

THE ISOLATION AND SYNTHESSES OF
2,5-DIACETYL BENZOFURAN

By

CHARLES THEODORE RAMMING

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Oklahoma State University

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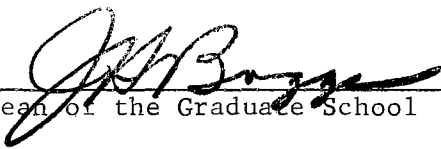
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2,5-DIACETYL BENZOFURAN

Thesis Approved:



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Dean of the Graduate School

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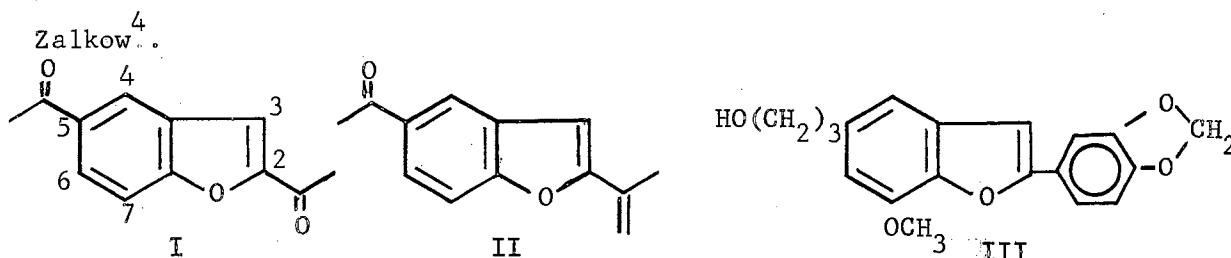
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HISTORICAL AND INTRODUCTION

2,5-Diacetylbenzofuran (I) has been isolated from rayless goldenrod (Aplopappus heterophyllus). This plant has been previously worked with by Couch¹ and others^{2,3,4} in interest of finding the compound which is responsible for "trembles" or "milk sickness" in humans and livestock. At the present time the compound responsible for this disease is still unknown.

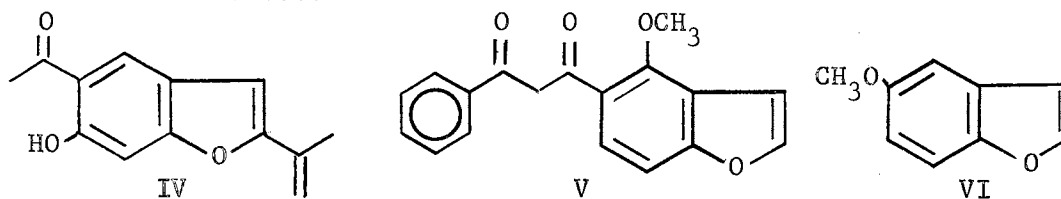
In the present work the isolation of the simple benzofuran I is somewhat unusual as there are only five other naturally occurring simple* benzofurans which are known and listed by Dean⁵ plus dehydrotremetone (II) which was isolated recently (1961) from white snake root (Eupatorium urticaefolium) by Bonner⁶ and also from rayless goldenrod by



The first simple benzofuran isolated was egonol (III), from the seed oil of the Egonoki (Styrax japonicus), in about 1938 by Okada. Kawai and co-workers have done extensive work on this compound and have successfully synthesized it⁷.

In 1939 euparin (IV) was isolated from the gravel root (Eupatorium purpureum) by Kamthong and Robertson⁸. It has also been isolated from

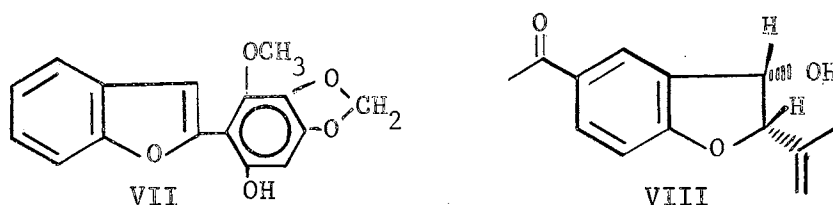
*By simple is meant a benzofuran with no additional fused rings.

Eupatorium cannabinum.

Pongamol (V) was isolated in 1954 from the seed oil (karanja oil) of Pongamia glabra by Seshadri and co-workers⁹ who also later synthesized it.¹⁰

The simplest of all natural benzofurans, 5-methoxybenzofuran (VI) was isolated from a fungus (Stereum subpileatum) of oak beer barrels in 1957 by Birkinshaw¹¹ who also synthesized it. This work was undertaken because the benzofuran VI imparted a strong, undesirable odor to the beer.

In 1958 Forbes and co-workers¹² isolated from bakers yeast 2-(6-hydroxy-2-methoxy-3,4-methylenedioxyphenyl) benzofuran (VII). Wagner and co-workers¹³ have synthesized this benzofuran (VII) using the Hoesch reaction.



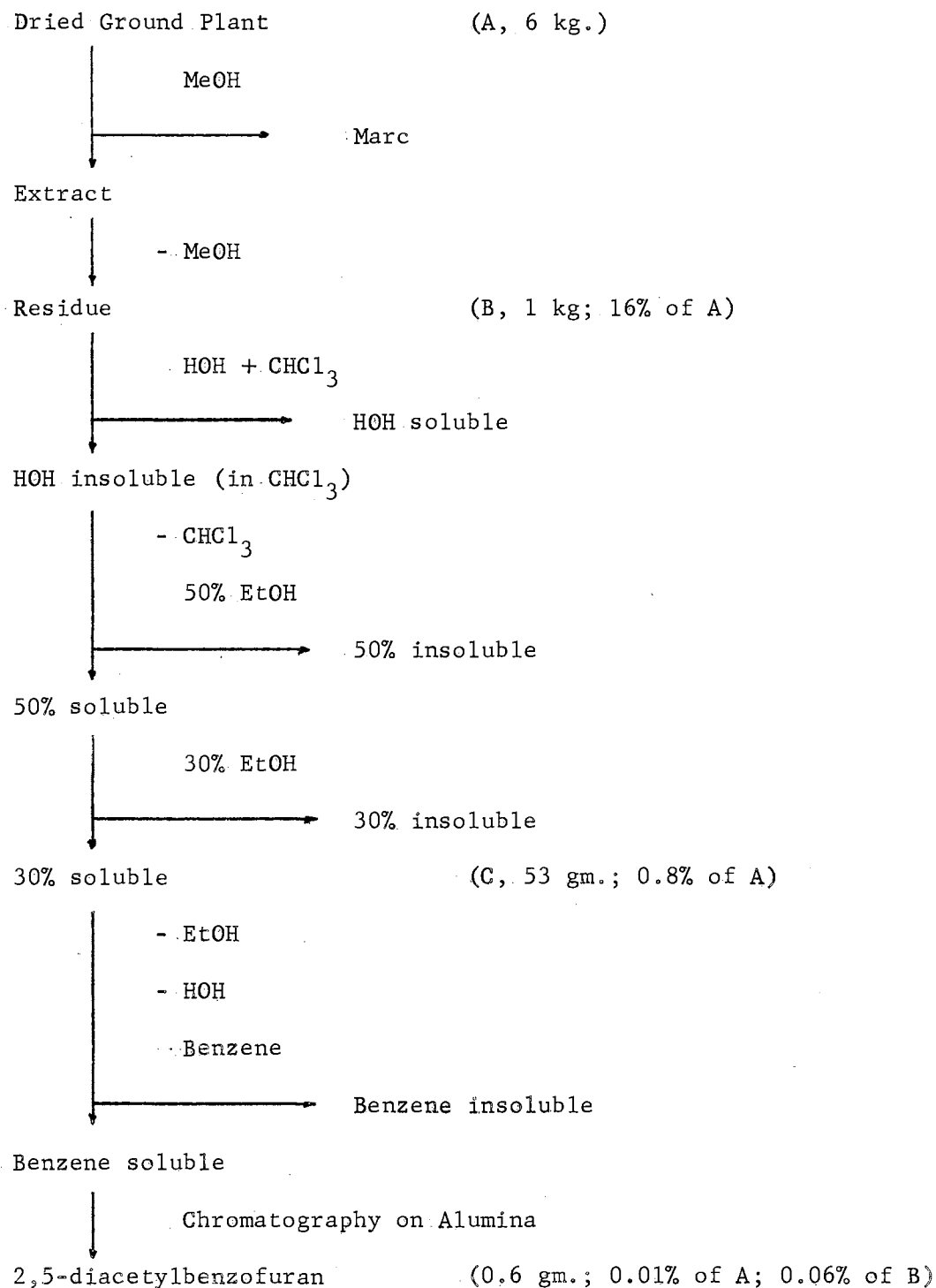
In addition to the benzofurans I and II, a 2,3-dihydrobenzofuran named toxol (VIII) has been isolated⁴ from the goldenrod plant. It has been shown to have the configuration as depicted in VIII¹⁴. Toxol and toxol acetate have both been degraded by ozonolysis followed by pyrolysis to 2,5-diacetylbenzofuran (I).⁴ Dehydrotremetone (III) has been degraded by osmium tetroxide glycolation followed by lead tetraacetate cleavage to I.⁴ Dehydrotremetone itself has not been synthesized. These degradations furnished the spectral and melting point data used to identify the isolated material (I).

