SYNTHESIS OF METHYLENEDIOXY AND DIMETHOXY COMPOUNDS

by

Demetrius G. Orphanos, B.Sc.

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Department of Chemistry
McGill University
Montreal.

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TO MY PARENTS

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GENERAL INTRODUCTION

It is a very well-known fact that numerous alkaloids contain as a substituent methylenedioxy and/or methoxy groups. Many of these substances possess a characteristic physiological activity and therefore are extensively used in medicine. The significance of these compounds has provided an impetus for extensive synthetic research by various schools to prepare new related substances of improved biological activity.

The fact that many physiologically active substances are oxazines, led us to believe that the combination of a dialkoxybenzene ring with an oxazine nucleus, might give rise to or increase biological activity. In the present work the object was to study the synthesis of a number of 6,7-dialkoxy-1,4-benzoxazin-2-ones and their dihydro-derivatives 2-phenomorpholones. This objective was achieved by means of the W. Wislicenus reaction in which 3,4-methylenedioxy-6-aminophenol and 3,4-dimethoxy-6-aminophenol respectively were condensed with a number of α-ketoesters to the corresponding benzoxazines.

Further, work was carried out on the conversion of the 6,7-dialkoxy-1,4-benzoxazin-2-ones obtained to the corresponding dialkoxy-2-phenomorpholones by low pressure catalytic hydrogenation. It was found that the success of this conversion was dependent on the kind of substituents attached in the 3-position.

In connection with the synthesis of the 6,7-dialkoxy-1,4-benzoxazin-2-ones, it was necessary to prepare 3,4-methylenedioxy-6-aminophenol and 3,4-dimethoxy-6-aminophenol as starting materials. No work on the synthesis of these compounds had been reported, and therefore their preparation was undertaken by low pressure catalytic hydrogenation of the corresponding 3,4-dialkoxy-6-nitrophenols.

The second part of this investigation was concerned with the preparation of a suitable phenethylamine system by which a 7,8-disubstituted-tetrahydroisoquinoline structure could be obtained.

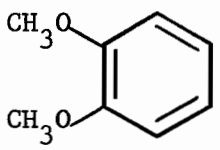
To attain this objective the following reaction sequences were adopted. Condensation of 6-bromopiperonal and acetopiperone in ethanolic sodium hydroxide solution gave 3,4-methylenedioxyphenyl-2-bromo-4,5-methylenedioxystyryl ketone and addition of hydrogen cyanide to the double bond resulted in the formation of β-(3,4-methylenedioxybenzoyl)-α-(2-bromo-4,5-methylenedioxyphenyl) propionitrile. The nitrile was then hydrolysed via the amide to the corresponding keto-acid which was reduced by Clemmensen's method to γ-(3,4-methylenedioxyphenyl)-α-(2-bromo-4,5-methylenedioxyphenyl) butyric acid. The ring closure of this substance to 1-oxo-6,7-methylenedioxy-2-(2-bromo-4,5-methylenedioxyphenyl)-1,2,3,4-tetrahydronaphthalene was effected by means of phosphorylchloride and interaction of this ketone with formamide, gave 1-formamido-6,7-methylenedioxy-2-(2-bromo-4,5-methylenedioxyphenyl)-1,2,3,4-tetrahydronaphthalene.

The infrared absorption spectra of the products obtained were determined and correlated with the structures assigned.

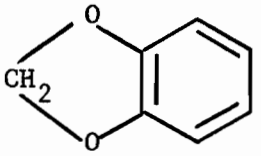
HISTORICAL INTRODUCTION

1. General

A great number of aromatic and heterocyclic compounds contain the dialkoxybenzene ring. The term dialkoxy is conventionally used in the place of methylenedioxy and o-dimethoxy groups. For the most part, these dialkoxy compounds are obtained by synthesis although many of them are frequently found as natural products. The simplest members of this class of compounds are represented by the veratrote (o-dimethoxybenzene) I and catechol methylene ether (methylenedioxybenzene) II which are often found as degradation products of naturally occurring substances such as alkaloids. No difficulties are encountered with the preparation of both



I



II

compounds which can be easily obtained from catechol. Interaction of o-dihydroxy compounds with methyl sulphate in methanolic sodium hydroxide solution produces veratrole derivatives (1,2,7),whereas the use of methylene sulphate (3,7) or methylene halides (4,5,6) results in methylenedioxybenzene compounds.

Dialkoxy compounds, as their structure indicates, belong to mixed phenolic ethers.

From a chemical standpoint, phenolic ethers are not usually attacked by alkalies. It has been demonstrated that simple dimethoxy or methylenedioxy compounds in agreement with their acetal (or ketal) structure, are stable toward bases.

Späth and Quietensky (8) have shown that dihydrosafrole is attacked very little by sodium ethoxide at 175° or by sodium hydroxide at 200°. However Robinson and Robinson (9,10) reported that, in an attempt to reduce 3,4-methylenedioxy-nitrobenzene with sodium methoxide in boiling methanol, the only isolated product was 5-nitroguaiacol. Substitution of the sodium methoxide for sodium ethoxide gave 5-nitro-2-ethoxyphenol. Also Helfer and Mottier (11) found that catechol methylene ether, and some of its derivatives, when heated at sufficiently high temperature with sodamide, produced dihydroxyphenols.

A method of dialkylation of phenolic ethers is based on the action of sodium in refluxing pyridine (12,13).

With concentrated mineral acids the phenolic ethers just as the aliphatic ethers, are decomposed. Hydriodic acid, is the acid most often used, and the fission always takes place in such a manner that the alkyl radical combines with the halogen. The quantitative estimation of the alkyl halide then serves for the determination of the phenolic ether groups, and is known as the Zeisel method.

$$C_6H_5OCH_3 + HJ \xrightarrow{130^\circ} C_6H_5OH + HJ$$

Späth and Quietensky (8) on the treatment of methylenedioxy compounds with concentrated mineral acids, found condensation products of high

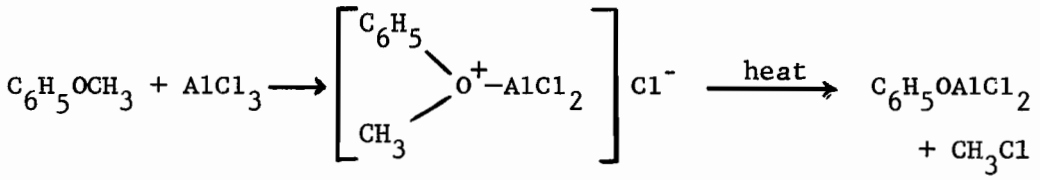
molecular weight which obviously were formed from the liberated HCHO with the phenolic parent substances. The HCHO comes from the methylenedioxy group.

Similar results to those above are reported by Fittig and Remsen (14,15), and, Ciamician and Silber (16).

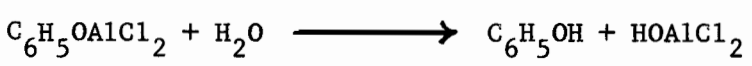
Splitting of the phenolic ethers can also be effected by the action of Grignard reagents (17, 18) or on heating the phenolic ethers with calcium oxide or barium hydroxide at 230^{o} (19).

Some methods of dialkylation of phenolic ethers which can also be used for methylenedioxy compounds, are based on the action of Friedel-Crafts reagents (Aluminum chloride (20,21), aluminum bromide (22) and zinc chloride (23)) in indifferent solvents such as benzene, nitrobenzene, chlorobenzene and carbon disulfite.

The dealkylation of the phenolic ethers by anhydrous aluminum chloride, either alone or in benzene or carbon disulfide under reflux, probably involves the mechanism (24).



$$C_6H_5OCH_3 + AlCl_3 \longrightarrow \left[\begin{matrix} C_6H_5 \\ \diagdown \\ O^{+}-AlCl_2 \\ \diagup \\ CH_3 \end{matrix}\right] Cl^{-} \xrightarrow{\text{heat}} C_6H_5OAlCl_2 + CH_3Cl$$



$$C_6H_5OAlCl_2 + H_2O \longrightarrow C_6H_5OH + HOAlCl_2$$

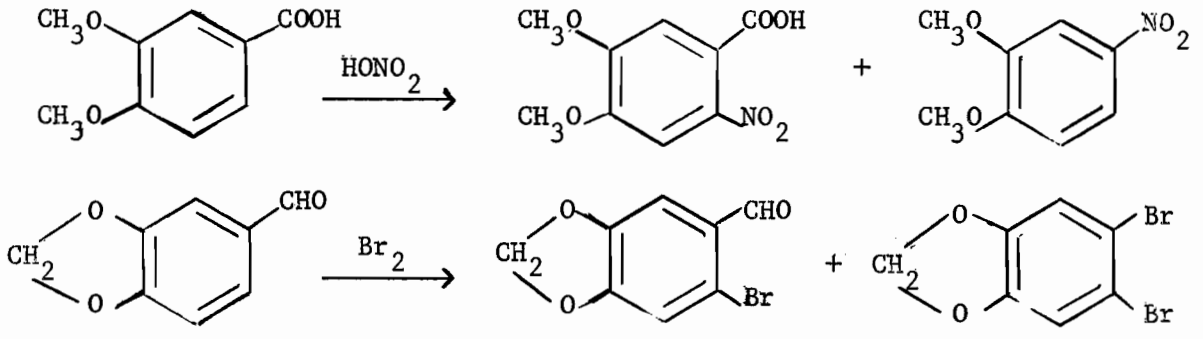
Physiological Activities of Phenol-ethers

There is considerable difference between the physiological activity of the aliphatic and aromatic ethers (25). Anisole and phenetole are toxic

and cause fatty degeneration of the liver and kidneys. Anethole is slightly antiseptic. In general the conversion to an ether of one or more of the hydroxyls in the polyhydric phenols increases the toxicity. Resorcinol dimethyl ether, for example, is more toxic than resorcinol. Compounds containing both an ether and a hydroxyl group possess activity between the phenols and the arylethers. The presence of a free hydroxyl, as in eugenol, increases the antiseptic and narcotic activity, as well as reducing the toxicity about one third. Thus guaiacol and monomethyl ether of homocatechol are irritant to mucous membranes, have antiseptic activity, are mildly anesthetic on injection, and in large doses cause paralysis and death in animals. Methylenedioxy ethers such as safrole are more strongly narcotic than eugenol, but the local irritant activity is less than that of anethole. Isosafrole has less narcotic activity than safrole perhaps because of the greater stability of the propenyl group over the allyl group.

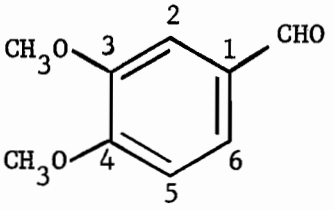
2. Orientation of Substituents in Dialkoxybenzene Ring

O-Dimethoxy and methylenedioxybenzene compounds have reactive benzenoid rings, which orient the incoming substituents in a unique manner. Two typical examples may be cited to illustrate this point (26, 27).



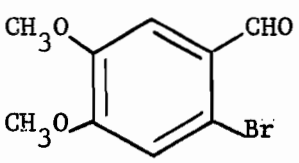
III IV

Veratraldehyde V provides the best example to explain this unpredictable orientation which appears at first sight to be anomalous according to the classical orientation rules (28).

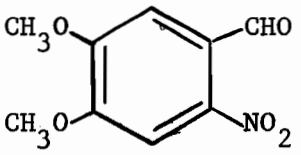


V

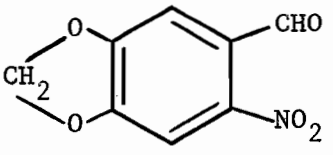
The methoxyl group in position 3 should direct an electrophilic attack to position 2 and 6, whereas the one in position 4 should instead direct the attack to position 5. Since the effects of these two groups ought therefore to cancel each other, we might expect that the orientation would be determined by the formyl group, and hence that the substitution would occur most rapidly at position 5. Experimentally, however, bromination leads to 6-bromoveratraldehyde, VI,(29) and nitration leads to 6-nitroveratraldehyde, VII,(30). Similarly, with piperonal, III, bromination gives 6-bromopiperonal, IV,(27) and nitration gives 6-nitropiperonal, VIII,(31). In each of these reactions, the orientation is therefore different from that expected.. These anomalies



VI



VII



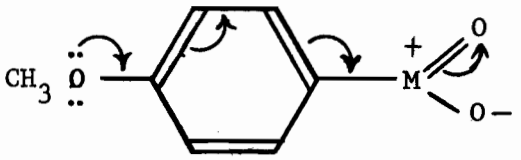
VIII

studied for the first time in 1917 by Jones and Robinson (32) were explained in the following way.

The influence of the one alkoxy-group which is in p-position to an electronegative group, is weakened so that the other alkoxy group controls

the direction taken by the reaction.

Later in 1925 Ray and Robinson (33), with the development of the electronic theory of conjugation, proposed a new interpretation for the partial neutralization of the directive power of the methoxy group by a nitro group situated in the p-position. They suggested that an electron shift from the ether oxygen was transmitted by means of the benzene nucleus to the nitro group as shown below.

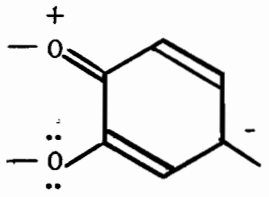


Although the argument of Ray and Robinson leads to the correct conclusion, a more careful examination shows that, the form just stated, is oversimplified and since 1925 much work has been done to solve this problem.

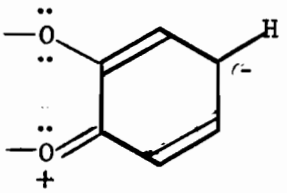
These arguments have arisen from the observation that electrophilic reagents prefer the 6-position in veratraldehyde, piperonal, sesamol (3,4-methylenedioxyphenol) (34), simply because alkoxyl groups activate para positions more effectively than ortho positions. There is, in fact, evidence that such a difference exists, since the bromination of phenol gives mostly p-bromophenol, and the nitration, especially when it is preceded by an initial nitrosation, also gives the para isomer (35, 36).

Wheland (37) taking into consideration all points of view, and discussing the whole problem in terms of the resonance theory, considers

that all interpretations are closely related, and that the susceptibility of the dialkoxy ring to attack by electrophilic reagents at para position to the oxygen atoms can be accounted for by resonance contributing structures of the type A and B



A



B

3. Infrared Absorption Spectra of Methylenedioxy and Dimethoxy Groups

Briggs, Colebrook, Fales and Wildman (38) following the original observation by Wildman and Kaufman (39) that compounds containing methylenedioxy groups exhibit characteristic maxima at about 1040 and 940 cm^{-1} in their infrared spectra, made a more detailed examination of this group. These investigators studied a number of analogous o-dimethoxy compounds and other methoxy compounds for comparison. The results obtained could be summarized as follows.

For the identification of the methylenedioxy group by infrared spectroscopy, twelve bands may be detected at about 3010, 2950, 2910, 2780, 1480, 1400, 1360, 1250, 1130, 1040, 926 and 719 cm^{-1}. Those at about 2950, 1400, 1360, and 1130 cm^{-1} may be absent or weak. All but the bands at 2780, 926, and 719 cm^{-1} are produced by either methylene or methyl (including methoxy) groups; therefore, these bands, particularly that at 926 cm^{-1}, are diagnostic of the methylenedioxy group.

From a comparison of these spectra of veratrole I and a number of other methoxy compounds, it may be concluded that ten major bands are

associated with methoxy groups attached to the aromatic nucleus - viz., a group of four bands in the 3000 cm^{-1} region at about 3003, 2950, 2915, and 2850 cm^{-1}, and six strong bands at about 1460, 1342, 1250, 1179, 1124, and 1028 cm^{-1}.

4. Synthesis of 3,4-Dialkoxyphenols

(a) 3,4-Methylenedioxyphenol (sesamol)

This substance, naturally occurring in sesame oil, has been synthetically obtained by two different methods starting either from piperonal or from 3,4-methylenedioxyaniline.

In 1936, Böeseken, Cohen and Kip (40, 41) studied the action of 20% peracetic acid on piperonal dissolved in acetic acid. The reaction temperature was kept constant at 30°. The product obtained was considered to be 3,4-methylenedioxyphenyl acetate. This conclusion suggested further alkaline hydrolysis to free the 3,4-methylenedioxyphenol. The yield reported on pure product, amounted to 60%.

Beroza (42) by a modification of the method of Böeseken, Cohen, and Kip, obtained the sesamol in a yield of 58%.

In recent years two patents (43, 44) have appeared claiming the preparation of sesamol in yields comparable to those obtained by the original investigators (40, 41). Here also the 3,4-methylene-dioxyphenyl acetate is reported to be the oxidation reaction product.

The second method is that followed by Takata and Matsuta (45). 3,4-Methylenedioxyaniline was diazotized in the usual manner, and the

diazonium salt was then decomposed to the corresponding 3,4-methylenedioxyphenol by means of a boiling mixture of copper sulphate, sulphuric acid, urea and water.

(b) 3,4-Dimethoxyphenol

Böeseken and Greup (46) obtained 3,4-dimethoxyphenol from veratraldehyde by an adaptation of the procedure given by Böeseken, Cohen and Kip (40) for the synthesis of the 3,4-methylenedioxyphenol. A 66 per cent yield is reported and 3,4-dimethoxyphenyl acetate to be the isolated reaction product which on alkaline hydrolysis gives the free phenol compound.

Later Meltzer and Doczi (47) obtained the 3,4-dimethoxyphenol in a yield of 55 percent by a modification of the original procedure (46). In this modification the reaction temperature was kept in the range of 40-45^{o} and the volume of the solvent was considerably increased. These authors claim 3,4-dimethoxyphenylformate as the reaction product which on alkaline hydrolysis is decomposed to free 3,4-dimethoxyphenol. Their claim was based on the reports of Wacek and Bezard (48). These latter investigators, in a study concerning the action of peracetic acid on a number of o-hydroxybenzaldehyde compounds, found as oxidation products the monoformates of the o-dihydroxyphenyl compounds.

Head and Robertson (49) and Clark (50) obtained 3,4-dimethoxyphenol in the following way: 3,4-dimethoxynitrobenzene was reduced to 3,4-dimethoxyaniline which in turn was diazotized, and the diazonium group was replaced by hydroxyl group. The yields obtained were very low and the product rather impure.

Baker and Evans (51) improved the yields of 3,4-dimethoxyphenol by decomposing the diazonium solution by means of a boiling copper sulphate solution.

5. Synthesis of 3,4-Dialkoxy-6-Nitrophenols

(a) 3,4-Methylenedioxy-6-Nitrophenol

Gertler, Alexander and Beroza (52) obtained this compound through a sequence of reaction steps, as follows.

3,4-Methylenedioxyphenol was acetylated to 3,4-methylenedioxyphenyl acetate by means of acetyl chloride in the presence of Pyridine. Dropwise addition of this acetate to a mixture of nitric acid and glacial acetic acid below 5^{o}, led to 3,4-methylenedioxy-6-nitrophenyl acetate. This in turn was hydrolysed by the action of ethanolic sodium ethoxide and neutralization of the resulting alkaline solution with hydrochloric acid, afforded the desired nitroprenol.

Arnold and Bordwell (53) obtained 3,4-methylenedioxyphenol by diazotizing the 3,4-methylenedioxy-6-nitroaniline, and then decomposing the resulting diazonium salt by boiling with copper sulphate solution.

(b) 3,4-Dimethoxy-6-Nitrophenol

This compound has been obtained in a number of different ways.

Arnold and Bordwell (53) obtained this compound by using the following method. 4-Acetamido-5-nitroveratrole was hydrolyzed by means of sulphuric acid to the corresponding amino compound. Diazotization of the latter and decomposition by the copper sulphate method followed by

steam distillation, gave the expected nitrophenol.

3,4-Dimethoxy-6-nitrophenol was obtained by Oliverio (54) from 4,5-dinitroveratrole on refluxing it in one per cent potassium hydroxide.

Another prepatation using as starting material veratrole is reported by Quelet and Aboul (55). The reaction steps were the following. Chlorination of veratrole followed by nitration, gave 3,4-dimethoxy-6-nitrochlorobenzene which on heating at 130^{o} with alcoholic sodium ethoxide yielded 4-methoxy-1,3-dihydroxy-6-nitrobenzene. This compound on methylation with methyl sulphate, afforded 3,4-dimethoxy-6-nitrophenol.

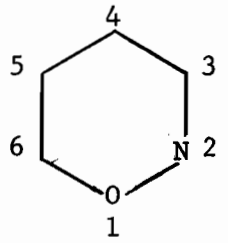
6. Benzoxazines

The chemical and structural relationship between benzoxazines and oxazines, suggests an introductory survey including both classes of compounds.

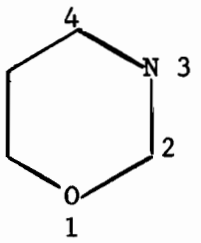
Interest in the oxazine series has been aroused largely from the fact that many important dyes, medicines, insecticides, etc. are derived from this heterocyclic compound. Detection of these heterocyclic rings in naturally occurring substances, has not been reported up to the present.

The oxazine ring system as defined by Widman (56) consists of a six-membered ring containing nitrogen, oxygen, and four carbon atoms all joined together by two double and four single bonds in one ring structure.

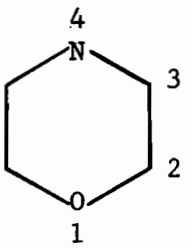
The relative position of the two heteroatoms in the ring, can give rise to the following ring structures.



1,2-Oxazine



1,3-Oxazine



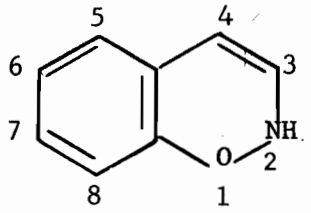
1,4-Oxazine

The naming and numbering, is that followed by the Ring index by Patterson, Capell and Walker (57). Occasionally for certain derivatives such as 1,4-tetrahydroxazine, the trivial name morpholine (58) is commonly used, but the numbering order is always in agreement with that given above.

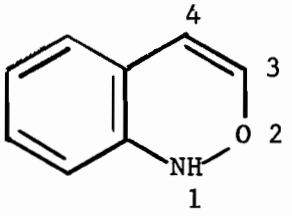
Ortho condensation of 1,2-, 1,3- and 1,4-oxazine with benzene ring, results in eight possible isomeric benzoxazines.

In the course of time and in different countries, various ways have been adopted for the numbering and naming of the isomeric benzoxazines.

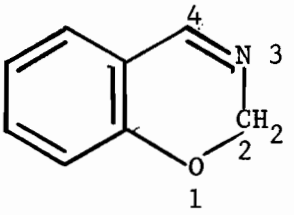
The nomenclature for all isomeric benzoxazines in accordance with the Ring index by Patterson, Capell and Walker (57) is shown by the following formulas. In Chemical Abstracts the position of the methylene group is denoted by supplementary H.



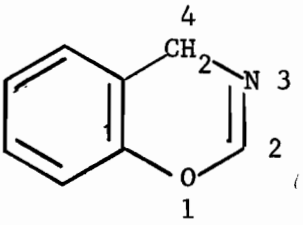
2H-1,2-benzoxazine



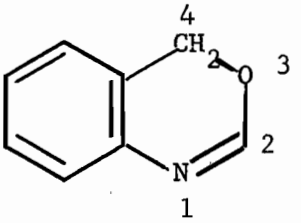
1H-2,1-benzoxazine



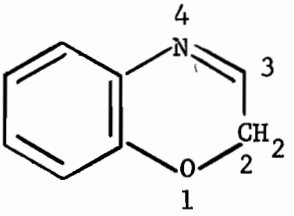
2H-1,3-benzoxazine



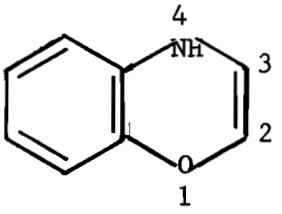
4H-1,3-benzoxazine



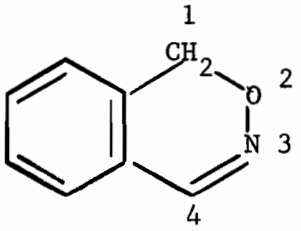
4H-3,1-benzoxazine



2H-1,4-benzoxazine



4H-1,4-benzoxazine



1H-2,3-benzoxazine

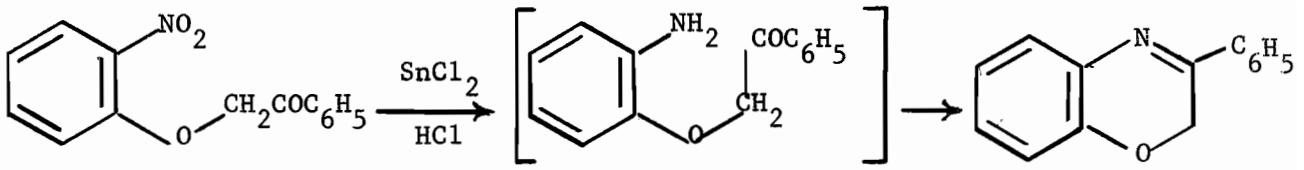
The existence of eight possible isomeric benzoxazines should apparently provide a great variety of chemical properties and even more of synthetic approaches.

In the following section, only those isomeric benzoxazines, possessing the 1,4-oxazine nucleus are reviewed because of their relation to the

interest of the present thesis.

(a) 2H-1,4-Benzoxazines

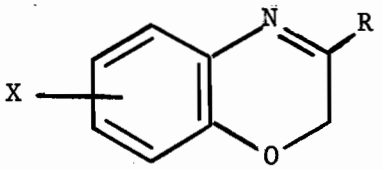
Synthesis of this type of derivative was first reported by Lellmann and Donner (59) in 1890. Condensation of o-nitrophenol with ω-bromoacetophenone yields o-nitrophenylphenacyl ether (IX) which by the action of stannous chloride and concentrated hydrochloric acid, is reduced to the corresponding amino compound which then is rapidly cyclized to 2H-3-phenyl-1,4-benzoxazine (X). The yields of 2H-1,4-benzoxazines obtained



IX X

by this general procedure are generally good (60).

The presence of the AsO_3H group in the 6- or 7-position make the substances pharmacological and some derivatives of the type (XI) have been described in the patent literature as being of value in the chemotherapy of trypanosome infections (61).



X = AsO_3H

R = alkyl

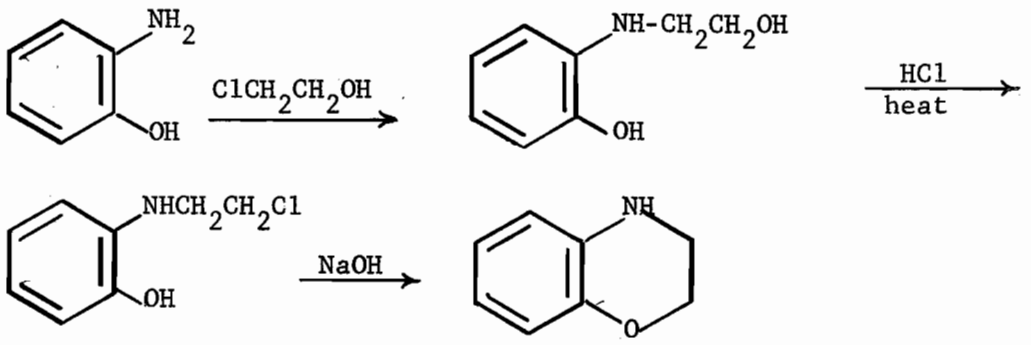
XI

(b) Reduced 2H-1,4- and 1,4-benzoxazines

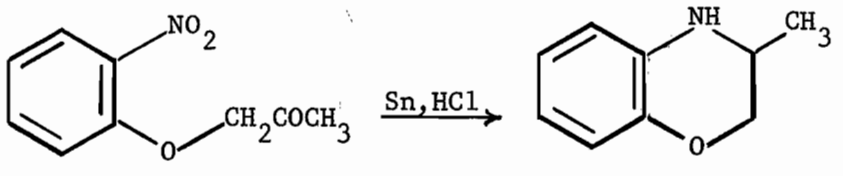
It is obvious that hydrogenation of the double bond of the heterocyclic part of the 2H-1,4- and 1,4-benzoxazines leads to the same compound commonly named phenomorpholine and alternatively benzomorpholine, phenemorpholine or phenmorpholine.

Although numerous derivatives of this group of benzoxazines have been synthesized, the number of references available is relatively small since most of them are listed in the patent literature.

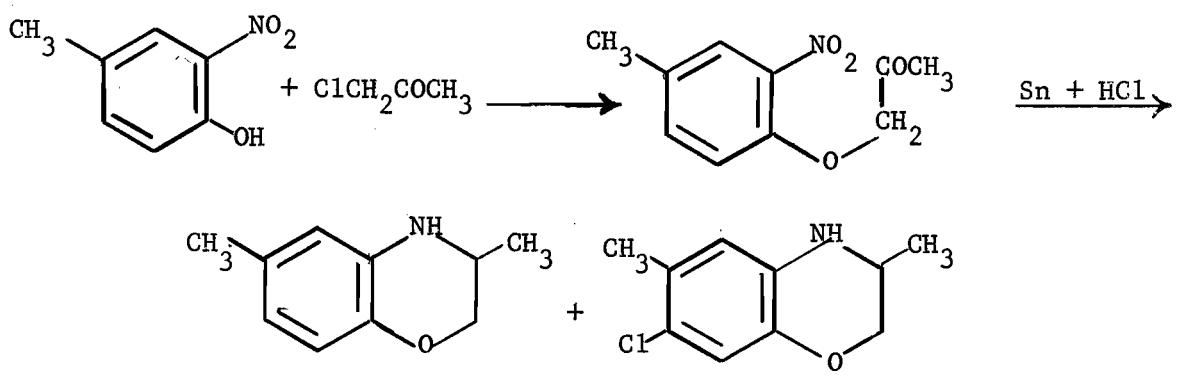
The parent compound phenomorpholine was first synthesized in 1899 by Knorr (58) by the following reaction scheme.



Phenomorpholine derivatives were prepared in 1898 by Stoermer and Brockerhof (60) by the treatment of o-nitrobenzoxyacetone with tin and concentrated hydrochloric acid. In 1912, Koenig and Becker (62) applied

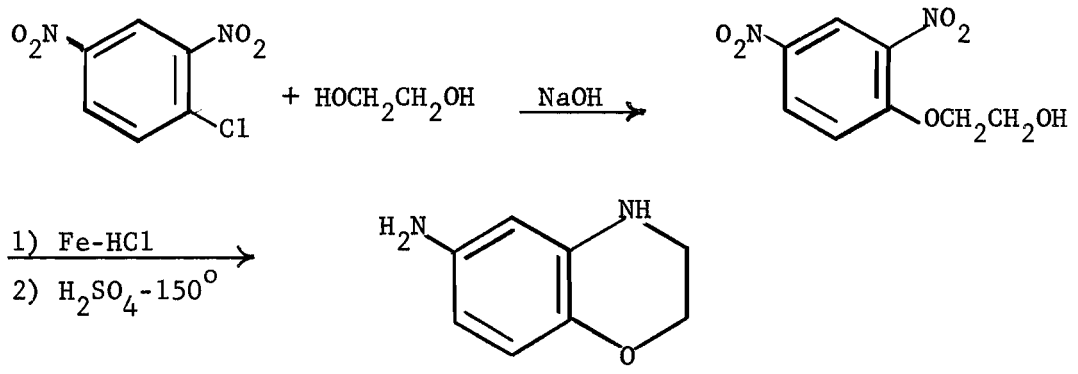


the reaction of Stoermer and Brockerhof to 2-nitro-4-methyl-benzoxy-acetone. The product obtained was found to be a mixture of 3,6-dimethyl-phenomorpholine and 3,6-dimethyl-7-chloro-phenomorpholine.



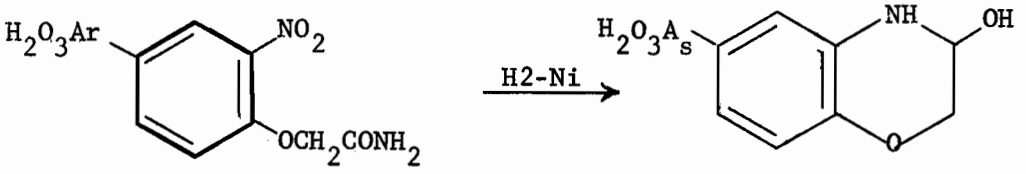
An almost similar process for the synthesis of phenomorpholines is that reported by Kunckell (63). o-Nitrobenzoxy-arylacetone on treatment with stannous chloride, gives 2H-3-aryl-1,4-benzoxazine which is then reduced to 3-aryl-phenomorpholine with tin and concentrated hydrochloric acid.

Fairborne and Toms (64) taking advantage of the mobility of the chlorine atom in the molecule of the 2,4-dinitrochlorobenzene, prepared 6-aminophenomorpholine in the following way.



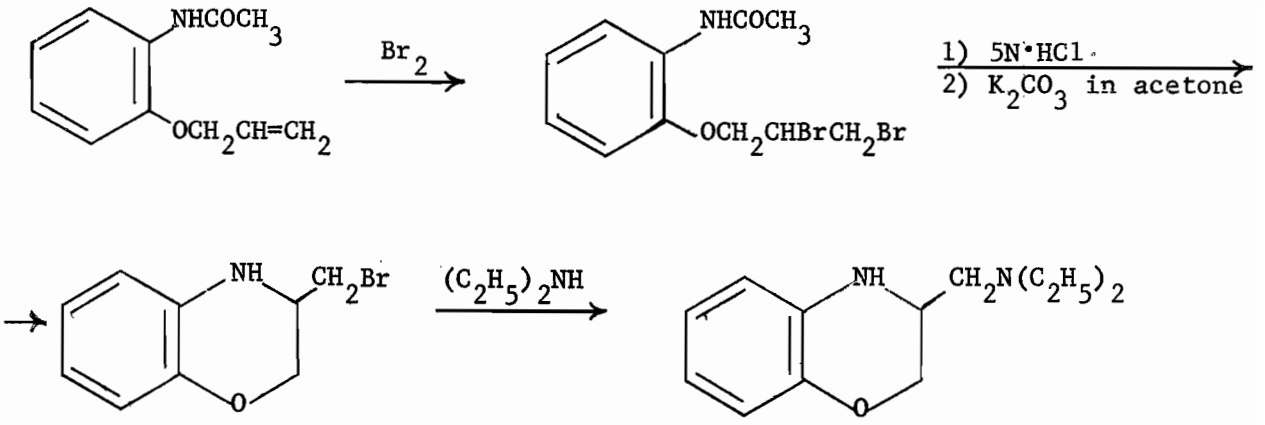
Catalytic reduction of o-nitrophenoxyacetates has also been successfully applied. Nickel, platinum, titanium, copper-chromium oxide, iron-cobalt, zinc-copper-chromium oxide, and molybdenum catalysts have all been used (65).

Sweet, Calkins and Banks (66) found that reduction of 2-nitro-4-arsonophenoxy-acetamide with hydrogen, using a Raney catalyst, in neutral solution results in the elimination of the amide group and the formation of 6-arsono-3-hydroxy-phenomorpholine. The last ring closure in which the

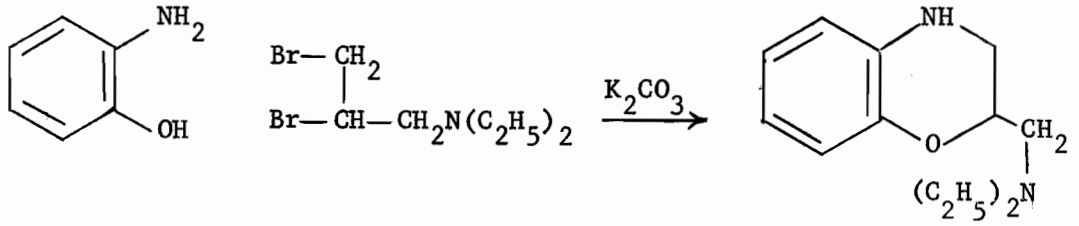


heterocyclic ring is closed at the nitrogen atom is typical of the majority of phenomorpholine syntheses.

Benoit and Bovet (67) prepared two isomeric phenomorpholine derivatives by approaches different from those described previously.



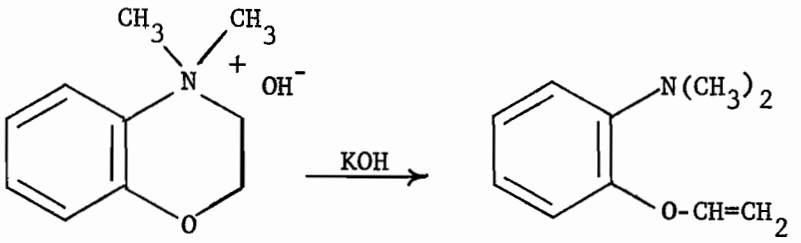
The isomeric 2-substituted phenomorpholine was prepared in a one step reaction.



Reactions of Phenomorpholine

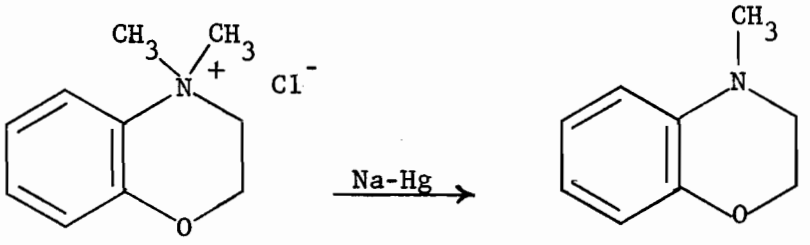
Phenomorpholine as might be expected from its structure, behaves like a typical secondary amine. Stoermer and Brockerhof (60) prepared several N-substituted-phenomorpholine compounds by applying reactions similar to those characteristic of the secondary amino group.

The behavior of phenomorpholine toward ring-opening reagents and on coupling with diazonium compounds is of some interest. Knorr (68), studying the behavior of 4,4-dimethyl-phenomorpholinium hydroxide toward hot potassium hydroxide, found o-vinyloxy-N,N-dimethyl-aniline as the reaction product. This ring cleavage is in contrast to the behavior of

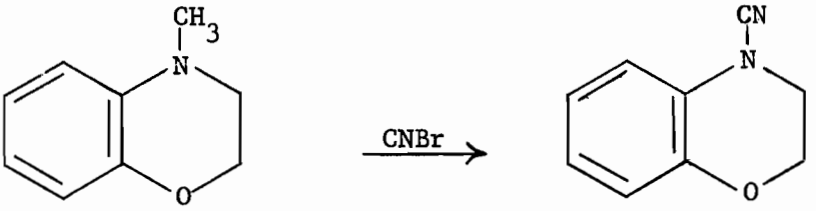


1,1-dimethyl-1,2,3,4-tetrahydroquinolinium hydroxide which only dissociates on heating with loss of methyl alcohol and formation of 1-methyl-1,2,3,4-tetrahydroquinoline (69). Brown and Seeman (69) studying the stability

of the phenomorpholine ring comparatively with that of 1,2,3,4-tetrahydroquinoline, found that reduction of 4,4-dimethylphenomorpholinium chloride with sodium amalgam, a reagent which brings about ring opening with the analogous tetrahydroquinoline compound, gives only 4-methylphenomorpholine.



With cyanogen bromide 4-methylphenomorpholine is only demethylated with no ring cleavage.

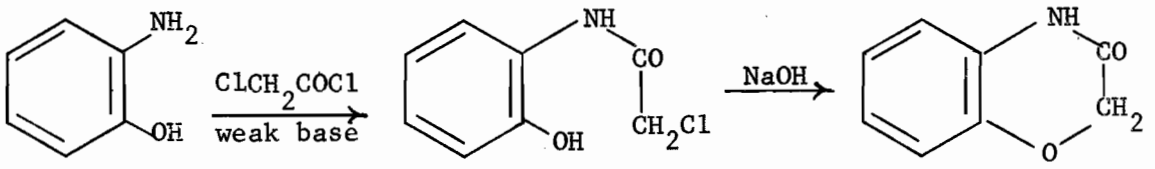


Derivatives with functional groups directly attached to the benzene ring are numerous. These functional groups are rarely introduced into the preformed phenomorpholine nucleus. As a rule the method generally employed, is the direct synthesis of such compounds by choosing the appropriately substituted aromatic portions.

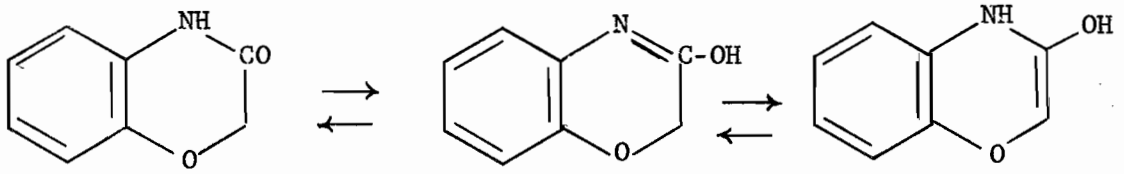
(c) 3-Phenomorpholone

The methods employed for the synthesis of 3-phenomorpholones are comparable to those for the preparation of phenomorpholine derivatives.

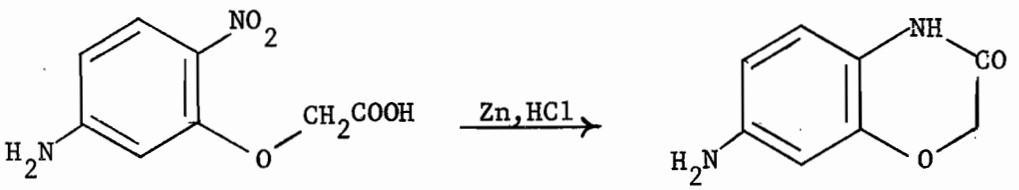
In 1926 Von Auwers and Frese (70) obtained the 3-phenomorpholone previously described by Aschan (71) by the action of sodium hydroxide on o-haloacylaminophenol which in turn was obtained by treatment of o-aminophenol and chloroacetyl chloride in the presence of a weak base.



In some early works (72, 73, 74) the 3-phenomorpholones were considered tautomeric with 3-hydroxy-4H-1,4-benzoxazines. However in 1936 spectrographic studies by Ramart-Lucas and Vantu (75) gave evidence that the amide formulation is to be preferred.

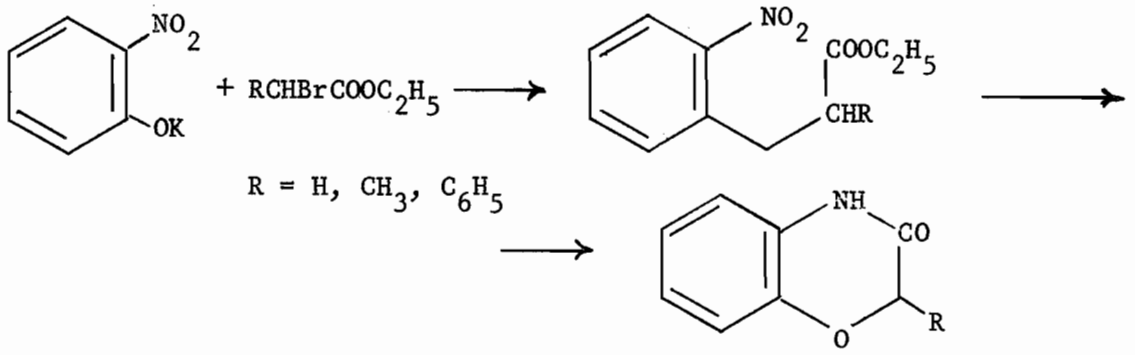


Howard (76) in 1897 described the synthesis of 6-amino-3-phenomorpholone by the following reaction scheme.



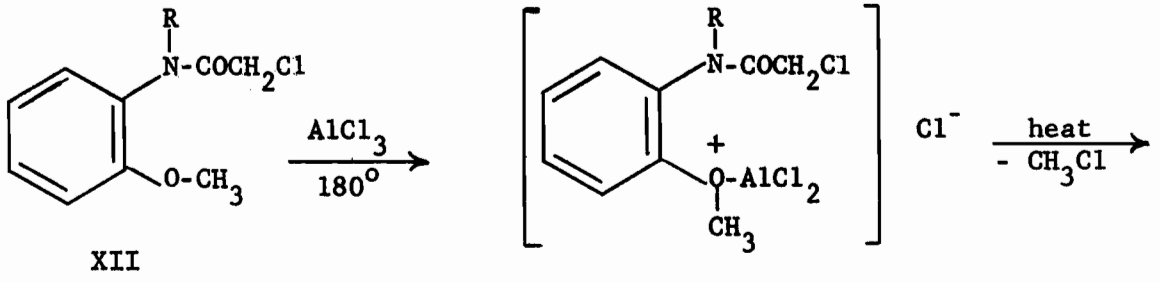
Newbery and Phillips (72) obtained Howard's compound from 4-nitro-2-aminophenol by chloroacetylation, followed by ring closure by means of alkali and subsequent reduction. This last procedure, similar to that of Von Auwers and Frese (70), is generally used and the yields of 3-phenomorpholones obtained are usually high (73, 74, 77, 78, 79, 80).

