1976

Attempted Synthesis Of Bostrycoidin

Herbert David Sheppard

ATTEMPTED SYNTHESIS OF BOSTRYCOIDIN

by

David Scott Sheppard

Department of Chemistry

Submitted in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

Faculty of Graduate Studies

The University of Western Ontario

London, Ontario

July 1975

ABSTRACT

Bostrycoidin is a dark red metabolite of both Fusarium bostrycoides and Fusarium solani D2 purple. It is a β azanthraquinone which is structurally related to javanicin and fusarubin. During an attempt to extend the pathway developed for the synthesis of javanicin, it was shown that chromic acid oxidized 3-methyl-5,7,8-trimethoxy-1-naphthol in higher yield than lead tetra-acetate. N-bromosuccinimide cleaved the para methoxyl groups of 3-methyl-1,4,5,7,8-pentamethoxynaphthalene in preference to bromination of the aromatic methyl. A new scheme was devised which introduced the critical carbon via a Stobbe condensation on 2,3,5 trimethoxybenzaldehyde followed by ring closure with acetic anhydride. A preliminary survey of possible reaction sequences for the construction of the heterocyclic ring was carried out starting with anisaldehyde. The acetonyl side chain was introduced to the trimethoxyl series via a Claisen rearrangement of ethyl 1-allyloxy-5,7,8-trimethoxy-3-naphthoate followed by oxidation first with N-bromosuccinimide and then with Jones' reagent. Reduction of the bromoketone resulted in cyclization of the side chain. Oxidative ring opening was carried out with several oxidizing agents to give the 5,8-dimethyl ether of the ester analogue of javanicin. Extension of this procedure to the 5,8-dimethyl ether of

fusarubin resulted in the loss of the C-11 carbon and subsequent cyclization of the side chain to give 4,9-diketo-2-methyl-5,6,8-trimethoxynaphtho (2,3-b) furan.

ACKNOWLEDGEMENTS

The author would like to express his appreciation to Dr. W. C. Howell for his supervision during the course of this work.

The stimulating discussions, the chemical advice and the encouragement provided by Dr. Paul de Mayo, particularly during the later stages of this work, are sincerely appreciated.

The contributions of Dr. J. F. King towards the preparation of the final draft of the manuscript are recognized.

The advice and assistance of other members of the Faculty and fellow graduate students is appreciated.

The support of the National Research Council of Canada in the form of studentships (1963-1966) is gratefully acknowledged.

Finally the author wishes to thank his wife Carolyn and his father Scott for their continuing encouragement and help which enabled this thesis to be completed.

D. D. Sheppard

CONTENTS

LIST OF FIGURES

Natural Occurrence of Quinones

The study of natural products has attracted the interest of scientists of varied disciplines. For the organic chemist, natural products have provided a challenge, not only because of the diversity of structures encountered, but also as the means for investigation of new reactions and reaction mechanisms.

The quinone pigments are the largest class of naturally occurring coloured substances, although, they make relatively little contribution to natural colouring. Many are found in the bark or underground portions of higher plants, while others are either present in the colourless quinol form, or are masked by other pigments.

Micro-organisms, particularly lower fungi, have provided a rich source of quinones, but they can be found in some higher fungi and few lichens. In the animal kingdom, quinones appear to be restricted to certain insects and marine animals. The shells of a variety of sea urchins are brightly coloured by calcium salts of substituted quinones.

There has been much speculation about the role played by quinones in the chemistry of living organisms. It is clear they behave in more than one way, but with the exception of a few isolated cases, their function is not completely understood. One chemical property common to all natural quinones is their ease of reduction and re-oxidation. The simultaneous occurrence of a quinone and the corresponding quinol in certain moulds suggests

intimate involvement in the oxidation-reduction processes of the organism. Quinones have been shown to affect respiratory systems, but no generalizations have been made.

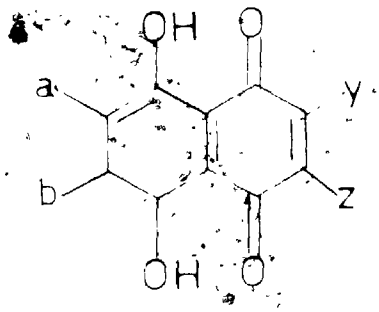
A second characteristic feature of quinones is their ability to undergo addition reactions. This is less important, since over half of the naturally occurring quinones do not possess the necessary free quinonoid position. Biological systems containing amine or thiol groups will usually react with those quinones capable of addition reactions. This is exemplified by the inhibition of enzymes by quinones.

Many quinones exhibit antibiotic activity. This is important in the protection of the organism that produces them, and is potentially beneficial to higher animals including man himself. This biological activity has provided the necessary incentive for structural determination, and the synthesis of many quinones.

Synthesis is an especially important aspect of quinone chemistry, because of the difficulties in obtaining enough pure compound from natural sources for clinical studies and commercial production. Synthetic routes have the added advantage of providing compounds which are not available from nature.

Historical Synthesis of Naphthazarins

Naphthazarins are a special class of naphthoquinones which have oxygen functions in the 5 and 8 positions. The parent compound, naphthazarin, is then 5,8-dihydroxy-

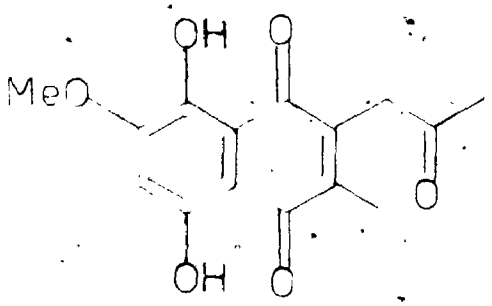


17

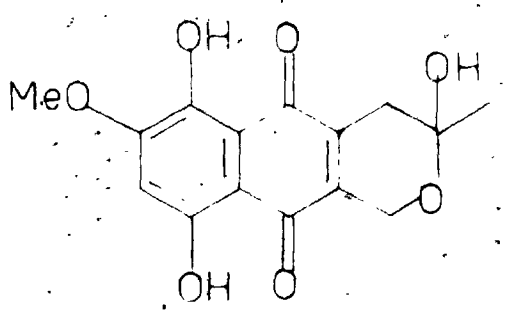
Friedel-Crafts reaction with maleic or succinic anhydrides or a Diels Alder reaction with a quinone will normally yield a mixture of two isomers. Unfortunately, these isomers are so similar that they are seldom easy to separate and identify. This is only of concern when a $\neq$ b and y $\neq$ z, but this situation arises sufficiently often to be of concern.

Synthesis of Javanicin

The three related fungal metabolites, javanicin 18, fusarubin 19 and bostrycoidin 20, are examples of compounds containing an unsymmetrical naphthazarin nucleus.

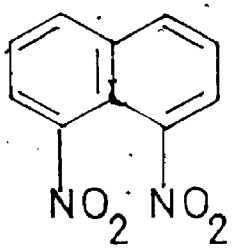


18



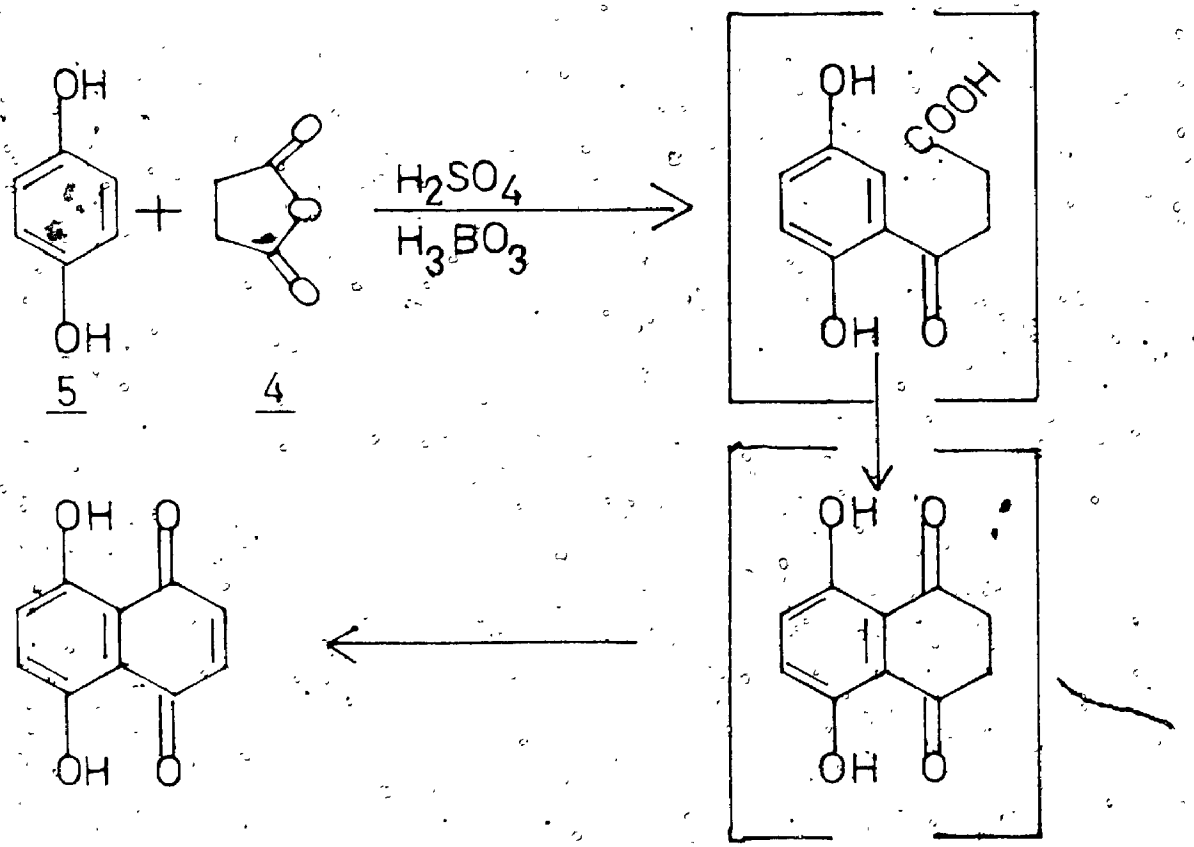
19

fuming sulphuric acid and a reducing agent such as aniline, phenylhydrazine or tin gave a poor yield of naphthazarin 1.

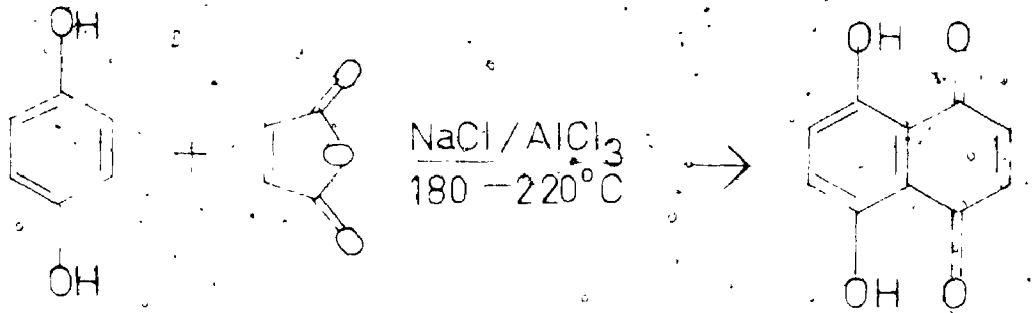


3

A seldom-used method first discovered by Dreyfus(5), and then later worked on by Ellis et.al.(6), involved the heating of a mixture of succinic anhydride 4, hydroquinone 5, sulphuric acid and boric acid. This reaction was assumed to proceed via the steps shown below. By far

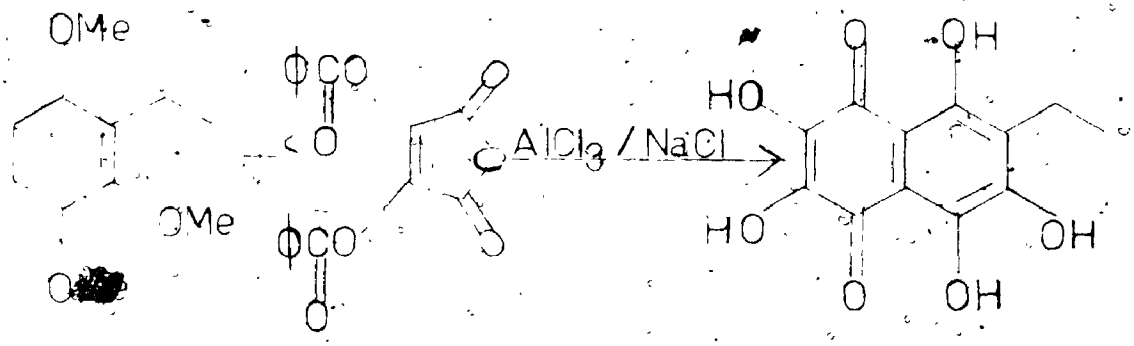


the most commonly used of any of the methods known was developed by Zahn and Ochwat (7). Maleic anhydride 6 was condensed with hydroquinone 5 using a melt of sodium chloride and aluminium chloride as the catalyst. This

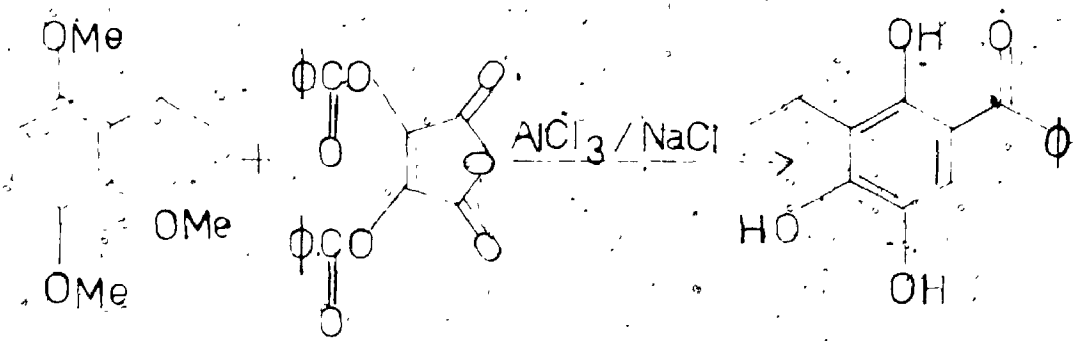


5 6

has been used successfully for naphthazarin itself and a variety of alkyl naphthazarins. Complex structures such as echinochrome A 9, have been synthesized by this

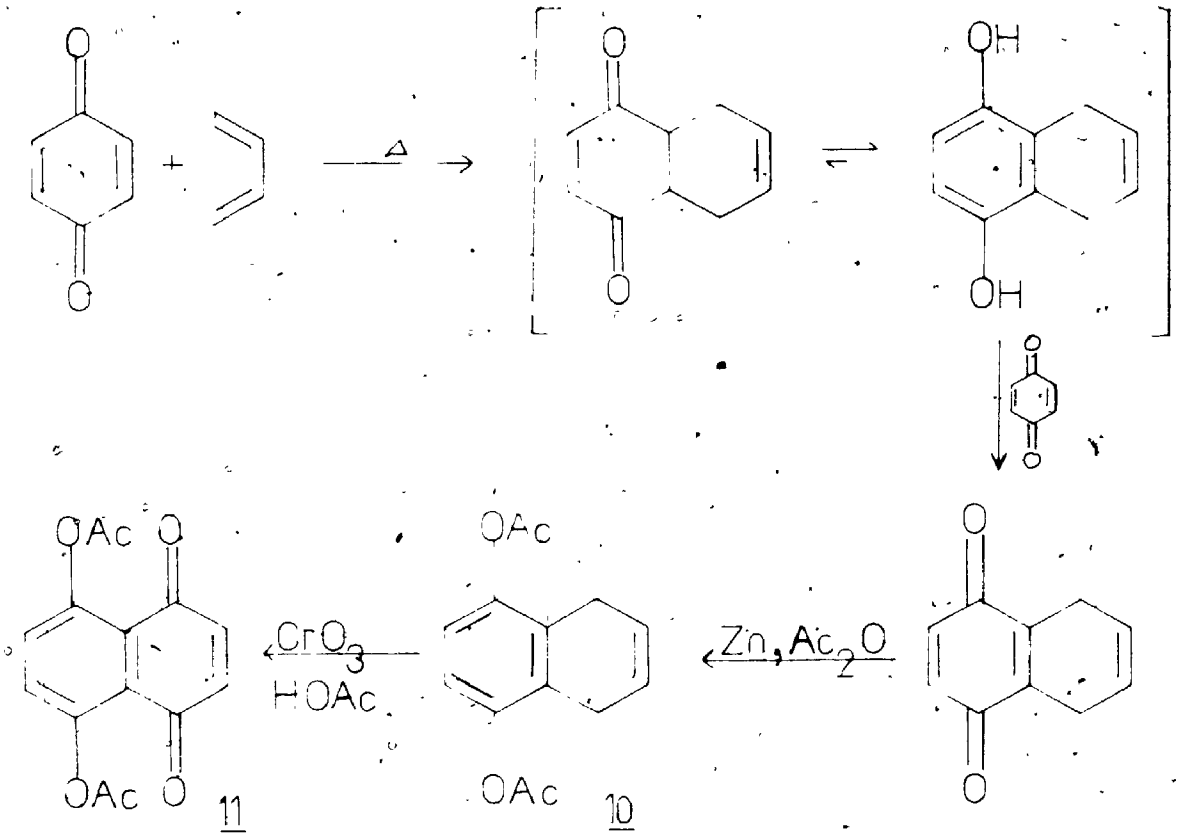


7 8 9



route (8). This yield was only 1% because of the unstable nature of the anhydride 8 and the competing acylation reaction illustrated.

An entirely different approach was used by Farina and co-workers (9,10). They used a Diels Alder addition followed by reductive acetylation of the adduct to prepare 1,4-diacetoxy-5,8-dihydronaphthalene 10, which was oxidized to the corresponding naphthazarin diacetate 11 with chromic acid. Methylnaphthazarin diacetate was pre-



pared in 75% yield using this route. A later reinvestigation of this system by Cort and Rodriguez (11), and this author (12), showed that the crude yield was indeed 75%, but the crude product was a mixture of several compounds, and the yield of the desired naphthazarin diacetate was only

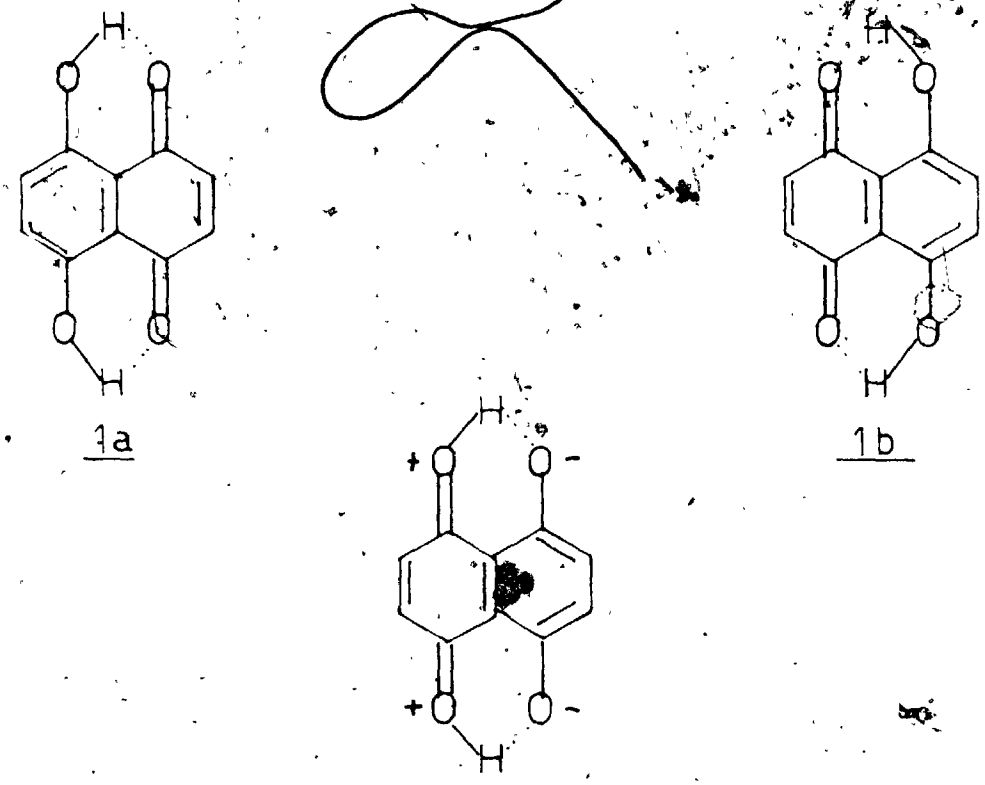
5-20% for simple cases.

A problem associated with all of these methods is their low yield. The severity of the conditions used in these procedures also rules out any chance of making the more labile compounds in the naphthazarin series. A large number of functional groups will not stand fuming sulphuric acid, nor can they be protected so that they will endure the reaction conditions for conversion of 1,5-dinitronaphthalenes to naphthazarins. The same argument holds true for the condensations using an aluminium chloride-sodium chloride melt for a catalyst. Even the seemingly milder conditions used by Farina (9,10) are too harsh for many functional groups.

A third problem associated with these routes is the lack of accessiblity of suitable starting materials. To give two examples, substituted 1,5-dinitronaphthalenes and 1,4-diacetoxy-5,8-dihydronaphthalenes are often very difficult to prepare.

Structure of Naphthazarin

Hadji and Sheppard (13) carefully analyzed the infrared spectrum of a mull of naphthazarin. The ν (OH) band at 2920 cm^{-1} suggested that the structure is either 1 a or 1 b rather than a resonance hybrid of the two forms as the latter should absorb below 1800 cm^{-1}. Although the hydrogen bonds are not symmetrical, the possibility that molecules may be periodically converted from one form to the other by occassional "tunnelling" of hydrogen atoms



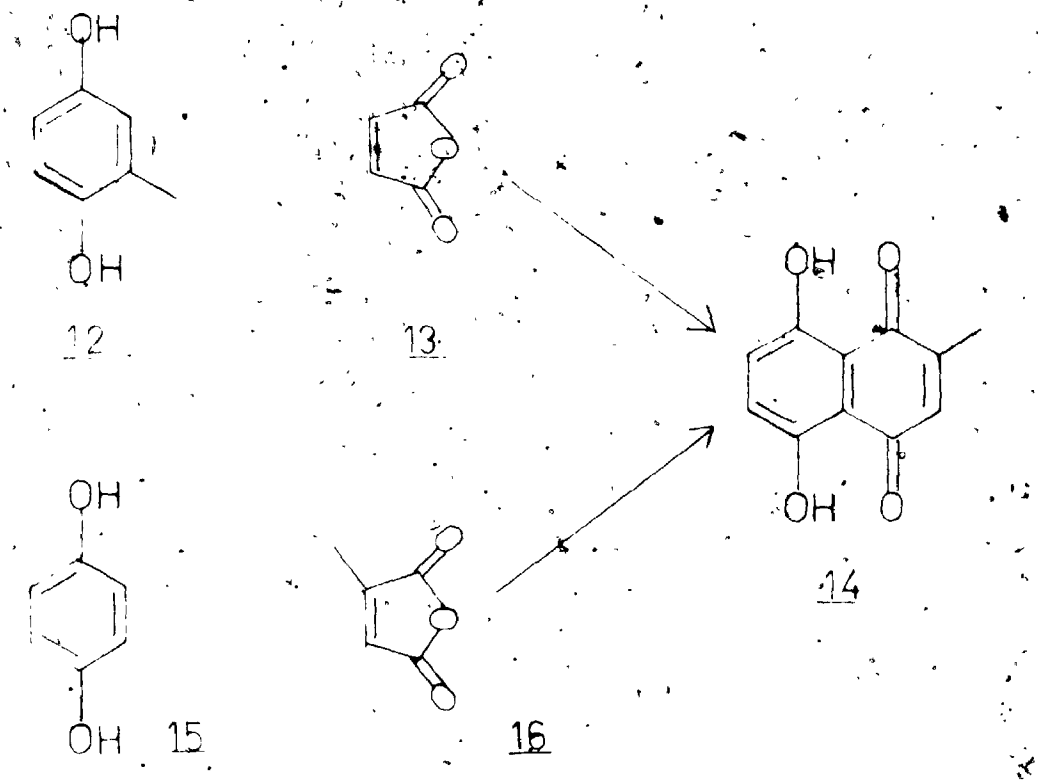
1a 1b

1c

between the two equivalent potential minima is not excluded. It is probable that resonance forms of the type 1 c contribute to the abnormally strong hydrogen bonding in these six membered chelate rings. The infrared spectra of quinones normally have an absorption band at 1675 cm^{-1} for the quinone carbonyl, but in the spectrum of naphthazarin the corresponding band is found at 1615 cm^{-1} (14). The proton magnetic resonance of naphthazarin has a signal at about 13 ppm which is downfield from the absorption of common naphthols (15). Methylation and acetylation of naphthazarin require much more vigorous conditions than those necessary for simple phenols (16). These facts are all consistent with strong hydrogen

bonding in naphthazarin.

