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STUDIES ON THE ALKYLATION OF QUINIZARIN

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ABSTRACT

Quinizarin a precursor to anthracyclines was subsequently alkylated with α, β-unsaturated aldehydes - crotonaldehyde, acrolein and ethyl acrylate using piperidinium acetate as a catalyst and ethanol as solvent. Quinizarin was synthesized using phthalic anhydride and parachlorophenol with concentrated sulphuric acid as solvent and catalyst in synergism with boric acid at 260^0C to give a yield of 36.3%, then reduced to leucoquinizarin using Sn in concentrated hydrochloric acid with glacial acetic acid as solvent and refluxed for five hours to give a yield of 35.6%. The alkylating reagent crotonaldehyde was synthesized by aldol condensation of acetaldehyde with concentrated sulphuric acid as catalyst at a yield of 27.1% while acrolein was synthesized by the dehydration of glycerol using potassium bicarbonate as catalyst at a yield of 94.8%. Leucoquinizarin was alkylated with crotonaldehyde, acrolein and ethyl acrylate using piperidinium acetate as a catalyst in ethanol. The alkylation with crotonaldehyde and ethyl acetate was done by reflux for three and five hours respectively and resulted in a 1, 4 addition and a subsequent aldol annelation reaction accompanied by a 1,3 sigmatropic shift to give a pentacyclic ring at a yield of 42.1% and 61% respectively. Acrolein gave a polymeric product.

Keywords: Quinizarin, leucoquinizarin, anthracyclines, crotonaldehyde, acrolein, ethyl acetate, 5,12-naphthacenedione, 7-Hydroxytrihydro-5,11-naphthacenedione, 9-Methyltriyhdro-5,11-naphthacenedione.

INTRODUCTION.

Anthracycline antibiotics are a class of drugs used in cancer chemotherapy derived from *“Streptomyces bacterium”, “Streptomyces peucetius”.*[1] These compounds are used to treat many cancers including leukaemia, lymphomas, breast, stomach, uterine, ovarian and lung cancers. The anthracyclines are among effective anticancer treatments ever developed and are useful against more types of cancer than any other class of chemotherapeutic agents. [2,3,4]

Anthracycline drugs include, dauorubicin, doxorubicin, epirubicin, idiarubicin, as represented in fig. 1.

Anthracyclines are among the most commonly used anti-cancer chemotherapeutic agents [5]. Doxorubicin and its derivative epirubicin are used in the treatment of breast cancer, childhood solid tumours, soft tissue sarcomas and its derivative idiarubicin, is used in the treatment of multiple myeloma, non-Hodgkin’s lymphomas and breast cancer. Doxorubicin exhibited the same kind of marked inhibitory effect on tumour growth as daunorubicin and was generally more potent. The clinical limitation, however, remains, as in the case of daunorubicin, the risk of cardiotoxicity that ranges from the insidious cardiomyophathy to irreversible heart failure. [6]. Other anthracycline derivatives include nemorbicin used for the treatment of heptocellular carcinoma.

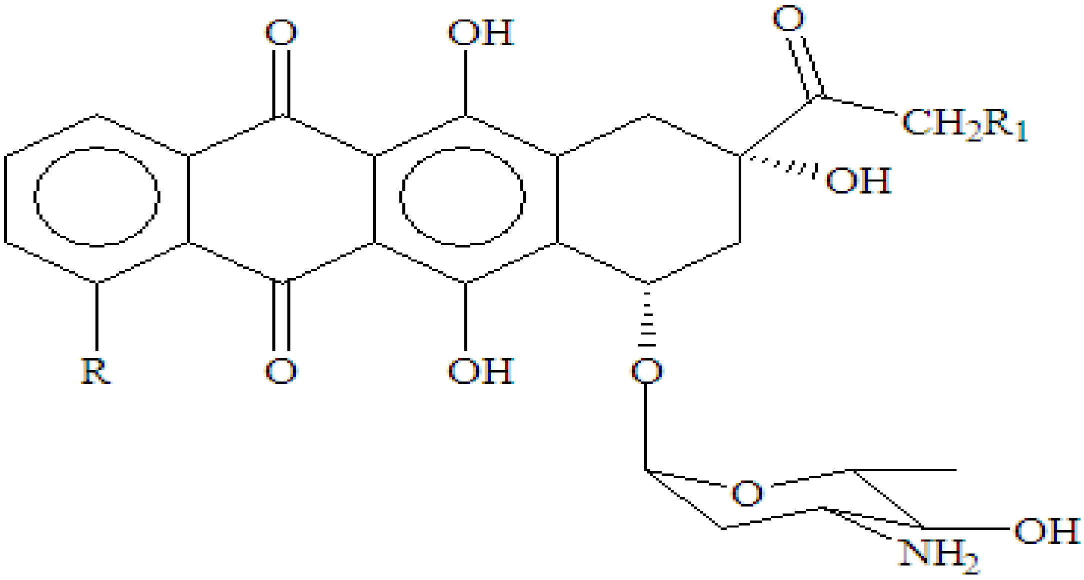


Figure 1: Structure of some Anthracycline

When: **1**. R=H, R_1= OH its Idriamycin

2. R = OMe, R_1= OH its Epirubicin

3. R = OMe, R_1 = H its Carminomycin or daunorubicin

4. R =H, R_1 = H its Idiarubicin.

Anthracyclines show four mechanisms of action:

1. Inhibition of DNA and RNA synthesis by interacting between base pairs of the DNA/RNA strand, thus preventing the replication of rapidly growing cancer cells. [7]
2. Inhibition of Tropoisomerase II enzyme preventing the relaxing of super coiled DNA and thus blocking DNA transcription and replication.
3. Iron-mediated generation of free radicals that damage the DNA, proteins and cell membranes [8]
4. Induction of histon eviction from chromatin that deregulates DNA damage response, epigenime and transcriptome. [9].

