parr shaker apparatus. Many solvents, including methanol, ethanol, THF and ethyl acetate, were used in the hydrogenation steps since the solubility of the compounds was not very good in any one of these polar solvents.

It was found necessary to isolate the amino-cinnamic ester and acetylate the amine before continuing the hydrogenation of the double bond of the cinnamate (Figure 18). The probability of catalyst poisoning due to absorption of the amine on the platinum catalyst is fairly high. Later studies with the p-nitro cinnamic acid went smoothly to saturated amine without the intermediate step when palladium

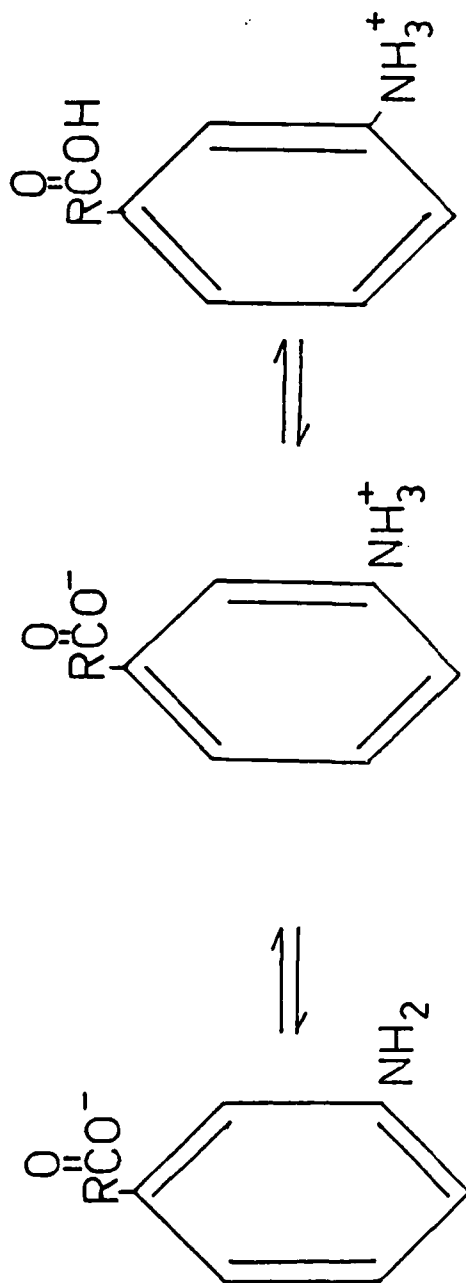


Figure 17

H₂ at 50 psi

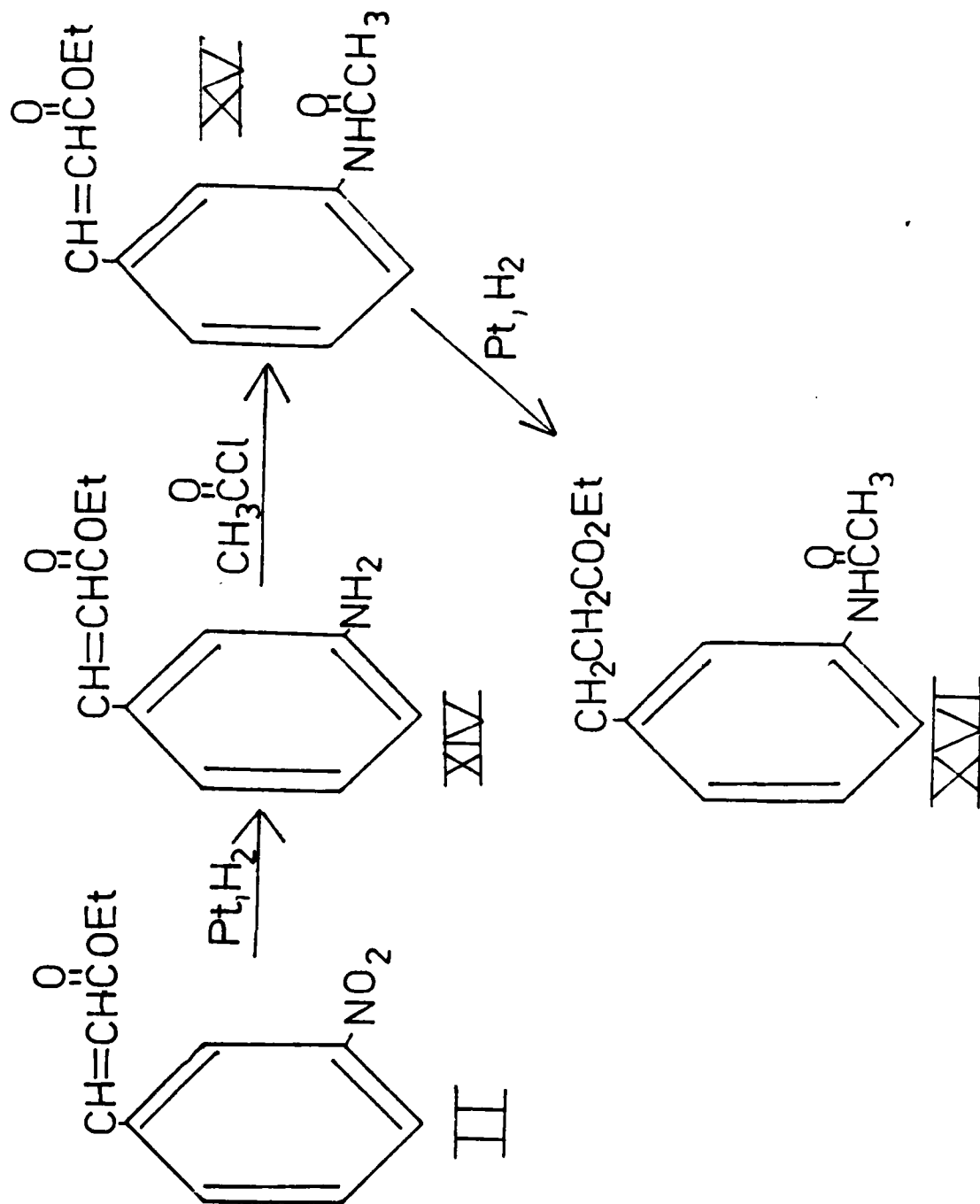


Figure 18

was the catalyst (Figure 19). Since platinum is a stronger adsorber than palladium this is consistent with this explanation.

The acetamidehydrocinnamate (IV) then had to be hydrolyzed back to the carboxylic acid (XIX) in order to prepare the ring closure precursor. Unfortunately, the conditions under which both esters and amides undergo hydrolysis in basic or acidic solutions are very similar.