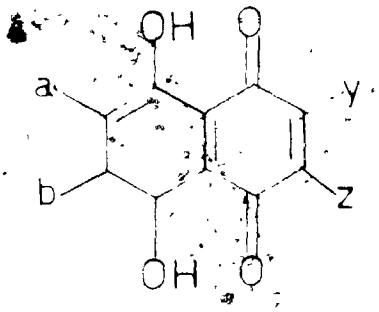
Macbeth et.al.(17) obtained methylnaphthazarin 14 from toluhydroquinone 12 and maleic anhydride 13, and also from hydroquinone 15 and citraconic anhydride 16. The ring bearing a particular substituent is predictable since electron releasing groups favour the quinone structure



and electron withdrawing groups favour the hydroquinone ring. These results are easily explained if the initial product can tautomerize to the most stable structure.

A total of six pairs of tautomers can be drawn for the generalized naphthazarin 17. These differ from one another only in the relative orientation of the four groups occupying the β positions.

Any synthetic route which consists of either a

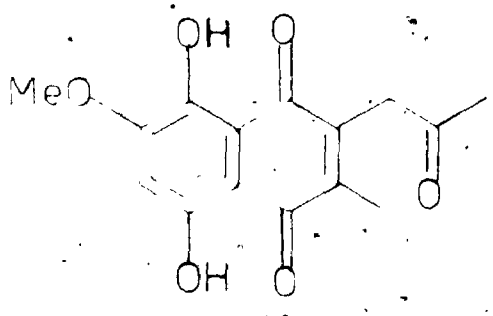


17

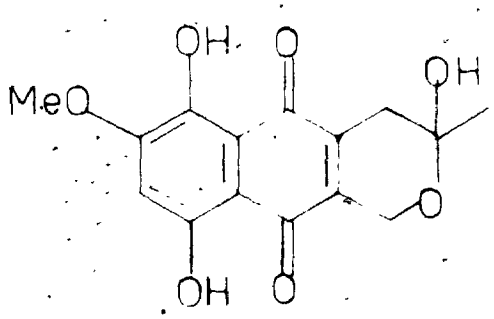
Friedel-Crafts reaction with maleic or succinic anhydrides or a Diels Alder reaction with a quinone will normally yield a mixture of two isomers. Unfortunately, these isomers are so similar that they are seldom easy to separate and identify. This is only of concern when a $\neq$ b and y $\neq$ z, but this situation arises sufficiently often to be of concern.

Synthesis of Javanicin

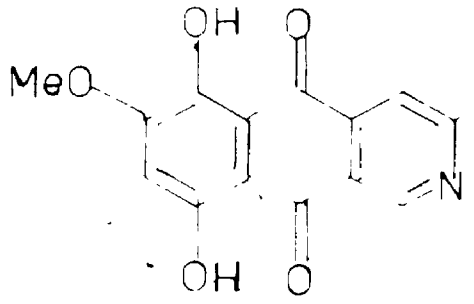
The three related fungal metabolites, javanicin 18, fusarubin 19 and bostrycoidin 20, are examples of compounds containing an unsymmetrical naphthazarin nucleus.



18



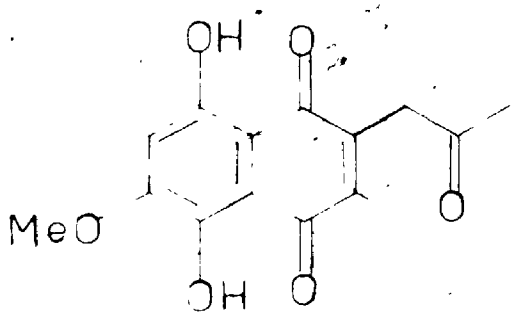
19



20

Interest in these compounds was aroused when biological testing showed all three to be bacteriostatic at low concentrations and bactericidal at higher concentrations (18). Unfortunately clinical studies had to be abandoned before completion because of a scarcity of material. Synthesis would provide sufficient material for further clinical work, and if rational, would prove the structures.

In 1964 Hardegger and co-workers published a series of papers (20,21,22,23) on synthetic methods which led to the complete synthesis of javanicin 18. A single paper (24) published the following year presented the synthesis of isojavanicin 21 and an improved scheme for javanicin.

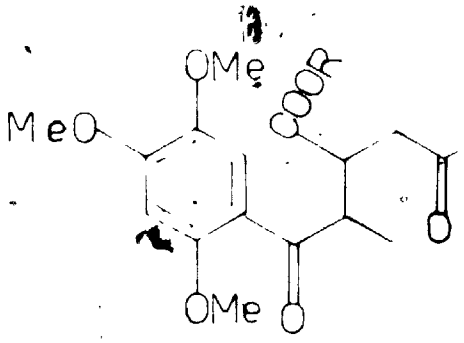


21

Since these papers form the basis for the present work, they warrant a detailed discussion.

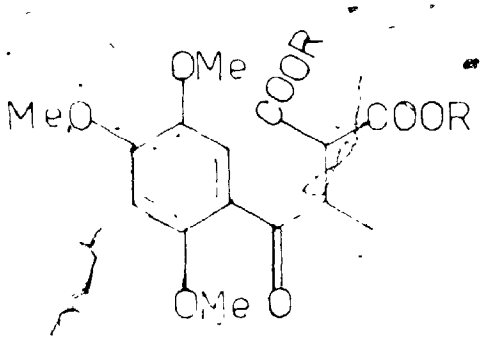
The basic approach to the problem was to start with a benzene ring substituted with oxygen functions in the 1,2 and 4 positions; this ring would become ring "A" in the final product. The remainder of the molecule was then built up by a series of selective reactions. The oxygen functions, particularly those which will occupy the peri positions of the naphthalene nucleus, must be present in an inert form during the synthesis, but should be easily convertible to phenols at the end. Methyl ethers were selected over benzyl ethers and acetates because of their smaller size and greater stability.

One straightforward pathway for the construction of the "B" ring appeared to be the well known cyclization of γ-phenyl butyric acid with polyphosphoric acid (25). The diketo ester 22 was prepared because cyclization would yield the correct carbon-oxygen skeleton. Unfortunately, the cyclization was unsuccessful, presumably because of electron withdrawal by the carbonyl group located ortho to the reaction site.

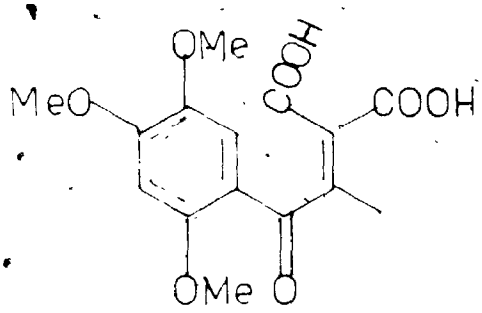


22

A similar system was also investigated. Preparation of the keto diester 23 was carried out in good yield. Alkaline hydrolysis of the diester was accompanied by some oxidation to give the unsaturated diacid 24. The oxidation was completed by treatment with bromine. Attempts to cyclize the diacid 24, or the corresponding monoacid were

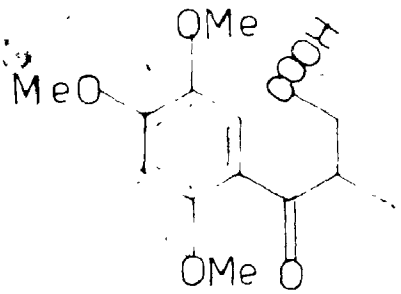


23

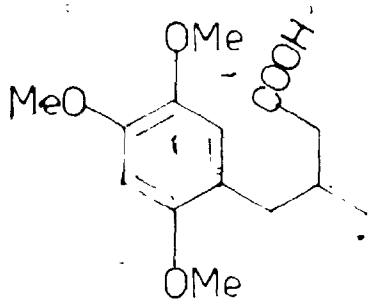


24

unsuccessful. Apparently the electron withdrawing carbonyl group ortho to the reaction site is sufficient to offset the electron releasing methoxyl groups and prevent the reaction. With this in mind, Hardegger et.al. (20) prepared the keto acid 25, and then removed the

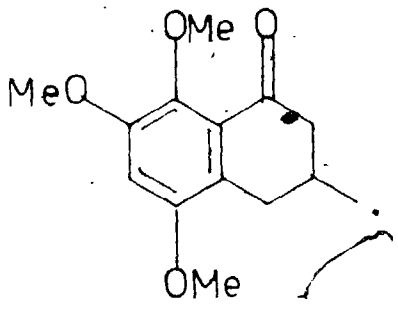


25



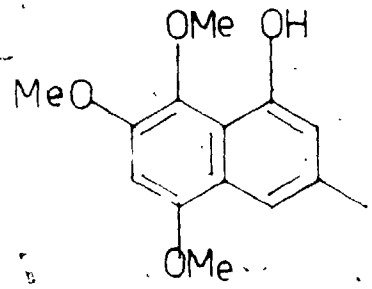
26

ketone group by catalytic hydrogenolysis to give the acid 26, which cyclized with polyphosphoric acid (25) to give 3-methyl-5,7,8-trimethoxy-1-tetralone 27 in good yield.

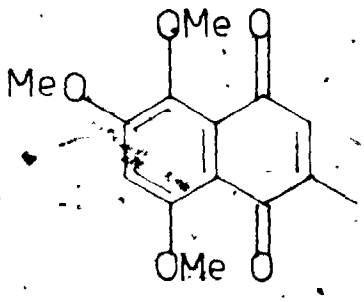


27

To complete the carbon-oxygen skeleton, an oxygen atom had to be introduced at C-4 and an acetonyl side chain was required at C-2. The major problem to be resolved was the determination of the sequence of reactions. The tetralone 27 was easily dehydrogenated to the corresponding naphthol 28 using palladium on charcoal as the catalyst. The quinone 29 was prepared from the naphthol



28

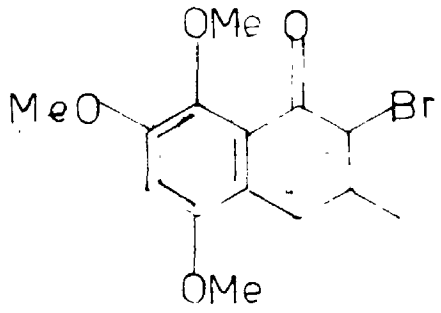


29

using lead tetraacetate as the oxidizing agent. Unfortunately the quinone 29 did not add acetoacetic ester under the conditions used successfully for 3-methyl-1,4-naphthoquinone.

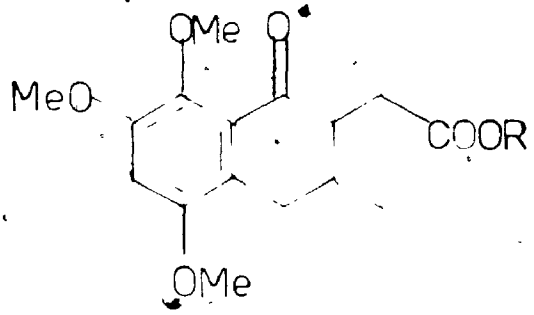
The possibility of adding the side chain before the oxidation step was also investigated. Bromination of the

tetralone 27 went smoothly to give the momobromo ketone 30.

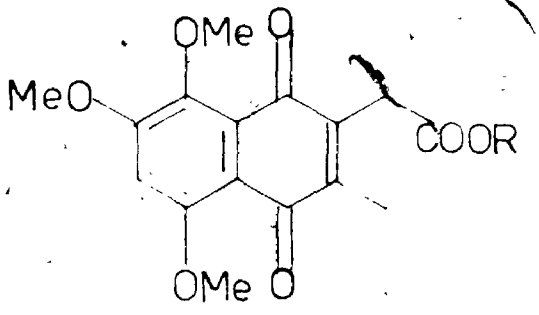


30

Treatment of the bromoketone with the sodium salt of acetoacetic ester resulted in the loss of hydrobromic acid to form the naphthol 28 rather than alkylation with acetoacetate. The sodium salt of malonate ester displaced the bromide to give a keto diester which was easily converted to the keto ester 31. Dehydrogenation and subsequent oxidation gave the corresponding quinone 32, but attempts to convert the side chain to an acetonyl group failed.



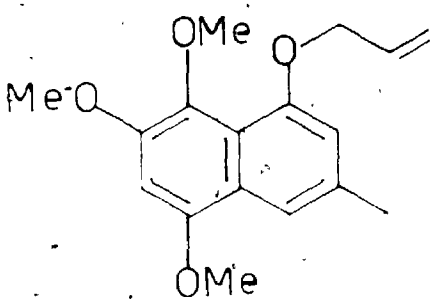
31



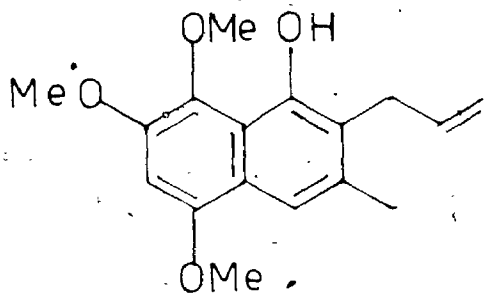
32

In order to investigate a different pathway, the naphthol 28 was treated with allyl bromide to give the allyl ether 33. Some difficulty was experienced in obtaining a good yield. A wide variety of conditions

consistently gave only 25% yield, but the starting material was easily recovered and recycled a number of times, thereby raising the overall yield to 65%. Rearrangement to the corresponding allyl naphthol 34 went smoothly.

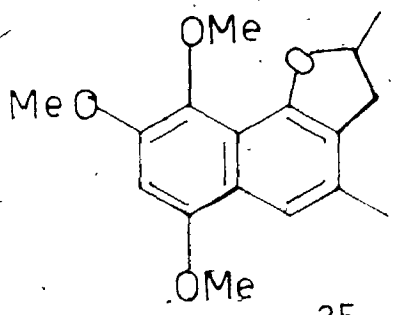


33

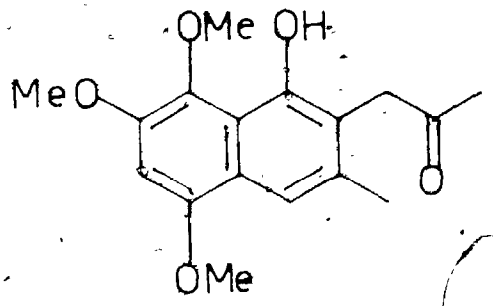


34

Two paths were then available, which differed only in the sequence of the steps. The first pathway investigated, involved conversion of the allyl side chain to an acetonyl group via the monobromide. Addition of hydrobromic acid to the allyl naphthol 34 was straightforward, but treatment of the crude bromide with triethylamine oxide resulted in a ring closure to form the dihydrofuran 35 in place of the acetonyl naphthol 36.



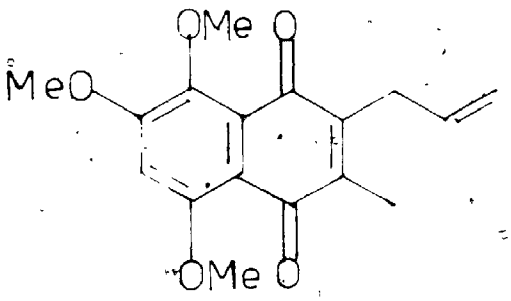
35



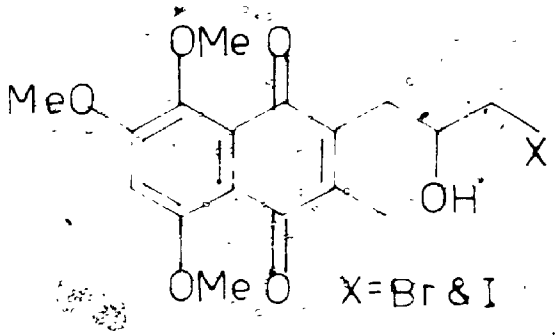
36

Treatment of the allyl naphthol 34 with one equivalent of hypobromous acid resulted in oxidation of the

naphthol to the corresponding quinone 37. Use of excess hypobromous acid gave the quinone bromohydrin 38 (X = Br).

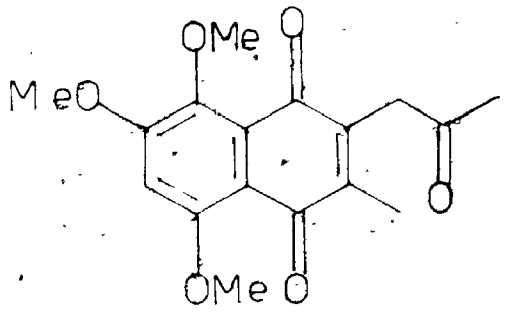


37



38

Higher yields of the two quinones 37 and 38 (X = I) were obtained when hypoiodous acid was used. The iodohydrin was oxidized in moderate yield with chromic acid. The iodine atom was then removed with hydrogen, palladium-charcoal and triethylamine to give the ketone 39 which is the 5,8-dimethyl ether of javanicin.

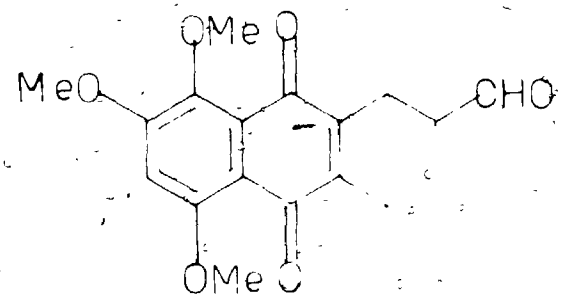


39

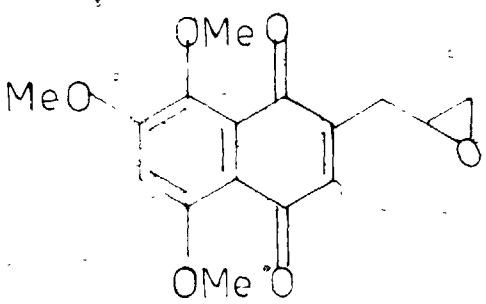
When the above described reduction reaction was carried out on the iodohydrin, a mixture of two products was obtained. Treatment of this mixture with chromic acid yielded the ketone 39 and the aldehyde 40.

One explanation is that the iodohydrin lost hydrogen iodide during the reduction to form the corresponding

epoxide 41, which then opened to give a mixture of the



40



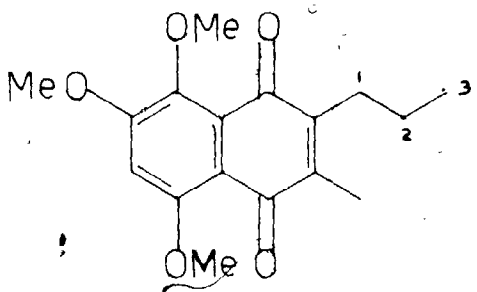
41

two possible alcohols. These in turn were oxidized by chromic acid to the ketone 39 and the aldehyde 40.

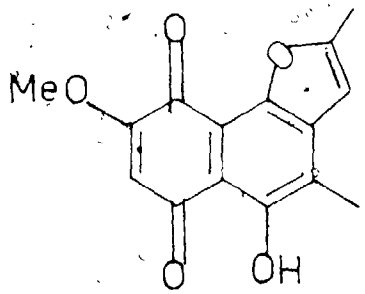
Methylation of natural javanicin gave a mixture of its 1,4-and 5,8-dimethyl ethers. The latter was shown to be identical to the synthetic ketone 39 by melting points and a mixed melting point. With only one of the two possible structures for the dimethyl ether synthesized, it was thought desirable to provide additional evidence because infrared, ultraviolet and proton magnetic resonance spectra were of little use in differentiating between two structures, which differ only in the relative positions of the methoxyl and the acetonyl groups.

Although hydrochloric acid in acetic acid was used successfully in cleaving the methoxyls in the quinone 42, the presence of a carbonyl function on C-2 of the side chain stopped the reaction completely. Hydriodic acid in boiling acetic acid attacked the triether only very slowly and no javanicin was isolated from the resinous product, whereas the use of mineral acid resulted in the ireversible cyclization of the side chain to give anhydro-

javanicin 43. The ether cleavage was finally carried



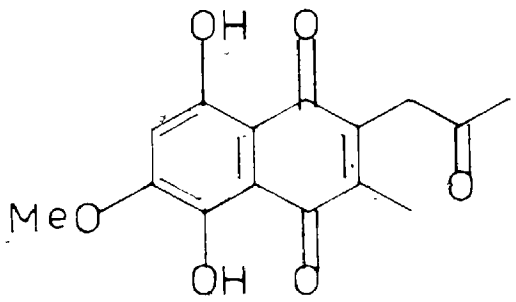
42



43

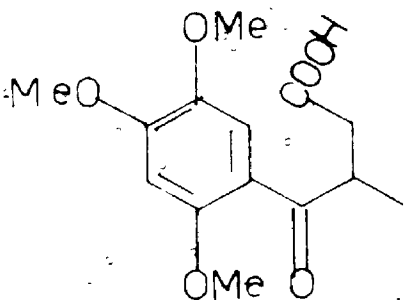
out with anhydrous aluminium chloride (26). Phenols bearing carbonyl functions in ortho or peri positons have a strong tendency to build stable metal complexes which can be decomposed into the hydrogen bonded phenol with hydrochloric acid (21). When javanicin 5,8-dimethyl ether was subjected to these conditions, the major product was javanicin and the minor one was anhydrojavanicin 43. Both were found to be identical to respective specimens from natural sources. Javanicin was thereby totally synthesized by a sequence of fifteen steps from vanillin with an overall yield of 1%.

In view of the difficulties encountered in positively confirming the structure of javanicin, it appeared worthwhile to Hardegger, et. al., to proceed with synthesis of the other isomer, isojavanicin, 21, in order that direct comparisons of both isomers with natural javanicin could be made. During this synthesis of isojavanicin, a shorter route to javanicin was uncovered (24). The basic approach was the same as before, but several of the operations were shortened. Acylation of 1,2,4 trimethoxybenzene with

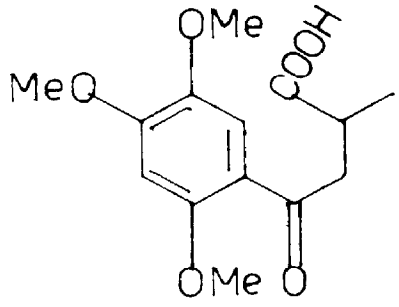


21

pyrotartaric anhydride under Friedel-Crafts conditions gave a mixture of two keto-acids 44 and 45.



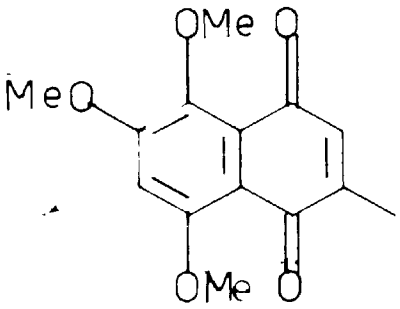
44



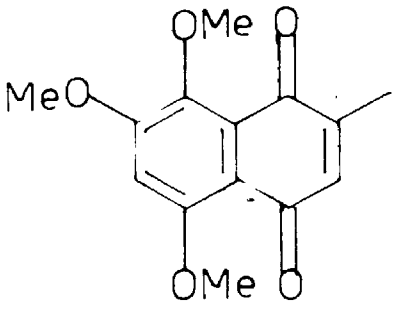
45

The ratio of the two was dependent on reaction conditions, but attack at the less hindered carbon of the anhydride was more facile which gave rise to a higher percentage of the ∝ methyl keto-acid 45. The keto acids were separated and transformed by a series of reactions already discussed into the two corresponding quinones 29 and 46.

In this synthetic scheme the greatest improvement lay in the manner in which the acetonyl side chain was formed. The Michael addition of acetoacetic ester to the quinone 29, previously found unsuccessful, went in 35%

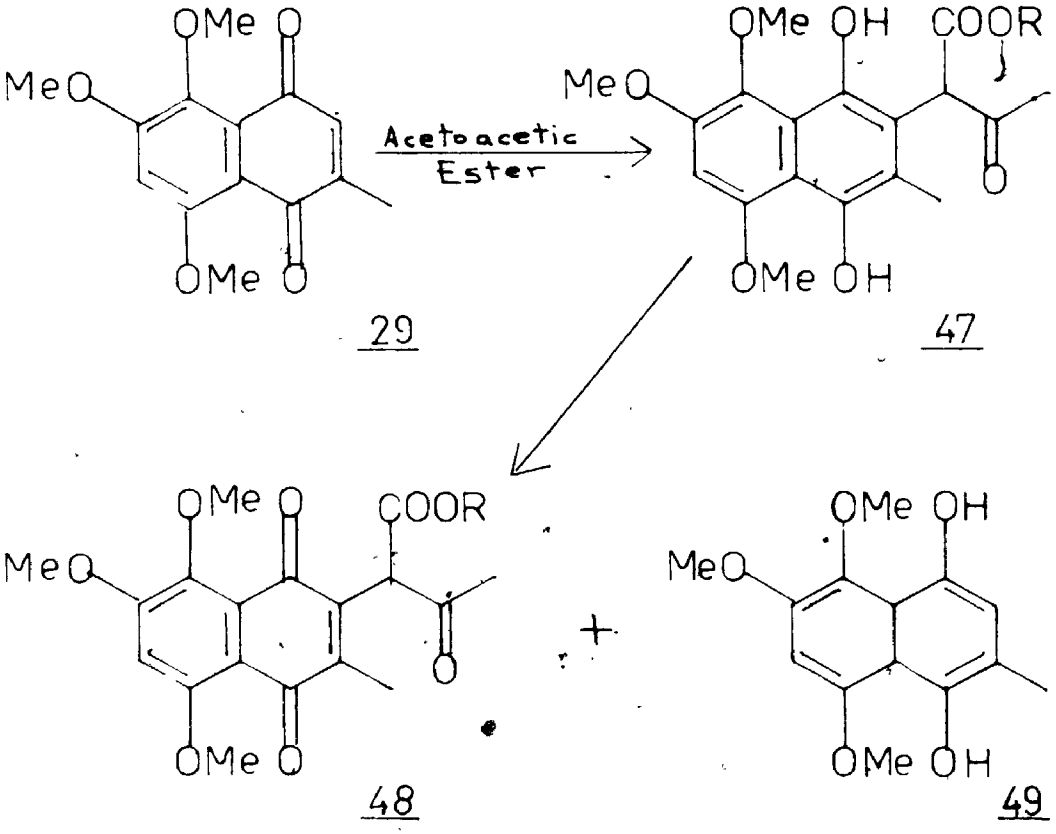


29



46

yield when tetrahydrofuran was used as the solvent. The apparently low yield is better understood when attention is drawn to the fact that half of the starting quinone acted as substrate while the other half acted as an oxidizing agent on the hydroquinone addition product initially formed 47, according to the following equation.