DISCUSSION AND RESULTS

A) Isolation

The compound 2,5-diacetylbenzofuran (I) was isolated from goldenrod by a modification of Couch's procedure¹. The plant was collected just north of the Pecos River in New Mexico during the month of August when it was in full bloom. The entire plant above ground was collected, dried, and ground with a hammer mill. The ground plant was then extracted with methanol in a large Soxhlet extractor. The methanolic extract was then treated as follows: (see Chart A). The methanol was distilled off and the residue washed with water containing a small amount of chloroform; then the water was decanted and, the chloroform distilled off; the resulting residue was dissolved in 50% ethanol, the solution filtered and the filtrate diluted to 30% ethanol and refiltered; the ethanol was distilled from the filtrate and the water decanted and the residue dissolved in benzene; the benzene solution was finally chromatographed on alumina. 2,5-Diacetylbenzofuran (I) was isolated from the fraction eluted from the column in 60% ether - 40% benzene, and crystallized after removing the solvent and allowing it to stand for some time. Along with I there was a large amount of an oily green material which was found to be best removed by washing with cold methanol and recrystallization of I from hot methanol. After several recrystallizations the compound was identified as I by comparison of its N.M.R. and I.R. spectra and melting point with those of I as prepared by Burke⁴. The fact that this compound (I) had

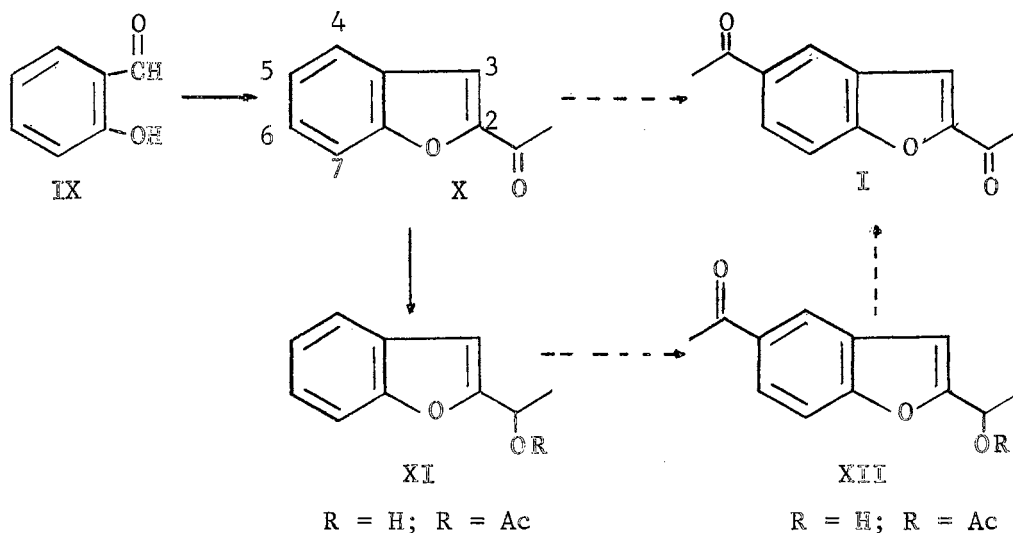
CHART A



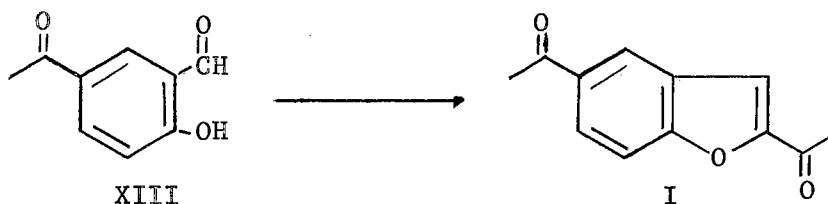
not been previously isolated seemed strange until it was noticed that it was unstable under saponification conditions and was therefore lost. Since this compound had been previously prepared only by degradation of natural compounds which themselves had not been synthesized and a sizeable amount was needed for testing, the total synthesis was undertaken as described below.

B) Attempted Syntheses

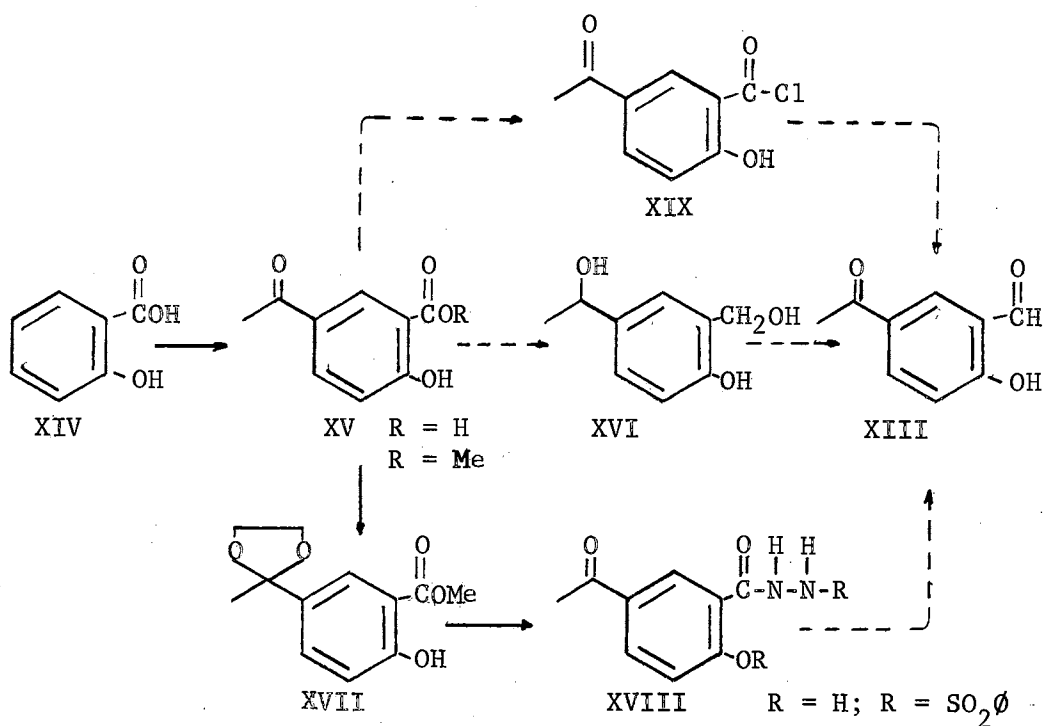
Salicylaldehyde (IX) was condensed with chloroacetone according to DeGraw and Bonner¹⁵ to give 2-acetylbenzofuran (X). Acylation of X in position 5 would result in the desired product I; however, acylation attempts with several reagents yielded no detectable I. Since the aromatic system of X is deactivated by the 2 acetyl group, the acylation was again attempted after the carbonyl group had been reduced to give the alcohol XI R = H and also on acetate of XI (R=Ac) to see if removal of the highly electron withdrawing carbonyl group would permit acylation. Under all of the conditions tried, a compound corresponding to XII R = Ac or H was never isolated.



Since all of the acylation attempts failed to go or resulted in polymerization, our next goal was the cyclization of aldehyde XIII with chloroacetone. Since aldehyde XIII was unknown the first problem became its synthesis.



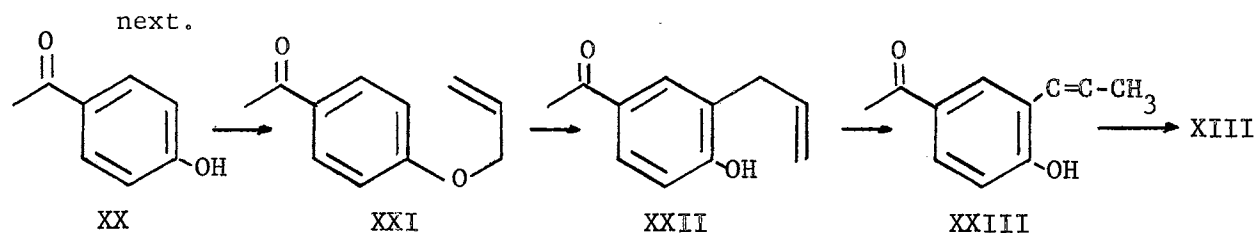
Acylation of salicylaldehyde (IX) would be expected to give the desired aldehyde XIII, but aldehydes in general are not readily acylable under Friedel-Crafts conditions, and another route was sought. Rosenmund¹⁶ reported that salicylic acid (XIV) could be acylated in the para-position to give XV (R = H) via the acetate of XIV through a Fries rearrangement. The methyl ester of XV (R = Me) was then made and an attempt made to convert it to the alcohol XVI by reduction with lithium aluminum hydride which could then be oxidized to the required aldehyde XIII. This sequence proved unsuccessful due to a number of problems. First, during the reduction the lithium salts of XVI precipitated out and did not allow the full reduction of XV (R = Me). Separation of the alcohol XVI, and other partially reduced compounds, from water by extraction proved difficult due to their great solubility in water. A method of efficiently separating the fully reduced from the partially reduced compounds presented another problem. In addition to these difficulties, more side products were obtained from the oxidation step and aldehyde XIII could not be obtained by this sequence of reactions.



Aldehydes can, in general, also be made from acids via the acid chlorides by catalytic or controlled hydride reduction. Therefore, an attempt was made to prepare acid chloride XIX from acid XV ($R = H$) by the method of Kirpal¹⁷ who prepared salicyl chloride from salicylic acid with thionyl chloride and catalytic amounts of aluminum chloride. This method, however, failed due to the low solubility of the acid XV ($R = H$) in thionyl chloride and therefore only the starting acid was recovered.

Aromatic aldehydes can also be prepared through the McFadyen-Stevens reaction¹⁸ which was also applied in this case. The methyl ester of XV ($R = Me$) was first treated with ethylene glycol to give the ketal XVII in order to protect the carbonyl group from reaction with hydrazine in the preparation of compound XVIII ($R = H$). Compound XVIII ($R = H$) was then treated with benzenesulfonyl chloride to give XVIII

(R = SO₂ϕ) which upon treatment with sodium carbonate should yield the aldehyde XIII. This method proved to be inefficient because the yield of XVIII (R = H) from XVII was only 10%. The decomposition of XVIII (R = SO₂ϕ) was not then undertaken in favor of the sequence described

