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THE SYNTHESIS OF 2-(3-FURYLOXYMETHYL) 1,3-DIOXOLANE

A THESIS
PRESENTED TO
THE FACULTY OF THE GRADUATE SCHOOL
UNIVERSITY OF THE PACIFIC

IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE
DOCTOR OF PHILOSOPHY

by

CARL EVERETTE CRIPE

March 1977

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CARL EVERETTE CRIPE

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This dissertation, written and submitted by

Carl E. Cripe

is approved for recommendation to the Committee on Graduate Studies, University of the Pacific

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Dated March 23, 1977

A SYNTHESIS OF 2-(3-FURYLOXY)1,3-DIOXOLANE

Abstract of Dissertation

Synthetic and naturally occuring substituted furans and tetrahydrofurans, especially fused tetrahydrofurans such as the 1,4:3,6-dianhydrohexitols, exhibit a variety of physiological activities and have industrial applications. However, fully unsaturated furo[3,2-b]furans are not known. An attempt to synthesize the parent fused ring compound was made.

Chloroacetaldehyde dimethyl acetal (I), by transacetalation with ethylene glycol, was used to prepare 2-(chloromethyl)1,3-dioxolane (II) which gave 2-(acetoxymethyl)1,3-dioxolane (III), with NaOAc and Li I. De-O-acetylation of III with methanolic methoxide resulted in 2-(hydroxymethyl)1,3-dioxolane (IV). Compounds II, III and IV were characterized by physical constants and IV was further characterized by its crystalline 2-nitrobenzensulfenyl and 2,4-dinitrobenzenesulfenyl derivatives.

3-Chloromercuryfuran (VII) and 3-iodofuran (VIII) were prepared by a modification of the method of Gronowitz and Sorlin, starting from furoic acid.

In an attempt to form 2-(3-furyloxymethyl)1,3-dioxolane (IX) in benzene from IV and VIII, in the presence of dibenzo-18-crown-6-ether, an unknown compound (X), thought to be a rearrangement product of the crown ether, was formed.

Compound IX, unstable in air at room temperature, was formed from IV and VIII in dimethoxyethane with NaH as base and a specially prepared $Cu^o/Cu_2O/CuO$ catalyst. In two attempts to form the furo[3,2-b]furan from IX in the presence of acid, the ether linkage was cleaved preferentially to the intended cleavage of the acetal function. Mechanisms for various steps in the synthetic sequence are discussed.

ACKNOWLEDGEMENT

I especially thank my long time friend Paul Kurtz, who was my first college chemistry teacher and one who has been a constant source of encouragement to me over the past twenty-five years. I have also greatly appreciated the instruction and the cordial and helpful treatment afforded me by the Chemistry Department of the University of the Pacific, chaired initially by beloved Dr. Emerson Cobb and now by Dr. Donald Wedegaertner.

My thanks also goes to Dr. Ram Babu, a former fellow graduate student who has been a consistent source of encouragement and help to me, to Mr. Neal Byington who has freely shared with me his expertise with instruments, to librarian Art Swann whose help with the literature search was beyond the call of duty, to Mrs. Dawn Mallard who patiently typed this manuscript, and to Dr. Karl Zimmerman whose dogged determination in the face of very considerable odds never ceases to amaze and challenge me.

My parents, Mary A. Cripe and the late John O. Cripe, neither of whom graduated from the eighth grade, did not help me directly in the field of chemistry but they gave me something to live by that has stood me in good stead in the laboratory and the classroom and beyond.

I owe a very great debt of appreciation to Dr. Paul Gross for his instruction and direction, for the many hours

of discussion, for his keen insights shared with me and for his cordiality and his willingness to help me not just in theory but also in the laboratory.

My family has made my graduate studies possible. Paul, Kevin and Ruth -- thank you each one very much for your patience, for your encouragement and for your help. Marjorie, we've gone a long way together and this is another thing we've shared in. This work is dedicated to you. If there were any way that two people could share one degree, then your name should be on there too. Thanks for everything.

C.E. Cripe

TABLE OF CONTENTS

CHAPTER I

INTRODUCTION

Furan is an unsaturated, five membered heterocycle, with the molecular formula C_4H_4O and with a dipole moment directed from the ring (positive pole) toward the oxygen atoms (negative pole).[13,133] It displays an ease of electrophilic substitution that caused Gilman[68] to describe it as superaromatic. However, it has a resonance energy less than one half that of benzene.[201] In view of its sensitivity to acids, resistance to bases, and participation in addition reactions, particularly 1,4-addition reactions, furan has also been viewed as an internal ether of a diene.[147a] Its resonance energy and the latitude of its reactions support the contention that furan (Figure 1) is properly designated as an aromatic.[93] Either of the unshared electron pairs may, to some extent, be delocalized into the ring, thus forming the sextet required by Huckel's 4n + 2 rule.[132] However, if one defines aromaticity in terms of susceptibility to induced ring currents, evidence of which may be gained by nmr spectroscopy, then furan displays a limited degree of aromaticity.[34]

Furan and a variety of substituted furans are found in nature. Joule and Smith's[109a] statement that the aromatic furan ring is not found in animal metabolism is open to challenge. Furan has been identified as one of the volatile components of chicken breast muscle[75] and compounds containing the furan moiety have been found in human urine.[148] Furthermore, dendrolasin, a 3-alkylfuran, has been isolated from ants.[62] Most naturally occuring furans are found as plant metabolites, especially terpenoids.[19a,15,91,114,196,205] Compounds containing the furan ring also exhibit a variety of physiologic activities in mammals. These include estrogenic activity,[120,169] cardiotonic activity,[128,141] hypoglycemic activity,[53] and, if the derivative tetrahydrofuran ring is considered, antitumor activity.[101]

The review articles and books used in the preparation of this thesis were varied in scope. Gilman and Wright[69] reviewed furan chemistry, through 1931, from the standpoint of nuclear substitution and orientation. Morton's book[147] on heterocyclic compounds devotes two chapters to furans and condensed furans and includes a partial review of the literature through 1943. The chapter on furans by Elderfield and Dodd,[46] in Elderfield's "Heterocyclic Compounds", Vol. I, was completed in 1950. A comprehensive treatise on furan compounds by Dunlop and Peters[44] was published in 1953. Bosshard and Eugster[19] reviewed developments in the synthesis and reactions of simple furan ring compounds from 1951-1963. Atcheson[1] and Joule and Smith,[109] in their books on heterocyclic chemistry, and Pelter,[165] in his chapter on oxygen heterocycles, include brief sections on furan and furan compounds. Palmer's[158] integration of the treatment of pyrroles, furans, and thiophenes and their benzo derivatives, includes a selective review of the literature through 1965. The most comprehensive recent treatise on the biological origin, synthesis and chemistry of furans is that by Livingstone,[123] published in 1973 as part of Rodd's Chemistry of Carbon Compounds. The book by Williams[203] is a technological review of the manufacture and use of compounds containing at least one furan ring and is based on U.S. patents from 1960 to 1973. Belen'kii's selective review[14] of thiophenes and furans, published in 1975, deals with direction and characteristics of electrophilic substitution reactions.

There are two major routes open for the synthesis of substituted furans.[19b] One of these employs substitution on an existing furan ring. Such an attack is usually electrophilic in nature. Variations on this general method may include, in subsequent steps, the removal of certain substituents (decarboxylation, decarbonylation, etc.) while leaving the desired one(s) in place and the alteration of side chain(s) or displacement of substituents after their attachment to the ring. The other general approach involves the formation of a furan ring where one did not previously exist and, in the process, choosing reactants

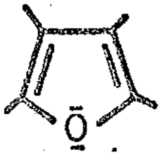


Figure 1

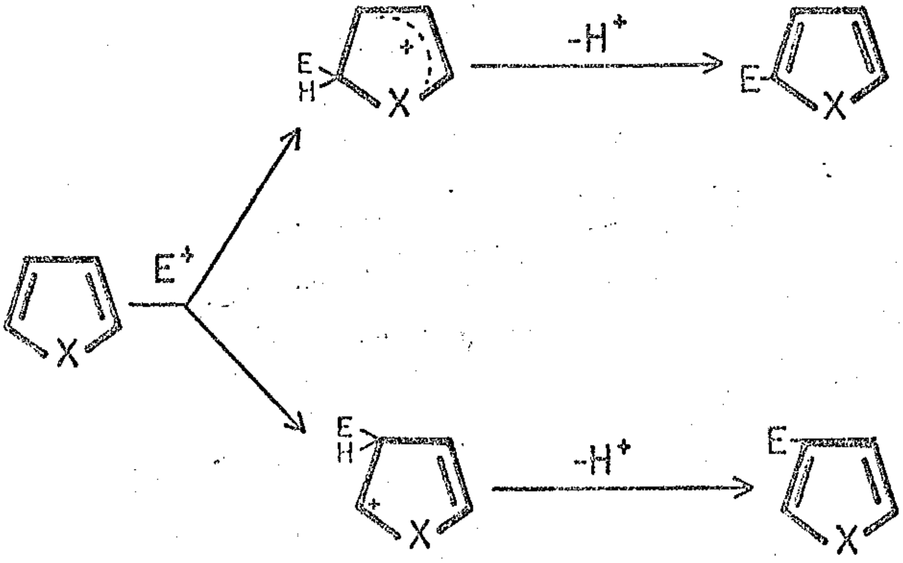


Figure 2

in such a way that the appropriate substituents are in place. The previously cited variations also apply to this approach.

The synthesis of 3-substituted furans has proven to be especially difficult.[155,179] For the methods that start from a preformed furan ring, this situation is due to the almost total lack of electrophilic attack on a β position if there is an open α position.[69a] This is explainable on the basis of the greater range of delocalization of the positive charge of the incoming electrophile[14a] (Figure 2). Methods involving the formation of a furan ring, with an appropriate 3-substituent in place, have also proven laborious, unsuited for large scale application, costly and erratic.[58]

A review of the "furan ring producing" methods that have been used or, in principle, may be used to produce 3-substituted furans reveals a variety of approaches. One of the oldest such methods is that of Paal and Knorr.[156] It most often involves furan ring formation from 1,4-dicarbonyl compounds, with the ultimate result that would be expected from the condensation of the dienolic form (Figure 3). The intermediate 1,4 dicarbonyl compound is formed from the reaction of an α-carbonyl carbanion with an α-halocarbonyl compound via C-alkylation. An example[167] is shown in Figure 4. However, Reichstein[168] demonstrated that, contrary to Sutter's original proposal,[189]

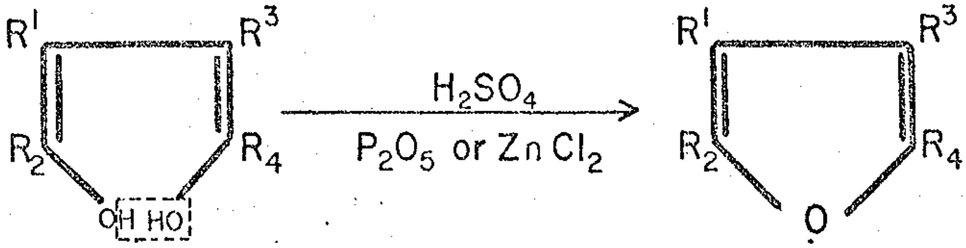


Figure 3

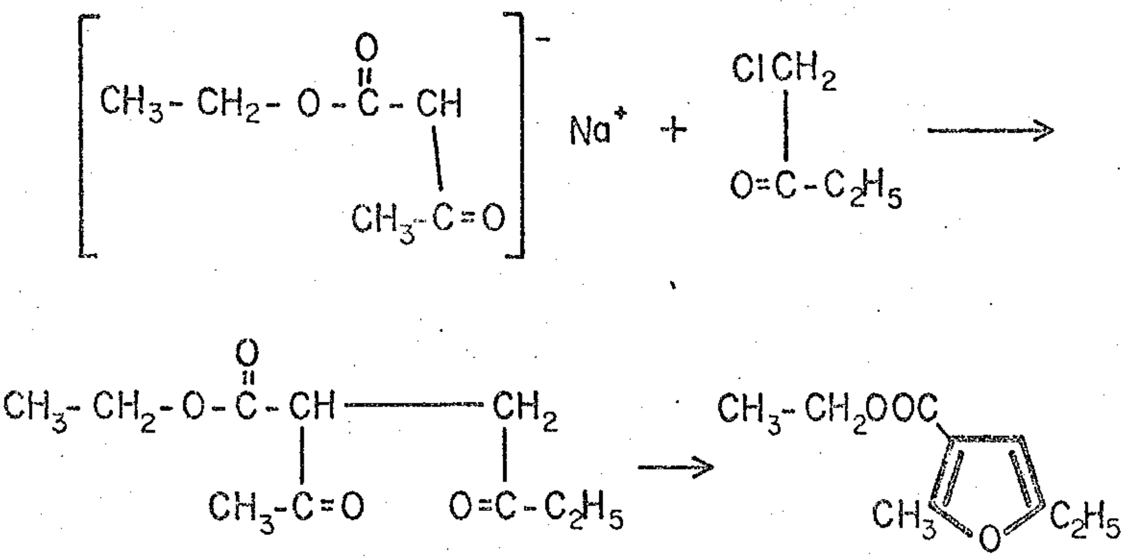


Figure 4

O-alkylation instead of C-alkylation occurs in the reaction of sodiodiethyloxaloacetate with ethylbromopyruvate yielding 2,3,4-tricarbethoxyfuran instead of the expected 2,3,5-tricarbethoxyfuran (Figure 5). This reaction pathway involves an intermediate which is not a 1,4-dicarbonyl compound. Other β-keto esters are known to condense with α-bromo carbonyl compounds via O-alkylation enroute to forming furans.[6,168] Hurd and Wilkinson,[102] in review of the work of Paal[156] and Feist,[54] established that acetoacetic ester reacted with chloroacetone in the presence of sodium ethoxide by initial C-alkylation, to give, after hydrolysis, as the final product, 2,5-dimethyl-3-furoic acid (Paal). However, if ammonia is used with the same two compounds, the initial step is O-alkylation and the final product is 2,4-dimethyl-3-furoic acid (Feist) (Figure 6).

A number of variations for the synthesis of substituted furans by dehydration and ring closure of 1,4-dicarbonyl compounds have been developed.[2,7,9,30,43,52,59,107,108,116,119,125,126,129,154,191,193]

As noted previously, the Feist-Benary[54] synthesis may be viewed as a variation of the Paal-Knorr[156] method. However, in the former the intermediate compound is formed by O-alkylation and, therefore, is not a 1,4-dicarbonyl compound. In this synthetic scheme an α-chloroketone or α-chloraldehyde (or a 1,2-dichloroether, which is a potential α-monochloroketone or α-monochloroaldehyde) is

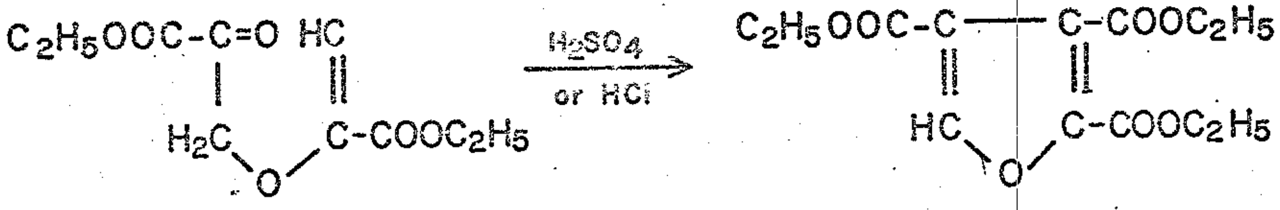
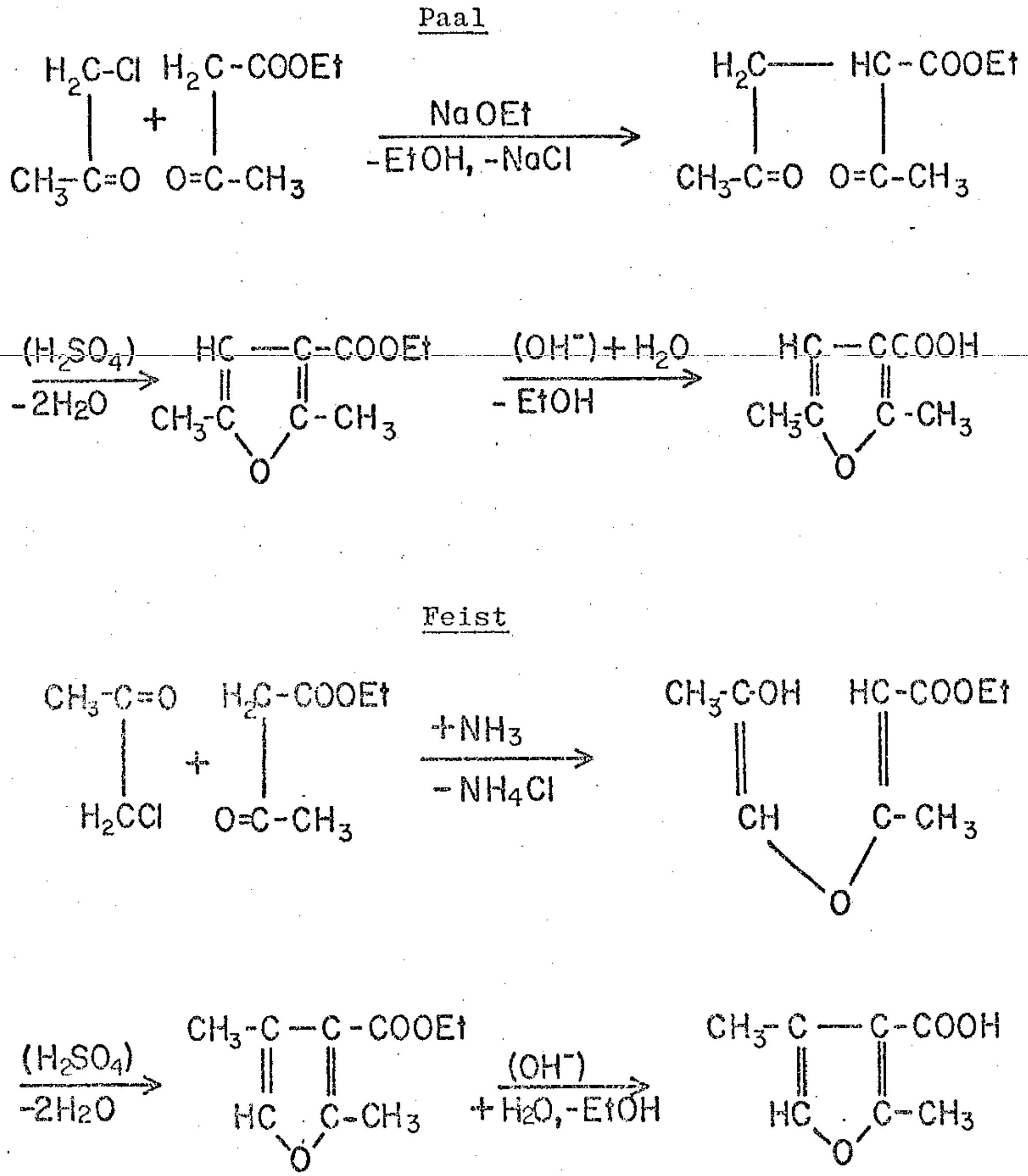


FIGURE 5



Paal

Feist

Figure 6

allowed to react with the appropriate CH-acidic carbonyl and ammonia. Here the selection of CH-acidic carbonyl compound is crucial. The choice of certain types (i.e. acetoacetic ester) leads primarily to the synthesis of pyrroles by involving the ammonia in the ring formation.[87] The choice of other types (i.e. acetone dicarboxylic ester) leads primarily to the synthesis of furans.[54]

The condensation of monosaccharides with β-keto esters is a method by which 2,3-disubstituted furans have been synthesized[74] (Figure 7).