A reagent was needed that would remove the ester function without disrupting the amide protecting group. The literature²⁹ suggested that LiI in dimethyl formamide (B.P. 153°C) would proceed by an S_N2 -like mechanism where the ester would cleave, while the amide underwent no reaction. This reaction was first tried with the ethyl ester (Figure 20) and spectra showed the ester still present.

The synthesis was repeated, but instead of LiI in dimethyl formamide SCN in dimethylsulfoxide was used in an attempt to utilize a stronger nucleophile and a higher boiling solvent in order to knock off the ethyl ester. Again, no acid function was detected.

The synthesis was repeated from the beginning utilizing methanol to give the methyl-m-acetamide hydrocinnamate. It has been reported³⁰ that the methyl ester more readily undergoes the S_N2 with LiI in higher yields. But again, the ester would not cleave after refluxing for three days (Figure 20).

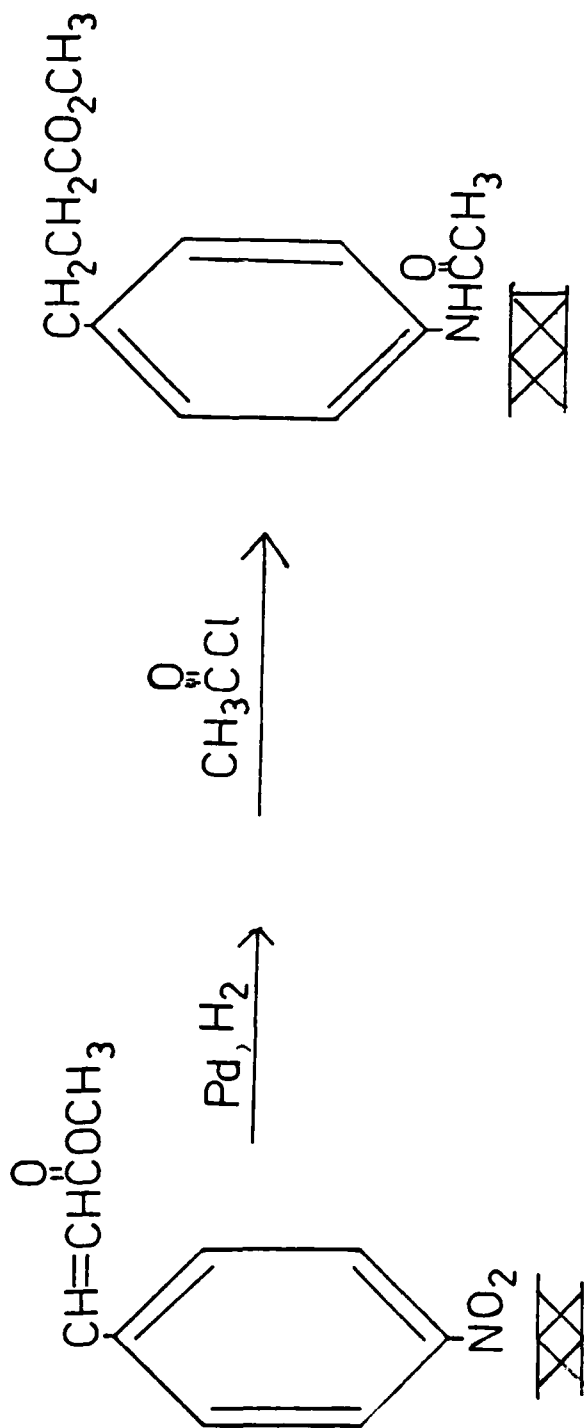
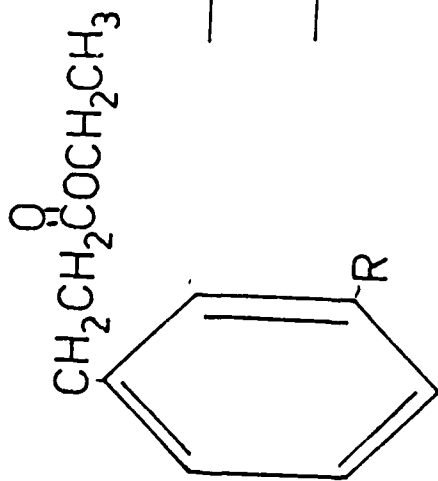