29 47

48 49

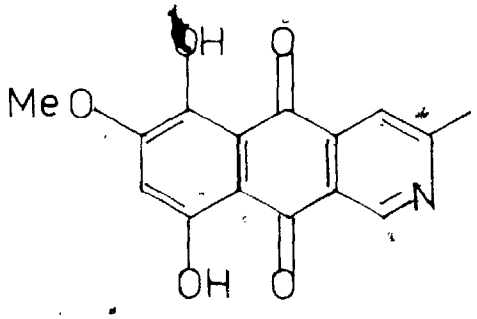
Use of the benzyl ester of acetoacetic acid allowed easy removal of the ester function. Treatment of the ester with hydrogen and a catalyst gave javanicin 5,8-dimethyl ether 39 smoothly. Javanicin was then obtained by the method used above.

Isojavanicin 21 was prepared via the same reactions, but quinone 46 was used as the substrate. Comparison of javanicin with isojavanicin showed their spectra to be virtually identical as expected. The melting points were different and the mixed melting point was depressed but it was very sharp, having only a two degree spread for an equimolar mixture.

The improved synthetic scheme consisted of eight steps instead of the fifteen steps in the first sequence. Unfortunately, the increase in yield is a modest 40%. The overall yield is still only 1.4%.

Structure of Bostrycoidin

Bostrycoidin 20 was first isolated in 1953 from



20

a culture of Fusarium Bostrycoides by Cajori and co-workers (18). Their curiosity was aroused by the biological

activity of this new pigment. It was particularly effective *in vitro* against a strain of tubercle bacillus (Mycobacterium tuberculosis var. hominis strain H 37). At low concentrations bostrycoidin was bacteriostatic, however, at higher concentrations it was definitely bactericidal. In addition it had the advantages of being stable at room temperature and of being able to withstand autoclaving. Preliminary investigations with mice suggested it was non-toxic and stable in the body, but the insolubility of the pigment in water led to an administration problem. The mouse was able to excrete the pigment quickly even when it was directly injected into the peritoneal wall with a hypodermic syringe. Unfortunately, a shortage of material forced the suspension of the biological tests before its effects on bacteria and living animals could be fully explored.

A few of the physical and chemical properties of bostrycoidin were investigated by Cajori and co-workers (19). The purified bright red crystals melted sharply at 243 to 244° and were found homogeneous when subjected to countercurrent distribution experiments. The amphoteric nature of the pigment was demonstrated by its solubility in strong acid to give an orange-red solution, and its solubility in strong base to give a deep purple solution. The presence of two phenolic hydroxyl functions was indicated by titrations, a ferric chloride test, and the formation of a diacetate with acetic anhydride. When an alcoholic solution of the compound was treated with

zinc dust and acetic acid the colour disappeared initially but reappeared on extended standing, which suggested the presence of a quinone group.

The infrared spectrum of a solution of bostrycoidin in chloroform was characteristic of the naphthazarin nucleus with bands at 1620 and 1585 cm^{-1}, but no bands at 3580 or 1660 cm^{-1}. A band at 1283 cm^{-1} was thought to be indicative of an aromatic methyl group. Further support for the presence of a naphthazarin nucleus was provided by the ultraviolet and visible spectra. A striking similarity was observed when the spectrum of bostrycoidin was compared to the spectra of solanione and javanicin, then thought to be different compounds, but later shown to be identical (27).

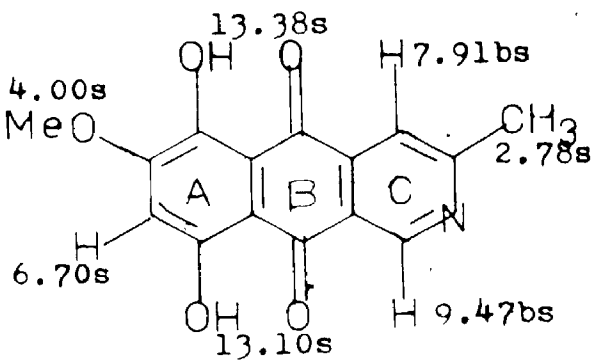
It was unfortunate that the test results which Cajori used to devise his molecular formula were not all correct. Microanalysis suggested $C_{17}H_{11}O_6$.OMe (rather than $C_{14}H_{11}O_4$ N.OMe). It is interesting to note that the Rast molecular weight determination, 305 ± 30, fits the correct structure at 285 better than the incorrect formula at 339. Negative tests were obtained for the presence of sulphur, halogen, metals and nitrogen. It is a pity that the solubility of the pigment in 20% aqueous hydrochloric or sulphuric acid did not suggest an exhaustive search for the presence of nitrogen instead of oxonium ion formation. Certainly, compounds containing hydroxyl groups will dissolve in strong acids such as sulphuric or phosphoric, but seldom are they basic enough to dissolve in two or

three normal hydrochloric acid.

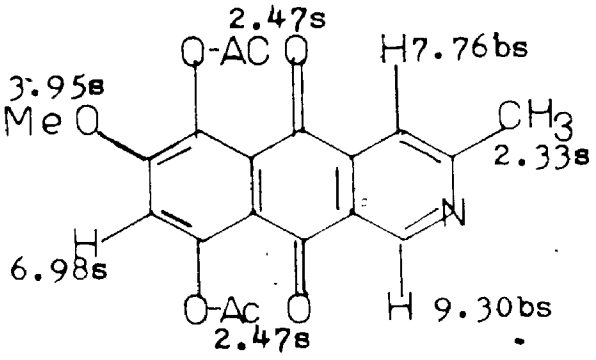
In later studies two investigators (28 a,b) independently proposed the correct molecular formula $C_{15}H_{11}NO_5$. The quinone function was confirmed by easy reduction (decolouration) of the pigment with sodium dithionite and easy re-oxidation (colouration) of the reduction product with air. The infrared spectrum of the pigment itself in a potassium bromide disc, and the spectrum of a chloroform solution of the corresponding diacetate confirmed the presence of the naphthazarin attached to a nitrogen. The most convincing evidence in support of the accepted structure for bostrycoidin was provided by the proton magnetic resonance (pmr) work of Arsenault (28a). The approach used was quite straightforward. The proton magnetic resonance spectrum of bostrycoidin and its diacetate were recorded, analyzed, and compared to the spectra of the best available models. Using only four models and the corresponding diacetates of three of these, Arsenault was able to provide an analogy for each proton in the system.

Figures I and II show the structures of the nine compounds involved in the study. The numbers and letters beside each proton designate in conventional terms the location, multiplicity, and coupling constants of the peak(s) in the pmr spectrum which correspond to the protons in question.

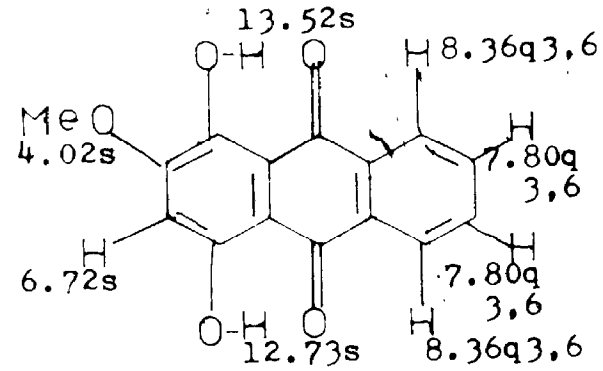
Structure 51 is an excellent model for ring A (lettering from left to right) of bostrycoidin 20. The corres-



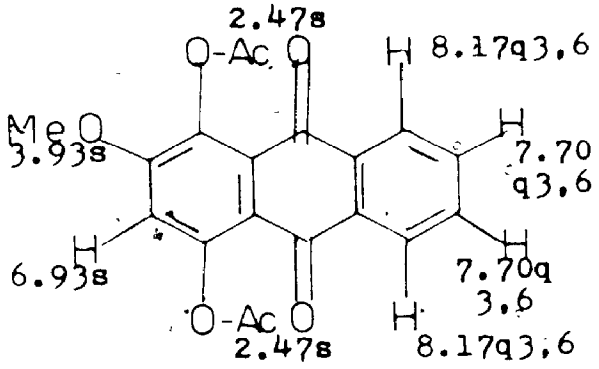
20



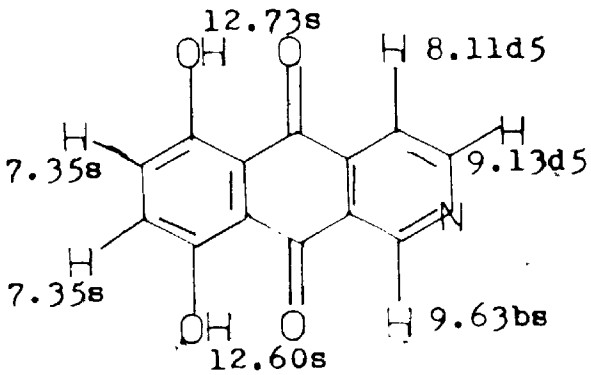
50



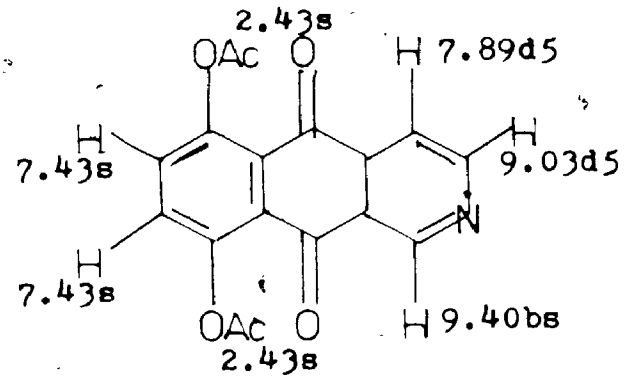
51



52

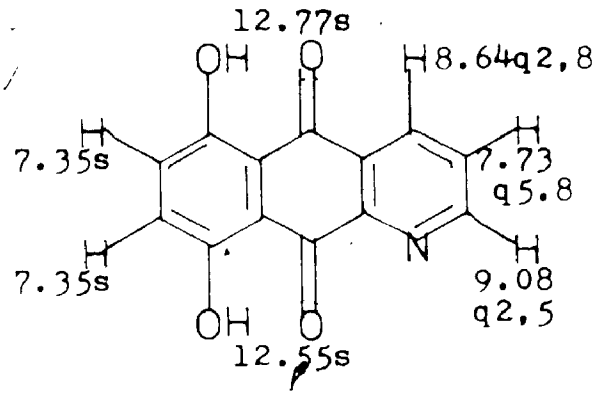


53

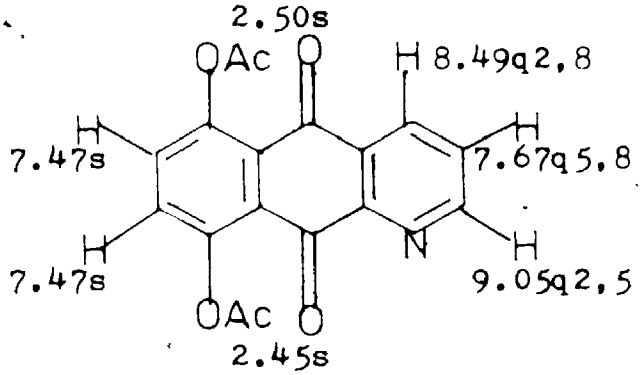


54

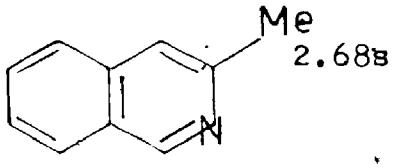
FIGURE I



55



56



57

s = singlet
bs = broad singlet
d5 = doublet J = 5 cps
q5,8 = quartet J = 5 and 8 cps

FIGURE II

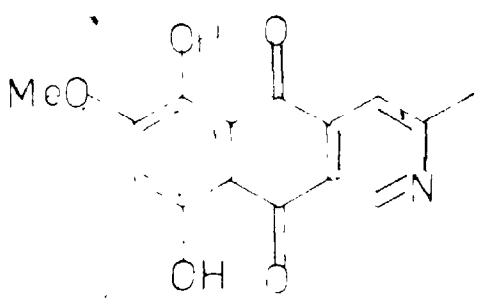
ponding protons in these two structures have the same multiplicity and very similar locations. It is interesting to observe that acetylation of compounds 20 and 51 produces two diacetates 50 and 52 respectively, which are very similar. The acetate methyls absorb in exactly the same location, supporting the claim that the structures have the same arrangement of atoms in ring A. This is further substantiated by the fact that the other comparable protons have shifted in the same direction by roughly the same amount.

Since ring B carries no protons, the only remaining concern is ring C. Unfortunately, a good model for ring C, i.e. a compound in which rings B and C are identical, is not readily available. A comparison of the C rings of structures 20, 53 and 55 suggests that bostrycoidin is most likely an isoquinoline. A quinoline structure similar to 55 would require that the two protons would have to be either ortho or meta with respect to one another. The spectrum of 55 suggests that the coupling constants of ortho protons are either 5 or 8 Hertz depending on location whereas meta protons have a coupling constant of 2 Hertz. Since the broad singlet designation normally refers to coupling of less than 1 Hertz, it is reasonable to suggest that the quinoline model is unsuitable.

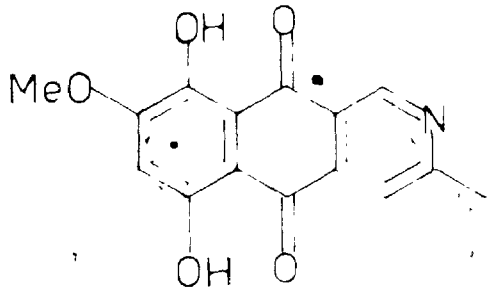
The isoquinoline model 53 indicates that there is no appreciable meta coupling between ring C protons in this system, although the picture is probably clouded slightly by the presence of strong ortho coupling.

Comparison of the spectra of compounds 20 and 57 suggests that the aromatic methyl is attached to C-3. This is further supported by inspection of the spectrum of compound 53. If the proton on C-3 were replaced with a methyl, the protons on C-1 and C-4 would compare very favourably with the corresponding protons in structure 20.

The evidence discussed up to this point has eliminated all but two possibilities for the structure of bostrycoidin 20 and 58. As was mentioned earlier, in



20



58

connection with Hardegger's work on javanicin, it is difficult to distinguish between structures of this type using only physical and spectroscopic methods. One good method for determining which of the possible structures is the correct one, involves synthesis from a known starting material via an unambiguous route. The best possible structural proof consists of synthesis of each of the possibilities and comparison of the naturally occuring material with each one.

Biosynthesis of Javanicin, Fusarubin and Bostrycoidin

Since one of the main motives for such a synthesis

is to provide a means for production of material for clinical testing, it is desirable to be able to predict which of the proposed structures is most likely to be the correct one. In this case one must rely on biogenetic theory for the prediction. Unfortunately, the biosynthesis of bostrycoidin has not yet been investigated, however, Gatenbeck and Bentley (29) have studied the biosynthesis of a close relative, javanicin, extensively.

Fusarium javanicum was cultured on media containing radioactive compounds. The resulting labelled javanicin was isolated, purified and then systematically degraded using the Zeisel reaction, the iodoform reaction, and Kuhn-Roth oxidations. Acetic acid obtained from the Kuhn-Roth oxidation was further degraded using the Schmidt reaction.

When the culture medium contained [Me - ^{14}C] methionine, the radioactive substrate was incorporated. When the labelled pigment was degraded with the Zeisel reaction, 97% of the activity was found in the methoxyl methyl. Kuhn-Roth oxidation showed only about 1% activity elsewhere in the molecule confirming the prediction that the C-15 methyl came from a C-1 donor such as methionine.

When [1 - ^{14}C] acetate was fed to the mould the results of Kuhn-Roth oxidation of the labelled javanicin produced were consistent with the presence of seven labelled atoms. Schmidt degradation of the acetic acid isolated indicated that the activity was divided about equally between the carboxyl carbon (56.8%) and the methyl carbon

(43.2%). Radioactivity was therefore present at C-11, or C-14, or both, as well as C-3, or C-13, or both. (see Figure III)

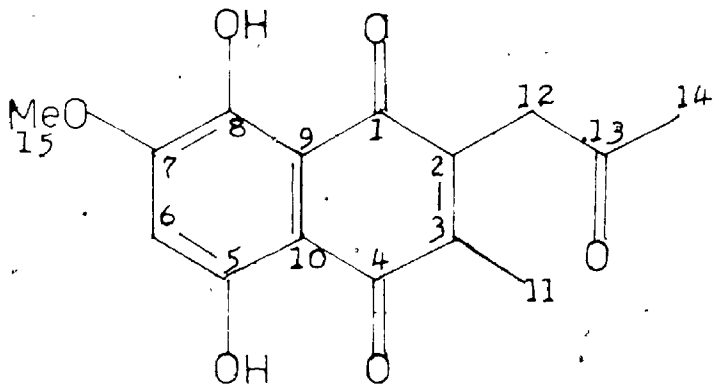
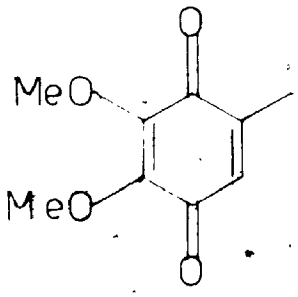


FIGURE III

Degradation of the javanicin labelled with [1 - ^{14}C] acetate with the iodoform reaction showed only 2.5% activity at C-14. It was therefore concluded that the Kuhn-Roth acetic acid activity originated almost exclusively from C-11 and C-13. The small amount of activity apparently present at C-14, as indicated by the iodoform reaction, probably came from C-11. Small amounts of iodoform are obtained from 5,6-dimethoxy-2-methyl-1,4-



benzoquinone 59 even though no acetyl function is present. Therefore, virtually none of the activity observed in the Kuhn-Roth acetic acid came from C-14.

This evidence indicates that javanicin was constructed from polyacetate with C-14 coming from an acetate methyl and C-11 stemming from an acetate carboxyl.

Experiments with [2-^{14}C] malonate were conducted to provide evidence for an acetate plus polymalonate pathway with an acetyl-CoA starter. This pathway requires no activity at C-14. The results were disappointing and inconclusive. Incorporation was low and activity was found equally distributed between C-3 and C-14.

If one accepts the polyacetate route with C-11 being derived from the reduction of a carboxyl carbon, then prediction of the structures of the three pigments javanicin 18, fusarubin 19, and bostrycoidin 20 follows. Figure IV shows a logical route for the construction of these compounds.

Cyclization of a polyacetate chain followed by oxidation at both C-1 and C-8 would give rise to the acid 60. The necessary methoxyl at C-7 is easily obtained by a C-1 alkylation of the hydroxyl with a donor such as methionine. Javanicin, fusarubin and bostrycoidin all differ from the corresponding acid 60 only in the level of oxidation of the carbon C-11. Javanicin is the product of a full reduction of the acid group in 60 to a methyl group. Interruption of the reduction at the aldehyde stage 62, followed by introduction of nitrogen and

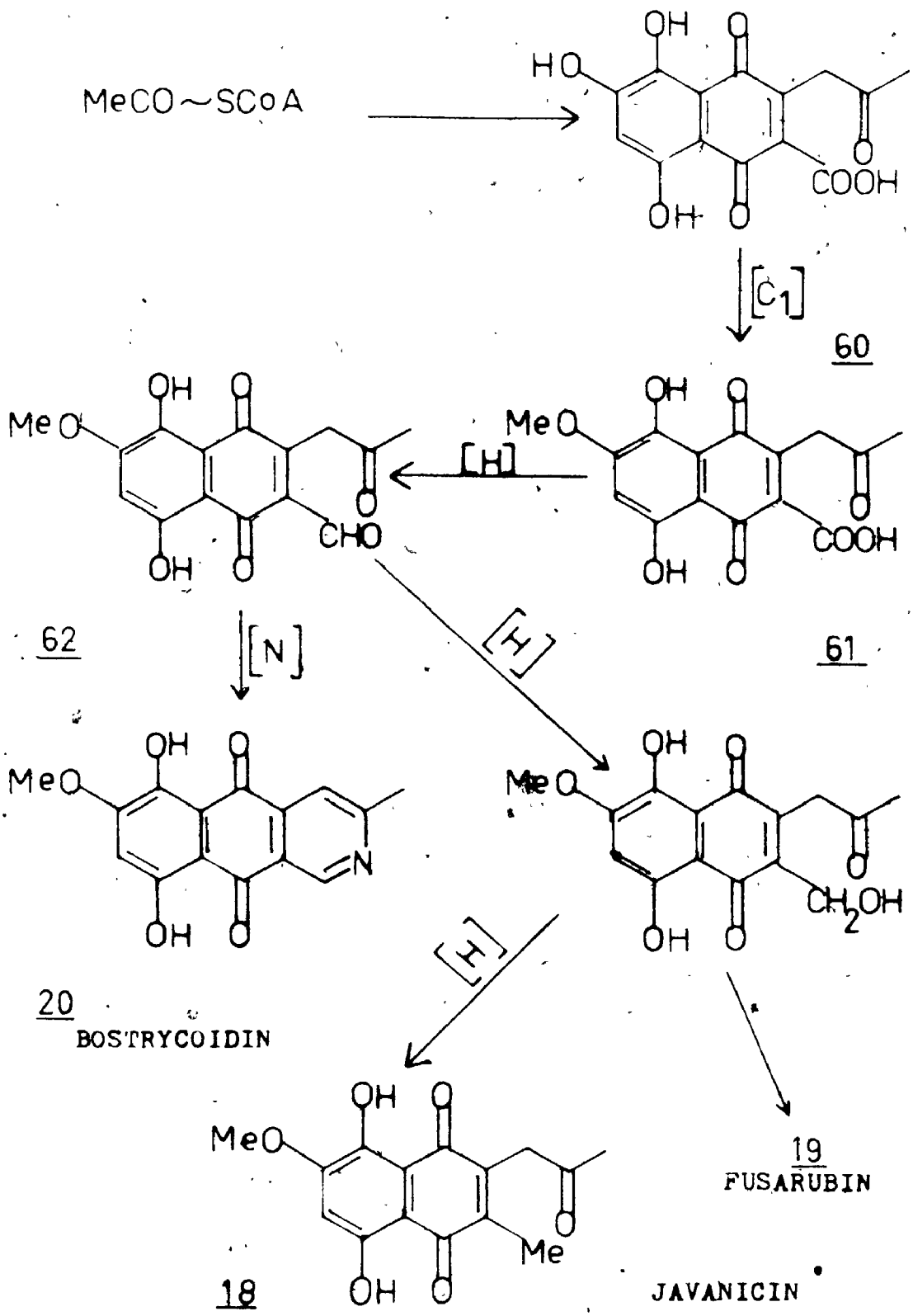

MeCO~SCoA
HO
OH
COOH
OH
[C1]
60
MeO
OH
[H]
CHO
OH
62
[N]
[H]
61
MeO
OH
N
OH
20
BOSTRYCOIDIN
MeO
OH
CH2OH
OH
[H]
19
FUSARUBIN
MeO
OH
Me
OH
18
JAVANICIN

FIGURE IV

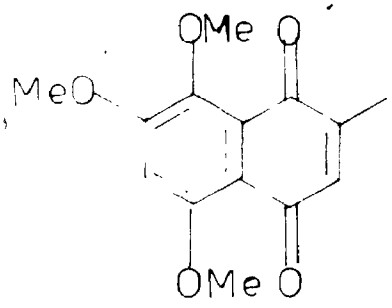
cyclization of the imine (nitrogen analogue of an aldehyde) would give rise to bostrycoidin 20. If the reduction were permitted to proceed to the alcohol stage before interruption, the resulting compound would be fusarubin 19. The structures predicted for javanicin and fusarubin by the polyacetate route have already been confirmed by synthesis. As yet the synthesis of bostrycoidin has not been completed.

