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STUDIES IN THE SYNTHESIS OF ALTERSCLANOL A AND RELATED COMPOUNDS

by

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A DISSERTATION

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Under the Supervision of Professor D. M. S. Wheeler

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TITLE

Studies in the Synthesis of Altersolanol A

and Related Compounds

BY

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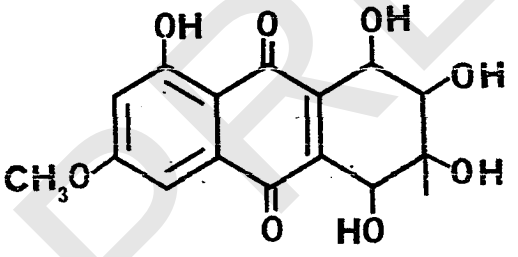
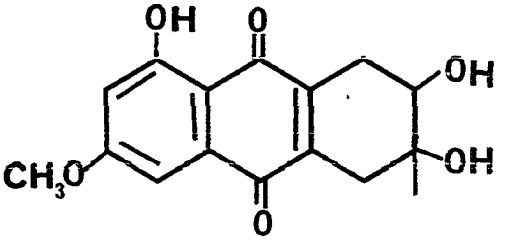
INTRODUCTION

In a previous work[1] the possible synthesis of two novel tetrahydroanthraquinones isolated by Stoessel[2] from Alternaria solania and in this laboratory[3] from Phomopsis junierova Hahn were discussed. These two compounds, altersolanol A and B (1a) (1b) were isolated by Stoessel from Alternaria solania , a fungal disease of solanceous plants along with three other anthraquinones.



1a



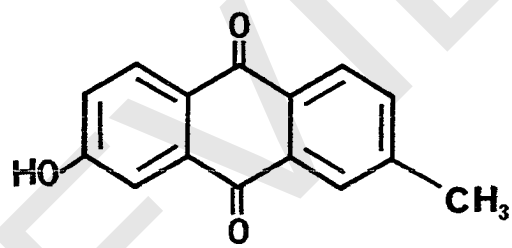
1b

Phomopsis junierova Hahn is the pathogen responsible for Cedar blight occuring mainly in the species Juniperia virginiana ,or eastern cedar and to some extent in evergreens[4]. The metabolite orignially isolated from

Phomopsis junerierova Hahn was named phomopsicin, but since has been found to be identical with altersolanol A by mixed melting point and by NMR[5].

With the isolation of altersolanol A in our department[6] attempts were begun to synthesize this unusual type of compound.

As is well known, anthraquinones comprise the largest group of quinone pigments which can be isolated from plants and fungi, the most common of which is emodin (1f).