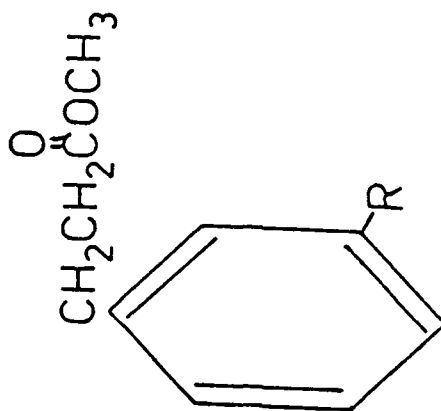
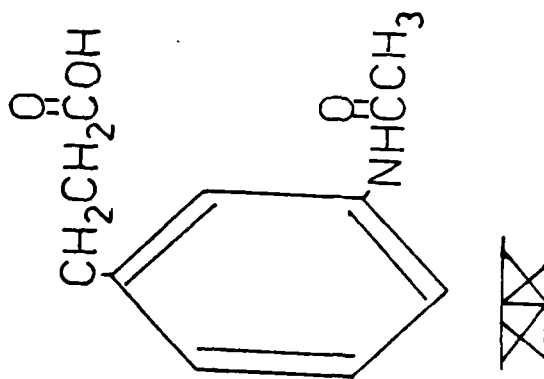
Figure 19

S_N2



LiI, DMF →

KSCN, DMSO →



LiI, DMF →

Figure 20

The methyl ester was finally hydrolyzed using an ethanolic solution of 50% KOH. Those very rugged reaction conditions hydrolyzed the amide also, but the amide was restored by treatment with acetic anhydride (Figure 21).

The m-acetamide hydrocinnamic acid (XIX) was then reacted with SOCl_2 to give the acid chloride. Following this the diazoketone (VI) was formed using the very dangerous and explosive reagent diazomethane (CH_2N_2). When (VI) is added in great dilution and slowly to boiling benzene containing catalytic amounts of CuCl , nitrogen is lost and the carbene adds intramolecularly to the phenyl ring. Rearrangement (Figure 15B) occurs and, because of the symmetry of the starting material, gave the 1,5 and 1,7-acetamido bicyclictrienone (VIII) isomers.

Upon column chromatographing, a great many impurities and by-products were found. A French group³¹ ran similar ring closure reactions and identified dimers and other by-products (Figure 14) from the reaction. We had great difficulty in spectroscopically identifying the purified acetamido bicyclictrienone. We also had the added problem of having to separate the two possible isomers of the compound at this point.

Concurrently the para compound was submitted to an analogous route. For the most part the reactions in the