Approaches to the Synthesis of Bostrycoidin

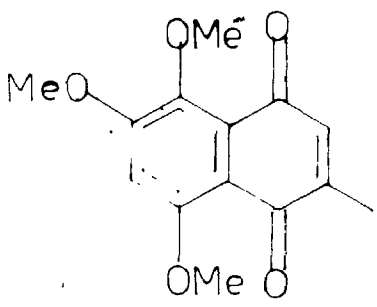
The close relationship of the moulds which produce these pigments as secondary metabolites, the apparent biogenetic relationship, and the obvious structural similarities of javanicin fusarubin and bostrycoidin all strongly suggest synthesis by a common pathway. Hardegger and co-workers have devised two synthetic routes to javanicin. The most efficient of these (24) consists of a mere eight steps with an overall yield of 1.4%, and while other approaches avoid the messy separations and appear to offer distinctive advantages in overall yield, it is probable that a logical extension of their work has the potential to furnish a quick structural proof for bostrycoidin, during which time a more practical scheme could be developed for the entire family including the parent acid 60 and the aldehyde 62 which was proposed as an intermediate for the biological pathway.

Synthesis of Bostrycoidin via the Hardegger Pathway

Hardegger's work afforded two quinones 29 and 46 which appear to be reasonable precursors for the synthesis



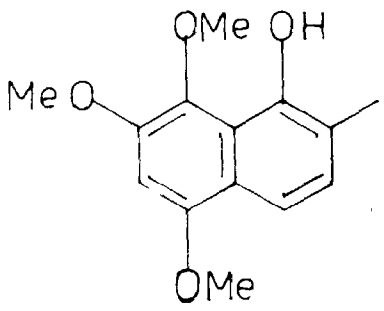
46



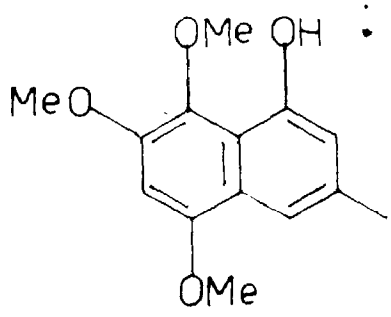
29

of bostrycoidin 20. The final choice between the two possibilities 29 and 46 will be influenced very strongly by the choice of the reaction for ring closure to create the isoquinoline ring.

Quinones 29 and 46 have been synthesized and fully characterized by Hardegger and co-workers, therefore no problems were anticipated in their preparation. Duplication of the scheme used by the Swiss chemists was no significant problem until the lead tetraacetate oxidations of the corresponding naphthols 28 and 63, were undertaken.



63



28

The first reaction attempted was conversion of the 2-methylnaphthol 63 to the quinone 46 with lead tetracetate in chloroform. The reaction product was an exceedingly complex mixture of a wide variety of compounds with none predominating to any extent. When this was observed, a cleaner reaction was sought and found.

When the naphthol 63 was treated with chromium trioxide in aqueous acetic acid under conditions similar to those used by Farina and co-workers (9,10), a smooth reaction proceeded to give the corresponding quinone 46 in good yield. The reaction was very clean, as demonstrated

by exhaustive thin layer studies, indicating a substantial improvement over the lead tetraacetate oxidation.

The same conditions allowed quantitative oxidation of the 3-methylnaphthol 28 to the quinone 29 with no difficulty. Since both of these quinones are known compounds, a discussion of physical and spectroscopic data is redundant. A technique was discovered which separated a mixture of the two quinones 29 and 46 cleanly, in spite of their marked structural similarity. If a mixture of the two quinones was spotted on a carefully prepared silica gel thin layer plate and developed with a mixture of ethyl acetate and hexane in a ratio of three to one, the resulting plate would show two distinct orange bands, one for each of the two quinones.

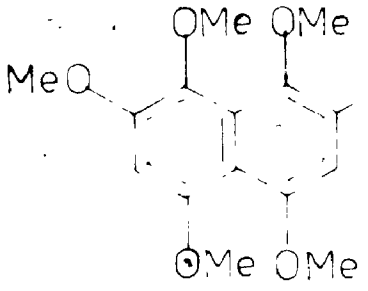
Comparison of the two quinones with bostrycoidin shows that the quinone methyl must be oxidized at some stage during the transformation. Since this is a key step if either of the two quinones are to be used as precursors, preliminary investigations of the oxidation reaction were initiated.

As was stated in the introduction, quinones and especially those with a free quinonoid position, are quite sensitive to a wide variety of reagents (30). Nucleophilic substitutions, addition reactions including dimerizations and reductions all occur with surprising facility. Thus, in order to carry out a selective oxidation, the quinone group must be blocked or masked so it can not interfere with, or be destroyed by the oxidation. Under normal

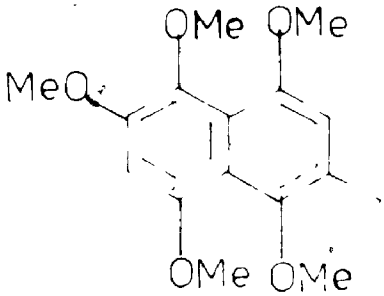
circumstances quinones are reduced to hydroquinones which are then acetylated, benzylated or methylated to make them inert (31). One of the most important factors to be considered in these specific cases is steric crowding. The substitution on the adjacent ring, particularly in the 5 and 8 positions, gives rise to strong peri interactions of a type which are well documented (32). The third methoxyl (in the 7 position) also adds significantly to the steric crowding which will facilitate removal of the proposed blocking groups, but will greatly impede their insertion. Reductive methylations are well known for their success in these crowded systems, and the resulting methoxyls are rather insensitive to acids or bases. Demethylation should not be a problem with the driving force exerted by the steric crowding.

Treatment of the quinone 46 with sodium dithionite, dimethyl sulphate and alcoholic potassium hydroxide (33) resulted in the formation of a new compound $C_{16}H_{20}O_5$ which contained an aromatic methyl group, five different methoxyl groups and two different aromatic protons (proton magnetic resonance spectrum). Comparison of this colourless crystalline material with the known reaction product 65 of the reductive methylation of the quinone 29 indicated that the new substance must be the expected pentamethyl ether 64. Reductive methylation of the quinone 29 under the same conditions gave the known pentamethyl ether 65 in good yield. The proton magnetic resonance and infrared spectra of the two pentamethyl

ethers 64 and 65 were virtually the same, but the melting points were very different.

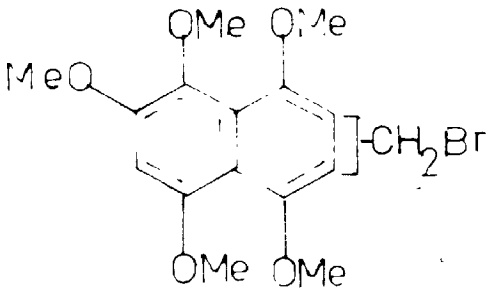


64

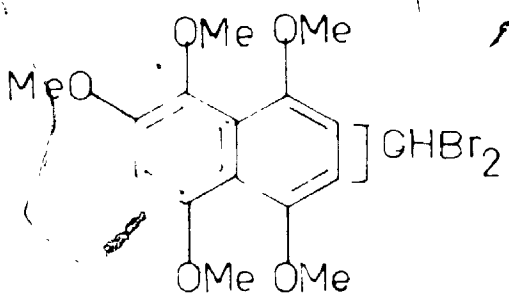


65

The next step was to oxidize the methyl group preferably to a carbonyl function while maintaining the highly oxygenated naphthalene ideally in its present form, but at least in a form which would be easily converted to the corresponding quinone. The first system studied involved use of N-bromosuccinimide which, via a free radical mechanism, should attack the aromatic methyl in preference to the ring itself (34). It is possible to obtain either a mono or a dibromo product 66 and 67 resp. from this reaction.



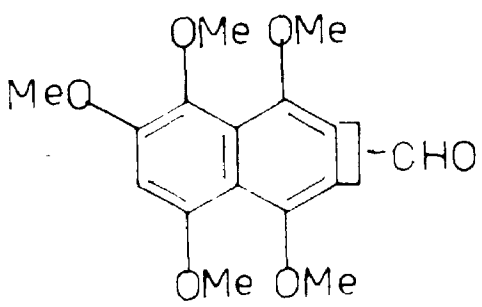
66



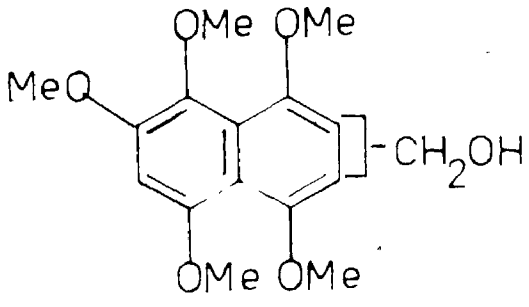
67

The dibromo compound 67 would be expected to be easily hydrolyzed to the desired aldehyde 68. On the

other hand the monobromo product would be converted to



68



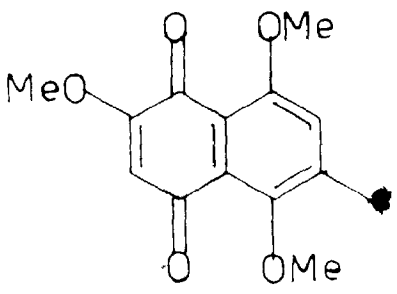
69

a carbonyl group by a wide variety of pathways which are usually one step longer than the route from the dibromo product.

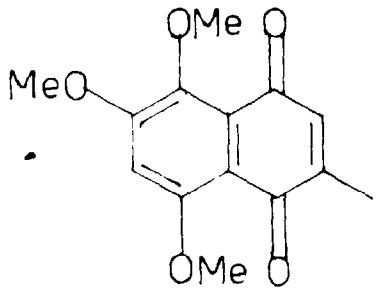
When the pentamethyl ether 65 was treated with 2 equivalents of N-bromosuccinimide in carbon tetrachloride with a trace of dibenzoyl peroxide as initiator in the absence of light at room temperature, the major product was 6-methyl-2,5,8-trimethoxy-1,4-naphthaquinone 70. The minor products were not identified. This came as a surprise because the oxygenated ring was not anticipated to be more reactive towards N-bromosuccinimide than the side chain. In an effort to shed more light on the reaction, control experiments were carried out. The pentamethyl ether 65 was dissolved in carbon tetrachloride and treated with a trace of dibenzoyl peroxide. The reaction mixture was a clean mixture of only two compounds in a roughly one to one ratio. The first was the quinone 70 mentioned above and the second was the quinone 29.

In the second control experiment, the pentamethyl ether 65 was dissolved in benzene and spotted on a silica

gel thin layer plate. After standing for a day, the



70



29

plate was developed in a mixture of chloroform and ethyl acetate. The starting material had been transformed into roughly equal quantities of the two quinones 29 and 70.

It is quite apparent that the methyl ethers lack the anticipated stability. They can be stored indefinitely in the dark, if they are recrystallized from an aliphatic hydrocarbon solvent, but solutions, especially those in chlorinated solvents such as methylene chloride or carbon tetrachloride, quickly turn orange on standing.

Acid catalyzed demethylations of aromatic ethers are well known (35), but normally the reaction conditions required are quite severe, a commonly used reagent being anhydrous aluminium chloride in nitrobenzene (23).

In all of the cases where the decomposition of the pentamethyl ether was observed, at least traces of acid were present, but the conditions were extremely mild. The abnormal sensitivity of the substrate towards acid must be attributed to the ease of addition of hydrogen ion to phenolic oxygen atoms, the relief of steric

compression provided by the reaction, and the ease with which the demethylated compound irreversibly oxidized to form a stable quinone structure.

Obviously, the methyl groups were not particularly effective in protecting the peri oxygens of this system. The chances of selectively oxidizing the aromatic methyl in the presence of the labile peri methoxyl groups appeared to be very slim. The quinones 29 and 70 were therefore not suitable precursors for the synthesis of bostrycoidin.

Since the aromatic methyl (C-11) was not easily functionalized in the presence of four peri methoxyls, it appeared advisable to either carry out the oxidation at an earlier stage, or introduce the carbon in question (C-11) in a higher oxidation state. The condensation reaction with pyrotartaric anhydride was not selective and the separation of the two isomers was not particularly clean, thus it appeared advantageous to develop a route which incorporated the troublesome carbon in a higher oxidation state, thereby avoiding both problems.

Bostrycoidin 20 is an isoquinoline. The accepted numbering system (28) designates the carbon being discussed as C-1, (Figure V). In bostrycoidin, C-1 exists in an oxidation state equivalent to an aldehyde. Since aldehydes are generally much too reactive towards a wide variety of reagents including oxidizing agents, reducing agents, acids and bases to be considered for a lengthy sequence of reactions, it seemed more reasonable to introduce C-1 to the skeleton in a more stable form. In this particular case, the carbon

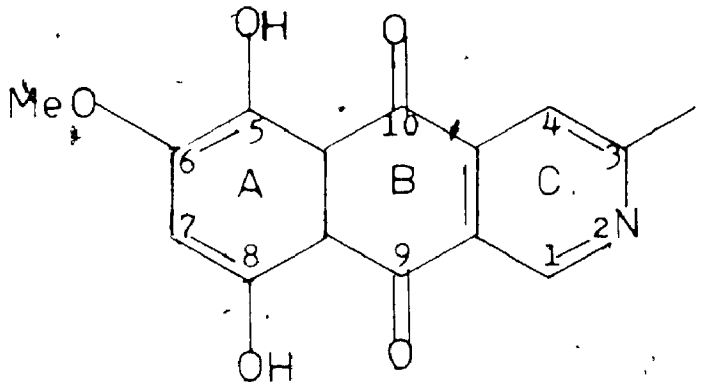


FIGURE V

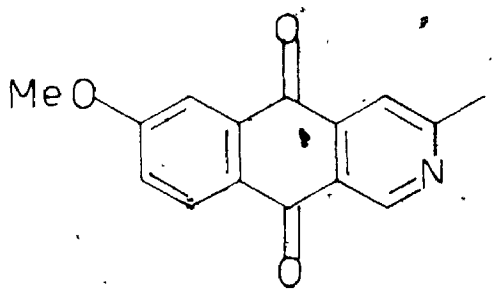
in question was benzylic in a number of the stages contemplated, which indicated that the next lower oxidation state (alcohol) would also be too reactive. In addition alcohols do not lend themselves well to the Aldol-Claisen condensations which are so useful in building up this type of skeleton. Use of an acid derivative should avoid both of these problems. A scheme was proposed which was analogous to the one used by Hardegger and co-workers (24).

Model System for Ring C Synthesis

In order to gain experience on the problems associated with the construction of the "C" ring of bostrycoidin, a model system was developed. It was necessary to determine the mode of formation of ring C (36) in order to define the exact nature of the precursor.

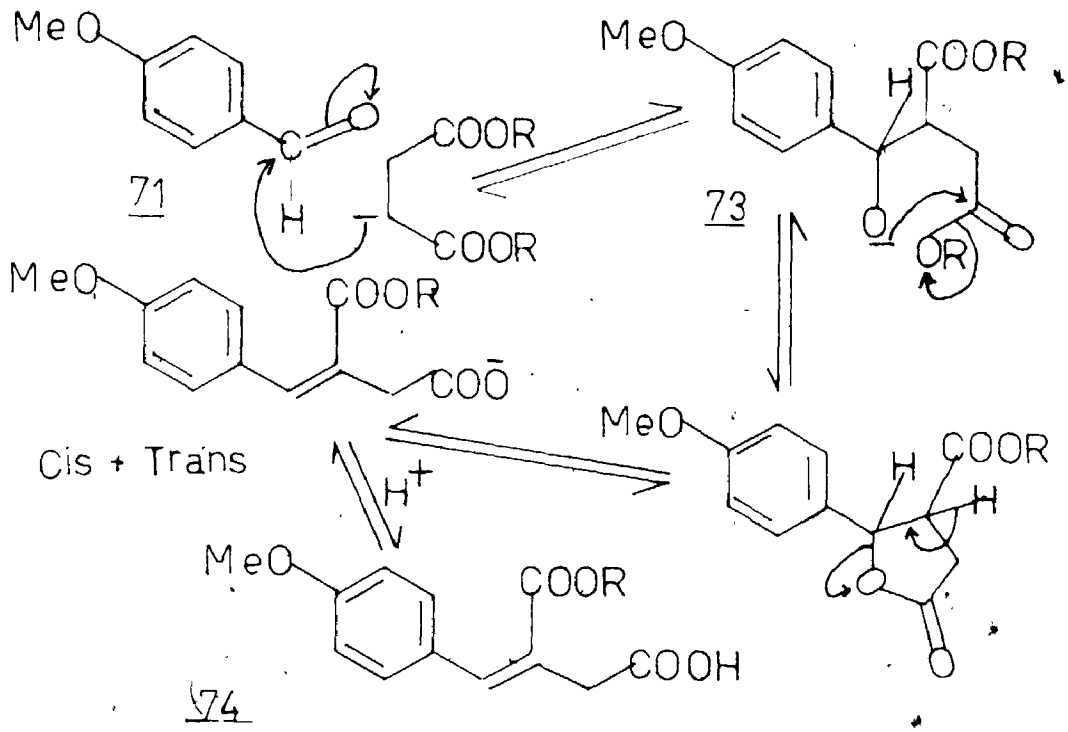
The starting material chosen was p-methoxybenzaldehyde 71 because it contained the methoxyl group

necessary to define the relative orientation of the "A" ring and the "C" ring in the final product of the model system 72. The route for the construction of ring B



72

of 72 was identical to that chosen for the trimethoxyl derivative. The necessary carbons were introduced via a Stobbe condensation using diethyl succinate (37). In the first step, the carbanion attacked the aldehyde carbonyl to form an adduct. Inspection of models showed that the negatively charged oxygen atom could form a five membered ring lactone 73 by attacking the carbonyl carbon of the ester group β to the initial carbanion. The lactone could then open to form the salt of the acid, which was finally isolated. The reaction product was a mixture of cis and trans isomers about the double bond. The initial condensation led to the formation of two chiral centres; both possible diastereomers were formed and these led to the two stereoisomers of the lactone 73, which in turn opened to the two geometrical isomers of the final product 74 (38). The existence of the two isomers was of little consequence, because the ring closure reaction conditions were such that isomerization could readily occur.



The formation of the lactone during the Stobbe condensation was a very helpful side reaction for two reasons. Since the two acid derivatives were different, choice of a reagent which would react with one in preference to the other was made easy. The second advantage is found in the work up of the reaction mixture. The product was very easily separated from any of the reagents and most of the side products by a simple bicarbonate extraction.

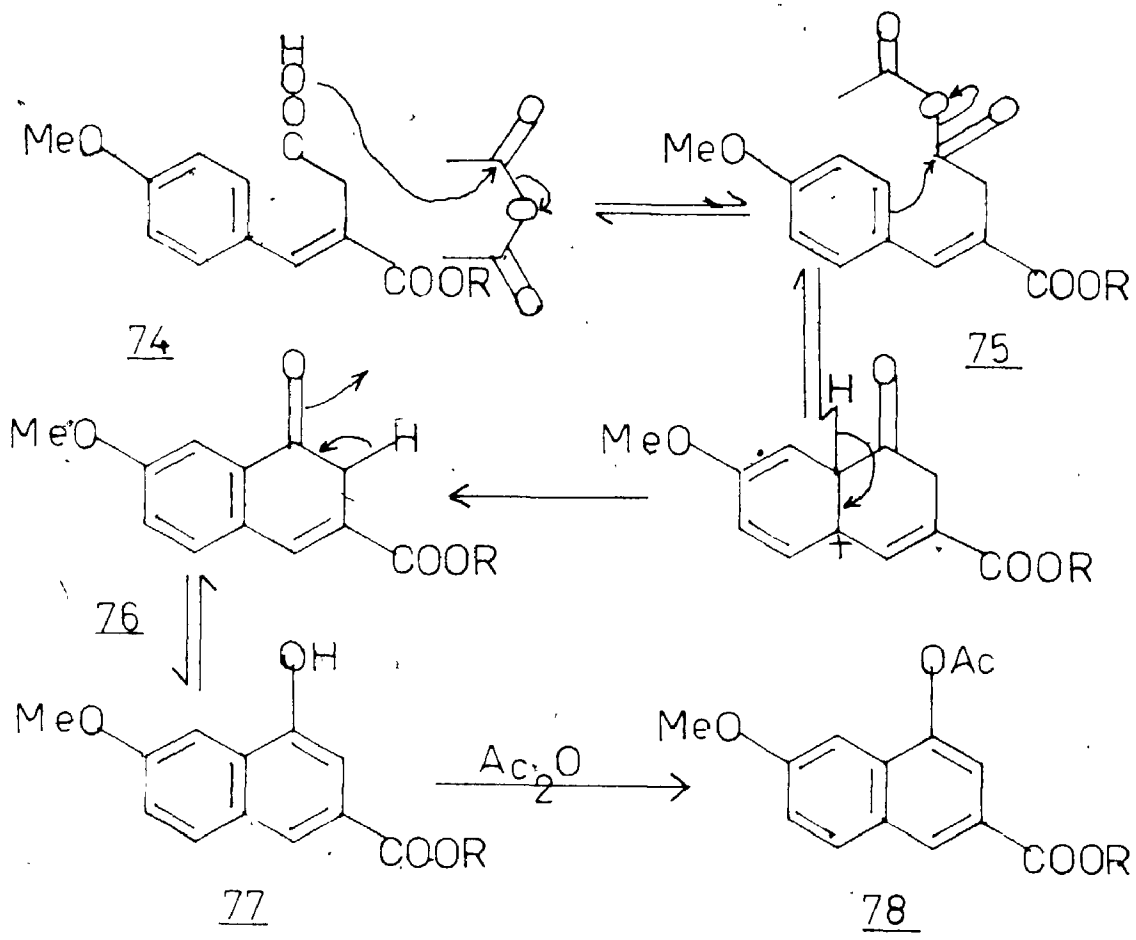
The cyclization reaction was found to go successfully using acetic anhydride both with and without anhydrous sodium acetate (37). Stronger acid cyclizing agents such as polyphosphoric acid or concentrated sulphuric acid were not employed for two basic reasons. It has

been shown earlier that methoxyl groups in several of the compounds discussed are especially sensitive to acid. Secondly, the use of strong acids would normally require the reduction of the side chain double bond before the cyclization could be carried out, because carbonyl groups α to the reaction site are known to deactivate systems sufficiently to prevent the reaction from occurring (25). Removal of the double bond would isolate the carbonyl from the ring and thereby destroy its effect.

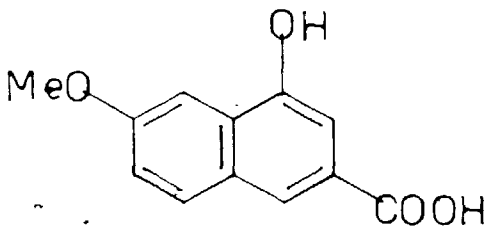
The first step in the cyclization reaction consisted of formation of the mixed anhydride 75. The anhydride was then attacked by the ring in either position ortho to site of the side chain to yield a ketone 76, which tautomerized to give the corresponding phenol 77. The free phenol was then readily acetylated with the large excess of acetic anhydride to give ethyl 1-acetoxy-7-methoxy-3-naphthoate 78. Only one product was obtained, because the two positions ortho to the side chain are equivalent and reaction at either site would give the same product.

The conversion of the ester to a nitrogen function was expected to require conditions which would hydrolyze the phenolic acetate, so a more effective blocking group had to be found to ensure that the phenol would not interfere.

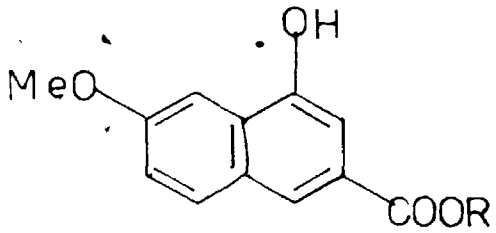
The ester 78 contains two different ester groups and it was necessary to cleave the phenolic acetate selectively while leaving the naphthoic ester untouched. Aqueous potassium hydroxide cleanly cleaved both esters



to give the corresponding phenol-acid 79, whereas filtration of the substrate on a column of neutral alumina selectively removed the acetate to give the phenol 77.



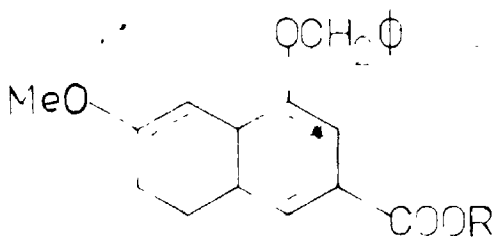
79.



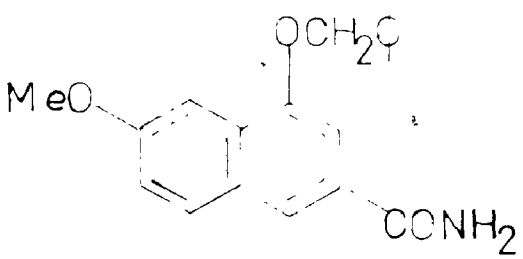
77.

An attempt to convert the ester group of compound 77 to the corresponding amide using ammonia, methanol and glycerin in a sealed tube (39) resulted in the formation of a polymer, which demonstrated the need for adequate protection of the free phenol.

The benzyl group was selected as the best protecting group. It is easily introduced and it can be removed by catalytic hydrogenolysis at the proper time. The phenol 77 (R = ethyl) was treated with potassium carbonate and benzyl bromide in dry acetone to give the benzyl ether 80 in good yield (40).