In recent times, the cardiotoxicity of doxorubicin has been found to be ameliorated by dexrazoxane and topoisomerase II interaction as pre-requisite in effective protection [10-15].

Owing to the cardiotoxicity of anthracyclines, there is interest in the synthesis of analogues with improved chemotherapeutic properties. A strategy for the synthesis of the tetracycline aglycone (anthracycline without the sugar moiety) starts with the 1,4-dihydroxy 9.10 anthraquinones (quinizarin), **5**. Which has the B, C, D rings of anthracycline in place leaving construction of the A alicyclic ring.

Previously the alkylation reactions used to introduce the alicyclic ring were carried out via Marschalk reaction [16]. This is a base –catalysed cross aldol under nitrogen at 50^0C with subsequent air exposure gave good conversions but the products were contaminated with an insoluble polymer. The low yield was a consequence of back oxidation of **6** to **5,** polymerization of the alkenes and the competitive addition of the base to alkenes

Unuigboje, A. [18] alkylated leucoquinizarin with furfural using piperidinium acetate as the base-catalyst, refluxing with propanol to yield the furfural derivative.

These types of reactions show promise in the preparation of a variety of substituted quinizarin derivatives which could prove to be valuable anthracycline precursor

condensation reaction, in which quinizarin is reduced to leucoquinizarin, **6,** with sodium dithionite which subsequently reacts with a carbonyl compound to give; after oxidation the 2-alkyl adduct**.**

Giles Arsenault, Douglas, A and Peter Huffen-Czupski et al [17] in a new approach to the synthesis of 2-alkylquinizarins showed the reaction of **6** with excess ethyl acrylate in ethanol

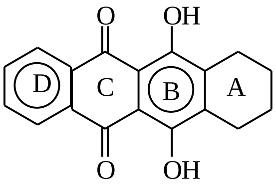


Fig. 2. The A - D Rings of Anthracyclines

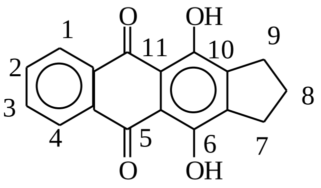


Fig. 3. Numbering of Trihydro-5,11-naphtnacenedione Ring System

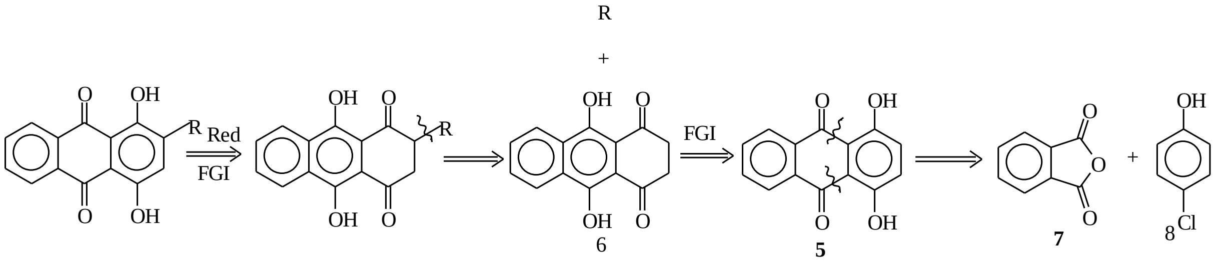


Fig. 4. Retrosynthetic Analysis of Quinizarin Alkylate.

Note: p-Chlorophenol is synthetic equivalent of hydroquinone

The formation of the A ring of the anthracyclines is dependent on the addition of alkyl substituents to the C-2 and C-3 positions of leucoquinizarin, **6,** which is the incipient B ring of anthracycline.

The retrosynthetic pathway is suggestive of the synthesis of quinizarin **5,** which was achieved by reacting readily available phthalic anhydride, **7,** with parachlorophenol, **8** and subsequent elaboration.

MATERIALS AND METHODS.

IR was done neat with Bruker alpha FTIR spectrometer.

^{1}H NMR and ^{13}C NMR were done with 400 MHz Bruker using $CDCl_3$ and DMSO as solvents based on the solubility of the product.

Melting point was taken in ℃ uncorrected

Preparation of Parachlorophenol, 8.

In a 1-litre round bottom flask was placed 500 ml (0.235 mol) of commercial household bleach solution (hypo) which contains 3.5% w/v of sodium hypochlorite. The flask was kept in a pail of ice and stirred rapidly till the temperature dropped below 10℃. With lights turned off, a solution of tert butyl alcohol (37 ml, 0.39 mol) and glacial acetic acid, was added in a single portion to the rapidly stirred bleach solution and stirring continued for about 3 minutes. The reaction mixture was poured into 1-litre separatory funnel, the lower aqueous layer was discarded and the top oily yellow organic layer was collected, first washed with 50 ml portion of 10% aqueous Na_2CO_3 and then with 50 ml of water. The product was dried over anhydrous $CaCl_2$ and filtered. The yield of the tert-butyl hypochorite, 99-100% pure was 24.97 g, (0.23 mol), 97.8 % yield.

In a round-bottom flask 27.89 g (0.295 mol) of phenol and 50 ml of 95% ethanol were placed. The phenol was dissolved in the ethanol and then 33 ml (0.295 mol) of tert-butyl hypochlorite was added in portions of 8 ml, at the beginning of the reaction and then 5 ml every 10 minutes over a period of 1 hour with continuous stirring. The reaction mixture was maintained at a temperature of 15℃ by immersing the reaction flask in a pail of chilled water. [19], followed by product recovery (24.7 g, 77.1%) through distillation at 210-225 ^{0}C.

IR (neat) ν cm^{-1}: 3316, 1590, 1401, 1217.