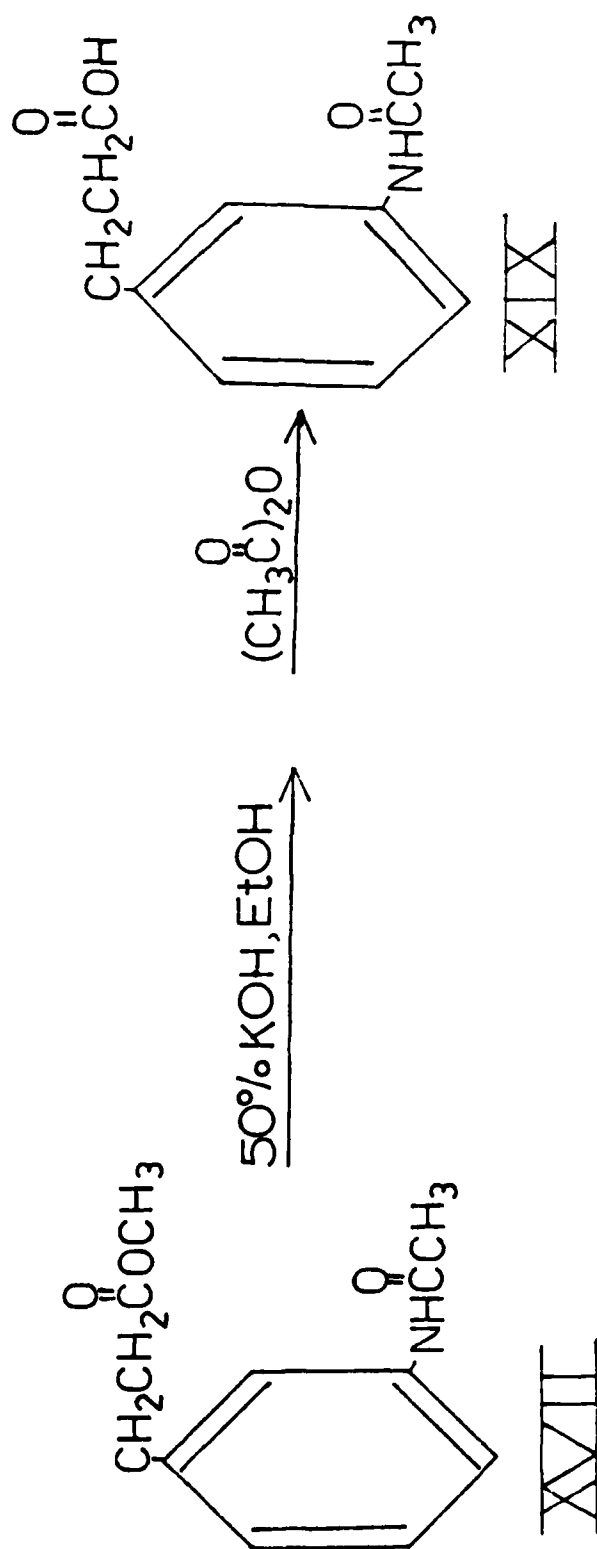


Figure 21

two routes were very similar. Some differences were noted, i.e., the hydrogenation of the double bond, followed by acetylation of the amine, could be completed in the first hydrogenation by using palladium instead of platinum (Figure 19). Also, the hydrolysis of the methyl ester was done with no loss to the amide in an ethanolic solution of 25% KOH refluxed for only two hours.

The ring closure on the para compound, though giving only one possible isomer, gave as many by-products as the meta-compound reaction.

The purification problem for these compounds after ring closure was great. As many as four columns were run on the product from the meta-acetamido diazoketone. The separated component that we believed was the most promising for the correct molecule was carried into a bromination reaction with N-bromosuccinimide in CCl_4 . Work up provided no material that could be characterized.

The para compound was purified by column chromatography after the ring closure reaction. But further studies were not made due to lack of time.

EXPERIMENTALA. Preparation of 1,5 and 1,7 azuloquinones1. Preparation of m-nitrocinnamic acid (Ia)³²

In a round-bottom flask 18g of fused potassium acetate, 45 ml acetic anhydride, and 0.3 moles m-nitrobenzaldehyde were mixed, refluxed in an oil bath at 155^o-160^oC for 15 minutes, then at 165-170^oC for 3 hours. While it was still hot, it was emptied into a large beaker, the flask rinsed with 400 ml of boiling water and added with 600 ml additional water to the beaker. The solid was filtered, the solution made basic in the 3N NaOH, and the solid returned to solution. The resultant solution was filtered through fluted paper, concentrated HCl was added until the solution was strongly acid. Overnight digestion on a hot plate improved the crystals which were filtered and dried in vacuum desicator. It was a gray solid;

YIELD: 75%; M.P.: (Lit.) - 204.5^oC

(Obs.) - 202-203^oC

IR: # KAR - 090881 - 01

2. Preparation of ethyl m-nitrocinnamate (II)³³

Into a 100 ml round-bottom flask was added 0.03 moles of m-nitrocinnamic acid and enough SOCl_2 to permit refluxing. SOCl_2 was removed by vacuum distillation. An excess of ethanol was added followed by slow addition of 0.03 moles of pyridine. After refluxing overnight and extraction with CH_2Cl_2 , the pyridine was removed by washing with water five times. CH_2Cl_2 layer was dried over Na_2SO_4 and rotaevaped. The residue was a solid;

YIELD: 60%; M.P.: (Lit.) 75-76°C
(Obs.) 71-72°C

IR: # KAR - 091781 - 01 NMR: # KAR - 093081 - 01

3. Preparation of methyl m-nitrocinnamate³³

Add to round-bottom flask 0.3 moles of m-nitrocinnamic acid and enough SOCl_2 to obtain a reflux. After refluxing 5 hours at 100°C, distill off the SOCl_2 (b.p. 79°C). Add enough CH_2Cl_2 to give a solution, then add 0.3 moles of pyridine very slowly. Finally add about 50 ml of methanol. Reflux with a mantle for approximately 45 mins. Extract (add more methylene chloride if necessary) with H_2O 5 times, and dry over Na_2SO_4 . Evaporate off CH_2Cl_2 and recrystallize in methanol. Alumina column run with CH_2Cl_2 -first band off is methyl ester. CH_2Cl_2 was removed,

rotaevaped and residue was yellow solid.