Dehydrogenations of dihydro and tetrahydrofurans have, in principle, the potential for the synthesis of 3-substituted furans, but have been sparsely applied and generally have given low yields.[19c] The dehydrogenation of a dihydrofuran to form the corresponding furan may also lead to tetrahydrofuran formation, and to hydrogenolytic ring opening[182,183] (Figure 8). However, undesireable side products have been minimized in the dehydrogenation of 2-ethyl-2,5-dihydrofuran[16] (Figure 9) and a good yield of 2-methylfuran has been obtained by the dehydrogenation of 2-methyltetrahydrofuran[17] (Figure 10). Paul[160] and Ghosh and Raha[73] have also obtained furans from the corresponding tetrahydrofurans. The addition of diazoalkanes, -esters or -ketones to 2(5H)-furanones, with thermal decomposition of the adducts followed by reduction of the resulting alkylated 2(5H)-furanones lead to 3-,2,3- and 3,4-substituted furans[164] (Figure 11). A synthesis of 3-alkylfurans has been developed

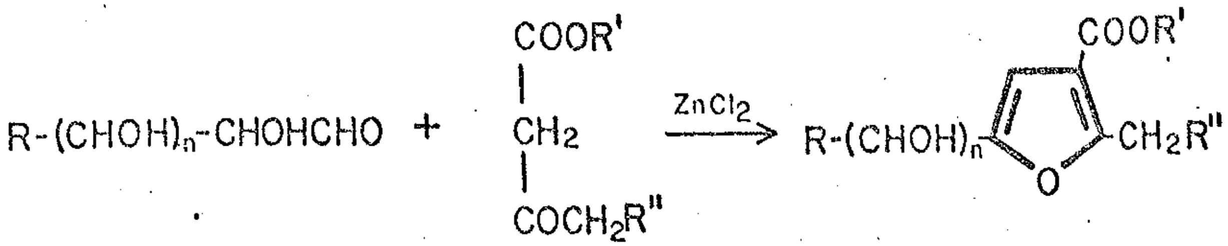


Figure 7

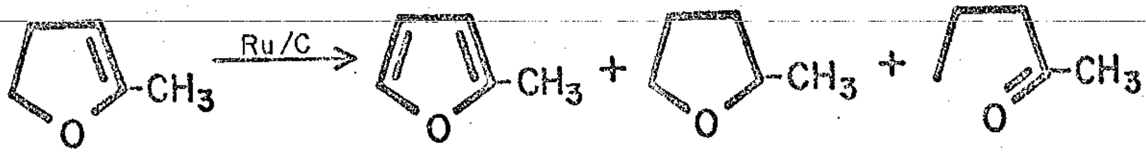
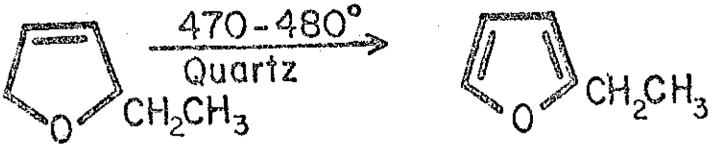


Figure 8



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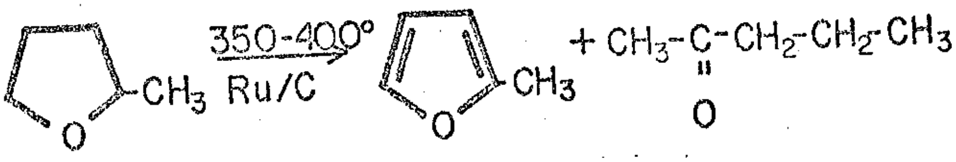


Figure 10

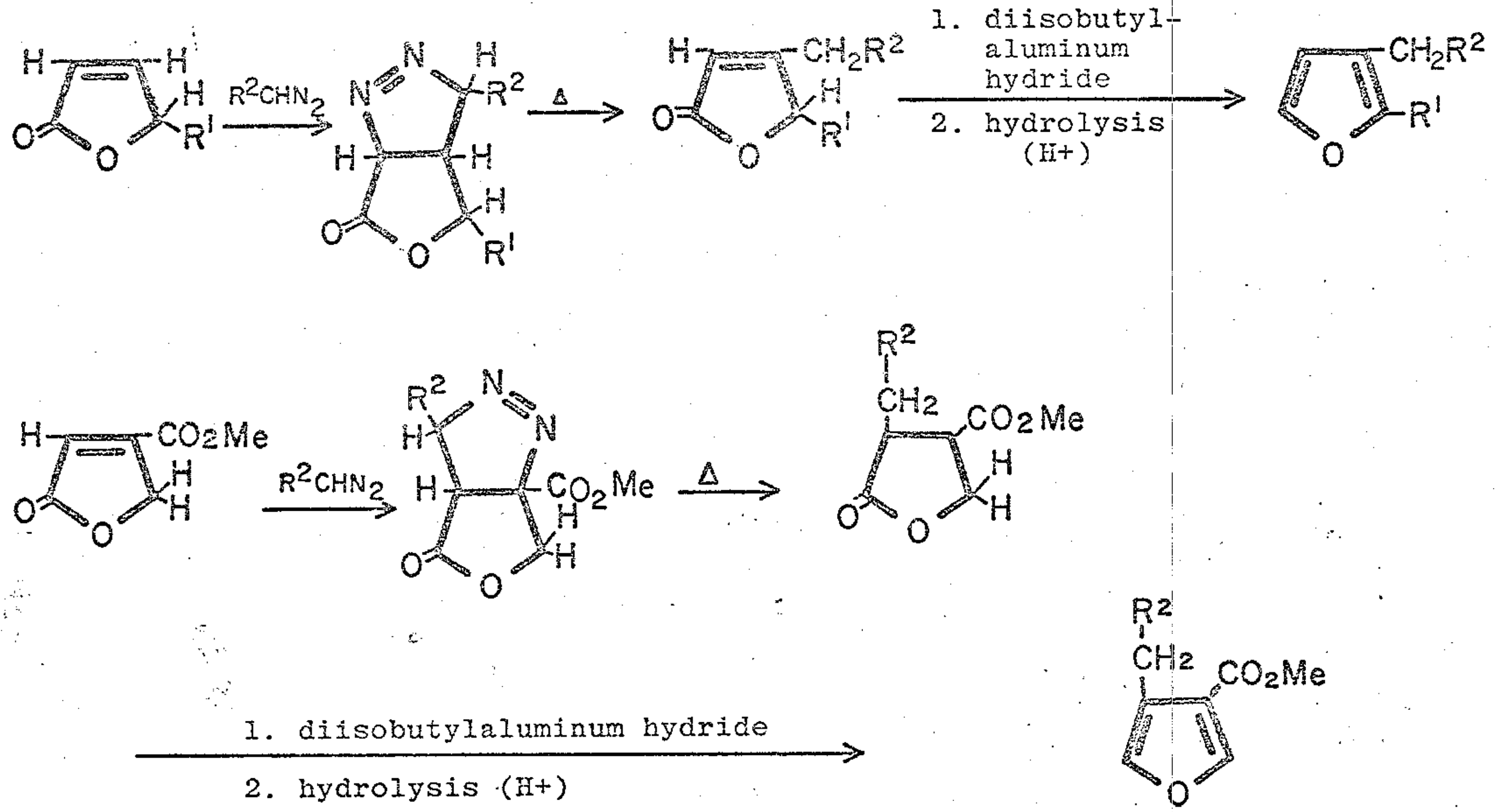

R^{2}CHN$_2$
Δ
1. diisobutylaluminum hydride
2. hydrolysis (H+)
CH$_2$R^2
R^1
R^{2}CHN$_2$
Δ
CO$_2$Me
1. diisobutylaluminum hydride
2. hydrolysis (H+)

Figure 11

from the tosylhydrazones of the corresponding 3-alkyltetrahydrofuran-4-ones. A mixture of the intermediate 3-alkyldihydrofurans is isolable in high yields[62] (Figure 12).

Formation of furans by the elimination of alcohol or water from dihydrofurans generally proceeds more smoothly and with better yields than by dehydrogenation. Thus, 2-alkoxyfurans have been prepared from 2,5-dialkoxy-2,5-dihydrofurans by pyrolytic and acid catalyzed alcohol eliminations[25,36,115,180] (Figure 13) and variously substituted furans have been synthesized from 3-hydroxydihydrofurans by the elimination of water under various conditions[41,161,194] (Figure 14). An interesting combination of dehydration-dehydrogenation leading to a 3-substituted product is the synthesis of 3-phenylfuran from 3-hydroxy-3-phenyltetrahydrofuran. In this instance sulfur in dimethylformamide effects dehydrogenation.[208]

Starting materials and intermediates containing epoxide rings have lead, via rearrangements, to the formation of 3-substituted furans. 3-Methyl furan has been synthesized by epoxide rearrangements from 3,4-epoxy-3-methylbutanal diethyl acetal[33] and from 4-carbomethoxy-3,4-epoxy-3-methylbutanal dimethyl acetal, followed by hydrolysis and decarboxylation. In a very similar way, three different 3-alkylfurans have been synthesized from 3,4-epoxy-1-butynes according to the following scheme in Figure 15.[140] The epoxy aldehyde intermediate is hypothetical. It will be noted, that anti-

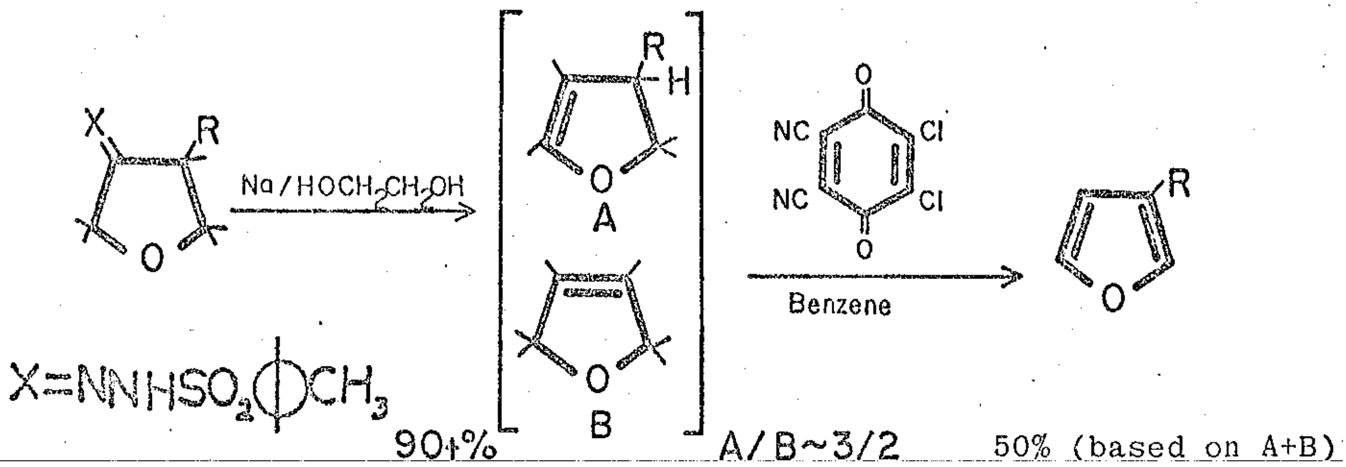


Figure 12

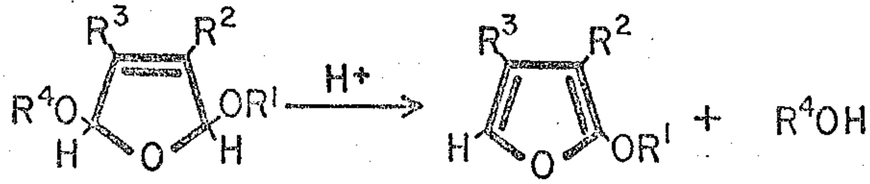


Figure 13

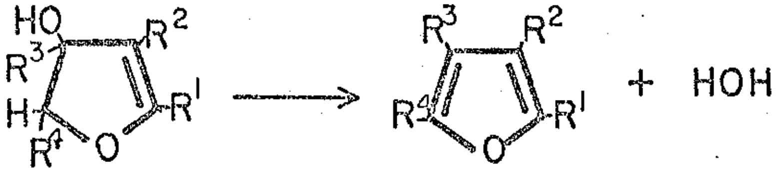


Figure 14

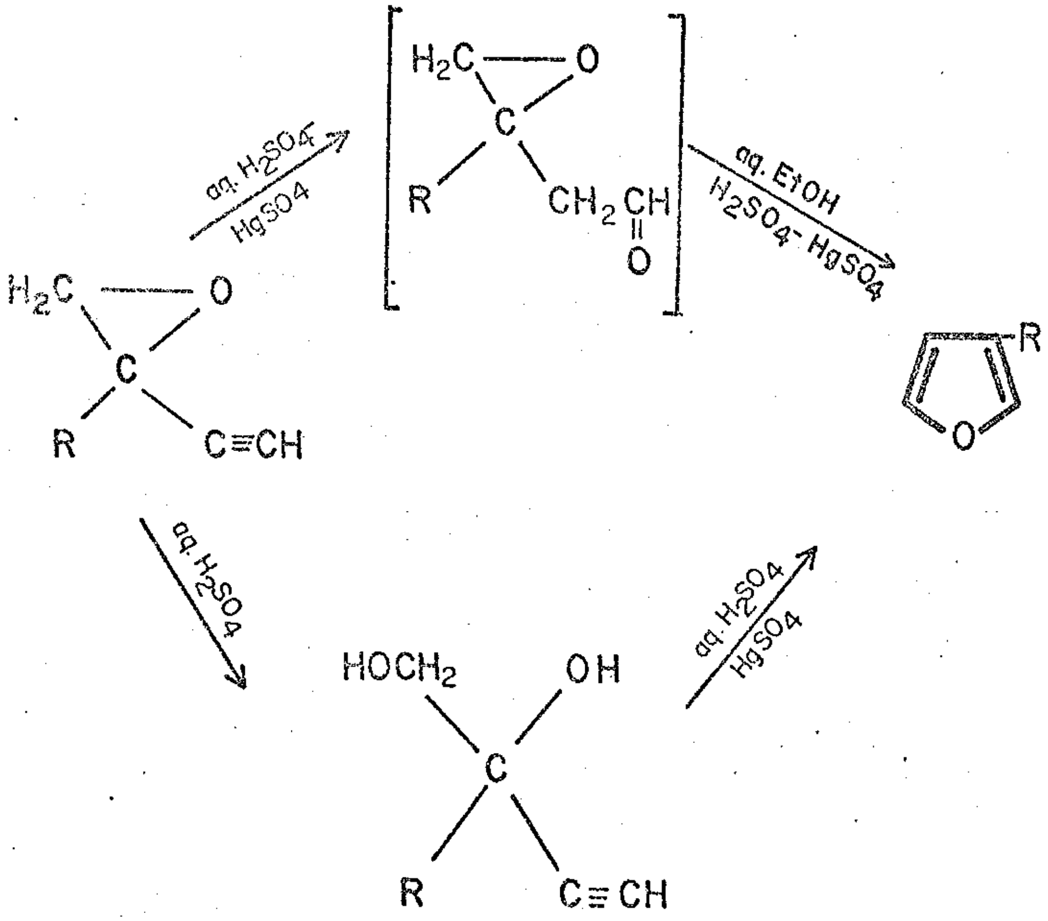


Figure 15

Markovnikov orientation of the addition to the triple bond must be postulated for either pathway. This could be accounted for by anchimeric assistance of the oxygen at 4-position in the easier formation of a 5-membered ring as compared to a 4-membered ring. Harris and coworkers[88,89] have demonstrated the formation and rearrangement of an epoxide ring compound in the synthesis of substituted furans from β-dicarbonyl compounds by reaction with dimethylsulfonium methylide. This reaction sequence, involving intermediate enol ethers of 3,4-epoxy-2,3-dialkylbutanones, has been worked out in some detail and is similar to the syntheses above (Figure 16). Unfortunately, this reaction is not too useful in the synthesis of 3-mono-substituted and 3,4-disubstituted furans, because of the competing formation of dihydropyran derivatives. However, a variation of it, in which n-butylthioenolethers are used, has worked well.[61]

Dare and coworkers[37] improved on the previous synthesis of 3-furoic acid from methyl coumalate and also developed a new ring closure method for synthesis of the furan nucleus, with the desired substituent in place, involving dehydration (Figure 17). R is a long chain alkyl or a keto group with the carbonyl adjacent to the ring. The synthesis of the 1,2,3,4-tetrol starting material was also reported by these authors.

The formation of furans by a sequence of a Diels-Alder reaction between an oxazole and an acetylene compound

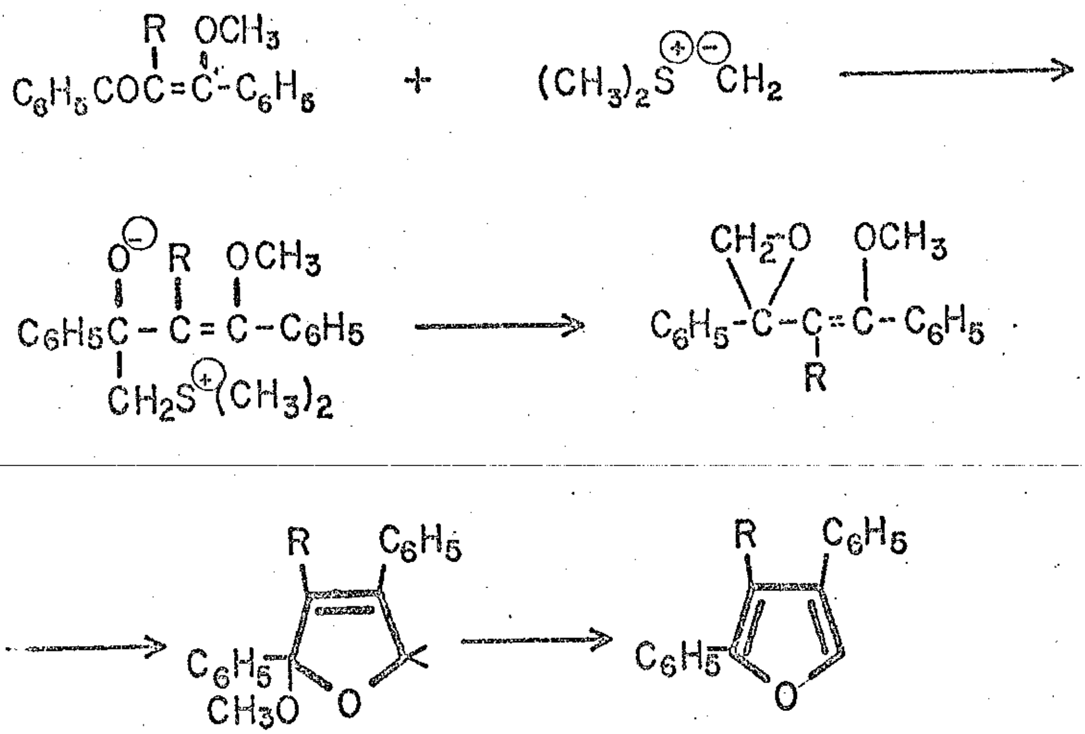


Figure 16

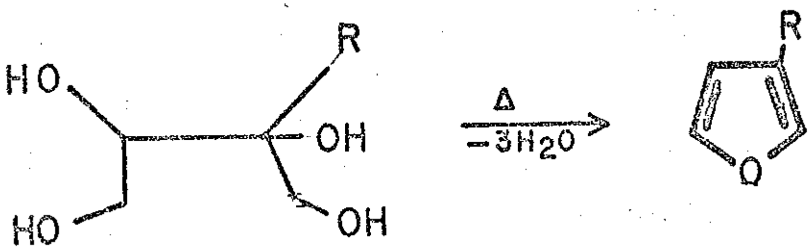


Figure 17

and a subsequent retro Diels-Alder reaction, is apparently dependent on the fact that the nitrile eliminated in the retro Diels-Alder reaction is a poor dienophile[76] (Figure 18). This reaction appears to be flexible enough for the synthesis of many substituted furans. However, the authors tried it only for a limited number of R groups. The most successful acetylenic dienophile was $MeO_2CC\equiv CCO_2Me$. The stability of the oxazole and the dienophile character of the substituted acetylene appear to be the major limiting factors. In an extension of this work[155] the method was found to be specific for the synthesis of 3-furoic acid (Figure 19) and 3-acetylfuran (Figure 20).