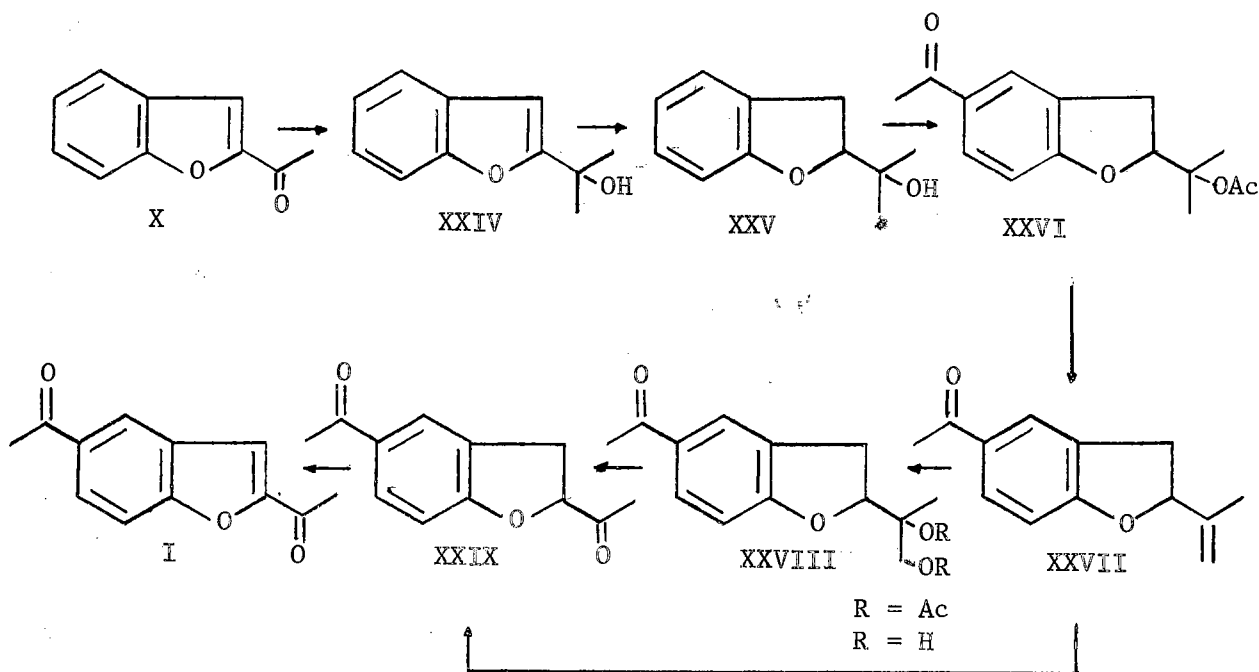


Phenol can be acylated according to the method of Schmid and Schmid¹⁹ to give p-hydroxyacetophenone (XX) or this material can be purchased commercially. The compound XX was then treated with allyl bromide to give the allyl ether XXI which underwent a Claisen rearrangement to give phenol XXII according to the method of Arnold and McCool²⁰. The allyl phenol XXII was then subjected to the usual conditions²¹ for rearrangement to the propenyl phenol XXIII. This gave XXIII in about 50% yield and therefore various methods were sought to increase the yield of XXIII. Crystallization and chromatography were unsuccessful with the mixture and therefore reaction conditions which would give 90% yield or better were sought. After many trials with various bases and solvents (see Table I), it was found that treatment of XXII with a methanolic KOH solution in a sealed tube at 130-140°C. for seven (7) days would give a product containing better than 90% XXIII. The propenyl phenol XXIII was then changed to aldehyde XIII by a one step cis dihydroxylation and oxidative clipping of the resulting glycol with sodium metaperiodate and a catalytic amount of osmium tetroxide according to the method of Pappo and Johnson²². Attempts to cyclize aldehyde XIII with chloroacetone were not undertaken since the desired 2,5-diacetylbenzofuran was successfully prepared by the

method presented in the next section.

C) Synthesis

The synthesis of 2,5-diacetylbenzofuran (I) has been accomplished by the route diagramed below.



The compound X prepared as previously described was treated with methyl magnesium iodide to give XXIV, which was hydrogenated in ethanol using freshly prepared²³ W-2 Raney nickel catalyst to give compound XXV. Compound XXV was then acylated with acetic acid and trifluoroacetic anhydride to give the crystalline compound XXVI. This sequence of reactions had previously been described by DeGraw²⁴. The acetate XXVI was then pyrolyzed at 330°C. according to Bowen²⁵ to give tremetone (XXVII). An attempt was then made to convert tremetone directly into the diketone XXIX with sodium metaperiodate and osmium tetroxide catalyst²². Since the yield of XXIX by this method was less than 20%, the three step oxidation described by Bonner, et al.¹⁴ was used giving

diketone XXIX in about 40⁺% yield. This method consisted of treating tremetone (XXVII) with silver acetate to give the diacetate XXVIII (R=Ac) which was hydrolyzed to the diol XXVIII (R = H). The diol XXVIII (R = H) was then oxidized to the diketone XXIX with lead tetraacetate. Dehydrogenation of XXIX with 5% Pd/C in an evacuated sealed tube gave compound I in about 68% yield. The melting points of the totally synthesized and the natural compounds are given below.

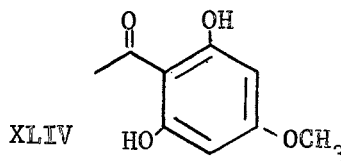
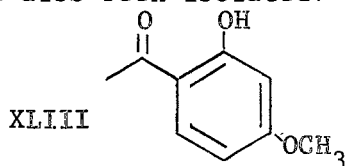
Natural I	M.P. 139-140°C.
Synthetic I	M.P. 138-139°C.
Mixed	M.P. 139-140°C.

The infrared, ultraviolet, and N.M.R. spectra were essentially identical as can be seen by examination of plates I through VI.

DISCUSSION OF BIOSYNTHESIS

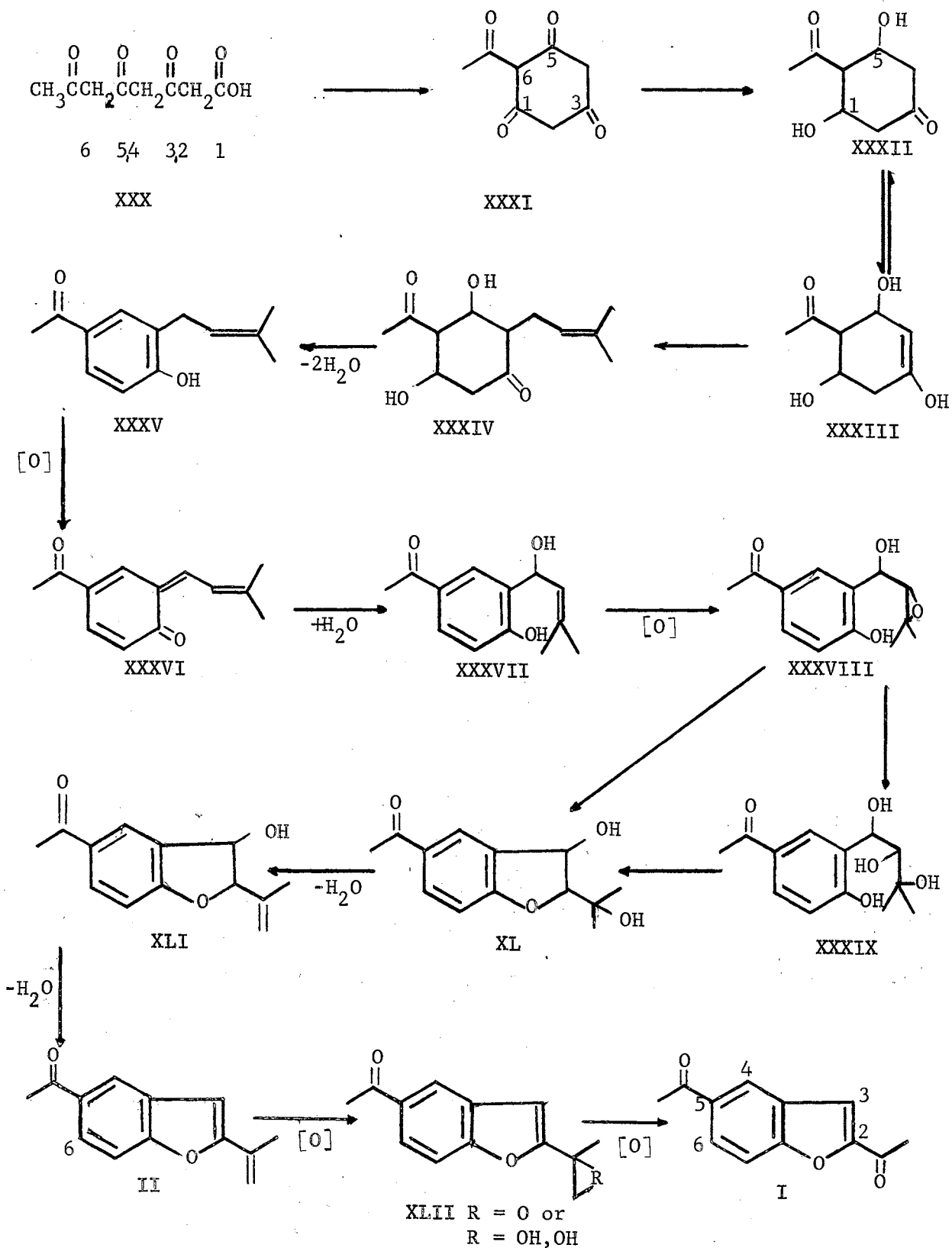
In Chart B a path for the biosynthesis of 2,5-diacetylbenzofuran (I) is shown. In this part we wish to discuss this pathway, pointing out various features of it.

Support for the formation of polyacetyl chains by living organisms is much and varied. In a review of the previous work, Richards and Hendrickson²⁶ discuss in detail the various possibilities of the formation of polyacetyl chains from acetate. The biosynthesis of I requires an eight carbon polyacetyl chain XXX, which forms the benzene ring and the 5-acetyl side chain in I. The formation of a benzene ring would then require the cyclization of XXX to XXXI. Richards and Hendrickson²⁶ describe this as a path-A cyclization which leads to a family of phenols, the acylphloroglucinols. Support for a structure of the type XXXI is given by the fact that peonol (XLIIII) and hydroxy-peonol (XLIV) have been isolated from Xanthorrhoea²⁷. A number of other similar compounds have also been isolated.²⁸



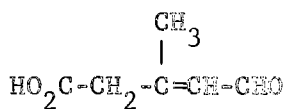
Transformation of XXXI to XXXII involve a reduction of the carbonyls at positions 1 and 5. Reduction at this point provides a method for aromatization of the ring with loss of the oxygen functions as water. Another way in which this could be accomplished would be by aromatization of XXXI by full enolization and then loss of the desired oxygen

CHART B

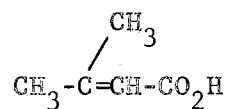


functions (1 and 5) through a reduction of an ester or glucoside, comparable to the hydrogenolysis of a tosylate. If such an enol aromatization occurred then the isoprenylation to give XXXV would have to take place on an aromatic ring and have to overcome the resonance energy of the benzene ring which it would not have to do if the enol form of XXXII (XXXIII) were the species being alkylated. It is also interesting to note that if only the carbonyl at 5 is reduced and lost as water and the carbonyl at 1 simply enolizes, then structure II would have a hydroxyl group at position 6 and this compound is euparin (IV) which has been isolated as discussed before⁸. However, this could also occur by the enol aromatization and loss of one hydroxyl by the reduction of some ester or glucoside.