80



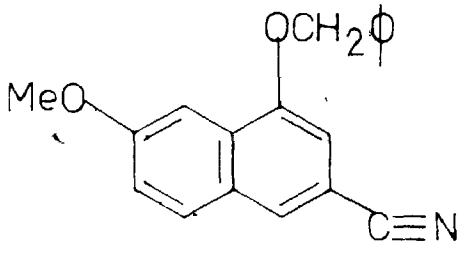
81

Formation of the corresponding amide 81 was carried out using a one step process or, alternatively, a three step process. The one step reaction consisted of heating the ester with methanol, glycerin, and ammonia in a sealed tube at about 120 degrees for eighteen hours (39). In the three step conversion the ester was first hydrolyzed with aqueous potassium hydroxide. The free acid was then treated with thionyl chloride to form the acid chloride, which without isolation or purification, was treated with ammonia to give the corresponding amide. Both methods

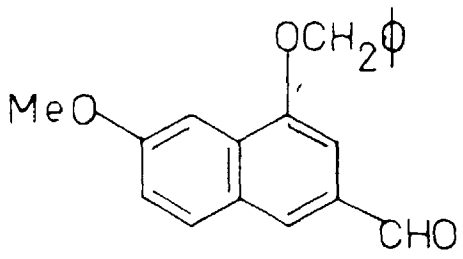
worked quite well and the only major factor to consider in the choice between them is scale. Small scale reactions are easily conducted in sealed tubes, but large scale sealed tube reactions are dangerous and finding suitable equipment is difficult. The steps in the three reaction sequence are so simple that it could be used on any scale.

Direct reduction of the amide 81 to the corresponding naphthyl amine was unsuccessful. Diborane (41) had no apparent affect on the substrate since starting material was recovered in high proportions from the reaction mixture. Lithium aluminium hydride (42,43) on the other hand cleaved the benzyl ether in preference to reduction of the amide group. The phenolic amide was not fully characterized, although the spectra suggested that the amide group was intact and the benzyl ether had disappeared.

The amide 81 was dehydrated to the nitrile 82 in good yield with thionyl chloride and pyridine (44).



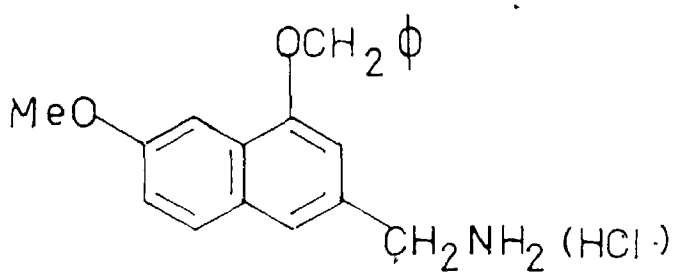
82



83

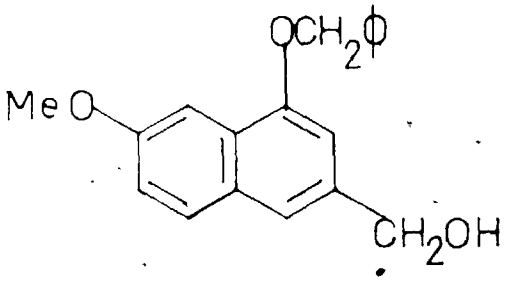
Reduction of the nitrile 82 with two moles of lithium aluminium hydride (45) gave a moderate yield of the aldehyde 83. If the amount of reducing agent was increased to a large excess and the reaction time was lengthened, a

low yield of the amine was isolated as the hydrochloride salt 84.

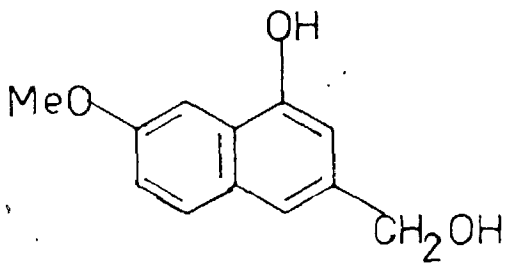


84

The aldehyde was made from the ester 80 in two easy steps. Treatment of the ester with excess lithium aluminium hydride (46) led to the formation of the desired



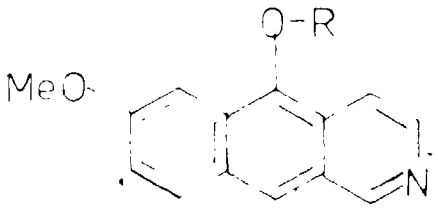
85



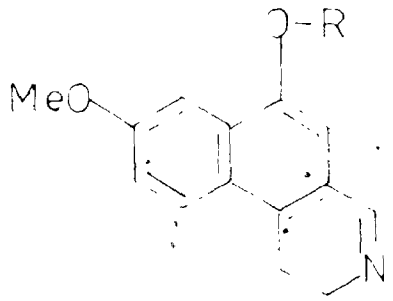
86

alcohol 85 in good yield. The reaction was a straightforward hydride reduction of an ester, although conditions had to be watched closely to minimize the formation of the diol 86. Lithium aluminium hydride is capable of causing the hydrogenolysis of the benzyl ether as we have seen earlier. Oxidation of the alcohol 85 with manganese dioxide (47) proceeded smoothly to give the same aldehyde 83 obtained from the partial reduction of nitrile 82.

Two routes to the β azanthracene were considered. The aldehyde 83 was the precursor for one pathway and the amine 84 was the precursor for the other. The greatest problem associated with ring formation in this simple case is the possibility of two different products depending on which site reacts to close the ring. In one case the azanthracene 87 would be produced, whereas ring closure at the alternative site would give the azaphenanthrene 88.



87



88

This problem exists in the more complicated trimethoxyl case as well. The obvious solution to the problem is to block the position para to the oxygen function in ring B, thereby preventing formation of the azaphenanthrene. Presumably, if the para site is more reactive in the ring closure reaction, then it follows that it would be reactive enough to undergo the substitution reaction required to introduce a blocking group.

The choice of blocking group is influenced by the nature of the groups in the peri positions of ring A because of the strong interactions between functional groups in peri positions (32). This consideration makes the choice of model appear rather unfortunate, since the

only difference between the model and the more complicated structure is the presence of two peri methoxyls in ring A of the latter compound. It was then decided that further work on the model system was unwarranted. The remainder of the discussion will then be completely devoted to the progress made in the preparation of suitable precursors for the synthesis of bostrycoidin.

New Route to Bostrycoidin

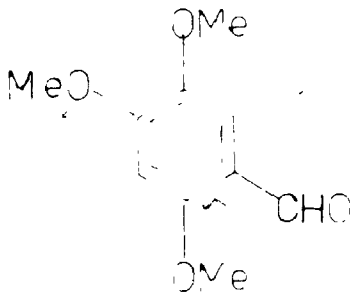
The starting material was the same 1,2,4-trimethoxybenzene used before, but the reaction sequence was chosen so that only one product was obtained in each step, thereby eliminating the need for tedious isomer separations.

A high yield of 2,4,5-trimethoxybenzaldehyde 89 was obtained by performing a Gattermann reaction (48) on 1,2,4-trimethoxybenzene. One can rationalize this result on the basis of electrophilic substitution theory. Of the three open positions in 1,2,4-trimethoxybenzene, only two are activated by two methoxyl functions, and of these C-3 is more sterically hindered than C-5, having two ortho methoxyls to interfere rather than one methoxyl and a hydrogen. Thus C-5 should be more susceptible to electrophilic attack than either C-3 or C-6, as is found.

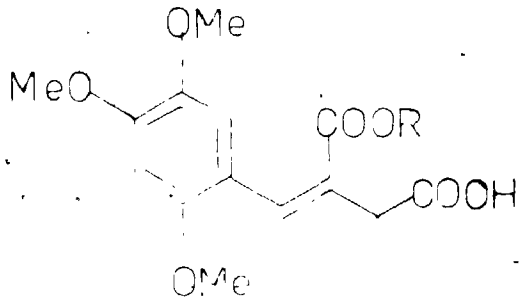
The reactions required to carry out the next three steps have been discussed in detail in the section devoted to the monomethoxyl series. Comments made in this section will not repeat previous arguments but rather single out

differences between the monomethoxyl and trimethoxyl compounds.

When 2,4,5-trimethoxybenzaldehyde 89 was subjected to the conditions for the Stobbe condensation (37), a dramatic difference in reaction rate from the reaction of anisaldehyde was anticipated. The additional methoxyl functions were expected to reduce the reactivity of the carbonyl carbon of the aldehyde via resonance effects. The reaction should also be expected to be slowed down because of the proximity of one of the additional methoxyls.



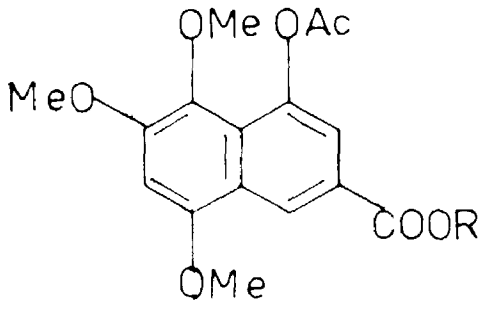
89



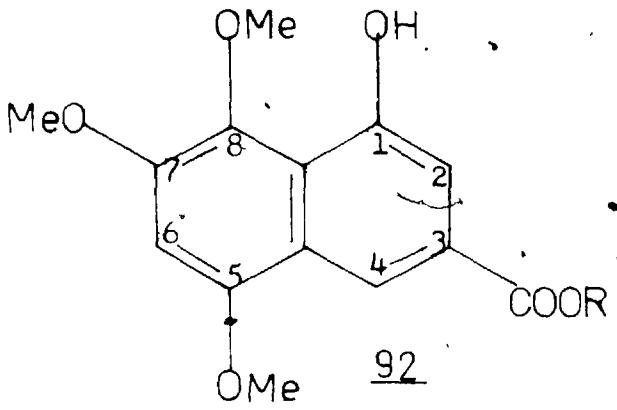
90

Accurate kinetic studies are beyond the scope of this work, but it was interesting to note that there were no differences observed in the two reactions when comparable conditions were maintained. Even in the trimethoxyl case, the reaction proceeded smoothly to give a good yield of the half ester 90.

The cyclization of the condensation product 90, proceeded smoothly to give a good yield of the diester 91. The additional two methoxyl groups in the trimethoxyl half ester 90 contribute to two opposing effects. The electron donation by the methoxyls certainly facilitates



91



92

the electrophilic attack of the mixed anhydride, but the size and proximity of the methoxyls give rise to steric effects which slow the reaction. In the monomethoxyl series, there are two identical sites where reaction can occur because of the symmetry of the system. The trimethoxyl case has only one potential reaction site, which means there is a restriction on the conformation of the molecule before reaction can occur, i.e. the probability is a factor of two smaller. Apparently, the opposing contributions made by the additional two methoxyls roughly cancel, since no large rate differences were observed between the two systems.

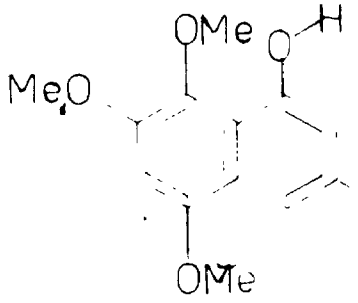
The selective hydrolysis of the acetate was necessary to prepare for the introduction of the three carbon side chain at C-2. Conversion of the acetate on C-1 to a free phenol would reduce steric interference for any reaction around C-2, and the election density would be significantly increased at C-2 via resonance and the inductive effect, thereby facilitating electrophilic substitution reactions. Of course, it was also a necessary prerequisite

for a Claisen rearrangement (49).

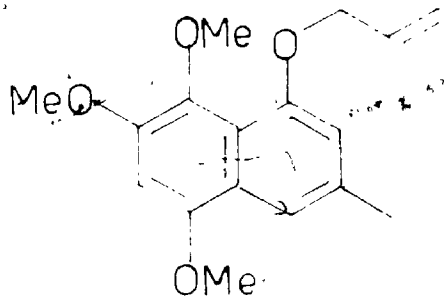
It was important to preserve the naphthoic acid function (at C-3) in the form of an ester group to prevent transesterification or decarboxylation reactions. Loss of the carbonyl carbon would destroy any chance of building ring C in such a way that the relative postions of the β methoxyl in ring A and the nitrogen in ring C would be known with certainty. Aqueous sodium hydroxide was found to be unselective, since both ester groups were smoothly cleaved in high yield. Selective cleavage of the acetate was carried out in over 90% yield by filtering the substrate on a column of neutral alumina using benzene as the solvent medium. Steric considerations suggest that the cleavage of the acetate in the more hindered trimethoxyl case should be more facile, since the reaction provides some relief to the crowding situation present in the acetate 91. In addition, the presence of an oxygen function at C-8 could accelerate the ester cleavage because of its ability to coordinate the lewis acid catalyst. The comparative ease with which the hydrolysis took place is indicated by the fact that the trimethoxyl naphthol 92 was never contaminated with the starting acetate 91 unless the alumina column was flooded, whereas, cleavage of the monomethoxyl acetate 78 often resulted in a mixture of unreacted acetate 78 and the desired naphthol 77, unless the column was eluted very slowly.

Some difficulty was anticipated in the preparation of the allyl ether 93 because of the problems Hardegger et.al. experienced with a close analogy (21). In order

to prepare the allyl ether 95 from the naphthol 94 in 72% yield, it was necessary to reflux the reaction mixture for 15 hours per cycle and recycle six times, a total of 90 hours reaction time. In contrast, the naphthol 92

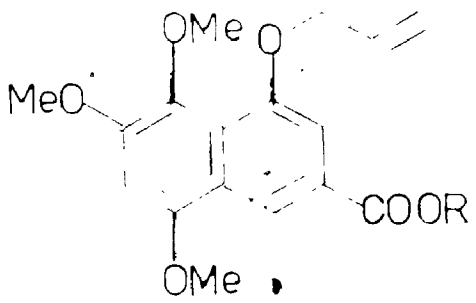


94

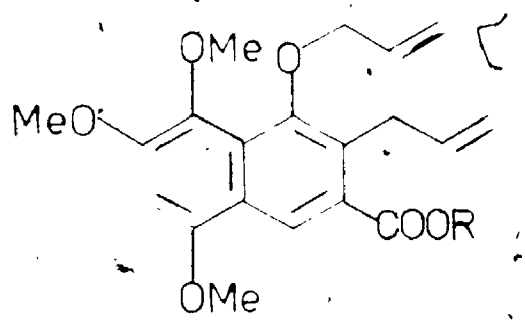


95

was alkylated in 82% yield after only 20 hours. The absence of starting naphthol 94 in the crude reaction product was demonstrated by extraction with ice cold Claisen's alkali (50) which was immediately neutralized with ice cold hydrochloric acid. The ester group apparently increased the acidity of the naphthol by inductive stabilization of the corresponding naphthoxide ion, thereby facilitating the alkylation reaction.



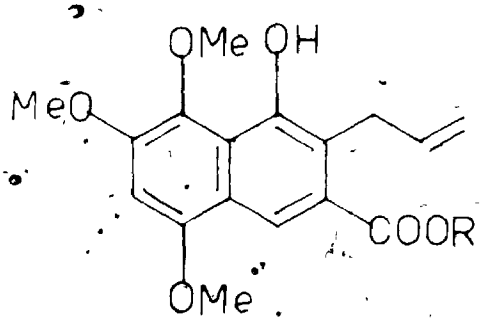
93



96

When the reaction was allowed to proceed for a longer time (72 hours), significant amounts of a new product

appeared. This was shown to be the diallyl compound 96. This substance could have arisen in two different ways. The O-alkylation could have been followed by a slower C-alkylation at C-2. On the other hand, O-alkylation could have been followed by a Claisen rearrangement, which would then be followed by a second O-alkylation. Evidence for the latter path was obtained by heating the allyl ether 93 at 100°. After 5 hours the reaction mixture was observed to contain about equal amounts of the starting allyl ether 93 and the product of the Claisen rearrangement 97. In light of this evidence, it is



97

reasonable to suggest that rearrangement occurred during the alkylation reaction.

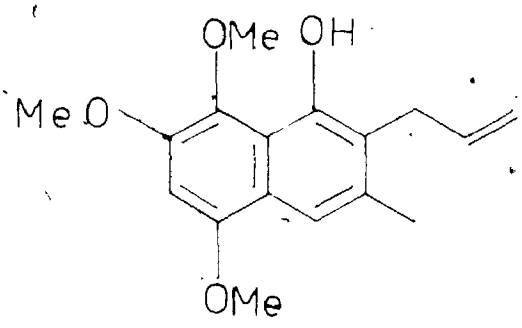
The allyl ether 93 decomposed when heated neat above its melting point, but it was possible to carry out the Claisen rearrangement in high yield using an inert nitrogen atmosphere and carefully purified N,N-diethylaniline as solvent (49). Hardegger et al (21) heated the allyl ether 95 at 210° for 6 hours to complete the reaction, but rearrangement of the ether 93 was complete after only 10 minutes at 200° and had a half life of

about 5 hours at 100°. Apparently, the ester group at C-3 facilitates the rearrangement as well as the alkylation of the naphthol.

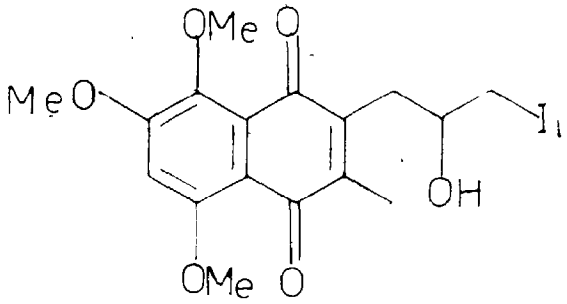
In many systems (49), the product of a Claisen rearrangement contains both the C-2 and C-4 allyl isomers provided that neither position of the substrate is blocked by another substituent. When the allyl ether 93 was heated, only the C-2 allyl product 97 was obtained, which is consistent with the experience of Hardegger and co-workers (21) in a similar system. The C-4 allyl isomer would contain a very unfavourable peri interaction between the methoxyl on C-5 and the allyl group on C-4 which is absent in the C-2 allyl isomer.

At this stage, it is necessary to introduce two oxygen atoms into the molecule in order to achieve the basic structure of the desired family of compounds. Ring "B" has to be oxidized from a naphthol to the corresponding 1,4-quinone, and the allyl side chain must be transformed into an acetonyl group. Hardegger et.al. (22) discovered that N-iodosuccinimide in a mixture of dimethylformamide, acetic acid and water oxidized the naphthol 98 to the quinone iodohydrin 99 in 42% yield, thereby introducing the two necessary oxygens simultaneously.

When these conditions were applied to the allyl naphthol 97, the product consisted of expected iodohydrin 101, and a new compound $C_{19}H_{21}O_6I$ in roughly equal



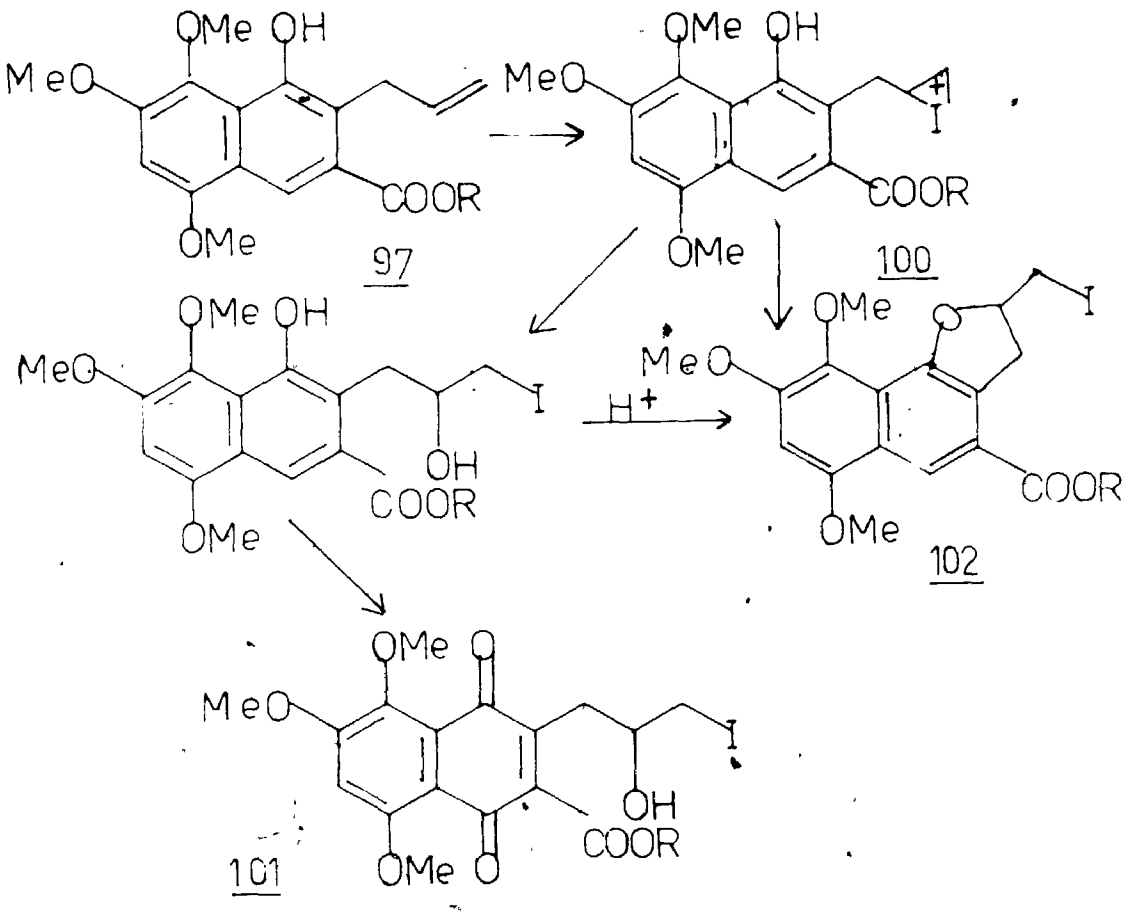
98



99

proportions. The latter compound was shown to contain an iodine atom, an ester function, three methoxyl groups, no quinone and no hydroxyl. This is easily rationalized if one looks at the reaction in a stepwise manner. The first step would be attack of the double bond by N-iodosuccinimide to form an intermediate iodonium ion 100. Attack by a water molecule could then occur at the secondary carbon (iodonium ions open by attack at a secondary carbon in preference to a primary carbon). The resulting iodohydrin would then be oxidized by two additional molecules of N-iodosuccinimide to give the corresponding 1,4 quinone observed in the reaction product. In an analogous manner, the iodonium ion can undergo intramolecular attack by the phenolic oxygen atom to give the new compound 102. This product would be stable to further oxidation by N-iodosuccinimide.

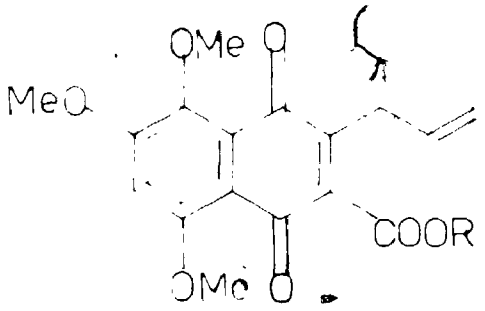
When Hardegger and co-workers (22) oxidized the allyl naphthol 98 with N-bromosuccinimide, they found a marked difference between the rate of oxidation of the naphthol and that of the double bond in the side chain. The



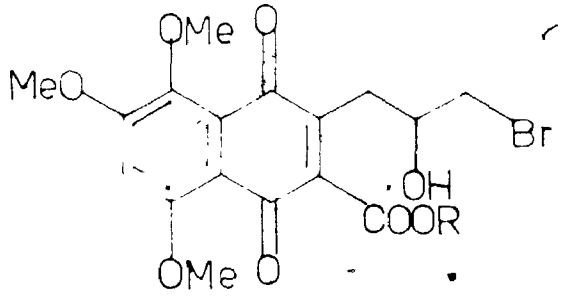
naphthol was oxidized to the corresponding 1,4 quinone in 30% yield when a mixture of dimethylformamide, acetic acid and water was used as solvent. Oxidation of the double bond to the corresponding bromohydrin required a higher temperature and a mixture of dioxane, water and perchloric acid for solvent. Even then the yield was only 9%.

When the allyl phenol 97 was used as substrate, the difference in rates was less pronounced. When the reaction was carried out with less than the necessary 3 equivalents of N-bromosuccinimide, there was a mixture of starting allyl phenol 97, allyl quinone 103 and quinone bromohydrin 104 after all the oxidizing agent was consumed. On

addition of more oxidizing agent, the first two components of the mixture disappeared and the quantity of the third increased to a maximum. This suggests that the rates of the two oxidations were similar. If either reaction were significantly faster than the other, only two of the three compounds would have been present in the reaction mixture when between two and three equivalents of oxidizing agent were used.