^{1}H NMR ($CDCl_3$) δ: 6.79-6.81(q of an A_2B_2, J= 3 Hz, 2H), 7.1-7.2 (q of an A_2B_2, J= 3 Hz, 2H)

^{13}C NMR ($CDCl_3$) δ: 115, 125.9 and 153.7

Reduction of Quinizarin to Leucoquinizarin, 6.

In a round-bottom flask were placed 20g (0.083 mol) of quinizarin, 16 g (0.013 mol) of mossy tin and 16 ml of concentrated HCl which were refluxed for 5 hours in 20 ml glacial acetic acid. During the heating period, the concentrated HCl was added in portions of 4 ml at the beginning of the reaction and heated for 1 hour followed by another 8 ml which were 4 ml portions each after every 1.5 hours, and the remaining 4 ml was added towards the end of the reaction.

The reaction mixture was then poured into 20 ml of ice-water slush and filtered by suction, while the crystals which also contained unreacted tin were washed with water to dissolve inorganic salts and acetic acid. The filtrate was extracted with 2 ×10 ml of dichloromethane and washed with 1×10 ml of aqueous Na_2CO_3 which was saturated with NaCl.

After drying over anhydrous $MgSO_4$, the dichloromethane was left overnight to evaporate. The resulting crystals were combined with original crystals and recrystallized with acetic acid, dried and weighed to give 7.2 g of leucoquinizarin. a yield of 35.6%. [18]

Melting point was 151-153℃.
^{1}H NMR (DMSO) δ: 13.66 (s, 2H, −OH), 8.23-8.3 (q of an A_2B_2, J= 3 Hz, 2H), 7.93-7.95 (q of an A_2B_2, J= 3 Hz, 2H), 3.09 (s – 4H).
^{13}C (DMSO) δ:202.96, 186.90, 157.11,153.95, 135.47, 135.15, 131.33, 129.74, 128.78, 127.03, 124,54, 112.89, 108.22

Synthesis of Crotonaldehyde, 9.

In a 250 ml flask was placed 100 ml of acetaldehyde and 60ml of conc sulphuric acid added in portions of 15 ml every 5 minutes over a period of one hour. The reaction was quenched with water (100 ml) and the aqueous layer was separated from the organic layer with a separatory funnel. $NaHCO_3$ (5 g) was added to the product to remove any excess sulphuric acid, then washed with 20 ml of brine water and product collected and dried over anhydrous magnesium sulphate, decanted and then distilled. The distillate was collected between 100-106℃, 20 ml (15.7 g, 27.1%) of crotonaldehyde [22]

^{1}H NMR ($CDCl_3$) δ: 9.43-9.45 (d –CHO), 6.1 -6.8 (m- 1H), 1.5 (d -3H)

Preparation of Acrolein, 10.

A 1-litre round bottom flask B and a 500ml round bottom flask C were immersed to about two-thirds their heighs in oil baths heated by Merck burners. Each was provided with a thermometer reaching to the bottom of the flasks.

Flask B was fitted with a two holed cork stopper, one of the holes was fitted with a 500 ml separatory funnel A and in the other hole a delivery tube C of 12 mm diameter. The tubes did not exceed 3 mm below the stopper connected with a separatory funnel, the delivery tube from B and the delivery tube E of 12 mm tubing leading to flask G. G was a 250 ml round bottomed flask immersed to two-thirds of its height in an oil bath heated by a Bunsen burner and also provided with two-holed cork stopper connected with tube E and delivery tube H. In the receiving flask I was put a pinch of hydroquinone before the final assembling of the apparatus. The flasks were charged as follows:

A weight of 200 g of freshly fused and finely powdered $KHSO_4$, 40 g of K_2SO_4, 60 g/46.8 ml of dry glycerol were charged to flasks B and D. The oil bath under B and D were heated to about 190-200℃ and under F to 110-120℃. When the reaction was well started 60 g (46.8 ml) of glycerol were placed in each separatory funnel and added dropwise during heating. After the first violent reaction abated (in about an hour) the baths of B and D were raised to about 215℃ and 230℃ and maintained there until no volatile product comes over (total time $4\frac{1}{2}$ hours). About 90 ml of pungent acrolein was recovered to give a yield of 94.8%. [20,21,23]

IR ν cm^{-1}: 3363, 2800, 1680.
^{1}H NMR (CDCL3), δ: 9.4 (s, CHO, 1H), 7.0 (t, vinylic, 1H), 7.2 (d, vinylic, 2H).
^{13}C (Neat) δ: 195, 58, 54.

Alkylation of Quinizarin with Crotonaldehyde: 9-Methyltrihydro-5,11-naphthacenedione, 11.

In a round bottom flask 20 ml of ethanol, 1g of leucoquinizarin (0.0041 mol), 0.003 piperidinium acetate (made from 0.19 ml of acetic acid and 0.34 ml of piperidine) and 0.012 mol (1ml) of crotonaldehyde were added followed by refluxing for 3 hours, after which the reaction mixture was allowed to cool to room temperature. The resulting crystals were collected by suction filtration followed by washing with aqueous HCl (5%) and water sequentially.

The filtrate was diluted with water and extracted with 2 × 50 ml of dichloromethane followed by washing with 2 x 50 ml of 5% NaOHaq then water. After drying the organic extract over anhydrous magnesium sulphate, the solvent was left to vaporise overnight, while the resulting crystals were combined with the initial and recrystallized from ethanol-acetone to give 0.65 g of orange crystals of the product which melted at 118-120℃.