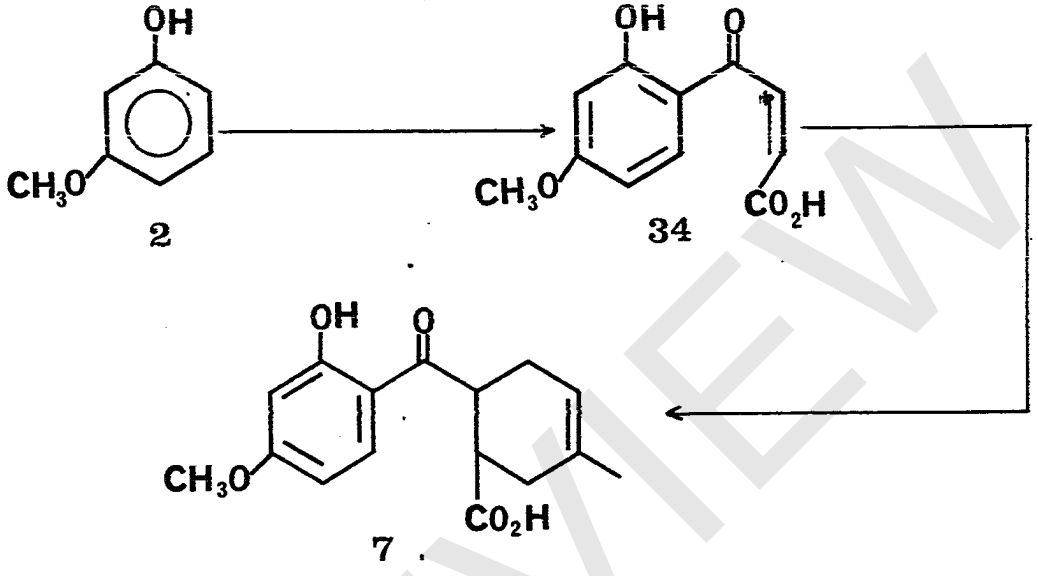


1f

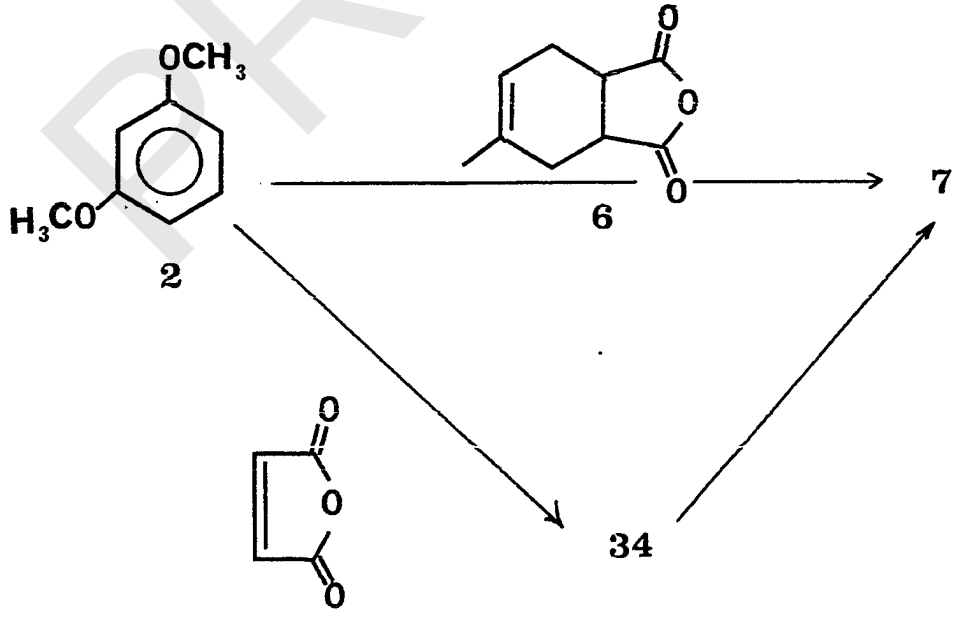
To date only three other compounds possessing a reduced ring system such as the metabolites isolated from Alternaria solani are known. The three other fungal metabolites isolated are; bostrycin (1C)[7], dehydrocaterarin (1D)[8], and tetrahydrocatenarin (1E)[7].

The synthesis of altersclanol B was attempted first since it appeared upon inspection that the overall reaction scheme would be much simpler than attemping to prepare and introduce the elaborate precursor of the tetrahydroxy functicn in ring C needed to complete the synthesis of altersclanol A. The synthesis of altersolanol B could be effectively acccmplished through one of three possible routes. The first, an CAB approach would involve acylation by a suitable precursor of ring A and functionality to introduce ring E readily (see below). The second possibilty utilizes an AEC ring attack with the introduction via acylation of ring B upon ring A and the later buildup of ring C through a Diels-Alder reaction on the naphthaquinone (49). The third synthesis proposed for altersolanol B would involve an ACB approach with a final ring closure to produce ring B. If any of these reaction sequences proves to be relatively straightfoward for altersclanol B the same reactions could be utilized to prepare altersolanol A without many modifications.

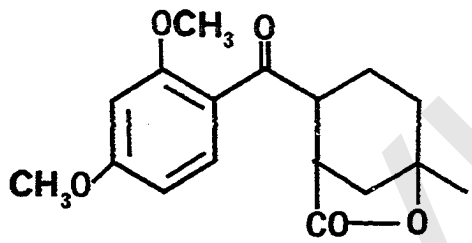
As was described in the masters thesis the CAB and the AEC attack schemes did not work while the ACB approach yielded the bicyclic compound (7) which could be used to produce altersclanol B.



Initially these three possible routes had been chosen to build up the bicyclic intermediate which would be needed to carry the synthesis to completion (2-7) (6-7).



When scheme I was attempted it was found that the Friedel-Crafts acylation did not yield 2-(2,4-dimethoxybenzoyl) 4-methyl 4-cyclohexene carboxylic acid (7), but instead gave the lactone 2-(2,4-dimethoxybenzoyl) 5-methyl, 6-oxa, 7-oxo bicyclo (3,2,1) octane (4).

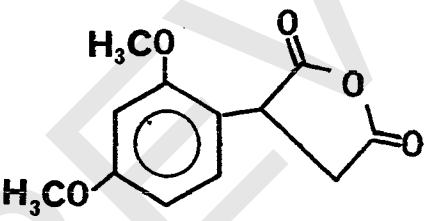


4

Abandoning this route 2-(2,4-dimethoxybenzoyl) 4-methyl 4-cyclohexenecarboxylic acid (7) was produced through scheme II. The orientation of the methyl in 2-(2,4-dimethoxybenzoyl) 4-methyl 4-cyclohexenecarboxylic acid (7) was confirmed by the formation of the appropriate lactone (4).

The first attempts at cyclization of 2-(2,4-dimethoxybenzoyl) 4-methyl 4-cyclohexenecarboxylic acid (7) with polyphosphoric acid resulted in the formation of a naphthalene derivative (38b) in which the isolated double bond had migrated into conjugation with the ring system. This result suggested that it would be better to remove the double bond before carrying out the cyclization. The way to do this would be to hydroxylate the double bond (7b), protect it as a cyclic carbonate (7c) and then perform the required cyclization to give (7d). From this point the synthesis of altersolanolanol B would be straightfoward; oxidation to the quinone (7e), demethylation of the ortho methoxy group (7f) and removal of the cyclic carbonate to yield altersolanol B (1b).