103

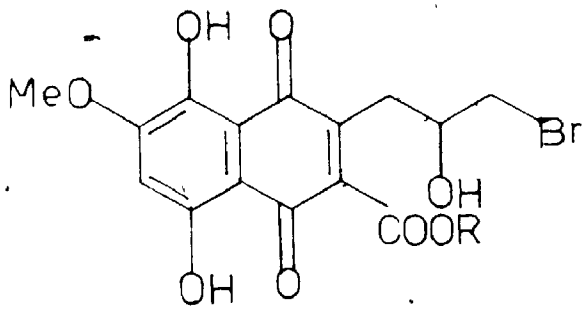


104

The reaction itself posed no great difficulties, but isolation and purification of the quinone bromohydrin was quite a different matter. The reaction was stopped by diluting with a large volume of water. Extraction with methylene chloride followed by washing several times with water removed most of the dimethylformamide and acetic acid. The remainder was removed by pumping down at room temperature in the dark since the quinone bromohydrin is susceptible to decomposition by heat and light. The succinimide was removed from the crude product without decomposition of the sensitive quinone bromohydrin by filtration through a column of deactivated thin layer silica gel. The silica gel was deactivated

by making a slurry in water and air drying before use in the column. The purified quinone bromohydrin was recrystallized from diethyl ether. Once purified and dried, this compound could be stored for months, if kept cold and dark.

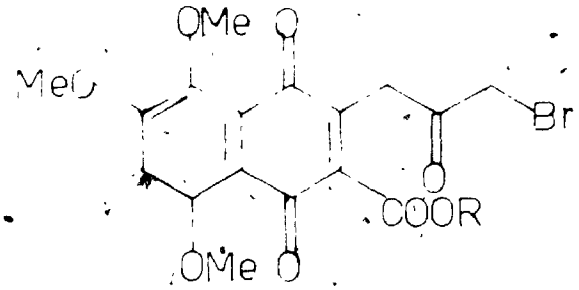
When pure quinone bromohydrin 104 was left in a closed, transparent glass vial on the bench top for several days it was observed that the brilliant orange solid had changed to a deep red solid without changing crystal form. A thin layer plate showed that all the quinone bromohydrin had disappeared and it was replaced by a single new product $C_{17}H_{17}O_8Br$. This new product contained a bromine, an ester function, only one methoxyl, a quinone, two aromatic hydroxyls and a single aromatic hydrogen. The two peri methoxyls had cleaved, presumably by the action of some hydrobromic acid which must have been liberated from the side chain by heat and light to give the naphthazarin 105.



105

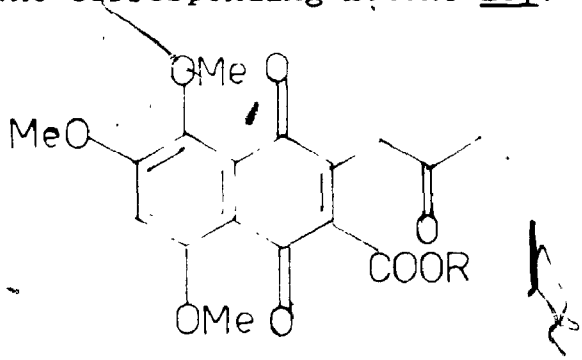
An oxidation of the secondary alcohol to the corresponding ketone and replacement of the bromine with hydrogen are the two remaining operations. Hardegger and co-workers (22) experienced fewer problems when the oxidation was

carried out before the reduction. When an acetone solution of the quinone bromohydrin 104 was treated with excess Jones' reagent (51), the oxidation proceeded quickly and smoothly in good yield (78%) to give the corresponding bromoketone 106. Purification of the crude product was difficult, since it decomposed quickly on even the specially prepared silica gel used for the quinone bromohydrin. Fortunately, the reaction was clean and the crude product could be crystallized from an ethyl acetate-hexane mixture.



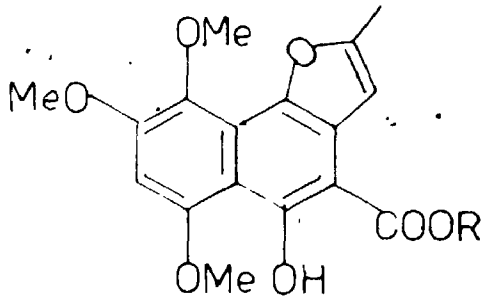
106

The last step was simple reduction of the bromoketone 106 to the corresponding ketone 107. Successful



107

completion of that step would give the dimethyl ether of the first member of the family 107. Modification of the ester group would give the other members of the family, namely, javanicin (methyl), fusarubin (hydroxymethyl), bostrycoidin (imine), and the corresponding aldehyde for which there is no common name. When the bromoketone 106 was treated with zinc dust and acetic acid (52), the red colour disappeared instantly and after 1.5 hours a colourless product $C_{19}H_{20}O_7$ was isolated in 83% yield. The proton magnetic resonance spectrum indicated the presence of an isolated ethyl group, a methyl coupled to a single hydrogen, a vinyl hydrogen coupled to a methyl, three methoxyls, an aromatic hydroxyl and an isolated aromatic hydrogen. The infrared spectrum indicated a hydroxyl and an ester, but no quinone. This evidence was consistent with 4-carboethoxy-5-hydroxy-2-methyl-6,8,9-trimethoxynaphtho (1,2-b) furan 108. The instant decolouration suggested a quick reduction of the quinone to the corresponding hydroquinone which, instead of remaining



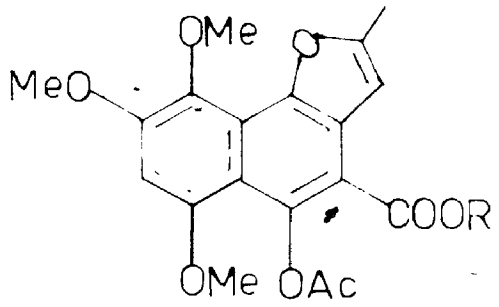
108

inert, cyclized to give a furan. At some time during the reaction, the bromide was also reduced. There was

insufficient evidence gathered to determine whether the bromine came off before or after the cyclization.

When the same reduction was attempted using hydrogen and either palladium on charcoal with 95% ethanol and a trace of triethylamine as solvent (53), or 5% palladium on strontium carbonate with ethyl acetate as solvent (54), the same result was obtained. The ease with which the cyclization occurred can be explained by the fact that the intermediate adduct readily lost water in an irreversible transformation to give a very stable aromatic product.

In an attempt to trap the hydroquinone as the diacetate (55), the reduction was carried out with zinc dust and 50% acetic anhydride in acetic acid. The only product isolated (68%) was 5-acetoxy-4-carboethoxy-2-methyl-6,8,9-trimethoxynaphtho (1,2-b) furan 109. The presence of peri interactions in this system would tend to increase the

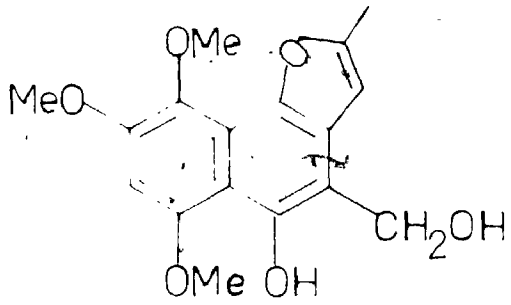


109

normal preference for the unimolecular cyclization over the bimolecular acetylation.

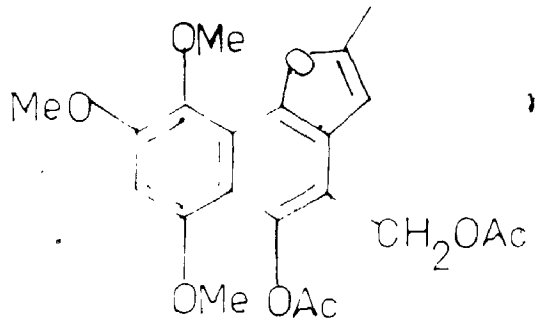
Formation of the furan should provide excellent protection for both the quinone and the acetonyl side

chain, while the ester group is reduced. In order to test the stability of the furan, the ester 108 was treated with excess lithium aluminium hydride in anhydrous ether (46) to give a good yield of a compound which was very unstable and difficult to purify. The proton magnetic resonance spectrum indicated the presence of three methoxyl groups, two single hydrogens which exchange with deuterium oxide readily, an isolated methylene, a methyl coupled with a single vinyl hydrogen, and finally an aromatic hydrogen. One interpretation of these data is that the anticipated diol 110 was obtained.



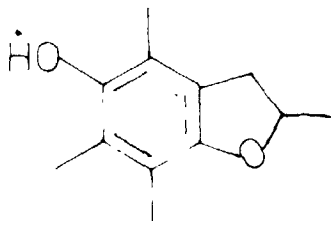
110

The diol 110 was treated with acetic anhydride and pyridine to give the corresponding diacetate 111 in 65% yield. Unfortunately, the diacetate was also difficult to purify. It did crystallize, but attempts to purify the product by recrystallization were unsuccessful. The infrared and proton magnetic resonance spectra indicated three methoxyl methyls, two acetate methyls, one vinyl methyl, one methylene, one vinyl hydrogen, one aromatic hydrogen, and no exchangeable hydrogens. Structure 111 is then consistent with the evidence available

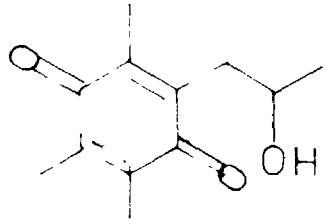


111

for the diacetate. It appears that a means of reducing the ester to the corresponding alcohol without disturbing the fundamental ring structure has been discovered. A synthetic route to several of the members of the family mentioned above has been found, provided the oxidative cleavage of the furan ring to regenerate the C-2 acetonyl quinone can be successfully carried out without skeletal rearrangement. Karrer et. al. (56) were able to oxidatively open the dihydrofuran 112 to give



112



113

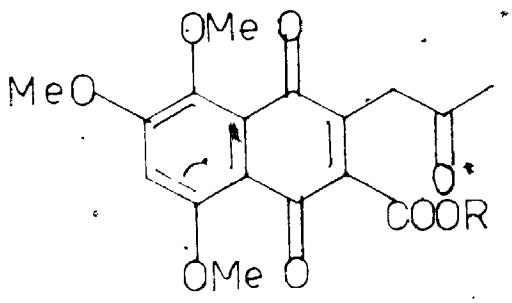
the quinone 113 with ferric chloride. When the oxidizing agent was changed to gold (III) chloride, there was a significant increase in the yield of the quinone 113.

Treatment of the ester 108 with gold (III) chloride

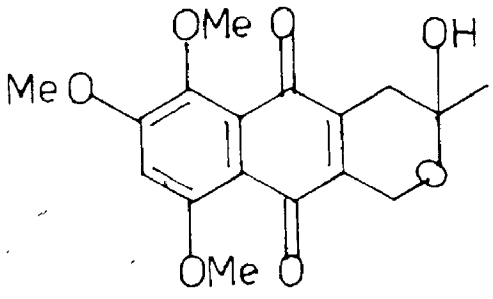
in aqueous ethanol at room temperature gave a 37% yield of a red oily compound. Infrared absorption at 1735 and 1665 cm^{-1} suggested the presence of an ester or ketone and a quinone respectively. The proton magnetic resonance spectrum indicated the presence of an ethyl group, three methoxyls, an isolated methyl group, an aromatic hydrogen and a methylene. The spectral evidence is consistent with structure 107 which is the 5,8 dimethyl ether of the ester analogue of javanicin. At least two other quinonoid compounds were observed in the thin layer chromatograms, but they were not characterized.

The ester 108 was also oxidized with ferric chloride in aqueous alcohol at room temperature. Work up of the reaction mixture followed by thin layer chromatographic isolation of the crude product gave 54% yield of the same quinone ester 107 that was isolated from the gold (III) chloride oxidation. The crude product also contained one of the unidentified quinones observed above.

The third reagent used to carry out the desired cleavage was 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)



107



114

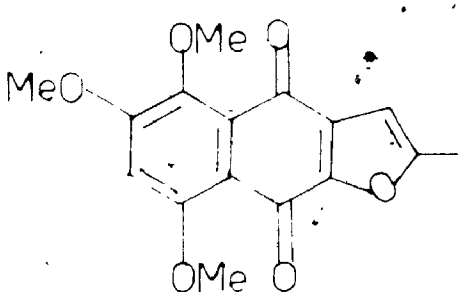
(57). In this reaction, the substrate 108 was mixed dry in a flask with two equivalents of DDQ. Since the reagent is sensitive to oxygen, the atmosphere over the dry chemicals was replaced with dry nitrogen before adding the methanol required for a reaction medium. During both the reaction time and work up, care was taken to minimize contact with oxygen and heat. Thin layer chromatography was used to separate 47% of the same quinone ester 107 that was isolated in the previous attempts. The unidentified quinone common to both of the previous reaction products was also observed in this product.

From the observations made in these cases, it may be concluded that a variety of reagents have the capability of opening the furan to regenerate the quinone and acetonyl groups without complication. Successful completion of this oxidative ring opening has yielded the 5,8 dimethyl ether of the ester analogue of javanicin and fusarubin.

Oxidative cleavage of the diol 110 was expected to give the 5,8 dimethyl ether of fusarubin 114. Treatment of the diol with DDQ in methanol yielded a red crystalline solid with a melting point of 218-219°. The infrared spectrum showed no absorption for a hydroxyl, a band at 2845 cm^{-1} indicating the presence of methoxyl(s), a band at 1662 cm^{-1} indicating a quinone and a band at 1550 cm^{-1} indicating an alkene or aromatic. The mass spectrum contained a parent peak at m/e of 302 which suggested the loss of sixteen mass units. The proton magnetic resonance spectrum gave a good indication of the structure of the

final product. The presence of three methoxyl groups was verified by characteristic singlet peaks between 3.87 and 3.98 ppm. Apparently, no major alterations were made to ring "A". This was further supported by the broad singlet absorption at 6.44 ppm. which has been found to be characteristic for the aromatic hydrogen on ring "A" throughout this study. Peaks at 2.42 and 6.44 ppm. suggested the presence of a vinyl methyl coupled to a single vinyl proton. No other absorption was observed.

Ring "A" surviving unchanged and ring "B" existing as a para quinone account for all but three carbons, one oxygen and four hydrogens. In order to be consistent with the pmr spectrum, the four hydrogens and three carbons must exist as a methyl and a single hydrogen attached to a double bond. Since no carbonyl or hydroxyl is involved in the attachment of the three carbon fragment to ring "B", the oxygen must be present in the form of an ether linkage. Structure 115 is consistent with all of the evidence available. Unfortunately, the reaction has



115

resulted in the loss of the critical carbon; the one which differentiates one member of the family (discussed earlier)

from another by virtue of its oxidation state and/or the nature of the heteroatom attached to it.

One possible explanation of the overall loss of sixteen mass units during the oxidation is described in figure VI. Ketonization of the ring B phenol group in the diol 110 would give the β hydroxyketone 116 which can exist in a conformation that is suitable for an intramolecular reverse aldol reaction via a six membered transition state resulting in the formation of the phenol 117 and formaldehyde. After loss of the critical carbon, hydride abstraction by DDQ in methanol (57) would give the intermediate ketal 118 which would decompose in the presence of traces of water to give the corresponding 1,4 quinone 119. No water was intentionally added to the reaction mixture, but during work up there was no attempt to exclude it.

Ring closure could occur via attack of the enol form of the acetonyl side chain on the ring as shown in figure VI. The resulting hydroquinone 120 would be oxidized to the corresponding quinone 115 either by DDQ or by air oxidation.

This pathway requires two moles of oxidizing agent. The reaction was carried out with only one equivalent of DDQ which suggests that the maximum yield should be only 50%. The 61% yield can be explained by the facile air oxidation of naphthohydroquinones referred to earlier.

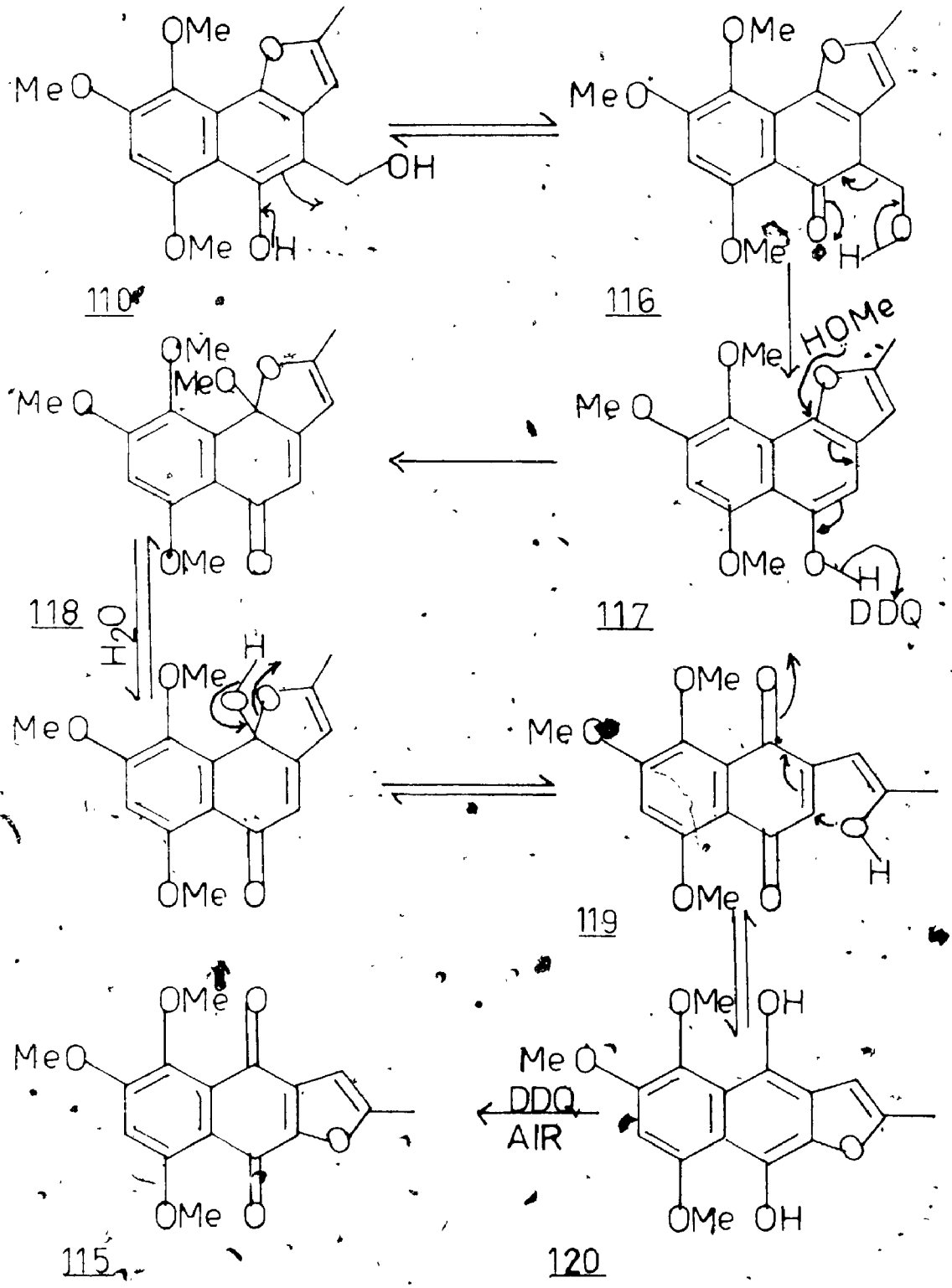

OMe
MeO
OH
OMe
OH
110
116
HOMe
H
DDQ
117
118
H_2O
119
DDQ
AIR
115
120

FIGURE VI

Conclusion

The pathway described in this work has at least in its present state, some deficiencies. It has led to the successful synthesis of the ester 107 and there is no reason to suspect a problem in the synthesis of javanicin. To obtain the members of the family containing sensitive functional groups such as fusarubin (hydroxymethyl), bostrycoidin (imine), and the corresponding aldehyde for which there is no common name, will require additional planning and experimentation in order to avoid problems such as the loss of the critical carbon just described.

EXPERIMENTAL

Infrared spectra were determined on either a Beckman IR-5a or on a Beckman IR-10 spectrophotometer. Proton magnetic resonance spectra were determined on either a Varian DP-60 or a Varian A-60 spectrophotometer. Molecular weights were determined using a Varian M66 mass spectrophotometer. The silica gel used for column chromatography was B.D.H. reagent grade unless other wise specified and the alumina used for column chromatography was Shawinigan reagent grade aluminium oxide. The silica gel used for thin layer chromatography was Camag kiesel gel DF-5 untreated in all cases except those where denaturing with dilute acid was specified. Petroleum spirits refers to B.D.H. solvent with a boiling range of 60-80°. Melting points were determined on a Thomas-Hoover uni-melt apparatus and are uncorrected.

Microanalyses were performed by A. B. Gygli, Toronto, Ontario.

I Synthesis of Bostrycoidin via the Hardegger Pathway

1. Oxidation of 2-Methyl-5,7,8-trimethoxy-1-naphthol 63

(a) With Lead Tetraacetate.

A solution of 370 mg of 2-methyl-5,7,8-trimethoxy-1-naphthol in a mixture of 15 ml of chloroform and 2.5 ml of glacial acetic acid was cooled to 0°, before adding 1.7 g of lead tetraacetate. The reaction mixture stood at -10° for twenty hours and a further twenty-four hours at 5° before acidification with concentrated hydrochloric acid. The resulting precipitate was removed by filtration and the filtrate was extracted with chloroform. The chloroform extract was washed three times with water, once with saturated bicarbonate solution and finally once again with water before drying. Concentration gave 353 mg of an orange-red solid. Thin layer chromatography using silica gel plates developed in chloroform indicated the presence of at least thirteen different compounds with none appearing to predominate significantly.

Elution of a silica gel column with 60 -80° petroleum spirits gave 27 mg (7%) of a red solid which was recrystallized from methanol to give deep red needles of 3-chloro-2methoxy-7-methyl-8-hydroxy-1, 4-naphthoquinone mp 149.5-150°; reported (24) mp 145°.

Elution with 50:50 benzene: petroleum spirits gave 23 mg (7%) of a red solid which was recrystallized from methanol to give deep red crystals of 8-hydroxy-7methyl-2-methoxy-1,4-napthoquinone mp 169-171°; reported (24) mp 175-177°. No other pure compounds were isolated or identified.

(b) With Chromic Acid.

A solution of 235 mg of 2-methyl-5,7,8-trimethoxy-1-naphthol in 30 ml of 80% (v/v) aqueous acetic acid was cooled in an ice bath and treated with a cold solution of 235 mg of chromic anhydride in 10 ml of 80% (v/v) aqueous acetic acid, dropwise with continuous stirring. After stirring for one hour in the ice bath, the reaction mixture was allowed to reach room temperature. After a further hour, the reaction mixture was poured into excess ice water and the resulting aqueous solution was extracted with chloroform. The extract was washed twice with saturated bicarbonate solution, and once with water before drying and evaporation to 250 mg (quantitative) of an orange solid. Thin layer analysis on silica gel plates with ethyl acetate as developing solvent indicated a single product. Recrystallization from petroleum spirits gave orange crystals of 2-methyl-5,7,8-trimethoxy-1,4-naphthoquinone 46 mp 131-132°; reported (24) 128-130°.

The same procedure was used to quantitatively oxidize 3-methyl-5,7,8-trimethoxy-1-naphthol 28 to 3-methyl-5,7,8-trimethoxy-1,4-naphthoquinone 29 mp 143-144°; reported (21) mp 143-144°.

2. Reductive Methylation of 2-Methyl-5,7,8-trimethoxy-1,4-naphthoquinone 46

A solution of 95 mg of 2-methyl-5,7,8-trimethoxy-1,4-naphthoquinone in 25 ml of 95% ethanol was treated first with 500 mg of sodium dithionite dissolved in 5 ml of water and then with 5 ml of dimethyl

sulphate. The reaction mixture was refluxed while a solution of 20 g of potassium hydroxide in 35 ml of water was added as quickly as the vigorous reaction would permit. A second solution of 500 mg of sodium dithionite in 5 ml of water was added before stirring under reflux for one and a half hours. The reaction mixture was cooled and diluted with water. The aqueous solution was extracted with chloroform and the extract was washed with water twice, dried and concentrated to give 99 mg (93%) of a yellowish oil. Filtration on a column of alumina with benzene gave 69 mg (65%) of 2-methyl-1,4,5,7,8-pentamethoxynaphthalene 64 mp 79-80°. Elution with ethyl acetate gave 11 mg of starting material.

ir ($CHCl_3$), 2840 (OMe) and 1610 (C=C).

pmr ($CDCl_3$), 2.53 (s,3), 3.95 (s,3), 4.00 (s,3), 4.08 (s,3), 4.11 (s,3), 4.17 (s,3), 6.87 (broad s,1), 7.01 (s,1).

Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.73; H, 6.90.

Found C, 65.74; H, 6.94.

Reductive methylation of 3-methyl-5,7,8-trimethoxy-1,4-naphthoquinone 29 using the same procedure gave a 56% yield of 3-methyl-1,4,5,7,8-pentamethoxynaphthalene 65 mp 124-125°; reported (21) mp 115-116°. The starting material was recovered in 15% yield.

3. Attempted Bromination of 3-Methyl-1,4,5,7,8-pentamethoxynaphthalene 65

A solution of 25 mg of 3-methyl-1,4,5,7,8-

pentamethoxynaphthalene in 4 ml of carbon tetrachloride was treated with 30 mg (2eq) of N-bromosuccinimide and 0.5 mg of dibenzoyl peroxide. The reaction mixture was shaken in the dark at room temperature for five hours before filtering. Concentration of the filtrate gave a yellow oil which contained at least six products by analysis on silica gel thin layer plates developed with ethyl acetate. Preparative thin layer chromatography followed by sublimation gave 10 mg (45%) of orange 6-methyl-2,5,8-trimethoxy-1,4-naphthoquinone 70 mp 171-171.5°; reported (24) 170°.