Newbery and Phillips (72) and Christiansen (81) obtained 3-phenomorpholones by reduction of o-nitrophenoxyacetic acids with iron and methyl alcoholic hydrochloric acids. Also a U.S. Patent (82) reports synthesis of 3-phenomorpholone derivatives by means of this reaction scheme.



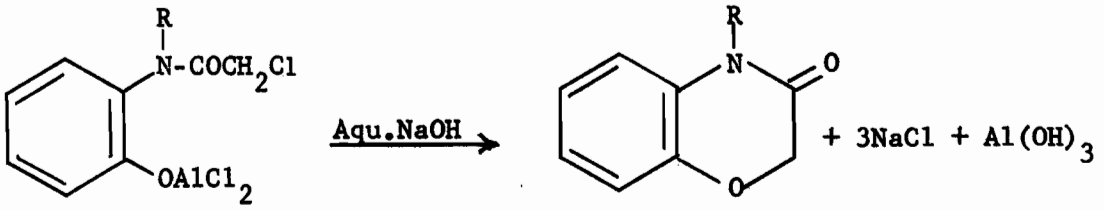
It has been reported by Cook, Loudon and McCloskey (83), and almost at the same time by Kretz, Muller and Schlittler (84), that the action of aluminum chloride on the chloroacetyl derivative of N-methyl-o-anisidine XII leads to the 3-phenomorpolone derivative XIII. The formation of 3-phenomoropholones from chloroacet-o-anisidides by reaction with aluminum chloride is a general reaction and the nitrogen atom of the anisidide may carry either a hydrogen or an alkyl

substituent (85). The reaction probably involves the mechanism.



XII

R = CH_3, H



XIII

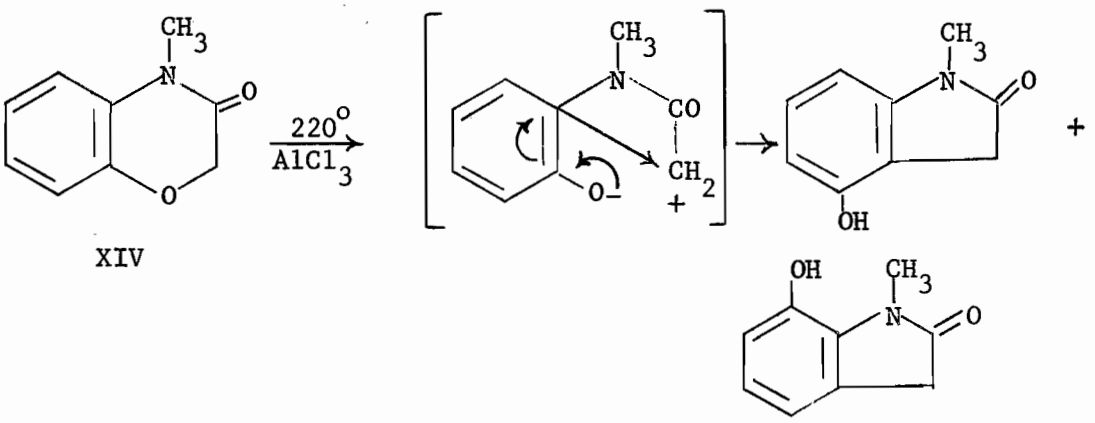
The reaction proceeds through demethylation to o-chloroacetamidophenol which, in the presence of aqueous alkali, yields 3-phenomorpholone.

Chemical Character of 3-Phenomorpholone

3-Phenomorpholone is readily N-methylated by methyl sulphate and alkali but, in general, methylation is best achieved by using methyl iodide and powered potassium hydroxide in acetone (85). N-Methyl-3-phenomorpholone being a cyclic amide, is readily reduced by lithium aluminum hydride, forming 4-methylphenomorpholine (85).

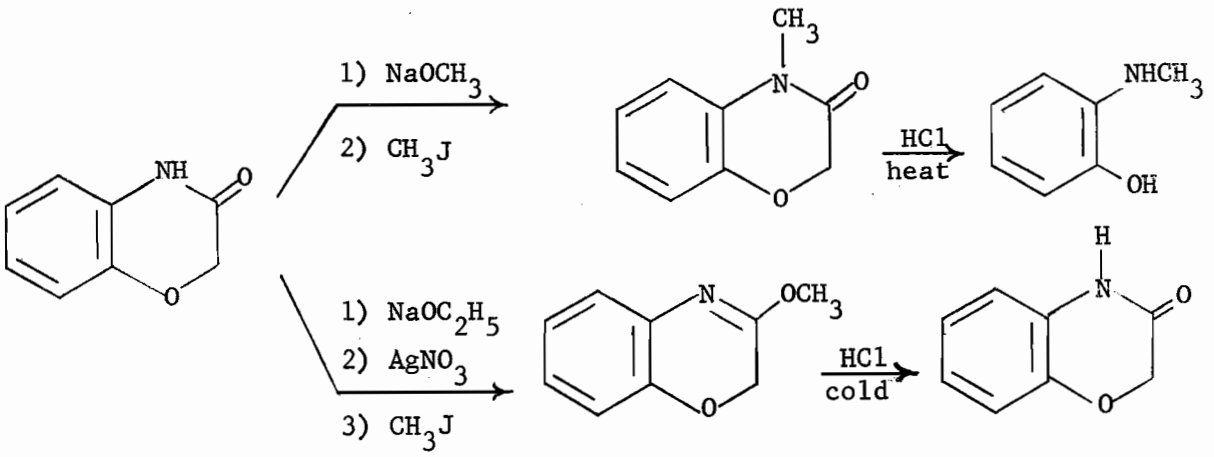
Cook, Loudon and McCloskey (83) found that N-methyl-3-phenomorpholone XIV heated up to 220° rearranges to a mixture of two isomeric

oxindoles. This reaction, which occasioned some earlier confusion (84), was later clarified (85) as proceeding as a special case of Stolle's oxindole synthesis (86).



XIV

3-Phenomorpholone on treatment with sodium methoxide and then methyliodide, gives N-methyl-3-phenomorpholone, whereas treatment first with sodium ethoxide and then with silver nitrate followed by methyl iodide, renders 2H-3-methoxy-1,4-benzoxazine (87). The assignment of these two isomeric structures was based on their behavior toward hydrochloric acid. The N-methyl derivative on treatment with hot concentrated hydrochloric acid,



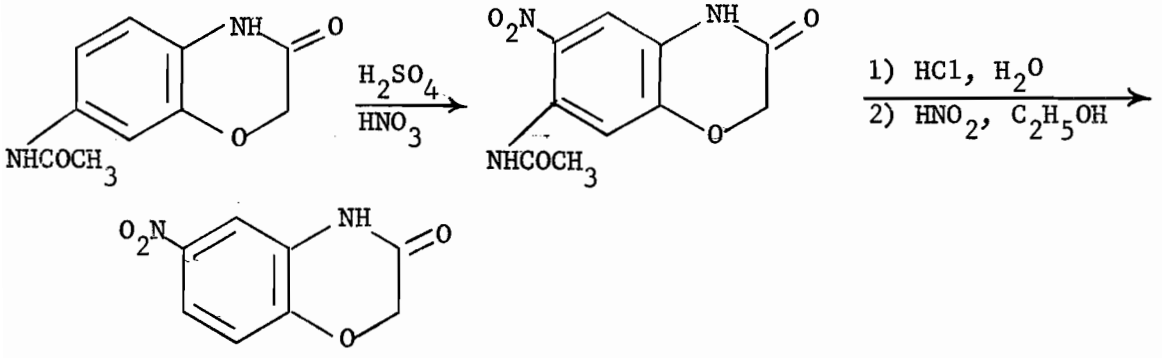
was cleaved to o-hydroxy-N-methylaniline, whereas the methoxy compound

regenerated 3-phenomorpholone with diluted hydrochloric acid.

Nitration of 3-phenomorpholones proceeds as usual in the benzene ring. However Balaban (88) reports that nitration of 3-phenomorpholone leads to a mixture of two nitro compounds melting at 235 and 155-157° respectively. The former is identical with the 6-nitro-3-phenomorpholone of Newbery and Philips (72) whereas the latter is not identical with any of the nitroderivatives carrying the nitro group in the benzene ring. On these grounds the author suggested, therefore that the compound of m.p. 155-157° is 2-nitro-3-phenomorpholone.

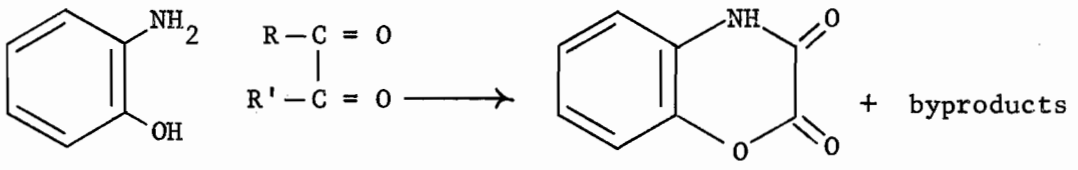
Nitration of 3-phenomorpholone-7-arsinic acid affords a mixture of two products one of which is the 8-nitroderivative and presumably the 6-nitroderivative is the other (74).

Balaban (88) reports that nitration of 7-acetamido-3-phenomorpholone gives only the 6-nitrocompound, whereas nitration of 8-acetamido-3-phenomorpholone gives a mixture of the 6- and 7-nitrocompounds. The structure of the 6-nitro-7-acetamido-3-phenomorpholone was shown by its transformation into the 6-nitro-3-phenomorpholone by the following reaction scheme.



(d) Phenomorphol-2,3-diones

Comparatively few derivatives of this substance have been reported. Condensation of o-aminophenols with oxalyl chloride, or monoethyl or diethyl oxalate, results in the formation of phenomorphol-2,3-diones. In this reaction some byproducts are formed depending on the type of α,β-dicarbonyl compound used (79,80).

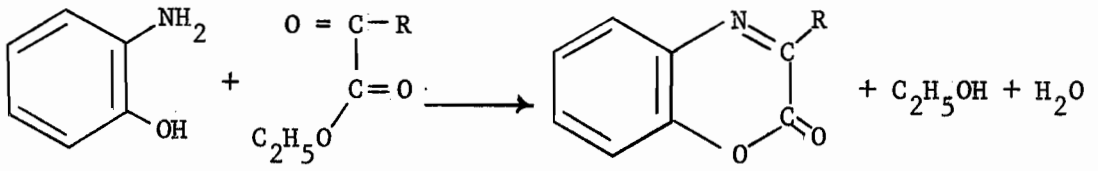


R = OC_2H_5, OH, Cl

R'= OC_2H_5, Cl

(e) 1,4-Benzoxazin-2-ones

1,4-Benzoxazin-2-ones are the products formed by the condensation of o-aminophenols with α-ketoesters. This reaction was discovered many years ago by Wislicenus et.al. (89,90) and the structure of these compounds was obvious from the mode of formation and the analytical data.



This condensation can also be achieved more conveniently by using hydrochlorides of the o-aminophenols with the sodium salt of the appropriate α-ketoester in alcoholic solution (91).

The 1,4-benzoxazin-2-ones are, as already indicated, prepared by simple, straightforward reactions. Generally the formation of these derivatives takes place very smoothly, in good yields, at temperatures ranging from room temperature to 100°, and they are readily isolated as coloured crystalline compounds possessing sharp melting points (91, 92). These chemical and physical properties suggest this reaction as a method for the isolation and characterization of o-aminophenols (92) and similarly it might be used for the characterization of α-ketoesters (91). Apart from this, the 1,4-benzoxazin-2-ones have not received much of attention since the time of Wislicenus' early work. The development of the field of chemotherapy has quite recently led to renewed interest in synthesizing more 1,4-benzoxazine compounds because of their close relationship to phenomorpholine.

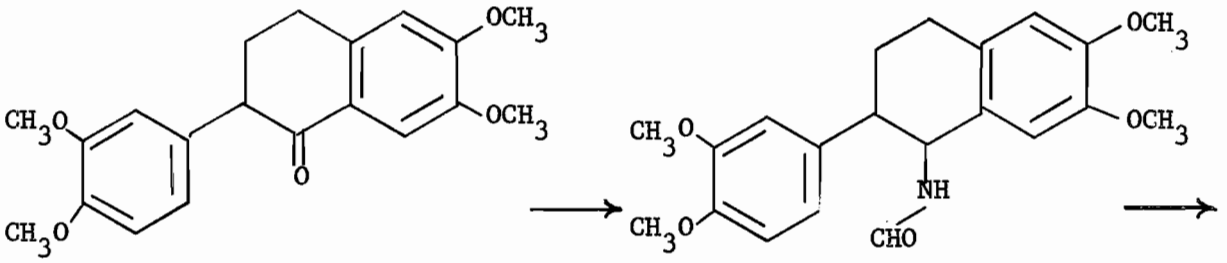
Recently, Biekert, Hoffmann and Meyer (91) applying the Wislicenus' condensation method, prepared several derivatives and a study concerning their chemical properties was undertaken. These investigators report an easy conversion of the 1,4-benzoxazin-2-ones to the corresponding 2-phenomorpholones by means of catalytic hydrogenation. This route to phenomorpholines reported, for the first time, should be of value considering the pharmacological properties of similar compounds (61). Furthermore the same workers found an approach to N-substituted-amino-alcohols by reductive cleavage of the 1,4-benzoxazin-2-ones with $LiAlH_4$.

The aromatic properties of these compounds have not been studied hitherto. Substitution by electrophilic agents would be expected to take place in the isocyclic portion of the molecule. Since the type of product thus formed is, as a rule, more simply prepared directly from an o-aminophenol bearing the desired substituent, no research on the substitution of 1,4-benzoxazin-2-ones by electrophilic reagents has been reported.

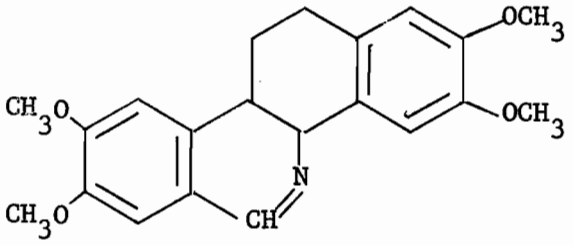
7. 3,4-Dialkoxyphenethylamines

The suggestion in 1930 by Bruchhausen and Bersch (93) that the alkaloid chelidonine has a benzo[c]phenanthridine ring system, was definitely confirmed by Späth and Kuffner (94). This type of structure established for the first time in natural products and later found in a number of alkaloids, soon attracted the interest of many investigators to study synthetic approaches (95). Thus in 1937 Richardson, Robinson, and Seijo (96) in their preliminary experimental studies described the synthesis of a substance XVII possessing the benzo[c]phenathridine ring system. It was obtained by condensing veratraldehyde and acetoveratrone to 3,4,3',4'-tetramethoxy-chalkone, which by addition of hydrogen cyanide yielded γ-keto-α-cyano-$\alpha\gamma$-diveratrylpropane, $C_6H_3(OMe)_2 \cdot CH(CN) \cdot CH_2 \cdot CO \cdot C_6H_3(OMe)_2$. This was hydrolysed successively to the corresponding amide and keto-acid, and the latter reduced by Clemmensen's method to $\alpha\gamma$-diveratryl butyric acid, $C_6H_3(OMe)_2 \cdot CH(COOH) \cdot CH_2 \cdot CH_2 \cdot C_6H_3(OMe)_2$ in which ring closure was effected by treatment with phosphoryl chloride, yielding 1-keto-6,7-dimethoxy-2-veratryl-1,2,3,4-tetrahydronaphthalene XV. The latter, either by direct

interaction with formamide or via the oxime and amine and treatment with formic acid, was converted into the desired phenethylamine structural system XVI, and in this the second ring closure was carried out in toluene solution by phosphoryl chloride to XVII.



XV XVI



XVII

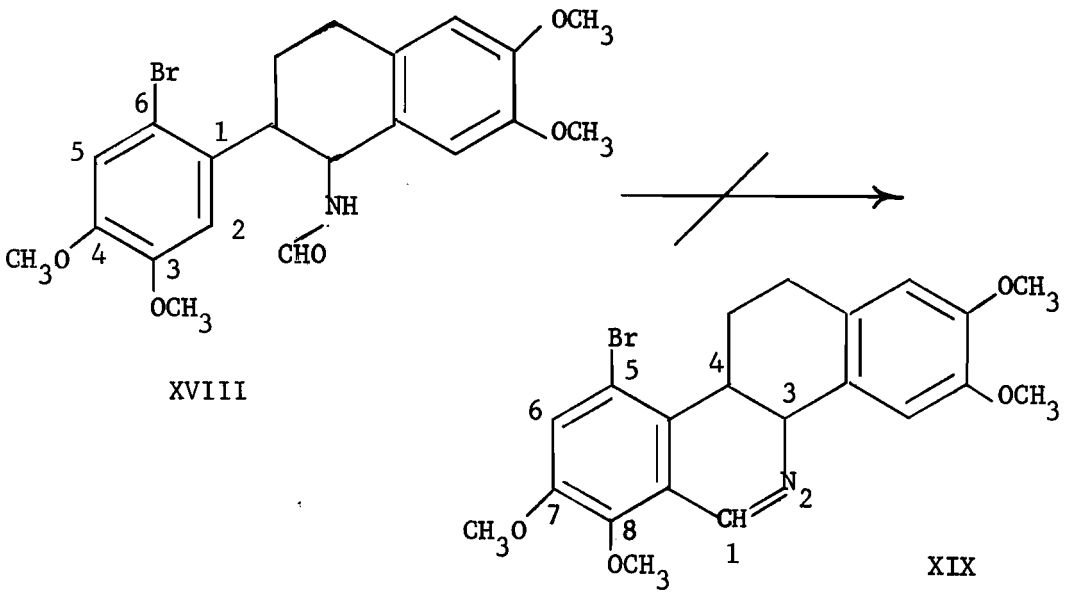
A few years later Bailey and Robinson (97) using as starting materials 6-bromoveratraldehyde and acetoveratrone, and following the same reaction sequences of Richardson, Robinson and Seijo, obtained the brominated 3,4-dimethoxyphenethylamine derivative (XVIII) with the object of inducing ring-closure in the 2-position of the varatryl nucleus, and so to obtain the proper configuration which is present in the chelidonine-sanquinarine group of alkaloids. Many attempts to cyclise the amide XVIII to the desired structural system XIX through a cyclodehydration, were unsuccessful. In those attempts the following cyclodehydration agents were used.

a) Phosphoryl chloride slone, or in toluene or in xylene.

b) Phosphoric anhydride in xylene.

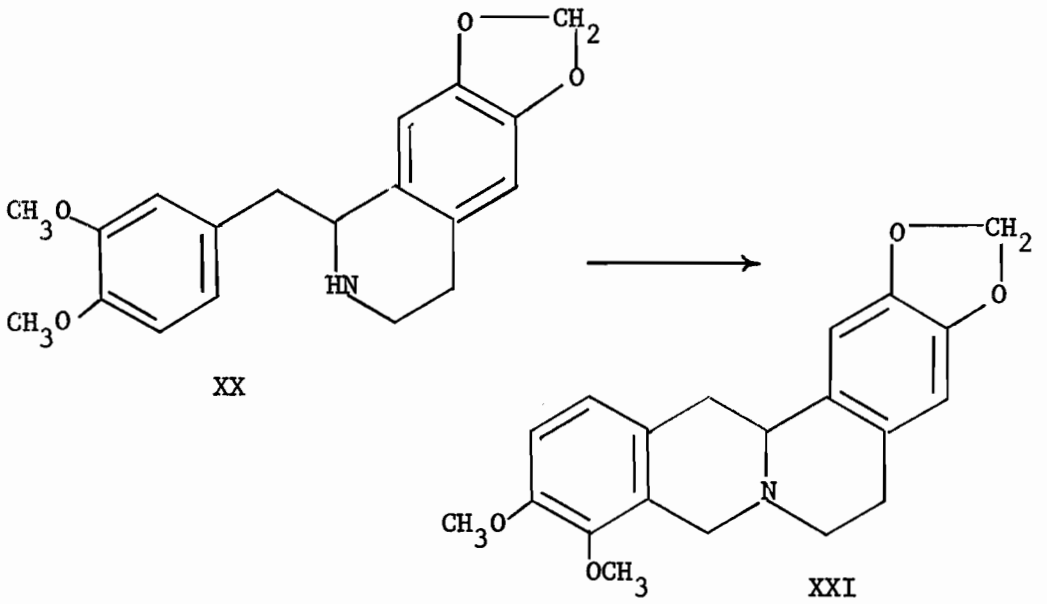
c) Phosphoric acid (syrupy), and

d) Phosphorus pentachloride in chloroform solution.



Ring closure in conformation with the isoquinoline portion of XIX is denoted as a 7,8-mode of cyclization. In this connection the literature reveals a few cases of reactions from which the products of such ring closure, are claimed to have the 7,8-dialkoxysubstituted isoquinoline structure. Such cyclization was reported by Pictet and Gams (98) who found that the treatment of the 3,4-dimethoxyphenethylamine derivative XX with methylal and hydrochloric acid, resulted in the formation of 7,8-dimethoxytetrahydroisoquinoline derivative, tetrahydroberberine XXI. Although the evidence for the identity of the product was convincing, the report was accepted with some reservation since it was contrary to

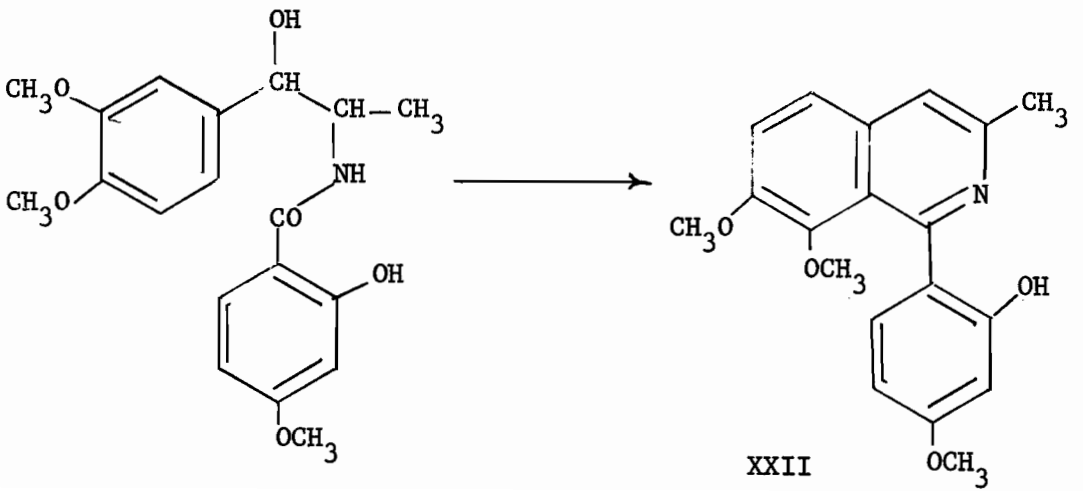
the behavior of closely related 3,4-dimethoxyphenethylamines (99, 100).



XX XXI

Howorth, Perkin and Rankin (101) failed in an attempt to duplicate the Pictet-Gams' synthesis. The only product isolated from the reaction was tetrahydropseudoberberine, the isomeric 6,7-dimethoxycompound.

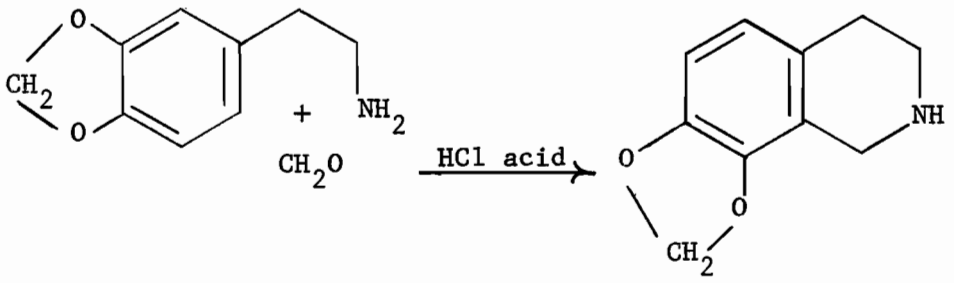
Another claim of a 7,8-mode of cyclization has been reported by Pfeiffer, Breitbach and Scholl (102). Structure XXII was assigned for the condensation product, on the basis of its non-identity with the known 6,7-isomeric compound which had been obtained by a direct method. However



XXII

Bruckner, Fodor, Kovacs, and Kiss (103, 104), obtaining the Pfeiffer, Breitbach and Scholl's compound, pointed out, that the 7,8-isoquinoline formulation was evidently erroneous, and that the product actually obtained was the 6,7-isomeride.

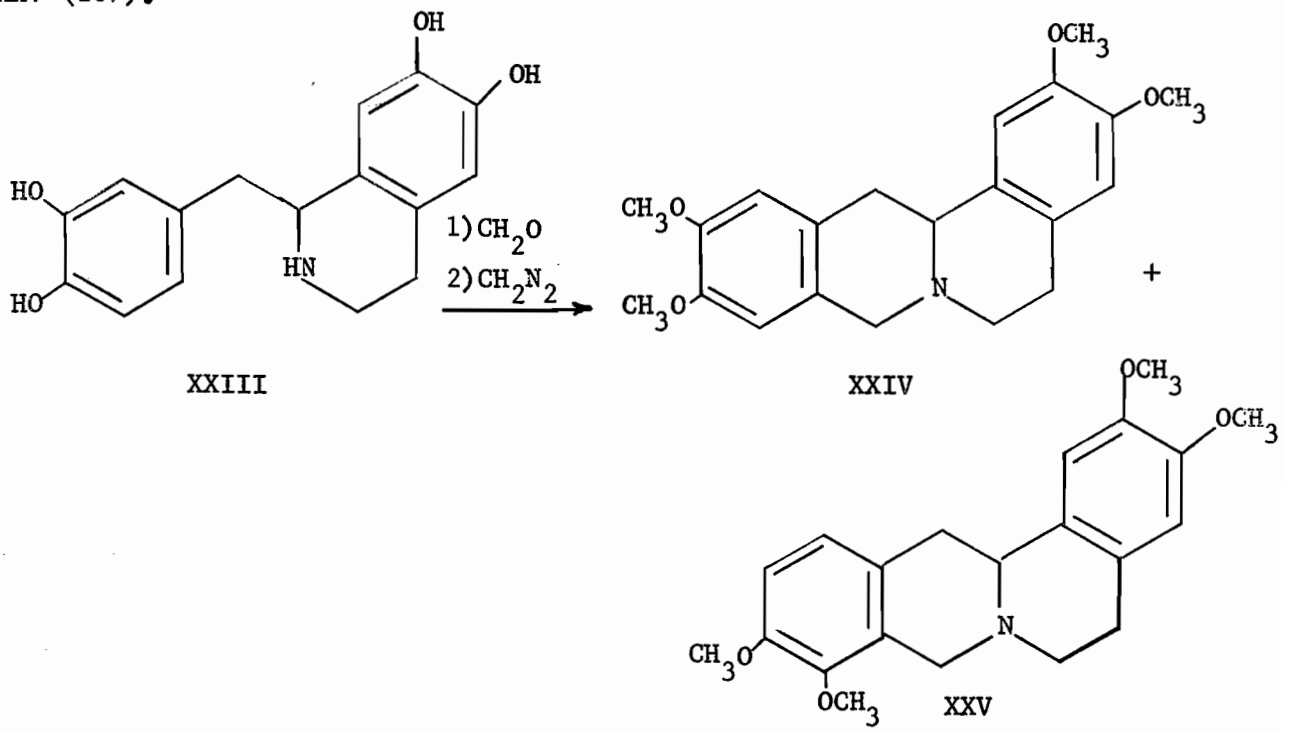
Another case of a 7,8-mode of cyclization has been reported by Buck (105) who claims that the product obtained from the reaction of 3,4-methylenedioxyphenethylamine and formaldehyde, possesses the 7,8-disubstituted isoquinoline structure. The assignment of this formulation was based on the discrepancies between the properties found and those concerning the 6,7-methylenedioxy-derivative.



Although the assigned structure has not been disproved, Gensler in Elderfield's Heterocyclic compounds (106) considers that in the light of available evidence, this formulation should be accepted with reservation. The same author discussing the cyclization of 3,4-dialkoxyphenethylamines to dialkoxyisoquinolines by means of the Bischler-Napieralski or Spengler syntheses, considers that only the 6,7-dialkoxyderivatives are favoured.

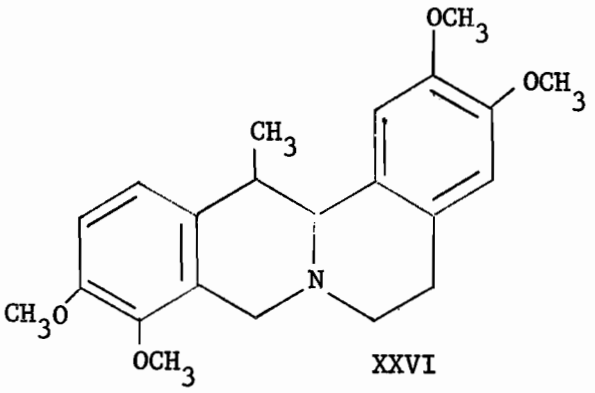
This limitation does not apply necessarily to the o-dihydroxy compounds, for which 7,8- as well as 6,7- ring closure appears quite possible.

Thus treatment of tetrahydropapaveroline XXIII with formaldehyde followed by methylation of the crude phenolic product with diazomethane gives small and equal amounts of XXIV and its isomeric compound tetrahydropalmatine XXV (107).



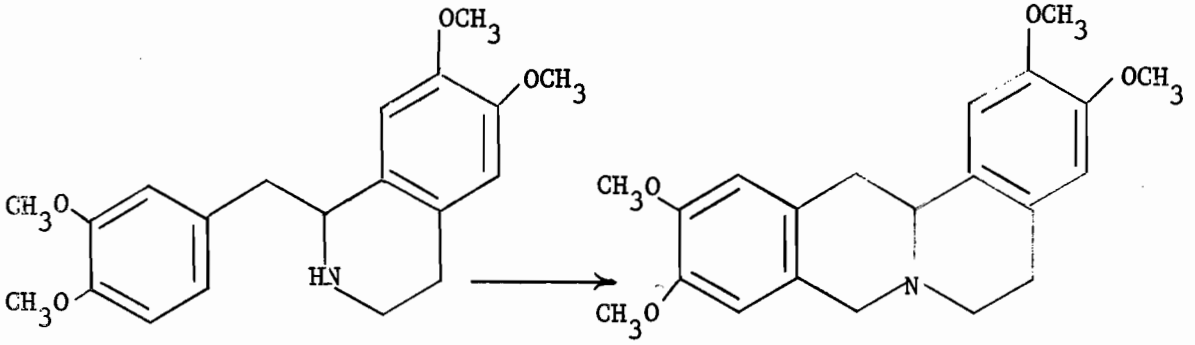
XXIII XXIV XXV

Späth and Kruta (107) applied the above sequence by which a 3,4-dihydroxyphenethylamine system replaced the corresponding methoxyl-substituted system in order to allow a 7,8-mode of cyclization, and succeeded in synthesizing one of the stereoisomers of corydaline XXVI. In contrast



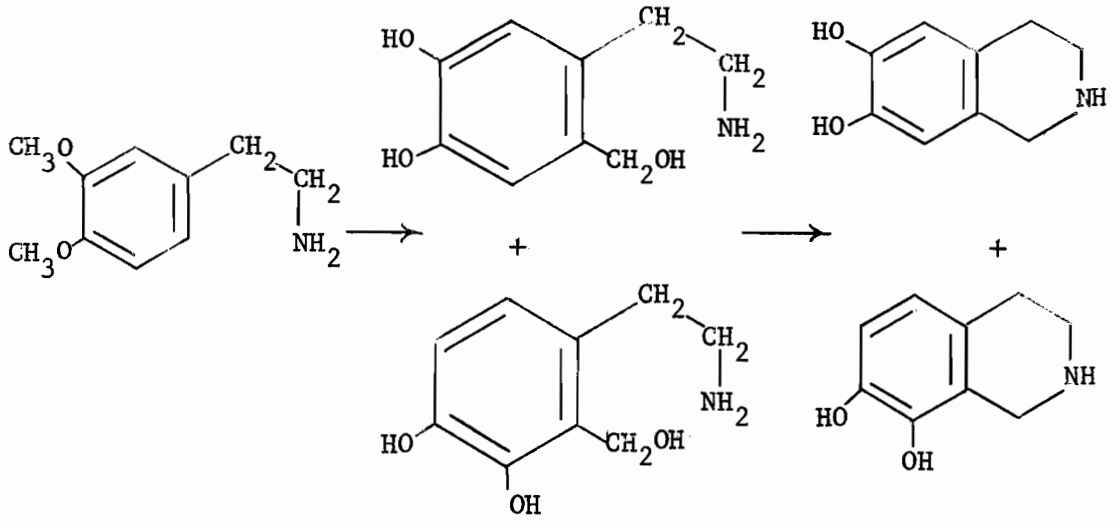
XXVI

When the same condensation was carried out with tetrahydropapaverine XXVII, a 3,4-dimethoxyphenethylamine, the only product isolated was the 6,7-dimethoxyisoquinoline derivative XXVIII (108, 109).

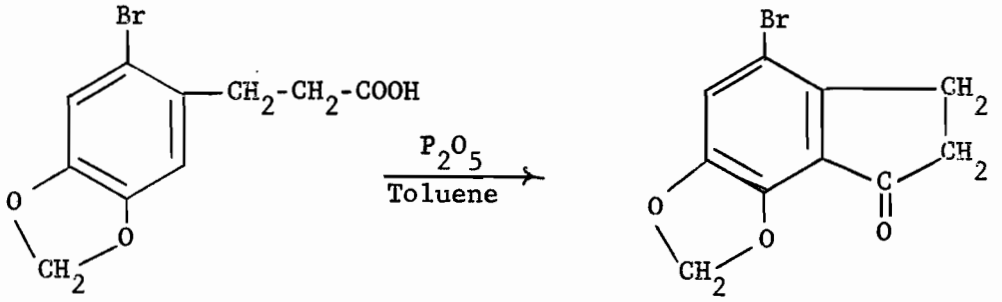


XXVII XXVIII

The ability of the 3,4-dihydroxyphenethylamines on treatment with formaldehyde to give cyclization products of both 6,7- and 7,8-modes, was interpreted by the mechanism shown below (110). In this mechanism the cyclization appears to proceed by way of aldehyde condensation with the nucleus (rather than with the amino group), followed by intramolecular interaction of the methylol and amino group.



The failure to obtain 7,8-dialkoxyisoquinolines directly from 3,4-dialkoxyphenethylamine systems, must be due to insufficient activation of the 2-position in the veratryl and piperonyl nucleus. However, the results of Haworth and Perkin (111) in the preparation of 4-bromo-6,7-methylenedioxy-1-hydrindone XXX from β-6-bromopiperonylpropionic acid XXIX, suggest that the 2-position in dialkoxyphenethylamines is not invulnerable, and should react, if suitable experimental conditions can be found.



XXIX XXX

DISCUSSION

PART I

6,7-Dialkoxy-1,4-Benzoxazin-2-Ones and Their Dihydroderivatives 6,7-Dialkoxy-2-Phenomorpholones

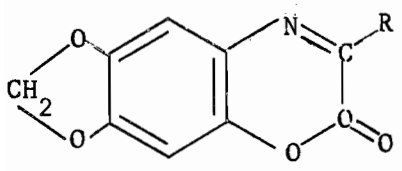
In the first phase of this investigation the synthesis of 1,4-benzoxazine-2-ones substituted by the methylenedioxy or two methoxy groups in the 6 and 7 positions was undertaken. It was thought that such heterocyclic compounds combining a dialkoxybenzene ring with an oxazine nucleus, might prove to have physiological activity.

The synthesis of these compounds involved the following two stages:

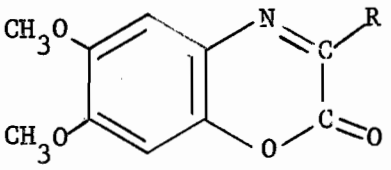
a) Preparation of 3,4-methylenedioxy-6-aminophenol and 3,4-dimethoxy-6-aminophenol;

b) Condensation of the 3,4-dialkoxy-6-aminophenols with various α-ketoesters.

These compounds are prepared for the first time by the methods described below and, have not been reported in the literature. Thery are represented by the general formulae XXXI, XXXII and are listed in Table I.



XXXI



XXXII

TABLE I

COMPOUND		R
6,7-Methylenedioxy-1,4-benzoxazin-2-one-3-acetic acid ethyl ester	XXXIII	$-CH_2COOC_2H_5$
6,7-Methylenedioxy-3-methyl-1,4-benzoxazin-2-one	XXXIV	$-CH_3$
6,7-Methylenedioxy-3-phenyl-1,4-benzoxazin-2-one	XXXV	$-C_2H_5$
6,7-Methylenedioxy-3-acetonyl-1,4-benzoxazin-2-one	XXXVI	$-CH_2COCH_3$
6,7-Methylenedioxy-3-phenacyl-1,4-benzoxazin-2-one	XXXVII	$-CH_2COC_6H_5$
6,7-Dimethoxy-1,4-benzoxazin-2-one-3-acetic acid ethyl ester	XXXVIII	$-CH_2COOC_2H_5$
6,7-Dimethoxy-3-methyl-1,4-benzoxazin-2-one	XXXIX	$-CH_3$
6,7-Dimethoxy-3-phenyl-1,4-benzoxazin-2-one	XL	$-C_2H_5$
6,7-Dimethoxy-3-acetonyl-1,4-benzoxazin-2-one	XLI	$-CH_2COCH_3$
6,7-Dimethoxy-3-phenacyl-1,4-benzoxazin-2-one	XLII	$-CH_2COC_6H_5$

1. Preparation of 3,4-Dialkoxy-6-Aminophenols

To prepare 3,4-methylenedioxy-6-aminophenol and 3,4-dimethoxy-6-aminophenol from piperonal and veratraldehyde respectively, the following synthetic path was chosen:

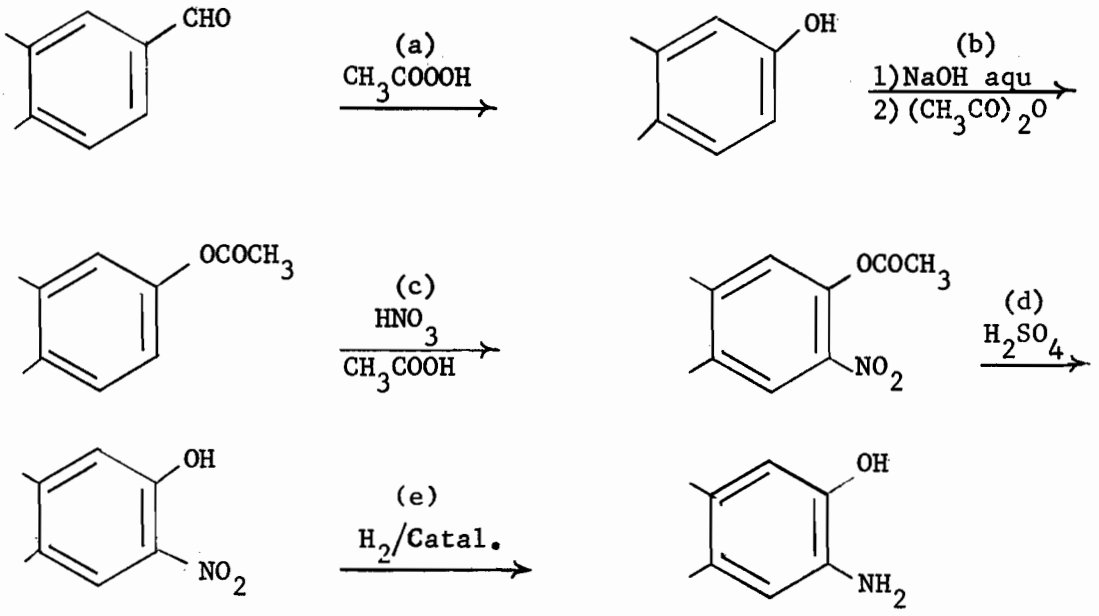
a) Replacement of the formyl group for hydroxyl by peracetic acid oxidation.

b) Acetylation of the hydroxyl group.

c) Nitration of the phenyl acetate in glacial acetic acid.

d) Hydrolysis of the 3,4-dialkoxy-6-nitrophenyl acetate to the free phenol compound.

e) Reduction of the nitro group to the corresponding amino group.



2. Preparation of 3,4-Dialkoxyphenols

Sesamol (3,4-methylenedioxyphenol), a substance naturally occurring in sesame oil was first prepared by Böeseken, Cohen and Kip (40,41) by treatment of piperonal with peracetic acid. Since that time, some modifications of this method have been developed, of varying degrees of complexity (42, 43, 44). All these modified procedures are basically similar to the original method which is outlined below.

Peracetic acid oxidation of piperonal in glacial acetic acid affords a dark brown reaction mixture from which a yellow oily compound is obtained after removal of the solvent and high vacuum distillation of the viscous residue. This yellow oily distillate was considered by some workers (40, 43, 44) to be sesamol acetate, while Beroza (42) thought

that is was probably either sesamol formate or sesamol acetate. In all cases it was further subjected to alkaline hydrolysis by refluxing it with ethanolic potassium hydroxide for some hours, to free the sesamol.

Following the original method as outlined by Böeseken et.al. (40, 41). many difficulties were encountered in the isolation procedure and the yields obtained were considerably lower than those reported. In no case was the reported sesamol acetate or sesamol formate obtained as the reaction product, but always the sesamol itself. This observation led to the simplification of the isolation procedure plus the recovery of the unreacted piperonal. The reaction was repeated a great number of times, and studied under a variety of experimental conditions, and the following observations were made.

a) The reaction never goes to completion, starting material being always recovered from the reaction mixture. By using a greater amount of peracetic acid than that established as optimum, the yields are noticeably lowered in favour of resinous byproducts.

b) Freshly prepared paracetic acid is remarkably more efficient.

c) The best yields (45-49%) were obtained when the amount of piperonal used was 50g and the reaction temperature between 32-38^{o}.

d) Yields can be reproduced if the reactions are carried out simultaneously, under strictly similar conditions, and especially using peracetic acid of the same preparation. Otherwise great differences may be found.

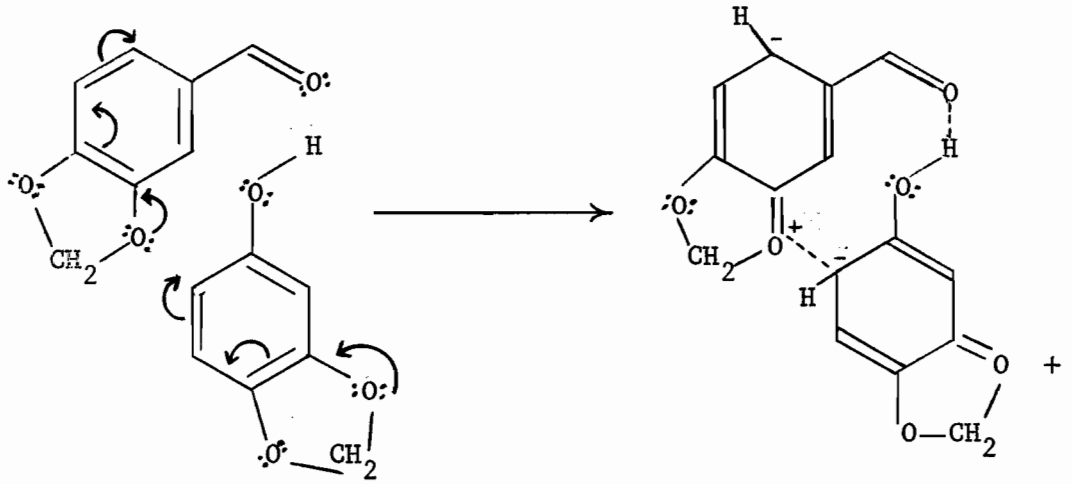
e) The substance reported as sesamol acetate or formate was proved to be an azeotropic mixture of sesamol and piperonal. The modification developed as described in the experimental part, leaves no doubt about the validity of this finding. The reported alkaline hydrolysis to which this mixture was subjected (40, 42, 43, 44) actually consisted in the conversion of the unreacted piperonal to 3,4-methylendioxy-benzyl alcohol and piperonylic acid, which undetected, were then easily removed by the various manipulations in the isolation procedure.

f) In this reaction small amounts of piperonylic acid are always formed.

g) Separation attempts of the mixture sesamol-piperonal by fractional distillation using a spinning band column (112) proved impracticable. This physical behavior of the two compounds when in a mixture, might be explained on the basis of their related individual chemical natures as follows:

From resonance data for the molecule of piperonal and those of related structure, it has been shown, that the important ionic resonance structure in aromatic substitution reactions, is that in which the molecule carries a negative charge at C-6 and a positive charge at the oxygen attached to C-3. Apparently such structures having separated centers of high and low electronic charge, are capable of holding together molecules of different compounds.