YIELD: 50%; M.P.: (Lit.) 123-124°C

(Obs.) 121-122°C

NMR: # KAR - 110181 - 01

4. Preparation of ethyl-m-aminocinnamate (XIV)

0.1 moles of (II) were dissolved in ETOH and a catalytic amount of 10% platinum on carbon was added.

The mixture was stirred while 5.8 liters of H₂ were added at atmospheric pressure. Catalyst was filtered off, and the solvent removed under vacuum.

YIELD: 97%; M.P.: Oil

IR: # KAR - 083181 - 01

5. Preparation of methyl-m-aminocinnamate

0.2 moles of methyl m-nitrocinnamate was dissolved in ethyl acetate containing a catalytic amount of 10% Pt on carbon. The mixture was placed in a Parr shaker and hydrogenated at 50 psig for twenty-four hours. Catalyst filtered by use of short column chromatography with silica gel. Ethyl acetate removed under vacuum.

YIELD: 95%; M.P.: Oil

NMR: # KAR 111081 - 01

6. Preparation of ethyl-m-acetamidocinnamate (XV)

0.09 moles of ethyl-m-aminocinnamate were dissolved in 75 ml of ether and 5 ml of pyridine. A slight excess of CH_3COCl (2 ml) was added slowly to the stirred solution. This was refluxed overnight and the ether layer washed with H_2O five times. The solution was dried over Na_2SO_4 and the ether removed under vacuum.

YIELD: 61%; M.P.: Oil (orange)

NMR: # KAR - 100181 - 02

IR: # KAR - 093181 - 01

7. Preparation of methyl-m-acetamidocinnamate

0.19 moles of methyl-m-aminocinnamate was dissolved in ether (200 ml) and a slight excess of pyridine and CH_3COCl were added in that order. The solution was stirred and refluxed for five hours. The ether layer was washed with H_2O , dried over Na_2SO_4 and rotaevaped.

YIELD: 57%; M.P.: Brown Oil

IR: # KAR - 111181 - 02

NMR: # KAR - 111181 - 01

8. Preparation of ethyl-m-acetamidohydrocinnamate (IV) -

0.054 moles of (XV) were dissolved in THF and a catalytic amount, 10% Pt/C was added. The solution was placed in a Parr shaker and reacted under H_2 at 50 psig for 24 hours. Catalyst was filtered with silica gel and the solvent removed under pressure.

YIELD: 95%; M.P.: Oil

IR: # KAR - 100181 - 01

NMR: # KAR - 100181 - 02

9. Preparation of methyl-m-acetamidohydrocinnamate (XVIII)

0.11 moles of methyl-m-acetamidocinnamate was dissolved in ethyl acetate and hydrogenated with 10% Pt/C and H₂ at 50 psig for 24 hours. It required several runs to saturate all of the material present. Catalyst filtered by silica gel column, solvent removed under pressure and white solid left.

YIELD: 96%; M.P.: (Lit.) Unknown

(Obs.) 78-80°C

IR: # KAR - 120181 - 01

NMR: # KAR - 112081 - 02

10. Preparation of m-acetamidohydrocinnamic acid

a. Attempt at hydrolysis of ethyl-m-acetamidohydrocinnamate with LiI in DMF.²⁹

Dried 40 ml of dimethylformamide (DMF) with P₂O₅ overnight. Dried all glassware in oven before use. In DMF, fresh distilled from P₂O₅, 0.5g of (IV) and 0.34g of LiI to DMF, let stir and reflux under N₂ gas for 48 hours. Solvent was stripped by vacuum distillation. IR: # KAR - 101381 - 01

b. Attempt at hydrolysis of ethyl-m-acetamidohydrocinnamate with KSCN in DMSO.²⁹

Dried DMSO over fresh molecular sieves. Distilled 50 ml and added 1.5g of (IV) and equimolar portion of KSCN.