4. Oxidation of 3-Methyl-1,4,5,7,8-pentamethoxynaphthalene 65

A solution of 3 mg of purified 3-methyl-1,4,5,7,8-pentamethoxynaphthalene in 1 ml of carbon tetrachloride was treated with about 0.5 mg of dibenzoyl peroxide. After shaking in the dark for six days the reaction mixture was evaporated down. The residue was analyzed on silica gel thin layer plates. Spots were observed which had the same intensity and one compound had the same R_f as 6-methyl-2,5,8-trimethoxy-1,4-naphthoquinone 70, while the other had the same R_f as 3-methyl-5,7,8-trimethoxy-1,4-naphthoquinone 29.

5. Decomposition of 3-Methyl-1,4,5,7,8-pentamethoxynaphthalene 65

A solution of 3 mg of 3-methyl-1,4,5,7,8-

pentamethoxynaphthalene in benzene was spotted on a silica gel thin layer plate. It was allowed to stand for 24 hours after developing. The colourless band for the starting material had turned orange. When the material was removed and analyzed on a fresh plate using 25% ethyl acetate in chloroform, spots corresponding to each of the quinones 70 and 29 were observed. No other compounds were identified.

II Synthesis of a Model System for Ring C Formation

1. Condensation of p-Methoxybenzaldehyde with Diethyl Succinate

Potassium (6.6 g) was dissolved in 100 ml of tertiary butanol and the resulting solution was refluxed and stirred while a solution of 18.2 g of p-methoxybenzaldehyde and 28 ml of diethyl succinate dissolved in 45 ml of tertiary butanol was added dropwise over 4 hours. The reaction mixture was stirred and refluxed overnight before cooling and diluting with water. The aqueous mixture was acidified with hydrochloric acid and then extracted with chloroform. The extract was washed thrice with water before drying and evaporation. The residue was dissolved in diethyl ether and washed four times with saturated sodium bicarbonate solution. The basic washings were neutralized with hydrochloric acid and extracted with chloroform. The extract was washed twice with water, dried with cotton wool and evaporated to give 38 g (quant) of the acid 74. Recrystallization from

ethanol gave colourless crystals mp 271-272°.

ir (nujol) 3300-2300 (broad O-H), 1667 cm^{-1} (unsaturated ester carbonyl).

pmr ($CDCl_3$), 1.33 (t,3, J=7Hz), 3.61 (s,2), 3.83 (s,3), 4.28 (q,2,J=7Hz), 6.90 (A_2B_2, 2,J=9.0 Hz), 7.33 (A_2B_2,2,J=9.0 Hz), 7.83 (broad s,1), 9.30 (s,1).

2. Preparation of Ethyl 1-acetoxy-7-methoxy-3-naphthoate 78

The 38 g of crude acid from the condensation reaction was treated with 150 ml of acetic anhydride and 5 g of anhydrous sodium acetate. The reaction mixture was refluxed overnight before cooling and pouring into 800 ml of ice water. The aqueous mixture was extracted with chloroform. The extract was washed twice with water, twice with saturated sodium bicarbonate solution and then once again with water before drying with cotton wool and evaporation to give 30.4 g (80%) of the diester 78. The product was easily purified by filtration on a column of silica gel using pure benzene as the solvent. Recrystallization from petrol gave colourless needles mp 100-101°.

ir ($CHCl_3$), 1776 (acetate C=O), 1715 (ester C=O), 1637 (aromatic C=C).

pmr ($CDCl_3$), 1.39 (t,3, J=7.0 Hz), 2.43 (s,3), 3.90 (s,3), 4.41 (q,2 J=7.0 Hz), 7.0 - 8.5 (m,5).

Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.67; H, 5.60.
Found C, 66.82; H, 5.51.

3. Preparation of Ethyl 1-hydroxy-7-methoxy-3-naphthoate 77

A solution of 30.2 g of ethyl 1-acetoxy-7-methoxy-3-naphthoate dissolved 500 ml of cyclohexane was put on a column of neutral alumina. Elution with benzene removed 11.7 g (28%) of ethyl 1-acetoxy-7-methoxy-3-naphthoate 78. Elution with chloroform removed 18.4 g (71%) of ethyl 1-hydroxy-7-methoxy-3-naphthoate 77. Recrystallization from benzene gave colourless cubes mp 156.5-157.5°.

ir ($CHCl_3$) 3571 (Sharp O-H), 3340 (broad O-H), 1695 (ester C=O), 1637, 1610 and 1590 cm^{-1} (aromatic C=C).

pmr (TFA), 1.51 (t, 3, J=7.0Hz), 4.12 (s,3), 4.55 (q,2, J=7.0Hz), 7.2-8.3(m, 5).

Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73.
Found C, 68.03 H, 5.62.

4. Preparation of Ethyl 1-benzyloxy-7-methoxy-3-naphthoate 80

A suspension of 2.7 g ethyl 1-hydroxy-7-methoxy-3-naphthoate, 2.7 g anhydrous potassium carbonate, 2.7 g benzyl bromide and 150 ml of dry acetone was refluxed for 24 hours. After cooling the reaction mixture was diluted with benzene filtered and evaporated

down. The residue was recrystallized from hexane to give 3.48 g (94%) of colourless needles of ethyl 1-benzyloxy-7-methoxy-3-naphthoate 81 mp 116-116.5°.

ir ($CHCl_3$), 1705 (ester C=O), 1637, 1610, and 1590 cm^{-1} (aromatic C=C).

pmr ($CDCl_3$), 1.39 (t,3, J=7.0Hz), 3.85 (s,3), 4.39 (q,2, J=7.0Hz), 5.24 (s,2), 7.0-8.5 (m,10).

Anal. Calcd for $C_{21}H_{20}O_4$: C, 74.98; H, 5.99.
C, 75.28; H, 6.00.

5. Hydrolysis of Ethyl 1-benzyloxy-7-methoxy-3-naphthoate 80

A solution of 600 mg ethyl 1-benzyloxy-7-methoxy-3-naphthoate in 20 ml of dioxane and 30 ml of 1N aqueous sodium hydroxide was allowed to stand in the dark at room temperature with occasional swirling for 72 hours before refluxing for ½ hour. After cooling and neutralization, the reaction mixture was extracted with chloroform. The extract was washed with water, dried and evaporated. The white solid residue was recrystallized from chloroform to give 505 mg (92%) of colourless needles, mp 235-236°, of 1-benzyloxy-7-methoxy-3-naphthoic acid.

ir (nujol) 3300-2500 cm^{-1} (acid O-H), 1685 (acid C=O), 1634, 1610 and 1590 cm^{-1} (aromatic C=C).

6. Preparation of 1-Benzyloxy-7-methoxy-3-naphthoamide 81

(a) From the acid.

A solution of 64 mg of 1-benzyloxy-7-methoxy-3-naphthoic acid, 60 mg of thionyl chloride, 2 drops of pyridine, and 25 ml of benzene was refluxed for 0,75 hours. After cooling, dry ammonia gas was bubbled through the solution for 20 minutes. The benzene was distilled off and the residue was dissolved in chloroform. The resulting solution was washed once with water, twice with saturated aqueous sodium bicarbonate solution, and once again with water before drying and evaporation. The white solid recrystallized from benzene to give 61 mg (98%) of white needles mp 187.5-188.5°.

ir ($CDCl_3$) 3497, 3390 (N-H), 1669 (amide C=O), 1631 and 1585 cm^{-1} (aromatic C=C)

pmr (TFA), 4.05 (s,3), 5.35 (s,2), 7.1-8.3 (m,10)

Anal. Calcd for $C_{19}H_{17}O_3N$: C, 74.25; H, 5.50; N, 4.56

Found C, 74.23; H, 5.72; N, 4.67

(b) From the ester 80

A Carius tube was charged with 45 mg of ethyl 1-benzyloxy-7-methoxy-3-naphthoate, 1 ml of methanol, 4 drops of glycerin, and 1 ml of liquid ammonia. The tube was sealed at liquid nitrogen temperature and then gently warmed to 122° for 18 hours. After cooling and opening the tube the contents were dissolved in chloroform. The extract was washed twice with water before drying and evaporation. The colourless solid residue mp 176-179.5° weighed 40 mg (93%). Recrystallization from benzene gave colourless needles mp 185.5-187°.

The mixed mp with the product of the acid chloride route was 186-188°.

7. Preparation of 1-Benzyloxy-7-methoxy-3-Cyanonaphthalene 82

A solution of 107 mg of 1-benzyloxy-7-methoxy-3-naphthoamide in 2 ml of pyridine was warmed to 50° before treatment with 20 drops of benzene sulphonyl chloride. The reaction mixture was allowed to stand for 5 hours before quenching in 120 mls of water. The aqueous solution was extracted with chloroform and the extract was washed twice with dilute sulphuric acid and once with water before drying with cotton wool and evaporation. The white residue was recrystallized from cyclohexane to give 95 mg (95%) of colourless crystals mp 114.5-115.5°.

ir ($CHCl_3$), 2227 (C≡N), 1629, 1605 and 1585 cm^{-1} (aromatic C=C).

pmr ($CDCl_3$), 3.92 (s,3), 5.25 (s,2), 6.9-7.8 (m,10).

Anal. Calcd for $C_{19}H_{15}O_2N$: C, 78.87; H, 5.23; N, 4.84.

Found : C, 79.21; H, 5.58; N, 4.85.

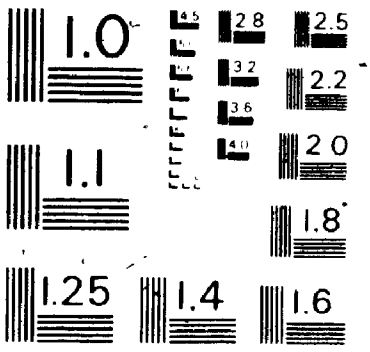
8. Preparation of 1-Benzyloxy-7-methoxy-3-naphthaldehyde 83

(a) Directly from the nitrile 82

A solution of 45 mg of 1-benzyloxy-7-methoxy-3-cyanonaphthalene in 15 ml of diethyl ether (freshly distilled from lithium aluminium hydride) was added slowly with stirring to a suspension of 11 mg of

2 2

OF/DE



lithium aluminium hydride in 10 mls of freshly distilled ether. The reaction mixture was stirred for 0.5 hours and then refluxed for an additional hour. The reaction was quenched with 1.5 ml of water and then 5 ml of 20% sodium hydroxide solution was added. The layers were separated and the aqueous layer was washed with ether. The combined ethereal solutions were washed twice with saturated sodium chloride solution, dried over anhydrous magnesium sulphate and evaporated to give a colourless oily residue. Thin layer chromatography using silica gel plates and 50% ethyl acetate and hexane indicated one major compound slower than the starting material. Preparative thin layer chromatography gave 18 mg (40%) of the starting material and 20 mg (45%) of colourless crystals mp 104-105° of 1-benzyloxy-7-methoxy-3-naphthaldehyde 83.

ir ($CHCl_3$), 2840 (OMe), 2720 (aldehyde C-H), 1686 (aldehyde C=O), 1630, 1610 and 1590 cm^{-1} (aromatic C=C).

pmr ($CDCl_3$), 3.96 (s,3), 5.35 (s,2), 7.5 (m,10) 10.07 (s,1).

Anal. Calcd for $C_{19}H_{16}O_3$: C, 78.06; H, 5.52.
Found C, 77.70; H, 5.31.

A D.N.P. derivative was prepared and recrystallized from chloroform mp 256-258°.

Calcd for $C_{25}H_{20}O_6N_4$: C, 63.55; H, 4.27; N, 11.86.

Found C, 63.12; H, 4.25;
N, 11.40.

(b) Via the alcohol 85

A suspension of 300 mg of lithium aluminium hydride in 60 ml of anhydrous ether was stirred for one hour before a solution of 1.00 g of ethyl 1-benzyloxy-7-methoxy-3-naphthoate in 60 ml of anhydrous ether was added dropwise with stirring over a period of two hours. The reaction mixture was stirred and refluxed for a further three hours before cooling and treating with 10 ml of water. A few drops of 10% aqueous sulphuric acid were added to complete the hydrolysis and the two layers were separated. The aqueous layer was extracted with ether five times. The extract was dried over anhydrous magnesium sulphate and evaporated down to give 0.82 g (93%) of almost colourless oily 1-benzyloxy-7-methoxy-3-naphthyl alcohol 85. The alcohol is somewhat unstable and quite pure (T.L.C.) so it was used in the next step without further purification.

ir ($CHCl_3$) 3600, 3450 (O-H) 1639, 1613 and 1592 cm^{-1} (aromatic C=C).

pmr ($CDCl_3$) 2.50 (bs, 1), 3.85(s,3), 4.68 (s,2), 5.16 (s,2), 7.3 (m, 10).

After dissolution of the alcohol in 100 ml of anhydrous diethyl ether, 32 g of freshly prepared active manganese dioxide was added. The resulting suspension was shaken overnight before filtration. The residue of

manganese dioxide was washed thoroughly with anhydrous ether and then the ethereal washings were concentrated to give a pale yellow oil. Filtration on alumina with ether followed by crystallization from petroleum spirits gave 0.59 g (72%) colourless crystals of 1-benzyloxy-7-methoxy-3-naphthaldehyde 83 mp 106-108°. A mixed melting point with the product from the nitrile reduction was 105-107°. The D.N.P. was prepared and recrystallized from chloroform mp 257-257.5°.

III Synthesis of Bostrycoidin Via A New Route

1. Preparation of 2,4,5-Trimethoxybenzaldehyde 89

Dry hydrogen chloride was bubbled through a stirred solution of 11.2 g of 1,2,4 trimethoxybenzene and 12.0 g of zinc cyanide in 250 ml of anhydrous ether at room temperature for 90 minutes. The ether was decanted off and replaced by an equal volume of water. The aqueous suspension was warmed and stirred for 45 minutes. After cooling the precipitate was collected and recrystallized from methanol to give 11.8 g (90%) of colourless needles of 2,4,5-trimethoxybenzaldehyde 89 mp 111.5-113°; reported (58) 113-115°.

2. Condensation of 2,4,5-Trimethoxybenzaldehyde 89 With Diethyl Succinate

Clean potassium (7.3 g) was dissolved in 150 ml of dry tertiary butanol in an atmosphere of dry nitrogen gas. The base was refluxed and stirred

under nitrogen during the dropwise addition of a solution of 15 g of 2,4,5-trimethoxybenzaldehyde and 16 g of diethyl succinate in 125 ml of dry tetrahydrofuran and for a furthur 12 hours after the addition was complete. After cooling the reaction mixture was poured into 500 ml of dilute sulfuric acid and the resulting aqueous solution was extracted five times with chloroform. The extract was washed once with water and then concentrated to a viscous yellow oil. This residue was dissolved in 750 ml of ether and washed four times with saturated sodium bicarbonate solution and once with water. These washings were immediately neutralized with dilute hydrochloric acid and extracted with chloroform five times. The extract was washed once with water, dried with cotton and concentrated to 32.15 g (110%) of an orange oil, ethyl 2-(2,4,5-trimethoxybenzylidene) succinate 90. This was used without further purification in the next step.

3. Cyclization of Ethyl 2-(2,4,5-trimethoxybenzylidene) Succinate 90

Ethyl 2(2,4,5-trimethoxybenzylidene) succinate (32.15 g) was refluxed in 350 ml of acetic anhydride for twelve hours. After cooling it was poured into 1500 ml of ice water and stirred for several hours during which time a solid precipitated. The aqueous suspension was extracted five times with chloroform. The extract was washed with water twice, with saturated sodium bicarbonate solution twice, and again with water

twice before drying with cotton and concentration to 27.0 g (87%) of a red solid.

Recrystallization from methanol gave colourless needles of ethyl 1-acetoxy-5,7,8-trimethoxy-3-naphthoate 91 mp 181-182°.

ir ($CHCl_3$), 2840 (OMe), 1764 (OAc), 1706 (COOR), 1626, 1605 cm^{-1} (C=C).

pmr ($CDCl_3$) 1.41 (t,3, J=7.0 Hz), 2.37 (s,3). 3.82 (s,3), 3.97 (s,6), 4.42 (q,2 J=7.0 Hz), 6.67 (broad s,1), 7.66 (d,1 J=1.5 Hz), 8.83 (d, 1, J=1.5 Hz).

Anal. Calcd for $C_{18}H_{20}O_7$: C, 62.06; H, 5.79.

Found: C, 61.81; H, 5.80.

4. Hydrolysis of Ethyl 1-acetoxy-5,7,8-trimethoxy-3-naphthoate 91

(a) Selective.

Crude ethyl 1-acetoxy-5,7,8-trimethoxy-3-naphthoate (551 mg) was dissolved in benzene and filtered on a column of alumina giving a pale yellow solid. Recrystallization from benzene gave 455 mg (94%) of pale yellow needles of ethyl 1-hydroxy-5,7,8-trimethoxy-3-naphthoate 92 mp 156-157°.

ir ($CHCl_3$), 3333 (OH), 2840 (OMe), 1720 (COOR), 1618 cm^{-1} (C=C).

pmr ($CDCl_3$), 1.40 (t,3, J=7.0 Hz), 3.94 (s,3), 3.98 (s,6), 4.40 (q,2, J=7.0 Hz), 6.55 (broad s, 1), 7.40 (d, 1, J=1.5 Hz), 8.37 (d,1, J=1.5 Hz).

9.61 (S,1, exchangeable with D_2O).

Anal. Calcd for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92.

Found C, 62.84; H, 6.00.

(b) Total.

Ethyl 1-acetoxy-5,7,8-trimethoxy-3-naphthoate (75 mg) was dissolved in 3 mls of dioxane. This solution was treated with 5 ml of 10% aqueous sodium hydroxide solution. The system was shaken overnight before diluting with 20 mls of water. The aqueous solution was extracted with ether twice, acidified with hydrochloric acid and then extracted with ether three times. The ethereal extract was washed once with water, dried with anhydrous magnesium sulphate and evaporated down to give 60 mg of a creamy white solid. This was recrystallized from ethyl acetate to give 52 mg (87%) of cream-coloured needles of 1-hydroxy-5,7,8-trimethoxy-3-naphthoic acid mp. 265-266°.

Anal. Calcd for $C_{14}H_{14}O_6$: C, 60.43; H, 5.07

Found C, 60.60; H, 5.26

5. Preparation of Ethyl 1-allyloxy-5,7,8-trimethoxy-3-naphthoate 93

Ethyl 1-hydroxy-5,7,8-trimethoxy-3-naphthoate (2.00 g), 6 g of anhydrous potassium carbonate, 6 g of freshly distilled allyl bromide and 40 ml of acetone (distilled from drierite) were combined and stirred under reflux in an atmosphere of dry nitrogen

gas for 22 hours. The reaction mixture was cooled, diluted with 400 ml of water and extracted with chloroform six times. The extract was washed once with water, filtered through cotton wool and concentrated to a pale yellow oily residue which solidified on standing.

This residue was dissolved in 250 ml of ether and washed three times with ice cold Claisen's alkali and three times with water. The washings were immediately neutralized with ice cold 6 normal hydrochloric acid.

The ethereal solution was diluted with an equal volume of chloroform, filtered through cotton wool and concentrated to give 2.2 g of a very pale yellow oil which solidified on standing. Recrystallization from hexane gave 1.68 g of ethyl 1-allyloxy-5,7,8-trimethoxy-3-naphthoate 93 mp 96-96.5°.

The mother liquors were chromatographed on a column of alumina made up in hexane. Elution with 50:50 hexane: benzene brought off a yellow oil, whereas, benzene brought off a pale yellow solid which was recrystallized from hexane then methanol to give 161 mg of the allyl ether 93 mp 95-96°.

Total yield 1.84 g (82%).

The acidified washings were combined and extracted with chloroform four times with chloroform. The extract was washed once with water, filtered through cotton and concentrated to give 98 mg of foul smelling brown oil. No starting material was detectable in this oil via tlc.

ir ($CHCl_3$), 2940 (Sharp C-H), 2850 (OMe), 1705 (COOR),

1620 and 1602 cm^{-1} (C=C).

pmr ($CDCl_3$), 1.43 (t,3, J=7.0 Hz), 3.87 (s,3), 4.00 (s,6), 4.47 (q,2, J=7.0 Hz), 4.77 (m,2), 5.47 (m,1), 5.78 (m,1), 6.08 (m,1), 6.75 (broad s,1) 7.53 (d,1, J=2 Hz), 8.67 (d, 1, J=2 Hz).

Anal. Calcd for $C_{19}H_{22}O_6$: C,65.88; H,6.40.

Found C,65.82; H,6.59.

6. Preparation of Ethyl 1-allyloxy-2-allyl-5,7,8-trimethoxy-3-naphthoate 96

Ethyl 1-hydroxy-5,7,8-trimethoxy-3-naphthoate (2.00 g) was treated exactly as above except that the reaction mixture was refluxed for 3 days. The crude neutral extract was chromatographed on alumina. Elution with hexane brought off a colourless solid which was recrystallized from hexane to give 108 mg (4.9%) of ethyl 1-allyloxy-2-allyl-5,7,8-trimethoxy-3-naphthoate 96 mp 81.5-82.0°. Elution with 50:50 hexane benzene brought off a pale yellow solid which was recrystallized from hexane to give 1.72 g (78%) of ethyl 1-allyloxy-5,7,8-trimethoxy-3-naphthoate 93 mp 95.5-96.5°.

ir ($CHCl_3$), 2940 (C-H), 2850 (OMe), 1710 (COOR), 1615 and 1595 cm^{-1} (C=C).

pmr ($CDCl_3$), 1.41 (t,3, J=7.0 Hz), 3.87 (s,3), 4.03 (s,3), 4.05 (m,2), 4.07 (s,3) 4.45 (q,2, J=7.0 Hz), 4.51 (m,2), 4.93 (m,1), 5.20 (m,1), 5.41 (m,1), 5.70 (m,1) 6.17

(m,2) 6.75 (broad s,1), 8.67 (s,1).

Anal. Calcd for $C_{22}H_{26}O_6$: C,68.38; H,6.78.

Found: C,68.34; H,6.80

7. Claisen Rearrangement of Ethyl 1-allyloxy-5,7,8-trimethoxy-3-naphthoate 93

(a) At 200°.

Ethyl 1-allyloxy-5,7,8-trimethoxy-3-naphthoate (7.5 g) was dissolved in 50 ml of diethyl aniline. The resulting solution was heated to 200° for 30 minutes in an atmosphere of nitrogen. After cooling the reaction mixture was diluted with 700 ml of ether. This ethereal solution was washed three times with cold 6 N hydrochloric acid and three times with water before dilution with 450 ml of chloroform and concentration to a brown oil, which solidified on standing. This residue was dissolved in 1 litre of hexane and put on a column of 20 g of alumina. Elution with hexane removed a pale yellow solid. Recrystallization from hexane gave 7.014 g (93.5%) of ethyl 2-allyl-1-hydroxy-5,7,8- trimethoxy-3-naphthoate 97 mp 78-79°.

ir ($CHCl_3$), 3400-3200 (broad O-H), 2940 (C-H), 2850 (OMe), 1712 (COOR), 1635 and 1610 cm^{-1} (C=C).

pmr ($CDCl_3$), 1.40 (t,3, J=7.0 Hz), 3.87 (m,2), 3.95 (s,6), 4.00 (s,3), 4.40 (q,2, J=7.0 Hz), 4.91 (m,1), 5.13 (m,1), 6.17 (m,1), 6.57 (broad s,1), 8.25 (s,1),

10.1 (s,1, exchangeable with D_2O).

Anal. Calcd for $C_{19}H_{22}O_6$: C,65.88; H,6.40.

C,65.73; H,6.53.

(b) At 100°.

Ethyl 1-allyloxy-5,7,8-trimethoxy-3-naphthoate (3 mg) was dissolved in 0.5 ml of diethyl aniline. The system was heated under dry nitrogen gas for five hours at 100°. After cooling a small aliquot was removed and diluted with chloroform. This solution was analyzed on a thin layer plate using chloroform as solvent. Charring with 50% sulfuric acid showed spots for starting material and product of equal intensity.

8. Oxidation of Ethyl 1-hydroxy-2-allyl-5,7,8-trimethoxy-3-naphthoate 97

(a) With N-iodosuccinimide.

Ethyl 1-hydroxy-2-allyl-5,7,8-trimethoxy-3-naphthoate (63 mg) was dissolved in 2 ml of a mixture of 90% dimethylformamide, 5% glacial acetic acid and 5% water and the resulting solution was treated with stirring with 125 mg of N-iodosuccinimide which had been freshly recrystallized from a mixture of purified dioxane and carbon tetrachloride. After stirring for 1½ hours, the reaction mixture was diluted with 100 ml water and extracted 5 times with methylene chloride. The extract was washed 5 times with water, filtered through cotton wool and evaporated down at 35° to 200 mg of red

oil. This oil was separated on 22 silica gel thin layer plates to give 25 mg (27%) of 3-carboethoxy-2-(-3-iodo-2-hydroxypropyl)-5,7,8-trimethoxy-1,4-naphthoquinone 101.

ir ($CHCl_3$), 3600-3200 (broad OH), 2940 (C-H), 2850 (OMe), 1730 (COOR), 1655 (Quinone), 1585 and 1555 cm^{-1} (characteristic doublet C=C)

A second faster moving band was removed from the plates to give 28 mgs (32½%) of 4-carboethoxy-2-iodomethyl-6,8,9-trimethoxynaphtho (1,2-b) furan 102. This material gave a positive Beilstein test after being recrystallized from benzene-hexane to give pale yellow crystals mp 155.5-156°.

ir ($CHCl_3$), No OH band, 2930 (C-H), 2840 (OMe), 1710 (COOR), 1623, 1600 and 1515 cm^{-1} (C=C).

pmr ($CDCl_3$), 1.43 (t, 3 J=7.0 Hz), 3.5-4.1 (m,5), 3.93 (s,3), 4.01 (s,3), 4.03 (s,3), 4.45 (q, 2 J=7.0 Hz), 6.68 (broad s, 1), 8.53 (s,1).