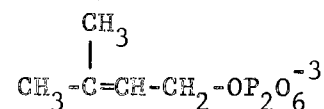
Isoprenylation of the enol XXXIII could then result in XXIV. Looking at I, it is observed that only a four carbon chain is needed to complete the carbon framework; however, for reasons to be pointed out subsequently, an isoprene unit is added at this point. The use of an isoprene unit as a building block in biosynthesis has long been known especially in terpenes and steroids. Richards²⁶ and Seshadri²⁹ agree that a large number of acetogenins, especially those with fused heterocyclic rings, contain isoprene units. The actual isoprenylating agent is unknown and different workers choose differing species. Seshadri²⁹ feels that it is an aldehyde of structure XLV or an equivalent form in which the double bond has been epoxidized or hydroxylated.



XLV



XLVI



XLVII

Robinson³⁰ suggested that it is senecioic acid (XLVI). Richards²⁶ notes that isopentenyl pyrophosphate (XLVII) could be the isoprenylating agent. Whatever the alkylating species is, a compound of structure XXXIV would result. A loss of two moles of water from XXXIV would result in the aromatic compound XXXV in which the carbonyl has enolized.

Subjecting XXXV to various oxidations which Richards³¹ and Seshadri²⁹ feel are in accord with biosynthetic processes, compound XXXVI is produced. The addition of water to XXXVI could then result in XXXVII which upon further oxidation could result in epoxide XXXVIII. Epoxide XXXVIII could be hydrolytically opened to XXXIX which could cyclize to XL or the epoxide XXXVIII could close directly to XL. Of course there are many other directions in which XXXV can be oxidized and cyclized to give other compounds, several of which are shown by Richards³¹.

Compound XL upon loss of a mole of water could result in XLI, and just such a compound has been isolated. Toxol (VIII) and its dehydration product dehydrotremetone (II), both have been isolated⁴ from the same plant from which I was isolated. This then gives much support for the alkylation of XXXIII by a five carbon unit rather than by a four carbon unit.

The further oxidation of II through the epoxide XLII (R = O) to the diol XLII (R = OH, OH) or to either without the other could result in I.

EXPERIMENTAL

Infrared spectra were recorded with a Beckman IR - 5A spectrometer; solids were taken in potassium bromide pellets, and liquids as films on sodium chloride crystals. The ultraviolet spectra were recorded with a Beckman DK - 1 spectrometer. Nuclear magnetic resonance (N.M.R.) spectra were recorded on a Varian A-60 N.M.R. spectrometer, using tetramethylsilane as an internal standard ($\delta = 0$) and the results are reported as dimensionless "chemical shift" units (δ). Melting points were obtained in sealed capillary tubes using a Thomas-Hoover apparatus and are uncorrected. Thin layer chromatograms (TLC) were made on 25 μ thick silica gel coated glass plates using 1:1 benzene-ether as the mobile phase unless otherwise noted, for detection was by iodine vapors.

A) Isolation

Rayless goldenrod was collected in August while in full bloom just west of Roswell, New Mexico, in and near the Bottomless Lakes Park. The entire plant above ground was cut, air dried, and then ground in a hammer mill with a 1/8 inch screen. The ground plant was extracted continuously with methanol in a large Soxhlet extractor. See Chart A for a diagram of the isolation sequence. In a typical run, two batches of three kilograms of ground plant were extracted and seventy-two hours with approximately ten liters of methanol each in two extractors. The methanol was removed from the extractors, combined, and the methanol

distilled off on a steam bath leaving approximately one kilogram of a tarry residue. This residue was then placed in a large beaker or flask, and an equal volume of chloroform added and then washed continuously with tap water until the water became clear. The water was then removed by decantation and the chloroform was distilled off on a steam bath. The residue resulting from this treatment was dissolved in 50% ethanol and filtered through glass wool while hot. Several portions of 50% ethanol were used. The filtrate (50% ethanol soluble) was then diluted with water until the resulting solution became 30% in ethanol and was then refiltered while hot. The 30% ethanol filtrate was then heated on a steam bath until all the ethanol had distilled off. The solution was cooled and the remaining water removed from the "heavy" residue (53 gm.) by decantation. From several such runs 410 gms. of the "heavy" residue was obtained and as much as possible (about 250 gms.) was dissolved in benzene. The benzene solution (saturated) was then placed on a column of 10 kg. of acid washed, activity I alumina (Merck). Fractions of 1000 ml. were taken as the solvent was changed stepwise from benzene to ether to methanol. The fractions were taken to dryness and allowed to stand for several days. The material eluted from the column with 60% ether-40% benzene deposited some crystals which were collected by filtration and then washed with cold methanol to remove a dark green oily material. The crystals (4.5 gm.) were then recrystallized from hot methanol and identified as 2,5-diacetylbenzofuran (I) by comparison of melting points, IR spectra, and N.M.R. spectra with I as prepared by Burke⁴. M.P. 139-140° C. $\nu_{\text{Max}}^{\text{KBr}}$ 3500, 1660, 1600, 1290, 1160, and 813 cm^{-1} . N.M.R. (DCCl_3): 2.64 δ (3 protons); 2.69 δ (3), and a multiplet from 7.5 to 8.4 δ (4). $\lambda_{\text{Max}}^{\text{EtOH}}$ 253 $\text{m}\mu$ ($\epsilon = 71,000$), 286 (34,000).

B) Syntheses

2 - Acetylbenzofuran (X). Salicylaldehyde (IX) (22 gm.) was dissolved in 88 ml. of absolute ethanol and to this was added 11 gm. of KOH in 63 ml. of hot methanol. The mixture was kept at 30-35° with a water bath and to the mixture was added dropwise with stirring 16.75 gm. (14.5 ml.) of chloroacetone. After stirring for one hour, 150 ml. of water were added and the methanol and ethanol distilled off under reduced pressure. The solution was then extracted with methylene chloride. The methylene chloride solution was then washed with water, 2% NaOH, more water, and then dried (MgSO₄). The methylene chloride was removed under vacuum and the residue crystallized twice from EtOH - HOH. A yield of 13.1 gm. (45%) of X resulted. M.P. 70-71° C (reported M.P. 72-73°)¹⁵
 $\nu_{\text{Max}}^{\text{KBr}}$ 3075, 1661, 1610, 1545, 1290, 1175, 1080, and 745 cm⁻¹. N.M.R. (CCl₄): 2.55 δ (3 protons) a multiplet from 7.3 to 7.9 δ (5 protons).

Attempted Acylations of X. (1) A mixture of 0.533 gm. of X, 0.34 gm. of glacial acetic acid, and 1.46 gm. of trifluoroacetic anhydride was stirred at room temperature for 4½ hrs. in a stoppered flask. After this time 7 ml. of ether was added, and the resulting solution was added dropwise to a rapidly stirred aqueous solution of sodium bicarbonate (in excess). More ether was added, the layers separated, and the ether dried (Na₂SO₄). After the ether was removed, 0.522 gm. of material resulted which TLC indicated to be the starting material X.

(2) A similar mixture as in part (1) was heated on a steam bath in a flask fitted with a condenser and drying tube for 5 hrs. After allowing the solution to cool, 10 ml. of chloroform was added and the chloroform solution then added to a stirred solution of sodium bicarbonate. The

layers were separated, the chloroform dried (Na_2SO_4) and then evaporated to give 0.629 gm. of a resinous material. TLC again showed the absence of I, the presence of the starting material X, and a large amount of a polymer.

(3) To 0.9 gm. of aluminum chloride, 25 ml. of carbon disulfide was added with stirring, keeping the flask at 27°C with a water bath. To this was added 0.25 ml. of acetyl chloride in 2 ml. of CS_2 . A solution of 0.533 gm. of X in 10 ml. of CS_2 was then added dropwise with stirring and cooling. After the addition was complete the mixture was refluxed on a steam bath for 4 hrs. To this was added 5 ml. of H_2O , 5 ml. of conc. HCl , and more water. The mixture was then extracted with 10 ml. of chloroform. The chloroform was washed with water, dried (Na_2SO_4) and evaporated to yield 0.490 gm. of material. TLC showed that no I was present and that the material was essentially starting material X.

1-(2-benzofuryl)-ethanol (XI R = H). A solution of 2.98 gm. of X in 40 ml. of methanol was added to a solution of 0.4 gm. of sodium borohydride in 10 ml. of methanol at 0°C . After 6 hrs., 30 ml. of 5% HCl (by volume) was added and the solution extracted with ether; the ether was washed 6-8 times with water, dried (Na_2SO_4) and evaporated. An oil (2.916 gm., 97%) resulted which upon standing solidified.

$\nu_{\text{Max}}^{\text{film}}$ 3300, 2955, 1600, 1455, 1255, 1075, 1008, 942, 880, and 805 cm^{-1} .
 N.M.R. (CCl_4): a doublet 1.52 δ (3 protons) ($J = 7\text{ c.p.s.}$), a singlet 3.68 δ (1) (disappears with D_2O), a doublet 4.88 δ (1) ($J = 7\text{ c.p.s.}$), a singlet 6.47 δ (1), a multiplet from 7.0 to 7.6 δ (4).

Attempted acylations of XI (R = H). (1) A solution of 1.005 gm. of XI (R = H) in 10 ml. of nitroethane, and 1 ml. of acetyl chloride was

stirred together for $\frac{1}{2}$ hr. and then added dropwise to a cold (0° C.) solution of 2 gm. aluminum chloride in 10 ml. of nitroethane. The mixture was kept at 0° C. and stirred for $\frac{1}{2}$ hr. and then poured on ice containing 5 ml. of conc. HCl. The mixture was then extracted with ether; the ether was washed with water, dried (MgSO_4), and the ether and nitroethane removed under vacuum. A mixture of 1.0777 gm. of material resulted which could not be identified.

(2) A solution of 1.00 gm. of XI ($R = H$) in 20 ml. of dry ether was cooled in an ice bath and 0.75 ml. of acetic acid was added with stirring. To the resulting solution, 3.35 ml. of trifluoroacetic anhydride in 5 ml. of ether was added and stirred overnight allowing the mixture to come to room temperature. About 1/10 of the ether was removed by vacuum without the application of heat and the stirring continued overnight again. After this time TLC indicated the absence of starting material and the mixture was poured into aqueous sodium bicarbonate. The layers were separated, the aqueous layer extracted with ether, and the ether portions combined. The ether solution was then washed with water, dried (MgSO_4), and the ether removed yielding 1.026 gm. of material. N.M.R. and I.R. showed it to be essentially XI ($R = \text{Ac}$). $\nu_{\text{Max}}^{\text{film}}$ 3100, 1745, 1600, 1460, 1375, 1240, 820, and 750 cm^{-1} . N.M.R. (CCl_4): doublet 1.59 δ ($J = 6.5 \text{ c.p.s.}$), singlet 1.05 δ , triplet 6.19 δ ($J = 6.5 \text{ c.p.s.}$), singlet 6.62 δ , multiplet from 7.0 to 7.7 δ .