Since the previous report[10] there have been several complications. When production of 2-(2,4-dimethoxybenzoyl) 4-methyl 4-cyclohexenecarboxylic acid (7) was increased to meet the demands of the synthesis it was discovered that the predominant product of the acylation was not 2,4-dimethoxybenzoylacrylic acid (6), but 2-hydroxy 4-methoxy benzoylacrylic acid (34), and that the conditions had to be completely controlled so that the acylation would successfully compete with the addition to the double bond of maleic anhydride to give the by-product (33).



33

Later on in the work it was felt that the free phenolic hydroxyl might be hindering the synthesis, and so the overall scheme has expanded to include concurrent synthesis utilizing 2-(2,4-dimethoxybenzoyl) 4-methyl 4-cyclohexenecarboxylic acid (7), 2-(2-hydroxy 4-methoxybenzoyl) 4-methyl 4-cyclohexenecarboxylic acid (8) and 2-(2,4-dimethoxy 5-methylcarboxamidebenzoyl) 4-methyl

4-cyclohexenecarboxylic acid (23). The 2-(2,4-dimethyoxy 5-methylcarboxamidebenzoyl) 4-methyl 4-cyclohexenecarboxylic acid (23) was synthesized in hopes of activating an unreactive 6 position in ring A. Overall what originally appeared to be a relatively straightfoward synthesis became extremely complicated and at times yielded unexplainable results.

DISCUSSION

SYNTHESIS OF THE CARBON SKELETON

In the Masters thesis[10] the first stage of the synthesis was the acylation of dimethoxybenzene with maleic anhydride to give 2-hydroxy 4-methoxybenzoylacrylic acid (34). In continuing the work it was found that the acylation of the aromatic substrate by maleic anhydride resulted in more difficulty than had previously been encountered. The literature reported conflicting data on the acylation of m-dimethoxy benzene. Rice and co-workers [11] found that the predominant product of the reaction in carbon disulide was the addition compound (32). While they isolated a low yield of 2,4 dimethoxybenzoylacrylic acid (6) they concluded that this was a minor product and that the predominant attack appeared to be electrophilic addition to the deactivated double bond of maleic anhydride. The addition product actually formed as the anhydride (32), but hydrolysis occurs during the work up to give the diacid (33).

Papa and co-workers[12] successfully acylated m-dimethoxy benzene to give 2,4-dimethoxybenzoylacrylic acid, but acylation was effected by use of the mono acid chloride rather than through direct attack by maleic anhydride.

Baddeley, Makar and Invenson[13] also reported a synthesis of 2,4-dimethoxybenzoylacrylic acid by a different route. The complex of aluminum chloride with maleic anhydride was prepared first and then decanted into a solution of dimethoxybenzene which was subsequently refluxed until evolution of hydrochloric acid fumes ceased.

When the acylation as described by Rice was attempted methlyene chloride was used instead of carbon disulfide as the solvent. Under these conditions a granular solid identified as (33) was isclated and identified by melting point and identical spectral data. Repetition of the acylation did not appreciably increase the yield of acrylic acid from what they originally reported.

When the acylation was performed using the conditions specified by Baddeley, Makar and Invenson no acrylic acid was collected as they reported, but an excellent yield of the product (33) was obtained and confirmed by the proton resonance spectrum and by mixed melting point.

When the acylation was repeated several times under rigorously anhydrous conditions no trace of 2,4-dimethoxybenzoylacrylic acid could be isolated, and subsequently it was found that it only succeeded in increasing the yield of the diacid (33) to a 90% yield.

It should be noted that the diacid remains through the usual procedures used to purify the acrylic acid. The diacid recrystallizes under the same conditions and from

the same solvents. The diacid differs from 2,4-dimethoxybenzoylacrylic acid by the relative rate of crystallization. It was found that if a mixture of both was recrystallized, the diacid will precipitate out immediately upon cooling, and there is enough time left to filter the solution, allow it to cool further and precipitate out the relatively pure 2,4-dimethoxybenzoylacrylic acid. Spectral examination of the initial precipitate has shown it to be almost pure diacid (33).

At this point it did not appear that an efficient procedure for preparing 2,4-dimethoxybenzoylacrylic acid had been found. After studying the literature and adapting the conditions specified by Dalal and Nargund[14], the reaction was at run ambient temperature while limiting the reaction time to four hours and by using, as suggested by Papa and co-workers[15], acetylene tetrachloride as a solvent. After several exploratory experiments, the acylation proceeded without major difficulty producing acrylic acids in 55% yield (see page 48).

The structure of the product (6) was confirmed by spectroscopic data. The ultra-violet spectrum showed the presence of a 2,4-dimethoxybenzoyl chromophore, the infra-red spectrum confirmed the presence of a conjugated ketone and an acid group; and the proton NMR revealed the peaks of two methoxy groups, an acid proton, 3 aromatic and