Furans have also been formed by ring contractions of δ-sultones, pyrones, and pyrylium salts. Thus furans substituted in the 2,3 and 4 positions have been formed from δ-sultones by the pyrolytic elimination of sulfur dioxide.[55,192,210] The δ-sultones are, in turn, formed by the action of sulfuric acid and acetic anhydride on α,β or β,γ-unsaturated ketones (Figure 21). Ring contractions of α-pyrones to furans require a suitable leaving group in the 3-position[11,21,37,51] (Figure 22). Although Broy and Mayer[21] found -OH and -Br to be adequate leaving groups in the formation of 2-furoic acid from 3-hydroxy-α-pyrone and 3-bromo-α-pyrone, Dare and coworkers[37] found that 3-bromo-5-carbomethoxy-α-pyrone but not 3-hydroxy-5-carbomethoxy-α-pyrone, would yield furan-2,4-dicarboxylic acid. The latter workers also found that

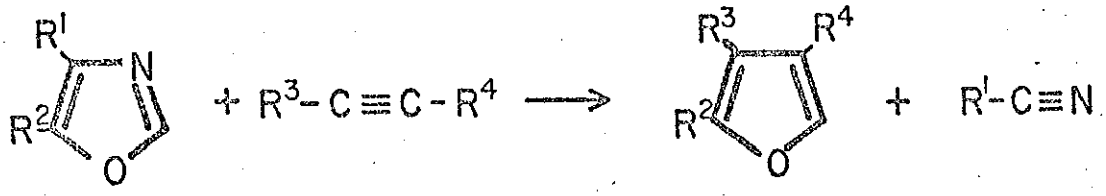


Figure 18

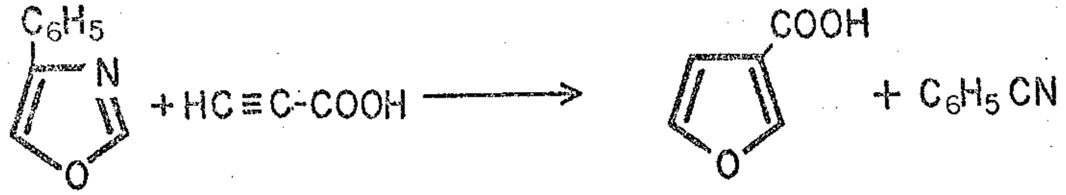


Figure 19

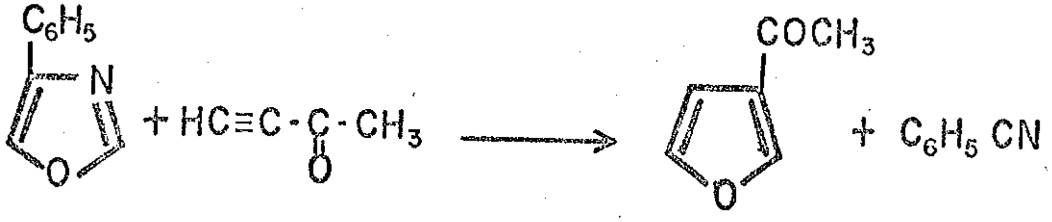


Figure 20

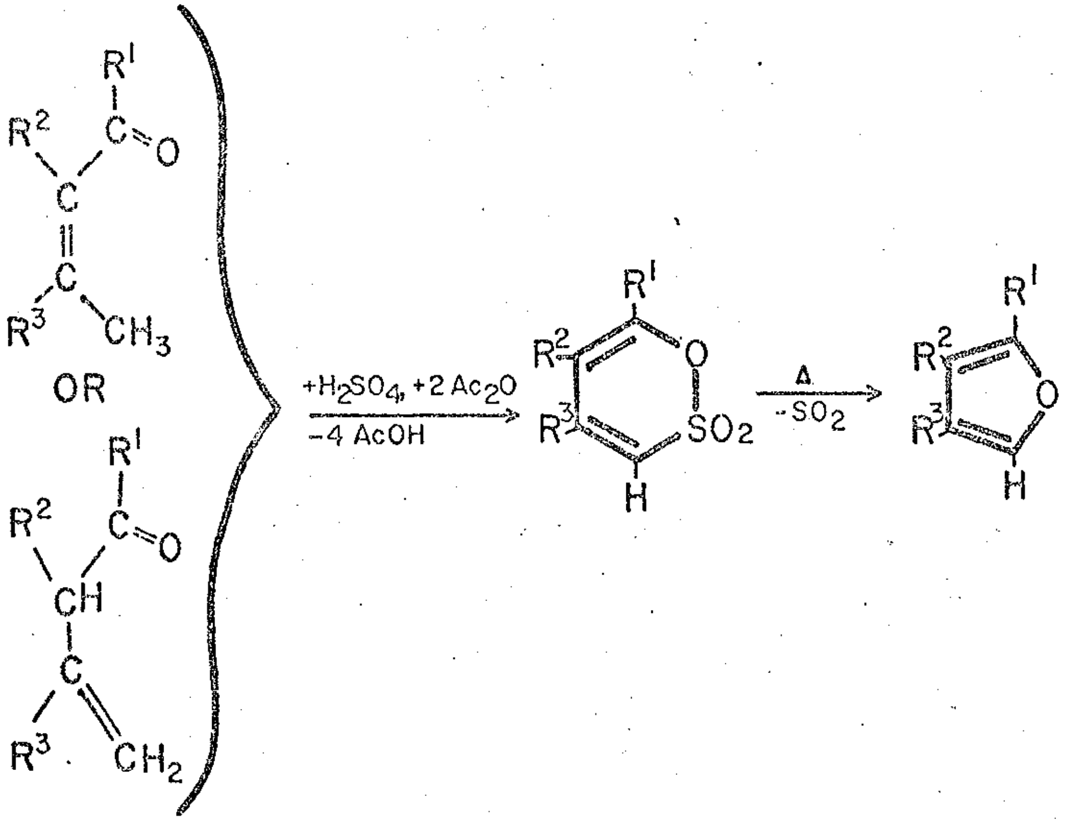


Figure 21

the base sodium methoxide led to the formation of acyclic end products, apparently in part because the 3-bromide was replaced by 3-methoxide, a considerably poorer leaving group. Photochemical conversions of γ-pyrones to 2-furaldehyde derivatives have also been reported.[157,209] A combination of the strong oxidizing agents, aqueous hydrogen peroxide and perchloric acid, are required for the ring contraction of pyrylium salts to furan derivatives.[12,181] The following mechanism is probably an improvement over the one proposed in the literature[12] (Figure 23). Recently, furan derivatives have been obtained from 1,3-dioxolanes by acid catalyzed pyrolysis[173] (Figure 24). Other methods, related to the ones already considered, have been reported.[5,18,90,104,142,175,176]

Synthetic routes to substituted furans, starting from already existing furan rings are usually, but not exclusively, electrophilic substitutions. Electrophilic substitutions on furan rings occur with greater ease than does electrophilic substitution on benzene.[72] However, since the furan ring is highly sensitive to acid attack[69c,123a] and oxidation,[8,20,35,51,123a] the electrophilic agent and the reaction conditions must be chosen carefully, or a mixture of polysubstituted furans, polymers and resinified materials may result from the reaction.[3,19,134,177] Single substitution, accomplished only under relatively mild conditions, lead almost invariably to 2-substituted products[27,39,109b] The indicated alkylation is one of a very [illegible]

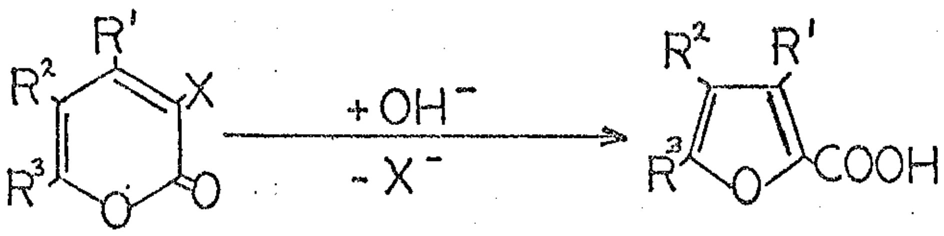


FIGURE 22

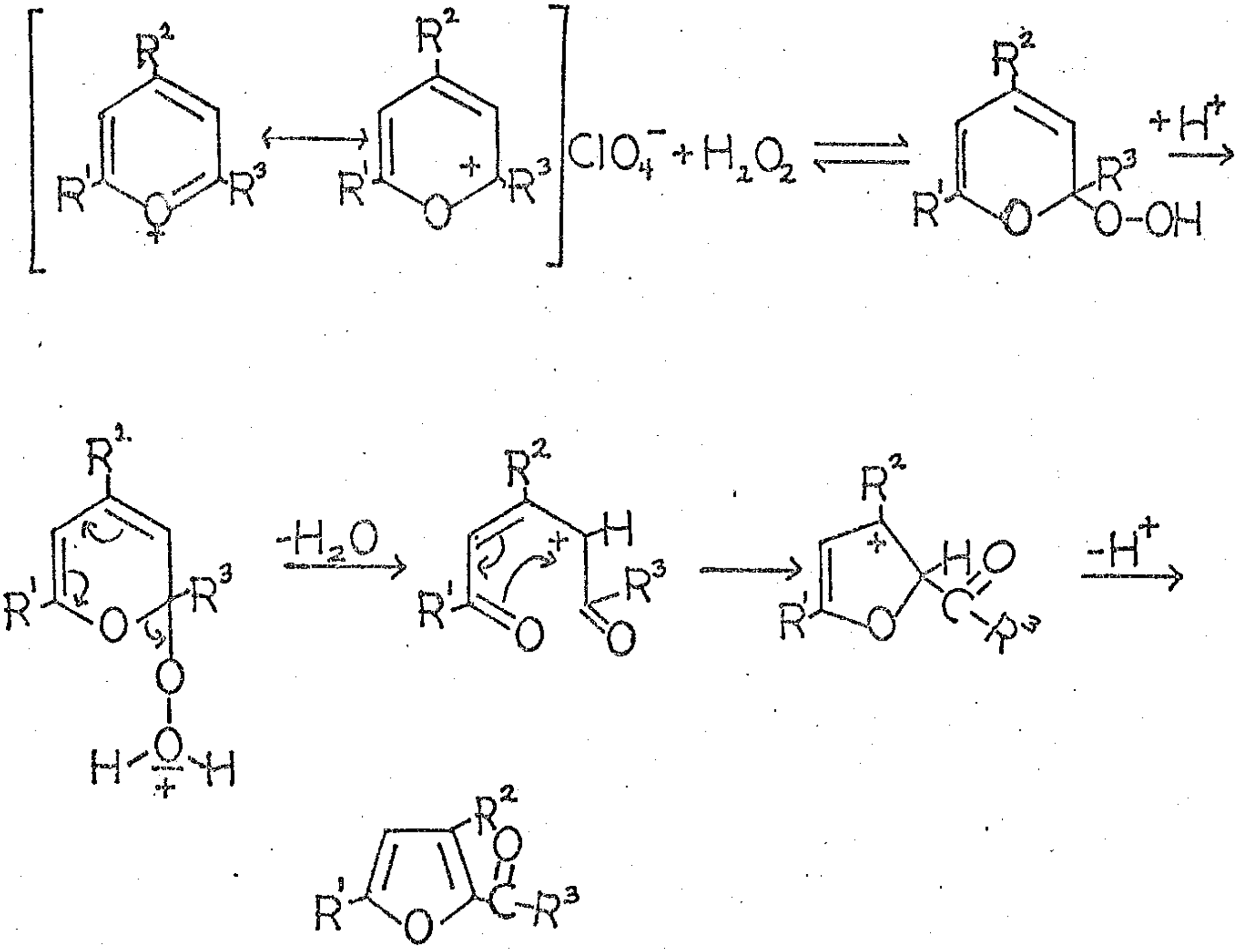


FIGURE 23

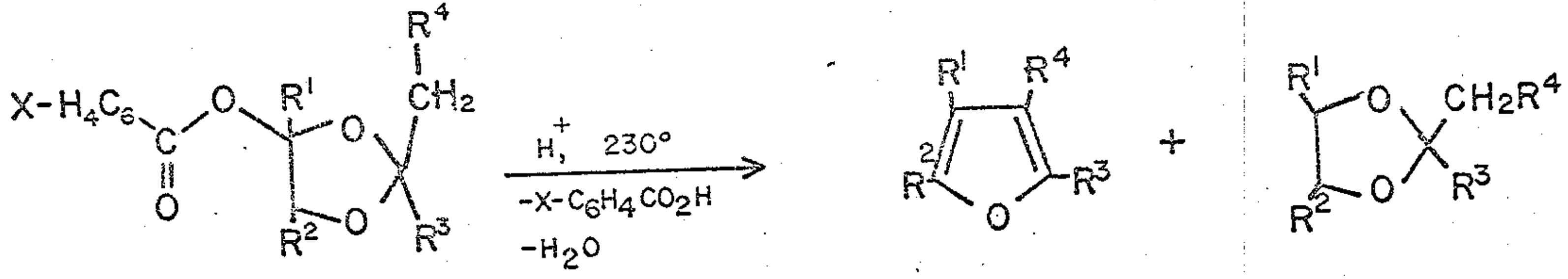


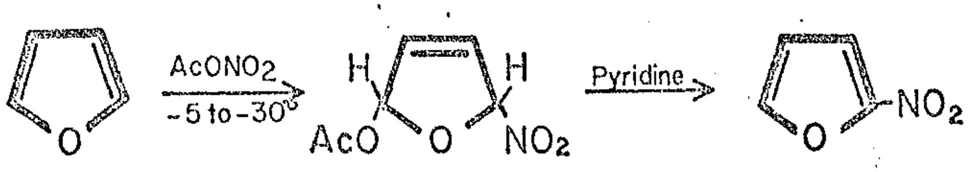
Figure 24

few instances in which a 3-monosubstituted product was shown to result from electrophilic substitution on furan (Figure 25).

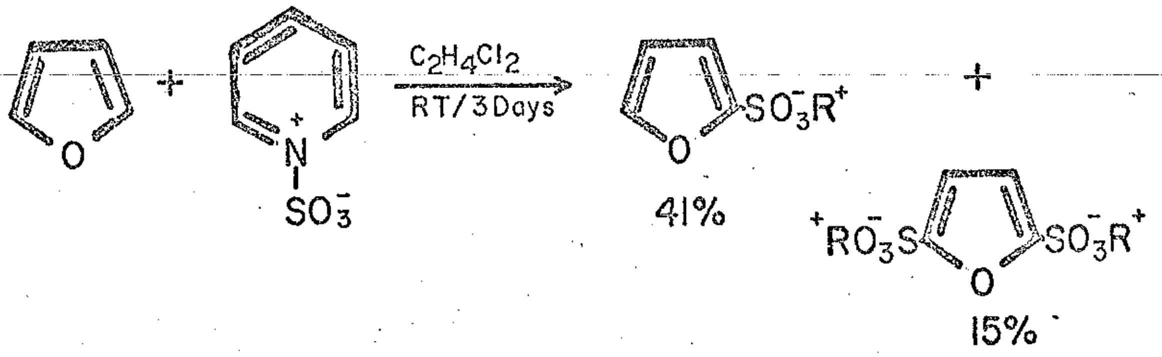
The substitutions take place either through addition followed by elimination, or by direct displacement, as in benzene[123b] (Figure 26).

Electrophilic substitution, in a 2-substituted furan, leads almost exclusively to a 2,5-disubstituted product, regardless of the directing character of the initial substituent.[44a,69d,82] However, occasionally contrary results have been reported[67] and Belen'kii[14b] suggested from an analogy with thiophene, that reversals of the apparent norm will be less uncommon as this matter is studied more carefully. Results to date, however, do not support his prediction. The reaction of ethyl-2-furoate with isopropyl chloride, first carried out by Gilman and Calloway,[66] illustrates that the substitution of an open α-position does occur even though the other α-position is substituted by an electron withdrawing group (Figure 27). In a β-monosubstituted furan, a second substituent will go into one of the two α positions. If the β-substituent has a -M effect (meta director for benzene), then the second substituent goes into the 5 position. If the initial substituent has a +I effect (ortho, para director for benzene) the incoming group substitutes in the 2 position.[19d,63] If both β positions are substituted the α-position next

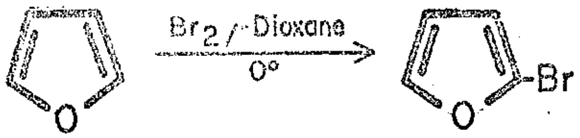
Nitration



Sulfonation



Halogenation



Alkylation

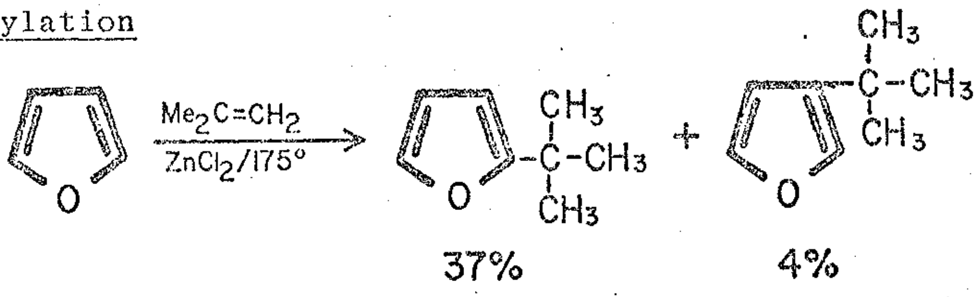


Figure 25

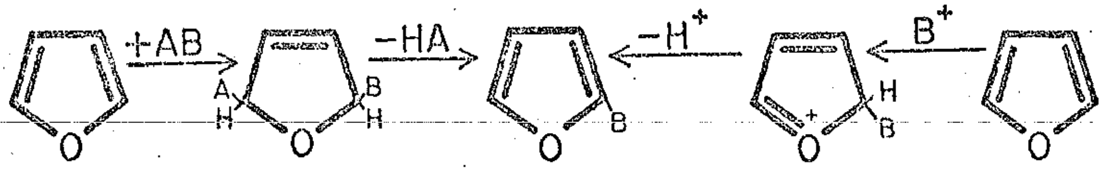


Figure 26

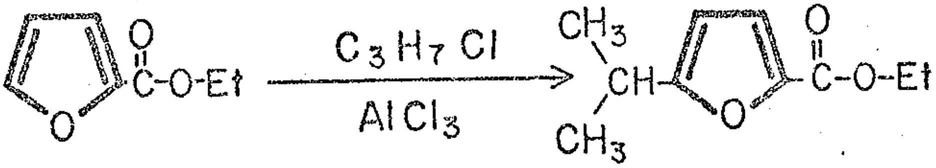


Figure 27

to the substituent with the greater +I effect is favored in further substitutions.[46b] If an α and a β position are substituted, the open α position is the primary target for a third substituent.[63,64] The substitution reactions discussed above are incapable of producing an appreciable quantity of a desired, 3-monosubstituted product. It should be noted that an electron withdrawing substituent stabilizes the furan ring[19f] and makes it more resistant to further substitutions.[19d] Although examples of ring stabilizations by electron donating groups are known,[109c] the general picture is one of activation and lesser ring stability accompanying electron donating substituents.[19g,109d]

Substitution of a third proton in an α,α-disubstituted furan leads to the introduction of β-substituents. The substituent with the larger +I effect will direct the incoming group to the adjacent β-position.[19d] If the α substituents can be readily removed (e.g. decarboxylation, decarbonylation) a 3-mono-substituted furan results.[24] This concept was the basis for the earliest syntheses of 3-bromofuran.[24,98,151,179] It is noteworthy here, that α substituents are more readily replaced by hydrogen than are β substituents, particularly carboxylic groups.[24,37,63,65,151,179] Also, tetraiodofuran has been used for the synthesis of 3-iodofuran.[28,29,174]

A unique method of synthesizing 3-iodofuran is that of Gilman and Wright[71] as modified by Gronowitz and Sorlin.[81] It involves the use of the neighboring 2-carboxyl as a vehicle for substituting the mercury atom into the 3-position of 2-furoic acid. This is followed by removal of the 2-substituent by decarboxylation. This opens the possibility for β -substitution when there is, concurrently, an open α position (Figure 28). Gilman and Wright[71] suggest the pathway for the formation of 3-chloromercuryfuran from furoic acid (Figure 29). Although this mechanism is speculative, and has been contested[81] no other has been proposed. The yield is quite low (12-15% based on $Hg(OAc)_2$) but the results are reproducible.[71,81] The 3-chloromercury derivatives of various alkylated furans have also been described.[195]

Displacement of one substituent by another has led to a variety of 3-substituted furans. Although 3-iodofuran does not form a Grignard reagent,[116] the iodine was displaced to give 3-methoxyfuran and 3-cyanofuran. After initial displacement of iodine with alkyl lithium to form 3-furyllithium, 3-furancarboxylic acid, 3-furanaldehyde, 3-methylfuran and 3-acetylfurans were synthesized.[80,81] The important intermediate, 3-furyllithium, has also been synthesized from 3-bromofuran,[58] and has been used to synthesize a variety of 3-substituted furans,[58,78,79] including a number of natural furan derivatives.[113,114,120,130,169] In one of these natural product syntheses, that of freelingyne, 3-furyllithium is converted to 3-furylcopper prior to further substitution. The above syntheses involved halogen-metal

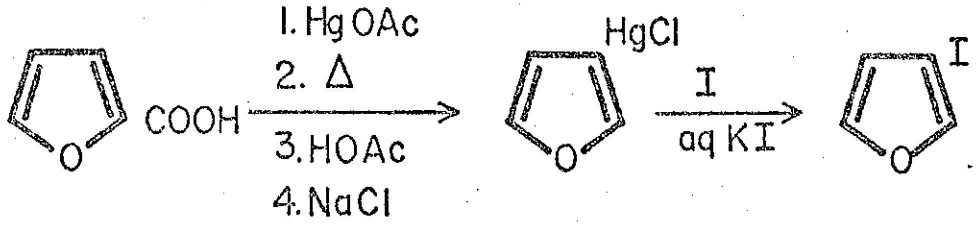


Figure 28

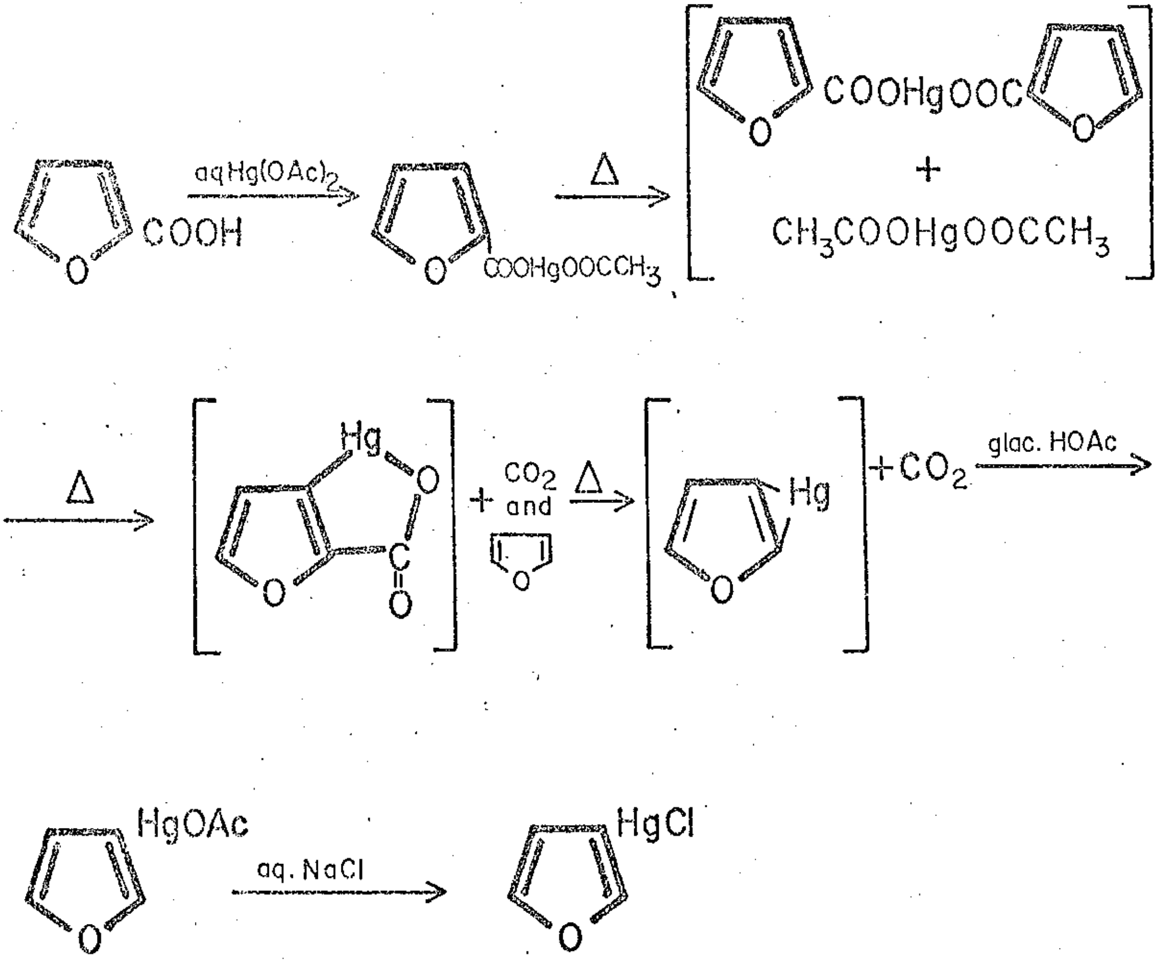


Figure 29

exchange with an alkyl lithium compound (usually n-butyllithium) at -70°. However, Davies and Davies[38] found that hydrogen-metal exchange occured, even in a halogen substituted furan, if lithium di-isopropylamide was the lithiating agent. 3-Furoic acid has also been produced but in less than 1% yield by the reaction of 3-iodofuran with sodium-potassium alloy, apparently producing a mixture of 3-sodio and 3-potassiofuran, followed by carbonation.[70] New 3-substituted furans have been produced by modification of substituents on existent 3-substituted furans.[83] Thus β-alkyl furans were prepared by treatment of 3-furoyl chloride with dialkylcadmium, followed by Wolff-Kishner reduction of the resulting β-furyl ketone.[84] In a multistep synthesis of 2-nitro-4-methylfuran from 3-furoic acid the intermediate structures were proposed[63] (Figure 30).