The scheme shown below could indicate the type of association which might occur in the case under discussion.



XLIII

The molecules of 3,4-methylenedioxyphenol and piperonal as depicted in XLIII, show an association where they are held together by hydrogen bonding between the carbonyl oxygen and the phenolic hydrogen, and another bond which arises from the centers of highest and lowest electron densities. Such a type of association might be responsible for the formation of an azeotropic mixture independent of the ratio of the two compounds with respect to each other. However, a full interpretation of the true nature of the azeotropic mixture arising from piperonal and 3,4-methylenedioxyphenol (sesamol), has not been attempted and the above explanation is offered only as a suggestion.

Following the directions of Böeseken and Greup (46), for the preparation of 3,4-dimethoxyphenol by means of peracetic acid oxidation of veratrole, a much lower yield than that reported was obtained.

Finally this method was modified in accordance with the procedure developed for the preparation of the 3,4-methylenedioxyphenol. The yield obtained was lower than that reported (50% as compared to 66%).

3. 3,4-Dialkoxyphenyl acetates

Sesamol acetate (3,4-methylenedioxyphenyl acetate) was prepared in 87% yield by the action of acetyl chloride on sesamol in the presence of pyridine (42). The anologous 3,4-dimethoxyphenyl acetate has been obtained in unreported yields, by boiling 3,4-dimethoxyphenol with acetic anhydride in the presence of a few drops of pyridine (2). Since it was thought more convenient to accomplish these acetylations by the interaction of acetic anhydride with the sodium salts of the phenolic compounds (113), this procedure was adopted, and the yields of both dialkoxyphenyl acetates were over 88%.

4. 3,4-Dialkoxy-6-nitrophenyl acetates

6-Nitrosesamol acetate (3,4-methylenedioxy-6-nitrophenyl acetate) has been prepared in a yield of 67% by the dropwise addition of sesamol acetate to a mixture of nitric acid and glacial acetic acid below $5^{o}C$ (52). Satisfactory nitrations are usually accomplished by this procedure; but in some instances, inversion in the mixing order, and use of higher temperatures ($30-45^{o}$), not only gives increased yields, but also emphasizes the fact that no special precautions are necessary (114). In this way a yield of 88% of a pure crystalline product was obtained which, without recrystallization, showed a m.p. $103-105^{o}$ (Reported m.p. in the literature $104-105^{o}$).

3,4-Dimethoxy-6-nitrophenyl acetate has not been reported previously, and its preparation was undertaken by following the procedure developed for the synthesis of the analogous 3,4-methylenedioxy-6-nitrophenyl acetate. The infrared spectrum of this compound was in agreement with the product expected, and the assignment of its structure was further established by hydrolysis of the acetate to the known 3,4-dimethoxy-6-nitrophenol which has been obtained by a direct route (53).

5. 3,4-Dialkoxy-6-Nitrophenols

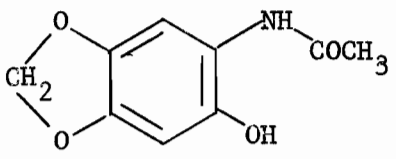
6-Nitrosesamol (3,4-methylenedioxy-6-nitrophenol) has been obtained by Gertler, Alexander and Beroza (52) in quantitative yield by the hydrolysis of 6-nitrosesamol acetate with ethanolic sodium hydroxide. The saponified mixture was neutralized with hydrochloric acid, and then left overnight. The same substance was obtained even more conveniently by refluxing the acetate with 20% sulphuric acid solution in ethanol for forty minutes. The hot reaction mixture was cooled, and the crystalline product which rapidly separated was filtered, washed with water and dried. In this way a quantitative yield was obtained of a pure crystalline product without any need for further purification.

3,4-Dimethoxy-6-nitrophenol has been obtained in a number of laborious ways (53, 54, 55). This compound was readily prepared by refluxing the corresponding acetate in a mixture of ethanol and 20% sulphuric acid. A nearly quantitative yield was obtained of a pure product melting at 144-145°. Reported melting points in the literature were: 142-3° (53), 143° (54), 144° (55).

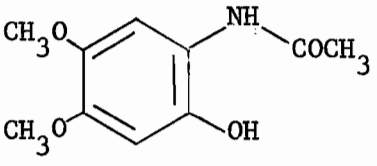
6. 3,4-Dialkoxy-6-Aminophenols

6-Aminosesamol (3,4-methylenedioxy-6-aminophenol) and 3,4-dimethoxy-6-aminophenol have not been described in the literature up to the present. Their preparation by reduction of the corresponding nitrocompounds, did not meet any difficulties, and all standard reducing agents were found to be effective. However the isolation of the free amines proved impracticable. The rapidity with which these bases decompose necessitates complete exclusion of atmospheric air, and manipulation in an absolutely inert or hydrogen atmosphere. Both amines were characterized through their anilides XLIV, XLV which were prepared by an adaptation of the procedure described by Hayes and Gewer (115) for the reductive acetylation of methyl α-oximinofuroylacetate to the acetyl derivative of the corresponding amine.

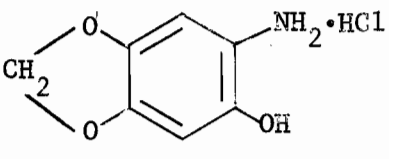
Characterization of these dialkoxy-aminophenols through their hydrochlorides, was found to be impracticable, since the salts formed proved to be very unstable. 3,4-Methylenedioxy-6-aminophenol hydrochloride XLVI was obtained as light gray colored powder which in a few days changed into a dark-gray colored compound. The freshly prepared hydrochloride became gradually dark on heating above 195° and at 210° completely decomposed to a black material.



XLIV



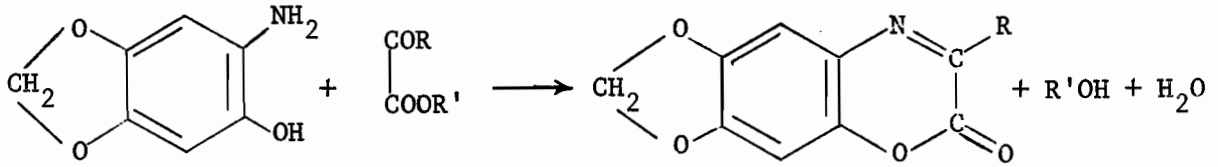
XLV

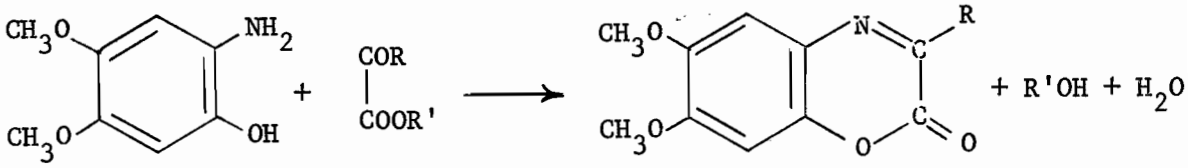


XLVI

7. Condensation of the 3,4-dialkoxy-6-aminophenols with α-ketoesters

To prepare 1,4-benzoxazin-2-ones substituted in the benzene ring by a methylenedioxy or dimethoxy group the appropriate α-ketoesters were condensed with 3,4-methylenedioxy-6-aminophenol or 3,4-dimethoxy-6-aminophenol respectively according to the general equations.





R = CH_3, C_6H_5, $CH_2COOC_2H_5$, CH_2COCH_3, $CH_2COC_6H_5$

R'= CH_3, C_2H_5

The constitution of these compounds was based on analogy, (89, 90, 91, 92) analytical data, and infrared spectra.

8. Preparation of 6,7-Dialkoxy-1,4-Benzoxazin-2-ones

The required 3,4-methylenedioxy-6-aminophenol and 3,4-dimethoxy-6-aminophenol as noted earlier were easily prepared quantitatively by catalytic reduction of the corresponding nitro derivatives. These 3,4-dialkoxy-6-aminophenols being extremely sensitive to oxidation,

were not isolated from the solution after hydrogenation, but were filtered in a nitrogen atmosphere in an ethanol-glacial acetic acid solution of the appropriate α-cetoester, and directly converted to the stable 6,7-dialkoxy-1,4-benzoxazin-2-ones. The presence of glacial acetic acid in the reaction mixture proved quite beneficial, since the yields obtained were much higher than those realized in its absence. The most pronounced effect of the glacial acetic acid in the reaction mixture, was the successful synthesis of the 6,7-dialkoxy-1,4-benzoxazin-2-ones possessing methyl or phenyl substituents in the 3-position, which otherwise could not have been prepared.

3,4-Methylenedioxy-1,4-benzoxazin-2-ones were obtained in high yields, in an almost pure state, at temperatures ranging from room temperature up to 60°, and the time required for the reaction was from a few seconds to six hours. By contrast, all 3,4-dimethoxy-1,4-benzoxazin-2-ones were prepared by heating at 70° for a long period of time. With these latter compounds, considerable amounts of dark decomposition products were formed, which were removed only with difficulty.

The reaction differences found between methylenedioxybenzoxazinones and dimethoxybenzoxazinones, in their preparation, are not completely understood, and only a solvent effect may be responsible.

Actually the condensation yielding the 3,4-methylenedioxy-1,4-benzoxazin-2-ones was accomplished in ethanol and glacial acetic acid, whereas the condensation yielding the 3,4-dimethoxy-1,4-benzoxazin-2-ones, was carried out in a mixture of methoxyethyleneglycol and glacial acetic acid. The presence of the methoxyethyleneglycol in the latter

condensation was unavoidable, because it was the solvent used in the preceding step for the hydrogenation of the 3,4-dimethoxy-6-nitrophenol.

Yield, reaction time, reaction temperature, melting point, and colour recorded for each 6,7-dialkoxy-1,4-benzoxazin-2-one compound, are listed in Table II.

6,7-Dialkoxy-1,4-benzoxazin-2-Ones, as would be expected from their structure, are highly coloured, and the kind of substituent in the 3-position seems to play an important role in the colour of the compound.

Both 6,7-dialkoxy-3-phenyl-1,4-benzoxazin-2-ones dissolved in acetone, show a strong blue-green fluorescence which, apparently, is due to the existence of a large conjugated system in their molecule. This effect, but with less intensity, is also obtained by dissolving these compounds in several other polar or inert solvents.

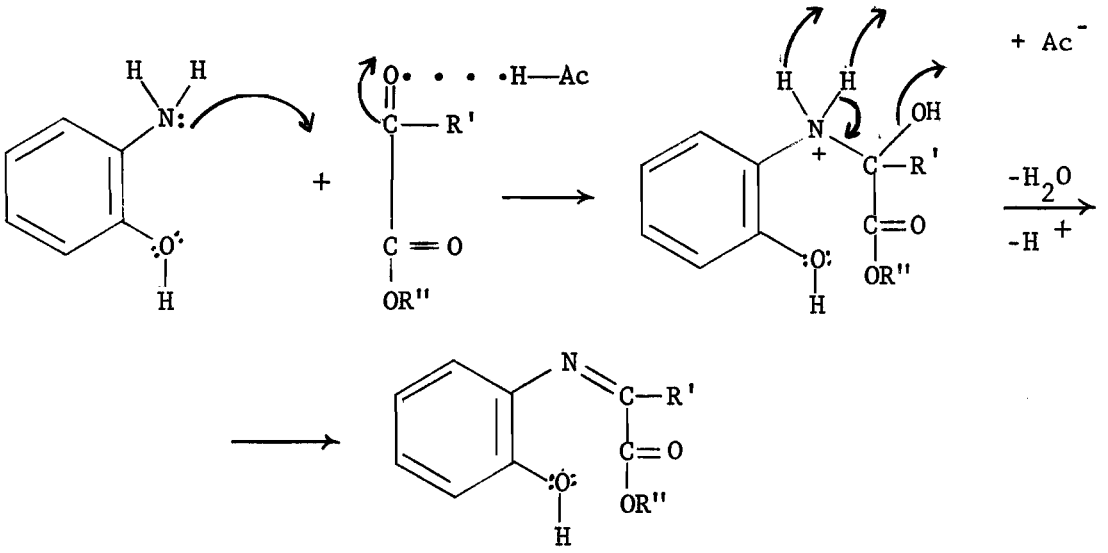
9. Mechanism of Condensation of O-Aminophenols with α-Ketoesters

The condensation of o-aminophenols and α-ketoesters proceeds at a slow rate in the absence of acids, however, the best yields of 1,4-benzoxazin-2-ones are obtained in the presence of glacial acetic acid.

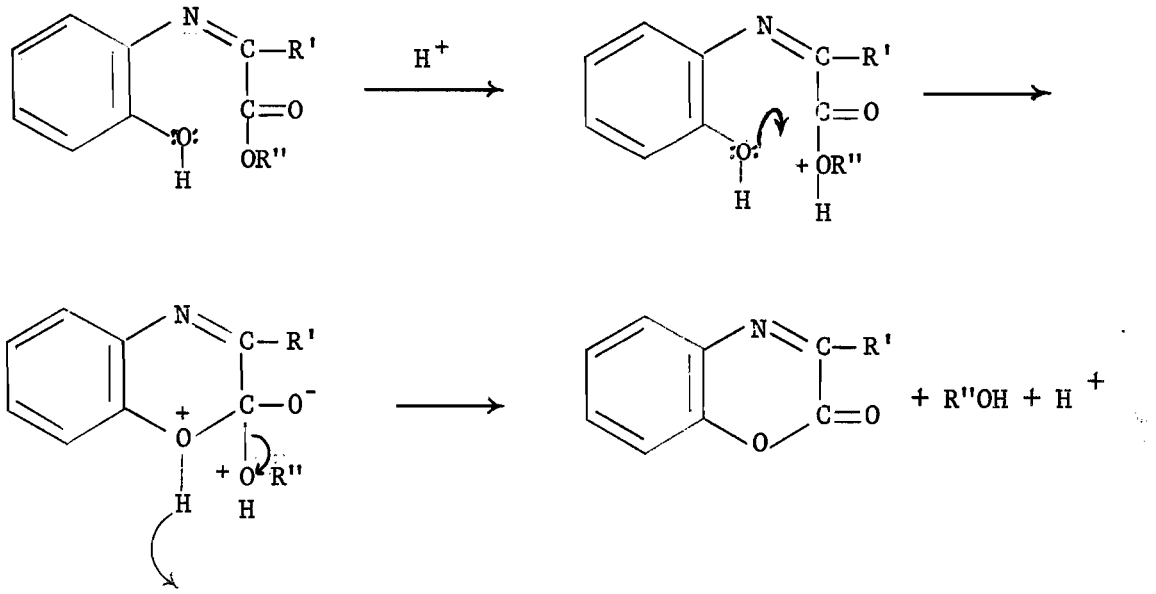
It is obvious that the first step of the interaction between the amino group and α-keto group is a general acid catalyzed reaction, and that o-minophenols can exhibit autocatalytic effect by virtue of their acidity. The second step is the acid catalyzed interaction of the phenolic hydroxyl group and the ester group of the α-ketoester; the latter reaction must be considered as a transesterification reaction

in which the alkoxyl group is expelled by the phenoxy group.

1st Step:



2nd Step:

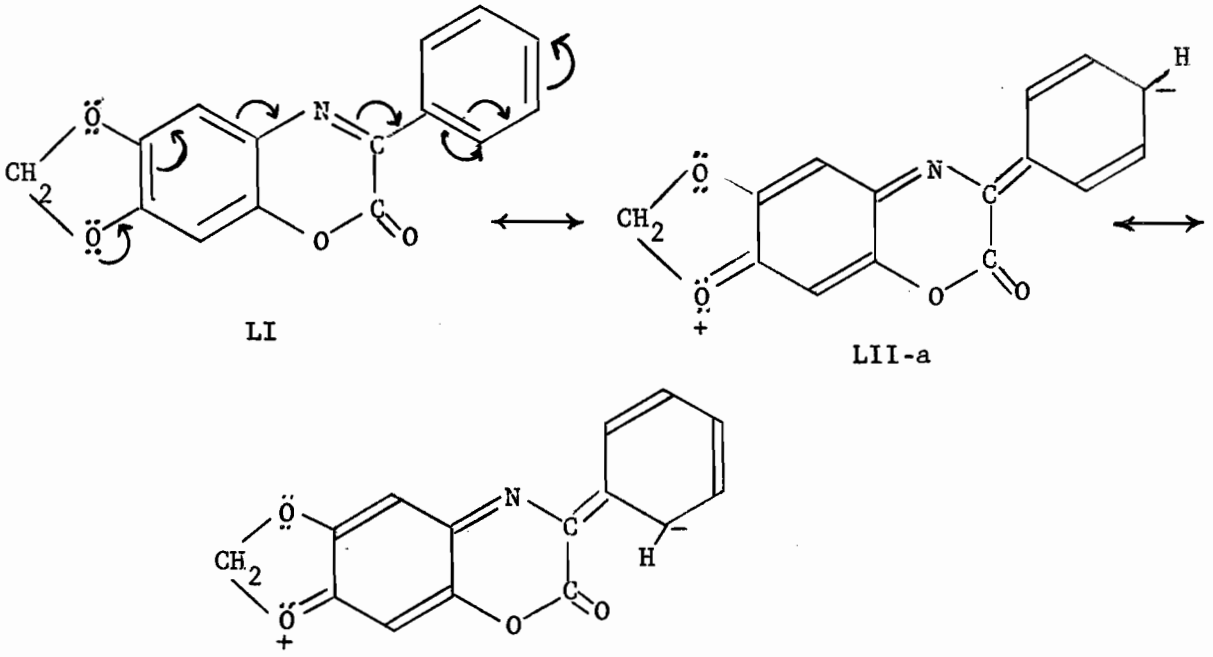


In the condensation of 3,4-dialkoxy-6-aminophenols with the various α-ketoesters, it was observed that when the group R' in the ketoester was a strong electron attracting group such as the acetonyl or phenacyl, the reaction proceeded with great ease and the yields were high, because of the -Is effect of the latter. The -Is effect renders the carbon atom of the keto group more reactive in the condensation by decreasing its electron density and hence increasing its electrophilic character.

10. Attempted nitration of 6,7-methylenedioxy-3-phenyl-1,4-Benzoxazin-2-One

It is well-known, that the electron releasing properties of the dialkoxy groups exert considerable influence upon the activity of other functional groups attached to the same benzene ring.

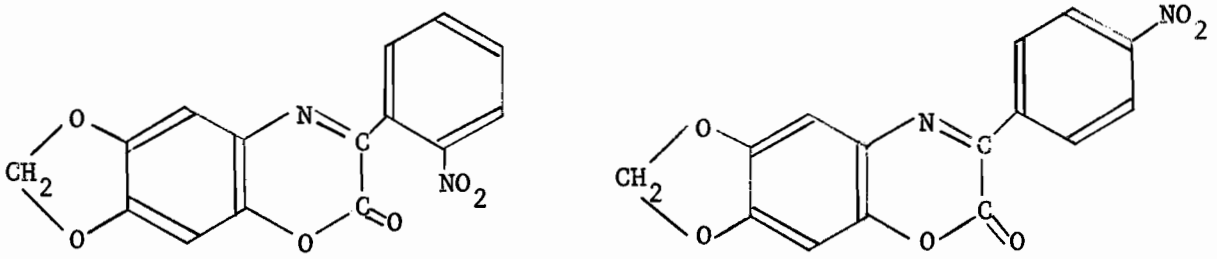
In order to determine if the activating effect of the methylenedioxy group could be transmitted through a propagation of electron displacements to the phenyl ring attached in the 3-position of the 6,7-methylenedioxy-3-phenyl-1,4-benzoxazin-2-one LI, a nitration of the latter was attempted. If the structures LII-a and LII-b contribute significantly to the resonance hybrid, a nitration, under conditions similar to those employed in the preparation of the 3,4-dialkoxy-6-nitrophenylacetates, would give the derivatives LIII-a and LIII-b. However in no case was a nitro compound obtained and the starting material was recovered unchanged.



LI

LII-a

LII-b



LIII-a

LIII-b

The resistance of the compound LI to nitration, suggests that the contribution of resonance structures LII-a and LII-b if present in the ground state of the molecule, must be low, and that the activating effect of the methylenedioxy group appears to be limited only to substituents which are directly attached on the same benzene ring.

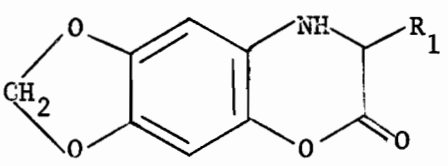
TABLE II

Yield, Reaction Temperature, Reaction Time, Color and m.p. of 6,7-Dialkoxy-1,4-Benzoxazin-2-Ones

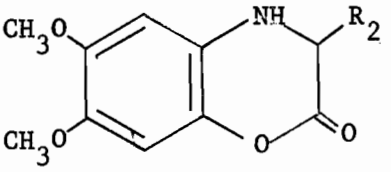
Compound	Percentage Yield	Reaction Temp.	Reaction Time	Color	M.P.
6,7-Methylenedioxy-3-methyl-1,4-benzoxazin-2-one	32	Room Temp.	12	Yellow	241-2°
6,7-Methylenedioxy-3-phenyl-1,4-benzoxazin-2-one	80.8	55-60°	6	Yellow	196-196.5°
6,7-Methylenedioxy-1,4-benzoxazin-2-one-3-acetic acid ethyl ester	91	Room Temp.	3	Yellow	164-165°
6,7-Methylenedioxy-3-acetonyl-1,4-benzoxazin-2-one	93	Room Temp.	1	Deep Orange	191-192°
6,7-Methylenedioxy-3-phenacyl-1,4-benzoxazin-2-one	99.3	Room Temp.	1	Red	260°
6,7-Dimethoxy-3-methyl-1,4-benzoxazin-2-one	8.1	65-70°	12	Yellow	188-189°
6,7-Dimethoxy-3-phenyl-1,4-benzoxazin-2-one	64.3	65-70°	12	Yellow	168°
6,7-Dimethoxy-1,4-benzoxazin-2-one-3-acetic acid ethyl ester	11.9	65-70°	12	Yellow	157-159°
6,7-Dimethoxy-3-acetonyl-1,4-benzoxazin-2-one	65	65-70°	12	Orange	187-188°
6,7-Dimethoxy-3-phenacyl-1,4-benzoxazin-2-one	81.5	65-70°	12	Red	175-176°

11. Low Pressure Hydrogenation of the 6,7-Dialkoxy-1,4-Benzoxazin-2-Ones to the Corresponding 6,7-dialkoxy-2-phenomorpholones

In the second phase of the present section, the catalytic hydrogenation of the 6,7-dialkoxy-1,4-benzoxazin-2-ones XXXIII, XXXIV, XXXV, XL to the corresponding 6,7-dialkoxy-2-phenomorpholones was achieved. These latter compounds represented by the general formulae LIV and LV are shown in Table III.



LIV



LV

$R_1 = CH_3$, C_6H_5, $CH_2COOC_2H_5$

$R_2 = C_6H_5$

TABLE III

Compound		M.P.
6,7-Methylenedioxy-2-phenomorpholone-3-acetic acid ethyl ester	LVI	110.5-111°
6,7-Methylenedioxy-3-methyl-2-phenomorpholone	LVII	177-179°
6,7-Methylenedioxy-3-phenyl-2-phenomorpholone	LVIII	191-192°
6,7-Dimethoxy-3-phenyl-2-phenomorpholone	LIX	116-117°

Synthesis of 2-phenomorpholones by catalytic hydrogenation of 1,4-benzoxazin-2-ones was first reported by Biekert et.al. (91). This hydrogenation was accomplished catalytically under a pressure of 50 atm. This method modified using a much lower pressure (0.2 atm.), was used for the hydrogenation of the dialkoxy-1,4-benzoxazin-2-ones XXXIII, XXXIV, XXXV, XL to the corresponding dialkoxy-phenomorpholones LVI, LVII, LVIII, LIX. Surprisingly hydrogenation of the dialkoxy-1,4-benzoxazin-2-ones XXXVI and XXXVII was not successful. The conditions for the hydrogenation of these compounds were varied as described in the experimental part of this thesis. However, hydrogenation was not effected by any of the changes, and use of temperatures 80-90^{o} under a pressure of 5 atm. resulted in extensive decomposition of the starting material.

12. Attempted nitration of 6,7-methylenedioxy-3-phenyl-2-phenomorpholone, and dehydrogenation by atmospheric oxygen of 6,7-dialkoxy-2-phenomorpholones to their parent dialkoxy-1,4-benzoxazinones.

The nitration of the colourless 6,7-methylenedioxy-3-phenyl-2-phenomorpholone was attempted using a procedure similar to that employed in the case of the 3,4-dialkoxyphenyl acetates. This reaction led instead to a nitroderivative, the coloured 6,7-methylenedioxy-3-phenyl-1,4-benzoxazin-2-one. The latter compound was identified by comparison of its infrared spectrum with that of a known sample, and further by melting point and mixed melting point determinations. This observed dehydration, was found not to be due to the nitric acid, but to air oxidation which was greatly accelerated by the acidic solvent.

Finally, it was found that all prepared 6,7-dialkoxy-2-phenomorpholones were readily dehydrogenated to their parent 6,7-dialkoxy-1,4-benzoxazin-2-ones, on their treatment in glacial acetic acid in an open

flask. This characteristic feature also occurs in the oxazine dyes where they can be reduced to leuco-compounds which, by reoxidation, even with air, are transformed into the original dyes.

Further, it was found that the time necessary for the dehydration varied for different substituents attached in the position 3 of the phenomorpholine nucleus; the dehydration with a methyl group takes place in the course of 8-10 hours, whereas with a phenyl or acetic acid ethyl ester group it is achieved in 3-5 hours.

13. Infrared Spectra

The infrared spectra of all compounds synthesized in the present part were recorded in the solid state using the KBr technique, and the frequencies of the maximum absorption bands are listed in Tables V - XI.

No attempt was made to discuss all absorption bands, but only the characteristic bands of new compounds.

14. Infrared Spectrum of 3,4-dimethoxy-6-nitrophenyl acetate

Two very strong bands occurring at 1525 and 1338 cm^{-1} in the spectrum of 3,4-dimethoxy-6-nitrophenyl acetate and which are absent in the spectrum of the parent compound, may be assigned to the asymmetrical and symmetrical stretching vibrations of the nitro group respectively (116).

In the carbonyl stretching region the strong peak at 1768 cm^{-1} was readily assigned to the acetate carbonyl group.

15. Infrared Spectra of 3,4-dialkoxy-6-hydroxyacetanilides

In the infrared absorption spectrum of 3,4-methylenedioxy-6-hydroxy-acetanilide XLIV, bands at 3270 cm^{-1} (m), 3090 cm^{-1} (m), 1648 cm^{-1}(m.sh), 1635 cm^{-1} (s) and 1565 cm^{-1} (v.s.), indicated the presence of a secondary amide group.

Examination of the spectrum of 3,4-dimethoxy-6-hydroxyacetanilide XLV in the N-H stretching region, showed a weak peak at 3365 cm^{-1} and a broad band of medium intensity at 3145 cm^{-1}. These bands were attributed to the bonded NH (trans) and NH (cis) stretching vibrations respectively. The peak of strong intensity at 1648 cm^{-1} with a shoulder at 1630 cm^{-1} was assigned to absorption by the amide carbonyl group.

16. Infrared spectrum of 3,4-Methylenedioxy-6-Aminophenol Hydrochloride

The spectrum of 3,4-methylenedioxy-6-aminophenol hydrochloride XLVI showed two absorption frequencies of medium intensity at 3540 and 3450 cm^{-1}. These absorptions may be assigned as being due to the simultaneous occurrence of two different types of association of the O-H group. A broad band of medium intensity at 3160 cm^{-1} and another sharp band at 2620 cm^{-1} were attributed to NH_3^+ stretching vibrations.

The medium bands at 1595 and 1298 cm^{-1} were readily assigned to NH_3^+ deformation frequencies.

17. Infrared Spectra of 6,7-Dialkoxy-1,4-Benzoxazin-2-ones

In general, all the 6,7-dialkoxy-1,4-benzoxazin-2-ones showed at least two bands between 1757 $\sim$ 1615 cm^{-1}. These absorption frequencies are listed in Table IV. The higher frequency band is attributed to the

stretching carbonyl absorption of the α,β-unsaturated δ-lactone system, while the second band arises from the stretching of the C=N function.

The frequencies recorded in Table IV for the α,β-unsaturated δ-lactone systems are in good agreement with the spectra of other α,β-unsaturated lactones (117, 118).

The dialkoxy-1,4-benzoxazin-2-ones XXXIII, XXXVI, XXXVII, XXXVIII, XLI and XLII, as it would be expected from their structure, do not show two carbonyl absorptions, but instead, a very strong band which obviously results from the overlapping of both frequencies occurring in the same region.

18. Infrared Spectra of 6,7-Dialkoxy-2-Phenomorpholones

The spectra of 6,7-dialkoxy-2-phenomorpholones as would be expected from their structure, show one strong band between 3360-3335 cm^{-1}, and another of very strong intensity at 1758 ~ 1745 cm^{-1}. These absorption frequencies are recorded in Table IV. The band occurring at higher frequencies was assigned to the NH stretching vibration whereas the second one of lower frequency was attributed to the stretching carbonyl absorption of the existed δ-lactone system.

An additional carbonyl absorption at 1730 cm^{-1} observed in the spectrum of 6,7-methylenedioxy-2-phenomorpholone-3-acetic acid ethyl ester, was readily assigned to the carbonyl acetate group.

TABLE IV

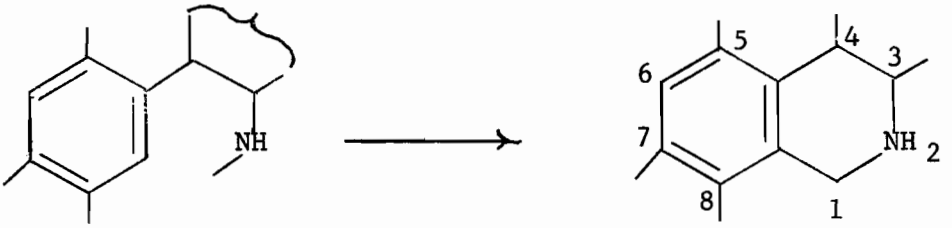
Positions of Absorption Maxima in the Infrared Spectra (cm^{-1}) of 6,7-Dialkoxy-1,4-Benzoxazin-2-Ones and their Dihydroderivatives 6,7-Dialkoxy-2-Phenomorpholoves

Compound	C=O Stretching of the α,β-unsaturated δ-lactone System	C=O Stretching of the saturated δ-lactone Sytem	C=N Stretching	NH Stretching
6,7-Methylenedioxy-1,4-benzoxazine-2-one-3-acetic ethyl ester	1755 v.s.		1632 v.s.	
6,7-Methylenedioxy-3-methyl-1,4-benzoxazin-2-one	1723 v.s.		1633 m.	
6,7-Methylenedioxy-3-phenyl-1,4-benzoxazin-2-one	1740 v.s.		1632 s.	
6,7-Methylenedioxy-3-acetonyl-1,4-benzoxazine-2-one	1743 v.s.		1632 v.s.	
6,7-Methylenedioxy-3-phenacyl-1,4-benzoxazine-2-one	1742 v.s.		1617 v.s.	
6,7-Dimethoxy-1,4-benzoxazine-2-one-3-acetic acid ethyl ester	1732 v.s.		1623 m.	
6,7-Dimethoxy-3-methyl-1,4-benzoxazin-2-one	1750 v.s.		1623 s.	
6,7-Dimethoxy-3-phenyl-1,4-benzoxazin-2-one	1724 v.s.		1617 s.	
6,7-Dimethoxy-3-acetonyl-1,4-benzoxazin-2-one	1742 v.s.		1627 v.s.	
6,7-Dimethoxy-3-phenacyl-1,4-benzoxazin-2-one	1750 v.s.		1615 v.s.	
6,7-Methylenedioxy-2-phenomorpholone-3-acetic acid ethyl ester		1745 v.s.		3360 s.
6,7-Methylenedioxy-3-methyl-2-phenomorpholone		1748 v.s.		3340 s.
6,7-Methylenedioxy-3-phenyl-2-phenormorpholone		1757 v.s.		3350 s.
6,7-Dimethoxy-3-phenyl-2-phenormorpholone		1748 v.s.		3335 s.

PART II

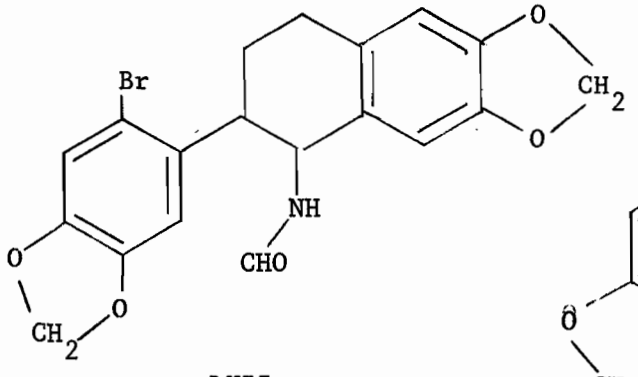
The 3,4-Methylenedioxyphenethylamine Skeletal System

The object of the second part of this investigation was the synthesis of a suitable phenethylamine system LX from which a 7,8-disubstituted-tetrahydroisoquinoline structure LXI might be obtained.

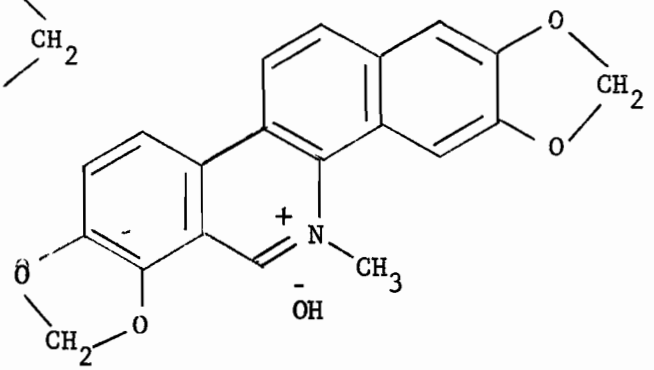


LX LXI

In the present work the synthesis of the 1-formamido-6,7-methylene-dioxy-2-(2-bromo-4,5-methylenedioxyphenyl)-1,2,3,4-tetrahydronaphthalene LXII possessing the desired phenethylamine structural system was adopted because of its relation to the alkaloid saquinarine LXIII.

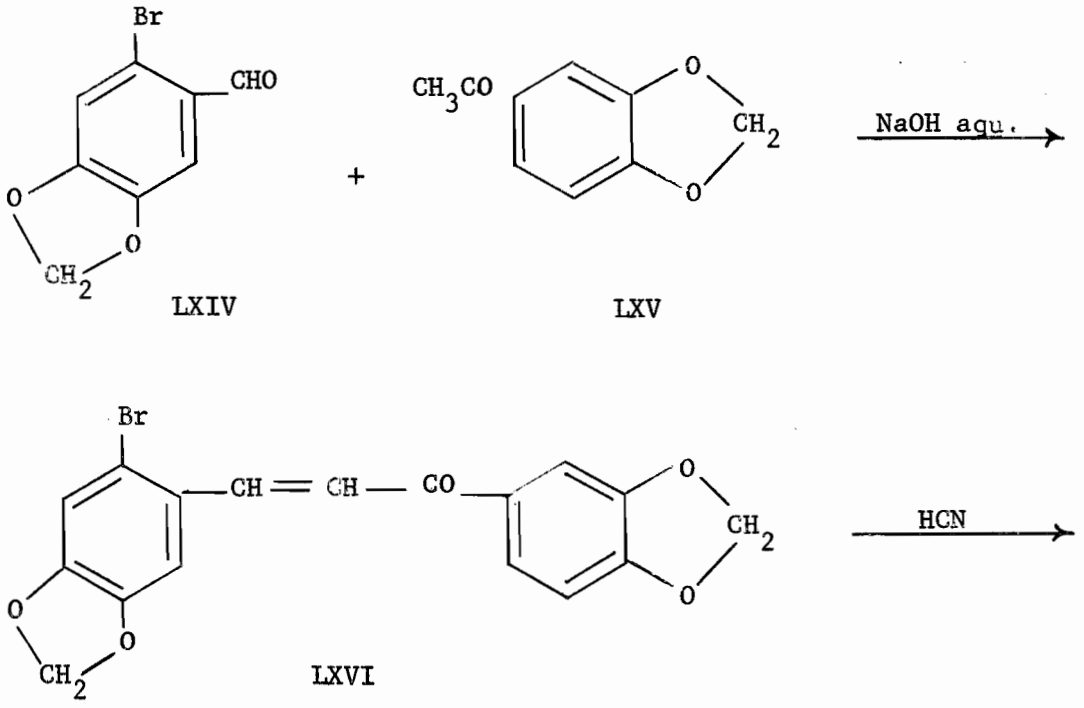


LXII



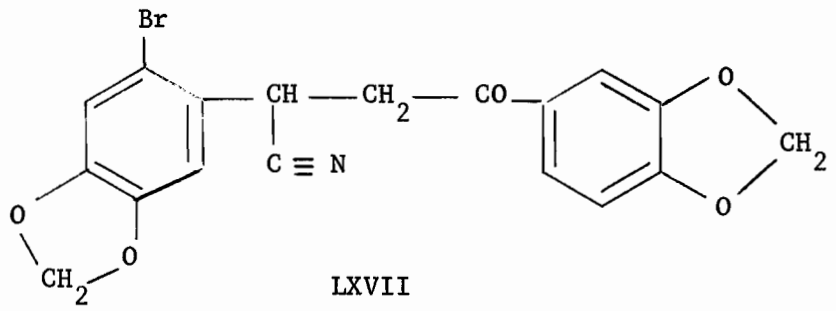
LXIII

Compound LXII was obtained by tracing the reaction scheme of Bailey and Robinson (97) for the preparation of 1-formamido-6,7-dimethoxy-2-(2-bromo-4,5-dimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene. Thus condensation of 6-bromopiperonal LXIV and acetopiperone LXV gave the chalcone LXVI and addition of hydrogen cyanide to the double bond resulted in the formation of the propionitrile LXVII. The nitrile was then hydrolysed by way of the amide LXVIII to the corresponding keto-acid LXIX which was reduced by Clemmensen's method to the derivative of butyric acid LXX. The latter on treatment with phosphorylchloride was cyclized to the tetralone derivative LXXI which in turn afforded the desired compound LXII by means of interaction with formamide.



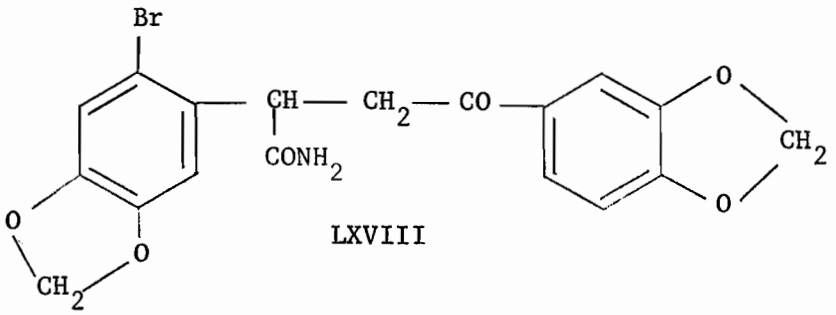
LXIV LXV

LXVI



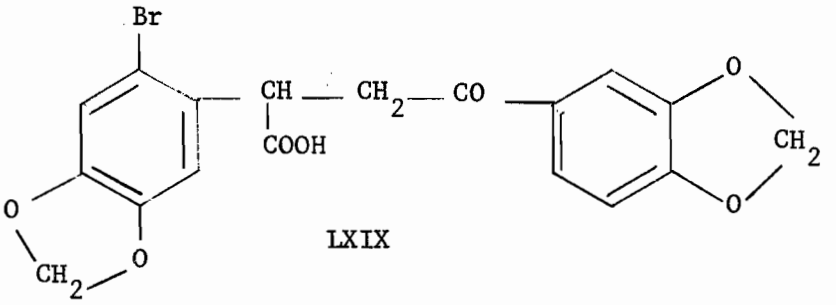
LXVII

$CH_3COOH + H_2SO_4$



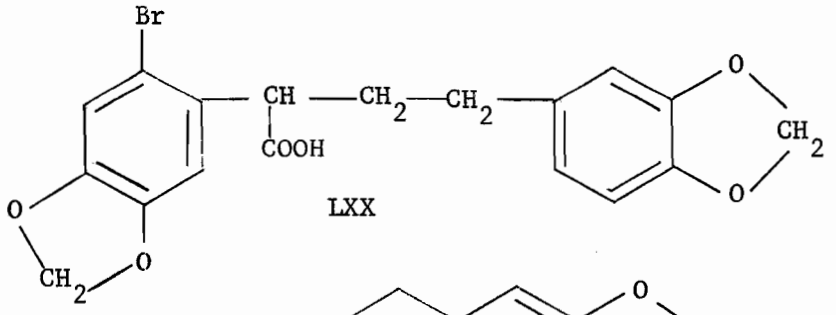
LXVIII

Ethanolic NaOH



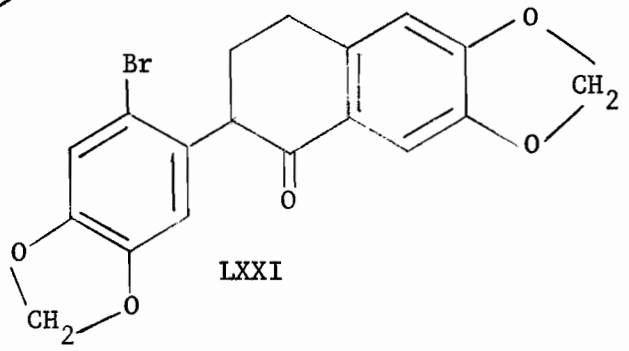
LXIX

Zn/HCl



LXX

$POCl_3$



LXXI

H_2NCHO

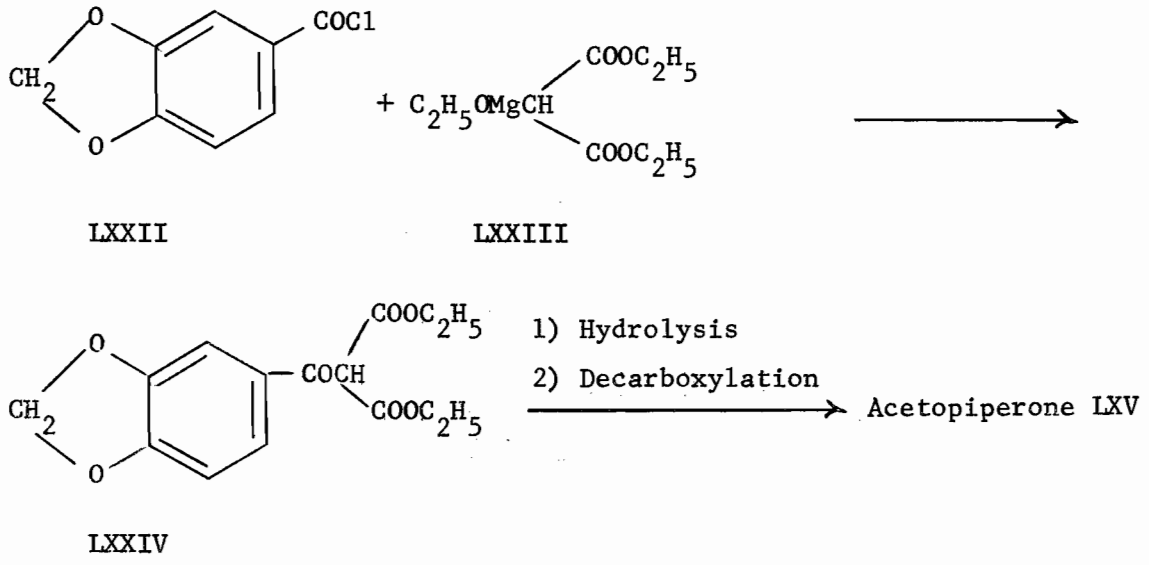
LXII

These compounds were prepared for the first time by the methods described below and have not been reported in the literature.