Let reflux and stir under N_2 for seven days. Solvent removed by vacuum distillation. IR: # KAR - 103081 - 01

c. Attempt at hydrolysis of methyl-m-acetamidohydrocinnamate with LiI and DMF.²⁹

2.32g of (XVIII) were added to freshly dried and distilled DMF containing an equimolar portion of LiI. All glassware used in reaction was dried in oven. Solution was refluxed and stirred under N_2 for 5 days. DMF removed by vacuum distillation. IR: # 120181 - 04

d. Preparation of m-acetamidohydrocinnamic acid (XIX)

Add 2.07g of (XVIII) to solution of 50g of KOH in 150 ml of 95% EtOH. Let reflux for 24 hours. Make the solution acidic by slowly adding conc. HCl. Evaporate off EtOH, extract acidic water layer with ether, dry with Na_2SO_4 , and remove ether under vacuum. Add 100 ml of freshly distilled, dry pyridine and an equimolar (with slight excess) amount of acetic anhydride (Figure 21) and let reflux 4 hours. Remove pyridine under reduced pressure and extracted with $CHCl_3$. $CHCl_3$ layer washed several times, extracted with 1M $CuSO_4$, dried over Na_2SO_4 and rotaevaped off under vacuum.

YIELD: 60%; M.P.: (Lit.) Unknown

(Obs.) 165-175^o (decomposed)

IR: # KAR - 031582 - 01

NMR: # KAR - 031182 - 01

11. Preparation of 5 and 7-acetamidobicyclo (5,3,0) deca - 1,7,9-trien-zone (VIII)²⁶

CH_2N_2 was prepared using the Diazald[®] kit and reagent. All work with diazomethane was carried out behind a safety shield and in a hood. 35 ml of ethylene glycol monomethyl ether and 20 ml of ether were added to a solution of 6g of KOH in 10 ml of H_2O . This solution was placed in a 100 ml long neck distilling flask fitted with a dropping funnel and the Diazald^R, (N-methyl-N-nitroso-p-toluenesulfonamide), distillation kit in a water bath at 70°C . At a rate equal to the distillation rate of the ether, a solution of 3g of Diazald[®] in 100 ml of ether is added through the dropping funnel. During distillation, the solution is stirred by a Teflon magnetic bar. The diazomethane is distilled over in the ether, which was collected in a two receiving flasks in series cooled in an ice/salt bath. The acid chloride (V) was dissolved in 250 ml of ether and added dropwise with stirring to the ether solution of CH_2N_2 (still in an ice/salt bath) over a period of one hour. The solution is then allowed to come to room temp. over one hour. The ether was distilled off while 250 ml of benzene was being added. When the ether was removed, the 250 ml benzene solution of (VI) was added dropwise over 7 hours into 2000 ml of refluxing benzene, containing 0.5g of CuCl , under N_2 and being stirred with a mechanical stirrer.

After 8 hours, solution filtered and benzene removed under vacuum. Black oil was left and upon thin layer chromatography with 15% ethyl acetate/petroleum ether gave at least 5 spots, indicating at least five products. Column chromatography with same solvents and silica gel gave some separation. Two other columns were run using CH_2Cl_2 /15% Pentane and CH_2Cl_2 /25% Pentane.

YIELD: 15%; M.P.: Orange Oil

IR: # KAR - 051182 - 02

NMR: # KAR - 051182 - 01

12. Attempted preparation of 2 bromo-6-acetamido-bicyclo-triemone (IX) -

Dissolve 0.2g of (VIII) in 50 ml of CCl_4 and add a equimolar portion of N-bromosuccinimide (NBS). Let reflux with stirring for 24 hours. Filter solid (succinimide) away from solution and remove CCl_4 under vacuum. NMR: # KAR - 051282 - 01. IR: # 052282-01.

13. Preparation of para-nitrocinnamic acid³² -

In a 500 ml round-bottomed flask add 50g of p-nitro-benzaldehyde, 20g of potassium acetate, and 50 ml of acetic anhydride. Air-cooled condenser reflux in a wax bath at 155° - 160°C for 15 minutes, then 165° - 170°C for 3 hours. While hot, place in 3000 ml beaker and rinse round-bottom with 300 ml of boiling water and add 600 ml more of water.

Make solution strongly basic, filter, make acidic, filter out precipitate.

YIELD: 78%; M.P.: (Lit.) 286°C
(Obs.) 283°-286°C

14. Preparation of methyl-p-nitrocinnamate (XX)³³ -

Add 0.23 moles of p-nitrocinnamic acid to enough SOCl_2 to induce refluxing. Let reflux for 5 hours and vacuum distill off SOCl_2 . Add an excess of methanol and an equimolar portion of pyridine. Let reflux overnight. Extract with CH_2Cl_2 , wash with H_2O five times, dry with Na_2SO_4 and run column on silica gel with CH_2Cl_2 as a solvent. Remove CH_2Cl_2 under vacuum.