A special case of blocking both α-positions, thus forcing β-substitution, and then removing the α-blockage, thus producing a 3-monosubstituted furan, involved the use of furan as a diene in a Diels-Alder reaction.[42,47,207] After 3-substitution the furan was "freed" by a reverse Diels-Alder reaction. This differs from the other substitution reactions under discussion not only in overall mechanism but in the fact that substitution occurs in a dihydrofuran rather than in a furan derivative. However, since the process starts and ends with an intact furan ring, it is included here. Using this approach, two syntheses of 3-bromofuran have been reported.[122,150]

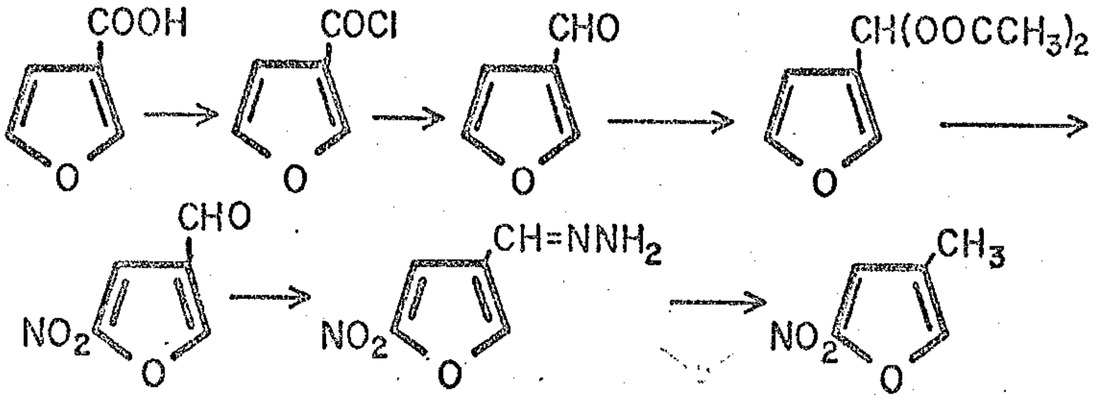


Figure 30

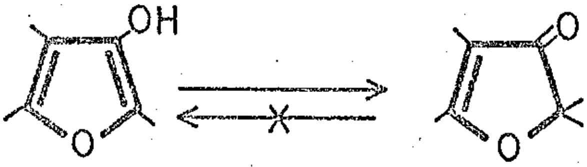


Figure 31

The synthesis of 3-hydroxyfuran[19h] would provide a seemingly logical route to the synthesis of 3-alkoxyfurans.[10] However its originally reported synthesis and properties[99] have not been reproduced.[10,127,190] Efforts to synthesize 3-hydroxyfuran by an alternate route have also met with failure.[172] However, when 3-methoxyfuran was hydrolyzed under mild conditions[100] the tautomeric α,β-unsaturated ketone resulted (Figure 31) rather than the enolic form which apparently does not exist in high concentration.

The synthesis of a variety of 2-alkoxyfurans, and their sensitivity to acid catalyzed ring opening reactions were reported by Manly and Amstutz.[131] The mechanism and end products of acidic hydrolysis of 2-alkoxyfurans are still a matter of controversy.[60,110] The only 3-alkoxyfuran that was synthesized and reported in the literature so far is 3-methoxyfuran.. It has been synthesized by the method of Fisher and Hodge[56] (Figure 32) and that of Gronowitz and Sorlin[81] (Figure 33).

An unusual 3-alkoxyfuran, would be furo[3,2-b] furan. Although neither this compound nor any fully unsaturated, substituted derivatives of it are known, numerous compounds containing this fused ring system, with a higher degree of saturation, have been synthesized. 1,4:3,6-dianhydro-D-mannitol(isomannide (1)), 1,4:3,6-dianhydro-D-glucitol (isosorbide (2)), and 1,4:3,6-dianhydro-L-iditol(isoidide (3)) were synthesized by Montgomery and Wiggins[144,145,202] (Figure 34). The synthesis of 1,4:3,6-dianhydro-D-iditol

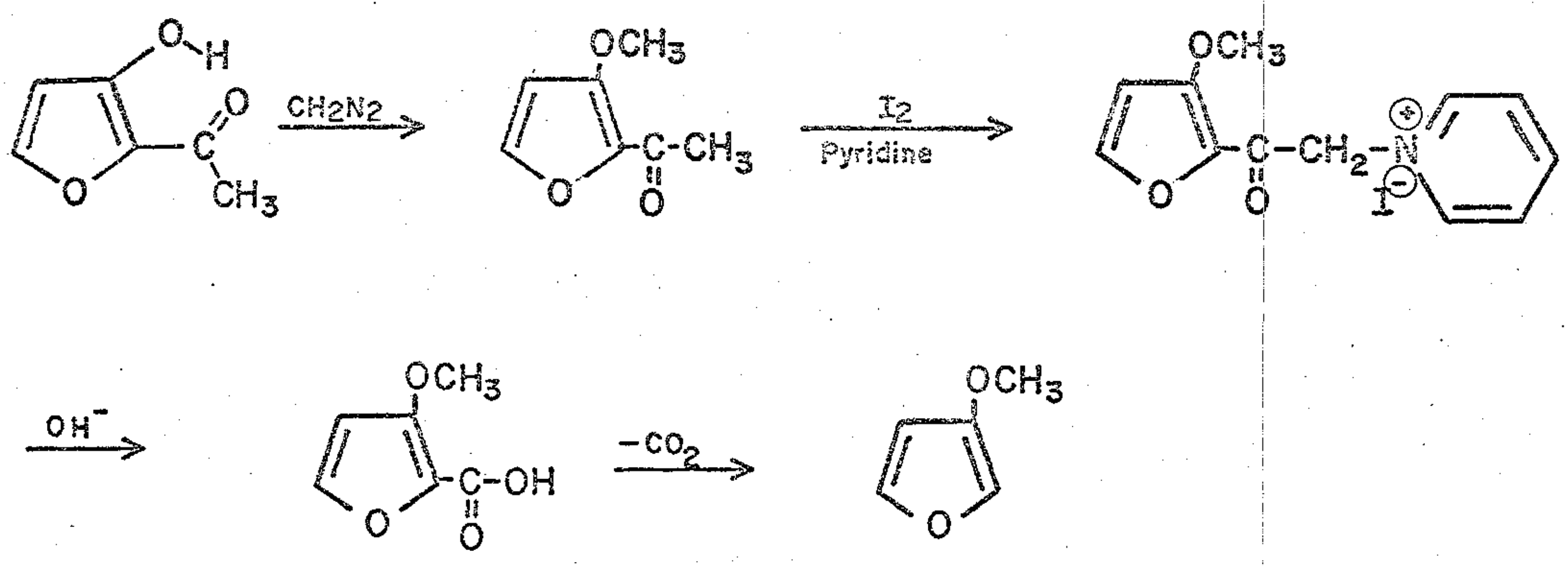


Figure 32

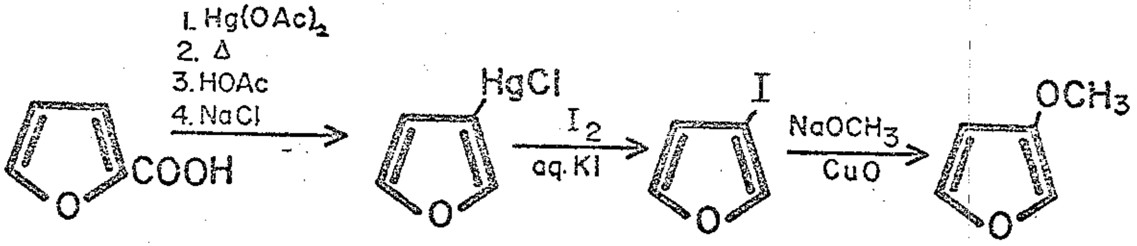
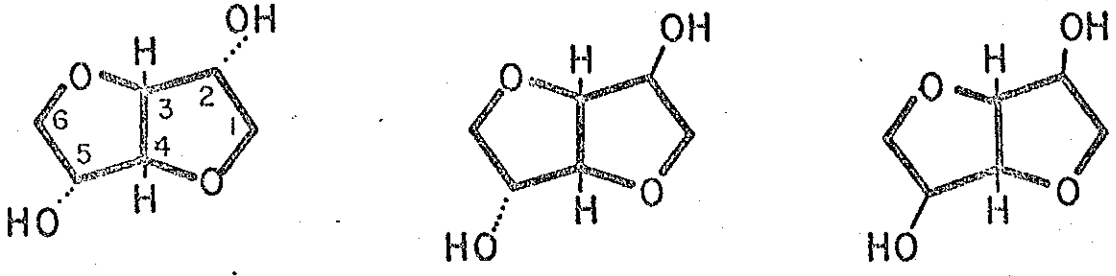


Figure 33

(D-isoidide) has also been reported.[95] The fused rings are nearly planar and are bent together at an angle of about 120°. Differences in the ease of substitution of -OH's at positions 2 and 5 are apparently related to these groups being endo (directed in toward the valley of the rings; more easily replaced due to the backside, SN-2 attack) or exo (directed away from the valley of the rings; less easily replaced by backside SN-2 attack).[103] Wiggins[202] also synthesized 2,5-dichloro-2,5-dideoxy-1,4,3,6-dianhydro-D-iditol from D-mannitol. Cope and Shen[32] reduced this compound to its hydrogenated analog which they named D-2,6-dioxabicyclo 3.3.0-octane(1,4:3,6-dianhydro-2,5-dideoxy-D-mannitol). These authors also synthesized L-2,6-dioxabicyclo 3.3.0-octane and extended the synthetic chemistry in both the D and the L series considerably. The saturated, hydrogenated compound containing this fused ring system has also been made starting from 1,6-hexanediol.[138,139] Numerous other isomers and derivatives containing this fused ring structure have been synthesized.[22,31,40,49,50,86,92,121,135,143,149,152,204] A compound that is especially close to the fully unsaturated ring system of interest is synthesized by the action of mercuric sulfate on the diacetylenic glycol[45] (Figure 35).

Some compounds with this general formula (Figure 36) have outstanding dispersant, surfactant, and emulsifying properties.[105,117] Others display physiologic properties,



1 2 3

Figure 34

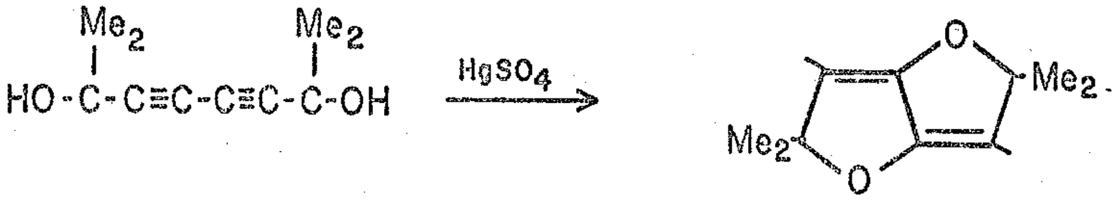


Figure 35

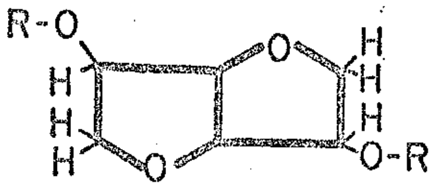


Figure 36

including stimulation of myocardial contraction,[188,206] and tumorigenesis,[178] and action as an effective osmotic diuretic.[153]

2-(Hydroxymethyl)1,3-dioxolane (1,3-dioxolane-2-methanol) was of interest in this study because of its possible use in the synthesis of 2-(3-furyloxymethyl)-1,3-dioxolane (Figure 37), a compound with obvious potential as an intermediate in the synthesis of furo [3,2-b] furan (Figure 38). Although the 1,3-dioxolane ring structure is used as a carbonyl protective group[112] and although 2-substituted derivatives of 1,3-dioxolane have long been known,[26,96,106,136,199] little was found in the literature on 2-(hydroxymethyl)1,3-dioxolane (Figure 39). Two uses of it were reported. One of these was in a process patented by Union Carbide.[85] The other involved a radical addition to the double bond of an enone[57] (Figure 40). The dioxolane alcohol has allegedly been detected in mixtures containing ethylene glycol and glycolaldehyde.[124,185]

The three reports of syntheses of 2-(hydroxymethyl) 1,3-dioxolane do not include a characterization of this product, except by b.p. at reduced pressure, and are unclear in preparative details and not suited for the laboratory.[96,118,137] Hill and Hibbert,[96] after describing the synthesis of 2-bromo-1,3-dioxolane, state without details that the corresponding alcohol can be easily obtained from this. McNamee and Blair,[137] in

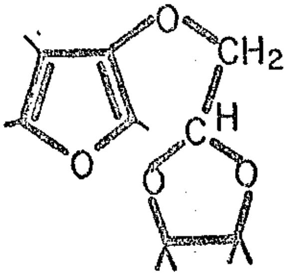


Figure 37

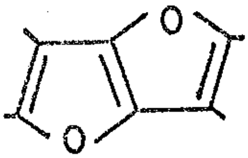


Figure 38

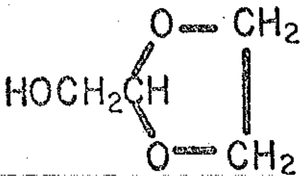


Figure 39

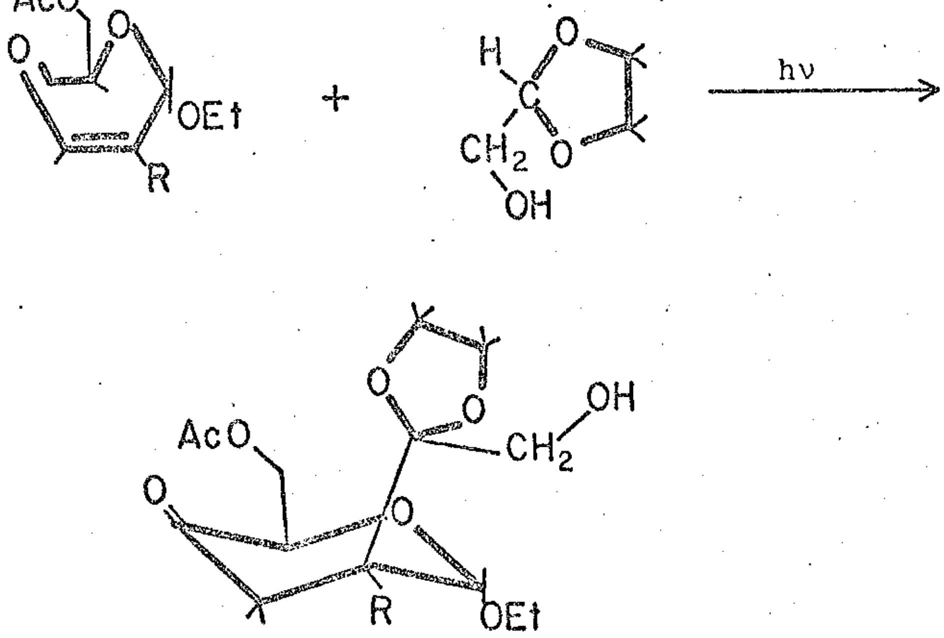


Figure 40

patents issued to Carbide and Carbon Chemicals Corp., state that the simultaneous dehydrogenation and dehydration of ethylene glycol in the presence of reduced Cu and Cr leads to the acetal alcohol. They define the fraction boiling at 97° under 30mm Hg as the alcohol but they do not characterize it further. Kuznetsov and Krasavtsev[118] mention in a table the synthesis of 2-(hydroxymethyl)1,3-dioxolane as one of a number of similar hydroxyaldehyde acetal syntheses starting from 1,2-dibromo-2-acetoxyethane (Figure 41). The starting material is unknown and characterizing constants for the product are not reported. Hardly qualifying as a synthesis is the report of Spath and Raschik[187] that they obtained 2-(hydroxymethyl)1,3-dioxolane as a byproduct in the synthesis of dioxane from dimeric glycolaldehyde. However, the compound was characterized by two solid nitrobenzoyl derivatives by these authors.

Aldrich Chemical Company, Inc., as recently as 1975, advertised 1,3-dioxolane-2-methanol in their Alfred Bader Library of Rare Chemicals, catalogue number S36, 919-5. In our laboratory this material proved to contain a number of components, produced no constant boiling fraction, and exhibited a strong carbonyl band in its i.r. spectrum. Correspondence with Aldrich brought the reply that the material contained water and had reacted to form ethylene glycol and glycolaldehyde, the latter

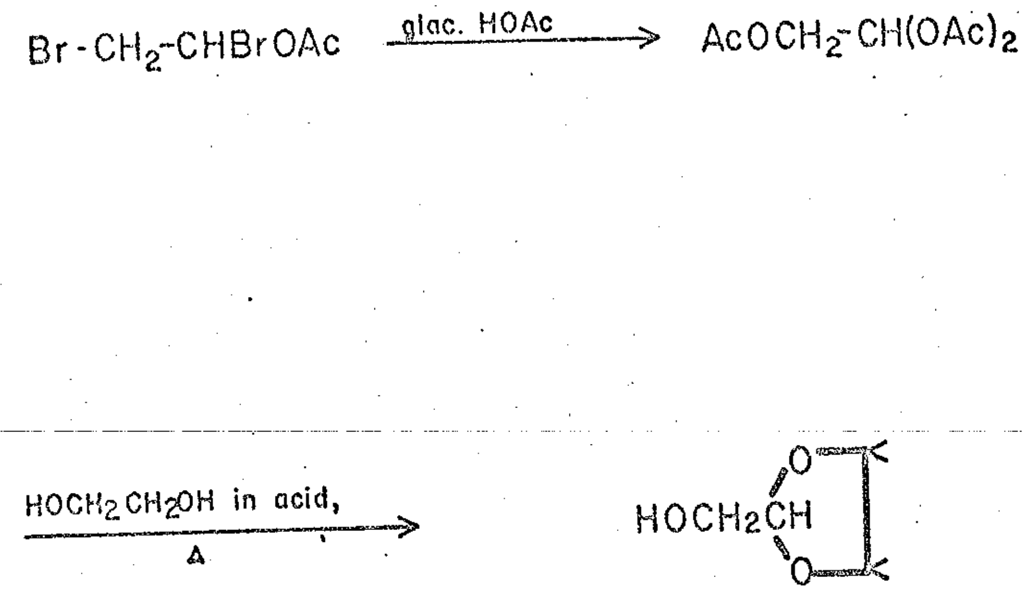

Br-CH2-CHBrOAc
glac. HOAc
AcOCH2-CH(OAc)2
HOCH2CH2OH in acid,
Δ
HOCH2CH

Figure 41

being oxidized to glycolic acid.[4] They also informed that the material was sold on an "as is" basis, that it was not analyzed prior to sale and that they were discontinuing it from their catalogue. A request concerning their source of supply went unanswered. Correspondence with the companies holding patents on this compound, one for it's synthesis[137] and the other for its use,[85] was also not productive in locating a source of supply.