^{1}H NMR δ: (DMSO) 13.65 (2H, −OH), 8.32-8.30 (q of an A_2B_2, J = 3 Hƶ, 2H), 7.87 -7.85 (q of an A_2B_2, J = 3 Hƶ, 2H), 2.4 (m, -3H), 2.09 (d, -4H. -CH_3- +).
^{13}NMR (DMSO) δ: 207.06, 202.95, 153.95, 131.33, 128.78, 124.52, `08.22, 36.02, 32.38,32.17

Alkylation of Qunizarin with Acrolein, 12.

In a round bottom flask 20 ml of ethanol, 1g of leucoquinizarin (0.0041 mol), 0.003mol piperidinium acetate (made from 0.19 ml of acetic acid and 0.34 ml of piperidine) and 0.012 mol

(0.6ml) of acrolein were placed. The flask was covered with a black cloth and was mechanically stirred at intervals for 24 hours at room temperature. The reaction was monitored using thin-layer chromatography. After 24 hours, the resulting crystals were collected by suction filtration followed by washing with aqueous HCl (5%) and water sequentially.

The filtrate was diluted with water and extracted with 2 × 50 ml of dichloromethane followed by washing with 5% NaOHaq 2 × 50 ml and then water. After drying the organic extract over anhydrous magnesium sulphate, the solvent was left to vaporise overnight, while the resulting crystals were combined with the initial and recrystallized from ethanol-acetone to give 0.1 g of dark red crystals which melted at 105-109℃.

Alkylation of Qunizarin with Ethyl Acrylate: 7-Hydroxytrihydro-5,11-naphthacenedione, 13.

In a 500 ml round bottom flask 20 ml of ethanol, 1g of leucoquinizarin (0.0041 mol), 0.003 mol.piperidinium acetate (made from 0.19 ml of acetic acid and 0.34 ml of piperidine) and 0.012 mol (1ml) of ethyl acrylate were added followed by refluxing for 5 hours, after which the reaction mixture was allowed to cool to room temperature. The resulting crystals were collected by suction filtration followed by washing with aqueous HCl (5%) and water sequentially.

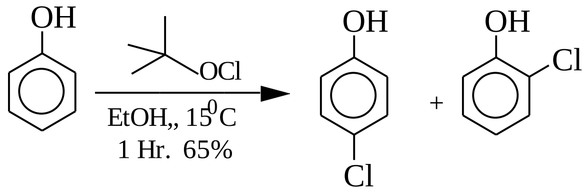
The filtrate was diluted with water and extracted with 2 × 50 ml of benzene followed by washing with 5% NaOHaq 2 × 50 ml and then water. After drying the organic extract over anhydrous magnesium sulphate, the solvent was left to vaporise overnight, while the resulting crystals were combined with the initial and recrystallized from ethanol-acetone to give 0.65 g of orange crystals which melted at 126-129℃.

^{1}H NMR δ: 13.65 (2H, -OH)), 8.31-8.29 (q of an A_2B_2, J = 3Hz, 2H), 7.98-7.96 (q of an A_2B_2, J = 3Hz, 2H) 5.01 (broad, 1H, -OH), 3.03 (t, 1H, vicinal to -OH), 2.4, m, 2H benzylic), 1.09 (multiplet, $-CH_2-$, 2H)

RESULTS AND DISCUSSIONS.

In the chlorination of phenol, the probability of polychlorination is low as the chloro group is deactivating. Ethanol has been reported by William [19] as one of the solvents that favors para substitution in the tert-butyl hypochlorite chlorination of phenol at an ortho-para ratio of 0.46. The yield of parachlorophenol was 65%. In ethanol there is solvent crowding of the hydroxyl group of the phenol due to hydrogen bonding which hinders the bulky tert-butyl hypochlorite from readily accessing the ortho-positions.

The product mixture was separated by simple distillation, since ortho-chlorophenol boils at 174.9℃ while para-chlorophenol boils at 220℃,



The IR spectrum shows the characteristic broad peak of hydroxyl group at 3316 cm^{-1}and the ^{1}H NMR shows 2 peaks which appear as doublets representing the 2 sets of equivalent protons on the benzene ring, The singlet which was to represent the hydroxyl group was not observed. In the ^{13}C NMR four peaks were seen, which represents the four non-equivalent C atoms of para-chlorophenol. The peak at δ 115.8 represents C-2 and C-6, that at δ 153.7 represents C-3 and C-5, while δ 125.9 represents the C- OH and δ 125.7 represents C-Cl.

The reaction between phthalic anhydride and parachlorophenol to produce quinizarin occurred in two steps – electrophilic and nucleophilic aromatic substitutions. In the electrophilic aromatic substitution, the sulphuric acid and boric acid both function as a catalyst. Boric acid and sulphuric acid increase the electrophilicity of the carbonyl carbons of phthalic anhydride by coordinating to the carbonyl oxygen. The para-chlorophenol has two ortho-para directors.

The carbonyl carbons are sequentially attacked by *p*-chlorophenol, followed by re-aromatization as in fig. 5.to give the chloro-quinizarin, 4-chloro-1-hydroxy-9,10-anthraquinone which is then converted to quinizarin via nucleophilic aromatic substitution by water. This conversion is facilitated by the presence of the carbonyl electron withdrawing group ortho to the chloride leaving group which stabilizes the negative charge formed by resonance. Water attacks the carbon bearing the chloride nucleophilically and the resonating electron pair was stabilized by the electron withdrawing carbonyl ortho to the chloride. The oxo anion formed accepts a proton from the hydroxonium ion through a 6-centre transition state, the chloride ion being a better leaving group than the resulting hydroxyl group, leaves on re-aromatization.

After quenching of the reaction, the boiling water in which the product was suspended, dissolved excess phthalic anhydride, leaving behind the quinizarin crystals.

Quinizarin was suspended in water and KOH was added for conversion to its soluble purple phenoxide ion. Care was taken to add KOH solution in drops until the red colour of the mixture just changed towards purple, to prevent a large excess of the base, which leads to formation of purpurin an insoluble dimer which diminishes the yield of the product..