YIELD: 63%; M.P.: (Lit.) 161°C
(Obs.) 158-160°C

NMR: # KAR - 102481 - 01

15. Preparation of methyl-p-acetamidohydrocinnamate (XXI)

Using several runs in the Parr shaker hydrogenation apparatus, ethyl acetate as a solvent, and palladium (Pd) on carbon as a catalyst, hydrogenate 0.14 moles of (XX). Remove the catalyst by short column with silica gel and evaporate the solvent under vacuum. Dissolve remaining orange/oil in 250 ml of anhydrous ether, add equimolar portions of acetyl chloride (CH_3COCl) and pyridine. Let

reflux overnight; wash five times with H_2O , dry ether with Na_2SO_4 , and remove ether under vacuum.

YIELD: 50%; M.P.: Yellow oil

NMR: # KAR - 040482 - 01

16. Preparation of p-acetamido hydrocinnamic acid -

0.07 moles of (XXI) were dissolved in 200 ml of 95% EtOH and allowed to reflux for 2.5 hours. The ethanol is removed by evaporation under vacuum after the solution is made acidic. The acidic water layer is then extracted with $CHCl_3$, the $CHCl_3$ is dried over Na_2SO_4 and removed under vacuum. White crystals.

YIELD: 55%; M.P.: 90-93°C

NMR: # KAR - 051782 - 01

17. Preparation of 6-acetamidobicyclo (5,3,0) deca-1,7,9-trien-zone²⁶

The procedure used was the exact same as for the 1,5 and 1,7-acetamido-6,cyclo-trienone (VIII). Column chromatography separated at least six products for the para-ring closure case.

CONCLUSIONS

The experimental work in this project fell short of the final objective because of time constraints. It is very likely that this synthetic route to azuloquinone can be successful.

Purification of each compound after every reaction in the synthesis proved to be the most frustrating and time-consuming aspect of this study. Once reaction conditions were optimized, repetition of the synthesis was no problem.

APPENDIX A
SPECTRAL DATA*

<u>SPECTRUM #</u>	<u>IR (cm⁻¹)</u>	<u>NMR (δ)</u>
090881-01	(KBr): s, 2600-3200(O-H); s, 1670-1720(C=O); s, 1630(C=O); s, 1525; s, 1300- 1350.	
091781-01	(KBr): m, 3400-3500; m, d, 2990, 3080; s, 1700-1740 (C=O); s, 1640(C=O); s, 1510-1550; s, 1300-1370; s, 1150-1200.	
093081-01		(CDCl ₃): trip, 1.36 (J=7.5Hz), area 3; quad, 4.32(J=7.5Hz), area 2; sing, 6.47, area 1; sing, 6.71, area 1; mult., 7.78, area 4.
110181-01		(CDCl ₃): sing, 3.84, area 3; sing, 6.47, area 1; sing, 6.71, area 1; mult., 7.75, area 4.
083181-01	Oil (Neat): s, 3200-5500; m, 2850-2980; s, 1710-1750 (C=O); s, 1600-1630; s, d, 1060, 1100.	

<u>SPECTRUM #</u>	<u>IR (cm⁻¹)</u>	<u>NMR (δ)</u>
111081-01		(CDCl ₃): mult., 2.60; sing, 3.60, area 3; mult., 6.45, mult., 6.90.
100181-03		(d ₆ -acetone): trip, 1.30, (J=7Hz), area 3; sing, 2.21, area 3; quad, 4.27 (J=7Hz), area 2; sing, 6.30, area 1; sing, 6.55, area 1; mult., 7.52, area 4.
093181-01	Oil (Neat): m, 3000; s, d, 1650, 1720 (C=O); m, 1380; m, 1250-1340; s, 1190.	
111181-02	Oil (Neat): m, 2975; s, 1650-1730 (C=O); m, d, 1600; s, 1550; s, d, 1300; s, 1440; s, 1170.	
111181-01		(CDCl ₃): sing, 2.20, area 3; sing, 3.83, area 3; sing, 6.43, area 1; sing, 6.74, area 1; mult., 7.71, area 4; sing, 8.97, area 1.
100181-01	Oil (Neat): m, 2900- 2950; s, d, 1650, 1730 (C=O); s, 1375; s, 11, 75	

<u>SPECTRUM #</u>	<u>IR (cm⁻¹)</u>	<u>NMR (δ)</u>
100181-02		(d ₆ acetone):trip, 1.17(J=7.5Hz),area 3;sing,2.17,area 3; mult.,2.70,area 4; quad,4.08(J=7.5Hz), area 2;mult.,7.10, area 4.
120181-02	(KBr):m,2970;s,1680- 1740;s,1580;s,1510; s,1485;s,1290-1350; s,1190.	
112081-02		(CDCl ₃):sing,2.19, area 3;mult.,2.75, area 4;sing,3.68, area 3;mult.,7.20, area 4;sing,9.13, area 1.
101381-01	Oil (Neat):w,3300; w,2960;s,d,1670-1735; m,d,1600;s,1550;m,d, 1390;m,1150-1200.	
103081-01	Oil (Neat):s,d,1670, 1735;m,d,1600;s,1550; m,d,1375;s,1030-1070.	
120181-04	Oil (Neat):w,3290;w, 2940;m,1740;s,1600- 1680;s,1550;s,1490; s,1400-1650;m,d,1300.	