CHAPTER II

STATEMENT OF PROBLEM

The decision to attempt the synthesis of furo[3,2-b]furan was based on four considerations. Firstly, there are an abundance of synthetic and naturally occuring compounds, especially carbohydrate derivatives, containing this ring system in a partially or fully saturated state. Secondly, some of these compounds are physiologically active and others are important industrially. Thirdly, no compound, synthetic or naturally occuring, containing the fully unsaturated nucleus has been reported. Yet this molecule has an uninterrupted chain of six carbon atoms and may conceivably be formed from certain hexose derivatives. By analogy with compounds containing the saturated ring, furo[3,2-b]furan may be physiologically active. Lastly, there is only one synthetic 3-alkoxyfuran, 3-methoxyfuran. Any intermediate successes toward the stated goal as well as achievement of the final objective will expand knowledge in the difficult area of 3-substituted furan synthesis especially in the presently unexamined area of 3-alkoxyfuran synthesis.

CHAPTER III

DISCUSSION AND RESULTS

The starting materials for the projected sequence shown in Figure 42, 3 iodofuran (VIII) and 2-(hydroxymethyl)1,3-dioxolane (IV), were thought to be easily accessible; in practice, the literature preparation of VIII proved to be quite elaborate and technically difficult,[81] and the alleged commercial source of IV, Aldrich Chemical Co., could not in fact supply this compound.[4] Since IV was not available commercially, was poorly characterized in the literature and no good laboratory synthesis was found, the synthesis and characterization had to be worked out.

Chloroacetaldehyde dimethyl acetal (I) may, in principle, be converted to 3-(hydroxymethyl)1,3-dioxolane via transacetalation with ethylene glycol and displacement of -Cl by -OH. In an initial experiment dry ethylene glycol, compound I and p-toluenesulfonic acid were stirred at reflux overnight in sufficient tetrahydrofuran (THF) to effect one phase. In order to shift the equilibrium in the direction of the cyclic acetal,[48,94,198,200] the condensate was continually passed through a calcium chloride filled porous thimble. Although this method worked fairly well if the calcium chloride was changed periodically, after saturation

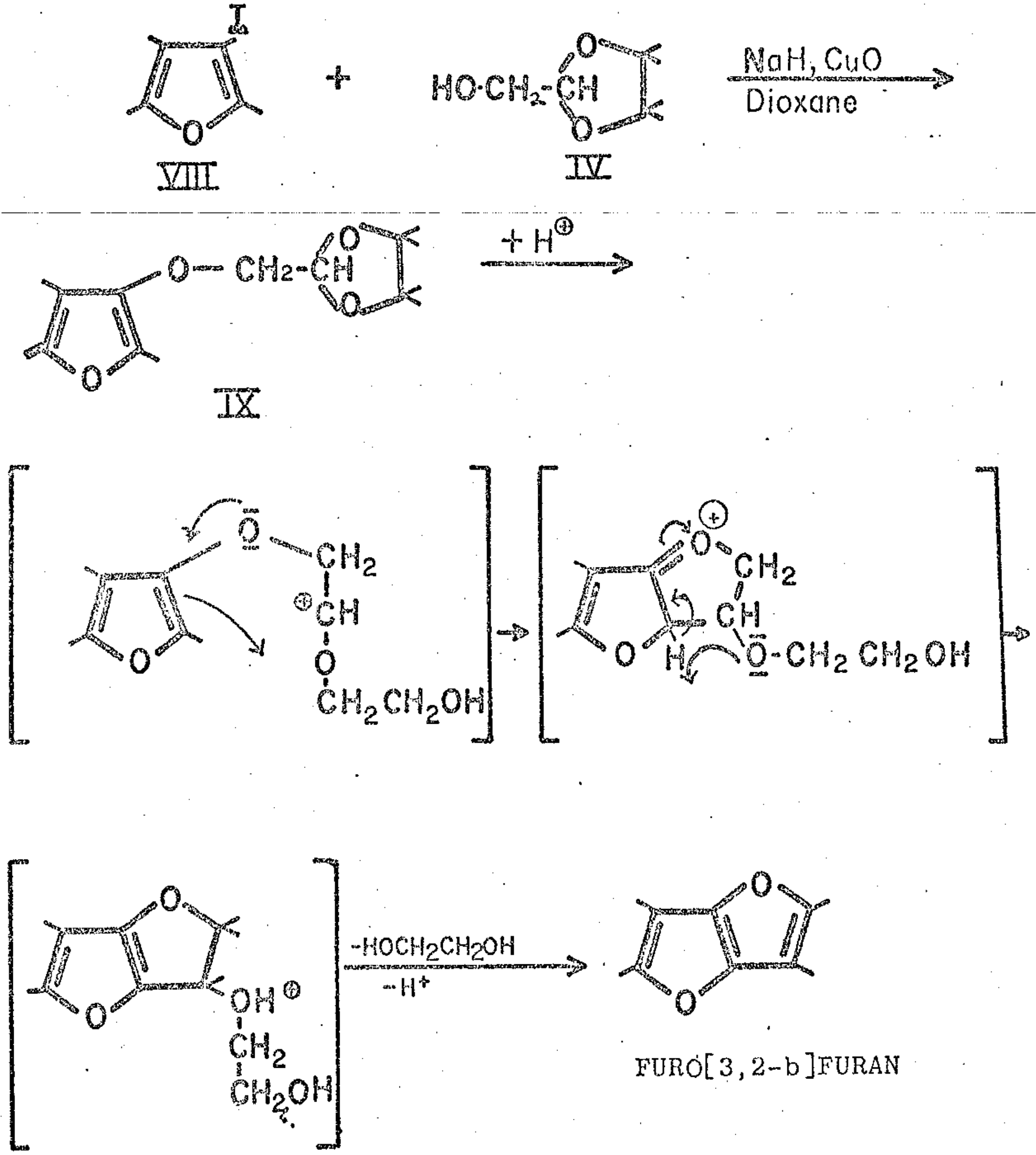

I
VIII
+
HO·CH₂-CH
IV
NaH, CuO
Dioxane
O—CH₂-CH
IX
+H⊕
CH₂
⊕CH
O
CH₂CH₂OH
⊕
O-CH₂ CH₂OH
H
OH ⊕
CH₂
CH₂OH
-HOCH₂CH₂OH
-H⁺
FURO[3,2-b]FURAN

Figure 42

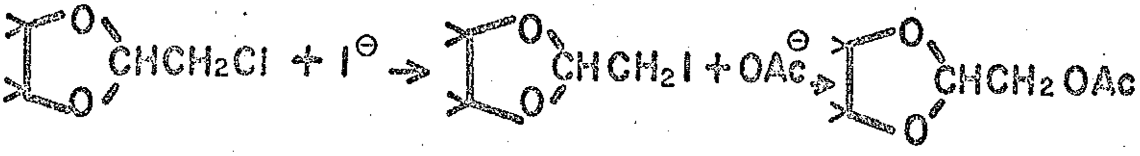
with methanol, the appreciable solubility of calcium chloride in THF was sufficient, in a period of 12 h, to leach enough calcium chloride from the thimble into the reaction flask to produce a two phase system, with a thick calcium chloride-ethylene glycol solution as the bottom layer. This problem was avoided by replacing the Soxhelet Extractor with a 15 inch Vigreaux Column fitted with a condenser and collection flask and replacing THF with the higher boiling dimethoxy ethane (DME). Methanol was distilled off with exclusion of moisture while most of the DME remained in the reaction vessel. 2-(Chloromethyl) 1,3-dioxolane (II) was obtained in 67% yield by neutralizing the acid in the residual liquid, washing out the excess ethylene glycol and distilling *in vacuo*.

An attempt was then made to substitute the -Cl directly by -OH. Since -Cl is not a particularly good leaving group and base may catalyze the elimination of HCl, a favorable outcome of the displacement was doubtful. The two phase system of II with aqueous KOH was stirred vigorously at room temperature for 3 days without a decrease in the base concentration in the aqueous phase. Heating at reflux for 3 additional days caused only a 24% base consumption. Efforts to complete the reaction at high temperature in a pressure vessel resulted in extensive decomposition. A concurrent effort to convert chloroacetaldehyde dimethyl acetal to the corresponding alcohol, hydroxyacetaldehyde dimethyl acetal, under the same reaction conditions was also unsuccessful.

An attempt was now made to displace the -Cl of compound I with acetate ion to give acetoxyacetaldehyde dimethyl acetal. Firstly, it was more economical to study the displacement conditions with the readily available I. Secondly, acetoxyacetaldehyde dimethyl acetal could possibly be conveniently de-O-acetylated to hydroxyacetaldehyde dimethyl acetal which might serve the intended synthetic purpose as well as IV, thus eliminating one synthetic step. A slurry from 1 part anhydrous NaOAc and 4 parts of a 15% solution of I in DMF was stirred and heated at reflux overnight. Partitioning of the reaction mixture between water and diethyl ether (DEE), drying the organic fraction overnight over Na_2SO_4, evaporation of DEE and distilling of residual liquid *in vacuo* produced a few drops of distillate boiling at 45-55° (approximately 20mm Hg). The ir spectrum of the distillate showed the presence of a band at ν_{max} 765 cm^{-1} identified with C-Cl stretching. However, there was also a band, ν_{max} 1750 cm^{-1}, identified as $-\overset{O}{\overset{\|}{C}}-$ stretching in an ester. This latter band was not present in the ir spectrum of the starting material. It appeared that substitution of -Cl by -OAc was possible but that the low solubility of NaOAc in DMF was a limiting factor. It is also possible that I was more resistant to displacement than II.

These results and considerations lead to an attempt to increase the OAc^- concentration in DMF by using a 50:50 mixture of LiOAc:NaOAc and proceeding as before. An attempt was made to displace -Cl by -OAc in both chloro compounds I and II. In the reaction with 2-(chloromethyl)1,3-dioxolane, after workup of the mixture as before, two fractions were collected, totalling about 2/3 of that projected for quantitative yield. They boiled from 67-80° and 80-97° (about 20mm Hg), respectively, and each gave a positive Beilstein test and showed evidence of both C-Cl and $-\overset{\overset{O}{\|}}{C}-$ in the ir spectrum. The smaller, higher boiling fraction gave a weaker Beilstein test and showed a greater ratio $\nu_{max}\ 1750\ cm^{-1}$ $(-\overset{\overset{O}{\|}}{C}-)/\nu_{max}\ 765\ cm^{-1}$ (C-Cl) than did the lower boiling fraction. The results of the reaction of chloroacetaldehyde dimethyl acetal with OAc^- were similar except that the boiling ranges of the product fractions were about 25° lower. In view of the apparent proximity of the boiling points of II and III and of I and acetoxyacetaldehyde dimethyl acetal (no reference to either projected product was found in the literature), a quantitative displacement of chloride by acetate was needed.

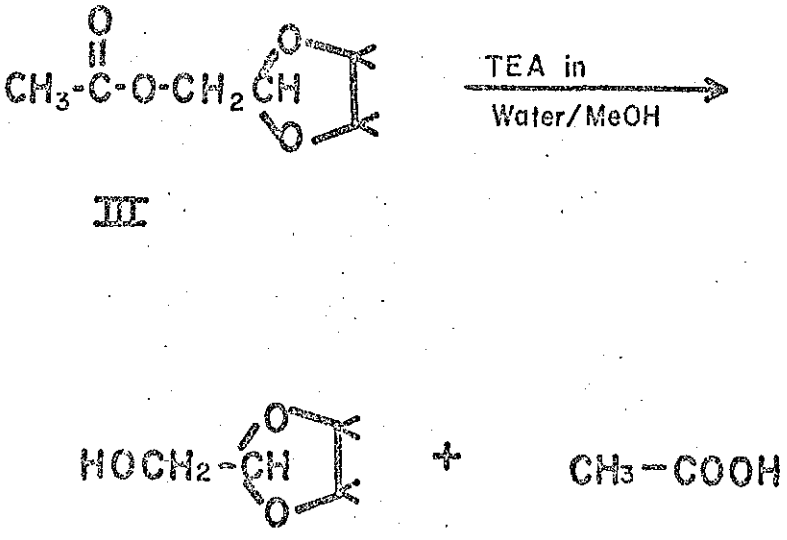
Alkali iodides have high solubility in DMF and iodide ion is a good nucleophile and a good leaving group. In a process similar to that previously tried, iodide could serve as a catalyst. The mechanism in Figure 43 was anticipated. NaOAc/LiI (∼4:1) was used and, otherwise, the procedures were carried out as before, with both I and II. In the reaction with II the initial yellow color faded completely, and the undissolved solid appeared white after 6 h, but yellow again after 42 h. These color changes were attributed to the intermediate formation of 2-(iodomethyl)1,3-dioxolane, with concurrent intermediate consumption of iodide ion. Work up as before gave III in 54% yield based on II. A narrow boiling range (96-98° at 20mm Hg), a negative Beilstein test, presence of the carbonyl band at ν_{max} 1750 cm^{-1} and consistent elemental analysis were indicative of complete conversion of starting material and purity of product. The attempt to carry out the analogous reaction on I resulted in a black, tarry mixture with relatively little product boiling in the expected range. Therefore attempts at synthesizing acetoxyacetaldehyde dimethyl acetal were discontinued. De-O-acetylations of carbohydrate derivatives have been carried out with aqueous methanolic triethylamine (TEA) at room temperature.[171] This technique was tried for the conversion of III to IV (Figure 44). The product IV is, predictably, a liquid and soluble in methanol and water and the acetal ring may be cleaved in the presence of acid. A procedure was devised for removing the HOAc formed in the course of the reaction. By evaporating off, under reduced pressure, methanol, TEA and HOAc with some water and replacing the aqueous-methanolic TEA periodically, four times, the acid formed was driven from the system. A fraction (36% yield) boiling from 89-95° (~ 20mm Hg) was finally collected. The ir spectrum indicated the presence of an -OH group (ν_{max} 3450 cm^{-1}) and of $-\overset{\overset{O}{\|}}{C}-$ (ν_{max} 1750 cm^{-1}). This evidence of uncoverted starting material, and the



II

III

Figure 43



III

IV

Figure 44

proximity of the boiling points of III and IV prompted us to try another procedure.

Transesterification with methanolic methoxide is a standard deacetylation method in carbohydrate chemistry.[170] Rigorously anhydrous conditions are imperative. Thus, 2-(acetoxymethyl)1,3-dioxolane (III) was dissolved in absolute methanol with a catalytic amount of sodium methoxide and the methyl acetate byproduct was distilled off. Neutralization by bubbling dry CO_2 through the liquid and distillation in vacuo produced IV in 78% yield based on III (Figure 45). The boiling point compared favorably with the literature value,[137] the ir spectrum showed absence of $-\overset{O}{\overset{\|}{C}}-$ (no ν_{max} 1750 cm^{-1}) and the presence of -OH (ν_{max} 3540 cm^{-1}) and the elemental analysis were consistent with the proposed structure of IV. Careful examination of the reaction mechanisms for formulation of compound III revealed that 2-hydroxy-1,4-dioxane was a possible structure for compound IV. Rearrangement of the dioxolane to a 1,4-dioxane structure could have occured during the preceeding step, displacement of Cl^- by ^-OAc, leading finally to a hemiacetal structure for IV (Figure 46). However, Fehling's Test, negative for a acetals but positive for hemiacetals, was negative, thus supporting the dioxolane structure.

The purities of this series of compounds were also checked by glc and tlc and the proposed structures were consistent with their nmr spectra. Hence this

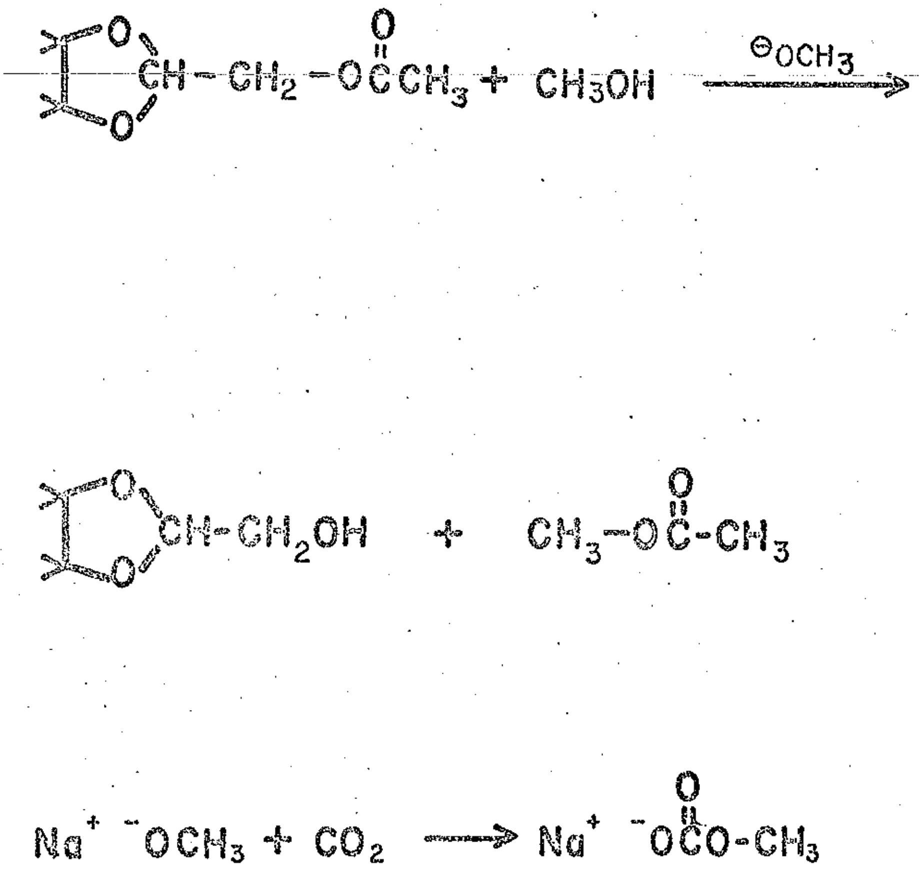


Figure 45

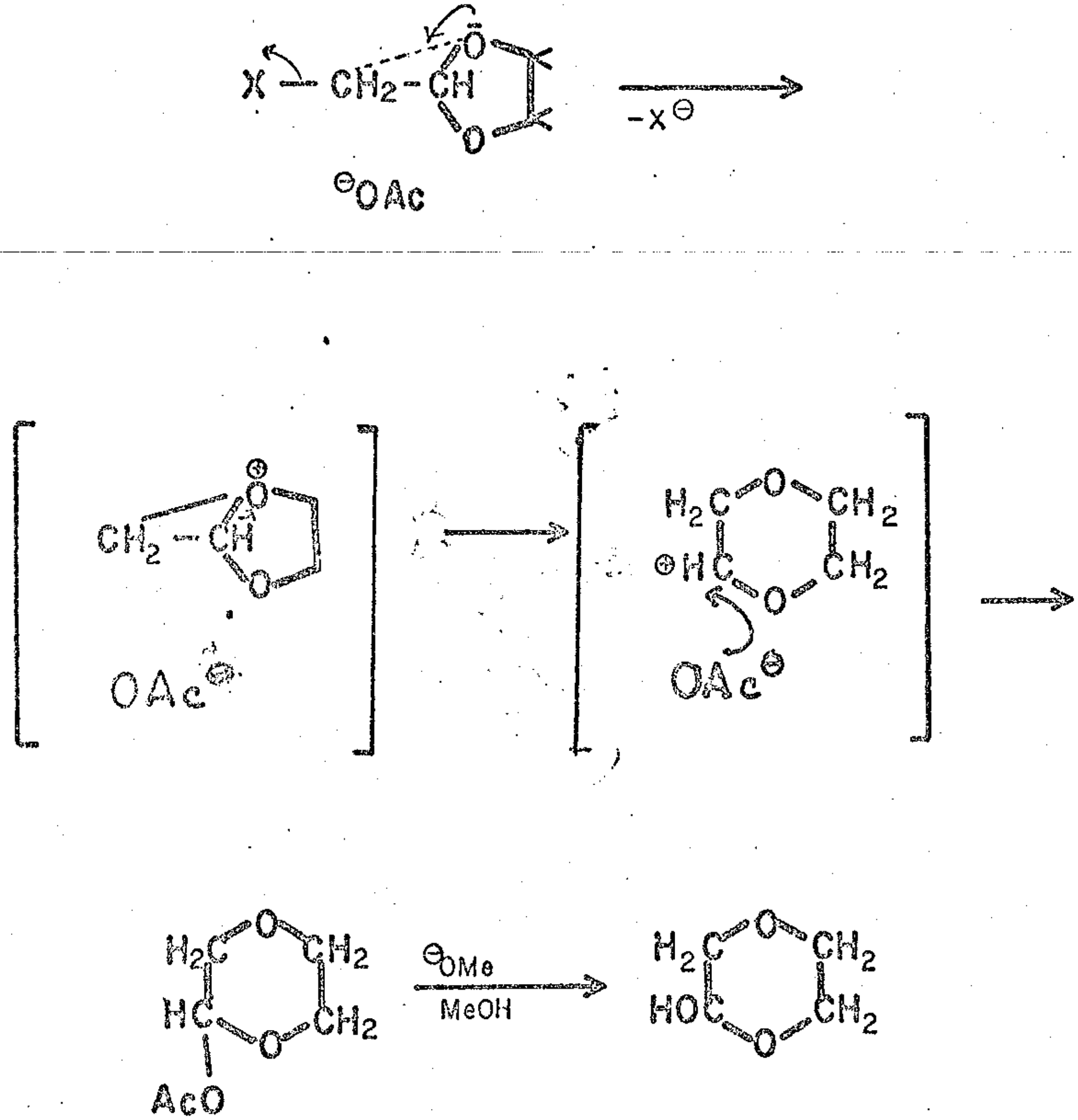

X — CH2 - CH
Ö
O
ΘOAc
-XΘ
⊕
O
CH2 — CH
O
OAcΘ
H2C
O
CH2
⊕HC
CH2
O
OAcΘ
H2C
O
CH2
HC
CH2
O
AcO
ΘOMe
MeOH
H2C
O
CH2
HOC
CH2
O

Figure 46

synthetic scheme proves to be a feasible synthesis of IV, with an overall yield, based on I, of 30% (Figure 47). All reagents and solvents used in this synthesis were readily available and relatively inexpensive.