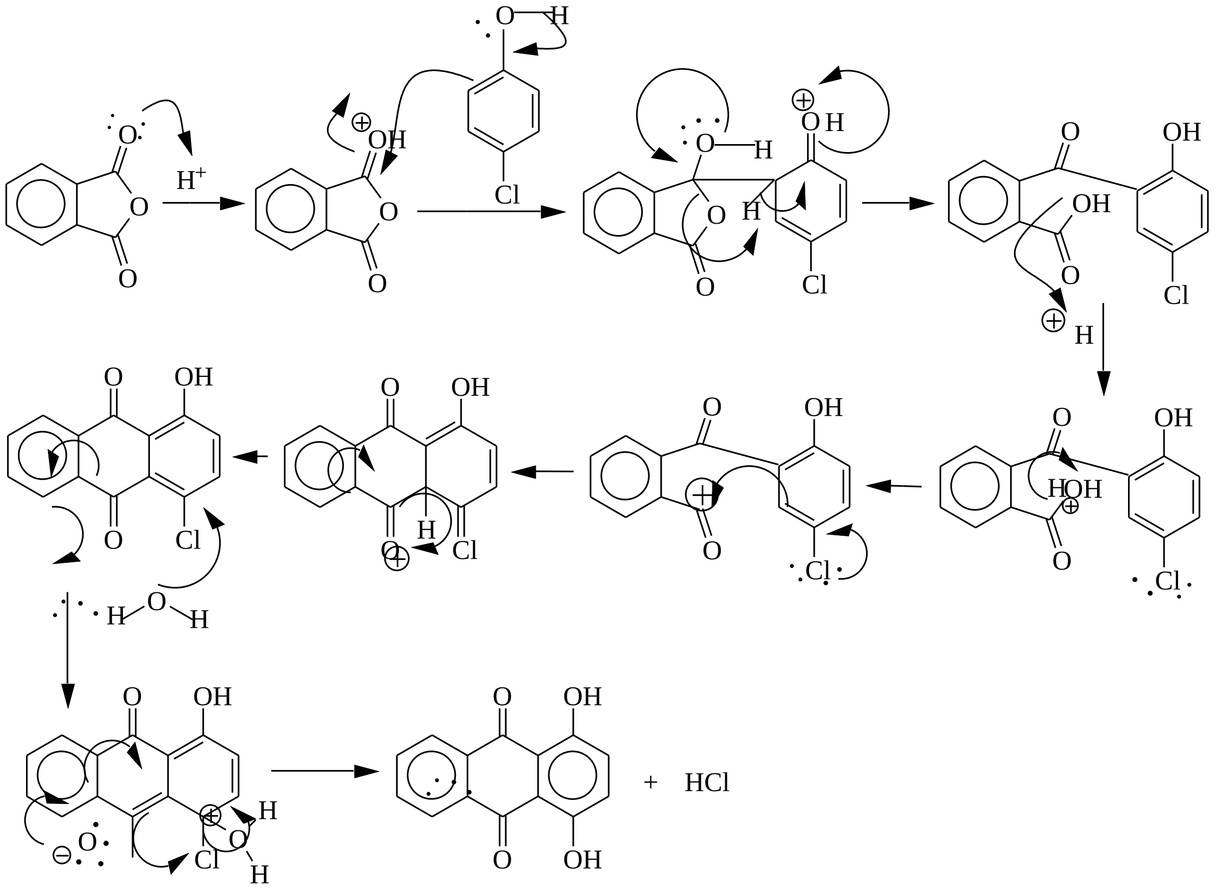


Fig. 5. Reaction Mechanism of Quinizarin Formation

Reduction of quinizarin to leucoquinizarin was effected with mossy Sn in conc. HCl. The ^{1}H NMR of quinizarin shows a singlet peak for the aromatic ring bearing the OH groups at δ 7.435 ppm while in leucoquinizarin, this peak appeared at δ 3.09 as singlet which is indicative of the alicyclic protons α to the carbonyl carbons.

Crotonaldehyde was prepared by the aldol condensation of acetaldehyde. The reaction was performed at room temperature, with conc. sulphuric acid added in portions to prevent the polymerization of the product which was washed with sodium bicarbonate to scavenge any protons left. Acetaldol (3-hydroxy butanal) which might have been formed in the course of the reaction boils at 83℃ and decomposes at 85℃, and so was eliminated during distillation of crotonaldehyde.at 102℃.

The yield was as low as 27.1% because acetaldehyde boils at 20℃ which is below room temperature, suggestive, of loss of considerable amount of reactant before the condensation could occur.

The preparation of acrolein from glycerol is a reversible dehydration reaction whose mechanism of formation is shown in Fig. 6. One of the conditions that favours the forward reaction is the removal of the product-water. Freshly fused $KHSO_4$ and K_2SO_4 were used because $KHSO_4$ being deliquescent will absorb water formed, thereby driving the reaction towards product. $KHSO_4$ also acts as a weak Bronsted-Lowry acid which catalyzes the reaction without undue polymerization of the vinylogue. To prevent the rapid polymerization of acrolein, the flask was covered with a black cloth, to protect it from light. Hydroquinone was also added to the product-receiving flask to prevents air oxidation. IR showed a peak at 1670 cm^{-1}, indicative of a conjugated carbonyl. PMR exhibited peaks at δ 5.4 ppm and a definitive singlet aldehyde peak at δ 9.5 ppm