The two substances 6-bromopiperonal and acetopiperone chosen as starting materials for the synthesis of 1-formamido-6,7-methylenedioxy-2-(2-bromo-4,5-methylenedioxyphenyl)-1,2,3,4-tetrahydronaphthalene were not readily available, and their preparation was undertaken.

6-Bromopiperonal was conveniently prepared by following the procedure of Orr-Bleankly, Robinson and Williams (27). According to this procedure piperonal was dissolved in glacial acetic acid and gradually treated at room temperature with bromine dissolved in glacial acetic acid. From this reaction two products were isolated; 6-Bromopiperonal was the main product and 4,5-dibromocatecholmethylene ether the minor one.

Acetopiperone has been prepared by a variety of synthetic routes (119, 120, 121, 122) with varying results as regards yield and purity of product. The methods of Shriner and Kleiderer (119), Klages (120) and Mameli (121) were attempted with unsatisfactory results. The yields obtained were very low and the product difficult to purify. Finally the most satisfactory procedure was found to be that of Drake and Tuemmler (123). In this procedure condensation of 3,4-methylenedioxy-benzoyl chloride LXXII with ethoxymagnesiomalonate LXXIII gave the keto-diester LXXIV which on boiling in a mixture of acetic acid, water and sulphuric acid was converted to acetopiperone LXV.



LXXII LXXIII

LXXIV

3,4-Methylenedioxybenzoyl chloride was prepared according to the procedure of Drake and Tuemmler (123) by refluxing piperonylic acid with 1.7 molar equivalents of pure thionyl chloride; the yield was slightly lower than reported (93.8% as compared to 98.5%). Piperonylic-acid was obtained by following the method described in Organic Syntheses (124).

To prepare ethoxymagnesiomalonate the procedure of Walker and Hauser (125) was used. This compound was obtained by refluxing a mixture of magnesium turnings, absolute ethanol, absolute diethylether and carbon tetrachloride. The mixing of the reagents was carried out by following a certain procedure, and the product formed was not isolated, but was directly converted to the diester of the 3,4-methylene-dioxybenzoylmalonic acid as outlined by Drake and Tuemmler (123). The yield obtained was slightly higher than reported (79.5% as compared to 78%).

1. Condensation of Piperonal with Acetopiperone

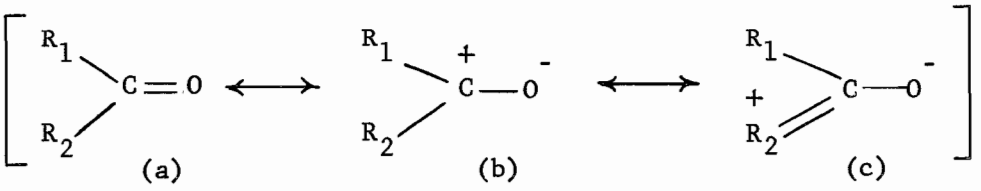
It is well-known that the reaction of an aromatic aldehyde and alkyl aryl ketone in the presence of aqueous alkali is a typical Claisen-Schmidt reaction which leads to the formation of α,β-unsaturated ketones. Thus, when an aqueous solution of sodium hydroxide was added to a boiling ethanolic solution of 6-bromopiperonal and acetopiperone, a pale yellow solid compound was separated which by analogy was formulated as 3,4-methylenedioxyphenyl 2-bromo-4,5-methylenedioxystryl ketone LXVI.

Kuhn, Lutz and Bauer (126) when determining the spectra of cis and trans benzalacetophenone in Nujol mull found, for each isomer, two bands in the region 1600-1700 cm^{-1}. The cis isomer showed bands at 1655 cm^{-1} (6.04 μ) and 1595 cm^{-1} (6.27 μ), the trans form at 1650 cm^{-1} (6.06 μ) and 1605 cm^{-1} (6.24 μ). The bands at 1655, 1650 cm^{-1} were attributed to the carbonyl absorptions and the bands at 1595, 1605 cm^{-1} to the ethylenic groups of the cis and trans isomers respectively.

In the carbonyl stretching region of the spectrum (KBr disk) of 3,4-methylenedioxyphenyl 2-bromo-4,5-methylenedioxystyryl ketone, a very strong peak at 1632 cm^{-1} with a definite shoulder at 1645 cm^{-1} was observed. The appearance of two carbonyl absorptions in the spectrum of LXVI is explicable only by assuming the presence of both geometric isomers (cis and trans). Further support for the cis and trans isomers was obtained from a consideration of the ethylenic stretching region. In the spectrum of LXVI two strong peaks were present at 1620 cm^{-1} and 1608 cm^{-1}. These were considered to be due to absorption

by the cis and trans ethylenic groups which reportedly, in benzalacetophenone, absorb at 1605 cm^{-1} and 1595 cm^{-1} respectively (126). Two medium peaks attributable to absorption by the cis and trans ethylenic groups were located at 996 cm^{-1} and 989 cm^{-1} in the spectra (126). Comparable bands at 993 cm^{-1} and 981 cm^{-1} in the spectrum of LXVI were likewise assigned. These conclusive infrared data suggest that the compound LXVI was prepared in a mixture of both (cis and trans) isomers.

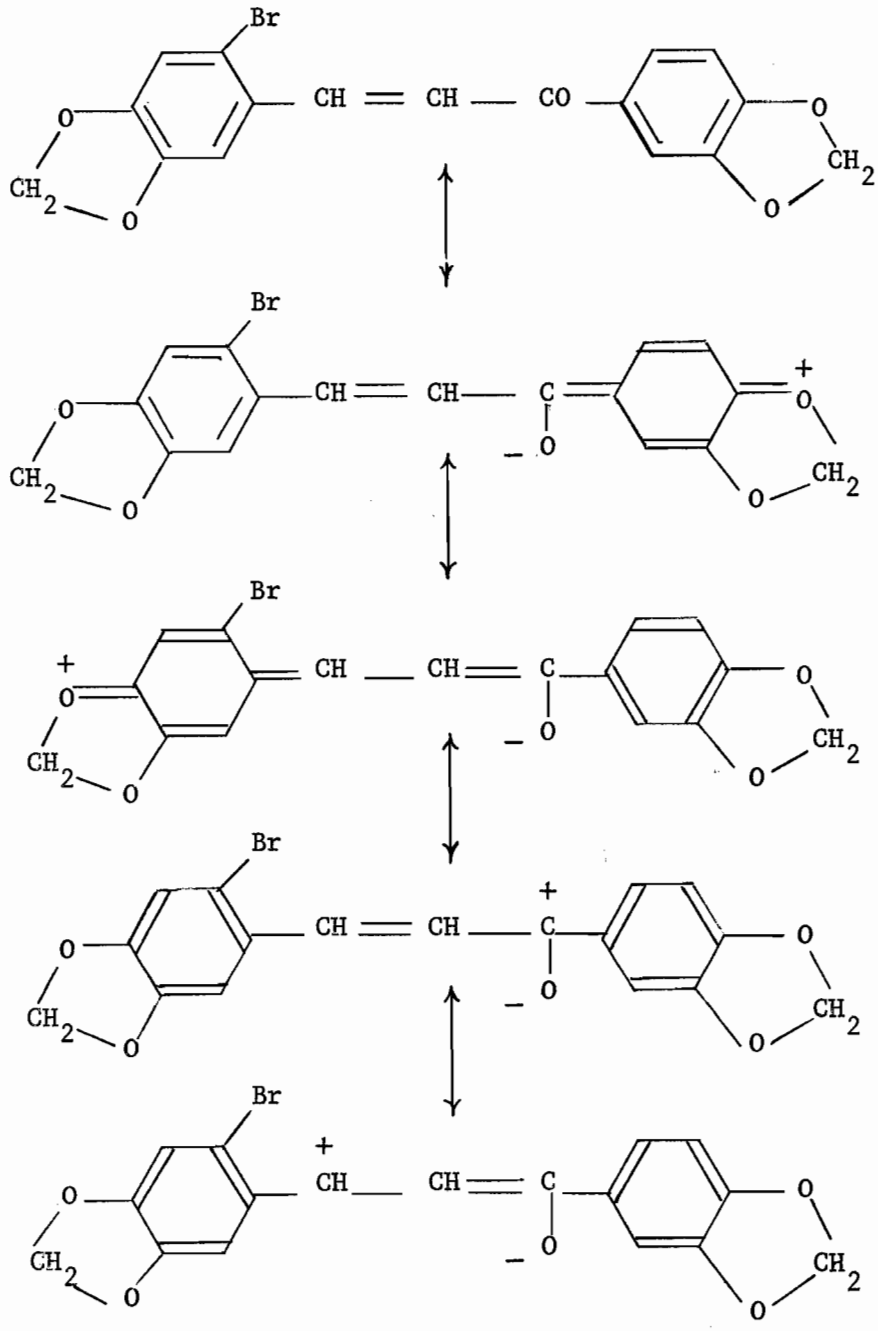
The carbonyl absorptions in the spectrum of LXVI were found to be much lower than those expected for a compound possessing the skeleton of a chalcone. Herbert and Kurth (127) established that the frequency of the carbonyl absorption in chalcones is much influenced by the phenyl substitution. In this connection Hartwell, Richards and Tompson (128) showed that the exact position of the carbonyl band is determined by the amount of single bond character possessed by the carbonyl bond. Thus in ketones (a) the double-bond character may be reduced whenever there is an increased opportunity for the contribution of the resonance structures (b) and (c). The participation of the resonance forms (b) and (c) in the resonance



hybrid depends on the electron-attracting or electron-repelling character of R_1 and R_2, and the greater the contribution of the ionic structures (b) and (c), the longer is the wave length at which the band will appear.

A consideration of the carbonyl compound LXVI, indicates it to be of the type which favors ionic structures similar to those assumed by Hartwell, Richards and Tompson (128), and a lowering in the carbonyl absorptions would

be normally expected. Therefore resonance structures such as LXXV, LXXVI, LXXVII, LXXVIII, may account for the shift in the carbonyl stretching band.



LXVI

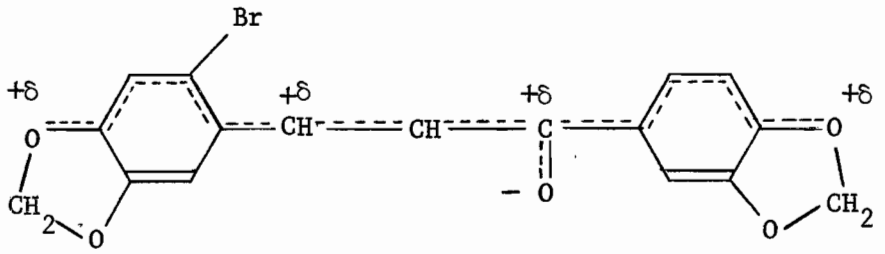
LXXV

LXXVI

LXXVII

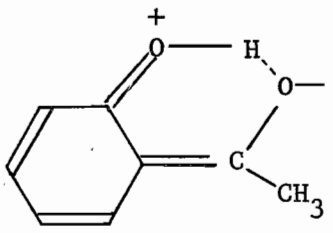
LXXVIII

According to the mesomeric theory, the resonance structures can be represented as in LXXIX.

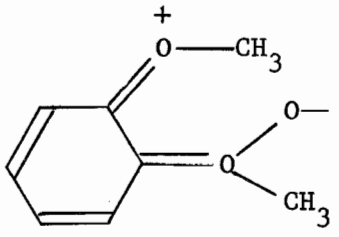


LXXIX

Further, Cordy (129) had noted that when a hydroxyl group is introduced ortho to the keto group in acetophenone, the carbonyl frequency is shifted from 1687 to 1635 cm^{-1}. This effect was attributed to hydrogen bonding between the hydroxyl group and the keto group. Rasmussen, Tunnicliff and Brattain (130) pointed out that the effect of hydrogen bonding on the C=O band is very small and the shift recorded by Gordy was due to the existence of a conjugated chelate system of the type as in LXXX. However Hergert and Kurth (127) found that methoxyacetophenone



LXXX

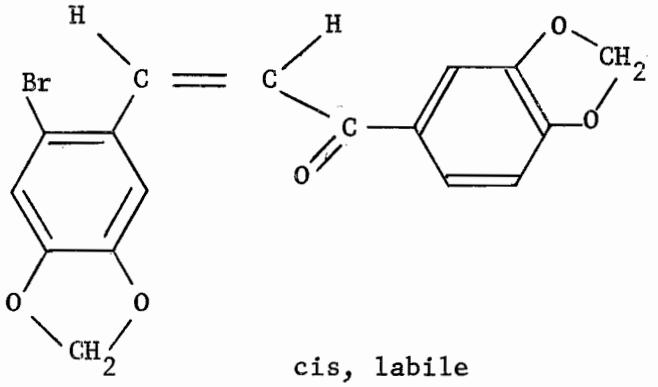


LXXXI

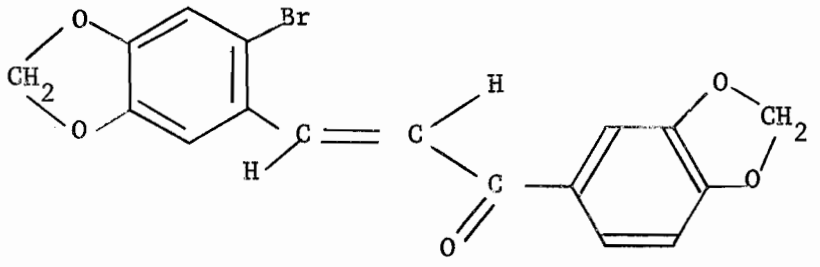
showed a band at 1649 cm^{-1} where obviously neither chelation nor hydrogen bonding was possible. They concluded therefore that the lowering in carbonyl frequency is due to the participation of resonance

forms of the type LXXX and LXXXI. This latter suggestion indicates that the shift of the carbonyl stretching frequency to lower wave lengths observed in the spectrum of LXVI, is mainly due to the participation of the resonance form LXXV.

Kuhn, Lutz and Bauer (126) in their spectroscopic studies of cis and trans benzalacetophenone, pointed out that the cis isomer, as would be expected from its structure, is the less stable, since the phenyl must overlap the carbonyl and cannot be coplanar with it. On these grounds the cis and trans formulations of the chalcone LXVI may be represented as follows.



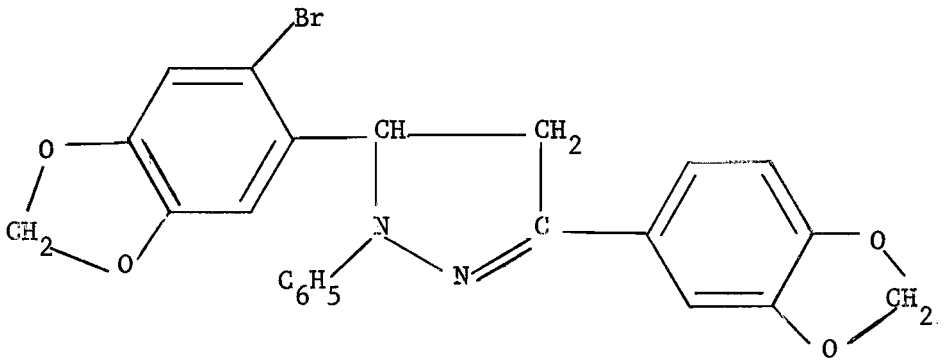
cis, labile



trans, stable

2. Reaction of 3,4-Methylenedioxyphenyl 2-Bromo-4,5-Methylenedioxystyryl ketone with phenylhydrazine

Attempts to prepare the phenylhydrazone of 3,4-methylenedioxyphenyl 2-bromo-4,5-methylenedioxystyryl ketone in the usual way, were unsuccessful. An adaptation of the procedure given by Richardson, Robinson and Seijo (96) for the preparation of the phenylhydrazone of 3,4-dimethoxyphenyl 3,4-dimethoxystyryl ketone, gave the pyrazoline LXXXII instead of the expected hydrazone.



LXXXII

The assigned structure LXXXII for the compound obtained, was supported by infrared data, and by the fact that the reaction of α,β-ethylenic carbonyl compounds with phenylhydrazine has been classified as a preparative method for pyrazolines (131). von Auwers and co-workers (132) studying this reaction, reached the conclusion that the pyrazoline is formed through the rearrangement of an unstable hydrazone and noted that in those cases where the latter can be isolated, its treatment with hot acetic acid may cause its rearrangement to the corresponding pyrazoline. Further, it has been found that the presence of

electron-releasing groups such as hydroxyl, alkoxyl and amino on either phenyl group of a chalcone makes the phenylhydrazone more labile and it can seldom be isolated, whereas electron withdrawing groups such as nitro and halogen stabilize the intermediate (133, 134, 135, 136).

3. Reaction of 3,4-Methylenedioxyphenyl 2-Bromo-4,5-Methylenedioxystyryl ketone with hydrocyanic acid.

Hydrocyanic acid does not readily react, in general with unsaturated hydrocarbons. The yields obtained are very low and high pressures and temperatures in the presence of metallic catalysts are necessary for the reaction to occur (137, 138, 139). The presence of a negative group in an unsaturated compound may affect the reactivity of the multiple bond to the point of rendering it capable of reaction with hydrocyanic acid. Thus hydrocyanic acid generated by the interaction of potassium cyanide and acetic acid, reacts with benzalacetophenone in alcoholic solution to form α-phenyl-β-benzoylpropionitrile (140, 141).

$$C_6H_5CH = CH \cdot CO \cdot C_6H_5 + HCN \longrightarrow C_6H_5CH(CN) \cdot CH_2CO \cdot C_6H_5$$

However, the addition of hydrocyanic acid to the double bond of alkoxy-substituted chalcones is relatively difficult to achieve as some workers have found (96, 97, 142).

Attempts to add hydrocyanic acid to the 3,4-methylenedioxyphenyl 2-bromo-4,5-methylenedioxystyryl ketone by an adaptation of the procedures given by Richardson, Robinson and Seijo (96), Bailey and Robinson (97) and in Organic Syntheses (143), were unsuccessful. Finally

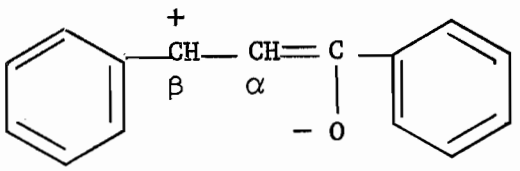
a procedure was developed according to which a methoxyethyleneglycol-tetrahydrofuran solution of the chalcone containing an equimolecular amount of glacial acetic acid was treated with an aqueous solution of sodium cyanide with gentle mechanical stirring and refluxing. After sodium cyanide had been added, the reaction mixture was allowed to stand for an additional hour on a hot (not boiling) water bath for the completion of the reaction.

A number of reactions of the chalcone with hydrocyanic acid were carried out in which the reaction time, and the amounts of methoxy-ethyleneglycol and tetrahydrofuran used as solvents, were varied. Eventually the conditions described in the experimental section were established as being optimum for the reaction, and the product β-(3,4-methylenedioxybenzoyl)-α-(2-bromo-4,5-methylenedioxyphenyl) propionitrile LXVII was obtained in an almost pure state as a white crystalline compound.

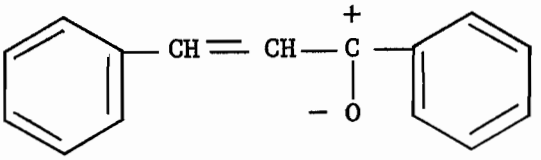
The difficulties encountered in the addition of hydrocyanic acid to the double bond of the alkoxysubstituted chalcones, are in contrast to the ease with which the addition proceeds in the case of the unsubstituted chalcone. These differences in reactivity are only explicable by assuming the mesomeric formulations LXXXV and LXXIX.

In benzalacetophenone, as its structure indicates, the most favoured resonance forms should obviously be LXXXIII and LXXXIV, whereas in 3,4-methylenedioxyphenyl 2-bromo-4,5-methylenedioxystyryl ketone the presence of the methylenedioxy groups fulfils the requirements for increased participation of more ionic resonance

structures among which the most important are those already assigned (LXXV, LXXVI, LXXVII, LXXVIII).

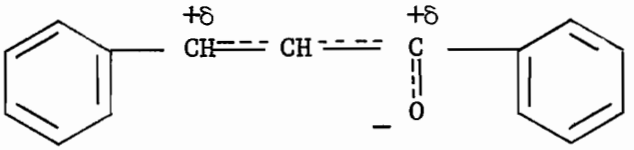


LXXXIII



LXXXIV

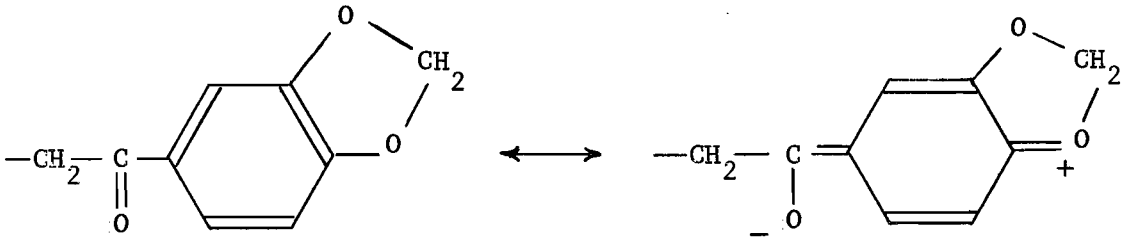
According to the mesomeric theory, the resonance structures LXXXIII and LXXXIV can be represented as in LXXXV.



LXXXV

A comparison between the mesomeric formulation LXXXV and LXXIX suggests that the β-carbon of the latter is rendered less positive than the equivalent atom of the former. It is clear now that such differences in electron density of the β-carbons of the compounds LXXIX and LXXXV should have considerable influence on the degree of their activation towards reagents capable of addition to double bonds. Thus the more positive the β-carbon the more easily the reaction can occur.

In the triple bond stretching region of the spectrum (KBr disk) of LXVII a very weak peak at 2260 cm^{-1} was observed. This frequency although high, has been recorded for some nitriles by Kitson and Griffith (144). They have also found that the intensity of C≡N band in various types of nitriles may vary from strong to undetectable. In general the band is strong in compounds containing C, H and N only, whereas the opposite effect is observed with nitriles containing oxygenated groups. The very strong band at 1670 cm^{-1} was assigned to the carbonyl absorption. This latter band was at a lower frequency (10 cm^{-1}) than the corresponding band of the unsubstituted aryl alkyl ketones. The lower frequency is explained in terms of the existence of the resonance structure LXXXVI (127).



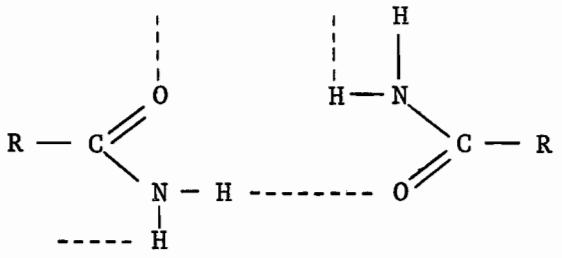
LXXXVI

4. β-(3,4-Methylenedioxybenzoyl)-α-(2-bromo-4,5-Methylenedioxyphenyl) Propionamide

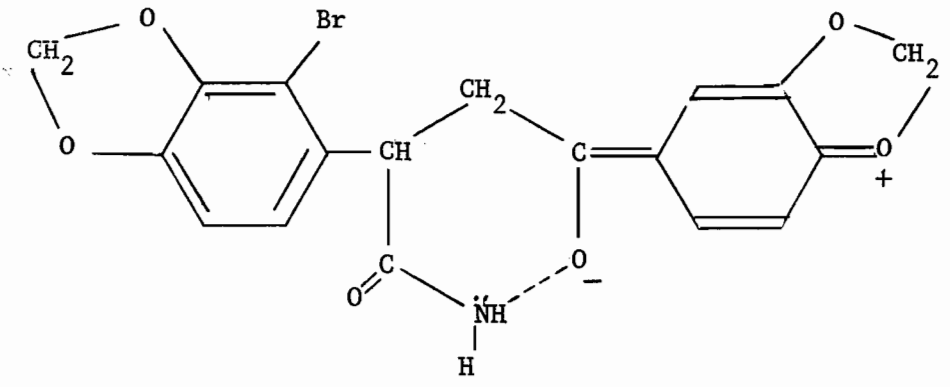
Treatment of an aliphatic nitrile with sulphuric acid diluted in a large volume of glacial acetic acid, results in the formation of the corresponding amide (97). By this procedure, β-(3,4-methylenedioxybenzoyl)-α-(2-bromo-4,5-methylenedioxyphenyl) propionamide LXVIII was

prepared in an almost quantitative yield.

It has been established that primary amides examined in solid state show strong bands at 3180 cm^{-1} and 3350 cm^{-1} (145). Richards and Thompson (146) attributed these frequencies as being due to two bonded N-H groups of a polymeric complex of the type shown below.



The polymeric association of primary amides in the solid state has been supported by x-ray measurements (147). Such a type of polymeric association seems to be less likely for the molecule of LXVIII which appears to satisfy all the requirements for the more stable intramolecular hydrogen bonding represented in LXXXVII.



LXXXVII

Of course the latter assumption of intramolecular association does not exclude the coexistence of any other type of dimeric or polymeric association. Such association appears likely from a consideration of the spectrum of LXVIII.

The infrared absorption spectrum (Kbr disk) of LXVIII exhibited a strong peak at 3480 cm^{-1}, a shoulder at 3380 cm^{-1}, a weak peak at 3305 cm^{-1} and another strong band at 3180 cm^{-1}. Only the latter frequency is in agreement with the reports in the literature. However Cleverley (148) in a detailed study of the free and bonded NH bands, reports that N-octanamide in chloroform has its free NH_2 absorptions at 3530 and 3415 cm^{-1}, but shows additional bands at 3498, 3345, 3300 and 3182 cm^{-1} which are plausibly interpreted as due to the simultaneous occurrence of different types of association. The complexity of the molecule of LXVIII appears to favour many different types of association, which apparently give rise to NH absorption frequencies comparable to those recorded by Cleverley. On these grounds the bands at 3480, 3380 and 3305 should also be attributed to N-H stretching frequencies.

In the carbonyl stretching range, a strong band at 1685 cm^{-1} and another very strong band at 1667 cm^{-1} were present. These two absorptions were due to the simultaneous presence of two carbonyl functions (amide and benzoyl-group) in the molecule of LXVIII and their differentiation was made as follows.

Richards and Thompson (146) studied the carbonyl frequency of primary amides in dioxan, and found for all of them an absorption close

to 1690 cm^{-1} in contrast to the 1650 cm^{-1} value found for the corresponding solids. This frequency has been denoted as the amide I absorption. The value 1650 cm^{-1} for primary solid amides has been substantiated by many workers (149). Only acetamide appears to absorb at 1694 cm^{-1} in the solid state and has been considered as an exceptional case. However the results of several workers (150) indicate that the amide I absorption is subjected to considerable alterations on change of state in which hydrogen bonding is broken and the carbonyl frequency of the amide group always absorbs at higher wave lengths than it does when it is hydrogen bonded. A consideration of these conclusions and of the formulation LXXXVII where the amide carbonyl is not involved in hydrogen bonding, indicates that the very strong band at 1685 cm^{-1} appearing in the spectrum (KBr disk) of LXVIII could reasonably be attributed to the amide I absorption.

The very strong absorption at 1667 cm^{-1} was assigned to the carbonyl function of the benzoyl group since similar absorption peaks are present in the spectra of the quite comparable compounds β-(3,4-methylenedioxybenzoyl)-α-(2-bromo-4,5-methylenedioxyphenyl) propionitrile LXVII and β-(3,4-methylenedioxybenzoyl)-α-(2-bromo-4,5-methylenedioxyphenyl) propionic acid. LXIX.

An additional strong band at 1613 cm^{-1} was present and was considered to be due to the amide II band. This band, attributed to NH_2 deformation frequencies is reported (146) to appear at slightly higher wave lengths, usually at 1620 cm^{-1}, but here also different types of association may be responsible.

5. β-(3,4-Methylenedioxybenzoyl)-α-(2-bromo-4,5-Methylenedioxyphenyl) Propionic Acid

This carboxylic acid was prepared by refluxing the corresponding amide in a mixture of ethanol and 10 per cent sodium hydroxide solution. The time required was about 20-24 hours and the reaction product was accompanied by considerable amounts of resinous materials. The yield in pure product was 58 per cent and is considered rather low for the type of the reaction. The low yield could be attributed to the extended refluxing of the compound under the alkaline conditions employed which are liable to produce some decomposition of the methylenedioxy group (9, 10). On the other hand the enolization of the carbonyl group of the benzoyl part of the molecule may be responsible for side reactions.

In the carbonyl stretching region of the spectrum (KBr disk) of LXIX a strong peak at 1713 cm^{-1} and another at 1670 cm^{-1} were observed. The band at 1713 cm^{-1} was readily assigned to the carboxylic acid carbonyl and the peak at 1670 cm^{-1} to the carbonyl absorption of the benzoyl group. The latter absorption occurred at the same frequency as the corresponding absorptions in the spectra of the comparable β-(3,4-methylenedioxybenzoyl)-α-(2-bromo-4,5-methylenedioxyphenyl) propionitrile LXVII and β-(3,4-methylenedioxybenzoyl)-α-(2-bromo-4,5-methylenedioxyphenyl) propionamide LXVIII.

An examination of the spectrum in the hydroxyl stretching region showed that the hydroxyl group is found completely in an associated form.

6. Clemmensen Reduction of β-(3,4-Methylenedioxybenzoyl)-α-(2-Bromo-4,5-Methylenedioxyphenyl) Propionic Acid LXIX to γ-(3,4-Methylenedioxyphenyl)-α-(2-Bromo-4,5-Methylenedioxyphenyl) Butyric Acid LXX

The carboxylic acid LXX was conveniently prepared by refluxing a mixture of β-(3,4-methylenedioxybenzoyl)-α-(2-bromo-4,5-methylenedioxyphenyl) propionic acid, toluene, water, hydrochloric acid, glacial acetic acid, and amalgamated zinc turnigs.

The reduction product was isolated as a highly viscous mass like a gel. This gel was exceedingly soluble in all common organic solvents and many attempts to obtain a solid compound were unsuccessful. Finally this uncrystallizable substance was dissolved in n-propylalcohol, and the solvent then removed under vacuum leaving a light brown amorphous solid. This brown solid, on crystallization from ethanol, afforded a white crystalline product in a high yield.

In the carbonyl stretching region in the spectrum (KBr disk) of LXX, only a single very strong peak at 1704 cm^{-1} was observed which was readily assigned to the carboxylic acid carbonyl group. The broad band at 3450 cm^{-1} was attributed solely to the presence of an associated hydroxyl group.

7. 1-Oxo-6,7-Methylenedioxy-2-(2-bromo-4,5-methylenedioxyphenyl)-1,2,3,4-Tetrahydronaphthalene LXXI

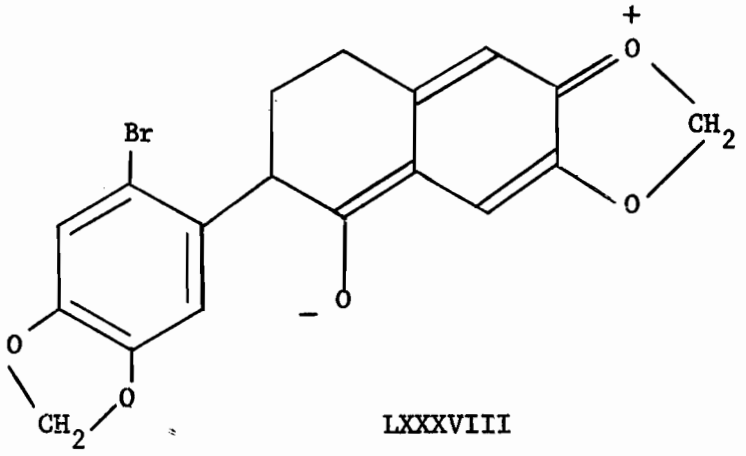
γ-(3,4-Methylenedioxyphenyl)-α-(2-bromo-4,5-methylenedioxyphenyl) butyric acid LXX was cyclized to 1-oxo-6,7-methylenedioxy-2-(2-bromo-4,5-methylenedioxyphenyl)-1,2,3,4-tetrahydronaphthalene LXXI by means of phosphoryl chloride. This procedure had been previously applied by

Robinson and Co-workers (97) for the cyclization of the γ-(3,4-Dimethoxyphenyl)-α-(2-bromo-4,5-dimethoxyphenyl) butyric acid to the 1-oxo-6,7-dimethoxy-2-(2-bromo-4,5-dimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene.

The cyclization product LXXI obtained was accompanied by considerable amounts of resinous materials, which caused difficulty in purification owing to failure to find any satisfactory solvent or mixture of solvents. Finally its purification was achieved after several recrystallizations from ethyl acetate. The yield of pure product obtained was 74 per cent and should be higher if the purification of the crude reaction product was less troublesome. The formulation of the compound as represented in LXXI was based on analogy (97). This substance on melting shows abnormal behavior; the most carefully purified material melts partly at 165-167°, resolidifies, and remelts again at 184-185°.

The compound LXXI being an α-tetralone derivative would be expected to show carbonyl absorption in the infrared near to 1703 cm^{-1} as the parent compound α-tetralone does (151). Instead, a very strong band at 1665 cm^{-1} was observed. This noticeable lowering in the carbonyl frequency is not surprising in view of the fact that all previously discussed compounds which possessed the methylenedioxybenzoyl function in their molecule showed their carbonyl absorptions in the narrow range of 1667-1670 cm^{-1}. This shift of the carbonyl absorption to lower wave lengths, indicates that the carbon-oxygen bond acquires a greater single bond character and consequently the resonance form

LXXXVIII should make a large contribution to the ground state of the molecule.



LXXXVIII

8. 1-Formamido-6,7-Methylenedioxy-2-(2-Bromo-4,5-Methylenedioxyphenyl)-1,2,3,4-Tetrahydronaphthalene LXII

Bailey and Robinson (97) applying the Leuckart reaction succeeded in obtaining in a good yield the 1-formamido-6,7-dimethoxy-2-(2-bromo-4,5-dimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene, by heating a mixture of 1-oxo-6,7-dimethoxy-2-(2-bromo-4,5-dimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene, formamide and ammonium sulphate. Attempts to apply this procedure to the preparation of the analogous 1-formamido-6,7-methylenedioxy-2-(2-bromo-4,5-methylenedioxyphenyl)-1,2,3,4-tetrahydronaphthalene LXII led to resinous materials. Very great difficulty was experienced in the preparation of this formamido compound, and many different procedures were tried. In the Leuckart reaction the usual catalysts such as ammonium formate, magnesium chloride and ammonium sulphate were applied without success. Crossley and Moore (152)

in a study concerning the factors affecting the Leuckart reaction, found that the addition of formic acid in the reaction of a ketone with formamide, decreases considerably the formation of resinous materials in favour of the expected product. Following these suggestions, a mixture of 1-oxo-6,7-methylenedioxy-2-(2-bromo-4,5-methylenedioxyphenyl)-1,2,3,4-tetrahydronaphthalene, formamide and formic acid was heated at 175-180^{o} for four hours. From this reaction mixture a colourless crystalline compound was obtained in a very low yield. By analogy (97) it was formulated as 1-formamido-6,7-methylenedioxy-2-(2-bromo-4,5-methylenedioxyphenyl)-1,2,3,4-tetrahydronaphthalene LXII.

The infrared spectrum (KBr disk) of this compound was quite unusual in so far as two absorption bands in the NH stretching region were present and no comparable example was found in the literature. These two absorption bands occurred at 3450 cm^{-1} and 3245 cm^{-1} and both were of medium intensity.

Ordinarily the NH frequency of secondary amides in the solid state shows only one band near to 3270 cm^{-1} and occasionally a second one of low intensity at 3080 cm^{-1} (153, 154). Absorption frequencies at higher wave length, usually between 3460-3420 cm^{-1} are only observed in very diluted solutions of secondary amides. Formanilide in very diluted solutions has been reported to absorb at 3408 and 3434 cm^{-1} (155) and the only correlation which should be found with the spectrum of the compound LXII, is the double absorption in the NH stretching region. However, in the solid state, in some cases, especially with complex molecules, the absorption frequency is determined largely by

the type of hydrogen bonding involved, and two or more absorptions can be found (156). On these grounds the bands at 3450 and 3245 cm^{-1} were attributed to the NH stretching frequencies.

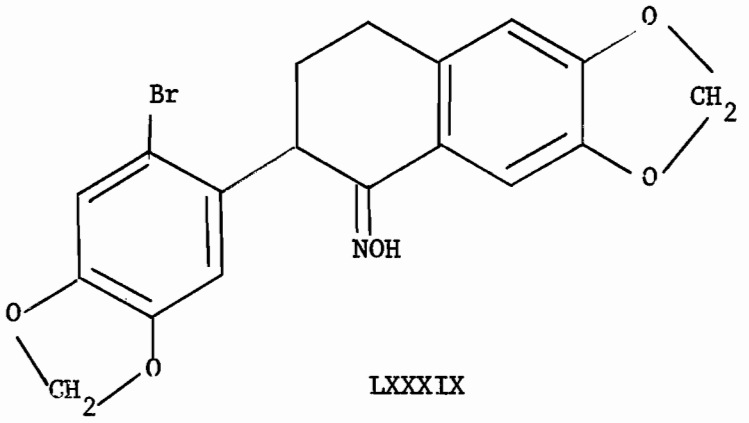
In the region from 1677 to 1549 three absorptions appeared. There was a definite shoulder at 1677 cm^{-1}, then a very strong band at 1658 cm^{-1}, and another of medium intensity at 1549 cm^{-1}. The bands at 1658 and 1549 cm^{-1} were readily assigned to the amide bands I and II respectively (153). The absorption at 1677 cm^{-1} is not well understood, and a reasonable explanation is hard to find.

9. 1-Oximino-6,7-Methylenedioxy-2-(2-Bromo-4,5-Methylenedioxyphenyl)-1,2,3,4-Tetrahydronaphthalene

Since the yields of LXII obtained by means of the Leuckart reaction were considered as insufficient to afford the necessary amount to permit further experimentation, an alternative route for preparing the compound was sought. Obviously such a route was the preparation of the 1-oximino-6,7-methylenedioxy-2-(2-bromo-4,5-methylenedioxyphenyl)-1,2,3,4-tetrahydronaphthalene LXXXIX from which, on reduction with $LiAlH_4$, it was hoped to obtain the corresponding amino compound. Interaction of the latter with formic acid could then easily result in the desired formamido derivative LXII.

The oximino compound LXXXIX was obtained in a high yield by adapting the pyridine method of oximation (157).

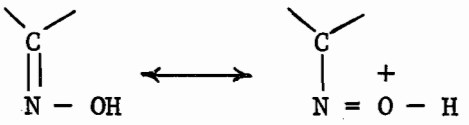
Infrared spectrum (KBr disk) of this oxime showed a medium structureless broad band between 3220 and 3290 cm^{-1}. This band could be assigned to the OH stretching mode of the oxime group, in agreement



LXXXIX

with the findings of Brown (158) who reported that aliphatic ketoximes absorb near to 3300 cm^{-1}. The position and the broadness of the band indicated the presence of the oximino-compound in an associated form through hydrogen bonding.

The weak band at 1623 cm^{-1} was considered to be due to the C=N stretching vibration. The low intensity of the band is explained in terms of the existence of the resonance structures XC and XCI. The



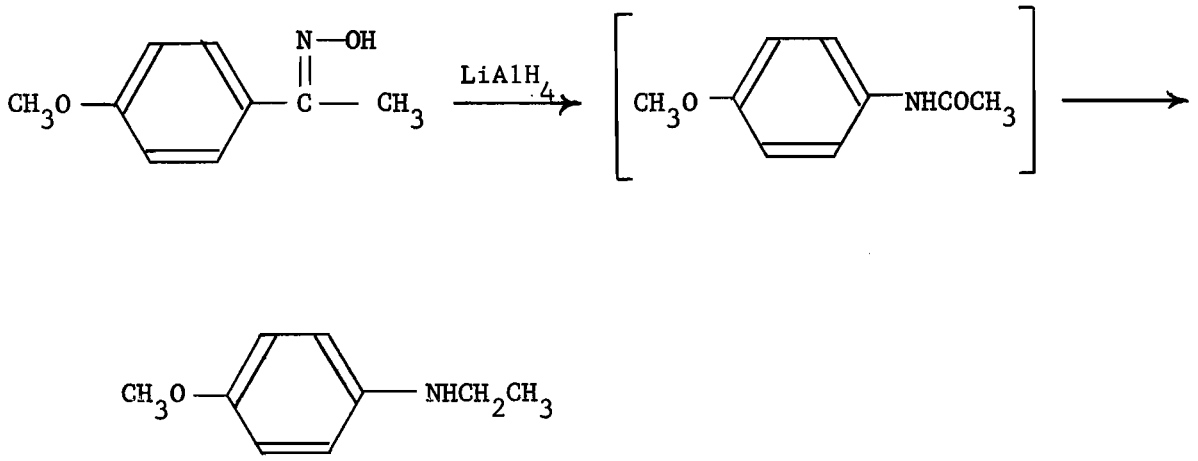
XC XCI

structure XCI reduces the double bond character of the C-N bond, and as a consequence, the absorption peak of the C=N is weakened (159). The medium intensity band at 948 cm^{-1} was assigned to the N-O vibration (158).

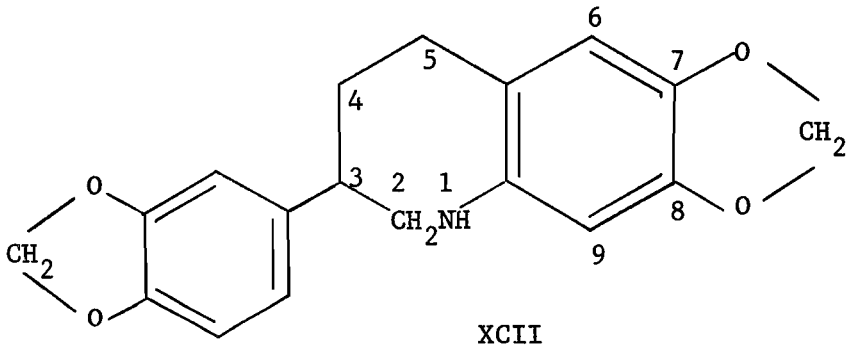
10. Treatment of 1-Oximino-6,7-Methylenedioxy-2-(2-Bromo-4,5-Methylenedioxyphenyl)-1,2,3,4-tetrahydronaphthalene with Lithium Aluminum Hydride in Dioxan.

In attempting to obtain 1-amino-6,7-methylenedioxy-2-(2-bromo-4,5-methylenedioxyphenyl)-1,2,3,4-tetrahydronaphthalene by reduction of the corresponding oxime with $LiAlH_4$ in dioxan, it was found surprisingly enough, that the product was not the anticipated one, but a debrominated compound for which analytical results and molecular weight determination were consistent with the molecular formula $C_{18}H_{17}N_1O_4$. The infrared spectrum of this compound showed in the N-H stretching region only one absorption which was sharp and of medium intensity. This absorption peak appeared at 3410 cm^{-1} and could be assigned to the N-H stretching vibration of a secondary amino group. This abnormal formation of a secondary amino group can be correlated with the findings of some Workers (160, 161). They found that secondary arylalkylamines were obtained by refluxing ether solutions of $LiAlH_4$ and certain substituted acetophenone oximes. Such anomalous formation of secondary amines has been interpreted as involving a Beckmann rearrangement before the reduction of the oximino group occurs. Lyle and Troscianiec (160) found that this rearrangement is greatly facilitated by the presence of electron releasing groups in the para-position of the acetophenone. The highest yields of secondary amines were obtained when the para-substituent in acetophenone-oxime was the methoxy group.