<u>SPECTRUM #</u>	<u>IR (cm⁻¹)</u>	<u>NMR (δ)</u>
031582-01	(KBr):s,3450-2900;s,1750; m,d,1550,1600;s,1485;m,d, 1250.	
031182-01		(d ₆ acetone)s,2.21, area 3;mult.,2.80, area 4;mult.,7.70, area 4.
051182-02	Oil (Neat):m,3400;w,2900; s,1700-1750;m,1600;s,d, 1450;m,850;s,800.	
051182-01		(d ₆ acetone) sing, 1.3,area 4;sing,3.05; area 4;sing,4.10, area 2;sing,3.72,area 2;trip,5.1,area 1; doub,6.45,6.55.
051282-01		(d ₆ acetone):sing, 1.3;sing,2.73;sing, 2.91;sing 3.71;sing, 4.10;mult.,7.55.
052282-02	Oil (Neat):w,2800-3600; s,1710;w,1430;m,1360; s,1180.	
102481-01		(CDCl ₃):s,3.87,area 3;sing,6.42,area 1; sing,6.71,area 1; mult., 8.00,area 4.

<u>SPECTRUM #</u>	<u>IR (cm⁻¹)</u>	<u>NMR (δ)</u>
051782-01		(d ₆ acetone):sing, 2.18,area 3;mult., 2.69(J=6Hz),area 4; mult.,7.35, area 4.

* Symbols: s = strong; m = medium; w = weak; sing = singlet;
doub,d = doublet; trip = triplet; etc.

ACKNOWLEDGMENTS

One can improve vastly in laboratory techniques and methods involved with setting-up reaction apparatus, purifying products and identifying each compound using extensive infrared, nuclear magnetic resonance, and mass spectroscopies. I truly believe I have learned more about practical chemistry in the past nine months than I have in three years of classroom chemistry. The experience of having done countless hours of research will, by far, be my greatest asset upon entering graduate or other education and for attacking other types of problems in the naval setting.

Thank-you -

For timely advice: Dr. T. H. Jones

Dr. G. T. Cheek

Captain R. Haddock, USMC

For technical assistance: Dr. Dale L. Campbell

For technical typing skills: Ms. Barb Knotts

For support: Family and Friends

Special Thank-you -

For being an advisor and mentor: Dr. C. F. Rowell

FOOTNOTES

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³³(a) S.M. McElvain and T.P. Carney, Journal of the American Chemical Society, 68(1946), p. 2599, (b) J. Horning, Organic Synthesis, Volume III, (New York: Wiley, 1957).

³⁴By manufacturer's directions.

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REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER	2. GOVT ACCESSION NO.	3. RECIPIENT'S CATALOG NUMBER
U.S.N.A. -TSPR; no. 115 (1982)	AD-A124253	3
4. TITLE (and Subtitle)	5. TYPE OF REPORT & PERIOD COVERED	
Syntheses of azuloquinones as an experimental determination for a theoretical prediction.	Final: 1981/1982	
	6. PERFORMING ORG. REPORT NUMBER	
	8. CONTRACT OR GRANT NUMBER(s)	
7. AUTHOR(s)	10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS	
Donovan, Joseph L.		
9. PERFORMING ORGANIZATION NAME AND ADDRESS	12. REPORT DATE	
United States Naval Academy, Annapolis.	29 July 1982	
	13. NUMBER OF PAGES	
	61	
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office)	15. SECURITY CLASS. (of this report)	
	UNCLASSIFIED	
	15a. DECLASSIFICATION/DOWNGRADING SCHEDULE	
16. DISTRIBUTION STATEMENT (of this Report)		
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18. SUPPLEMENTARY NOTES		
Accepted by the U. S. Trident Scholar Committee.		
19. KEY WORDS (Continue on reverse side if necessary and identify by block number)		
Quinone Chemistry, Organic Azuloquinones		
20. ABSTRACT (Continue on reverse side if necessary and identify by block number)		
<p>Quinones are chemical compounds utilized throughout naturally occurring biological systems in energy-transferring reduction/oxidation reactions. Quinones are also being tested in the area of anti-tumor agents. Azuloquinones are unknown quinones which may provide the specific energy that may match metabolic values.</p> <p>Azuloquinone is a compound that has received a great deal of attention in theoretical chemistry recently. Quantum mechanical predictions on the</p>		

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relative energies and stabilities of the eleven possible isomers of azuloquinone have preceded the experimental determination of the measured energies for these compounds. The intent in this project was to synthesize several isomers of azuloquinone by simply varying the starting material conformation. Though the synthesis was not completed, there is extensive progress towards isolating isomeric azuloquinone and the route has been substantiated as a feasible way to synthesize azuloquinones.

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