Anal. Calcd for $C_{19}H_{21}O_6I$: C, 48.42; H,4.49.

Found: C, 48.07; H,4.51.

(b) With N-bromosuccinimide.

Ethyl 1-hydroxy-2-allyl-5,7,8-trimethoxy-3-naphthoate (221 mg) was dissolved in 11 ml of dimethylformamide, 0.8 ml of water and 0.8 ml of glacial acetic acid. N-bromosuccinimide (358 mg) was added and the flask was swirled until it dissolved. The reaction

was allowed to proceed at room temperature in the dark for 3 hours before diluting it with 450 ml of water. The aqueous solution was extracted five times with methylene chloride. The extract was washed twice with water, filtered through cotton and concentrated on a rotary evaporator at 35° to a red oil. This oil was then pumped down with a vacuum pump for 2 hours. The resulting red oil was dissolved in ethyl acetate and filtered on a column of treated kiesel-gel*. The ethyl acetate was removed at reduced pressure and the resulting red oil was crystallized from ether to give 246 mg (84%) of 3 carboethoxy-2-(3-bromo-2-hydroxypropyl)-5,7,8-trimethoxy-1,4-naphthoquinone 104 mp 119-120°.

ir ($CHCl_3$), 3600-3400 (broad OH), 2940 (C-H), 2850 (OMe), 1730 (COOR), 1655 (Quinone), 1585 and 1555 cm^{-1} (characteristic doublet C=C).

pmr ($CDCl_3$) 1.38 (t,3 J=7.0 Hz), 3.80 (s,3), 3.92 (s,3), 393 (s,3), 4.38 (q,2 J=7.0 Hz), 6.70 (broad s,1).

Anal. Calcd for $C_{19}H_{21}O_8Br$: C,49.91; H,4.63, Br,17.48.
Found: C,49.67; H,4.61; Br,17.45.

9. Preparation of 2 Allyl-3-carboethoxy-5,7,8-trimethoxy-1,4-naphthoquinone 103

*The kiesel-gel with binder and ultraviolet indicator was made into a slurry with water. After air drying for 12 hours it was ready for use.

A solution of 31 mg of ethyl 2-allyl-1-hydroxy-5,7,8-trimethoxy-3-naphthoate 97 in 0.5 ml of dimethylformamide, 25 μl of water and 25 μl of glacial acetic acid. A solution of 47 mg of N-bromosuccinimide in one ml of dimethylformamide was added to the former solution dropwise. The reaction was allowed to proceed for one hour. Testing a drop of reaction mixture on a strip of damp starch iodide paper indicated an absence of oxidizing agent. The reaction mixture was diluted with 50 ml of water and then extracted with chloroform. The extract was washed with water twice, dried with cotton wool and evaporated down to an orange oil. Separation on thin layer plates gave 14 mg (43%) of 2-allyl-3-carboethoxy-5,7,8-trimethoxy-1,4-napthoquinone 103.

ir ($CHCl_3$) 2940 (C-H), 2850(OMe), 1730(COOR), 1650 (quinone), 1613, 1587 and 1558 cm^{-1} (C=C).

pmr ($CDCl_3$) 1.35 (t,3 J=7.0 Hz), 3.50(m,2), 3.85(s,3), 3.97 (s,6), 4.38(q,2 J=7.0 Hz), 5.13 (m,2), 6.0 (m,1) and 6.73 (broad s,1).

Also separated were 15 mg (37%) 3-carboethoxy-2-(-3-bromo-2-hydroxypropyl)-5,7,8-trimethoxy-1,4-naphthoquinone 104 and 6 mg (20%) of starting material 97.

10. Spontaneous Decomposition of 3-Carboethoxy-2-(-3-bromo-2-hydroxypropyl)-5,7,8-trimethoxy-1,4-naphthoquinone 104

A sample of 51 mg of 3-carboethoxy-2-(-3-bromo-2-hydroxypropyl)-5,7,8-trimethoxy-1,4-naphtho-

quinone was left standing in a colourless transparent vial on the bench top. After one day, it was noted that the colour had changed from a brilliant orange to a deep red while still remaining in the same crystalline form. A thin layer chromatogram showed the bromohydrin 104 had completely disappeared being replaced with a faster moving purple compound. Two crystallizations of the crude material from benzene-hexane resulted in the formation of two types of crystals, brilliant red rosets mp 182-183 and brown needles. The total yield of 3-carboethoxy-2-(-3-bromo-2-hydroxypropyl)-5,8-dihydroxy-7-methoxy-1,4-naphthoquinone 105 was 29 mg (60%). The brown variety was a mixture of decomposition product and the red type, however, attempts at separation of the two by crystallization was unsuccessful. The red crystals gave a positive Beilstein test and an alcoholic solution turned blue on addition of sodium hydroxide solution.

ir ($CHCl_3$), 3500-3100 (broad OH), 2940(C-H), 2850(OMe), 1725 (COOR), 1670(quinone), 1628 and 1585 cm^{-1} (C=C).

pmr ($CDCl_3$) 1.40 (t,3, J=7.0 Hz), 3.2-4.0 (m,5), 3.86 (s,3), 4.45 (q,2 J=7.0 Hz), 5.27 (m,1); 6.1(s;1), 13.30 (s,1), 13.35 (s,1).

mass spectrum doublet m/e 410 & 412

11. Oxidation of 3-Carboethoxy-2-(-3-bromo-2-hydroxypropyl)-5,7,8-trimethoxy-1,4-naphthoquinone 104 with Jones' Reagent

Jones' reagent (10 ml) was added to a solution of 110 mg of 3-carboethoxy-2-(-3-brom-2-hydroxypropyl)-5,7,8-trimethoxy-1,4-naphthoquinone dissolved in 10 mls of acetone which had been distilled from potassium permanganate.

Stirring was continued for 5 minutes before diluting the reaction mixture with 100 ml of water. The aqueous acetone was extracted five times with methylene chloride. The extract was washed three times with water, filtered through cotton and evaporated to 112 mg of a red oily residue. This oil was crystallized from ethyl acetate-hexane to give 86 mg (78%) of crimson red needles of 3-carboethoxy-2-(-3-bromoacetonyl)-5,7,8-trimethoxy-1,4-naphthoquinone 106 mp 167-168°.

ir ($CHCl_3$), 2940 (C-H), 2850 (OMe), 1730 (C=O and COOR), 1660 (Quinone) 1590 and 1555 cm^{-1} (characteristic doublet C=C).

pmr ($CDCl_3$), 1.35 (t,3, J=7.0 Hz), 3.80 (s,3), 3.87 (s,2), 3.95 (s,6), 4.04 (s,2), 4.37 (q,2, J=7.0 Hz), 6.73 (broad s,1).

Anal. Calcd for $C_{19}H_{19}O_8Br$: C,50.19; H,4.21; Br,17.55.
Found: C,50.11; H,3.95; Br,17.57.

12. Reduction of 3-Carboethoxy-2-(-3-bromoacetonyl)-5,7,8-trimethoxy-1,4-naphthoquinone 106

Zinc dust (1 gm) was added with stirring to a solution of 195 mg of 3-carboethoxy-2-(-3-bromoacetonyl)-5,7,8-trimethoxy-1,4-naphthoquinone dissolved

in 25 ml glacial acetic acid. This system was stirred at room temperature for 1½ hours before removing the solid by filtration. The solid was washed several times with glacial acetic acid. The filtrate was diluted with 500 ml of water and extracted with methylene chloride. The extract was washed once with water, twice with saturated sodium bicarbonate solution and once again with water before filtration through cotton wool and evaporation to a brownish yellow crystalline solid. This was recrystallized twice from methanol to give 128 mg (83%) pale yellow needles of 4-carboethoxy-5-hydroxy-2-methyl-6,8,9-trimethoxynaphtho (1.2-b) furan 108 mp 157-158 °.

ir ($CHCl_3$), 3200-2700 (broad O-H), 2940 (C-H), 2850 (OMe), 1647 (COOR), 1624 and 1584 cm^{-1} (C=C).

pmr ($CDCl_3$) 1.50 (t,3, J=7.0 Hz), 2.55 (d,3, J=1.0 Hz), 3.95 (s,3), 4.03 (s,6), 4.51 (q,2, J=7.0 Hz), 6.63 (broad s,1), 6.80 (q, 1, J=1.0 Hz), 1.29 (s,1 exchangeable with D_2O)

Anal. Calcd for $C_{19}H_{20}O_7$: C,63.33; H,5.59.
Found: C,63.38; H,5.89.

13. Preparation of 5-Acetoxy-4-carboethoxy-2-methyl-6,8,9-trimethoxynaphtho (1,2-b) furan 109

A solution of 20 mg of 3-carboethoxy-2-(-3-bromoacetonyl)-5,7,8-trimethoxy-1,4-naphthoquinone

dissolved in 50% (v/v) glacial acetic acid in acetic anhydride, was treated with 50 mg of zinc dust and then was stirred for 3 hours at room temperature under an atmosphere of nitrogen gas. The reaction mixture was then refluxed for 1½ hours before cooling and pouring into 100 ml of water. The aqueous solution was extracted with methylene chloride. The extract was then washed with water once before filtering through cotton and evaporation to give 16 mgs of yellow oil which solidified on standing. Recrystallization from methanol gave 12 mg (68%) of 5-acetoxy-4-carboethoxy-2-methyl-6,8,9-trimethoxynaphtho (1,2-b) furan 109 mp 170-171°.

ir ($CHCl_3$), 2940 (C-H), 2850 (OMe), 1760 (OAc), 1710 (COOR), 1618 and 1585 cm^{-1} (C=C).

pmr ($CDCl_3$), 1.42 (t,3, J=7.0 Hz) 2.55 (d,3, J=1.0 Hz), 3.88 (s,3), 3.92 (s,3), 3.97 (s,3), 4.38 (q,2, J=7.0 Hz), 6.58 (broad s,1), 6.83 (q,1, J=1.0 Hz).

Anal. Calcd for $C_{21}H_{22}O_8$: C,62.68; H,5.51.
Found: C,62.87; H,5.86.

14. Reduction of 4-Carboethoxy-5-hydroxy-2-methyl-6,8,9-trimethoxynaphtho (1,2-b) furan 108 with Lithium Aluminium Hydride

A solution of 70 mg of 4-carboethoxy-5-hydroxy-2-methyl-6,8,9-trimethoxynaphtho (1,2-b) furan dissolved in 60 ml of diethyl ether was treated with excess lithium aluminium hydride. The reaction mixture was heated

under reflux for 3 hours. After cooling in an ice bath 30 ml of a solution of sodium potassium tartrate was added dropwise at first. The two layers were separated and the aqueous phase was washed five times with ether. The ethereal extract was washed three times with water and once with saturated sodium chloride solution before diluting with chloroform and evaporating to dryness at room temperature to give 60 mg (96%) pale yellow 5-hydroxy-4-hydroxymethyl-2-methyl-6,8,9-trimethoxynaphtho (1,2-b) furan 110.

This material was quite pure and attempts to further purify it by crystallization and chromatography failed.

ir ($CHCl_3$), 3580, 3380 (O-H), 2940 (C-H), 2840 (OMe), 1630 and 1600 cm^{-1} (C=C).

pmr ($CDCl_3$) 2.49 (d,3, J=1.0 Hz), 3.12 (broad band, 1, exchangeable with D_2O), 3.90 (s,6), 3.93 (s,3), 4.90 (s,2), 6.47 (broad s,1), 6.50 (q,1, J=1.0 Hz), 9.28 (broad s,1, exchangeable with D_2O).

15. Acetylation of 5-Hydroxy-4-hydroxymethyl-2-methyl-6,8,9-trimethoxynaphtho (1,2-b) furan 110

A solution of 10 mg of 5-hydroxy-4-hydroxymethyl-2-methyl-6,8,9-trimethoxynaphtho (1,2-b) furan in 3 ml of pyridine was treated with 0.5 ml of acetic anhydride. After mixing, the reaction mixture was allowed to stand at room temperature for 12 hours before pumping to dryness using a vacuum pump. The oily residue was separated via

tlc using 10% ethyl acetate in chloroform to give 8 mg (65%) of a pale yellow oil, which began to crystallize slowly on standing. Attempts to further purify this 5-acetoxy-4-acetoxymethyl-2-methyl-6,8,9-trimethoxynaphtho-(1,2-b) furan 111 by recrystallization were unsuccessful.

ir ($CHCl_3$), 2900 (C-H), 2800 (OMe), 1757, 1730 (OAc), 1605 and 1590 cm^{-1} (C=C).

pmr ($CDCl_3$), 2.05 (s,3), 2.39 (s,3), 2.55 (d,3), J=1.0 Hz), 3.93 (s,3), 3.97 (s,3), 4.02 (s,3), 5.35 (s,2), 6.63 (q,1, J=1.0 Hz).

16. Oxidation of 4-Carboethoxy-5-hydroxy-2-methyl-6,8,9-trimethoxynaphtho (1,2-b) furan 108

(a) With Gold(III) Chloride.

A solution of 37 mg of 4-carboethoxy-5-hydroxy-2-methyl-6,8,9-trimethoxynaphtho (1,2-b) furan in 7 ml of 95% ethanol was treated with 100 mg of gold (III) chloride dissolved in 2 ml of water. After stirring 2.5 hours at room temperature, the reaction mixture was poured into water and extracted with methylene chloride. The extract was washed twice with water, filtered through cotton wool and evaporated down to 51 mg of a red oil. Separation on silica gel thin layer plates using 25% ethyl acetate in chloroform gave 14 mg (37%) of red oily 2-acetonyl-3-carboethoxy-5,7,8-trimethoxy-1,4-naphtho-quinone 107. Two other quinonoid compounds were observed, but not identified.

ir $CHCl_3$), 2930 (C-H), 2850 (OMe), 1735 (COOR) and

(C=O), 1665 (C=O, Quinone), 1585 and 1555 cm^{-1} (C=C characteristic doublet).

pmr ($CDCl_3$), 1.25 (t,3 J=7.0 Hz), 2.27 (s,3), 3.81 (s,3), 3.95 (s,6), 4.31 (q,2 J=7.0 Hz), 5.0 (broad s,2), 6.73 (broad s,1).

(b) With Ferric Chloride.

A solution of 5.0 mg of the furan 108 was dissolved in 2.5 ml of 95% ethanol was stirred at room temperature during the addition of a solution of 47 mg of ferric chloride in 2 ml of water. Stirring was continued for 3½ hours before pouring the reaction mixture into water and extracting with methylene chloride. The extract was washed once with water, filtered through cotton wool and evaporated down to give 7 mg of an orange oil. Separation on a silica gel thin layer plate using 25% ethyl acetate in chloroform gave 2.8 mg (54%) of red oily 2-acetonyl-3-carboethoxy-5,7,8-trimethoxy-1,4-naphthoquinone 107. Comparison of the two samples of this quinone by tlc and infrared spectra showed them to be identical. One of the unidentified quinones isolated in part (a) was also found in part (b).

(c) With 2,3 Dichloro-5,6-dicyanobenzoquinone.

A sample of 10.0 mg of furan 108 was put into a flask containing 6.25 mg 2,3 dichloro-5,6-dicyanobenzoquinone. The flask was flushed with dry nitrogen gas and sealed with a rubber septum. Using a

syringe, 0.5 ml of methanol was added to the solids. After swirling briefly the reaction mixture was allowed to stand overnight at room temperature. The reaction mixture was pumped to dryness with a vacuum pump using one's hand as the only source of heat for the flask. Separation of the crude product on silica gel thin layer plates gave the two compounds observed in parts (a) and (b). The yield of 2-acetonyl-3-carboethoxy-5,7,8-trimethoxy-1,4-naphthoquinone 107 was 4.9 mg (47%). The weight of the as yet unidentified quinone observed in parts (a) and (b) found was 3.0 mg.

17. Oxidation of 5-Hydroxy-4-hydroxymethyl-2-methyl-6,8,9-trimethoxynaphtho (1,2-b) furan 110

(a) With 2,3-Dichloro-5,6-dicyanobenzoquinone.

To a stirred solution of 60 mg of 5-hydroxy-4-hydroxymethyl-2-methyl-6,8,9-trimethoxynaphtho (1,2-b) furan in 10 ml methanol was added 44 mg 2,3-dichloro-5,6-dicyanobenzoquinone. The reaction mixture was stirred at room temperature for 20 minutes before evaporating to dryness at 25°. The residue was stirred with benzene and the insoluble 2,3 dichloro-5,6-dicyanobenzohydroquinone was removed by filtration. The filtrate was evaporated to give 58 mg of a red oil. Allowing this oil to stand for several hours in a small amount of benzene resulted in the formation of 27 mg of red crystals. The mother liquors were separated on silica gel thin layer plates

by developing them twice in pure ethyl acetate to give 18 mg of red oil. This was combined with the above solid and recrystallized from benzene to give 35 mg (61%) of red crystals mp 218-219° of 4,9 diketo-2-methyl-5,6,8-trimethoxynaphtho (2,3-b) furan 115.

ir ($CHCl_3$), 2940 (C-H), 2845 (OMe), 1662 (C=O), 1550 cm^{-1} (C=C).

pmr ($CDCl_3$), 2.42 (d,3, J=1.0 Hz), 3.87 (s,3), 3.95 (s,3), 3.98 (s,3), 6.44 (broad s,1), 6.44 (q,1, J=1.0 Hz).

m/e parent peak 302

(b) With Ferric Chloride

A solution of 45 mgs of diol in 15 ml of 95% ethanol was treated with a solution of 50 mg ferric chloride (hexahydrate) in 3 ml of water. The reaction mixture was stirred at room temperature for 3 hours before pouring into water and extracting with methylene chloride. The extract was evaporated down to give 34 mg of reddish orange solid. Recrystallization from benzene-hexane gave 31.5 mg (73%) of reddish orange crystals mp 215.5-217.5° of 4,9 diketo-2-methyl-5,7,8-trimethoxynaphtho (2,3-b) furan 115. A mixed melting point with the furan isolated in part (a) 216-218°. All spectra of the two compounds were identical.

REFERENCES

1. Z. Roussin, Comptes Rendus, 52, 1033 (1861).

2. T. Kuroda and M. Wada, Sci. Papers Inst. Phys. Chem. Res., Tokyo, 34, 1740 (1938).

3. D. B. Bruce and R. H. Thomson, J. Chem. Soc., 1089 (1955).

4. H. E. Fierz-David and W. Stockar, Helv. Chim. Acta, 26, 92 (1943).

5. H. Dreyfus, Chem. Abs., 24, 1393 (1930). F. P. 667917 (1929).

6. G. H. Ellis, H. C. Olpin, and E. W. Kirk, Chem. Abs., 27, 3952 (1933). U. S. 1,911,945 (1933).

7. K. Zahn and P. Ochwat, Annalen, 462, 72 (1928).

8. K. Wallenfels and A. Gauhe, Ber. 76, 325 (1943).

9. F. Farina, M. Lora-Tamayo and C. Suarez, Tetrahedron Letters, 19, 9 (1959).

10. F. Farina, M. Lora-Tamayo and C. Suarez, Anales Real Soc. Espan. fis. quin. Ser. B, 59, 167 (1963).

11. L. A. Cort and P. A. B. Rodriguez, J. Chem. Soc. (C), 949 (1967).

12. Unpublished Results of the author.

13. D. Hadzi and N. Sheppard, Trans. Faraday Soc., 50, 911 (1954).

14. K. Nakanishi, Infrared Absorption Spectroscopy - Practical, Holden-Day, Inc., San Francisco (1962).

15. L. M. Jackman, Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry, Pergamon Press Inc., New York (1959).

16. F. Radt, Elsevier's Encyclopaedia of Organic Chemistry, Series III Volume 12 B., Elsevier Publishing Company, Amsterdam (1952), p. 3184.

17. A. K. Macbeth, J. R. Price and F. L. Winzor, J. Chem. Soc., 325 (1935).

18. M. A. Hamilton, M. S. Knorr and R. A. Cajori, Antibiotics and Chemotherapy, 3, 853 (1953).

19. F. A. Cajori, T. T. Otani and M. A. Hamilton, J. Biological Chem., 208, 107 (1954).

20. E. Hardegger, K. Steiner, E. Widmer, H. Corrodi, Th. Schmidt, H. P. Knoepfel, W. Rieder, H. J. Meyer, F. Kugler and H. Gempeler, Helv. Chim. Acta., 47, 1996, (1964).

21. E. Hardegger, K. Steiner, E. Widmer and Th. Schmidt, Helv. Chim. Acta., 47, 2017 (1964).

22. E. Hardegger, K. Steiner, E. Widmer and A. Pfiffner, Helv. Chim. Acta., 47, 2031 (1964).

23. E. Hardegger, E. Widmer, K. Steiner and A. Pfiffner, Helv. Chim. Acta., 47, 2031 (1964)

24. E. Widmer, J. W. Meyer, A. Walser and E. Hardegger, Helv. Chim. Acta., 48, 538 (1965).

25. F. D. Popp and W. E. McEwen, Chem. Rev., 58, 321 (1958).

26. C. Hartmann and L. Gattermann, Chem. Ber., 25, 3531 (1892).

27. R. H. Thomson, Naturally Occurring Quinones, Butterworths Scientific Publications, London (1957), p. 120.

28a G. P. Arsenault, Tetrahedron Letters, 45, 4033 (1965).

b W. C. Howell, private communication.

29. S. Gattenbeck and R. Bentley, Biochem. J., 94, 478 (1965).

30. E. H. Rodd, Chemistry of Carbon Compounds, Volume III, Part B, Elsevier Publishing Company, Amsterdam (1956) chapter XI.

31. J. F. W. McOmie, Advances in Organic Chemistry Methods and Results, 3, 191 (1963).

32. V. Balasubramaniyan, Chem. Rev., 66, 567 (1966).

33. J. A. Labudde and C. Heidelberger, J. Am. Chem. Soc., 80, 1225 (1958).

34. L. Horner and E. H. Winkelmann, Angew. Chem., 71, 349 (1959).

35. R. J. Burwell, Chem. Rev., 54, 615 (1954).

36. R. H. Manske, Chem. Rev., 30, 145 (1942).

37. R. G. Cooke and W. R. Owen, Aust. J. Chem., 15, 486 (1962).

38. L. S. El-Assal and S. A. M. El-Wahhab, J. Chem. Soc., 849 (1960).

39. M. Gordon, J. G. Miller and A. R. Day, J. Am. Chem. Soc., 71, 1245 (1949).

40. R. A. Baxter, G. R. Ramage, and J. A. Timson, J. Chem. Soc., 530 (1949).

41. H. C. Brown and P. Heim, J. Am. Shem. Soc., 86, 3566 (1964).

42. M. S. Newman and T. Fukunaga, J. Am. Chem. Soc., 82, 693 (1960).

43. V. M. Micovic and M. L. J. Mihailovic, J. Org. Chem. 18, 1190 (1953).

44. C. R. Stephens, E. J. Bianco and F. J. Pilgrim, J. Am. Chem. Soc., 77, 1701 (1955).

45. M. W. Bullock, J. J. Hand and E. L. R. Stokstad, J. Am. Chem. Soc., 78, 3693 (1956).

46. W. G. Brown, Organic Reactions, Vol. 6, John Wiley and Sons, New York, (1951) p. 469.

47. E. P. Papadopoulos, A. Jarrar and C. H. Issidorides, J. Org. Chem., 31, 615 (1966).

48. G. A. Olah and S. J. Kuhn, Friedel-Crafts and Related Reactions, G. A. Olah ed. Vol. III pt. 2. Interscience Publishers, New York (1964) chapter 38.

49. D. S. Tarbell, Chem. Rev., 27, 495 (1940).

50. L. Claisen, Ann., 418, 96 (1919).

51. A. Bowers, T. G. Halsall, E. R. H. Jones and A. J. Lemin, J. Chem. Soc., 2548 (1953).

52. G. Stork and F. H. Clarke, J. Am. Chem. Soc., 83, 3114 (1961).

53. M. Freifelder, Practical Catalytic Hydrogenation, Wiley-Interscience, New York (1971) chapter 20.

54. R. L. Augustine, Catalytic Hydrogenation, Marcel Dekker Inc., New York (1965) chapter 6.

55. H. O. Huisman, Rec. Trav. Chim., 69, 1133 (1950).

56. P. Karrer, R. Escher, H. Fritzsche, H. Keller, B. H. Ringier and H. Salomon, Helv. Chim. Acta 21, 939 (1938).

57. D. Walker and J. D. Hiebert, Chem. Rev., 67, 153 (1967).

58. N, A. Starkovsky, J. Org. Chem., 27, 3733 (1962).