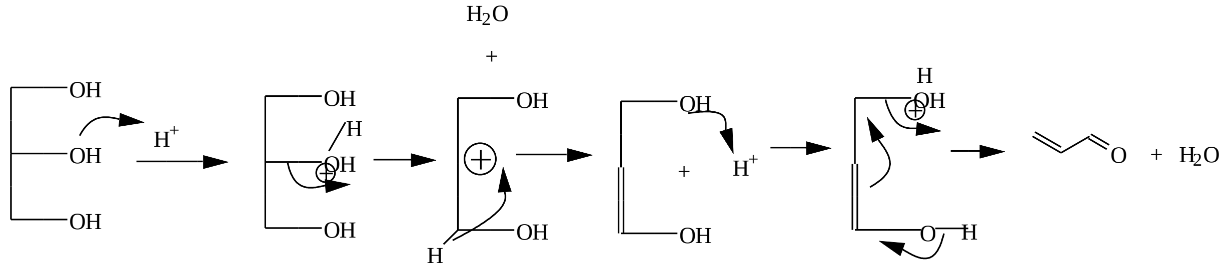


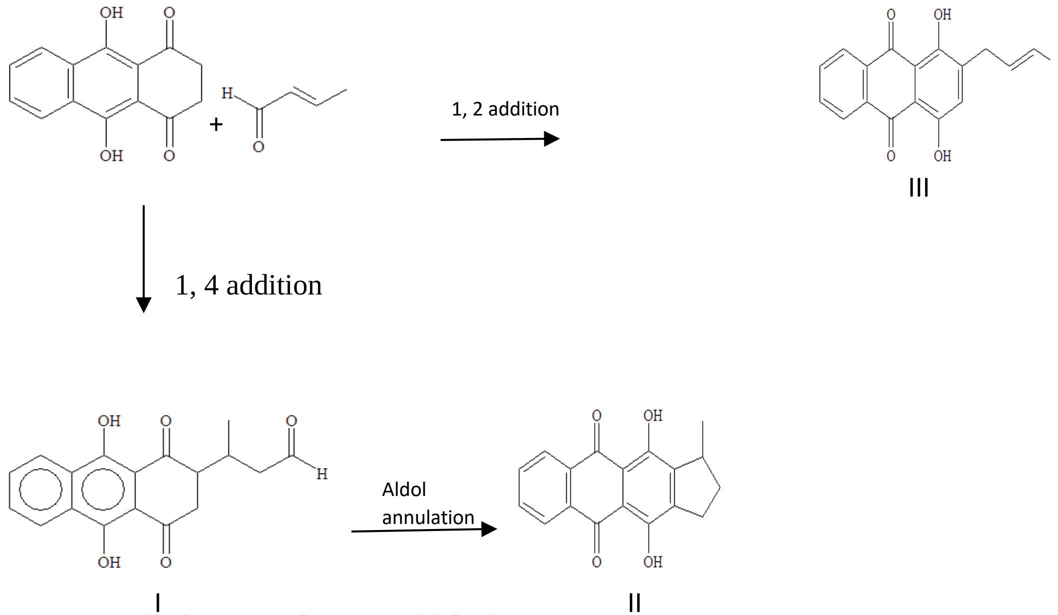
Fig. 6. Reaction Mechanism of Acrolein Formation

The alkylation of quinizarin was carried out using piperidinium acetate which harbours both acid and base catalysts. Piperidinium acetate is made up of an acid (piperidinium ion) and a base (carboxylate ion). The piperidinium ion protonates the carbonyl oxygen making the carbonyl carbon more electrophilic, the carboxylate ion, then abstracts a proton from the carbon α to the carbonyl to give an enolate ion which subsequently reacts with the α, β unsaturated carbonyl. Both piperidine and carboxylic acid are regenerated.

In a conjugated carbonyl system, there are two electrophilic sites which can react with potential nucleophiles: directly at the carbonyl carbon to give a 1, 2 addition, or at the end of the conjugated system to give a 1, 4 addition

Attack at the carbonyl carbon, is usually faster but produces the less stable kinetic product. In conjugate addition, the more resonance stable thermodynamic product results [24].

Typically, kinetic control, involves lower temperatures and shorter reaction times which ensures the fastest reactions occur, while thermodynamic control involves higher temperatures and longer reaction times.