Compound IV was further characterized by the syntheses of two solid derivatives. Alkyl esters of 2,4-dinitrobenzenesulfenic acid have been used to characterize the corresponding alcohols[111] and the 2-nitrobenzenesulfenic acid esters are also fairly stable.[211] Therefore, 2-(2-nitrobenzenesulfenyloxy) methyl-1,3-dioxolane (V) and 2-(2,4-dinitrobenzenesulfenyloxy)methyl-1,3-dioxolane (VI) were synthesized by an adaptation of the procedure used by Pasto for synthesizing sulfenamides[159] (Figure 48). There were difficulties encountered in the synthesis of V which were not found with VI. The 2-nitrobenzenesulfenyl chloride, although labeled 99%, was impure (tlc). Recrystallization from hot heptane did not completely purify the reagent as shown by tlc and m.p. 70-72°C (reported by Aldrich: m.p. 74-76°). Crystals of V, uniform by tlc, were obtained in low yield, only after numerous recrystallizations of the crude sulfenyl ester from benzene, water, heptane, methylcyclohexane, and CH_2Cl_2. Synthesis of Compound VI proceeded more smoothly, from purification by recrystallization from hot methylcyclohexane of the 2,4-dinitrobenzenesulfenyl chloride starting material, to the obtaining of a crystalline product homogeneous by tlc. This is reflected in the better yield.

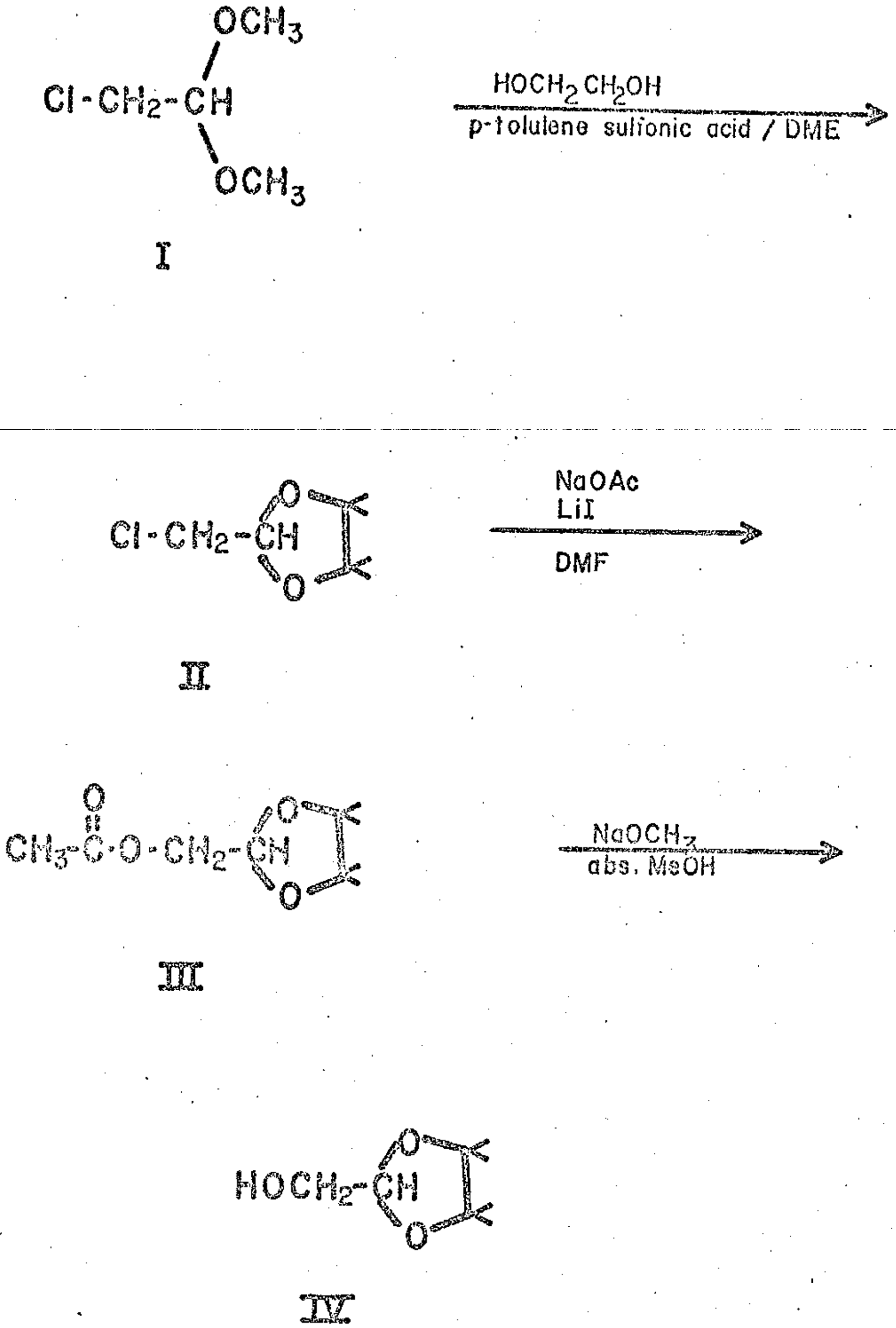
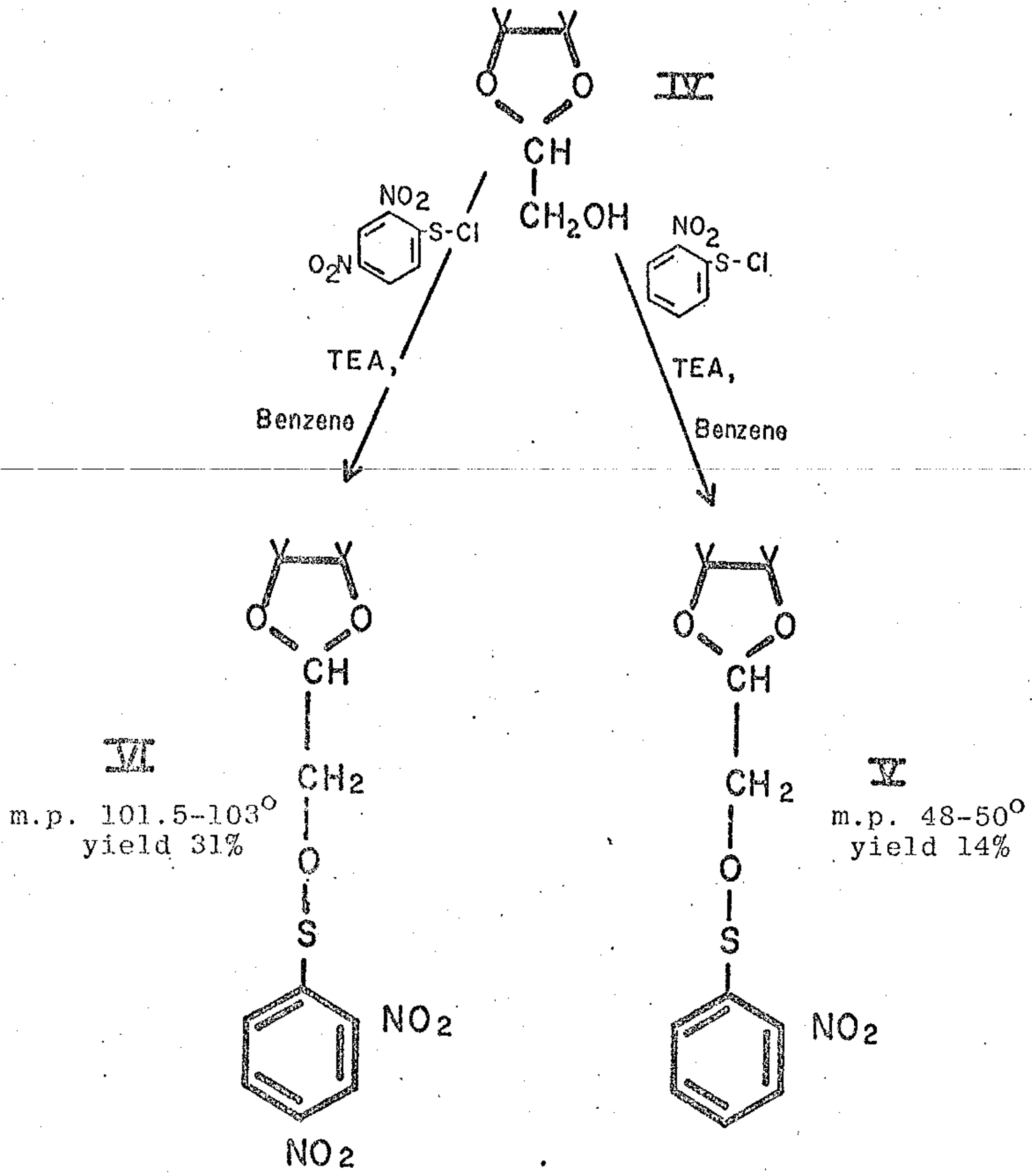

OCH3
Cl-CH2-CH
OCH3
I
HOCH2CH2OH
p-toluene sulfonic acid / DME
Cl-CH2-CH
O
O
II
NaOAc
LiI
DMF
O
CH3-C-O-CH2-CH
O
O
III
NaOCH3
abs. MeOH
HOCH2-CH
O
O
IV

Figure 47



VI
m.p. 101.5-103°
yield 31%

V
m.p. 48-50°
yield 14%

Figure 48

If either of these compounds should prove to be of use as part of a continuing synthetic scheme, there is little doubt that both of the above procedures can be improved.

The second major problem in the synthesis of compound IX was the commercial unavailability of 3-iodofuran (VIII). Although there is a relatively simple procedure for obtaining 3-iodofuran (VIII) from 3-bromofuran[186] (Figure 49) we were unable to obtain 3-bromofuran commercially until near the end of this study. Although methods are available for the synthesis of 3-bromofuran starting from furan[122,150] and dibromo and bromo furoic acids[150,179,186] they are either laborious and give low yields[58] or they involve, at some point, Diels-Alder adducts of 3-bromofuran and maleic anhydride which are subject to rearrangements which could block the formation of 3-bromofuran.[47] Therefore, we favored a synthesis of 3-iodofuran (VIII) by the method of Gilman and Wright[71] as adapted by Gronowitz and Sorlin.[81] Modifications of this procedure have recently been used by Bell and coworkers,[15] who warned that mercuric salts used in this synthesis could explode during dry pyrolysis. This apparently does not apply at temperatures below 140°. In fact our oil bath temperature reached 175° on one occasion without incident. We could not agree with the claim of these authors[15] that their modification doubles the yield of 3-chloromercuryfuran (VII) compared to that obtained by Gronowitz and Sorlin.[81] Bell and coworkers[15] apparently failed to realize that Gronowitz and Sorlin[81] based their % yield of VII on mercuric acetate. If this correction is made the yields are comparable. In order to duplicate the reported yields (~15%) we had to mix the solutions of mercuric acetate and furoic acid hot (because of the low water solubility of furoic acid). Pyrolysis was continued for 36 h at an oil bath temperature of 140°, stirring after addition of acetic acid was continued for 36 h, the suspension containing crude 3-acetoxymercuryfuran was filtered before addition of NaCl, and filtration and drying of the precipitate was followed by exhaustive extraction with ether. 3-Chloromercuryfuran (VII), with aqueous I_2/KI, gave 3-iodofuran, after steam distillation.[81]

The synthesis of 2-(3-furyloxymethyl)1,3-dioxolane (IX), by a Williamson copper-catalyzed ether synthesis, was analogous to the synthesis of 3-methoxyfuran[81] (Figure 50). Although 2-methoxyfuran has not been synthesized by this approach[131] it has been used successfully in the preparation of 2-methoxythiophene[184] and 3-methoxythiophene.[77] A four centered mechanism, involving simultaneous coordination of the O of the alkoxide and the I of 3-iodofuran (VIII) by Cu is suggested here (Figure 51). Gronowitz and Sorlin[81] found the ideal molar ratio of CuO catalyst to VIII to be greater than 1. In the successful effort to synthesize IX, a special catalyst (prepared by us) with a large surface area, containing coprecipitated Cu°, Cu_2O and CuO, was used.

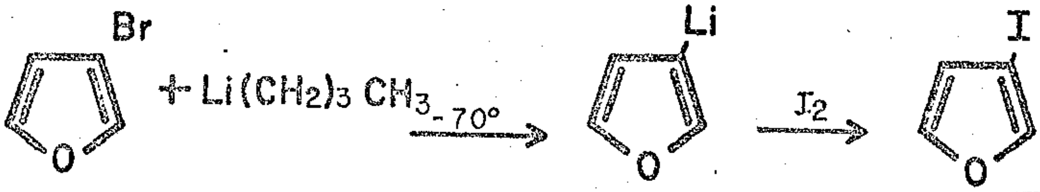


Figure 49

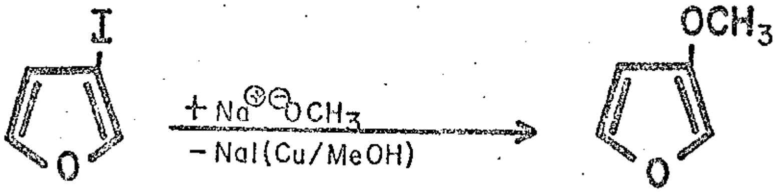


Figure 50

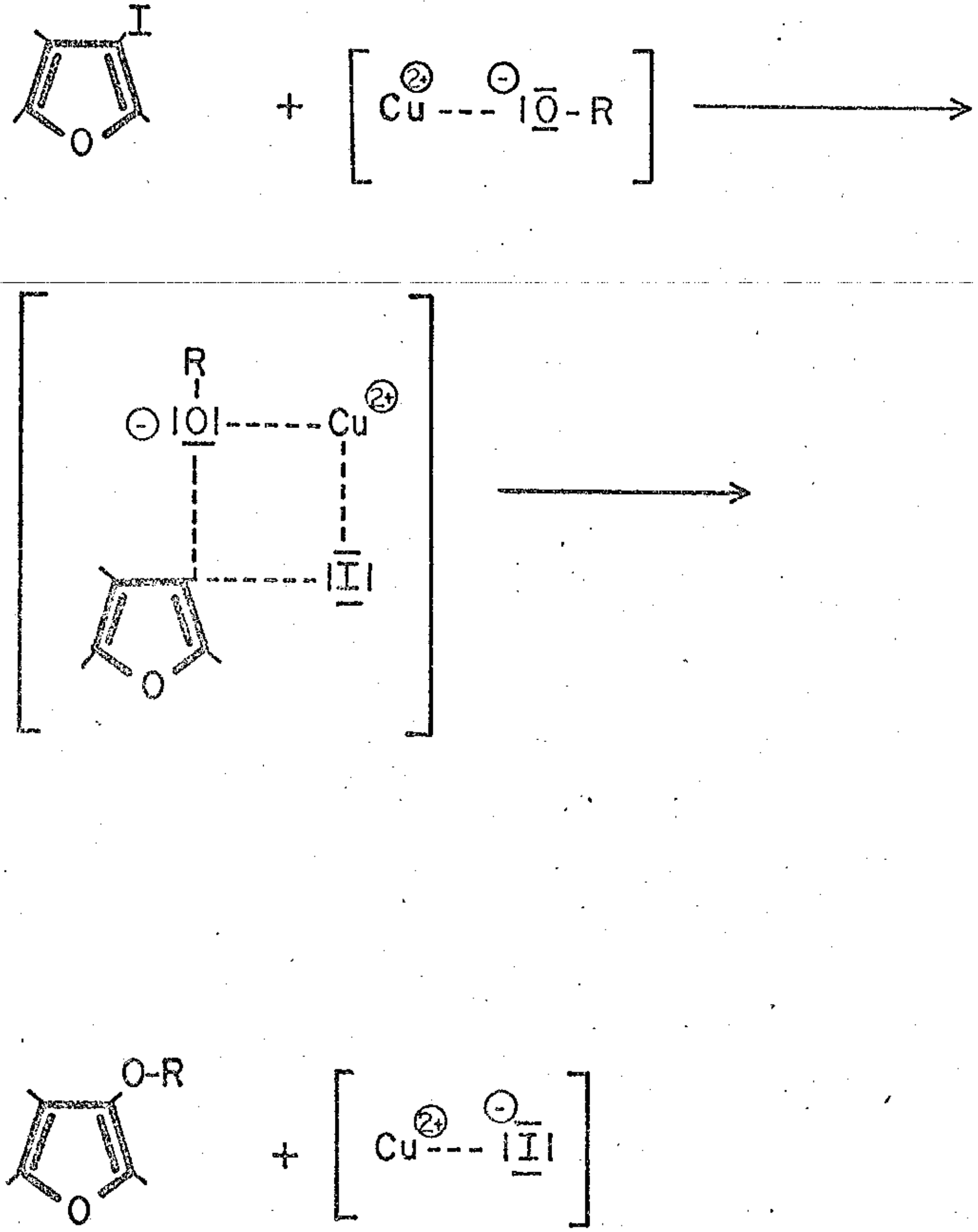


Figure 51

In a first attempt to synthesize IX, commercial CuO was used as catalyst and NaH was used to form the alkoxide of 2-(hydroxymethyl)1,3-dioxolane in THF, which was found to be a fair solvent for the alkoxide. The alkoxide/CuO slurry was heated at reflux with 3-iodofuran (VIII) for six days. Periodically the pH-value was checked and additional VIII added. When a pH of 8 was reached it was concluded that most of the alkoxide had reacted. Throughout the reaction there were two major products (tlc) which appeared to increase with time. Separation of these two substances by preparative tlc produced two homogeneous substances (tlc) in 100 mg quantities. However, neither of these materials were UV absorbent on the tlc plates with UV indicator, as had been the case with all other furan compounds checked, and the nmr spectra of both showed no furan protons. The two substances, obviously not IX, were not investigated further.

It was assumed now that accessibility of the alkoxide of IV to 3-iodofuran (VIII) was important and that ether solvents would solvate the alkoxide too much and might even destroy it by the peroxide they contained. Thus benzene was substituted for THF, CuO was eliminated and potassium-t-butoxide was used in place of NaH. Dibenzo-18-crown-6-ether,[161] known to solubilize ionic substances in benzene by complexation of alkali metal ion was predicted to leave the alkoxide in an unsolvated and very active state. The alkoxide of IV was predicted to be a more stable anion than t-butoxide. Also, steric hindrance in the possible competing formation of 3-(t-butoxy)furan would favor production of the desired compound (IX). An atmosphere of N_2 excluded the possibility of air oxidation in this attempted synthesis. Since IV and VIII remained substantially unreacted after prolonged reflux of the stirred mixture the base content was increased and t-butanol was removed by azeotropic distillation, as evidenced by the nmr spectrum of the distillate. Gas chromatography continued to indicate IV and VIII in the residual material whereas tlc indicated a growing number of components with additional reflux time. Separation of these components included extraction followed by distillation in vacuo of the fraction containing the lower boiling components and column chromatography of the fraction containing the higher boiling components. The small amount of distillate showed four components on tlc and one of these had a mobility identical with that of IX synthesized by a later procedure. The largest, most readily crystallizable fraction collected by column chromatography had the same empirical formula as dibenzo-18-crown-6-ether but was obviously not this compound because of different melting point, different R_f values and different crystalline properties. The unknown compound X may be an isomer of the crown ether formed by rearrangement or cleavage. Compound X was obviously hygroscopic, being liquid in its anhydrous form and crystalline in its hydrated form. It was observed in this attempted synthesis that dibenzo-18-crown-6-ether and potassium t-butoxide have a mutual solubilizing effect on each other in benzene, a phenomenon noted by Pedersen,[162] although his observations did not include this particular example. Since very little IX was formed in this attempt it appears that copper catalysis is essential for the synthesis of 3-alkoxy furans. Although crown ethers are known to cleave and/or rearrange at high temperatures in the presence of O_2,[163] the here observed apparent isomerisation is new. This cleavage on isomerisation is supported by the failure to reclaim more than a tiny fraction of the crown ether used and the apparent absence of structural features attributable to IV and VIII in X. Interestingly, X was evidently present (tlc) in the reaction mixture after the first 24 h of heating.