Since the molecule LXXXIX contains all the requirements for a Bechmann rearrangement comparable to that of p-methoxy-acetophenone



oxime, the compound $C_{18}H_{17}N_1O_4$ might be formulated as in XCII

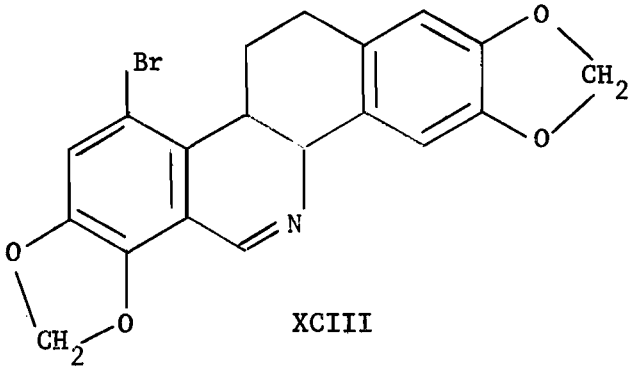


XCII

Support for the position of the secondary amino group in the molecule of XCII was also obtained from the results of Russell and Thompson (155), who have examined both the intensity and frequency of N-H stretching absorption of the secondary amino group in a wide range of compounds. They found that in aliphatic secondary amines the frequency falls in the range 3310-3350 cm^{-1} with low intensity.

In alkylarylamines the frequency rises and can be found in the range of 3422-3450 cm^{-1} and the intensity increases by a factor of 50. Consequently, the latter findings suggest that the band at 3410 cm^{-1} in the spectrum of $C_{18}H_{17}NO_4$ is due to a secondary amino group directly attached to a benzene ring. Furthermore, Witkop and Patric (162) have quoted a band at 1613 cm^{-1} (6.2 μ) as being typical of the structural element C_6H_5-NH-C< where C does not have a double bond. A similar band at 1612 cm^{-1} in the spectrum of the compound $C_{18}H_{17}NO_4$ could be also assigned. This last suggestion is also support for the formulation of $C_{18}H_{17}NO_4$ as represented in XCII. The nomenclature for this compound in accordance with the Ring Index by Patterson, Capell and Walker (57) is as follows: 7,8-Methylenedioxy-3-(3,4-methylenedioxyphenyl)-2,3,4,5-tetrahydro-1H-1-benzazepine.

11. Attempted Cyclodehydration of 1-Formamido-6,7-Methylenedioxy-2-(2-Bromo-4,5-Methylenedioxyphenyl)-1,2,3,4-Tetrahydronaphthalene LXII to a 7,8-Methylenedioxyisoquinoline Derivative XCIII



XCIII

1-Formamido-6,7-methylenedioxy-2-(2-bromo-4,5-methylenedioxy-phenyl)-1,2,3,4-tetrahydronaphthalene LXII the key compound to obtaining XCIII, was only available in minute amounts. This fact inhibited experimentation attempts under a variety of reaction conditions and cyclization agents by means of which the structure XCIII was hoped to be obtained. Accomplishment of a single experiment by using polyphosphoric acid as cyclodehydration agent led to an unidentifiable brownish waxy material, and there was no evidence to indicate that the desired product XCIII had been formed.

TABLE 5

Infrared Absorption Maxima of

3,4-Methylenedioxy-6-aminophenol hydrochloride

3,4-Methylenedioxy-6-hydroxyacetanilide

6,7-Methylenedioxy-1,4-benzoxazin-2-one-3-acetic acetic acid ethyl ester

6,7-Methylenedioxy-3-methyl-1,4-benzoxazin-2-one

Positions of Absorption Maxima (cm^{-1}) in the Infrared Spectra of

3,4-Methylenedioxy-6-aminophenol hydrochloride	3,4-Methylenedioxy-6-hydroxy-acetanilide	6,7-Methylenedioxy-1,4-benzoxazin-2-one-3-acetic acid ethyl ester	6,7-Methylenedioxy-3-methyl-1,4-benzo-xazin-2-one
3540 m. (sh.)	3270 s.	2925 v.w.	3105 v.w.
3450 m.	3090 s.	1755 s.	3060 m.
3160 m. (br.)	2920 m. (sh.)	1660 m. (sh.)	2925 w.
2995 s. (sh.)	1648 m. (sh.)	1632 s.	1723 v.s.
2940 v.s.	1635 s.	1515 s.	1633 m.
2700 v.w. (br.)	1607 v.s. (br.)	1498 s.	1565 m.
2620 m.	1565 v.s.	1440 v.w. (br.)	1501 s.
2560 v.w. (sh.)	1515 v.s.	1416 w.	1480 v.s.
1662 w.	1457 s.	1401 v.w.	1460 s.
1628 w.	1435 v.s.	1371 w.	1415 m.
1595 m.	1388 s.	1300 s.	1403 w.
1507 v.s.	1350 s.	1256 v.s.	1380 s.
1494 w.	1305 m.	1220 v.w.	1300 s.
1464 s.	1257 s.	1186 w.	1283 s.
1435 w. (br.)	1222 s.	1170 m.	1260 v.s.
1340 w.	1180 v.s.	1135 m.	1242 m.
1298 m.	1124 w.	1047 m.	1228 m.
1195 v.s.	1087 w.	1032 m.	1163 v.s.
1168 m.	1041 s.	945 w.	1120 s.
1030 v.w.	1013 m.	932 m.	1085 v.w.
1022 v.w.	970 m.	885 v.w.	1037 v.s.
1073 w.	932 s.	847 m.	1001 m.
1043 m.	880 m.	835 v.w.	936 s.
937 s.	857 s.	822 w.	905 m.
869 s.	840 m. (sh.)	766 m.	892 s.
857 w.	832 s.	740 v.w.	857 m.
	803 w.	710 v.w.	827 m.
	774 m.	683 m.	807 v.w.
	752 w.		795 v.w.
	720 w.		765 m.
	708 w.		732 v.w.
			724 v.w.
			687 v.w.

TABLE 6

Infrared Absorption Maxima of

6,7-Methylenedioxy-3-phenyl-1,4-benzoxazin-2-one

6,7-Methylenedioxy-3-acetonyl-1,4-benzoxazin-2-one

6,7-Methylenedioxy-3-phenacyl-1,4-benzoxazin-2-one

3,4-Dimethoxy-6-nitrophenyl acetate

Positions of Absorption Maxima (cm^{-1}) in the Infrared Spectra of

6,7-Methylenedioxy-3-phenyl-1,4-benzoxazin-2-one	6,7-Methylenedioxy-3-acetonyl-1,4-benzoxazin-2-one	6,7Methylenedioxy-3-phenacyl-1,4-benzoxazin-2-one	3,4-Dimethoxy-6-nitrophenyl acetate
3075 v.w.	3075 v.w.	2918 v.w.	3096 w.
3030 v.w.	2925 v.w.	1742 v.s.	2996 w.
2930 w.	1743 v.s.	1642 m.	2950 m.
1740 v.s.	1645 m. (sh.)	1617 v.s.	2850 w.
1632 s.	1632 v.s.	1600 v.w.	1768 v.s.
1600 v.w.	1585 v.s.	1593 m.	1613 m.
1582 v.w.	1505 m.	1552 m.	1596 s.
1510 m. (sh.)	1490 v.s.	1510 m.	1525 v.w.
1502 s.	1447 w.	1490 s.	1468 m.
1478 v.s.	1410 w.	1451 m.	1450 m.
1459 s.	1358 w.	1415 m.	1407 v.w.
1420 m.	1327 s.	1402 w.	1370 s.
1404 m.	1291 s.	1330 s. (sh.)	1338 v.s.
1320 v.w.	1253 v.s.	1323 s.	1277 v.s.
1305 v.w.	1235 s.	1310 m.	1254 m.
1278 v.s.	1210 w. (sh.)	1293 m.	1232 s.
1236 m.	1181 m.	1253 v.s.	1210 v.s.
1184 v.s.	1165 s.	1195 s.	1195 v.s.
1162 v.w.	1033 s.	1182 s.	1172 s.
1125 m.	995 v.w.	1162 s.	1157 m. (sh.)
1082 w.	932 m.	1070 v.w.	1082 s.
1035 v.s.	870 m.	1054 w.	1038 w.
1005 w.	832 w.	1033 s.	1013 m.
980 s.	812 v.w.	1004 v.w.	995 m.
883 w.	775 w.	944 v.w.	910 s.
864 s.	740 m.	928 m.	883 s.
825 w.	730 m.	873 v.w.	869 w.
800 s.		855 m.	838 w.
755 w.		820 v.w.	800 s.
735 w.		825 w.	770 w.
721 v.w.		764 v.w.	755 w.
693 w.		745 w.	682 v.w.
683 m.		735 s.	664 m.
		720 v.w.	

TABLE 7

Infrared Absorption Maxima of

3,4-Dimethoxy-6-hydroxyacetanilide

6,7-Dimethoxy-1,4-benzoxazin-2-one-3-acetic acid ethyl ester

6,7-Dimethoxy-3-methyl-1,4-benzoxazin-2-one

6,7-Dimethoxy-3-phenyl-1,4-benzoxazin-2-one

Positions of Absorption Maxima (cm^{-1}) in the Infrared of

3,4-Dimethoxy-6-hydroxyacetanilide	6,7-Dimethoxy-1,4-benzoxazin-2-one-3-acetic acid ethyl ester	6,7-Dimethoxy-3-methyl-1,4-benzoxazin-2-one	6,7-Dimethoxy-3-phenyl-1,4-benzoxazin-2-one
3365 v.w.	3090 v.w.	3075 w.	3080 v.w.
3145 w. (br.)	3000 w.	3010 v.w.	3035 v.w.
3025 v.w.	2935 v.w.	2920 v.w.	2938 v.w.
1648 s.	1732 v.w.	2935 v.w.	2835 v.w.
1630 m. (sh.)	1623 m.	1750 v.s.	1724 v.s.
1609 s.	1603 v.w.(sh.)	1685 v.w.	1685 v.w.
1555 v.s.	1563 s.	1623 s.	1617 s.
1538 v.s.	1545 v.w.	1565 s.	1598 m.
1520 m. (sh.)	1510 s.	1508 s.	1578 w.
1475 s.	1468 s.	1470 m.	1535 w.
1451 s.	1453 w.	1453 s.	1513 v.s.
1438 m. (sh.)	1427 w.	1422 m.	1497 w. (sh.)
1418 v.s.	1415 w.	1385 m. (sh.)	1465 s.
1385 m.	1385 m.	1375 s.	1446 s.
1357 s.	1376 m.	1300 s.	1423 w.
1299 m.	1340 s.	1266 s.	1390 s.
1265 s.	1309 s.	1252 s.	1323 w. (sh.)
1237 w.	1274 s.	1212 m.	1305 m.
1213 v.s.	1250 s.	1203 s.	1290 s.
1206 v.s.	1223 m.	1180 w.	1280 v.s.
1197 m. (sh.)	1209 s.	1152 s.	1252 s.
1181 m.	1185 m.	1166 w.	1218 s.
1158 v.w.	1170 m.	1096 w.	1205 s.
1127 m.	1160 m.	1035 w.	1186 m.
1046 w. (sh.)	1152 m.	1020 s.	1159 s.
1035 s.	1111 v.w.	980 s.	1105 w.
1021 m.	1091 m.	914 m.	1075 w.
996 s.	1033 m.	874 s.	1036 w.
971 w.	1007 v.s.	845 m.	1013 s.
885 m.	968 w.	823 w.	1005 m.
875 m.	938 v.w.	772 m.	985 s.
832 s.	907 w.	760 m.	930 v.w.
760 m.	865 s.	697 w.	902 w.
	855 w.		851 s.
	812 v.w.(sh.)		845 m. (sh.)
	802 w.		818 v.w.
	773 w.		800 s.
			765 w.
			751 w.
			702 w.
			685 m.

TABLE 8

Infrared Absorption Maxima of

6,7-Dimethoxy-3-acetonyl-1,4-benzoxazin-2-one

6,7-Dimethoxy-3-phenacyl-1,4-benzoxazin-2-one

6,7-Methylenedioxy-2-phenomorpholone-3-acetic acid ethyl ester

6,7-Methylenedioxy-3-methyl-2-phenomorpholone

Positions of Absorption Maxima (cm^{-1}) in the Infrared Spectra of

6,7-Dimethoxy-3-acetonyl-1,4-benzoxazin-2-one	6,7-Dimethoxy-3-phenacyl-1,4-benzoxazin-2-one	6,7-Methylenedioxy-2-phenomorpholone-3-acetic acid ethyl ester	6,7-Methylenedioxy-3-methyl-2-phenomorpholone
2975 v.w.	3070 v.w.	3460 v.w.	3340 s.
2840 v.w.	2935 w.	3360 s.	3078 w.
1742 v.s.	2840 v.w.	3090 w.	3000 w.
1627 v.s.	1750 v.s.	2905 w.	2950 v.w.
1593 s. (br.)	1700 v.w.	2820 w. (sh.)	2890 w.
1580 s. (br.)	1615 v.s.	1745 v.s. (sh.)	2850 v.w.
1518 v.s.	1600 m. (sh.)	1730 v.s.	2788 v.w.
1468 s.	1590 s.	1655 v.w.	1748 v.s.
1448 s.	1545 m.	1630 v.w.	1650 v.w.
1420 m.	1523 s.	1514 v.s.	1506 s.
1380 s.	1510 m. (sh.)	1495 s.	1492 s.
1363 m. (sh.)	1495 v.w. (sh.)	1480 w. (sh.)	1458 w.
1326 s.	1471 m.	1457 v.w.	1402 v.w.
1292 s.	1455 m.	1432 v.w.	1378 m.
1252 v.s.	1420 m.	1413 m.	1333 m.
1200 s.	1375 s.	1398 v.w.	1315 s.
1185 w.	1325 s.	1378 s.	1280 m.
1175 w.	1292 s.	1335 s.	1228 v.s.
1152 m.	1270 m. (sh.)	1302 s.	1193 v.s.
1110 m.	1255 v.s.	1268 s.	1166 v.s.
1035 w.	1240 m. (sh.)	1238 s.	1150 m. (sh.)
1010 s.	1220 v.w.	1203 s.	1107 w.
995 sh.	1202 s.	1180 v.s.	1083 v.w.
935 m.	1184 m.	1165 v.s.	1038 v.s.
913 sh.	1155 m.	1030 v.w.	961 w.
842 s.	1118 w.	1060 v.w.	935 s.
815 w.	1060 m.	1038 s.	900 m.
795 w.	1026 m.	1030 s.	856 s.
772 w.	1003 s.	955 v.w.	835 m.
747 s.	950 w.	935 s.	774 w.
	874 v.w.	915 v.w.	728 m.
	837 m.	869 m.	718 w.
	825 v.w.	850 s.	678 m.
	813 v.w. (sh.)	823 w.	
	783 w.	786 w.	
	743 s.	733 w.	
	700 w.	715 v.w.	
		700 w.	

TABLE 9

Infrared Absorption Maxima of

6,7-Methylenedioxy-3-phenyl-2-phenomorpholone

6,7-Dimethoxy-3-phenyl-2-phenomorpholone

3,4-Methylenedioxyphenyl-2-bromo-4,5-methylenedioxystyryl ketone

2-Phenyl-3-(2-bromo-4,5-methylenedioxyphenyl)-5-(3,4-methylene-dioxyphenyl)pyrazoline

Positions of Absorption Maxima (cm^{-1}) in the Infrared Spectra of

6,7-Methylenedioxy-3-phenyl-2-phenomorpholone	6,7-Dimethoxy-3-phenyl-2-phenomorpholone	3,4-Methylenedioxyphenyl-2-bromo-4,5-methylenedioxy styryl ketone	2-Phenyl-3-(2-bromo-4,5-methylenedioxy)-5-(3,4-methylenedioxyphenyl)pyrazoline
3350 s.	3335 s.	2930 w.	2900 w.
3080 w.	3080 v.w.	1645 m. (sh.)	1603 v.s.
3050 w.	3020 w.	1632 v.s.	1567 w.
3000 v.w.	2955 w.	1620 m.	1507 v.s.
2915 w.	2910 m. (sh.)	1608 m.	1485 v.s.
2950 v.w.	2845 w.	1603 m. (sh.)	1460 v.s.
2790 v.w.	1748 v.s.	1507 v.s.	1414 w.
1757 v.s.	1642 w.	1482 v.s.	1492 m.
1680 v.w.	1608 v.w.	1443 s.	1355 w.
1650 v.w.	1523 v.s.	1418 s.	1320 m.
1615 v.w	1505 m. (sh.)	1353 w.	1185 v.w.
1595 v.w.	1472 m.	1293 s.	1145 v.w.
1552 v.w. (sh.)	1460 w.	1268 v.s. (sh.)	1130 w.
1518 s.	1450 m.	1260 v.s.	1108 m.
1510 s.	1403 m.	1240 s. (sh.)	1077 w.
1498 s.	1315 s.	1208 w. (sh.)	1042 v.s.
1460 m.	1306 s.	1170 w.	1005 w.
1427 w.	1296 m.	1127 m.	986 v.w.
1400 w.	1245 v.s.	1116 m.	940 m.
1300 s.	1213 v.s.	1042 v.s.	908 v.w.
1288 s.	1190 v.s.	993 m.	878 w.
1276 m.	1140 s.	981 m.	870 w.
1227 v.s.	1098 w.	935 s.	843 w. (sh.)
1180 v.s.	1077 w.	905 m.	840 w.
1130 s.	1037 w.	881 v.w.	817 m.
1080 w.	1005 s.	861 s.	748 s.
1042 s.	955 m.	852 m.	724 v.w.
1007 v.w.	917 v.w.	837 v.w.	695 w.
950 m. (sh.)	890 v.w.	817 w.	
942 s.	855 m. (sh.)	810 w. (sh.)	
923 w.	845 s.	792 v.w.	
880 m.	823 w.	740 m.	
851 s.	776 m.	722 v.w.	
832 w. (sh.)	760 w.	703 v.w.	
823 w.	720 m. (sh.)	603 w.	
792 v.w.	702 s.		
775 w.			
765 w.			
730 s.			
702 s.			

TABLE 10

Infrared Absorption Maxima of

β-(3,4-Methylenedioxybenzoyl)-α-(2-bromo-4,5-methylenedioxyphenyl)propionitrile

β-(3,4-Methylenedioxybenzoyl)-α-(2-bromo-4,5-methylenedioxyphenyl)propionamide

β-(3,4-Methylenedioxybenzoyl)-α-(2-bromo-4,5-methylenedioxyphenyl)propionic acid

γ-(3,4-Methylenedioxyphenyl)-α-(2-bromo-4,5-methylenedioxyphenyl)butyric acid

Positions of Absorption Maxima (cm^{-1}) in the Infrared Spectra of

β-(3,4-Methylenedioxybenzoyl)-α-(2-bromo-4,5-methylenedioxyphenyl)propionitrile	β-(3,4-Methylenedioxybenzoyl)-α-(2-bromo-4,5-methylenedioxyphenyl)propionamide	β-(3,4-Methylenedioxybenzoyl)-α-(2-bromo-4,5-methylenedioxyphenyl)propionic acid	γ-(3,4-Methylenedioxyphenyl)-α-(2-bromo-4,5-methylenedioxyphenyl) butyric acid
3098 v.w.	3480 s.	3450 w. (br.)	3450 w. (br.)
3060 v.w.	3380 v.w.	3098 v.w.	3010 w. (sh.)
2940 w.	3305 w.	3020 w.	2905 s.
2900 w.	3180 s.	2910 m.	1704 v.s.
2260 v.w.	2918 m.	2760 v.w.	1630 v.w.
1670 v.s.	2780 v.w.	2660 v.w.	1615 v.w.
1622 v.w.	1685 v.s.	1713 v.s.	1508 v.s.
1604 s.	1667 v.s.	1670 v.s.	1498 s. (sh.)
1507 v.s.	1613 s.	1607 s.	1487 v.s.
1482 v.s.	1508 v.s.	1508 v.s.	1460 v.w.
1455 v.s.	1485 v.s.	1483 v.s.	1448 m.
1413 s.	1448 v.s.	1452 v.s.	1425 v.w.
1380 w.	1417 s.	1410 m.	1412 w.
1356 m.	1392 w.	1390 v.w.	1398 w.
1347 s.	1376 s.	1358 m.	1365 v.w. (br.)
1312 v.w.	1357 m. (sh.)	1326 m.	1332 m.
1265 v.s.	1348 m. (sh.)	1252 v.s.	1310 m.
1245 s.	1300 m.	1242 s. (sh.)	1280 m.
1235 s. (sh.)	1277 m. (sh.)	1210 v.w. (sh.)	1240 v.s.
1217 s. (sh.)	1263 v.s.	1185 w.	1210 w.
1165 v.w.	1240 s.	1145 w.	1187 m.
1150 w.	1206 w.	1115 w.	1148 v.w. (sh.)
1140 w.	1195 w.	1042 v.s.	1123 s.
1118 s.	1145 w.	1007 w.	1102 w.
1042 s. (sh.)	1118 s.	997 w. (sh.)	1042 v.s.
1033 v.s.	1103 m.	974 w.	1022 m.
1007 s.	1082 v.w.	938 m.	960 v.w. (sh.)
967 w.	1040 v.s.	899 v.w.	935 s.
932 m.	1008 w.	883 w.	916 m.

β-(3,4-Methylenedioxybenzoyl)-α-(2-bromo-4,5-methylenedioxyphenyl)propionitrile	β-(3,4-Methylenedioxybenzoyl)-α-(2-brono-4,5-methylenedioxyphenyl)propionamide	β-(3,4-Methylenedioxybenzoyl)-α-(2-bromo-4,5-methylenedioxyphenyl)propionic acid	γ-(3,4-Methylenedioxyphenyl)-α-(2-bromo-4,5-methylenedioxyphenyl) butyric acid
925 m.	993 w.	868 m.	866 m.
903 w.	970 w.	825 m.	848 m.
883 s.	933 s.	810 w.	820 m.
855 w.	912 w.	770 v.w.	813 m.
807 v.s.	898 w.	735 v.w.	805 m.
755 v.w.	879 m.	699 w.	770 v.w.
733 v.w.	873 w. (sh.)		760 v.w.
720 w.	860 m.		724 v.w.
685 w.	850 w.		
	845 v.w.		
	837 v.w. (sh.)		
	820 m. (sh.)		
	815 s.		
	765 w.		
	730 w.		
	708 v.w.		
	683 w.		

TABLE 11

Infrared Absorption Maxima of

1-Oxo-6,7-methylenedioxy-2-(2-bromo-4,5-methylenedioxyphenyl)-1,2,3,4-tetrahydronaphthalene

1-Oximino-6,7-methylenedioxy-2-(2-bromo-4,5-methylenedioxyphenyl)-1,2,3,4-tetrahydronaphthalene

1-Formamido-6,7-methylenedioxy-2-(2-bromo-4,5-methylenedioxyphenyl)-1,2,3,4-tetrahydronaphthalene

7,8-Methylenedioxy-3-(3,4-methylenedioxyphenyl)-2,3,4,5-tetrahydro-1H-1-benzazepine

Positions of Absorption Maxima (cm^{-1}) in the Infrared Spectra of

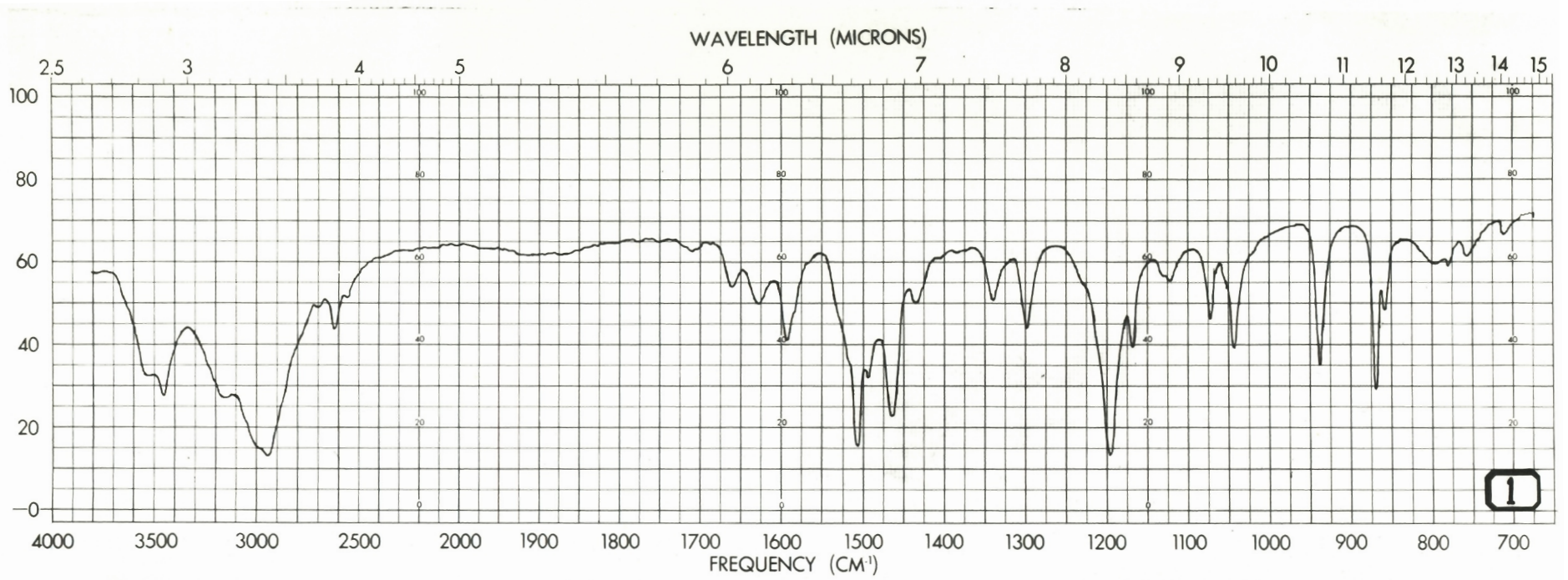
1-Oxo-6,7-methylenedioxy-2-(2-bromo-4,5-methylenedioxyphenyl)-1,2,3,4-tetrahydronaphthalene	1-Oximino-6,7-methylenedioxy 2-(2-bromo-4,5-methylenedioxyphenyl)-1,2,3,4-tetrahydronaphthalene	1-Formamido-6,7-methylenedioxy-2-(2-bromo-4,5-methylenedioxyphenyl)-1,2,3,4-tetrahydronaphthalene	7,8-Methylenedioxy-3-(3,4-methylene dioxyphenyl)-2,3,4,5-tetrahydro-1H-1-benzazepine
3070 v.w.	3290 w. (br.)	3450 m.	3410 m.
2990 v.w. (br.)	3220 w. (br.)	3245 m.	2908 m.
2925 m.	3065 w.	3058 w.	2860 w. (sh.)
2780 v.w.	2910 m.	2900 m.	2790 v.w.
1665 v.s.	1623 w.	1677 s. (sh.)	1635 v.w.
1613 s.	1505 v.s.	1658 v.s.	1623 v.w.
1505 v.s.	1484 v.s.	1549 m.	1612 w.
1478 v.s.	1440 w.	1508 s.	1511 s.
1460 v.w. (sh.)	1410 w.	1487 v.s.	1500 s. (sh.)
1452 v.w. (sh.)	1487 s.	1445 v.w.	1488 v.s.
1437 m.	1352 w.	1414 w.	1445 s.
1410 m.	1339 v.w.	1398 m.	1400 w.
1392 s.	1287 m.	1385 m.	1374 v.w.
1370 v.w. (sh.)	1274 m.	1341 w.	1353 m.
1348 s.	1238 v.s.	1300 v.w.	1305 v.w.
1338 m. (sh.)	1220 m. (sh.)	1285 v.w.	1290 w.
1298 w.	1192 v.w. (sh.)	1255 v.s.	1250 v.s.
1280 w. (sh.)	1165 w.	1230 s.	1243 m. (sh.)
1258 v.s.	1148 w.	1183 w.	1225 s.
1236 v.s.	1115 m.	1153 w.	1190 v.s.
1218 v.w. (sh.)	1083 v.w.	1115 m.	1175 s.
1204 v.w.	1040 v.s.	1068 w.	1112 w.
1166 w.	1022 m.	1040 v.s.	1085 w.
1150 w.w. (sh.)	1003 s.	985 v.w.	1070 v.w.
1121 m.	957 m.	960 v.w.	1037 v.s.
1098 m.	948 m.	939 m.	993 w.
1076 v.w.	935 m.	922 m.	932 s.
1036 v.s.	919 m.	892 v.w.	865 m.
989 w.	880 m.	870 w.	835 w.
972 v.w.	860 m.	863 w.	820 w.
935 v.s.	835 m.	833 w.	812 m.
893 m.	790 v.w.	822 v.w.	758 w.
865 m.	775 v.w.	777 v.w.	751 w.
855 w.	746 v.w.		735 w.
835 m.	732 w.		
798 w.			
774 w.			
752 w.			
700 w.			

FIGURE 1

Infrared Absorption Spectra of

1. 3,4-Methylenedioxy-6-aminophenol hydrochloride

2. 3,4-Methylenedioxy-6-hydroxyacetanilide


WAVELENGTH (MICRONS)
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100 80 60 40 20 0
4000 3500 3000 2500 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700
FREQUENCY (CM-1)
1

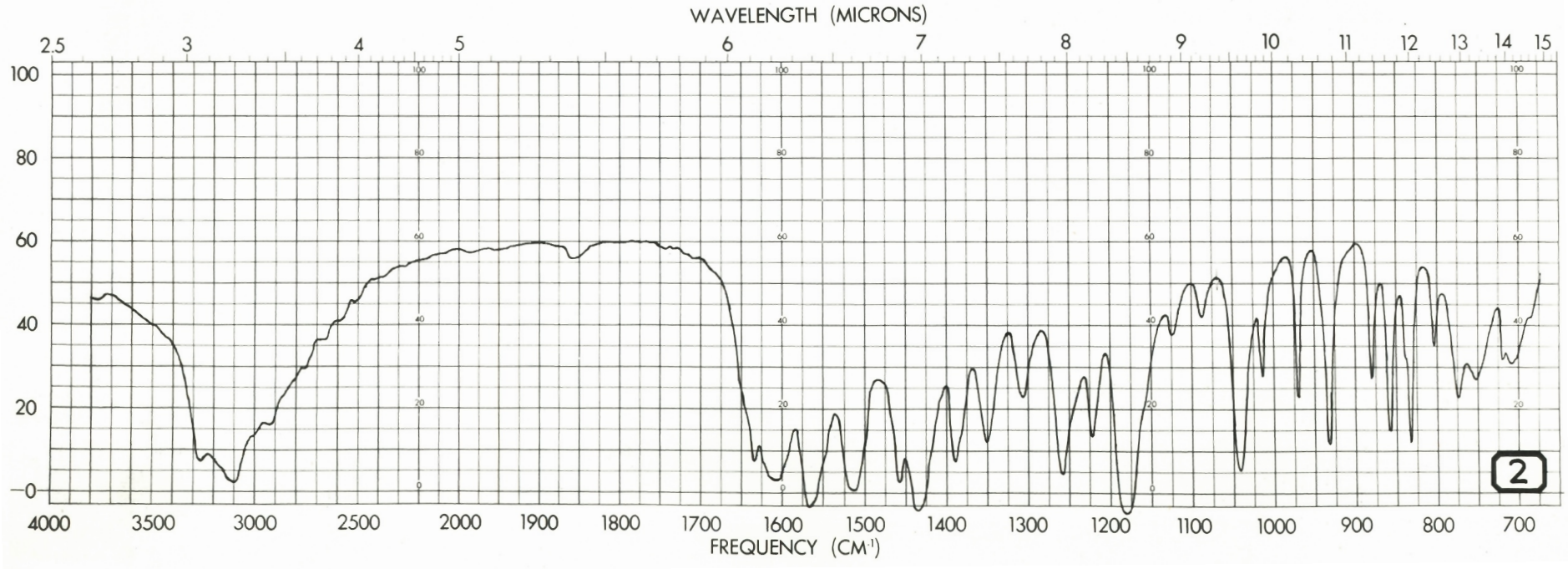
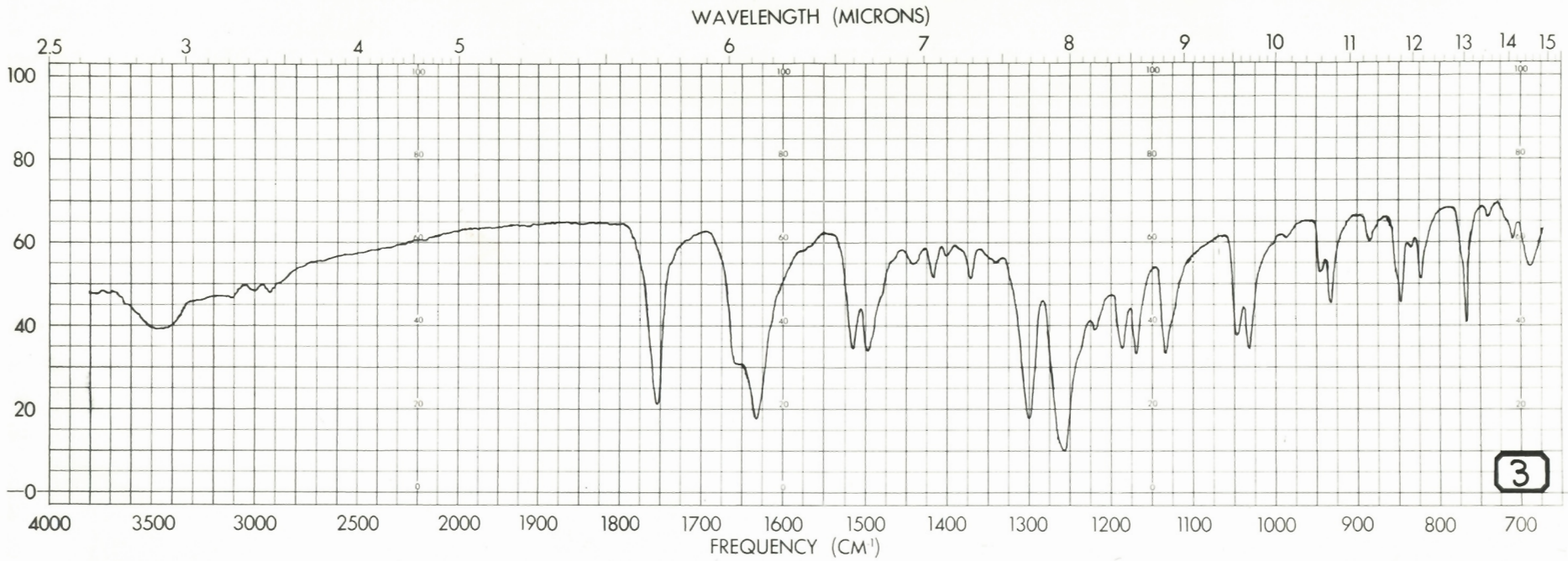

WAVELENGTH (MICRONS)
2.5 3 4 5 6 7 8 9 10 11 12 13 14 15
100 80 60 40 20 0
4000 3500 3000 2500 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700
FREQUENCY (CM-1)
2

FIGURE 2

Infrared Absorption Spectra of

3. 6,7-Methylenedioxy-1,4-benzoxazin-2-one-3-acetic acid ethyl ester

4. 6,7-Methylenedioxy-3-methyl-1,4-benzoxazin-2-one


WAVELENGTH (MICRONS)
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100 80 60 40 20 0
4000 3500 3000 2500 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700
FREQUENCY (CM⁻¹)
3

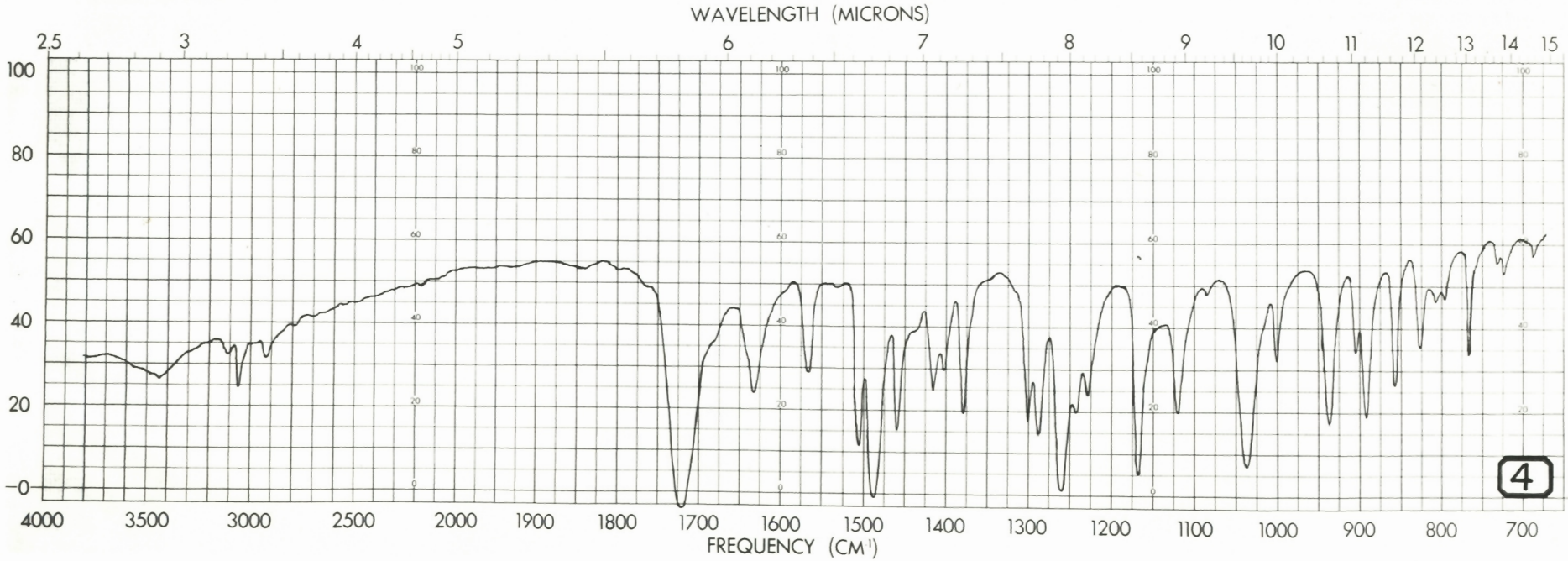
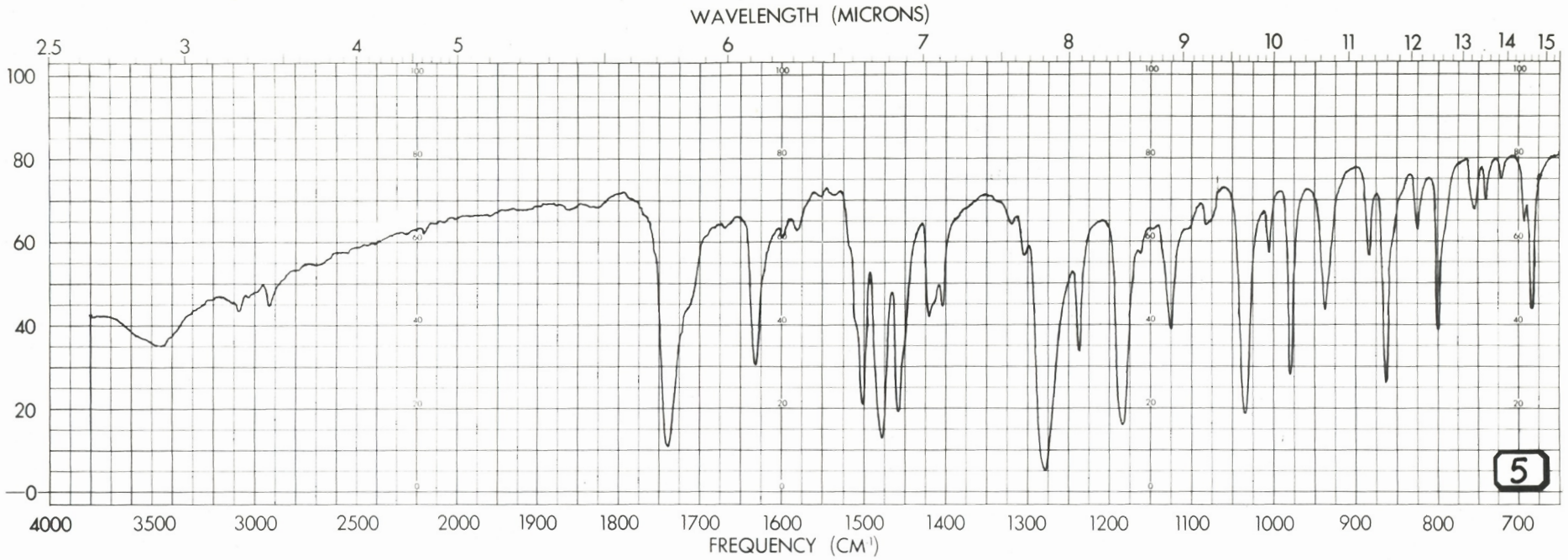

WAVELENGTH (MICRONS)
2.5 3 4 5 6 7 8 9 10 11 12 13 14 15
100 80 60 40 20 0
4000 3500 3000 2500 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700
FREQUENCY (CM⁻¹)
4

FIGURE 3

Infrared Absorption Spectra of

5. 6,7-Methylenedioxy-3-phenyl-1,4-benzoxazin-2-one

6. 6,7-Methylenedioxy-3-acetonyl-1,4-benzoxazin-2-one


WAVELENGTH (MICRONS)
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5
6
7
8
9
10
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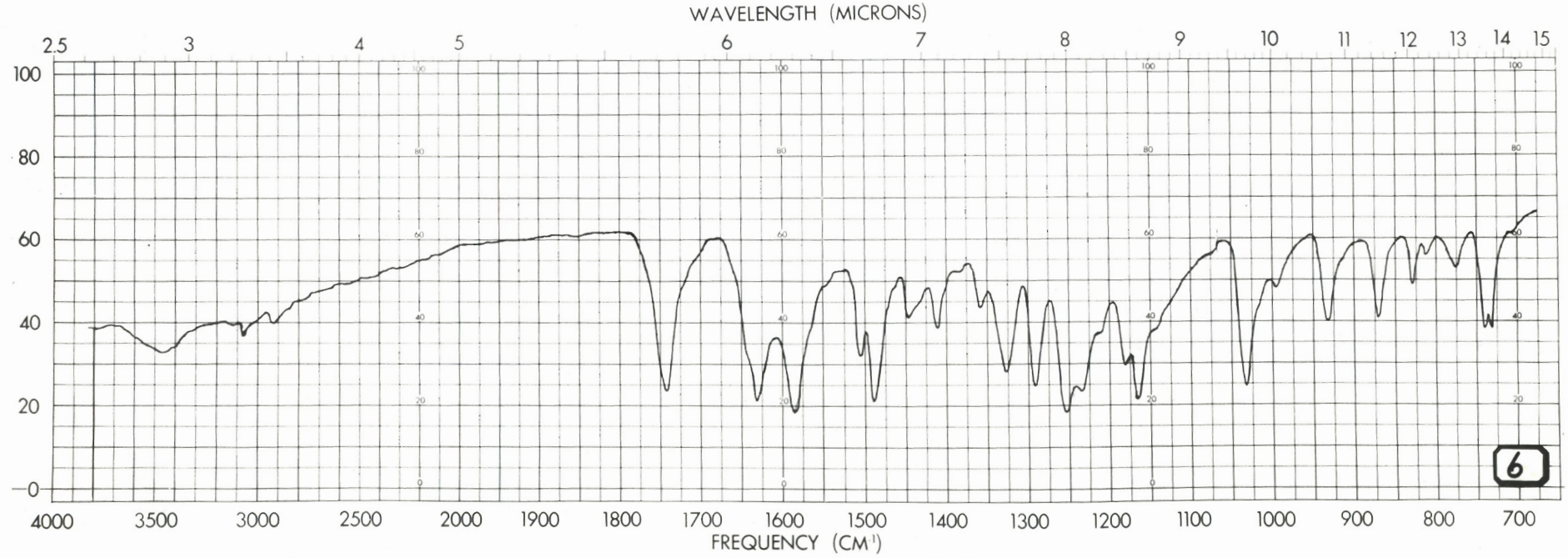
13
14
15
100
80
60
40
20
0
4000
3500
3000
2500
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
FREQUENCY (CM-1)
5