1,2 vs 1,4-Alkylation With Crotonaldehyde

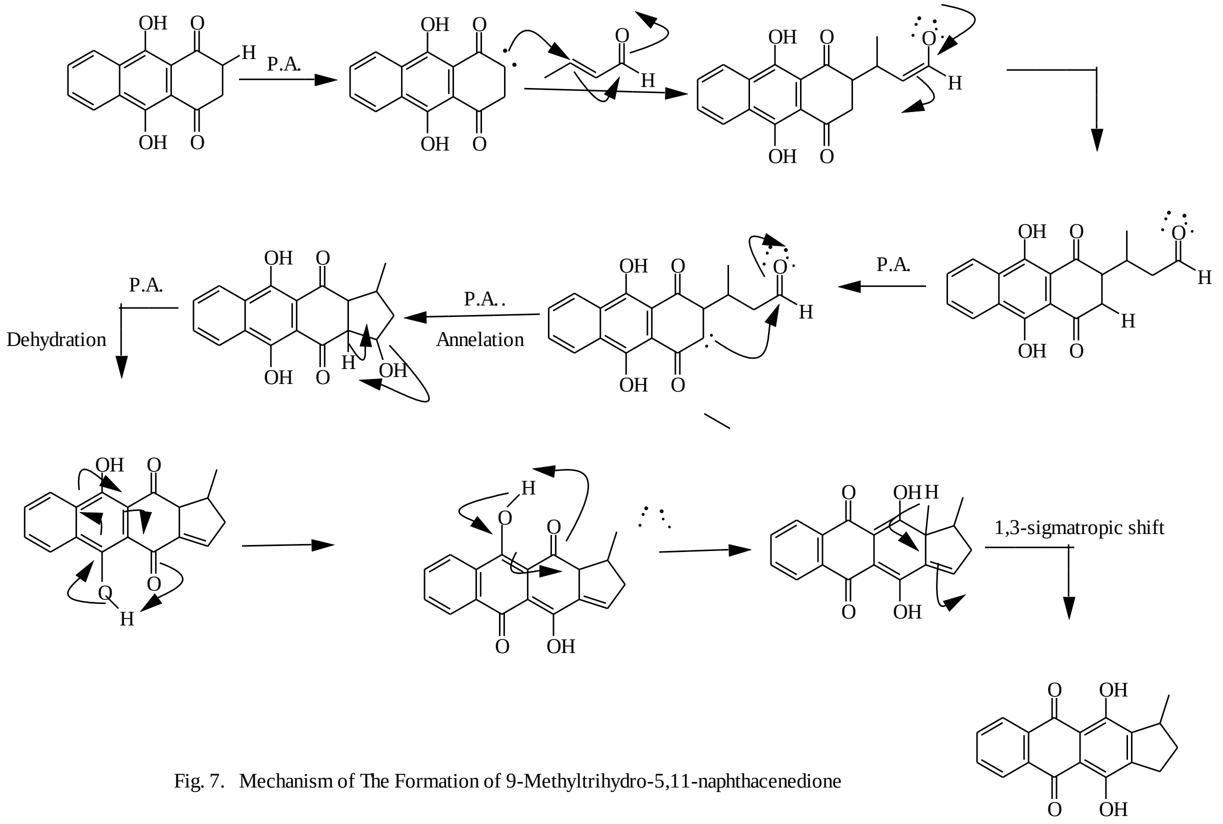


Fig. 7. Mechanism of The Formation of 9-Methyltrihydro-5,11-naphthacenedione

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Another factor that favours 1,4 addition is the nature of the nucleophile; the attraction between nucleophiles and electrophiles is governed by two related interactions: electrostatic attractions between positive and negative charges and orbital overlap between the HOMO of the nucleophile and the LUMO of the electrophile. Nucleophiles containing small electronegative atoms (such as O or Cl) tend to react under predominantly electrostatic control while large nucleophiles containing larger atoms (including S of thiols, P) are predominantly subject to control by orbital overlap. Hence, the term, hard and soft; nucleophiles describe the small and large atoms respectively.

Electrophiles too can be classified as hard or soft, the carbonyl carbon of an α, β unsaturated carbonyl is said to be hard because it has a high partial positive charge, while the β carbon is a softer electrophile which will react by orbital overlap between the HOMO of the nucleophile and the LUMO of the electrophile. [25,26].

In the reaction of leucoquinizarin and crotonaldehyde, the product of the 1, 4 addition should show a peak at 9 ppm for the aldehydic proton in the ^{1}H NMR; but this peak was absent, rather a doublet at δ 2.097 ppm which integrated as 4H, representing the methyl group attached to position 9, in product **11** appears. At δ 2.5 ppm, a multiplet that integrates as 3 protons appears representing the benzylic protons. The methylene protons at position 8 (located on the pentacyclic ring system) were embedded in the methyl signal.

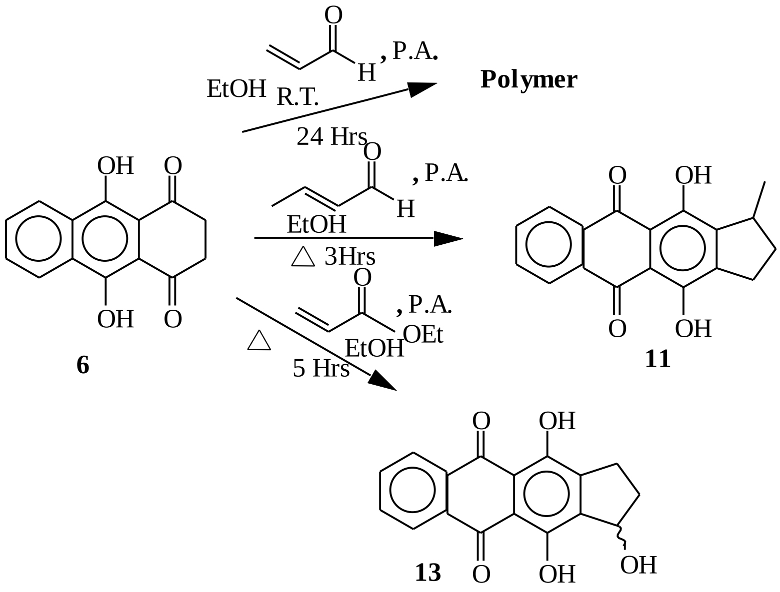

Fig. 8. Alkylation Reactions

This suggests that the reaction did not stop at 1, 4 addition but proceeded to aldol annelation. Laurence M. et al [22] with the alkylation of 5-hydroxyquinizarin showed that the alkylation of quinizarin is regioselective in favour of C-2; they examined the Marschalk condensation of propionaldehyde with leucoquinizarin and obtained the 2-propyl derivative, but Marschalk et al [16], showed that with formaldehyde the C-2 and C-3 positions were both alkylated, they further showed that subsequent to the alkylation of C-2, alkylation occurs at the C-3 position, with formation of 2,3 dimethyl quinizarin.[27]

Let's analyse the possibility of a 1,2- addition using Molecular Orbital Theory. Electrons move from the HOMO of the nucleophile to the LUMO of the unsaturated carbonyl. In the LUMO of the unsaturated carbonyl the largest coefficient is on the β carbon of the α, β-unsaturated system, and it is therefore the β carbon that nucleophiles attack to give a stable thermodynamic product [26]. The second largest coefficient is on the C=O carbon atom and it will not be surprising if the nucleophile attacks there as well. In the reaction of ethyl acrylate with leucoquinizarin, the 1, 2- addition product should show peaks for the C=C protons in conjugation with the carbonyl which should appear as a doublet and a triplet somewhere between δ 5-7 ppm, but this was evidently absent.