Acetate XI ($R = \text{Ac}$). A mixture of 2.9 gm. XI ($R = H$), 6 ml. of acetic anhydride, and 5 ml. of pyridine were stirred at room temperature for 6 days. The mixture was then added to 50 ml. of water and extracted with ether. The ether was washed with water, a small amount of 5% HCl,

more water, and then dried (MgSO_4). The ether was removed yielding 2.3 gm. of material whose N.M.R. indicated to be 66% XI (R = Ac) and 33% XI (R = H). The mixture was not separated but used directly in the acylation attempt next described. See part (2) of attempted acylations of XI (R = H) for a better method of preparation and spectral data of XI (R = Ac).

2 - Hydroxy - 5 - acetylbenzoic acid (XV R = H). Aspirin (acetyl salicylic acid) (20 gm.) was added to a cold (0°C) stirred solution of 30 gm. of aluminum chloride in 100 ml. of nitroethane. The temperature was raised to 45°C . and held there for one hour. After 4 hrs. the mixture was poured into a stirred ice-HCl mixture. The solution was adjusted to a pH of 3 and the precipitate which formed was removed by filtration. After recrystallization from ethanol-water, 12.5 gm. (65% yield) of XV (R = H) resulted. M.P. $218-219^\circ\text{C}$. $\nu_{\text{Max}}^{\text{KBr}}$ 2825 (broad), 1680, 1650, 1600, 1290, 1230, 843, 807, and 718 cm^{-1} .

Methyl - 2-hydroxy - 5 acetylbenzoate (XV R = Me). Acid XV (R = H) (5.83 gm.) was treated with excess ethereal diazomethane. The solution was allowed to stand overnight, was filtered, and the ether slowly evaporated to leave 5.698 gm. (91% yield) of a crystalline material. M.P. $40-45^\circ\text{C}$. $\nu_{\text{Max}}^{\text{KBr}}$ 3150, 1690, 1590, 1445, 1095, 960, 840, and 798 cm^{-1} . N.M.R. (CCl_4): singlet 2.50 δ ($J = 9.5$), singlet 11.09 δ .

Attempted reduction of XV (R = Me). A solution of 5.16 gm. of XV (R = Me) in 50 ml. of dry ether was added to 1.5 gm. of lithium aluminum hydride in 80 ml. of dry ether at room temperature. A yellow precipitate formed and 25 ml. of tetrahydrofuran was added to help

redissolve the precipitate. Most of the precipitate remained and the mixture was stirred for 2 days. Wet ether was slowly added, followed by water, and 50 ml. of 4% sulfuric acid. The mixture was extracted with ether, and the ether dried (Na_2SO_4). After removing the ether and traces of tetrahydrofuran, 3.14 gm. of material resulted which was used directly as described below.

Attempts to oxidize the reduction products of XV (R = Me). (1)

A solution of 1.66 gm. of the above reduction product in 18 ml. of pyridine was added dropwise to 5.963 gm. of chromium trioxide in 60 ml. of pyridine. The mixture was stirred during the addition and then allowed to stand at room temperature for 16 hrs. At this time, 300 ml. of water was added and the mixture extracted with a large amount of ether. The ether was washed with water, 10% HCl, more water and then dried (MgSO_4). Upon evaporation of the ether 0.677 gm. of unidentified material resulted.

(2) A solution of 1.0 gm. of the above reduction product in 100 ml. of chloroform was stirred with 7 gm. of active manganese dioxide as prepared according to Sondheimer³² for 6 hrs. The mixture was filtered, and the filtrate dried (Na_2SO_4). The chloroform was then removed yielding 0.6 gm. of unidentified material.

Attempted preparation and reduction of XIX. Acid XV (R = H)

(2.994 gm.) was placed in a flask fitted with a condenser and a stirrer. To this was added 0.02 gm. of aluminum chloride and 3 ml. of thionyl chloride. The mixture was thoroughly stirred and kept at a temperature of 45-55° C. for 3 hrs. During this time the acid did not dissolve as expected. The excess thionyl chloride was then removed under vacuum and

the residue dissolved in 25 ml. of dry tetrahydrofuran (THF). The mixture was then cooled in a dry ice-acetone bath and 9.938 gm. of lithium aluminum tritertiary butoxy hydride in 40 ml. of THF was added in 45 minutes. The solution was allowed to stir for 2 hrs. and come to room temperature. It was then poured on ice and filtered, the precipitate (aluminum hydroxide) being washed with ethanol. Acidification of the filtrate with 6% sulfuric acid and extraction with ether yielded 1.153 gm. of material upon evaporation of the ether. The infrared spectrum indicated the material to be the starting acid (XV R = H). This was confirmed by TLC after treating the material with diazomethane, making the methyl ester (XV R = Me).

Preparation of XVIII (R = SO₂∅). A mixture of 1.033 gm. of ester XV (R = Me), 0.02 gm. of p-toluene sulfonic acid, 20 ml. of benzene, and 2 ml. of ethylene glycol was refluxed for 17 hrs. with a Dean Stark trap. The benzene and excess ethylene glycol were removed under vacuum and the residue (XVII) heated with 1.7 ml. of hydrazine in 10 ml. of MeOH at reflux temperature for 8 hrs. during which time part of the methanol was allowed to escape. The mixture was cooled, dissolved in 8 ml. of H₂O, and the precipitate which formed after standing was removed by filtration. The 0.104 gm. of precipitate (XVIII R = H) was suspended in 1.5 ml. of pyridine and ½ ml. of benzenesulfonyl chloride was added with stirring. The mixture was poured on iced HCl (5 ml. of conc. HCl), stirred, and the precipitate removed by filtration, washed with 1 ml. of 5% HCl and 2 ml. of water and then dried. A yield of 0.257 gm. (9.3% from XV, R = Me) of a cream colored solid (XVIII, R = SO₂∅) resulted which had a melting point of 145-150° C. with decomposition.

p-Hydroxyacetophenone (XX). A solution of 20 gm. of vacuum-dried phenol in 100 ml. of nitroethane was cooled under tap water and to this was added dropwise 17 ml. of acetyl chloride with cooling in an ice bath. Aluminum chloride (50 gm.) was then added in small portions with vigorous stirring and continued cooling. The mixture was stirred for one hour and then allowed to stand for 24 hrs. The mixture was then cooled again and ice and water slowly added with stirring. The mixture was warmed on a steam bath after adding 25 ml. of conc. HCl and then filtered. The layers were separated and the water layer extracted with ether. The oil and the ether were combined and evaporated. The residue was dissolved in ether and the ether extracted with 5% NaOH. The basic extract was acidified with sulfuric acid and extracted with ether. The ether solution was then dried (MgSO_4) and decolorized with several portions of norite. Evaporation of the ether yielded 25.82 gm. of XX which was recrystallized from benzene-petroleum ether (3:1) M.P. $107-108^\circ\text{C}$. (Reported M.P. $106-107^\circ$).¹⁹

Allyl ether of XX (XXI). A mixture of 12.5 gm. of XX, 8.2 ml. of allyl bromide, 13.8 gm. of anhydrous potassium carbonate, and 15 ml. of acetone was refluxed on a steam bath for 8 hrs. Water (50 ml.) was added and the mixture cooled and then extracted with ether. The ether solution was washed with water, 5% NaOH, more water, and then dried over anhydrous potassium carbonate and decolorized with norite. Evaporation of the ether yielded 16.15 gm. of XXI. B.P. $110-120^\circ\text{C}$ @ 0.3 mm Hg. (reported B.P. $146-147^\circ$ @ 10 mm Hg)²⁰. $\nu_{\text{Max}}^{\text{film}}$ 2845, 1680, 1600, 1510, 1420, 1360, 1180, and 835 cm^{-1} . N.M.R. (CCl_4): singlet $2.42\ \delta$ (3 protons), doublet at $4.52\ \delta$ ($J = 4.5\text{ c.p.s.} : 2$), triplet at $5.35\ \delta$

($J = 9$ c.p.s.; 2), a multiplet at 5.89 δ , doublets at 6.87 and 7.86 δ ($J = 9$ c.p.s.; 2 protons each).

Allyl phenol XXII. The allyl ether XXI (16.15 gm.) was heated to reflux under a nitrogen atmosphere for 4½ hrs. The temperature of the pot material rose from 193° to 222° and then dropped. Upon cooling the material solidified and was dissolved in ether with stirring. The ether was extracted with 5% NaOH, washed with water, dried, and evaporated to give 3.00 gm. of the starting ether XXI. The basic extract was acidified with 6% H₂SO₄ to a pH of 3 and extracted with ether. The ether was decolorized with norite, dried with MgSO₄, and evaporated yielding 13.00 gm. of XXII which was recrystallized from MeOH-H₂O (3:10). M.P. 114-116° C. (reported M.P. 115-116° C)²⁰. $\nu_{\text{Max}}^{\text{KBr}}$ 3130, 1650, 1580, 1290, 1240, 1125, 920, and 815 cm⁻¹. N.M.R. (DCCl₃): singlet 2.59 δ (3 protons), doublet 3.49 δ ($J = 6$ c.p.s.; 2), singlet 5.05 δ (1), singlet 5.28 δ (1), doublet 7.00 δ ($J = 9$ c.p.s.; 1), singlet 7.8 δ (3).

General procedure for attempted rearrangements of XXII to XXIII as tabulated in Table I. A solution of 1 gm. of XXII in 10 ml. of the solvent was added to the base dissolved in approximately 10 ml. of the solvent. (For pyridine the addition was made to the hot solvent. For methanol the addition was made at room temperature.) The mixture was then heated to the specified temperature for the time designated. After cooling an equal volume of water was added, the mixture extracted with ether, and the aqueous portion acidified with 6% sulfuric acid to a pH of about 3 and then extracted with ether. The ether was then dried (MgSO₄) and evaporated to yield the phenolic mixture of XXII and XXIII. The percentage of XXII and XXIII was determined by N.M.R.

TABLE I

Solvent	Base	Mole Ratio of Base to XXII	Rx time in hours	Rx temp. in °C.	% Rear- rangement to XXIII
MeOH	KOH	<u> </u> ^a	7	90	60
MeOH	NaOMe	2.0:1	6	80	55
MeOH	KOMe	3.0:1	24	65-80	67
Pyridine	KOH	2.0:1	5	100	56
Pyridine	KOH	3.0:1	5	110	45
Pyridine	KOH	6.0:1	15½	110	54
Pyridine	KOH	3.0:1	16	115	60
EtOH: MeOH(2:1)	KOH	2.1:1	6	85	60
H ₂ O	KOH	3.9:1	100	100	25 ^b

^aMeOH saturated with KOH.