WAVELENGTH (MICRONS)
2.5
3
4
5
6
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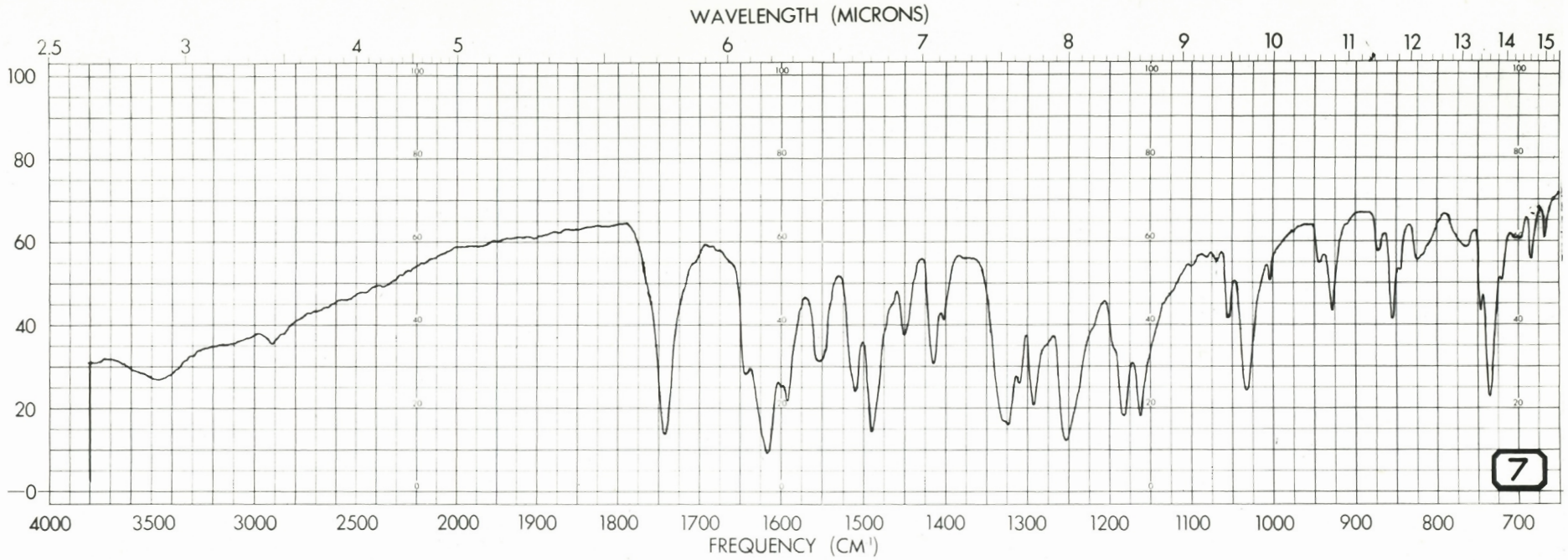
8
9
10
11
12
13
14
15
100
80
60
40
20
0
4000
3500
3000
2500
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
FREQUENCY (CM-1)
6

FIGURE 4

Infrared Absorption Spectra of

7. 6,7-Methylenedioxy-3-phenacyl-1,4-benzoxazin-2-one

8. 3,4-Dimethoxy-6-nitrophenyl acetate


WAVELENGTH (MICRONS)
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5
6
7
8
9
10
11
12
13
14
15
100
80
60
40
20
0
4000
3500
3000
2500
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
FREQUENCY (CM⁻¹)
7

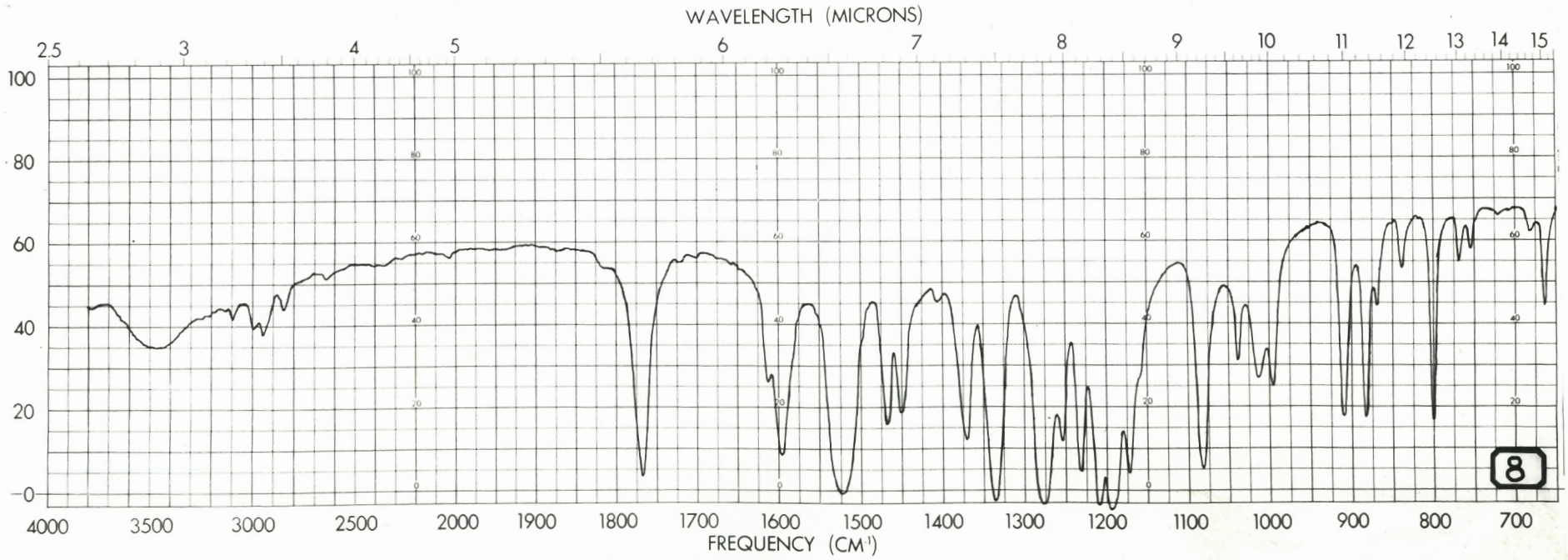
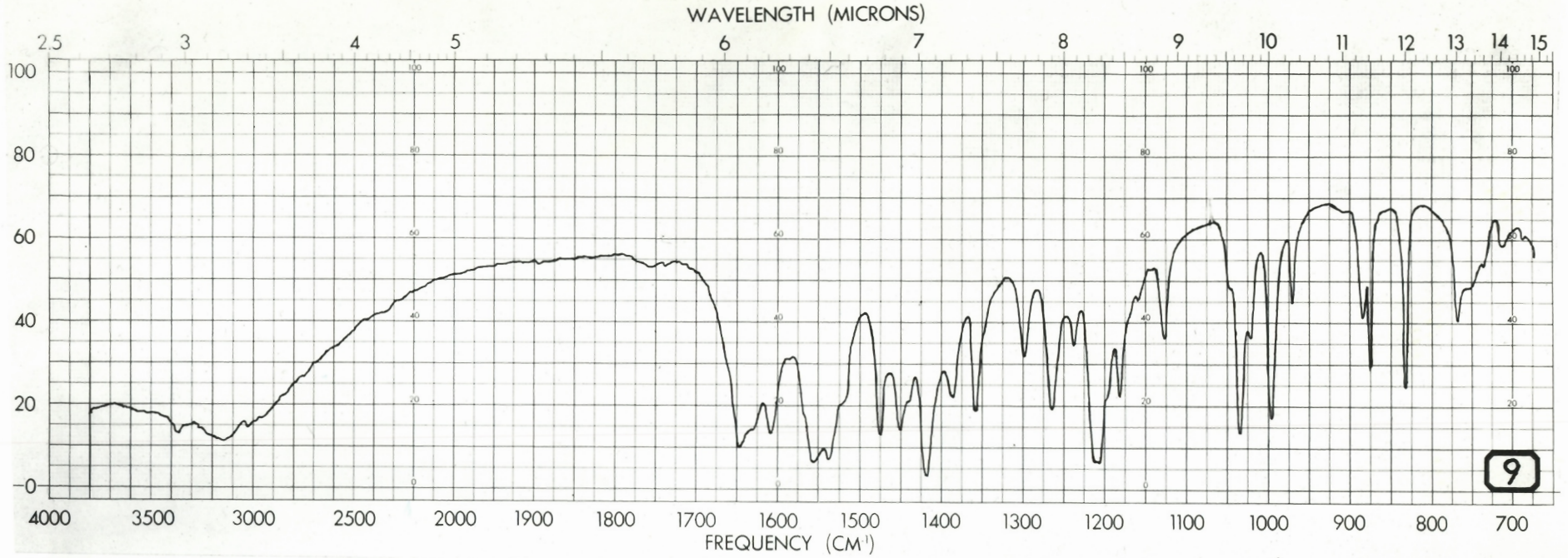

WAVELENGTH (MICRONS)
2.5
3
4
5
6
7
8
9
10
11
12
13
14
15
100
80
60
40
20
0
4000
3500
3000
2500
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
FREQUENCY (CM⁻¹)
8

FIGURE 5

Infrared Absorption Spectra of

9. 3,4-Dimethoxy-6-hydroxyacetanilide

10. 6,7-Dimethoxy-1,4-benzoxazin-2-one-3-acetic acid ethyl ester


WAVELENGTH (MICRONS)
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100 80 60 40 20 0
4000 3500 3000 2500 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700
FREQUENCY (CM-1)
9

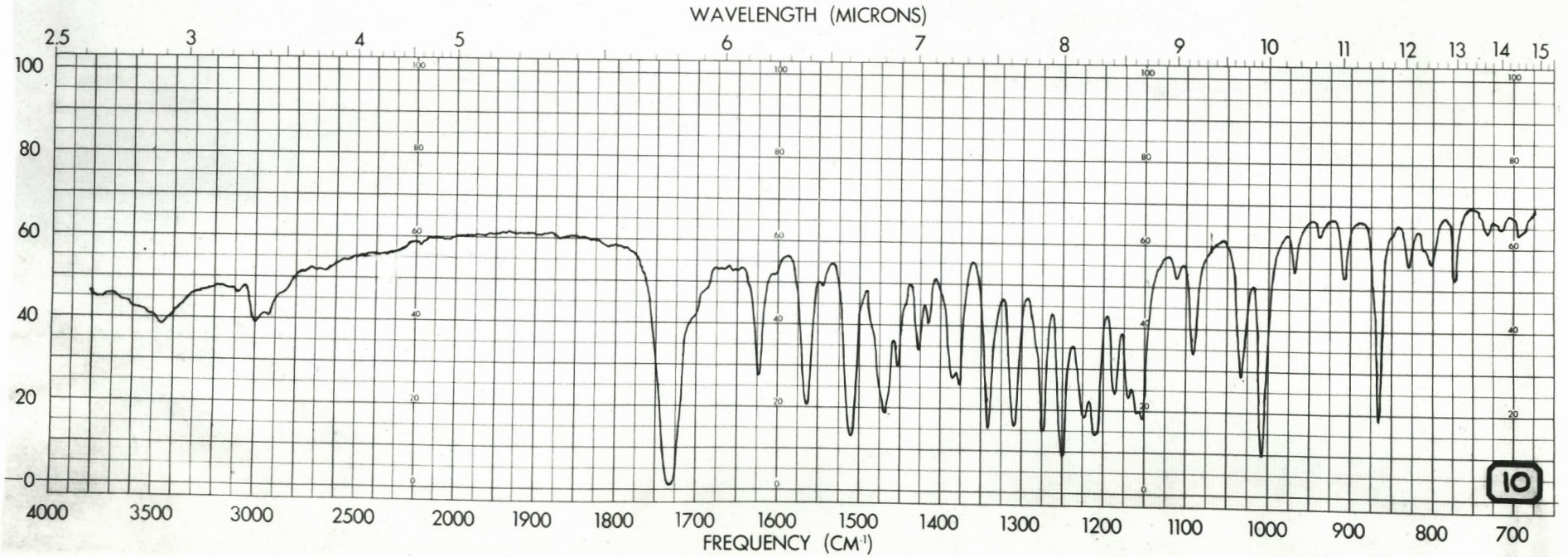
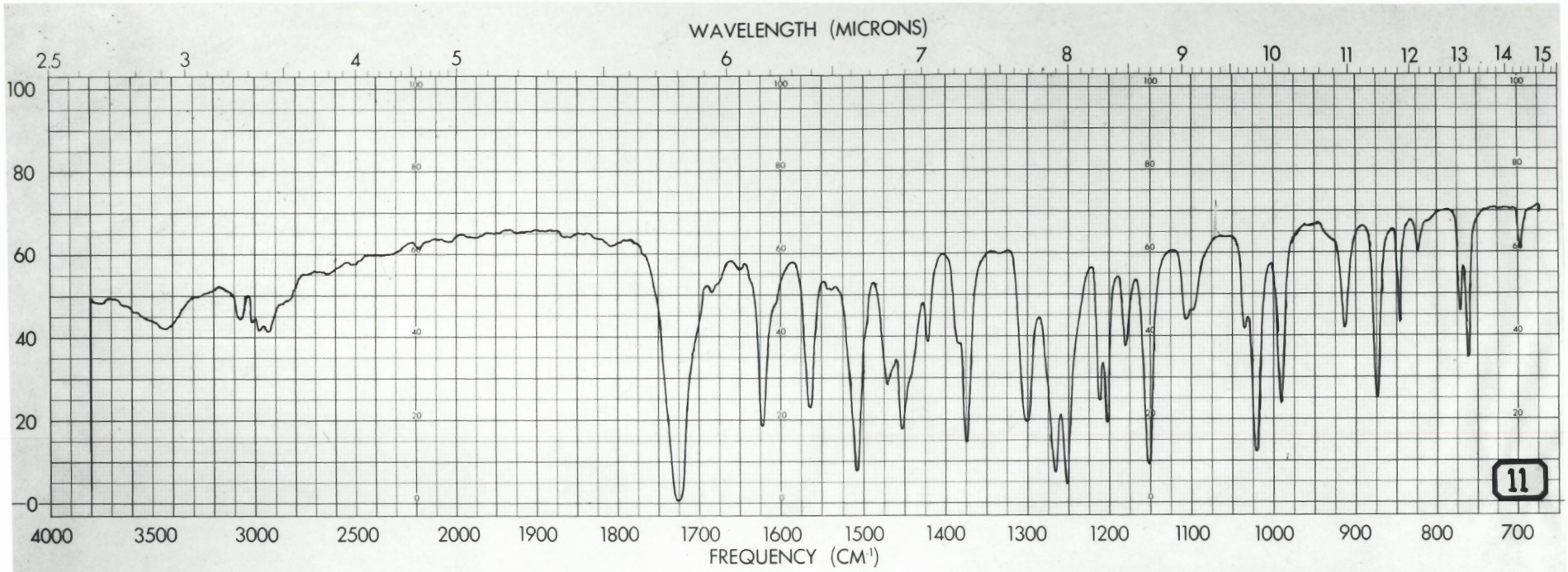

WAVELENGTH (MICRONS)
2.5 3 4 5 6 7 8 9 10 11 12 13 14 15
100 80 60 40 20 0
4000 3500 3000 2500 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700
FREQUENCY (CM-1)
10

FIGURE 6

Infrared Absorption Spectra of

11. 6,7-Dimethoxy-3-methyl-1,4-benzoxazin-2-one

12. 6,7-Dimethoxy-3-phenyl-1,4-benzoxazine-2-one


WAVELENGTH (MICRONS)
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100 80 60 40 20 0
4000 3500 3000 2500 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700
FREQUENCY (CM-1)
11

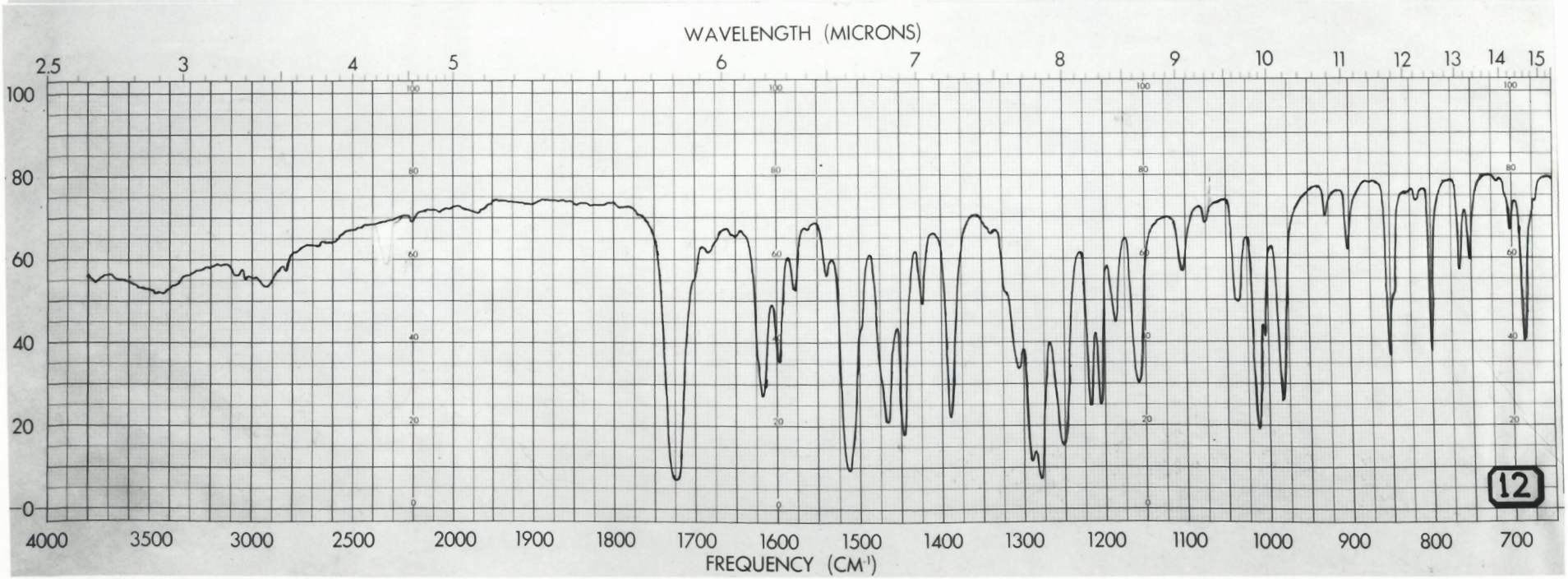
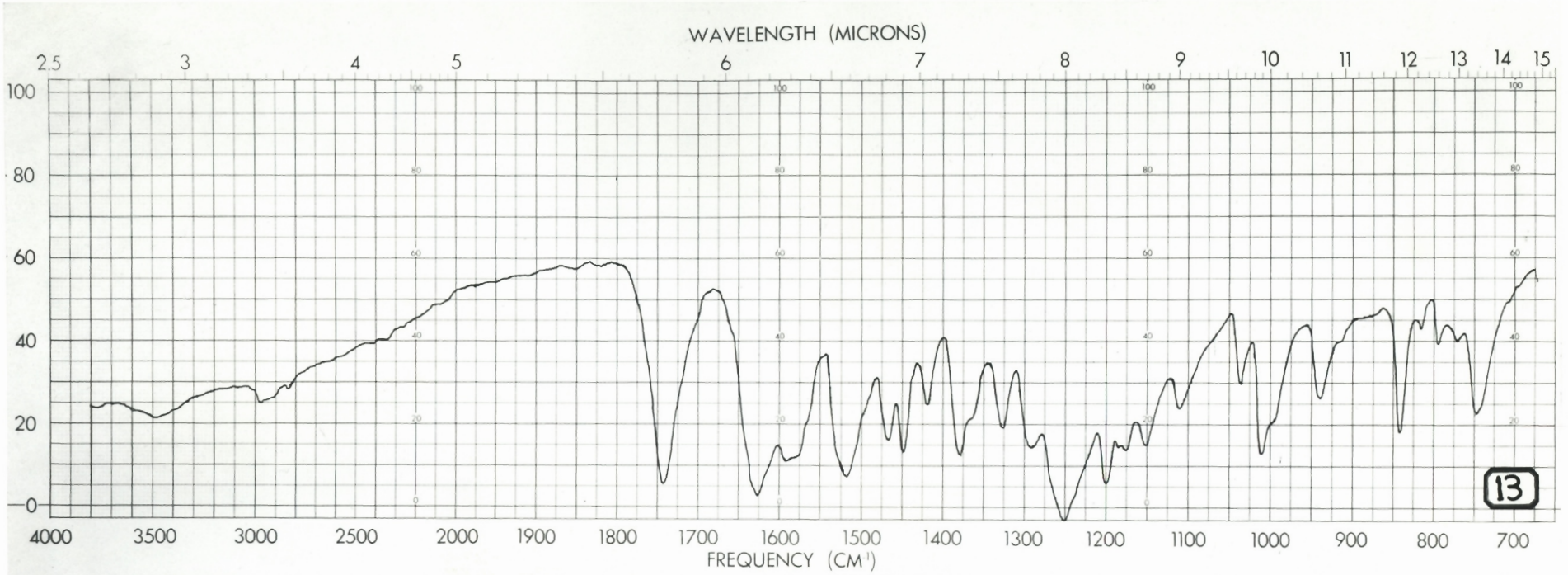

WAVELENGTH (MICRONS)
2.5 3 4 5 6 7 8 9 10 11 12 13 14 15
100 80 60 40 20 0
4000 3500 3000 2500 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700
FREQUENCY (CM-1)
12

FIGURE 7

Infrared Absorption Spectra of

13. 6,7-Dimethoxy-3-acetonyl-1,4-benzoxazin-2-one

14. 6,7-Dimethoxy-3-phenacyl-1,4-benzoxazin-2-one


WAVELENGTH (MICRONS)
2.5 3 4 5 6 7 8 9 10 11 12 13 14 15
100 80 60 40 20 0
4000 3500 3000 2500 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700
FREQUENCY (CM⁻¹)
13

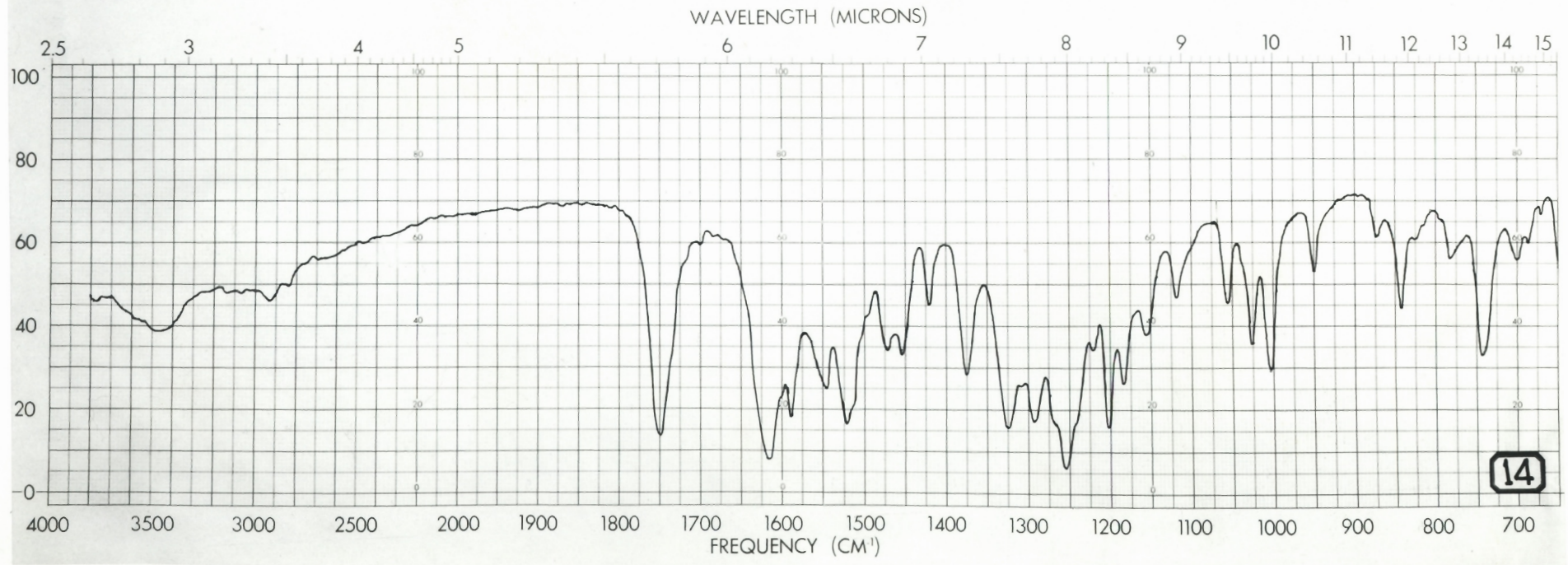
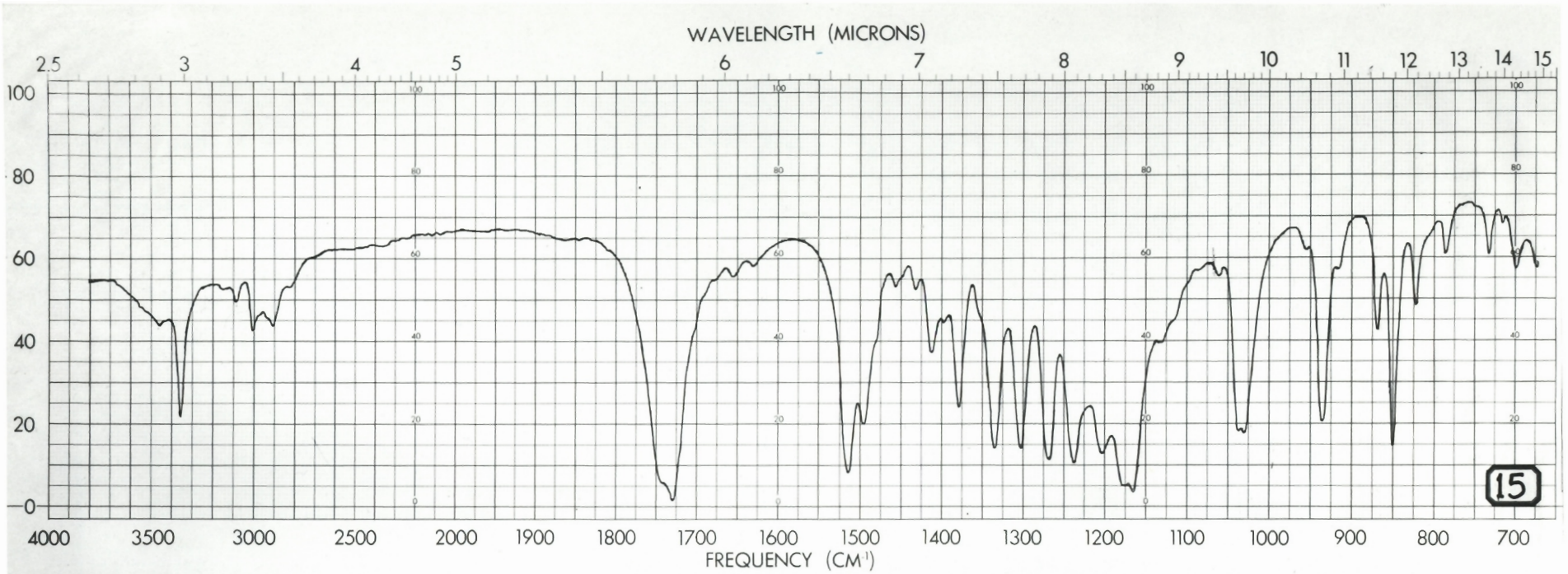

WAVELENGTH (MICRONS)
2.5 3 4 5 6 7 8 9 10 11 12 13 14 15
100 80 60 40 20 0
4000 3500 3000 2500 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700
FREQUENCY (CM⁻¹)
14

FIGURE 8

Infrared Absorption Spectra of

15. 6,7-Methylenedioxy-2-phenomorpholone-3-acetic acid ethyl ester

16. 6,7-Methylenedioxy-3-methyl-2-phenomorpholone


WAVELENGTH (MICRONS)
2.5 3 4 5 6 7 8 9 10 11 12 13 14 15
100 80 60 40 20 0
4000 3500 3000 2500 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700
FREQUENCY (CM-1)
15

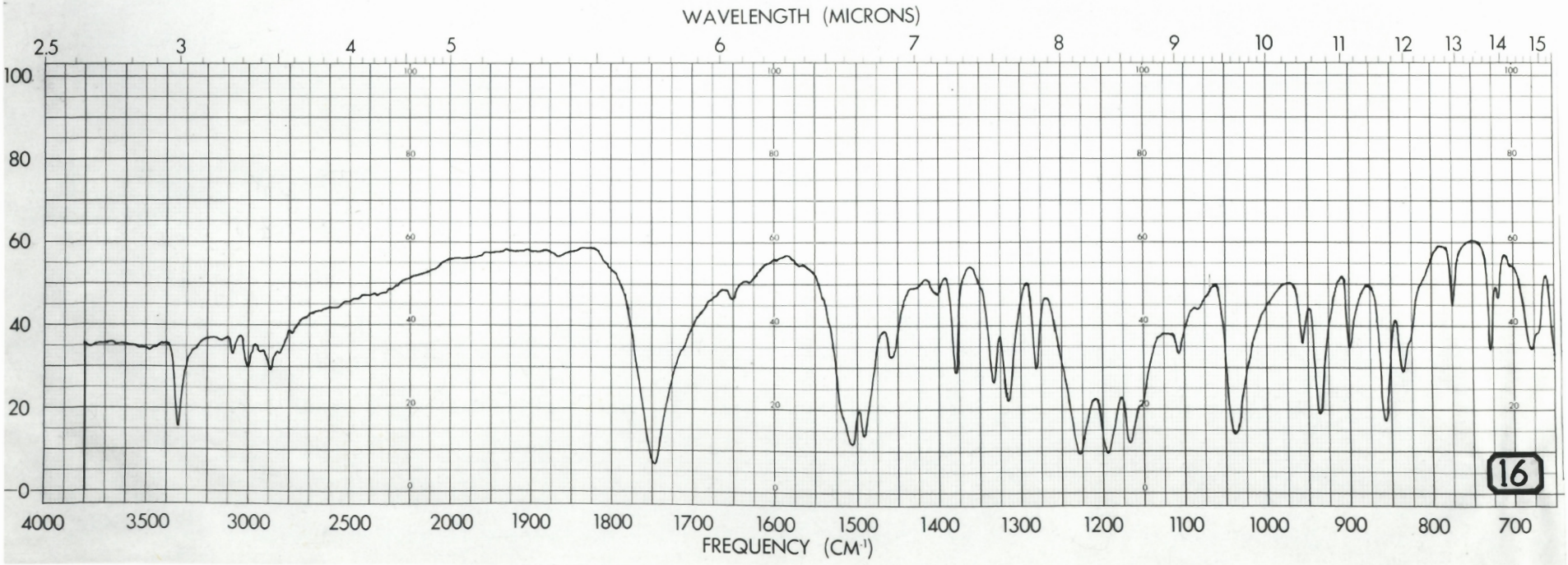
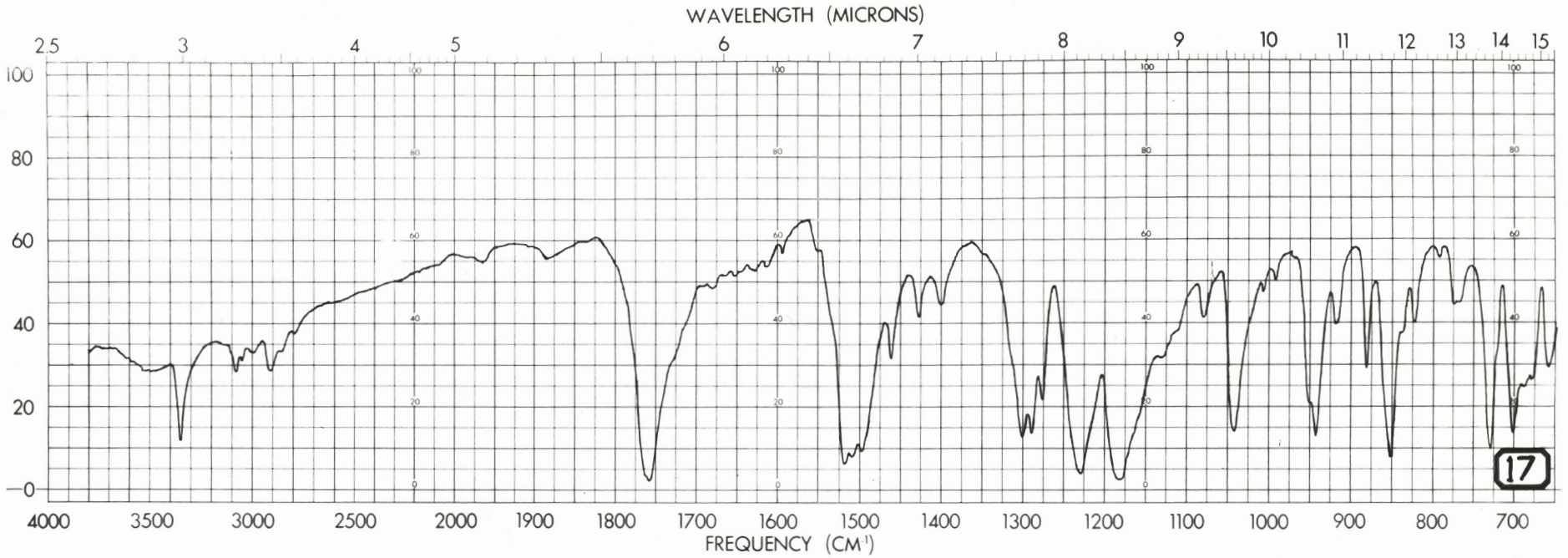

WAVELENGTH (MICRONS)
2.5 3 4 5 6 7 8 9 10 11 12 13 14 15
100 80 60 40 20 0
4000 3500 3000 2500 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700
FREQUENCY (CM-1)
16

FIGURE 9

Infrared Absorption Spectra of

17. 6,7-Methylenedioxy-3-phenyl-2-phenomorpholone

18. 6,7-Dimethoxy-3-phenyl-2-phenomorpholone


WAVELENGTH (MICRONS)
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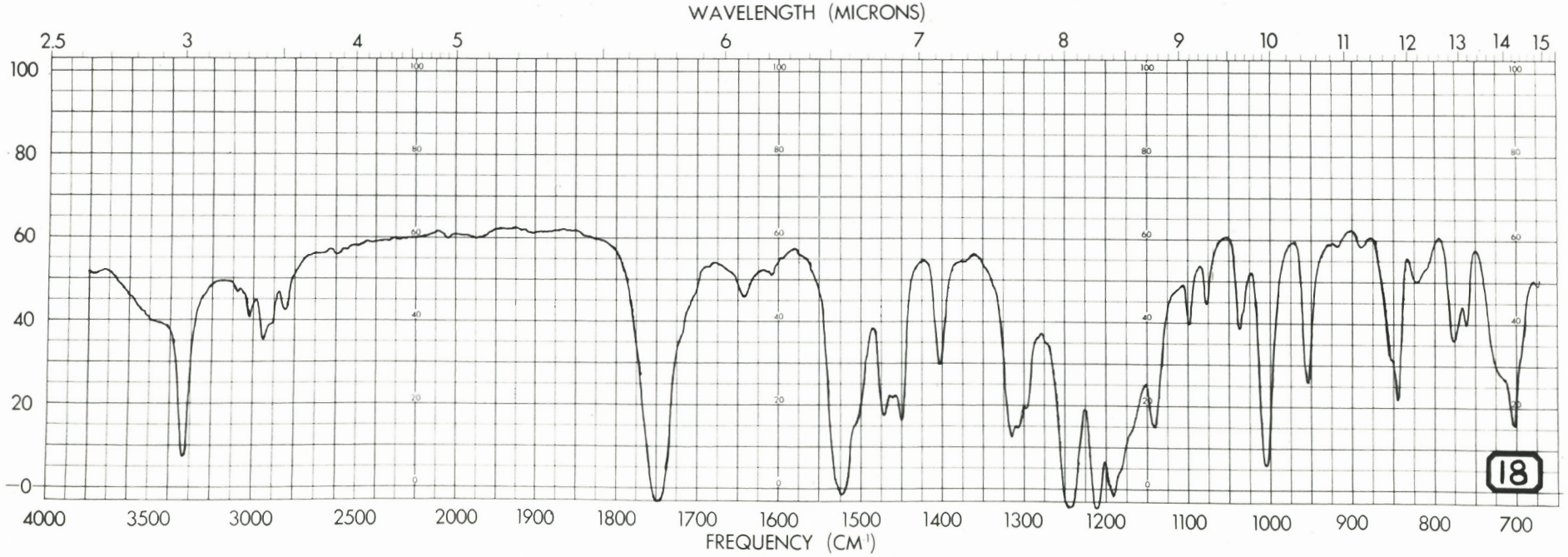
700
FREQUENCY (CM-1)
17


WAVELENGTH (MICRONS)
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20
0
4000
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3000
2500
2000
1900
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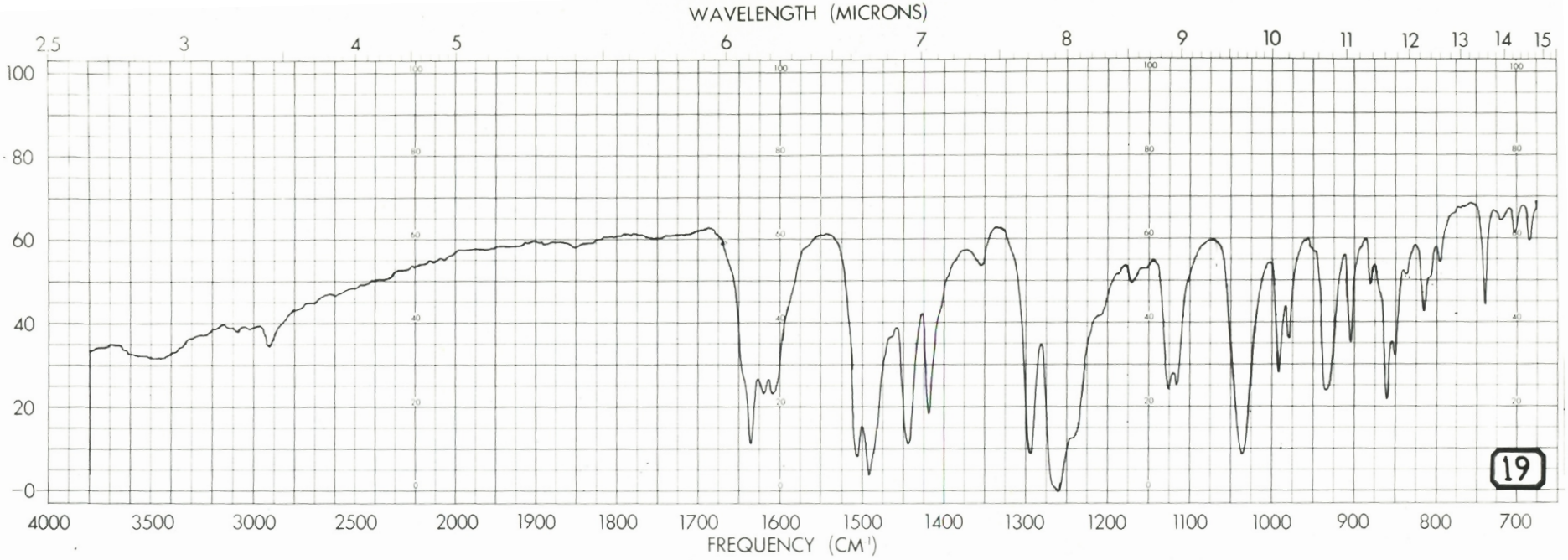
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
FREQUENCY (CM-1)
18

FIGURE 10

Infrared Absorption Spectra of

19. 3,4-Methylenedioxyphenyl 2-bromo-4,5-methylenedioxystyryl ketone

20. 2-Phenyl-3-(2-bromo-4,5-methylenedioxyphenyl)-5-(3,4-Methylenedioxyphenyl) pyrazoline


WAVELENGTH (MICRONS)
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4000 3500 3000 2500 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700
FREQUENCY (CM⁻¹)
19

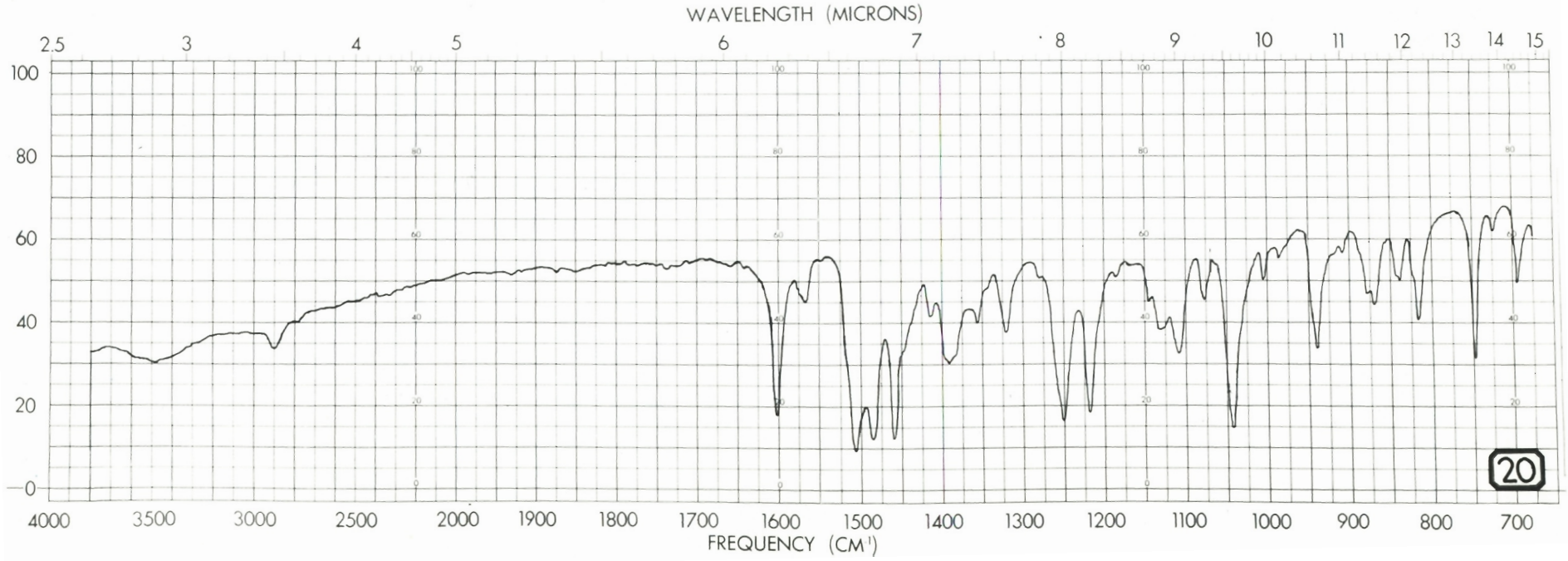
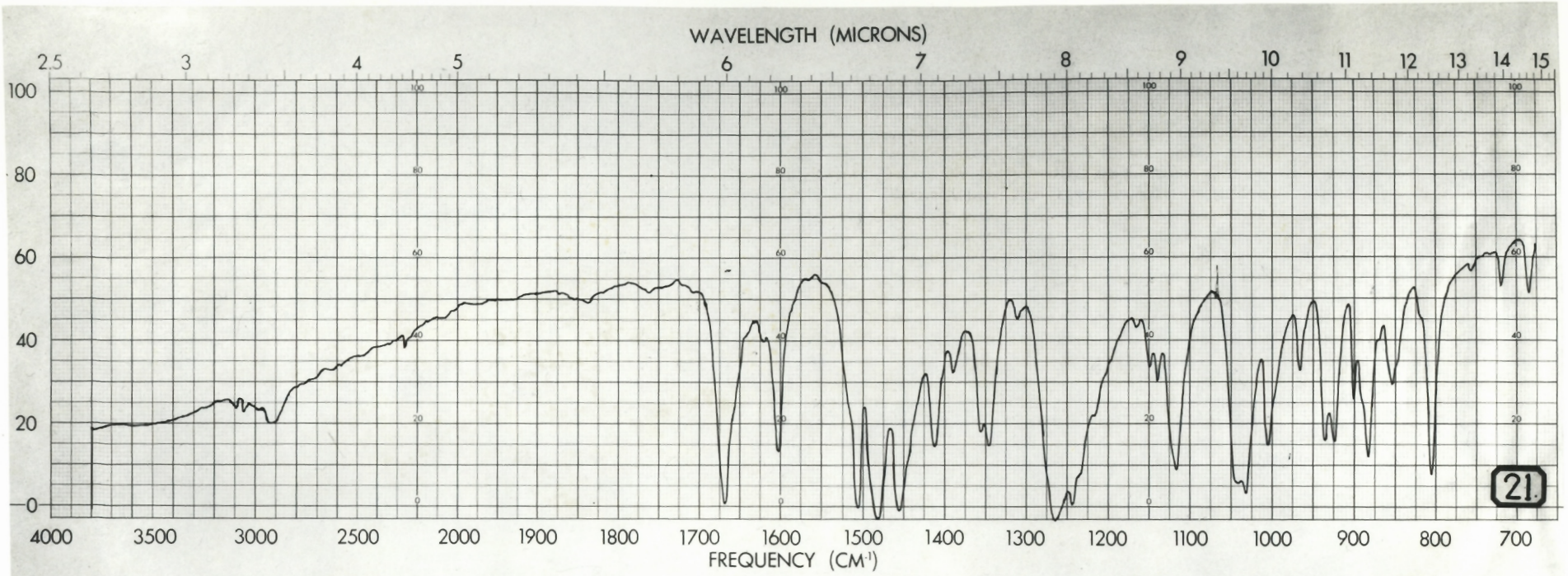