The third approach to the synthesis of IX took into account the evident need for a copper catalyst, but one more efficient than the commercial CuO catalyst previously used. Also, this author has experienced difficulties with the use of THF, both as a reaction and as a tlc solvent. This appears to be related not only to rapid peroxide formation but also to a high solubility of the peroxides formed in the parent THF. In view of these considerations, impure copper oxide, as described in the general experimental part, was used. The deliberate admixture of Cu_2O was supposed to decrease the crystallinity of CuO and increase the surface area and activity of the catalyst. Apparently[184] it is the copper, with its d-orbitals, that is essential for a catalysis of this type and not specifically CuO. A sacrifice in the solubility of the alkoxide of 2-(hydroxymethyl)1,3-dioxolane (IV) was made by the choice of 1,2-dimethoxyethane (DME) as solvent but it was hoped that the avoidance of problems encountered with THF would justify this choice.

The possible problems of cleavage and/or rearrangement of IV due to oxidation by CuO or the strong basic action of NaH were checked by refluxing IV with each and with both together for a prolonged period. In each case IV was the only component present (tlc and glc) after refluxing and the two low yield products obtained in the first effort at the synthesis of IX were found to be absent by tlc. The reaction was carried out under dry N_2.

After stirring and refluxing for 20 h, a new component was observed by tlc. Additional reflux time did not substantially change the tlc pattern. Distillation *in vacuo* produced a small amount (6% yield, assumed to be IX) of liquid boiling from 130-155° (~20mm Hg) and enriched in the component noted above by tlc. The liquid darkened upon standing and solidified when placed in the refrigerator. A larger batch was run with greater care and produced 2-(3-furyloxymethyl) 1,3-dioxolane (IX), uniform on tlc and boiling at 92-94° (1mm Hg), in 24% yield. Again it was observed that IX yellowed upon standing at room temperature and solidified upon cooling (Figure 52).

Attempts at the synthesis of furo[3,2-b]furan were now made. In the first of these a projected property of the desired product was taken into account. Furo[3,2-b]furan would be a furan analog of naphthalene (Figure 53). As such it would be expected to sublime readily. If comparative vapor pressures of benzene and furan are considered analogous, furo[3,2-b]furan should sublime considerably more readily than naphthalene. Hence, a solid acid catalyst (an intimate mixture of dried silica gel and crude p-tosyl anhydride) was impregnated with IX in a micro-sublimation apparatus. The solid mixture was warmed gently (pressure 1mm Hg) while the cold finger was kept at -20° and rigorously dry conditions were maintained. It was known[100] that careful acid hydrolysis of 3-methoxyfuran leads to the following cleavage (Figure 54). A similar result might be expected in our case. However, acetal cleavage could be expected to compete favorably with hydrolysis. After ethylene glycol elimination, ring closure by electrophilic attack on the 2 position of furan[19d,69] by a carbonyl carbon, and water elimination would seem reasonable. And if, as expected, furo[3,2-b]furan sublimes readily under these conditions, it would be removed, as soon as it is formed, from the acid conditions favoring further cleavage. In this reaction the liquid drop that accumulated on the cold finger had the

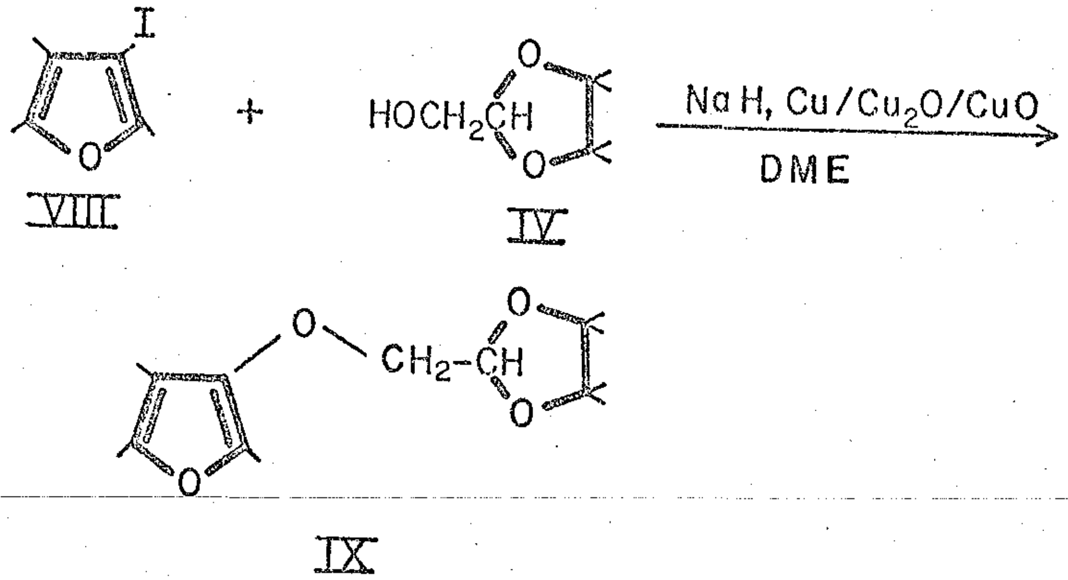


Figure 52

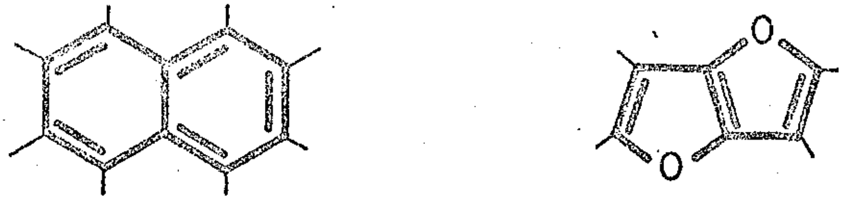


Figure 53

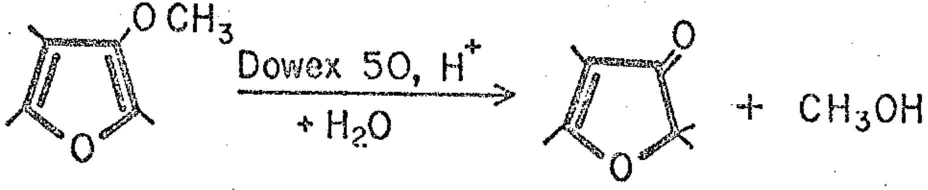


Figure 54

same R_f values as IV (tlc, three systems). Apparently hydrolysis at the "normal" ether linkage did occur. The silica gel-acid catalyst, although dried over P_2O_5, was apparently not totally anhydrous and cleavage likely occured according to the suggested mechanism (Figure 55). The postulated 3(2H)-furanone was not isolated. Under milder acidic conditions, in an aqueous-organic two phase system, where any furo[3,2-b]furan formed would be away from the acid and essentially totally in the organic layer, and where IX would only partially be in the aqueous layer at any given time, it was hoped that acetal cleavage and formation of furo[3,2-b]furan might still be achieved. A 3% solution of citric acid constituted the aqueous phase, the organic phase initially being IX in CCl_4. Vigorous stirring produced a multicomponent system in the organic phase that was monitored by tlc during the experiment. Several of the spots on the tlc increased dramatically in intensity at the outset of the reaction, but they faded rapidly with prolonged reaction time. Thin layer chromatography of the aqueous phase again showed material with the same R_f values as IV.

An analysis based on ir and nmr spectra confirms the postulated structures for compounds II, III, IV and IX. Infrared bands characteristic of each proposed structure are present in the spectra and these are noted in the experimental section. The nmr spectrum of the compound postulated as 2-(chloromethyl)1,3-dioxolane (II) shows

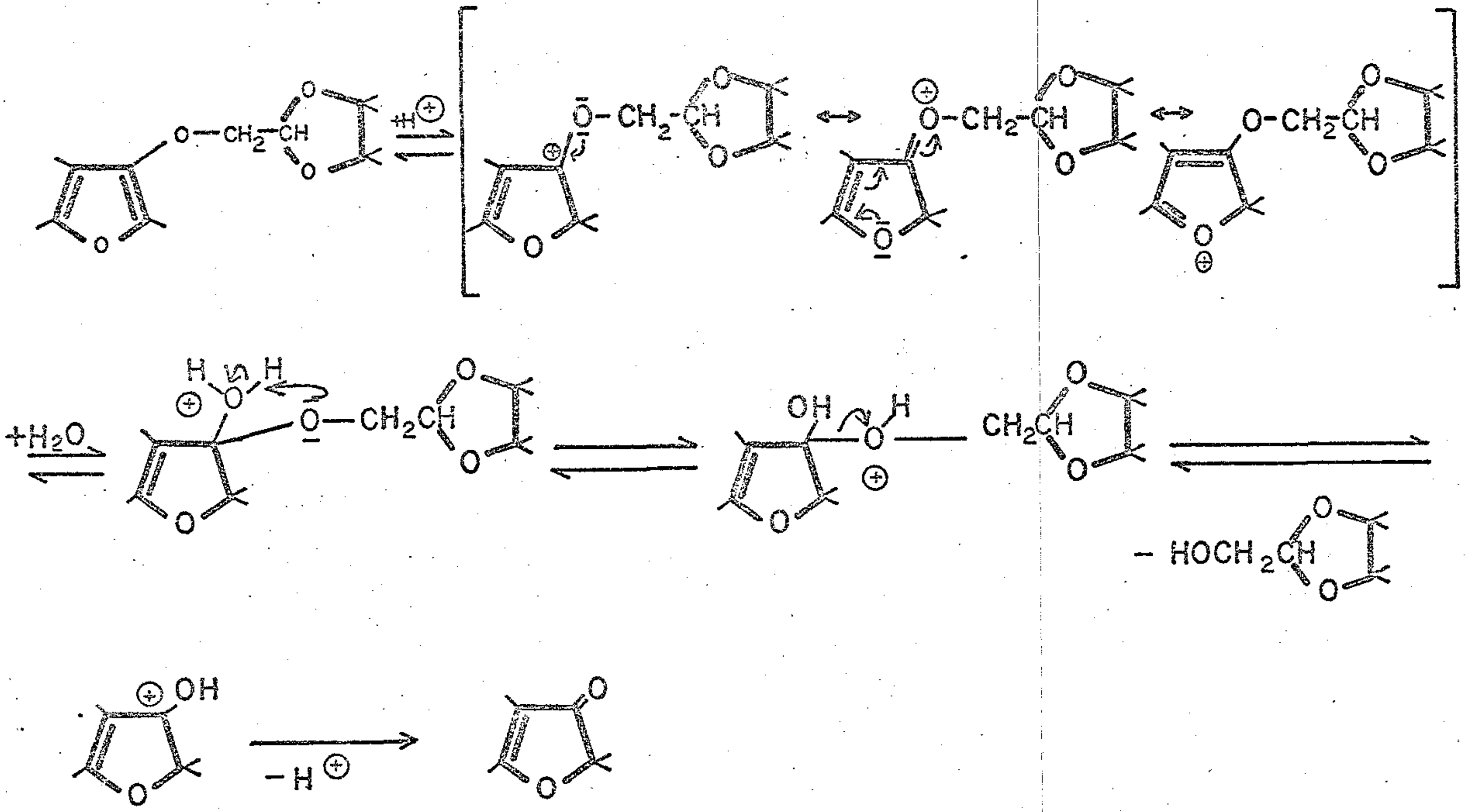


Figure 55

three types of protons, a one proton triplet at δ 5.2, a four proton doublet at δ 4.00-4.04 and a two proton doublet at δ 3.60-3.64. The absorbance of the ring proton on the 2-position of the dioxolane ring predictably would be shifted downfield to the greatest extent because of the inductive deshielding effect of the two neighboring oxygen atoms, and would be a triplet because of the neighboring methylene group. The position and splitting of the four proton peak at δ 4 and the two proton peak at δ 3.6 are consistent with the two endocyclic methylene groups and the exocyclic methylene of the chloromethyl group, respectively.

The compound projected as 2-(acetoxymethyl)1,3-dioxolane (III) has an nmr spectrum in accord with this structure. The unsplit, three proton peak at δ 2.04 is expected for the methyl protons in an acetate. The remaining peaks are much the same as in II except that the peak for the exocyclic methylene is apparently shifted downfield to near δ 4 as compared to 2-(chloromethyl)1,3-dioxolane (II) and 2-(hydroxymethyl)1,3-dioxolane (IV). This is consistent with chemical shifts induced by acetoxy groups. Compounds II and III display absorption maxima in their ir spectra which support the assigned structures (see experimental section).

The nmr spectrum for 2-(hydroxymethyl)1,3-dioxolane (IV) would be expected to be similar to that of compound II except for an unsplit, single proton peak representing the hydroxyl proton. This is in fact the spectrum of the compound designated compound IV with the unsplit single proton peak at δ 4.2 evidently representing the hydroxyl proton. The expanded, offset spectrum of compound IV (see spectra) confirms this assignment.

Support for the 2-(3-furyloxymethyl)1,3-dioxolane structure for compound IX includes the assignment of the twin peaks at δ 7.28+ and δ 7.24- to the protons at positions 5 and 2 on the furan ring and the assignment of the one proton peak at δ 6.3 to the proton at position 4 on the furan ring. This is supported by the reported nmr spectrum of 3-methoxyfuran[82] and the spectra of 3-bromofuran,[166] 3-iodofuran and 3-methylfuran.[82] All of these spectra show similar relative but not identical chemical shifts for these proton peaks, regardless of the substituent. The one proton triplet at δ 5.2, as previously, is identified with the ring proton on the 2 position of the dioxolane ring. What appears to be a six proton quadruplet at δ 3.83-3.93 is considered an overlap of the doublet from the four protons of the two dioxolane ring methylene groups with the doublet from the exocyclic methylene. This is analogous to the situation in compound III and for good reason. In III the absorbance of the exocyclic methylene protons was thought to be shifted downfield (compared to the situation in compounds II and IV) because they were adjacent to the ester moiety. Here they are apparently shifted downfield to approximately the same extent because they are adjacent to the furyloxy group. Evidence supporting this analogy is also found in the ir spectrum where compound IX gives a very strong band at 1600 cm^{-1}, in the carbonyl region, evidently due to the carbon carbon double bond. In contrast to these observations, the pattern of peaks in the nmr spectra for 2-methoxyfuran and other 2-substituted furans is distinctly different.

The structure of compound X was not established. However, indications for it being isomeric with dibenzo-18-crown-6-ether do not depend only on its elemental analysis. The major nmr peaks in compound X, although split differently, are located at the same δ values as the peaks representing the benzene protons, δ 7.2, and the methylene protons, δ 4.0-4.4, in dibenzo-18-crown-6-ether. That compound X is much more hygroscopic and apparently, therefore, has a much better facility for hydrogen bonding than the crown ether, is evident from the noted physical properties (hydrates and crystallizes in the atmosphere, dehydrates and liquifies in the presence of $CaCl_2$ and P_2O_5) and the ir spectrum from 2850 to 3550 cm^{-1}. The ir spectrum also provides evidence for the presence of (an) hydroxyl group(s). The definitive structure for this compound remains unknown.

Although this study has failed in the attempt to synthesize furo[3,2-b]furan, it has provided an instructive comparison of the relative stabilities to acid catalyzed cleavage of positions "a" and "b" in compound IX (Figure 56). The ether linkage at "a" is readily cleaved, in mild acid with the primary contact being across a phase boundary, whereas some IV, with acetal linkages intact, survived several days dissolved in the same medium. With the apparent rugged character of IV one must question whether the material so designated and received in this laboratory from Aldrich was ever obtained. Hence, another value of this study has been the development of a new, suitable laboratory synthesis for IV and the further physical and chemical characterization of this compound. The discovery that homogeneity of all of the compounds used here may be checked by tlc is certainly a convenience for anyone working with them. The tlc of the two solid derivatives of IV was particularly interesting in this respect. On the tlc each of the compounds appeared as a yellow spot, indicating the presence of nitro group(s). Under the UV lamp the same region was visible by extinction of the uv fluorescence of the indicator mixed with the silica gel. Upon spraying and warming this same area charred, suggesting the 1,3-dioxolane-2-methyl-moiety. The synthesis and characterization of compound IX constitutes the synthesis of the second known 3-alkoxyfuran and presents the opportunity for further explorations, if a way can be found to cleave the acetal ring without first cleaving the 3-ether linkage. However that may be, the observations presented here tend to corroborate and extend the information on the hydrolysis of 3-alkoxyfurans, even under very mild conditions.

In further attempts to synthesize furo[3,2-b]furan or its derivatives dehydration followed by dehydrogenation of the 1,4:3,6-dianhydrohexitols (Figure 57) may be a good route.

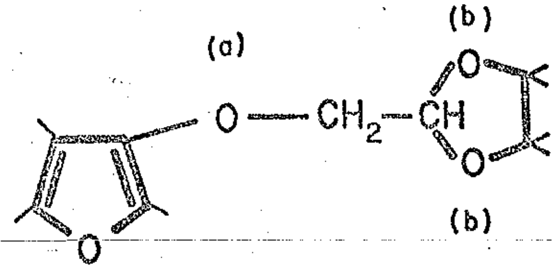


Figure 56

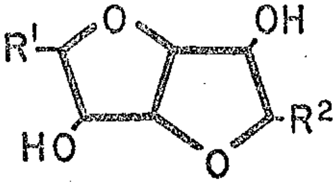


Figure 57

CHAPTER IV

EXPERIMENTAL PROCEDURES

Melting points were taken in a Thomas-Hoover melting point apparatus, Model 6404H, and are uncorrected. Refractive indices were determined on a Bausch and Lomb Refractometer, Model 33.45.58 and are corrected to n_D^{20}. Infrared (ir) spectra are recorded with Perkin-Elmer spectrophotometers, Models 137 and 337. The potassium bromide pellet technique was used on compounds V, VI, VII and X and compounds I, II, III, IV, VIII and IX were run as a neat liquid. The nuclear magnetic resonance (nmr) spectra were obtained with a JEOL Minimar-100 100MHz nuclear magnetic resonance spectrophotometer. The homogeneities of all compounds synthesized, with the exception of VII, were determined by thin layer chromatography using Analtech Precoated Thin Layer Chromatography Plates (0.25 mm).

Compound VIII was detected on the plates by extinction of the ultraviolet fluorescence of a zinc-silicate indicator. Compounds I-IV were detected on the plates by spraying with a sulfuric acid/methanol (1/9) mixture, and charring on a hot plate at 120° for 15 min.

Compounds V,VI,IX and X were detected by the extinction of ultraviolet fluorescence with subsequent spraying and charring. Homogeneities of compounds I-IV, VIII and IX were also checked by gas chromatography. All but IX were chromatographed on a Carle glc apparatus, Model 6500, using both the polar column (5 ft, 1/8 in. dia., 8% carbowax 1540 on 90-100 mesh anachrom ABS) and the nonpolar column (5 ft, 1/8 in. dia., di-N-butylphthalate on 90-100 mesh anachrom ABS) at column temp. of 140°. The homogeneity of compound IX was checked on a Pye-Unicam glc apparatus fitted with a silica gel packed column (6 ft, 1/8 in. dia., porosity 50-80 mesh) at column temperature of 120°. The thick layer chromatography purification in the attempted reaction of compound VIII with compound IV was achieved on a precoated plate (Merck silica gel G.S., 1mm). The column material used in the chromatographic isolation of compound X was "Baker Analyzed Reagent" Silica gel powder (60-200 mesh). The uses and adaptations of any of the above techniques for charting the progress and/or direction of reaction are indicated in the separate procedures.

Starting materials chloroacetaldehyde dimethyl acetal (Aldrich; 97%) and furoic acid (Aldrich; 99.5%) were used without further purification. Other reagents used without further purification were sodium acetate (J.T. Baker; anhydrous, purified), lithium iodide (Alfa Products, Ventron; anhydrous, 99+%), triethylamine (MCB; bp 88-90°), acetic acid (Aldrich; glacial, 99.8%), mercuric acetate (Aldrich, 98%), iodine (MCB; U.S.P. crystals), potassium iodide (Baker and Adamson; min 99.5%), cupric oxide (used in the attempted reaction of VIII with IV - Baker and Adamson; min 99.0%), potassium-t-butoxide (Aldrich, mp 256-258 dec), sodium hydride (Alfa Inorganics, Ventron; 57% emulsion), and citric acid (Baker; analyzed reagent). Of the reagents purified prior to use, ethylene glycol was distilled (2X) *in vacuo*, *o*-nitrobenzenesulfenyl chloride (Aldrich; 99%) and 2,4-dinitrobenzenesulfenyl chloride (Aldrich; 98%) were recrystallized (2X) from hot hexane, and dibenzo-18-crown-6-ether (Aldrich; 98%) was recrystallized from hot benzene. The deliberately impure CuO, used in the synthesis of IX, was prepared by adding $CuSO_4 \cdot 5H_2O$ (MCB, reagent grade; 250 g, 1 mole) and NaOH (Mallinckrodt, reagent grade; 110 g, 2.75 mole) to a hot (98°), stirred mixture of water (700 ml) and Cu metal (15.9 g, 0.25 mol - J.T. Baker; purified powder), cooling to room temp., filtering by centrifugation, washing free of alkali, air drying, powdering in a mortar and drying *in vacuo* over P_2O_5 at 101.5° for 48 h.