^bN.M.R. integrator not working properly and this is an estimation.

Rearrangement of XXII to XXIII. A solution of 5.48 gm. of XXII, 8.08 gm. of KOH, and 54 ml. of MeOH were sealed in a heavy walled tube and heated for 7 days at 130-140° C. The tubes were cooled, opened, and the contents added to an equal volume of water. The precipitated silicates were filtered out and washed with water and ether. The filtrate was extracted with ether and the ether washed with base. The aqueous portions were combined and acidified with 6% sulfuric acid to a pH of about 3, and then extracted with ether. The ether solution was dried (MgSO₄) and decolorized with norite. Evaporation of the ether yielded 4.938 gms. (90% yield) of material which N.M.R showed to be 90-95% XXIII. N.M.R. (CHCl₃): doublet at 1.89 δ (J = 5 c.p.s.; 3), singlet 2.61 δ (3), no protons from δ = 3.5 to 6.0.

Aldehyde XIII. A solution of 1 gm. of XXIII in 25 ml. of dioxane-water (3:1) was mixed with 0.25 gm. of osmium tetroxide in 20 ml. of the same solvent at room temperature. After 5-10 minutes the solution turned black and 2.56 gm. of solid NaIO₄ was added in small portions over a period of 2 hrs. at intervals of 5-10 minutes. The mixture was then stirred for 4 hrs. A small amount of H₂S gas was then introduced, precipitating black osmium sulfide. The mixture was filtered and extracted with ether. The ether was washed with water, dried (MgSO₄) and evaporated. The IR (ν_{Max}^{film} 3020, 2875, and 1650) and N.M.R. singlet δ 10.07) showed the presence of an aldehyde (XIII) which was not further characterized.

2-Benzofuryl - 2-propanol (XXIV). A solution of 6.482 gm. of 2-acetylbenzofuran (IX) in 35 ml. of dry (Na) ether was added dropwise to a methyl Grignard solution made by adding 3.75 ml. of methyl iodide

to 1.406 gm. of Mg. in 40 ml. of ether. After the addition was completed, the mixture was stirred for one hour and then poured on 50 gm. of ice in 60 ml. of 1 N HCl. The mixture was extracted with ether and the ether washed with a dilute solution of NaHSO_3 , saturated NaHCO_3 , and water. The ether was then dried (Na_2SO_4) and used directly in order to avoid dehydration during removal of the ether.

2-(2,3-Dihydrobenzofuryl)-2-propanol (XXV). The above ethereal solution was mixed with 25 ml. of absolute ethanol and the ether removed. The total volume was brought up to 60 ml. with absolute ethanol and one-half teaspoon of freshly prepared W-2 Raney nickel added. The mixture was stirred in an atmospheric hydrogenation apparatus until 900 ml. of hydrogen was taken up. The catalyst was filtered out and the ethanol removed yielding a colorless oil of 6.79 gm.

2-(2,3-Dihydro-5-acetylbenzofuryl)-2-propyl acetate (XXVI). To a mixture of 4.4 ml. of glacial acetic acid and 11 ml. of trifluoroacetic anhydride, was added dropwise 6.79 gm. of XXV with cooling in a water bath. The solution was stirred for the addition and then allowed to stand for three hrs., after which time it was poured into a solution of 24 gms. NaHCO_3 in 150 ml. of water. The mixture was extracted with ether, and the ether dried (Na_2SO_4), and evaporated to give 3.015 gm. (30% yield) of XXVI after recrystallization from benzene-Skelly "B" (7:3). M.P. 95°C . (reported M.P. $95-96^\circ\text{C}$)²⁴ $\nu_{\text{Max}}^{\text{KBr}}$ 1740, 1680, 1620, 1275, and 1250 cm^{-1} . N.M.R. (CCl_4): doublet 1.50 δ (J - 5 c.p.s.; 6 protons) singlet 1.95 δ (3), singlet 2.45 δ (3), doublet 3.20 δ (J = 9 c.p.s.; 2), triplet 5.08 δ (J = 9; 1), doublet 6.76 δ (J = 9; 1) singlet 7.76 δ (2).

Tremetone (XXVII). Acetate XXVI (2.367 gm.) was placed in an indented test tube with a nitrogen atmosphere and heated in a Wood's metal bath at 330°C. for 10 minutes. It was allowed to cool and the contents were dissolved in ether, which was then washed with 5% NaOH, water and then dried (Na_2SO_4). Evaporation of the ether yielded 1.805 gm. (99% yield) of an oil which N.M.R. showed to be greater than 90% XXVII. $\nu_{\text{max}}^{\text{film}}$ 2590, 1680, 1620, 1500, 1450, 1370, 1275, 1240, 1170, 1130, 960, 910, and 820 cm.^{-1} . N.M.R. (CCl_4): singlet 1.85 δ (3), singlet 2.53 δ (3), multiplet 3.27 δ (2), multiplet 5.19 δ (3), doublet 6.86 δ ($J = 9$ c.p.s.; 1), singlet 7.86 δ (2). This synthesis of tremetone is essentially the same as that reported by Bowen.²⁵

2,5-Diacetyl-2,3-dihydrobenzofuran (XXIX). (1) A solution of 1.00 gm. tremetone (XXVII) in 25 ml. of dioxane-water (3:1) was mixed with 0.25 gm. of osmium tetroxide in 20 ml. of the same solvent. After 10-15 minutes, during which the solution slowly turned black, 2.30 gm. of solid NaIO_4 was added in small portions at 20 minute intervals in about 4 hrs. The mixture was stirred overnight and a small amount of H_2S gas was added, precipitating black osmium sulfide. The solution was filtered and extracted with ether, and the ether washed well with water and then dried (MgSO_4). Evaporation of the ether yielded 0.824 gm. of material which was chromatographed on 40 gms. of acid washed alumina. Impure XXIX (0.17 gm. less than 20% yield) was eluted from the column with ether-benzene (3:17).

(2) A solution of 1.019 gm. tremetone (XXVII) in 50 ml. of acetic acid, 1.285 gm. of iodine and 1.85 gm. of silver acetate was stirred at room temperature for one hour. A solution of 0.1 ml. water and 2.5 ml. of

acetic acid was then added and the mixture refluxed for 30 minutes. It was cooled, filtered free of silver salts, evaporated under vacuum, dissolved in ether, washed with saturated potassium carbonate, dried (MgSO_4), and the ether evaporated to give 1.178 gm. of an amber oil (XXVIII R = Ac).

The above amber oil was then dissolved in 100 ml. of MeOH and added to a solution of 3.90 gm. of KOH in 10 ml. of water and warmed at 55°C . for 1 hr. The volume was reduced to 100 ml. under vacuum and then extracted with ether. The ether was dried (MgSO_4) and evaporated leaving 0.653 gm. of a white crystalline solid (XXVIII R = H). M.P. $123-128^\circ\text{C}$. (Reported¹⁴; M.P. $125-130^\circ\text{C}$., recrystallized M.P. $137-138^\circ\text{C}$.)

A solution of the above material (0.653 gm.) in 10 ml. of acetic acid and 50 ml. of benzene, was stirred with 2.17 gm. of crude lead tetraacetate at room temperature for 1 hour. To this was added 100 ml. of ether and 30 ml. of saturated potassium carbonate (dropwise) and stirred for 30 minutes. The brown precipitate was filtered out and the filtrate extracted with ether. The ether was dried (MgSO_4) and evaporated yielding 0.600 gm. of a light yellow oil. The oil was extracted with Skelly "B" at room temperature to give 0.353 gm. (40% yield) of the diketone XXIX. This synthesis of XXIX is the same as reported by Bonner, et al.¹⁴

2,5-Diacetylbenzofuran (I). A mixture of 0.176 gm. of XXIX and 0.355 gm. of 5% palladium on charcoal was sealed under vacuum in a heavy walled tube and the tube heated for $1\frac{1}{2}$ hrs. at $215-220^\circ\text{C}$. After cooling the contents were dissolved in acetone and the catalyst filtered out. The acetone was evaporated yielding 0.085 gm. (50% yield) of a solid. Two crystallizations from MeOH yielded material identical with the

natural I. M.P. 138-139°. Mixed M.P. 139-140°C with natural I. $\nu_{\text{max}}^{\text{KBr}}$
3500, 1660, 1600, 1290, 1160, 813 cm^{-1} . N.M.R. (DCCl_3): 2.64 δ (3
protons), 2.69 δ (3), and a multiplet from 7.5 to 8.4 δ (4). $\lambda_{\text{max}}^{\text{EtOH}}$ 253 $\text{m}\mu$
($\epsilon = 71,000$), 286 (34,000).