WAVELENGTH (MICRONS)
2.5 3 4 5 6 7 8 9 10 11 12 13 14 15
100 80 60 40 20 0
4000 3500 3000 2500 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700
FREQUENCY (CM⁻¹)
20

FIGURE 11

Infrared Absorption Spectra of

21. β-(3,4-Methylenedioxybenzoyl)-α-(2-bromo-4,5-methylenedioxyphenyl)propionitrile

22. β-(3,4-Methylenedioxybenzoyl)-α-(2-bromo-4,5-methylenedioxyphenyl)propionamide


WAVELENGTH (MICRONS)
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4000 3500 3000 2500 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700
FREQUENCY (CM-1)
21

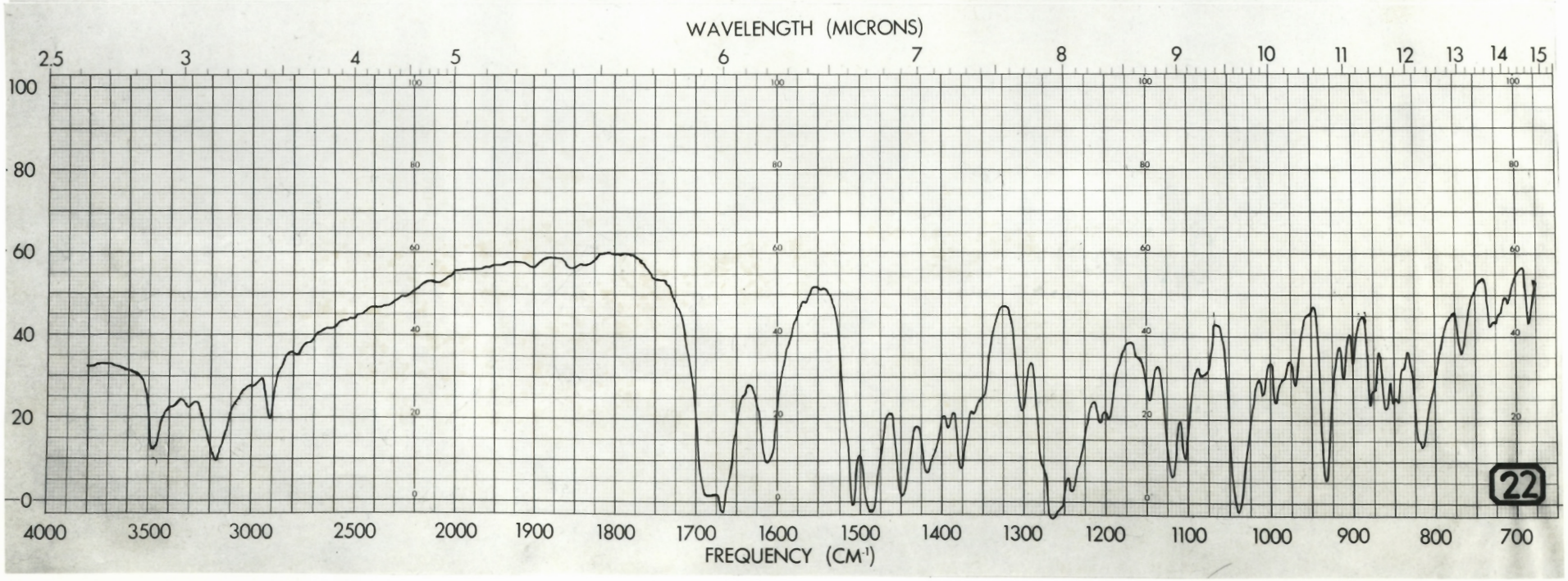
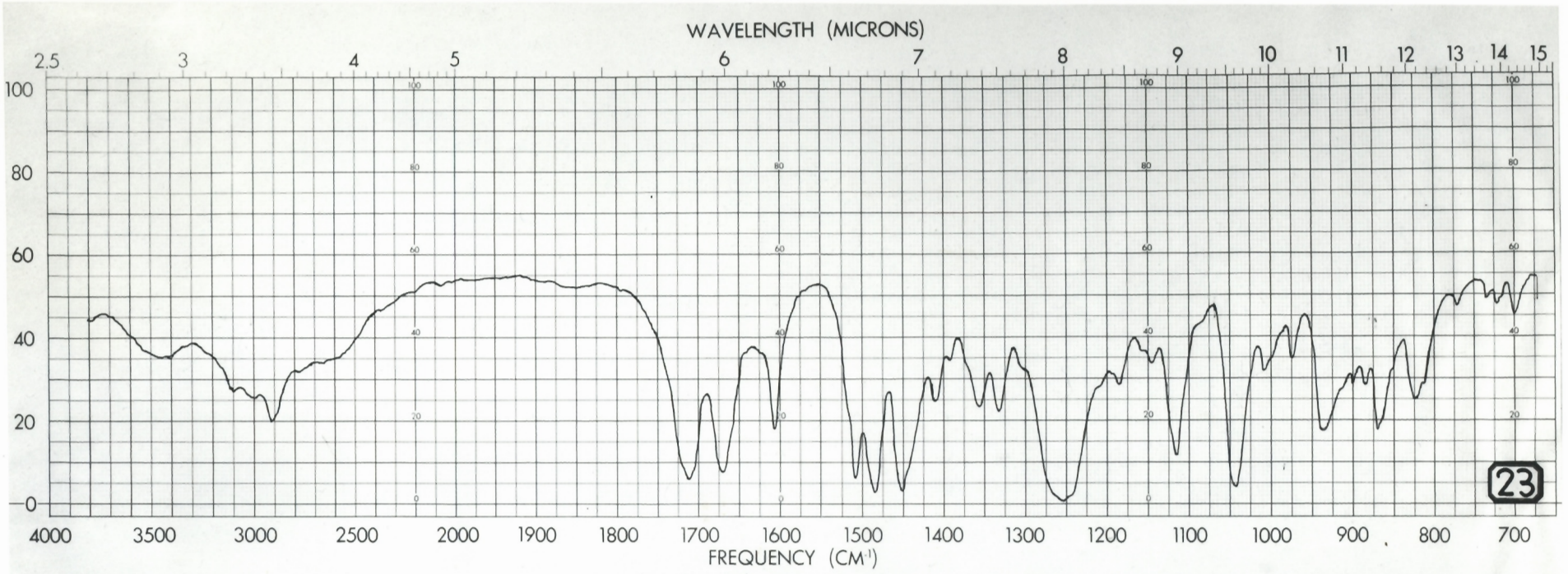

WAVELENGTH (MICRONS)
2.5 3 4 5 6 7 8 9 10 11 12 13 14 15
100 80 60 40 20 0
4000 3500 3000 2500 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700
FREQUENCY (CM-1)
22

FIGURE 12

Infrared Absorption Spectra of

23. β-(3,4-Methylenedioxybenzoyl)-α-(2-bromo-4,5-methylenedioxyphenyl) propionic acid

24. β-(3,4-Methylenedioxyphenyl)-α-(2-bromo-4,5-methylenedioxyphenyl) butyric acid


WAVELENGTH (MICRONS)
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4000 3500 3000 2500 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700
FREQUENCY (CM-1)
23

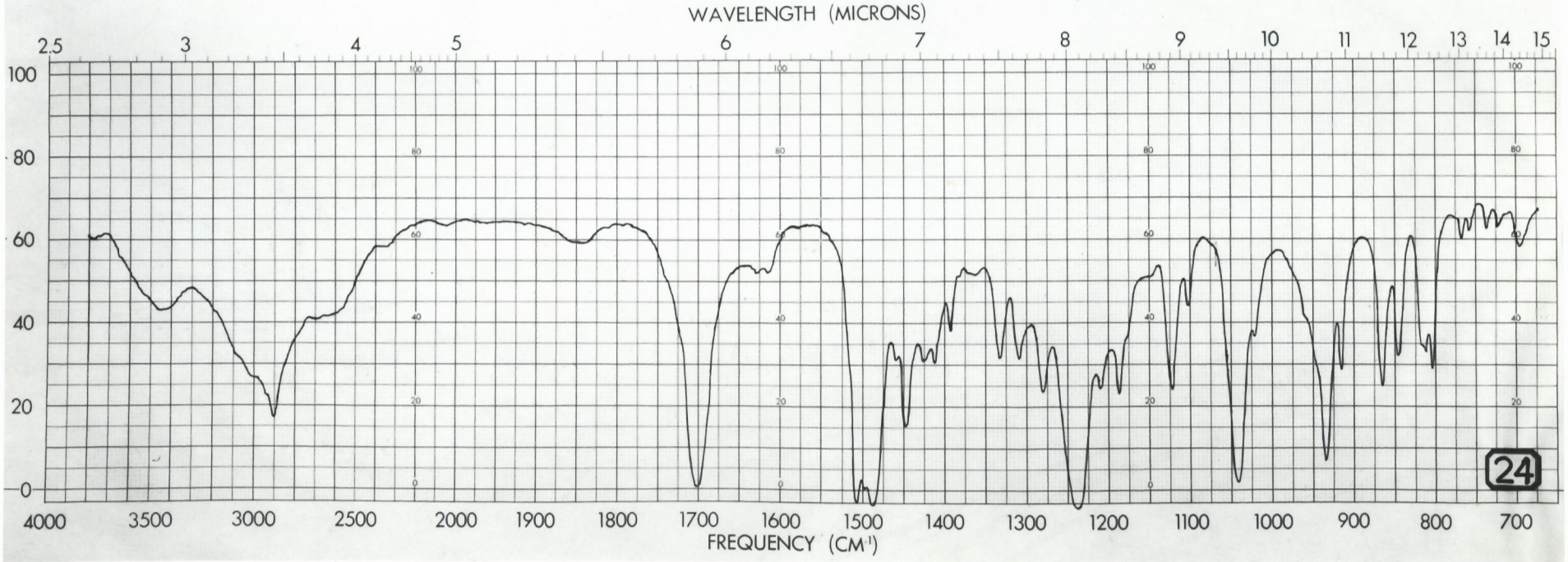
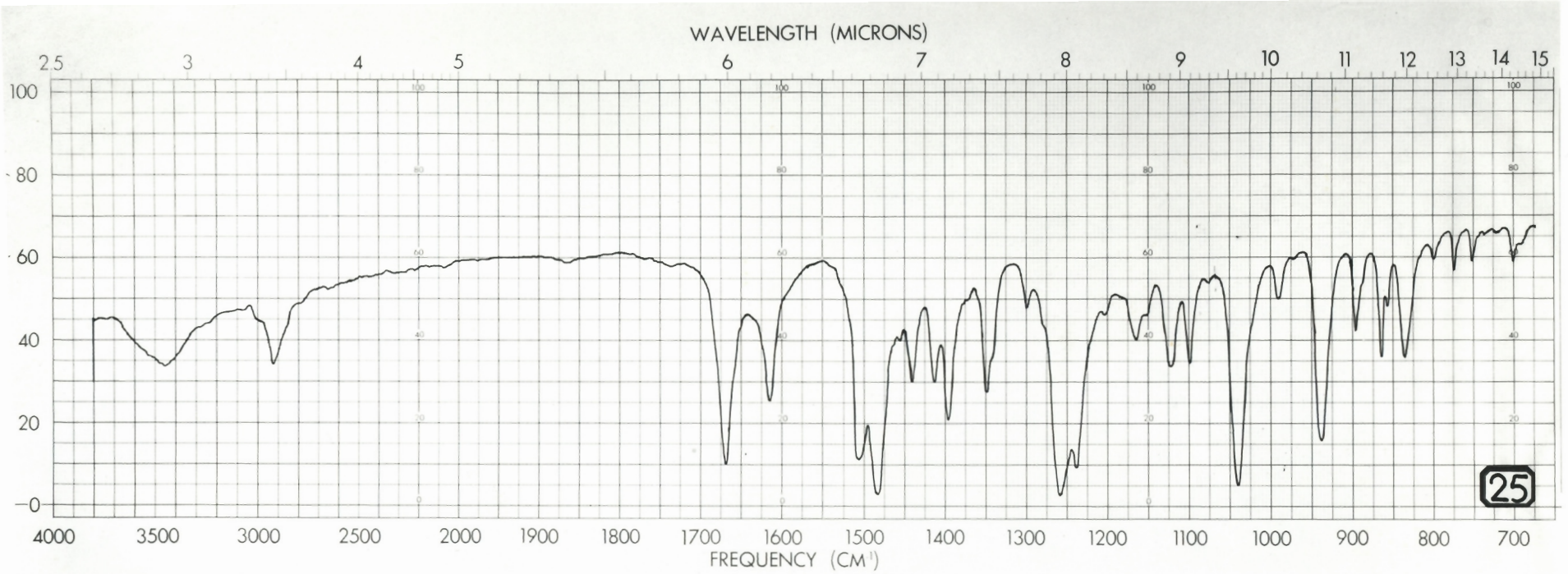

WAVELENGTH (MICRONS)
2.5 3 4 5 6 7 8 9 10 11 12 13 14 15
100 80 60 40 20 0
4000 3500 3000 2500 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700
FREQUENCY (CM-1)
24

FIGURE 13

Infrared Absorption Spectra of

25. 1-Oxo-6,7-methylenedioxy-2-(2-bromo-4,5-methylenedioxyphenyl)-1,2,3,4-tetrahydronaphthalene

26. 1-Formamido-6,7-methylenedioxy-2-(2-bromo-4,5-methylenedioxyphenyl)-1,2,3,4-tetrahydronaphthalene


WAVELENGTH (MICRONS)
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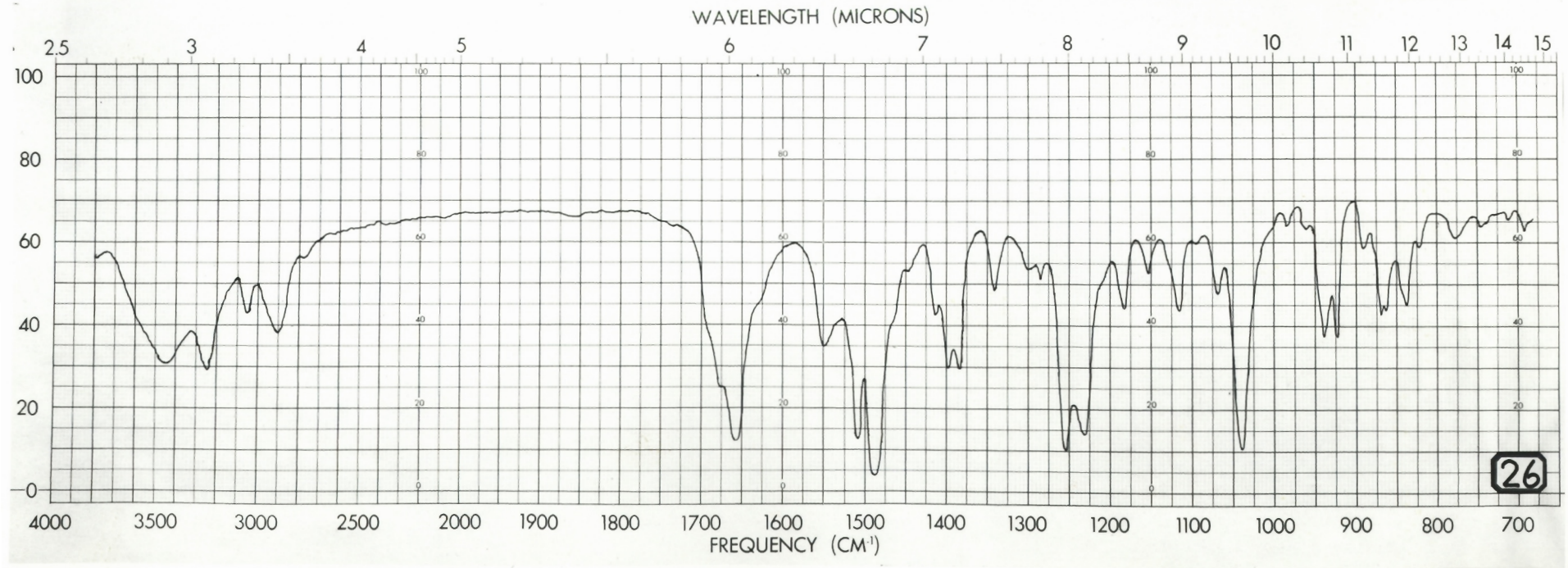
100 80 60 40 20 0
4000 3500 3000 2500 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700
FREQUENCY (CM-1)
25


WAVELENGTH (MICRONS)
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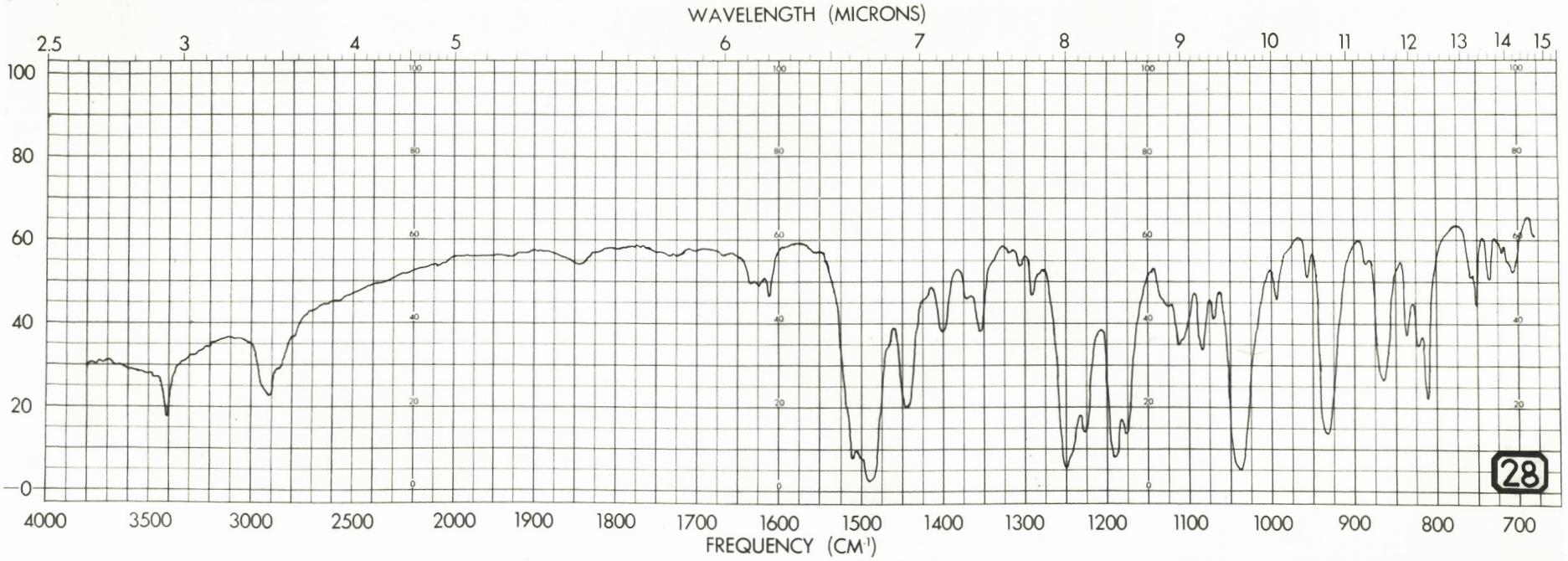
100 80 60 40 20 0
4000 3500 3000 2500 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700
FREQUENCY (CM-1)
26

FIGURE 14

Infrared Absorption Spectra of

27. 1-Oximino-6,7-methylenedioxy-2-(2-bromo-4,5-methylenedioxyphenyl)-1,2,3,4-tetrahydronaphthalene

28. 7,8-Methylenedioxy-3-(3,4-methylenedioxyphenyl)-2,3,4,5-tetrahydro-1H-1-benzazepine.


WAVELENGTH (MICRONS)
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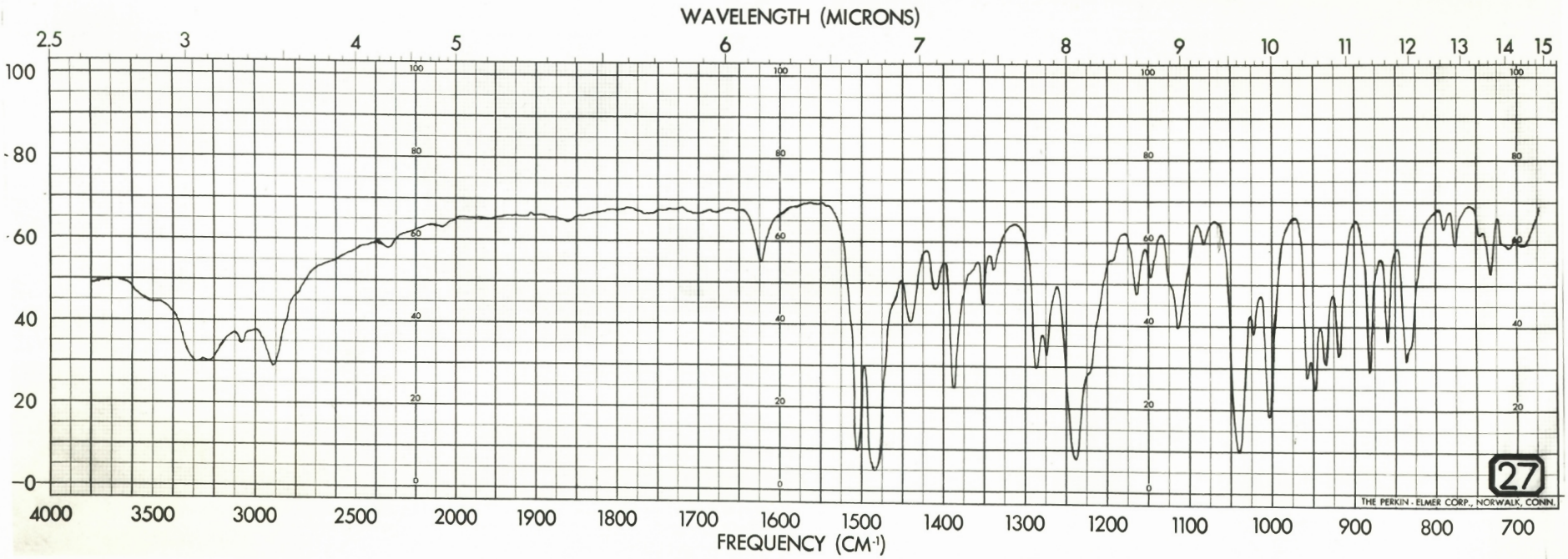
100 80 60 40 20 0
4000 3500 3000 2500 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700
FREQUENCY (CM-1)
28


WAVELENGTH (MICRONS)
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100 80 60 40 20 0
4000 3500 3000 2500 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700
FREQUENCY (CM-1)
27
THE PERKIN-ELMER CORP., NORWALK, CONN.

EXPERIMENTAL

All melting points were determined in a Thiele-Dennis melting point tube containing Dow Corning silicone fluid No. D.C. 550. The reported melting points were corrected by using the set of melting point standards supplied by the Bayer Company, Leverkussen, Germany.

Carbon, hydrogen and nitrogen microanalyses as well as molecular weight determinations, were carried out in the Alfred Bernhardt Laboratory in Mülheim (Ruhr), West Germany, except for dialkoxybenzoxazine compounds and 3,4-dialkoxy-6-hydroxyacetarylides. The latter were analyzed by Dr. C.Daessle in his microanalytical laboratory in Montreal.

Infrared Spectra

The infrared spectra were recorded by means of a Perkin-Elmer Model 21 double beam spectrophotometer equipped with a sodium chloride prism.

All the spectra were taken in the solid state and the potassium bromide pellet technique was used. The potassium bromide (400 mg) was mixed with 1-2 mg. of the substance in a ground glass stoppered tube in the presence of 3 steel balls and then shaken for 3 minutes in a Perkin-Elmer vibrator.

The pellets were formed by applying a pressure of 20.000 lbs/sq. in. for three minutes.

The setting of the instrument during the recording were as follows: resolution, 927; response, 1; gain 5; speed, 5-6; suppression, 0. The

scale used was: 100 cm^{-1}/1 cm. in the absorption range 4000-2000 cm^{-1} and 100 cm^{-1}/4 cm. in the range of 2000-650 cm^{-1}.

The absorption maxima of the bands listed in Tables 5, 6, 7, 8, 9, 10, 11, are characterized by the following abbreviations:

v.w. (very weak); w.(weak); m.(medium); s.(strong);

v.s. (very strong); br. (broad); sh. (shoulder).

PART I

A. Synthesis of 6,7-Dialkoxy-1,4-Benzoxazin-2-Ones

The synthesis of 6,7-dialkoxy-1,4-benzoxazin-2-ones involved the following steps.

a) Preparation of 3,4-dialkoxyphenols

b) Preparation of 3,4-dialkoxyphenyl acetates

c) Preparation of 3,4-dialkoxy-6-nitrophenyl acetates

d) Preparation of 3,4-dialkoxy-6-nitrophenols

e) Preparation of 3,4-dialkoxy-6-aminophenols

f) Preparation of 6,7-dialkoxy-1,4-benzoxazin-2-ones

1. 3,4-Methylenedioxyphenol (Sesamol)

The method described by Böeseken, Cohen and Kip (40, 41) was modified.

In a 1 liter three-necked flask equipped with a thermometer extending to the bottom, a mechanical stirrer and an air condenser connected at the upper end with an exit tube leading to the hood, 50 g. (0.333 mole) of piperonal were dissolved with stirring in 200 ml of glacial acetic acid. When all the solid had dissolved, the stirrer was replaced by a dropping funnel which contained 145 g. (0.38 mole) of freshly prepared 20 per cent peracetic acid solution. The piperonal-acetic acid solution was brought up to 32°C and the peracetic acid was added in protions of 20-25 ml with occasional shaking. About 3 hours

were required for the addition; the temperature was kept between 32° and 38°. After the addition of the first portion of peracetic acid, the temperature was raised slowly to about 38° and then was allowed to fall to 32° before the next portion of peracetic acid was added.

During the progress of the reaction the solution changed progressively from colourless at the beginning to light yellow, light brown, and finally to a dark brown colour.

After all the peracetic acid had been added, the reaction mixture was left for a further 24 hours at room temperature and was then distilled under reduced pressure (water aspirator) to free it from acetic acid as completely as possible. The remaining dark brown viscous oil mixed with toluene or benzene (250 ml), was stirred for 15 minutes during which time most of the resinous byproducts separated to a thick highly viscous mass. After separation and distillation of the solvent, the residual dark brown oil subjected to high vacuum distillation, gave 40.5 g of a yellow oil boiling at 110-114° under a pressure of 2 mm. At the end of the distillation the temperature was raised to 130-145° and piperonylic acid distilled, most of which solidified in the delivery arm of the distillation flask and in smaller amounts in the condenser. This piperonylic acid, collected and crystallized from methanol, gave a melting point 226-7° (1.2 gr).

The yellow oil obtained from the high vacuum distillation, was poured into a separatory funnel and shaken vigorously with 150 ml of 10 per cent sodium hydroxide solution, and was then extracted three times with 50 ml portions of diethylether. The combined ether extracts,

washed with water and dried over potassium sulphate, left 13.1 gr of unreacted piperonal after removal of the solvent.

The alkaline layer, acidified with 20 per cent sulphuric acid solution, was then extracted with diethylether (200 ml). The ether extract, washed three times with 50 ml portions of 5 per cent sodium bicarbonate solution and then with water, was dried over potassium sulphate. Removal of the ether first by distillation on a steam bath and then at room temperature under reduced pressure, afforded a colourless to light yellow oil which with evolution of heat rapidly solidified to pure sesamol with a m.p. 64-65°. The melting point reported in the literature was 65.8° (40), 63° (42). Yield 22.5 g. (48.9%).

2. Attempted Separation of the Mixture Sesamol-Piperonal by Fractional Distillation

The mixture of sesamol-piperonal obtained in the previous reaction, failed to be separated by fractional distillation by means of a Spinning Band Column (112). Nearly the whole mixture distilled in the narrow range of 96-97° under a pressure of 2.5 mm.

3. Preparation of 20 Per cent Peracetic Acid Solution

20 per cent Peracetic acid solution was prepared in accordance with the directions given by Böeseken, Cohen and Kip (40).

Peracetic acid free of explosive Ac_2O_2 was prepared by adding acetic anhydride (433 g.) in small amounts to a 50 per cent solution of hydrogen peroxide containing p-toluenesulfonic acid (0.5 g.) and allowing the temperature to fall back to 35° after each addition. Addition of

glacial acetic acid (24 g.) to this mixture, gave a solution of 20 per cent peracetic acid. The final mixture was left for a further 24 hours before use.

4. 3,4-Dimethoxyphenol

The method of Böeseken and Greup (46) was modified.

The apparatus consisted of a 1 liter three-necked flask fitted with an air condenser connected at the upper end with an exit tube leading to the hood, a thermometer extending to the bottom and a mechanical stirrer.

In the flask were placed 56 g. (0.333 mole) of veratraldehyde and 250 ml of glacial acetic acid. The mixture was stirred until all the solid had dissolved. The stirrer was replaced by a dropping funnel containing 145 g. (0.38 mole) of freshly prepared 20 per cent peracetic acid solution. The veratraldehyde-acetic acid solution was heated up to 32° and the peracetic acid was added in portions of 20-25 ml over a period of about 2 hours with occasional shaking. After the addition of the first portion of peracetic acid, the temperature rose to about 40° and a dark solution resulted. The temperature was allowed to fall to 32° before the next portion of the peracetic acid was added.

After all the peracetic acid had been added, the reaction mixture was allowed to stand at room temperature for a further 24 hours, and was then distilled under reduced pressure to free it from acetic acid as completely as possible. The remaining dark brown viscous oil, taken up in diethylether (200 ml) and washed twice with 100 ml portions of water, was then dried over potassium sulphate. Removal of the ether on a steam bath followed by high vacuum distillation afforded 39.8 g. of

a yellow oil boiling at 118-127° under a pressure of 2 mm. This intermediate oily product was poured into a separatory funnel and shaken vigorously for 10 minutes with 160 ml of 10 per cent sodium hydroxide solution, and then extracted three times with 50 ml portions of diethylether. The combined ether extracts, washed with water and dried over potassium sulphate, afforded, after removal of the solvent, 11.5 g of a white crystalline compound which was identified as unreacted veratraldehyde.

The aqueous alkaline layer was boiled for 10 minutes, cooled, and acidified with 20 per cent sulphuric acid solution. The separated 3,4-dimethoxyphenol was extracted from the acidic solution with 200 ml of diethylether. The ether extract was washed three times with 50 ml. portions of 5 per cent sodium bicarbonate solution and then with water and dried over potassium sulphate. Removal of the ether left 25.8 g. (50%) of crude 3,4-dimethoxyphenol melting at 71-76°. Crystallization from carbon tetrachloride gave a melting point 79-80°. The melting points reported in the literature were: 78-80° (47), 80-81 (51), 81.5 (46).

5. 3,4-Methylenedioxyphenyl Acetate (Sesamol Acetate)

The acetylation of 3,4-methylenedioxyphenol was accomplished according to the general procedure outlined by Vogel (113).

In a 250 ml two-necked flask fitted with a mechanical stirrer, 13.8 g. (0.1 mole) of 3,4-methylenedioxyphenol were dissolved with stirring in 60 ml of 10 per cent sodium hydroxide solution. When all the solid had dissolved, the solution was cooled by addition of about

70 g. of crushed ice. To the clear cooled solution, 15 g. (0.15 mole) of acetic anhydride was added in a single portion, and the whole mixture was vigorously stirred for 10 minutes. The milky reaction mixture was poured into a separatory funnel, and extracted with carbon tetrachloride (40 ml). The lower layer containing the sesamol acetate in carbon tetrachloride was separated and shaken with saturated sodium bicarbonate until effervescence had ceased.

The extract obtained after drying over anhydrous magnesium sulphate and removal of carbon tetrachloride under reduced pressure, was subjected to high vacuum distillation. 3,4-Methylenedioxyphenyl acetate was distilled at $112^{o}/2.5$ mm. Refractive index n_D^{20} 1.5281. Reported n_D^{25} 1.5265 (42). Yield 16.6 g (92%).

6. 3,4-Dimethoxyphenyl Acetate

15.4 g. (0.1 mole) of 3,4-dimethoxyphenol were acetylated by following the procedure employed in experiment 5 for the preparation of the 3,4-methylenedioxyphenyl acetate. The crude acetate was distilled at $128^{o}/2$ mm and partially solidified on cooling to room temperature. This semisolid product was pure enough to be used for the next step, and consequently, no further purification was carried out.

Yield 17.4 gr. (88%). Reported m.p. 44^{o} (2).

7. 3,4-Methylenedioxy-6-Nitrophenyl Acetate

The method of Gertler, Alexander and Beroza (52) was modified.

3,4-Methylenedioxyphenyl acetate (18 g.; 0.1 mole) dissolved in glacial acetic acid (60 ml) was gradually treated at room temperature

with 11 g. (0.12 mole) concentrated nitric acid (sp.g. 1.42, 70% nitric acid) in 20 ml of glacial acetic acid. The resulting clear orange solution was stirred for a further 3 hours and then poured into cold water (400 ml). One hour later the pale yellow precipitate was collected, washed thoroughly with water and dried. The dried product weighed 20.6 g. and melted at 103-105°.

Recrystallization from ethanol afforded a pale yellow well formed crystalline compound melting at 104-105°C. Yield 19.8 g. (88%). Reported m.p. 104-105° (52).

8. 3,4-Dimethoxy-6-nitrophenyl acetate

No previous synthesis of this compound has been reported.

3,4-Dimethoxyphenyl acetate 19.6 g. (0.1 mole was dissolved in 60 ml. of glacial acetic acid. To the rapidly stirred solution, kept at 20-25°, 11 g. (0.12 mole) of concentrated nitric acid (sp.g. 1.42, 70% nitric acid) in 20 ml of glacial acetic acid was added during the course of 30 minutes and stirring was continued for two more hours. A few minutes after the first addition of the nitric acid-acetic acid solution into the nitration mixture, the nitrophenyl acetate started to separate as a pale yellow crystalline solid. The entire contents of the flask were then transferred to a 600 ml beaker and 300 ml of water was added. The pale yellow precipitate was collected on a Büchner funnel, washed thoroughly with water, and dried in the dark. It weighed 21.9 g. and melted at 115-118°C. After crystallization from ethanol, pale yellow prisms were obtained which melted at 117-118°. Yield 20.7 g. (85.4%). On exposure to light a more intense yellow colour develops on the surface of the crystals.

Anal. Calc'd for $C_{10}H_{11}NO_6$	C, 49.79;	H, 4.59;	N, 5.81%
Found	C, 49.51;	H, 4.47;	N, 6.08%

9. 3,4-Methylenedioxy-6-Nitrophenol

A mixture of 3,4-methylenedioxy-6-nitrophenyl acetate (22.5 g.) 0.1 mole), ethanol (220 ml) and 20 per cent by volume sulphuric acid solution (125 ml) was refluxed on the water bath for forty minutes. The hot reaction solution deposited golden yellow crystalline needles on cooling. The precipitated crystalline product was filtered off and washed thoroughly with cold water. The product was dried first in the air and then in vacuum. It weighed 17.5 g. (96%) and melted at 94-96°.

After crystallization from 60 per cent ethanol, it melted at 95-96°. Reported m.p. were 82-84° (53) and 93-94° (52).

Extraction of the mother liquors with ether (100 ml) and removal of the solvent, gave an additional amount of 0.6 g. melting at 92-93°. Thus the total yield obtained was 18.1 g. (98.3%).

10. 3,4-Dimethoxy-6-Nitrophenol

24.1 gr. (0.1 mole) of 3,4-dimethoxy-6-nitrophenyl acetate were hydrolysed to 3,4-dimethoxy-6-nitrophenol under conditions similar to those employed in experiment 9. During the hydrolysis some of the product separated in yellow crystalline needles. The product obtained without recrystallization showed a m.p. 144-145° which remained unchanged after recrystallization from a mixture of ethanol-water (2:1). Yield 19.4 g. (97.8%). Reported melting points in the literature were: 142-3° (53), 143° (54), 144° (55).

11. 3,4-Methylenedioxy-6-Hydroxyacetanilide

The procedure described by Hayes and Gever (115), for the reductive acetylation of methyl α-oximinofuroyl acetate was adapted for the synthesis of 3,4-methylenedioxy-6-hydroxyacetanilide.

1.83 g. (0.01 mole) of 3,4-methylenedioxy-6-nitrophenol was mixed with glacial acetic acid (50 ml) and acetic anhydride (1.1 g.; 0.011 mole). The nitrogroup was reductively acetylated, using 0.015 g. of 10 per cent palladium-on-carbon, employing the Parr-hydrogenation apparatus at room temperature and a hydrogen pressure of 3 atmospheres. Although the uptake of hydrogen was complete in about 7-8 minutes, the hydrogenation mixture was shaken for a further 20 minutes. Some of the anilide crystallised during the course of the reaction. The reaction mixture was therefore dissolved in hot ethanol and the catalyst removed by filtration of the hot solution through a preheated funnel. The solution was concentrated under reduced pressure (water aspirator) to a semi-solid state, diluted with water (100 ml) and filtered.

The nearly white product obtained, after washing with water and drying, had a m.p. 206-208°. Crystallization from ethanol-water (1:1) afforded a cotton-like white crystalline compound melting at 209-211°C. Yield 1.78 gr. (91%).

Anal. Calc'd for $C_9H_9NO_4$	C, 55.39;	H, 4.64; N, 7.18%
Found	C, 55.17;	H, 4.75; N, 7.33%

12. 3,4-Dimethoxy-6-Hydroxyacetanilide

The procedure followed in experiment 11 was also applied for the preparation of this compound.

A mixture of 1.99 g. (0.01 mole) of 3,4-dimethoxy-6-nitrophenol, 5 ml of glacial acetic acid, 1.1 g. (0.011 mole) of acetic anhydride and 0.015 g. of 10 per cent palladium-on-carbon, was hydrogenated at room temperature under a hydrogen pressure of 3 atmospheres. Although the uptake of hydrogen was complete in about 7-8 minutes, the hydrogenation mixture was shaken in the hydrogenation apparatus for a further 20 minutes. The catalyst was filtered and the solvent removed by distillation in vacuo. The residual oil on stirring with 10 ml of benzene, crystallized to give 1.90 g. (90%) of a white powder melting at 132-135°. For analysis, the material was recrystallized from benzene to yield colourless needless of melting point 137-138°.

Anal. Calc'd for $C_{10}H_{13}N_1O_4$ C, 56.86; H, 6.20; N, 6.63%

Found C, 57.08; H, 6.04; N, 6.41%

13. 3,4-Methylenedioxy-6-Aminophenol Hydrochloride

0.5 g. of 3,4-methylenedioxy-6-nitrophenol, 0.01 g. of 10 per cent palladium-on-carbon and 250 ml of absolute diethyl ether were shaken at room temperature under a hydrogen pressure of 3 atmospheres. The hydrogenation of the nitrogroup to the amino group was complete in about 2 hours. This conversion was easily detected from the disappearance of the nitrophenol yellow colour from the hydrogenation mixture. The catalyst was removed by filtration in an atmosphere of nitrogen or hydrogen.

Into the flask containing the clear filtrate, hydrogen chloride was introduced until no more solid separated. The white crystalline hydrochloride of the 3,4-methylenedioxy-6-aminophenol was collected and washed with 5 ml of benzene, and was then dried in vacuum. The product weighed 0.45 g. and on heating above 195° started to become gradually dark and at 210°C had completely decomposed to a black material.

Anal. Calc'd for $C_7H_8N_1Cl_1O_3$ N, 7.39%

Found N, 7.51%

14. Reduction of 3,4-Methylenedioxy-6-Nitrophenol to the Corresponding Amino Compound

(a) Reduction with platinum oxide or palladium-on-carbon as catalysts.

A solution of 1.83 g. (0.01 mole) of 3,4-methylenedioxy-6-nitrophenol in 50 ml of 96% ethanol was placed in the reaction bottle of the catalytic hydrogenation apparatus, and 0.015 g. of platinum oxide or 0.015 g. of 10% palladium-on-carbon was added. The mixture was shaken with hydrogen at room temperature and a pressure of 3 atmospheres until three molecular equivalents had been absorbed. The disappearance of the yellow colour from the solution served as the best indicator to show the completion of the reduction. The time required was about 10 minutes. Removal of the catalyst by filtration in a nitrogen atmosphere, afforded a colorless solution. Despite many efforts to isolate the reduction product (3,4-methylenedioxy-6-aminophenol) by removal of the solvent in a nitrogen atmosphere, led to failure. A dark gray solid was always obtained, which, on contact with air, was rapidly decomposed to a black powder.

(b) Reduction with Raney-Nickel

A mixture of 1.83 g. (0.01 mole) of 3,4-methylenedioxy-6-nitrophenol, 50 ml of 96% ethanol and 0.2 g. of Raney-nickel was hydrogenated at 80-90°, at an initial pressure of 3 atmospheres. The time required for the uptake of three molecular equivalents was about 1 hour. The complete reduction of the nitrocompound was best detected from the disappearance of its yellow colour from the solution. On removal of the catalyst by filtration in a nitrogen atmosphere, a colourless solution was obtained, which, when used directly in reactions with α-ketoesters, gave cyclization products whose yields indicated the quantitative preparation of 3,4-methylenedioxy-6-aminophenol. (cf. experiment 20)

15. Reduction of 3,4-Dimethoxy-6-Nitrophenol to the Corresponding Amino Compound

The procedures (a) and (b) employed in the previous experiment 14 for the catalytic reduction of the 3,4-methylenedioxy-6-nitrophenol, were also adopted for the reduction of the 3,4-dimethoxy-6-nitrophenol with only one slight modification. As a result of different solubilities, the 50 ml of 96% ethanol were replaced by 70 ml of methoxyethyleneglycol.

Attempts to isolate the 3,4-dimethoxy-6-aminophenol led as in experiment 14, to black powder.

B. Synthesis of 6,7-Dialkoxy-1,4-Benzoxazin-2-Ones

3,4-Methylenedioxy-6-aminophenol and 3,4-dimethoxy-6-aminophenol were condensed with the following α-ketoesters to the corresponding 1,4-benzoxazin-2-ones.

(a) Diethyl oxalacetate (163, 164)

(b) Ethyl pyruvate (165)

(c) Ethyl benzoylformate (166)

(d) Methyl acetopyruvate (167)

(e) Methyl benzoylpyruvate (167)

16. 6,7-Methylenedioxy-1,4-Benzoxazin-2-One 3-Acetic Acid Ethyl Ester

At room temperature and in a nitrogen atmosphere 1.88 g. (0.01 mole) of diethyl oxalacetate dissolved in 10 ml of glacial acetic acid were mixed with an ethanolic solution of 3,4-methylenedioxy-6-aminophenol (0.01 mole). On mixing an orange coloured solution was formed which rapidly deposited a yellow crystalline solid. The flask containing the reaction mixture was tightly closed and shaken for 5 minutes, and then allowed to stand at room temperature for a further 3 hours. The solid material which separated was collected on a filter, washed with ethanol and dried. After recrystallization from hot ethanol or even better a mixture of ethanol-methoxyethyleneglycol (1:1), it gave 2.51 g. (91%) of fine silky canary-yellow coloured crystalline needles melting at 164-165°.