Since the possibility of the 1, 2- addition has been ruled out, we are left with the 1, 4- addition which is thermodynamically favoured since it is

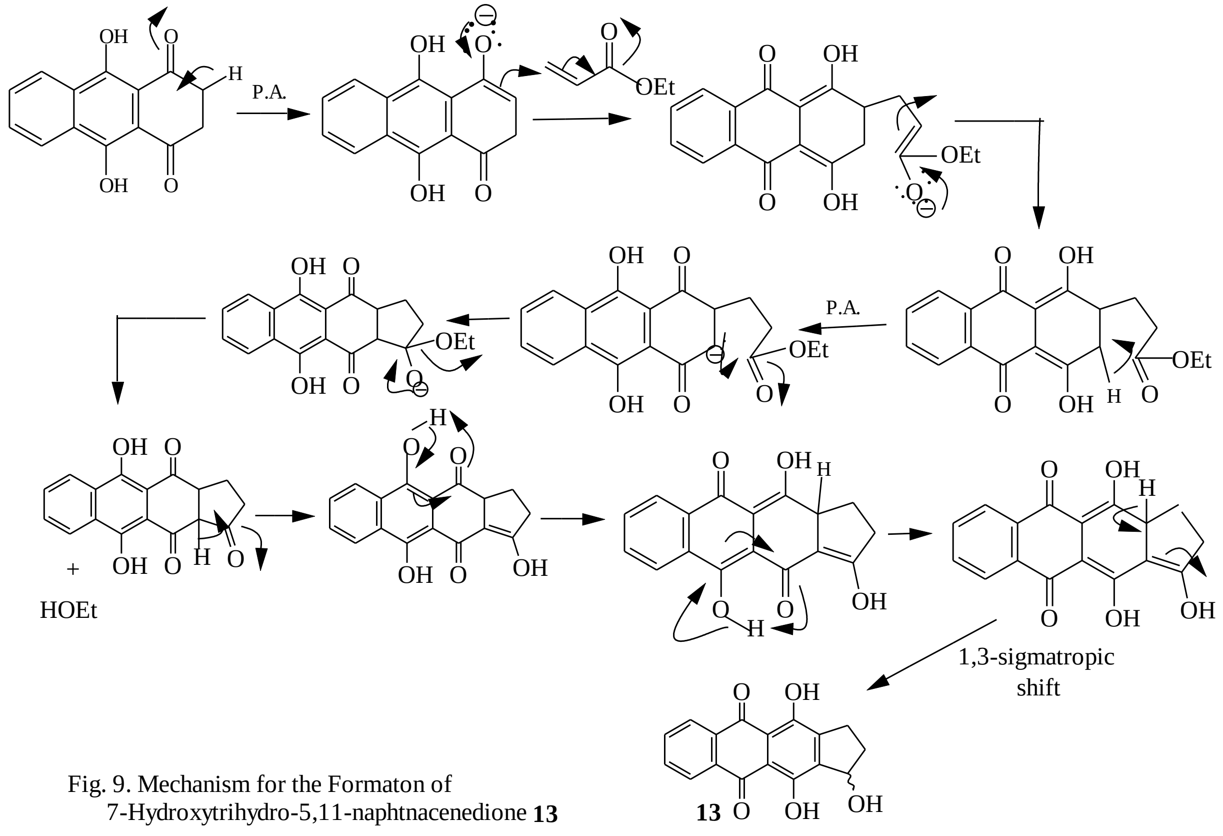

Fig. 9. Mechanism for the Formaton of 7-Hydroxytrihydro-5,11-naphtnacenedione **13**

more stable. The conditions of the reaction - high temperature and long reaction time - also favour the 1, 4- addition product [26].

Analysing the ^{1}H NMR spectrum of the product, the characteristic triplet and quartet of the ethyl ester of a 1,2-adduct was absent. The spectrum showed a broad spectrum at δ 5 ppm which integrated as 1H representing the -OH peak. A multiplet at 3.03 integrated as 1, representing the proton vicinal to -OH. At 2.04 ppm appeared a multiplet that integrated as 2 H representing the benzylic protons and the peak at 1.09 which integrated as 2H represents the methylene protons of the pentacyclic ring. (see fig. 9, Mechanism of Formation of 7-Hydroxytrihydro-5,11-naphthacenedone, **13)**. Quinizarin aromatic peaks for the rings bearing the -OH groups were absent; so also was the leucoquinizarin alicyclic hydrogens alpha to the carbonyls. The peaks for the aromatic protons in leucoquinizarin which appeared at δ 8.33 - 8.31 and 7.73 - 7.70 ppm gave way to the peaks which appeared at δ 8.31-8.29 and 7.98-7.96 ppm.

This leaves us with the Clasein annelation product. The 1, 4 - addition actually took place, but did not end there, an intramolecular Claisen condensation occured. The cyclopentene ring so formed, being a five membered ring is quite stable since it has a bond angle of 108^0, which is very close to the tetrahedral 109.5^0. The intramolecular reaction which is favoured by virtue of unimolecular over bimolecularity took place, leading to annelation to form the stable 5-membered ring. After formation of the enol, there is a 1,3-sigmatropic shift which aromatizes the phenolic ring and places H at the C that bears the OH (see fig. 9.).

The sequence of reactions is:

i. 1,4-vinylogous addition reaction
ii. Claisen condensation (intramolecular)
iii. Enolization
iv. 1,3-sigmatropic shift
v. Aromatization.

CONCLUSION.

The conversion of quinizarin to leucoquinizarin provides a fast entry for alkylation by vinylogues which undergo 1,4-addition and subsequent annelation for formation of the A ring of anthracyclines.

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