Plate I

Nuclear Magnetic Resonance Spectrum of Natural 2,5-Diacetylbenzofuran

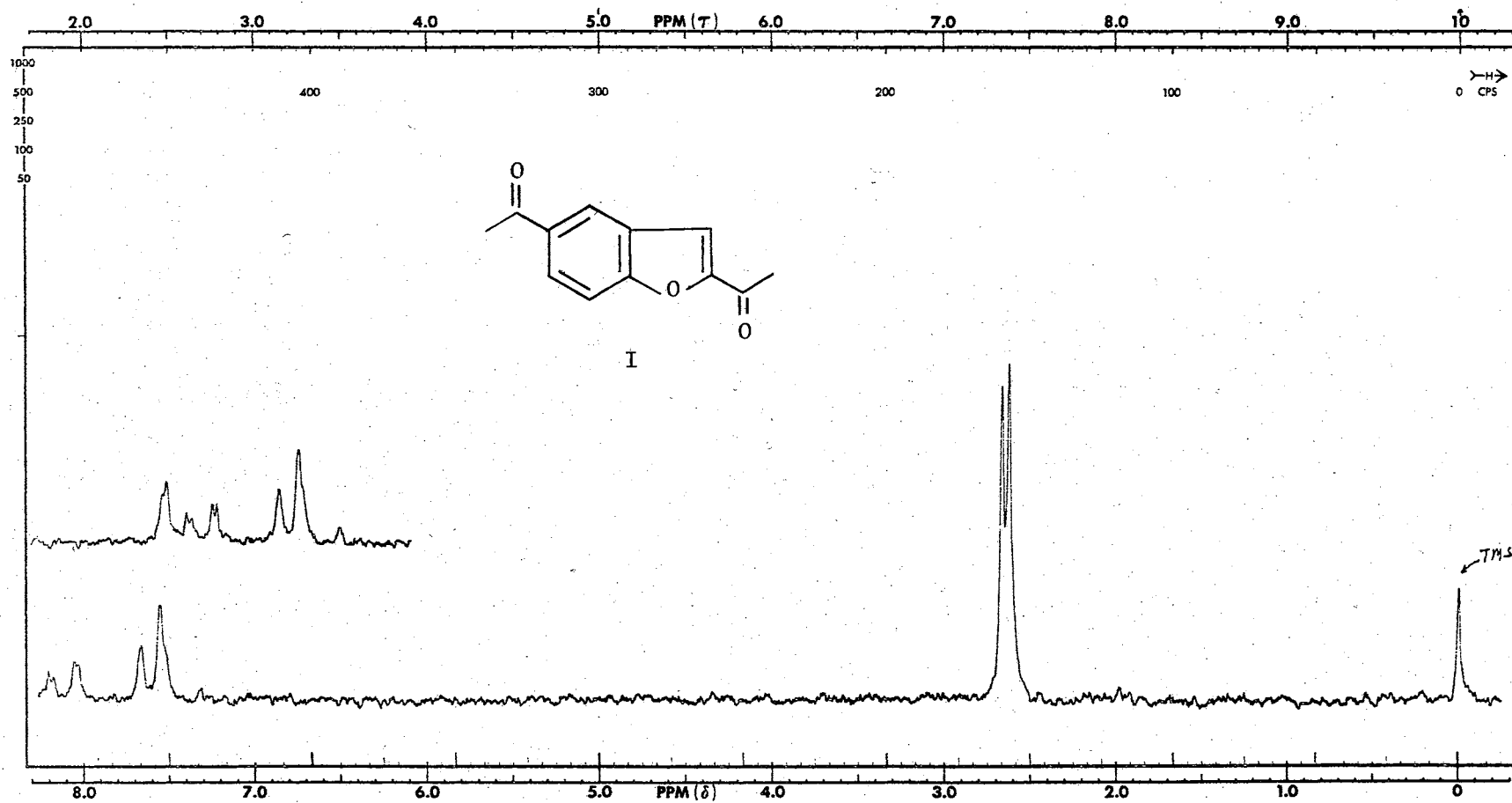


Plate II

Nuclear Magnetic Resonance Spectrum of Synthetic 2,5-Diacetylbenzofuran

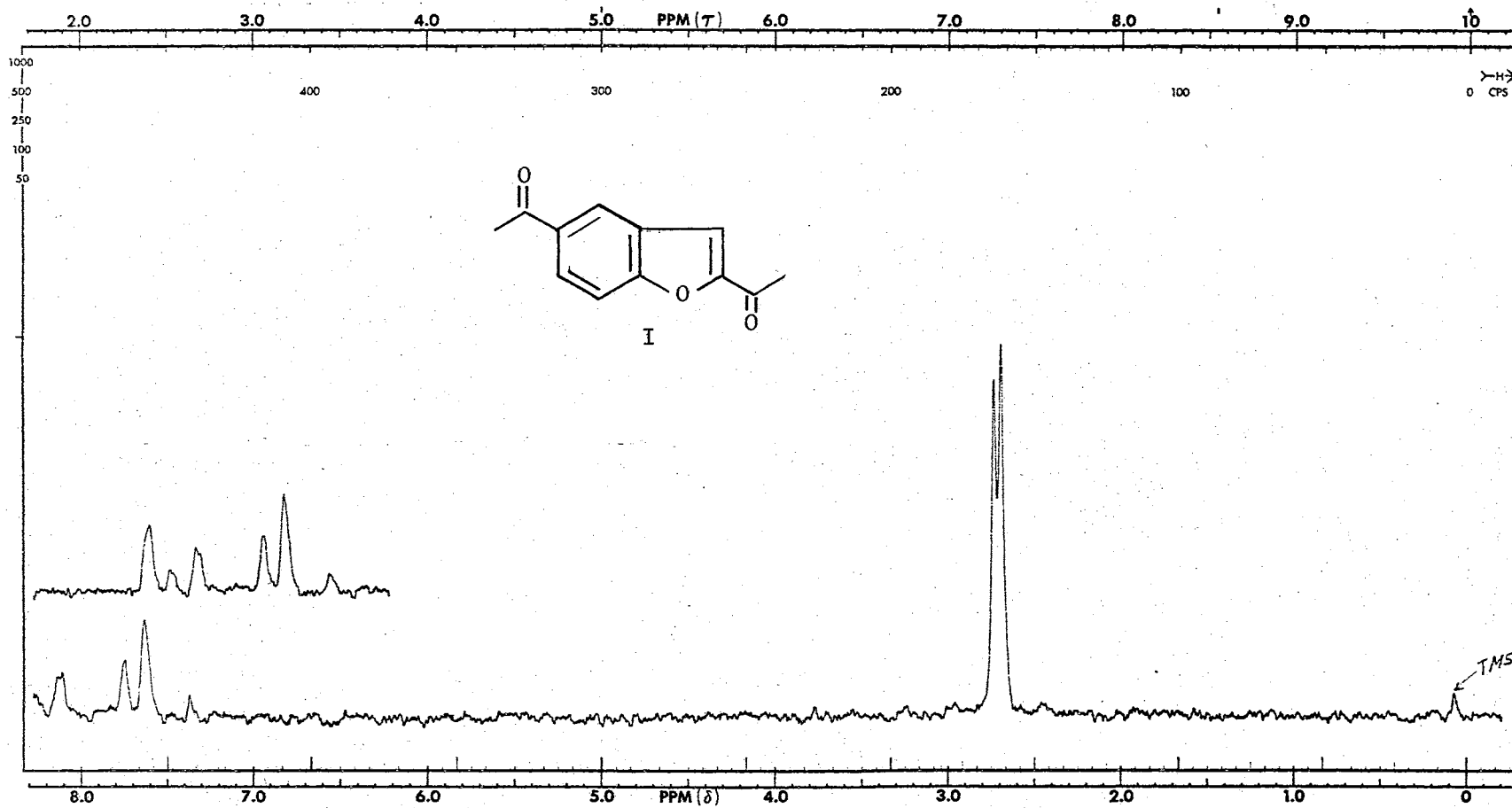


Plate III

Ultraviolet Spectrum of Natural 2,5-Diacetylbenzofuran

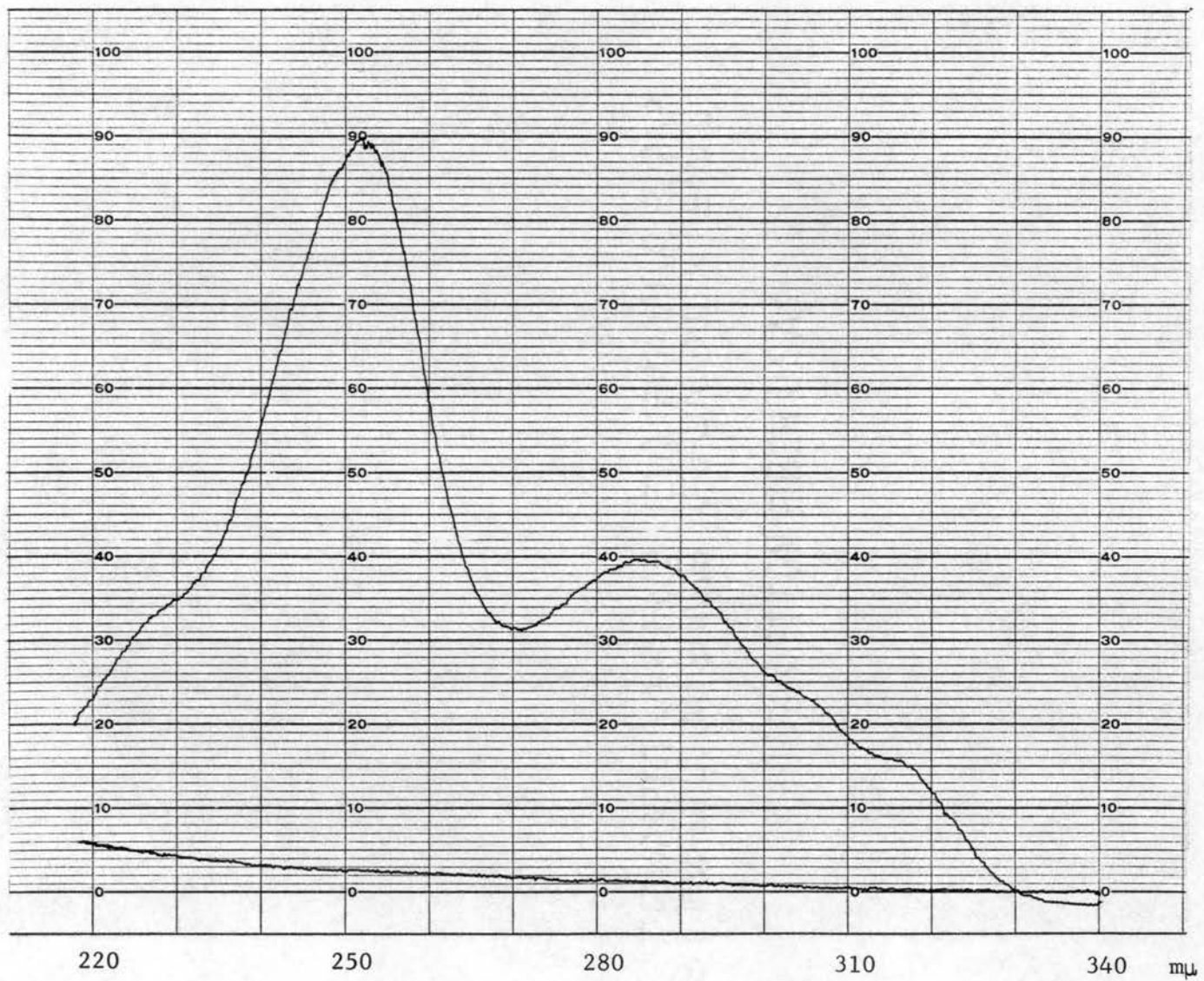


Plate IV

Ultraviolet Spectrum of Synthetic 2,5-Diacetylbenzofuran

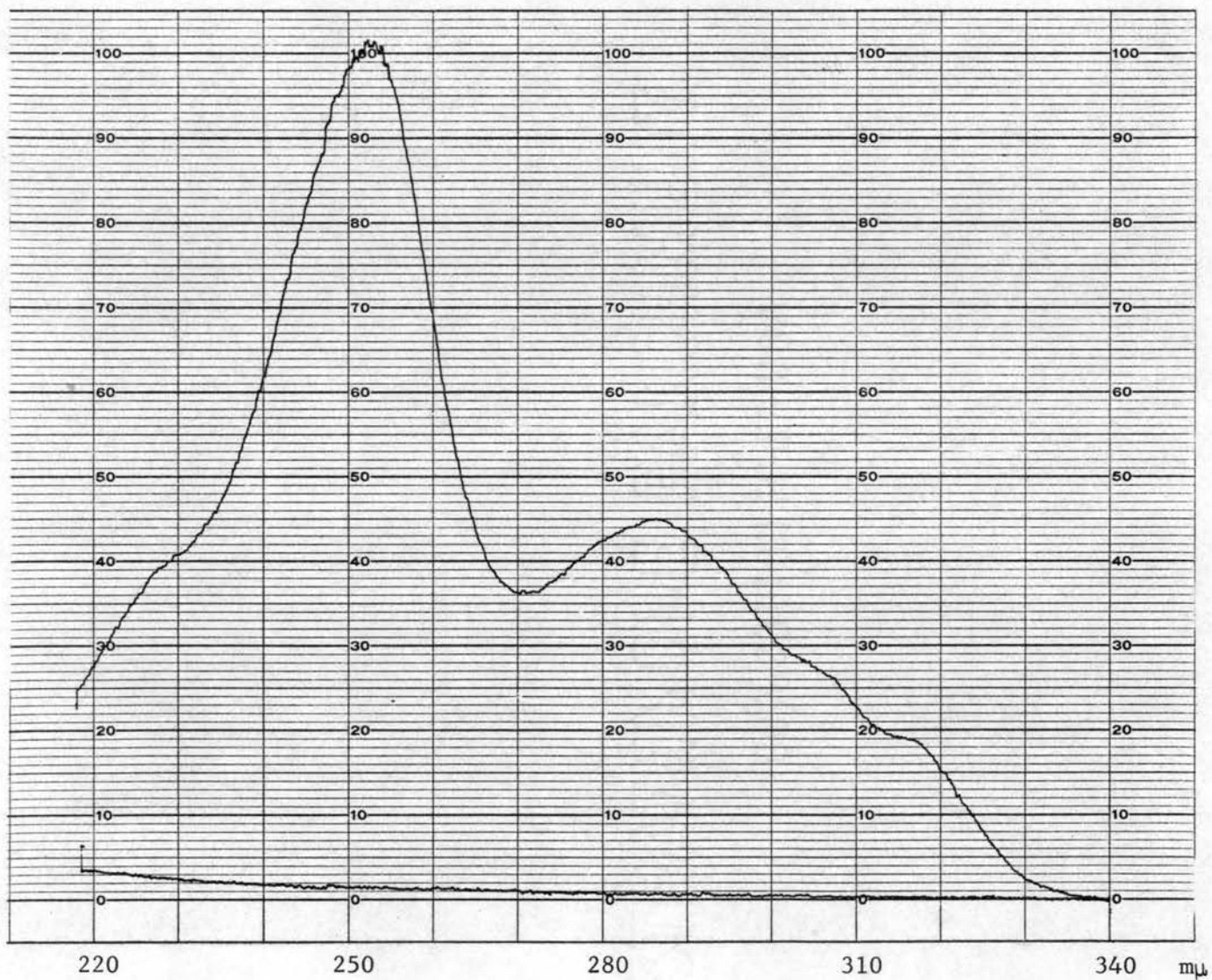


Plate V

Infrared Spectrum of Natural 2,5-Diacetylbenzofuran

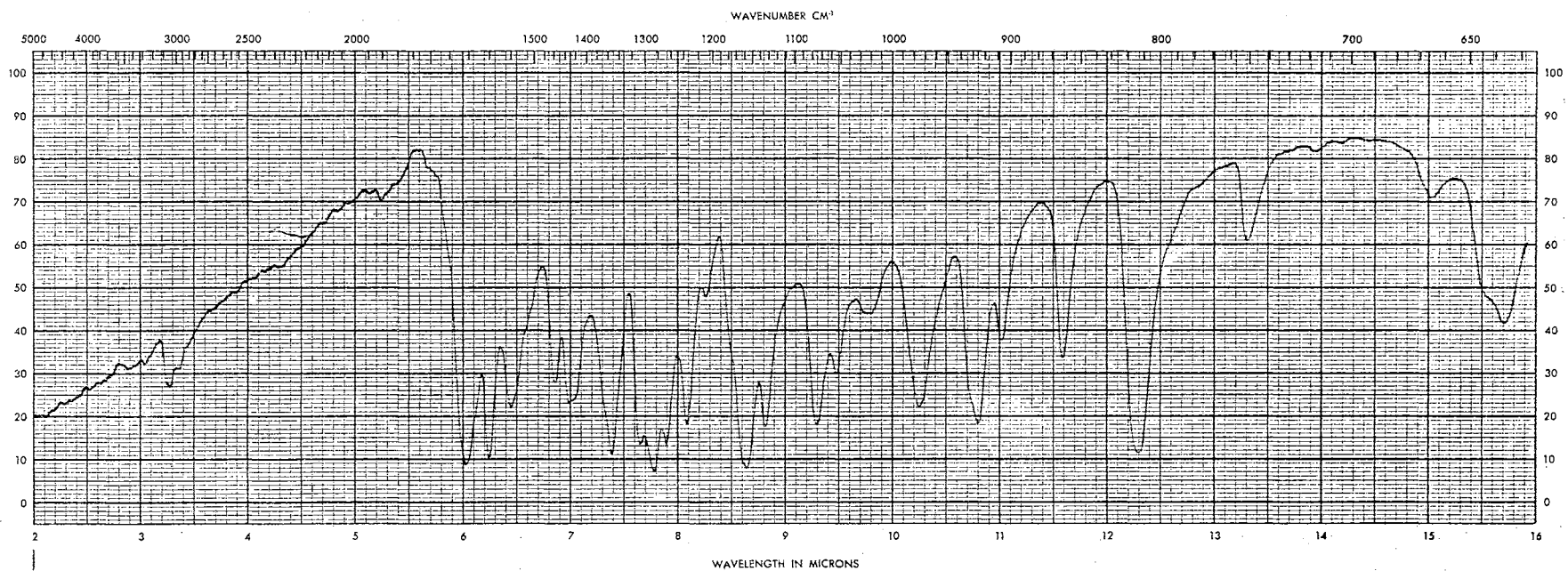
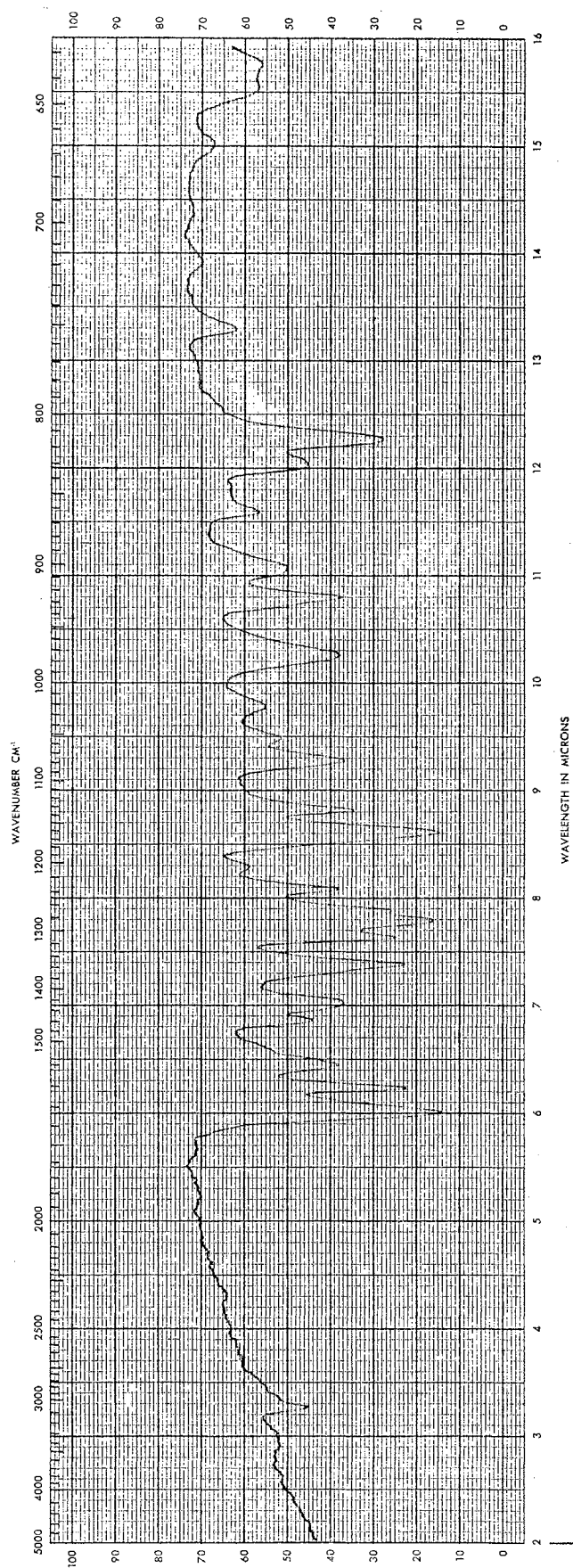


Plate VI

Infrared Spectrum of Synthetic 2,5-Diacetylbenzofuran



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VITA

Charles Theodore Ramming

Candidate for the Degree of

Master of Science

Thesis: THE ISOLATION AND SYNTHESIS OF 2,5-DIACETYLBNZOFURAN

Major Field: Chemistry

Biographical:

Personal Data: Born in Miami, Oklahoma, March 30, 1941 to Clarence A. and Adeline Ramming.

Education: Graduated from Lahoma High School, Lahoma, Oklahoma in 1959; received the Bachelor of Science degree from Oklahoma State University with a major in Chemistry in 1963; completed the requirements for the Master of Science degree in August, 1965.

Professional Experience: A laboratory technician in the wheat protein testing laboratory of the Enid Board of Trade, Enid, Oklahoma, for the summer of 1962. An undergraduate teaching assistant for one semester. A graduate teaching assistant for three semesters. A graduate research assistant for two summers and one semester.

Professional Societies: Phi Lambda Upsilon.