Anal. Calc'd for $C_{13}H_{11}NO_6$	C, 56.32; H, 3.99; N, 5.05%
Found	C, 56.51; H, 3.88; N, 5.10%

17. 6,5-Methylenedioxy-3-Methyl-1,4-Benzoxazin-2-One

Working as in experiment 16, the ethanolic solution containing the 3,4-methylenedioxy-6-aminophenol (0.01 mole) was mixed with 1.3 g. (0.011 mole) of ethylpyruvate dissolved in 10 ml of glacial acetic acid. On mixing an orange colored solution resulted which after a few minutes of shaking deposited a yellow-greenish solid. After standing overnight, the product was filtered, dissolved in a large amount of ethanol and boiled with charcoal. Removal of the charcoal by filtration afforded a clear yellow solution which on cooling in an ice-water bath deposited 0.445 g. (32%) of yellow crystalline needles melting at 241-242°. Recrystallization from ethanol did not change the melting point.

Anal. Calc'd for $C_{10}H_7N_1O_7$ C, 58.54; H, 3.34; N, 6.83%

Found C, 58.23; H, 3.28; N, 6.96%

18. 6,7-Methylenedioxy-3-Phenyl-1,4-Benzoxazin-2-One

At room temperature and in a nitrogen atmosphere 2 g. (0.011 mole) of ethyl benzoylformate dissolved in 10 ml of glacial acetic acid, were mixed with 1.53 g. (0.01 mole) of 3,4-methylenedioxy-6-aminophenol dissolved in 50-70 ml of ethanol. The ethanolic solution of the 3,4-methylenedioxy-6-aminophenol was obtained as described in experiment 14. The flask containing the reaction mixture was tightly closed, shaken for a few minutes, and then heated at 55-60° on a water bath for 6 hours. At the end of the heating time a deep orange solution was obtained which after standing overnight at room temperature deposited a yellow crystalline product. The precipitate was collected on a

Büchner funnel, taken up in acetone and boiled with charcoal. Removal of the charcoal by filtration through a preheated funnel gave a yellow solution with a strong blue-green fluorescence. This solution was partially concentrated by distillation until yellow needles appeared and then was cooled down in a dry-ice-bath for a few minutes. The 6,7-methylenedioxy-3-phenyl-1,4-benzoxazin-2-one was collected on a filter and in an almost quantitative yield; washed with ethanol and dried. It weighed 2.16 g. (80.8%) and melted at 196-196.5°. Recrystallization from hot ethanol did not improve the melting point.

Anal. Calc'd for $C_{15}H_9N_1O_4$	C, 67.42;	H, 3.39;	N, 5.24%
Found	C, 67.58;	H, 3.42;	H, 5.36%

19. 6,7-Methylenedioxy-3-Acetonyl-1,4-Benzoxazin-2-One

An ethanolic solution of 1.53 g. (0.01 mole) of 3,4-methylenedioxy-6-aminophenol, obtained as in experiment 14, was added to a solution of 1.5 g. (0.01 mole) methyl acetopyruvate in 10 ml glacial acetic acid, contained in a 250 ml Erlenmeyer flask. The experiment was conducted at room temperature in a nitrogen atmosphere. On mixing the two solutions, a deep orange coloured crystalline compound rapidly separated. The flask containing the reaction mixture was tightly closed, shaken for a few minutes and then allowed to stand at room temperature for an extra hour.

The product was filtered with suction, washed with ethanol and dried. It weighed 2.29 g. (93%) and melted at 191-192°. Recrystallization

from hot acetone did not improve the melting point.

Anal. Calc'd for $C_{12}H_9NO_5$ C, 58.30; H, 3.67; N, 5.66%

Found C, 58.07; H, 3.90; N, 5.86%

20. 6,7-Methylenedioxy-3-Phenacyl-1,4-Benzoxazin-2-One

This compound was obtained by following the procedure applied in experiment 19. From the condensation of 2.1 g. (0.01 mole) methyl-benzoylpyruvate and 1.53 g. (0.01 mole) of 3,4-methylenedioxy-6-aminophenol, a red shiny crystalline compound was obtained melting at 260°. It weighed 3.07 g. (99.3%). Recrystallization from hot acetone, gave no improvement in the melting point.

Anal. Calc'd fro $C_{17}H_{11}NO_5$ C, 66.02; H, 3.58; N, 4.53%

Found C, 65.95; H, 3.46; N, 4.70%

21. 6,7-Dimethoxy-1,4-Benzoxazin-2-One Acetic Acid Ethyl Ester

1.99 g. (0.01 mole) of 3,4-dimethoxy-6-nitrophenol were catalytically reduced as described in experiment 15. The hydrogenation solution containing 0.01 mole of 3,4-dimethoxy-6-aminophenol, was freed from catalyst and mixed with a solution of 1.88 g (0.01 mole) diethyl oxalacetate in 10 ml of glacial acetic acid. The flask containing the reaction mixture was tightly closed and then heated at 65-70° on a water bath for 12 hours. The red solution on standing overnight in a refrigerator, deposited yellow crystalline needles. The product was collected on a Büchner funnel and then taken up in methanol and boiled with charcoal. Removal of the charcoal by filtration afforded a yellow

solution which on cooling in a dry-ice-acetone bath gave 0.35 g. (11.9%) of shiny yellow needles melting at 157-159°. Recrystallization from hot methanol did not change the melting point.

Anal. Calc'd for $C_{14}H_{15}NO_6$	C, 57.33;	H, 5.15;	N, 4.77%
Found	C, 57.05	H, 5.11;	N, 5.02%

22. 6,7-Dimethoxy-3-Methyl-1,4-Benzoxazin-2-One

From the condensation of 1.3 g. (0.011 mole) of ethylpyruvate and 1.69 g. (0.01 mole) of 3,4-dimethoxy-6-aminophenol, following the procedure of experiment 21, a yellow crystalline compound was obtained melting at 188-189°. Yield 0.18 g. (8.1%). Recrystallization from hot methanol left the melting point unchanged.

Anal. Calc'd for $C_{11}H_{11}NO_4$	C, 59.73;	H, 5.01;	N, 6.33%
Found	C, 59.92;	H, 5.17;	N, 6.47%

23. 6,7-Dimethoxy-3-Phenyl-1,4-Benzoxazin-2-One

From the condensation of 2 g. (0.011 mole) benzoylformate and 1.69 g. (0.01 mole) of 3,4-dimethoxy-6-aminophenol, following the procedure of experiment 21, a yellow substance in fine crystalline needles was obtained melting at 168°. Yield 1.82 g. (64.3%). Recrystallization from hot methanol did not change the melting point. The compound when dissolved in acetone, exhibits a strong blue-green fluorescence.

Anal. Calc'd for $C_{16}H_{13}NO_4$	C, 67.83;	H, 4.62;	N, 4.94%
Found	C, 67.63;	H, 4.70;	N, 5.13%

24. 6,7-Dimethoxy-3-Acetonyl-1,4-Benzoxazin-2-One

At room temperature and in a nitrogen atmosphere 1.5 g. (0.01 mole) of methyl acetopyruvate dissolved in 10 ml of glacial acetic acid, were mixed with 1.69 g. (0.01 mole) of 3,4-dimethoxy-6-aminophenol dissolved in methoxyethyleneglycol. The latter compound in methoxyethyleneglycol was obtained as described in experiment 15.

The flask was tightly closed and shaken for one minute and then heated for 12 hours at 60-70° on a water bath. After the heating period most of the solvent was removed by distillation under reduced pressure. The residue (about 30 ml) was placed in a refrigerator for 2-3 hours during which time a red solid was precipitated. The product was collected on a Büchner funnel, washed with diethylether and dried. It weighed 1.88 g. (71.4%) and melted at 180-183°. 6,7-Dimethoxy-3-acetonyl-1,4-benzoxazin-2-one was crystallized from ethanol as orange needles melting at 187-188°. Yield 1.71 g. (65%).

Anal. Calc'd for $C_{13}H_{13}NO_5$	C, 59.31;	H, 4,98;	N, 5.32%
Found	C, 59.03;	H, 4.90;	N, 5.52%

25. 6,7-Dimethoxy-3-Phenacyl-1,4-Benzoxazin-2-One

From the condensation of 1.69 g. (0.01 mole) 3,4-dimethoxy-6-aminophenol and 2.1 g. (0.01 mole) methyl benzoylpyruvate, working as in experiment 24, a red solid was obtained which weighed 2.65 g. (81.5%) and melted at 171-173°. For analysis, a small sample was dissolved in a large volume of diethylether, boiled with charcoal and filtered.

Evaporation of the ether to a quarter of its volume, gave a deep red crystalline compound melting at 175-176°.

Anal. Calc'd for $C_{18}H_{15}NO_5$	C, 66.45;	H, 4.65;	N, 4.30%
Found	C, 66.69;	H, 4.84;	N, 4.16%

26. Attempted Nitration of 6,7-Methylenedioxy-3-Phenyl-1,4-Benzoxazin-2-One

A solution of 0.5 g. concentrated nitric acid (sp. gr. 1.42, 70% nitric acid, 0.0052 mole) in 5 ml of glacial acetic acid was added in one portion to a solution of 0.67 g. (0.0025 mole) of 6,7-methylenedioxy-3-phenyl-1,4-benzoxazin-2-one in 20 ml of glacial acetic acid contained in a 100 ml Erlenmeyer flask. The mixture was stirred for 3 hours at room temperature and then poured into 200 ml of water. The yellow precipitate was collected directly on a Büchner funnel, washed with water and dried. It weighed 0.58 g. and was found to be the starting material unchanged.

27. 6,7-Methylenedioxy-2-Phenomorpholone-3-Acetic Acid Ethyl Ester

A suspension of 1.38 g. (0.005 mole) of 6,7-methylenedioxy-1,4-benzoxazin-2-one-3-acetic acid ethyl ester in 100 ml of absolute ethanol was placed in the reaction bottle of the catalytic hydrogenation apparatus and 0.1 g. of 10% palladium-on-charcoal was added. The mixture was shaken with hydrogen at room temperature and a pressure of 0.3 atmospheres until one molecular equivalent had been absorbed. The disappearance of the yellow colour of the benzoxazinone from the hydrogenation solution, served as the best indicator for the completion

of reduction The time required was about 30 minutes. Removal of the catalyst by filtration in a nitrogen atmosphere, gave a colourless solution. This solution was concentrated to one fourth its volume under reduced pressure at room temperature. For this purpose a film evaporator was used. The residue in which most of the product had separated as white crystals, was cooled in an ice-water bath and then filtered under suction in a nitrogen atmosphere. The white crystalline compound was washed with 5 ml of light petroleum ether and dried in vacuo. It weighed 1.29 g. (92%) and melted at 110.5-111°C. Recrystallization from benzene did not raise the melting point. 6,7-Methylenedioxy-2-phenomorpholone-3-acetic acid ethyl ester found to be sensitive to air oxidation.

Anal. Calc'd for $C_{13}H_{13}NO_6$	C, 55.91;	H, 4.69;	N, 5.02%
Found	C, 55.98;	H, 4.75;	N, 5.20%

28. 6,7-Methylenedioxy-3-Methyl-2-Phenomorpholone

From the hydrogenation of 0.5 g. 6,7-methylenedioxy-3-methyl-1,4-benzoxazin-2-one, 50 ml of absolute ethanol with 0.05 g. of 10% palladium-on-charcoal as catalyst, and working as in experiment 27, a white crystalline compound was obtained melting at 177-179°. Yield 0.46 g. This compound was sensitive to air oxidation.

Anal. Calc'd for $C_{10}H_9NO_4$	C, 57,97;	H, 4.38;	N, 6.76%
Found	C, 57.96;	H, 4.41;	N, 6.95%

29. 6,7-Methylenedioxy-3-Phenyl-2-Phenomorpholone

From the hydrogenation of 0.5 g. 6,7-methylenedioxy-3-phenyl-1,4-benzoxazin-2-one, 50 ml of absolute ethanol with 0.05 g. of 10% palladium-on-charcoal as catalyst, and working as in experiment 27, a white crystalline compound was obtained melting at 170.5-171°. Yield 0.47 g. This phenomorpholone also proved to be very sensitive to air oxidation.

Anal. Calc'd for $C_{15}H_{11}NO_4$	C, 66.91;	H, 4.12;	N, 5.20%
Found	C, 67.16;	H, 4.08;	N, 5.11%

30. 6,7-Dimethoxy-3-Phenyl-2-Phenomorpholone

From the hydrogenation of 0.5 g. 6,7-Dimethoxy-3-phenyl-1,4-benzoxazin-2-one, 50 ml of absolute ethanol with 0.05 g. of 10% palladium-on-charcoal as catalyst, and working as in experiment 27, a white crystalline compound was obtained melting at 116-117°. Yield 0.45 g. This compound was very sensitive to air oxidation.

Anal. Calc'd for $C_{16}H_{15}NO_4$	C, 67.35;	H, 5.30;	N, 4.91%
Found	C, 67.17;	H, 5.23;	N, 5.15%

31. Attempted Hydrogenation of 6,7-Methylenedioxy-3-Acetonyl-1,4-Benzoxazin-2-One

The attempted hydrogenation of this compound by using the conditions employed in experiment 27, resulted in recovery of the starting material. Further the conditions for the hydrogenation of this compound were varied by using as solvents methoxyethyleneglycol, tetrahydrofuran, glacial acetic acid, dioxane or acetone, or alternatively by using platinum oxide

as catalyst. However, hydrogenation was not effected by any of these changes and hydrogenation at temperatures 80-90° under a pressure of 5 atmospheres, caused extensive decomposition of the starting material.

32. Attempted Hydrogenation of 6,7-Methylenedioxy-3-Phenacyl-1,4-Benzoxazin-2-One

All hydrogenation attempts led to the same negative results as in experiment 31.

33. Attempted Nitration of 6,7-Methylenedioxy-3-Phenyl-2-Phenomorpholone

A solution of 0.5 g. concentrated nitric acid (sp. g. 1.42, 70% nitric acid) in 5 ml of glacial acetic acid was added in one portion to a solution of 0.2 g. of 6,7-methylenedioxy-3-phenyl-2-phenomorpholone in 10 ml of glacial acetic acid contained in a 50 ml Erlenmeyer flask. The mixture was stirred for 3 hours at room temperature and then poured into 100 ml of water. The yellow precipitate was collected on a Büchner funnel, washed with water and dried in vacuo. It weighed 0.46 g. and melted at 193-195°. The infrared spectrum of this compound was the same as that of the 6,7-methylenedioxy-3-phenyl-1,4-benzoxazin-2-one which had been prepared in experiment 18. Further a mixed melting point determination with an authentic sample of 6,7-methylenedioxy-3-phenyl-1,4-benzoxazin-2-one did not show any depression of the m.p.

34. Dehydrogenation of 6,7-Methylenedioxy-2-Phenomorpholone-3-Acetic Acid Ethyl Ester to 6,7-Methylenedioxy-1,4-Benzoxazin-2-One-3-Acetic Acid Ethyl Ester

0.1 gr. of 6,7-Methylenedioxy-2-phenomorpholone-3-acetic acid ethyl ester in 10 ml of glacial acid, was stirred for 5 hours at room temperature. The resulting yellow solution on pouring in 50 ml of water, separated a yellow solid. This yellow solid was collected on a filter, washed with a few drops of methanol and dried. It had a m.p. 160-163^{o} and its infrared spectrum was the same as that of the 6,7-methylenedioxy-1,4-benzoxazin-2-one-3-acetic acid ethyl ester prepared in experiment 16. Further, no depression of the m.p. was observed of a mixed m.p. determination with an authentic sample of 6,7-methylenedioxy-1,4-benzoxazin-2-one-3-acetic acid ethyl ester.

35. Dehydrogenation of

(a) 6,7-Methylenedioxy-3-methyl-2-phenomorpholone,

(b) 6,7-Methylenedioxy-3-phenyl-2-phenomorpholone, and

(c) 6,7-Dimethoxy-3-phenyl-2-phenomorpholone to the corresponding 6,7-dialkoxy-1,4-benzoxazin-2-ones.

Working as in experiment 34, all three above mentioned phenomorpholones were converted to the corresponding 6,7-dialkoxy-1,4-benzoxazin-2-one. It was found that the time necessary for the conversion varied for different substituents attached in the 3-position of the phenomorpholone nucleus; the conversion with a methyl group takes place in the course of 8-10 hours, whereas with a phenyl group it is achieved in 3 hours.

PART II

36. 3,4-Methylenedioxyphenyl 2-Bromo-4,5-Methylenedioxystyryl Ketone

This compound was prepared by following the procedure of Bailey and Robinson (97) for the synthesis of 3,4-dimethoxyphenyl 2-bromo-4,5-dimethoxystyryl ketone.

Into a 3 liter three-necked flask set on a boiling water bath and fitted with an efficient stirrer and a separatory funnel, were placed 1.5 l. of 96 per cent ethanol, 114.5 g. (0.5 mole) of 6-bromopiperonal (27) and 82 g. (0.5 mole) of acetopiperone (123). The mixture was stirred until all the solid had dissolved. To the boiling ethanolic solution, with vigorous stirring, 150 ml of 8 per cent sodium hydroxide solution was added by means of the separatory funnel. A yellow solid separated almost immediately. The mixture was kept vigorously stirred, until it was so thick that stirring was no longer effective (about 10-15 minutes). Stirrer and bath were removed and the mixture was left overnight at room temperature. The yellow material was filtered with suction on a Büchner funnel, washed with alcohol followed by water until the washings were neutral to litmus and then with 100 ml of ethanol. The crude chalcone, after drying in the air and then in vacuo, weighed 152 g. (81%) and melted at 155-157°. The crude material so obtained was pure enough to be used for the next stage.

3,4-Methylenedioxyphenyl 2-bromo-4,5-methylenedioxystyryl ketone crystallized from hot xylene in fine pale yellow prisms melting at 158-160°C.

Anal. Calc'd for $C_{17}H_{11}O_5Br$	C, 54.42;	H, 2.95%
Found	C, 54.34;	H, 2.83%

37. 2-Phenyl-3-(2-Bromo-4,5-Methylenedioxyphenyl)-5-(3,4-Methylenedioxyphenyl) Pyrazoline

The phenylhydrazone of 3,4-methylenedioxyphenyl 2-bromo-4,5-methylenedioxystyryl ketone could not be prepared in the usual way, and an adaptation of the pyridine method of oximation (158) resulted in the related pyrazoline LXXXVII.

A mixture of 1 g. 3,4-methylenedioxyphenyl 2-bromo-4,5-methylenedioxystyryl ketone, 1 g. of phenylhydrazine hydrochloride and 5 ml of pyridine, was heated on a steam bath for 5 hours. After cooling, the crystalline product was collected, washed with a few drops of ethanol, and dried in vacuum. It weighed 0.45 g. (35.1%) and melted at 211-213°.

The pyrazoline crystallized from ethyl acetate in fine pale yellow prisms melting at 216-218°.

Anal. Calc'd for $C_{23}H_{16}BrN_2O_4$	C, 59.49;	H, 3.47;	N, 6.03%
Found	C, 59.29;	H, 3.53;	N, 5.80%

38. β-(3,4-Methylenedioxybenzoyl)-α-(2-bromo-4,5-Methylenedioxyphenyl) propionitrile

The procedure of Bailey and Robinson (97) for the preparation of β-(3,4-dimethoxybenzoyl)-α-(2-bromo-4,5-dimethoxyphenyl) propionitrile was adopted under modified conditions.

Into a 2-liter three-necked flask set on a water bath and fitted with a stirrer, a reflux condenser connected at the upper end with an exit tube leading to the hood and a separatory funnel, were placed 187.6 g. (0.5 mole) of 3,4-methylenedioxyphenyl 2-bromo-4,5-methylenedioxystyryl ketone, 800 ml of methoxyethyleneglycol, 400 ml of tetrahydrofuran and 30 g. of glacial acetic acid. The mixture was heated and stirred until all the solid had dissolved and a clear green yellow solution had been obtained. To this clear solution with heating and gentle stirring, a solution of 55 g. of sodium cyanide in 120 ml of water was added from the separatory funnel over a period of about 5-7 minutes. Ten minutes after all the sodium cyanide had been added, stirring was interrupted and the mixture was kept hot (at about 70°) for an extra hour. During this time, the initial greenish colour changed to a dark brown. The flask was removed from the water bath and allowed to cool slowly at room temperature and then placed in a refrigerator for 5-6 hours. The white crystalline material which had separated, was collected on a Büchner funnel, washed first with ethanol and then with water until the washings were free from sodium cyanide (silver nitrate test). It weighed 175.2 g. (85%) and melted at 139-142°. This product was pure enough to be used for the next step.

β-(3,4-Methylenedioxybenzoyl)-α-(2-bromo-4,5-methylenedioxyphenyl) propionitrile crystallized from acetone in colourless needles melting at 144-147°.

Anal Calc'd for $C_{18}H_{12}BrNO_5$	C, 53.75;	H, 3.01%
Found	C, 53.80;	H, 2.98%

39. β-(3,4-Methylenedioxybenzoyl)-α-(2-Bromo-4,5-methylenedioxyphenyl) Propionamide

The procedure of Bailey and Robinson (97) for the preparation of β-(3,4-dimethoxybenzoyl)-α-(2-bromo-4,5-dimethoxyphenyl) propionamide was adopted.

Into a 1 liter round bottom flask equipped with a mechanical stirrer and a separatory funnel, were placed 40.2 g. (0.1 mole) of β-(3,4-methylenedioxybenzoyl)-α-(2-bromo-4,5-methylenedioxyphenyl) propionitrile and 300 ml of glacial acetic acid. To this vigorously stirred suspension at room temperature 35 ml of concentrated sulphuric acid was gradually added from the separatory funnel for 10 minutes; any rise in the temperature being checked by cooling. Ten minutes after all the sulphuric acid has been added, the stirrer was stopped and the resulting greenish solution was poured with stirring into 1.5 liters of cold water. The nearly white precipitate was collected on a Büchner funnel, washed thoroughly with water and dried. It weighed 41.4 g. (98.5%) and melted at 193-194° with decomposition. The crude material so obtained, was pure enough to be used for the next stage.

β-(3,4-Methylenedioxybenzoyl)-α-(2-bromo-4,5-methylenedioxyphenyl) propionamide crystallized from methoxyethyleneglycol in a white fine

crystalline powder melting at 204-205° with decomposition.

Anal. Calc'd for $C_{18}H_{14}BrNO_6$	C, 51.44;	H, 3.36;	N, 3.33%
Found	C, 51.23;	H, 3.47;	N, 3.33%

40. β-(3,4-Methylenedioxybenzoyl)-α-(2-Bromo-4,5-Methylenedioxyphenyl) Propionic Acid

A mixture of 42 g. (0.1 mole) of β-(3,4-methylenedioxybenzoyl)-α-(2-bromo-4,5-methylenedioxyphenyl) propionamide, 300 ml of 96% ethanol and 250 ml of 10% sodium hydroxide solution was refluxed on a water bath until evolution of ammonia had ceased. The time required was about 20-24 hours. The alkaline solution was cooled, diluted with twice its volume of water, and filtered. It was then acidified with 5N-hydrochloric acid. The precipitated solid material was filtered on a Büchner funnel, washed thoroughly with water and dried. It weighed 28.2 g.

β-(3,4-Methylenedioxybenzoyl)-α-(2-bromo-4,5-methylenedioxyphenyl) propionic acid crystallized from a mixture of glacial acetic acid-ethanol (1:1) or glacial acetic acid-water (2:1) in white hard prisms, melting partly at 146-148°, resolidifying, and remelting again at 176-179°. Yield 24.2 g. (57.7%).

Anal. Calc'd for $C_{18}H_{13}BrO_7$	C, 51.32;	H, 3.11%	
Found	C, 51.30;	H, 3.06%	

41. γ-(3,4-Methylenedioxyphenyl)-α-(2-Bromo-4,5-Methylenedioxyphenyl)-Butyric Acid

A mixture of 42.1 g. (0.1 mole) of β-(3,4-methylenedioxybenzoyl)-α-(2-bromo-4,5-methylenedioxyphenyl) propionic acid, 300 ml of toluene,

5 ml of glacial acetic acid, 75 ml of water, 150 ml of concentrated hydrochloric acid and 150 gr. of amalgamated zinc turnigs, was placed in 1-liter flask set on a water bath and fitted with a separatory funnel and a reflux condenser connected to a gas absorption trap.

The mixture was refluxed for 48 hours during which time at 12-hour intervals three 50 ml portions of concentrated hydrochloric acid were added. After cooling the toluene layer, separated from the aqueous layer, it was washed with water and then extracted 5 times with 50 ml portions of saturated sodium carbonate solution. Acidification of the combined sodium carbonate extracts with dilute hydrochloric acid, afforded an oil which in a few minutes became a highly viscous brownish mass. This product on drying in vacuo failed to give any solid compound. The crude material so obtained, holds persistently a small amount of toluene which prevents its crystallization. In order to remove the toluene, the highly viscous product was dissolved in 100 ml of n-propylalcohol and the solvent then evaporated as completely as possible. The remaining residue, dried in vacuo, gave on trituration an amorphous brownish solid material which crystallized from ethanol in colourless prisms melting at 126.5-128°. Yield 35.8 g. (87.9%).

Anal. Calc'd for $C_{18}H_{15}BrO_6$	C, 53.09;	H, 3.71%
Found	C, 53.16;	H, 3.82%

42. 1-Oxo-6,7-Methylenedioxy-2-(2-Bromo-4,5-Methylenedioxyphenyl)-1,2,3,4-tetrahydronaphthalene

The procedure of Bailey and Robinson (97) for the preparation of 1-oxo-6,7-dimethoxy-2-(2-bromo-4,5-dimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene was adopted.

Into a 1-liter round bottom flask set on a water bath and fitted with a reflux condenser connected at the upper end with an exit tube leading to the hood, was placed a mixture of 40.7 g. (0.1 mole) of γ-(3,4-methylenedioxyphenyl)-α-(2-bromo-4,5-methylenedioxyphenyl) butyric acid and 120 ml of phorphoryl chloride. The mixture was refluxed for five minutes and then left to cool. The resulting dark green solution was poured onto 1 kg of crushed ice and left overnight. The nearly white solid was collected on a Büchner funnel, washed thoroughly with water and dried. It weighed 34.5 g. and no characteristic m.p. was obtained. The crude product, five times recrystallized from hot ethylacetate, gave a white fine crystalline compound melting partly at 165-167°, resolidifying, and remelting again at 184-185°. Yield 28.8 g. (74%).

Anal. Calc'd for $C_{18}H_{13}BrO_5$ C, 55.55; H, 3.36%

Found C, 55.75; H, 3.48%

43. 1-Oximino-6,7-Methylenedioxy-2-(2-Bromo-4,5-Methylenedioxyphenyl)-1,2,3,4-Tetrahydronaphthalene

A mixture of 3.9 g. (0.01 mole) 1-oxo-6,7-methylenedioxy-2-(2-bromo-4,5-methylenedioxyphenyl)-1,2,3,4-tetrahydronaphthalene, 4 g. of hydroxylamine hydrochloride and 20 ml of pyridine, was heated on a boiling water bath for 5 hours. The hot reaction mixture was cooled, diluted with

100 ml of water and acidified with dilute hydrochloric acid. The white precipitate was collected on a filter, washed thoroughly with water and dried. The crude oxime so obtained crystallized from a mixture of ethanol-tetrahydrofuran (1:1) in white well formed prisms melting at 232-234°. Yield 3.88 g. (96%).

Anal. Calc'd for $C_{18}H_{14}O_5NBr$ C, 53.48; H, 3.49; N, 3.46%

Found C, 53.63; H, 3.70; N, 3.68%

44. 1-Formamido-6,7-Methylenedioxy-2-(2-bromo-4,5-Methylenedioxyphenyl)-1,2,3,4-tetrahydronaphthalene

In a 100 ml three-necked flask fitted with a reflux condenser, a thermometer extending to the bottom and a separatory funnel, were placed 3.9 g. (0.01 mole) of 1-oxo-6,7-methylenedioxy-2-(2-bromo-4,5-methylenedioxyphenyl)-1,2,3,4-tetrahydronaphthalene, 25 ml of formamide and 5 ml of 90% formic acid. The whole mixture was heated for 4 hours at 175-180° by means of an electric heating mantle. During the heating time, at 1-hour intervals, two 5 ml portions of 90% formic acid were added in order to maintain a slightly acidic reaction mixture. The warm mixture was cooled, diluted with water and extracted twice with two 50 ml portions of chloroform. The chloroform extract was washed with water and dried over sodium sulphate. Removal of the solvent left a highly viscous oil which dried first in vacuo and then recrystallized three times from a mixture of ethanol-dioxan (1:1) afforded a colourless crystalline compound melting at 245-246°. Yield 0.27 gr. (6.9%).

Anal. Calc'd for $C_{19}H_{16}BrNO_5$ C, 54.56 H, 3.86 N, 3.35%

Found C, 54.48 H, 3.70 N, 3.58%

45. Attempted Preparation of 1-Amino-6,7-Methylenedioxy-2-(2-Bromo-4,5-Methylenedioxyphenyl)-1,2,3,4-Tetrahydronaphthalene

Two grams (0.052 mole) of crushed lithium aluminum hydride was weighed into a tared 50 ml Erlenmeyer flask, and 80 ml of anhydrous dioxan added. This mixture was transferred into a 500 ml three-necked, round-bottomed flask which was provided with a nitrogen inlet tube, a reflux condenser protected by a calcium chloride drying-tube, and a dropping funnel also fitted with a calcium chloride drying-tube. The apparatus had been swept out thoroughly by a stream of dry nitrogen. The lithium aluminum hydride-dioxan mixture was refluxed in a nitrogen atmosphere with stirring by means of a magnetic stirrer for 1/2 hour. Then a solution of 2.0 gr. (0.005 mole) of 1-oximino-6,7-methylenedioxy-2-(2-bromo-4,5-methylenedioxyphenyl)-1,2,3,4-tetrahydronaphthalene in 80 ml of anhydrous dioxan was added dropwise with stirring in a nitrogen atmosphere over a period of 30 minutes. The resulting reaction mixture was refluxed under these conditions for a further 30 minutes. After cooling to room temperature, wet dioxan was added to the mixture dropwise, with vigorous stirring. The voluminous white precipitate was filtered with suction, and the cake on the filter washed thoroughly with ether. The filtrate was transferred to a separatory funnel, and extracted with ether. After being dried overnight over anhydrous sodium sulphate, the ethereal extract was filtered and evaporated under reduced pressure in a nitrogen atmosphere. An oily residue remained and was dried in vacuo. The crude product so obtained, on trituration with a few mls of methanol, afforded a solid brownish compound which collected and dried, gave a m.p. 150-153°. This material dissolved in

ethanol and boiled with charcoal, afforded after filtration a colourless ethanolic solution from which a white crystalline compound separated on partial removal of the solvent. In this way 0.37 g. of a white crystalline substance were obtained melting at 157-158°C. Recrystallization from ethanol did not change the melting point. This product was not the anticipated one, but a debrominated compound for which analytical results and molecular weight determination were consistent with the molecular formula $C_{18}H_{17}N_1O_4$. A consideration of its infrared spectrum with some comparable data in the literature, suggests that this compound is 7,8-methylenedioxy-3-(3,4-methylenedioxyphenyl)-2,3,4,5-tetrahydro-1H-1-benzazepine.

Anal. Calc'd for $C_{18}H_{17}NO_4$	C, 69.43;	H, 5.50;	N, 4.50
Found	C, 69.31;	H, 5.59;	N, 4.49

Molecular weight calc'd for $C_{18}H_{17}NO_4$, 311

Found 319

46. <u>Attempted Cyclodehydration of 1-Formamido-6,7-Methylenedioxy-2-(2-Bromo-4,5-Methylenedioxyphenyl)-1,2,3,4-Tetrahydronaphthalene to a 7,8-Methylenedioxyisoquinoline Derivative by using Polyphosphoric Acid as Cyclization Agent</u>

To 4 g. of polyphosphoric acid contained in a 10 ml beaker at room temperature was added 0.42 g. (0.001 mole) of 1-formamido-6,7-methylenedioxy-2-(2-bromo-4,5-methylenedioxyphenyl)-1,2,3,4-tetrahydronaphthalene. The mixture was stirred thoroughly with a strong spatula for 15 minutes and left for 6 hours at room temperature. The dark paste was then transferred into 20 ml of ice water with thorough

stirring and trituration, and the beaker was rinsed with small portions of cold water. The product which separated from the cold water as a black precipitate was extracted with five 10 ml chloroform. The combined chloroform extracts were washed successively with 10 ml of water, 10 ml of 10% sodium bicarbonate solution and finally with 5 ml of water. The chloroform solution was dried over potassium sulphate and filtered. The chloroform was removed by distillation on a steam bath first at atmospheric pressure and finally under reduced pressure. The dark gummy residue was taken up in 10 ml of ethanol and boiled with charcoal. The charcoal was filtered off and the solvent was removed. A brownish waxy material was obtained which on treatment with a few drops of methanol failed to deposit any crystals, and there was no evidence to indicate that the desired product XCIII had been formed.

SUMMARY AND CONTRIBUTION TO KNOWLEDGE

1. The synthesis of 1,4-benzoxazin-2-ones substituted either by the methylenedioxy or two methoxy groups in the 6 and 7 positions was achieved.

The synthesis of these compounds involved the following two stages:

(a) Preparation of 3,4-methylenedioxy-6-aminophenol and 3,4-dimethoxy-6-aminophenol. These compounds were obtained by low pressure catalytic hydrogenation of the corresponding nitrocompounds. Both amino compounds were characterized by means of their acetanilides which were obtained by reductive acetylation of the corresponding nitrocompounds using a palladium on charcoal catalyst. 3,4-Methylenedioxy-6-aminophenol was also characterized by its hydrochloride.

(b) Condensation of 3,4-dialkoxy-6-aminophenols with various α-ketoesters. These condensations were carried out in polar solvents (ethanol was used for the methylenedioxy compounds and methoxyethyleneglycol for the dimethoxy compounds) in the presence of glacial acetic acid.

2. In the condensation of 3,4-dialkoxy-6-aminophenols with α-ketoesters, it was found that the nature of the latter compounds is the main factor governing the speed of the reaction and the yield of the product obtained.

3. All 6,7-dialkoxy-1,4-benzoxazin-2-ones prepared are highly coloured and the nature of the substituent in the 3-position appears to be responsible for the intensity of the colour.

4. 6,7-Methylenedioxy-3-phenyl-1,4-benzoxazin-2-one and 6,7-dimethoxy-3-phenyl-1,4-benzoxazin-2-one dissolved in acetone or other certain solvents, show a remarkable blue-green fluorescence. This effect may be attributed to the large conjugated system of double bonds in their molecules.

5. The method of peracetic acid oxidation of piperonal to sesamol (3,4-methylenedioxyphenol) was modified. It was found that this reaction never goes to completion, starting material being always isolated from the reaction mixture. By using a greater amount of peracetic acid than that established as the optimum, the yield of the desired product is noticeably lowered in favour of resinous byproducts. Furthermore, it was established that the oxidation reaction product was the free phenolcompound and not its acetate or formate as was believed. This finding suggested a suitable modification in the isolation process by which the unreacted piperonal was conveniently recovered.

From this reaction small amounts of piperonylic acid can be isolated.

Moreover, the best yields in sesamol were obtained by conducting the reaction at a higher and wider range of temperatures.

6. The method for the preparation of 3,4-dimethoxyphenol was improved by adopting the modified procedure employed for the preparation of 3,4-methylenedioxyphenol.

7. The method for the preparation of 3,4-methylenedioxy-6-nitrophenyl-acetate was improved to obtain higher yields by carrying the nitration at room temperature and altering the original order of the mixing of the reagents.

8. 3,4-Dimethoxy-6-nitrophenyl acetate was obtained in a high yield by adopting the modified procedure for the preparation of 3,4-methylene-dioxy-6-nitrophenyl acetate.

9. The method for the preparation of 3,4-methylenedioxy-6-nitrophenol was improved by carrying out the hydrolysis in a mixture of ethanol and 20% sulphuric acid. The refluxing period for the hydrolysis was 30 minutes and a quantitative yield was obtained.

10. A new procedure for the preparation of 3,4-dimethoxy-6-nitrophenol was developed, and a nearly quantitative yield was obtained. This compound was obtained by hydrolysis of the corresponding phenyl acetate in a mixture of ethanol and 20% sulphuric acid.

11. In order to determine the active positions in the molecule of 6,7-methylenedioxy-3-phenyl-1,4-benzoxazin-2-one, a nitration of this compound was attempted. The reaction conditions were similar to those employed for the nitration of 3,4-methylenedioxyphenyl acetate to obtain 3,4-methylenedioxy-6-nitrophenyl acetate. In no case a nitrocompound

was obtained and the starting material was recovered unchanged.

12. 6,7-Methylenedioxy-2-phenomorpholone-3-acetic acid ethyl ester, 6,7-methylenedioxy-3-methyl-2-phenomorpholone, 6,7-methylenedioxy-3-phenyl-2-phenomorpholone and 6,7-dimethoxy-3-phenyl-2-phenomorpholone were conveniently prepared by catalytic hydrogenation of the corresponding 6,7-dialkoxy-1,4-benzoxazin-2-ones. The hydrogenation was carried out in ethanol, using palladium on carbon as catalyst and a pressure slightly higher than atmospheric.

13. Attempts to prepare the 6,7-methylenedioxy-3-acetonyl-2-phenomorpholone and 6,7-methylenedioxy-3-phenacyl-2-phenomorpholone from the corresponding 6,7-methylenedioxy-1,4-benzoxazin-2-ones varying the reaction conditions (temperature, solvent, catalyst, pressure) were unsuccessful.

14. It was found that the 6,7-dialkoxy-2-phenomorpholones prepared in the present work were readily dehydrogenated to their parent 6,7-dialkoxy-1,4-benzoxazin-2-ones by means of atmospheric oxygen. This dehydrogenation is greatly accelerated by treatment of the former compounds in glacial acetic acid.

15. The condensation of 6-bromopiperonal with acetopiperone in ethanolic sodium hydroxide solution resulted in the formation of 3,4-methylenedioxyphenyl 2-bromo-4,5-methylenedioxystyryl ketone.

16. β-(3,4-methylenedioxybenzoyl)-α-(2-bromo-4,5-methylenedioxyphenyl) propionitrile was obtained by the addition of hydrogen cyanide to the

double bond of the 3,4-methylenedioxyphenyl 2-bromo-4,5-methylenedioxystyryl ketone using a mixture of methoxyethyleneglycol and tetrahydrofuran as solvent.

17. β-(3,4-Methylenedioxybenzoyl)-α-(2-bromo-4,5-methylenedioxyphenyl) propionamide was obtained from the corresponding nitrile by treatment of the latter with a mixture of glacial acetic acid and sulphuric acid.

18. β-(3,4-Methylenedioxybenzoyl)-α-(2-bromo-4,5-methylenedioxyphenyl) propionic acid was obtained by alkaline hydrolysis of the corresponding amide in refluxing ethanol.

19. γ-(3,4-Methylenedioxyphenyl)-α-(2-bromo-4,5-methylenedioxyphenyl) butyric acid was prepared by Clemmensen's reduction of the β-(3,4-Methylenedioxybenzoyl)-α-(2-bromo-4,5-methylenedioxyphenyl)propionic acid.

20. Attempts to prepare the phenylhydrazone of the 3,4-methylenedioxyphenyl 2-bromo-4,5-methylenedioxystyryl ketone using pyridine as solvent, resulted in the formation of the 2-phenyl-3-(2-bromo-4,5-methylenedioxyphenyl)-5-(3,4-methylenedioxyphenyl) pyrazoline.

21. 1-Oxo-6,7-methylenedioxy-2-(2-bromo-4,5-methylenedioxyphenyl)-1,2,3,4-tetrahydronaphthalene was synthesized by refluxing the γ-(3,4-methylenedioxyphenyl)-α-(2-bromo-4,5-methylenedioxyphenyl) butyric acid in phosphoryl chloride.

22. The reaction of 1-oxo-6,7-methylenedioxy-2-(2-bromo-4,5-methylenedioxyphenyl)-1,2,3,4-tetrahydronaphthalene with formamide in the

presence of formic acid resulted in the formation of the 1-formamido-6,7-methylenedioxy-2-(2-bromo-4,5-methylenedioxyphenyl)-1,2,3,4-tetrahydronaphthalene.

23. 1-Oximino-6,7-methylenedioxy-2-(2-bromo-4,5-methylenedioxyphenyl)-1,2,3,4-tetrahydronaphthalene was obtained by applying the method of oximation to 1-oxo-6,7-methylenedioxy-2-(2-bromo-4,5-methylenedioxyphenyl)-1,2,3,4-tetrahydronaphthalene.

24. Attempts to reduce the 1-oximino-6,7-methylenedioxy-2-(2-bromo-4,5-methylenedioxyphenyl)-1,2,3,4-tetrahydronaphthalene to the corresponding primary amine by means of lithium aluminum hydride in dioxan, led to a debrominated compound of which infrared spectrum showed the presence of a secondary amino group instead of the expected primary. Analytical results and molecular weight determination of this compound were consistent with the molecular formula $C_{18}H_{17}NO_4$. A consideration of its infrared spectrum with some comparable data in the literature, suggests that this compound is 7,8-methylenedioxy-3-(3,4-methylenedioxyphenyl)-2,3,4,5-tetrahydro-1H-1-benzazepine. The formation of this compound is explicable only by assuming a Beckmann rearrangement before the reduction of the oximino group occurs.

25. During this investigation, the following new compounds were prepared and characterized.

3,4-Methylenedioxy-6-aminophenol hydrochloride.

3,4-Methylenedioxy-6-hydroxyacetanilide.

3,4-Dimethoxy-6-nitrophenyl acetate.

3,4-Dimethoxy-6-hydroxyacetanilide.

6,7-Methylenedioxy-3-phenyl-1,4-benzoxazin-2-one.

6,7-Methylenedioxy-1,4-benzoxazine-2-one-3-acetic acid ethyl ester.

6,7-Methylenedioxy-3-methyl-1,4-benzoxazin-2-one.

6,7-Methylenedioxy-3-acetonyl-1,4-benzoxazin-2-one.

6,7-Methylenedioxy-3-phenacyl-1,4-benzoxazin-2-one.

6,7-Dimethoxy-1,4-benzoxazin-2-one-3-acetic acid ethyl ester.

6,7-Dimethoxy-3-methyl-1,4-benzoxazin-2-one.

6,7-Dimethoxy-3-phenyl-1,4-benzoxazin-2-one.

6,7-Dimethoxy-3-acetonyl-1,4-benzoxazine-2-one.

6,7-Dimethoxy-3-phenacyl-1,4-benzoxazine-2-one.

6,7-Methylenedioxy-2-phenomorpholone-3-acetic acid ethyl ester.

6,7-Methylenedioxy-3-methyl-2-phenomorpholone.

6,7-Methylenedioxy-3-phenyl-2-phenomorpholone.

6,7-Dimethoxy-3-phenyl-2-phenomorpholone.

3,4-Methylenedioxyphenyl 2-bromo-4,5-methylenedioxystyryl ketone.

2-Phenyl-3-(2-bromo-4,5-methylenedioxyphenyl)-5-(3,4-methylenedioxyphenyl) pyrazoline.

β-(3,4-Methylenedioxybenzoyl)-α-(2-bromo-4,5-methylenedioxyphenyl) propionitrile.

β-(3,4-Methylenedioxybenzoyl)-α-(2-bromo-4,5-methylenedioxyphenyl) propionamide.

β-(3,4-Methylenedioxybenzoyl)-α-(2-bromo-4,5-methylenedioxyphenyl) propionic acid.

γ-(3,4-Methylenedioxyphenyl)-α-(2-bromo-4,5-methylenedioxyphenyl) butyric acid.

1-Oxo-6,7-methylenedioxy-2-(2-bromo-4,5-methylenedioxyphenyl)-1,2,3,4-tetrahydronaphthalene.

1-Formamido-6,7-methylenedioxy-2-(2-bromo-4,5-methylenedioxyphenyl)-1,2,3,4-tetrahydronaphthalene.

1-Oximino-6,7-methylenedioxy-2-(2-bromo-4,5-methylenedioxyphenyl)-1,2,3,4-tetrahydronaphthalene.

7,8-Methylenedioxy-3-(3,4-methylenedioxyphenyl)-2,3,4,5-tetrahydro-1H-1-benzazepine.

26. The infrared absorption spectra of the products obtained in this investigation were determined in potassium bromide and were correlated with the structure assigned.

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