All of the solvents used were purified, prior to use, by the methods elaborated by Vogel,[197] with the following exceptions: dimethylformamide (Mallinckrodt; bp 152-155°), methylcyclohexane (MCB; practical) and heptane (MCB; practical). The N_2 used was Linde, Union Carbide Corp. (High Purity Dry Grade).

2-(Chloromethyl)-1,3-dioxolane(II): Chloroacetaldehyde dimethyl acetal (I, 228.5 ml, 2 mol) and *p*-toluenesulfonic acid monohydrate (4.60 g, 0.0242 mol) were dissolved in absolute dimethoxyethane (320 ml) and dry ethylene glycol (226 ml, 4 mol). This mixture was slowly distilled (6.5 h) through an aluminum covered Vigreux column (bath temp 105-149°; distilling vapor temp 65-85°) until 600 ml of distillate were collected. The undistilled material was stirred and neutralized with saturated aqueous KCl containing copious amounts of K_2CO_3 (4 x 60 ml). The organic phase was diluted with CH_2Cl_2 (150 ml). This solution was dried overnight, with shaking, over anhydrous $CaCl_2$, filtered by suction and concentrated under atmospheric pressure. The residual liquid was distilled *in vacuo* giving II (165.5 g; 67%); bp 61-62° (22mm Hg; literature bp 72° at 29mm Hg[198]), n_D^{20} 1.4485; d^{29} 1.2350; ir (neat) 760 (C-Cl), 1050, 1150 (C-O-C) and 2900, 2970 cm^{-1} (CH_2); nmr (neat) δ 5.2 (t, 1, O-C$\underline{H}$-O), 4.02 (d, 4, O-C$\underline{H_2}$-C$\underline{H_2}$-O), and 3.62 ppm (d, 2, Cl-C$\underline{H_2}$).

Anal. Calcd. for $C_4H_7O_2Cl$ (122.55): C, 39.20; H, 5.76; Cl, 28.93.

Found: C, 39.58; H, 5.88; Cl, 28.95.

Attempts at preparation of IV from II. Compound II (10.0 g, 0.084 mol) was allowed to react with aqueous, or alcoholic (MeOH, t-BuOH) aqueous KOH at reflux temperatures or in an autoclave at 175-180°. Incomplete displacement of chlorine was noted by continued presence in isolated organic fractions. Under forcing conditions, complete displacement of chlorine was noted by absence in the small isolated organic fraction (~ 1 ml). When an attempt was made to distill this sample in vacuo, extensive decomposition occurred. No constant boiling fraction could be obtained.

Attempt at preparation of III from II. Compound II (10.0 g, 0.08 mol) was dissolved in a stirred suspension of anhydrous sodium acetate (6.5 g, 0.08 mol) and anhydrous lithium acetate (6.5 g, 0.1 mol) in dimethylformamide (80 ml). The mixture was heated at reflux (bath temp 110-140°) for 65 h and extracted with diethyl ether (3 x 50 ml). The combined ether extracts were dried overnight over anhydrous Na_2SO_4, filtered and the ether removed in vacuo at room temp. Distillation in vacuo (about 25mm Hg) produced 3 fractions (3.7 g, 67-80°; 1.0 g, 80-94°; 0.2 g, 94-97°). Each fraction gave a positive Beilstein test (indicative of starting material) and showed a $-\overset{O}{\overset{\|}{C}}-$ band in the ir spectrum (possibility of the desired ester). There was no further work up because of incomplete conversion of starting material and low yield of possible product, 2(acetoxymethyl)-1,3-dioxolane.

2(acetoxymethyl)-1,3-dioxolane (III): Compound II (24.6 g, 0.2 mol), sodium acetate (26 g, 0.317 mol) and lithium iodide (8 g, 0.060 mol) in dimethylformamide (60 ml) were stirred and heated at reflux for 42 h (bath temp 120-140°). The mixture was partitioned between diethyl ether and water. Each of three successive ether extracts (125 ml) was washed with two portions (50 ml) of water or previously used aqueous wash. Each aqueous portion was used twice, once each on successive extracts. The water phase was then added to the aqueous dimethylformamide mother liquor for further ether extraction. The combined ether extracts were shaken with saturated aqueous $NaHSO_3$ (10 ml) and were neutralized by shaking with saturated K_2CO_3 (200 ml) for 0.5 h. The organic phase was dried over anhydrous Na_2SO_4 overnight, filtered and the bulk of the solvent removed *in vacuo* (bath temp to 85°). The remaining liquid (about 35 ml) was distilled *in vacuo* and gave III (15.8 g, 54%); bp 96-98° (20mm Hg), n_D^{20} 1.4316; d^{22} 1.1894; ir (neat) 1050, 1150 (C-O-C), 1235 (ester C-O) and 1740 (ester C=O), (absent C-Cl); nmr (neat) δ 5.15 (t, 1, O-C$\underline{H}$-O), 4.1 (d, 2, O=C-O-C$\underline{H_2}$), 3.97 (d, 4, O-C$\underline{H_2}$-C$\underline{H_2}$-O), and 2.04 ppm (s, 3, C$\underline{H_3}$-C=O).

Anal. Calcd. for $C_6H_{10}O_4$ (146.14): C, 49.31; H, 6.90.
Found: C, 49.30; H, 6.75.

Attempt to deacetylate III with TEA/water. Compound III (5.33 g, 0.036 mol) was dissolved in a solution of water (5.0 ml) and triethylamine (TEA, 5.7 ml, 0.041 mol) and the stirred mixture remained at room temp for 18 h. The mixture was distilled *in vacuo* (about 100 mm Hg; bath temp 80-130°) with additions of TEA in water-methanol (20% in a 1:1 mixture; 5 x 5 ml) as needed to insure alkalinity and to maintain one phase. Distillation was then continued until there was no further evidence of water removal and the residual liquid was neutral to brom cresol purple. The clear, light brown liquid was dissolved in diethyl ether (15 ml) and dried overnight over anhydrous K_2CO_3. Filtration produced a clear, faintly yellow liquid from which the ether was removed by distillation. The remaining material was distilled *in vacuo*. An ir spectrum of the distillate (1.36 g, 89.5-94.5°, 20mm Hg) showed the ester carbonyl band of the starting material (III) and the -OH band of the projected deacetylated product, 2(hydroxymethyl)-1,3-dioxolane (IV). Low yield (total 35.8%), incomplete deacetylation and the apparent proximity of the boiling point of III made further efforts as separation impractical.

2(Hydroxymethyl)-1,3-dioxolane (IV): Metallic sodium (100 mg) was dissolved in absolute methanol (50.0 ml) and III (12.0 g, 0.082 mol) was added. The solution was refluxed, with exclusion of moisture, for 17 h and distilled.

Distillate (30 ml) in the range 57.5-65° (bath temp 100-110°) was collected. Additional absolute methanol (50.0 ml) was added to the undistilled solution (~ 20 ml) and distilled off until about 10 ml of undistilled material remained. Dry CO_2 was bubbled through the residual liquid for 45 min, effecting a pH change from 11 to 9. Distillation under CO_2 *in vacuo* gave IV (6.65 g; 78%): bp 86.5-88.5° (20mm Hg; literature bp 98° at 29mm Hg[137]), n_D^{20} 1.4453; d^{22} 1.2197; ir (neat) 1055, 1145 (C-O-C), 2895, 2965 (CH_2) and 3440 cm^{-1} (OH), absent (C=O); nmr (neat) δ 5.02 (t, 1, O-C$\underline{H}$-O), 4.19 (s, 1, O$\underline{H}$), 4.0 (d, 4, O-C$\underline{H_2}$-C$\underline{H_2}$-O), and 3.61 ppm (HO-C$\underline{H_2}$).

Anal. Calcd. for $C_4H_8O_3$ (104.10): C, 46.15; H, 7.75.
Found: C, 46.15; H, 7.62.

2-(2-Nitrobenzenesulfenyloxy)methyl-1,3-dioxolane (V): Compound IV (1.0 ml, 0.0105 mol) and 2-nitrobenzenesulfenyl chloride (1.90 g, 0.0100 mol) were dissolved in dry benzene (10 ml). A solution of triethylamine (1.4 ml, 0.01 mol) in benzene (5 ml) was added dropwise, with stirring, during 15 min. The mixture was stirred at room temp for 49 h and filtered by suction through glass fiber filter paper. Hexane (10 ml) was added to the filtrate. The solution was refrigerated overnight and the benzene-hexane mother liquor was decanted from the orange, viscous liquid and yellow crystals which had formed. This material was dissolved in cold benzene (min vol) and washed with water (3 times with 1/2 vol). The washes were discarded. Hexane (125 ml) was added to the benzene phase and the solvents were slowly removed in vacuo (20mm Hg, bath temp 50°) on a rotary evaporator until 50 ml remained. Additional hexane (25 ml) was added and yellow crystals and viscous, orange liquid again formed. Evaporation on a rotary evaporator continued until only opaque, viscous, orange liquid remained. This material was extracted three times with a mixture of hot heptane (95 ml) and methylcyclohexane (20 ml). After recrystallization in a dry ice-ethanol bath and collection of the crystals, the supernatant was twice reused for extraction. A fourth extraction of the orange, semi-solid material was carried out with fresh, hot methylcyclohexane (75 ml) and a fourth crop of crystals were obtained. The combined heptane and methylcyclohexane mother liquors, after two successive reductions in volume, in vacuo on a rotary evaporator, followed by refrigeration overnight and filtration, produced a fifth and sixth crop. The combined crystals were twice recrystallized from a minimal amount of CH_2Cl_2 by addition of heptane (4 vol), reduction of volume (1/2) on a rotary evaporator and overnight refrigeration. The product was now uniform by tlc and was air dried on a buchner funnel. This gave V (0.35 g; 13.6%); mp 48-50°; ir (KBr) 1150 (C-O-C), 1330 (NO_2), 1585 (aromatic C=C), 2875, 2945 (CH_2), and 3080 cm^{-1} (aromatic CH), absent (OH).

Anal. Calcd. for $C_{10}H_{11}NO_5S$ (257.27): C, 46.69; H, 4.31; N, 5.44; S, 12.46.

Found: C, 47.2; H, 4.39; N, 5.60; S, 12.68.

2-(2,4-Dinitrobenzenesulfenyloxy)methyl-1,3-dioxolane (VI): Compound IV (1 ml, 0.0105 mol) and 2,4-dinitrobenzenesulfenylchloride (2.35 g, 0.01 mol) were dissolved in dry benzene (10 ml). A solution of triethylamine (1.4 ml, 0.01 mol) in benzene (5.0 ml) was added dropwise, with stirring, during 30 min. The mixture was stirred at room temp for 27 h and filtered by suction through glass fiber filter paper. Heptane (2 vol) was added, the mixture was refrigerated for 48 h and the precipitate was filtered off by suction. The crude sulfenyl ester (2.2 g) was extracted with hot absolute ethanol (3 x 15 ml). Water (60 ml) was added to the stirred extract. Crystallization began and continued during 24 h of refrigeration. The crystals were dried *in vacuo* over $CaCl_2$ and dissolved in CH_2Cl_2 (50 ml). The solution was stirred with silica gel (60-200 mesh, 10.0 g). The mixture was filtered by suction and the silica gel was washed with additional CH_2Cl_2 (5 x 15 ml) on the funnel. The washings and the filtrate were diluted with hexane (150 ml). This solution was evaporated *in vacuo* on a rotary evaporatory. A residual volume of 100 ml was refrigerated overnight and gave crystals which were recrystallized from a minimal amount of CH_2Cl_2

by addition of hexane to give, after drying in vacuo over $CaCl_2$, VI (0.923 g, 30.5%): mp 101.5-103°; ir (KBr) 1140 (C-O-C), 1335 (NO_2), 1590 (aromatic C=C), 2875 (CH_2) and 3085 cm^{-1} (aromatic CH), absent (OH).

Anal. Calcd. for $C_{10}H_{10}N_2O_7S$ (302.26): C, 39.74; H, 3.33; N, 9.27; S, 10.61.

Found: C, 39.81; H, 3.41; N, 9.42; S, 10.68.

3-Chloromercuryfuran (VII): This compound was prepared by a modification of the procedure of Gronowitz and Sorlin[80] (itself a modification of the procedure of Gilman and Wright[70]). A solution of furoic acid (528 g, 4.62 mol) in hot water (4.75 l) was slowly added to a stirred solution of mercuric acetate (750 g, 2.31 mol) in hot water (12 l). The precipitate was filtered off, and dried to give a mercuric salt (740 g), which was pyrolyzed in a three necked 3 l flask, fitted with a mechanical stirrer, thermometer and a condenser arranged for distillation, by heating in an oil bath at 140° for 36 h. After cooling to room temperature acetic acid (95%, 950 ml) was added and stirring continued for 36 h. The mixture was poured into water (8.3 l) and filtered. Saturated sodium chloride solution was added to the filtrate until no more precipitate formed. The precipitate was filtered and air dried. The resulting crude VII (308 g) was divided into six equal portions and extracted (72 h min-

144 h max) with diethyl ether in a Soxhlet apparatus. The times varied depending on continuing evidence of extractable material. After evaporation, solid product (169 g) was obtained, which was recrystallized from ethanol (95%, 4 l) to give VII (101.9 g; 14.5%): mp 182.5-184.5° (literature mp 183-184°, yield 15%);[81] ir (KBr) 1575 (aromatic C=C) and 3130 cm^{-1} (aromatic CH).

3-Iodofuran (VIII): This compound was prepared from 3-chloromercuryfuran (VII, 25.0 g, 0.082 mol) by the procedure of Gronowitz and Sorlin,[80] which gave 12.01 g (75.5%), bp 137-139° (765mm Hg) (literature bp 137-139° at 765mm Hg, yield 75%);[81] ir (neat) 1575 (aromatic C=C) and $3150 cm^{-1}$ (aromatic CH).

Attempted reaction of VIII with IV: A mixture of IV (2ml, 0.022 mol) and NaH (0.265 g, 0.011 mol) was dissolved in tetrahydrofuran (8 ml) and VIII (0.86 ml, 0.009 mol) and CuO (0.848 g, 0.011 mol) were added. After the stirred mixture was heated at reflux for 42 h the pH appeared to be slightly lower than the original value (approximately 14) and a tlc showed two product spots moving faster than IV (in 1 THF:3 hexane). Additional VIII (0.43 ml, 0.0045 mol) was added and the mixture was heated at reflux for 82.5 h. The pH (~10) and the tlc (the two product spots appear darker) indicated continued reaction but the glc (polar column and nonpolar column, 140°) continued to show only IV, VIII and solvent. Again VIII (0.43 ml, 0.0045 mol) was added, the stirred mixture was heated at reflux 17.5 h and the pH (~8) and the tlc and glc (same patterns as before) were again checked. None of the three product spots (a faint third one now in evidence) quenched phosphorescence on tlc prior to charring. Tetrahydrofuran was evaporated off under N_2 and replaced by CH_2Cl_2 (equal vol). After washing with water (3 x equal vol) the organic phase was dried overnight over $CaCl_2$ and filtered by suction. A tlc, upon charring, indicated quantitative removal of unreacted IV and the presence of the two original, faster running products. After the removal of CH_2Cl_2, by evaporation under N_2, the residual material (0.6 g) was subjected to thick layer chromatography in petroleum ether/tetrahydrofuran (3:1) and tlc confirmed the clean separation of these two fractions. An nmr spectrum of each solid material (0.1 g) in $CDCl_3$ showed the absence of furan protons, hence no further efforts at purification and identification were made.

<u>2-(3-furyloxymethyl)-1,3-dioxolane</u> (IX): Compound IV (8.1 ml, 0.12 mol) and VIII (6.2 ml, 0.065 mol) were dissolved in absolute dimethoxyethane (60 ml) and copper oxide catalyst (5.8 g, prepared as described in the general part) and NaH (1.43 g, 0.06 mol) were added to the stirred solution.

The mixture was heated at reflux for 20 h. Additional VIII (0.5 ml, 0.005 mol) was added and heating at reflux was continued for 16 h. The mixture was filtered by suction and most of the solvent was distilled off through a column (bath temp to 130°; distilling vapor temp to 85°). The residual liquid (15 ml) was dissolved in CH_2Cl_2 (85 ml). A solid precipitate was filtered off. The aqueous phase of the filtrate was extracted with CH_2Cl_2 (2 x 2 ml) and the extracts were added to the organic phase, which was in turn washed with water (2 x 30 ml). The organic phase was dried overnight over anhydrous Na_2SO_4, filtered, and concentrated by distillation through a column under N_2 (distilling vapor temp to 43°). The residual liquid (15 ml) was further concentrated by distillation *in vacuo* under N_2 (distilling vapor temp to 50°; 20mm Hg). The remaining undistilled liquid (4 ml), upon distillation *in vacuo* under N_2, gave IX (2.5 g; 25%): bp 92-94° (1mm Hg); mp 25-27°; ir (neat) 1155 (C-O-C), 1600 (aromatic C=C), 2910, 2950 (CH_2) and 3170 cm^{-1} (aromatic CH), absent (OH); nmr (CCl_4) δ 7.28 (s, 1, C=C$\underline{H}$ at position 5 on furan ring), 7.24 (s, 1, C=C$\underline{H}$ at position 2 on furan ring), 6.3 (s, 1, C=C$\underline{H}$ at position 4 on furan ring), 5.2 (t, 1, O-C$\underline{H}$-O), and 3.83-3.93 ppm (evidently d, 4, O-$\underline{CH_2}$-$\underline{CH_2}$-O *and* d, 2, C=C-O-$\underline{CH_2}$).

Anal. Calcd. for $C_8H_{10}O_4$ (170.17): C, 56.47; H, 5.92.

Found: C, 56.47; H, 5.89.

Reaction of IX with acid (Heterogenous catalysis): An intimate solid mixture of crude *p*-tosyl anhydride (200 mg, 0.6 mmol based on the anhydride) and silica gel (2 g; 60-200 mesh) was dried over P_2O_5 *in vacuo* at 101.5° for 24 h. The dried mixture was transferred to a micro sublimator and impregnated with IX (100 mg, 0.6 mmol) from a small tipped medicine dropper. The apparatus was evacuated (1 mm Hg). The coolant consisted of ethanol rapidly recirculating through an ethanol, dry ice bath (lowest temp attained -20°). The mixture was warmed (bath temp 60°) for 30 min. The solid mixture turned black and a drop of liquid formed on the cold finger. Thin layer chromatography of the liquid in two solvent systems (1 THF:3 hexane; absolute diisopropyl ether) showed only one spot with the same R_f value as IV. The residual, darkened solid was extracted with CH_2Cl_2. The extract, on tlc, showed many faint spots.

Reaction of IX with acid (Liquid two phase system): Compound IX (100 mg, 0.6 mmol) in CCl_4 (1 ml) was stirred vigorously with an aqueous solution of citric acid (1 ml, 5%) at room temp for 19 h. Thin layer chromatography of the organic phase in three solvent systems (diisopropyl ether; CH_2Cl_2; 1 diethyl ether:9 pentane) revealed at least five components in addition to unreacted IX. After efficient stirring of the two phase system for an additional 23 h, tlc revealed a pattern similar to the previous one, with the following exception: The second fastest moving spot (in the three tlc systems) was much more intense. This spot quenched phosphorescence prior to charring. Rapid stirring at room temp was continued for 54 h (total 96 h). Thin layer chromatography of the organic phase produced a pattern in which all spots were markedly decreased in intensity. This was especially true of those identified with IX and with the second fastest moving spot, the one previously observed to increase in intensity with reaction time. Both were only faintly discernable on very heavy spotting (4 x heavier than previously). Thin layer chromatography of the aqueous phase revealed the presence of IV.

Unknown compound X obtained by reaction of IV, VIII, t-butoxide and crown ether: Dibenzo-18-crown-6-ether (10.6 g, 0.03 mol) and potassium-t-butoxide (3.32 g, 0.03 mol) were added, with stirring, to dry benzene (135 ml) under N_2. After the mixture was warmed (bath temp 75°) and filtered hot by suction, IV (3.25 mol, 0.034 mol) was added to the filtrate. The stirred mixture was warmed (bath temp 75°) under N_2 and, after an unsuccessful attempt to remove t-butanol by azeotropic distillation with benzene, the original volume was restored with fresh benzene. Compound VIII (2.5 ml, 0.026 mol) was added and the stirred mixture was heated (bath temp gradually increased from 75° to 95°)

under N_2 for 50 h. Addition of potassium-t-butoxide (1.78 g, 0.016 mol) and benzene (30 ml), heating at reflux (bath temp 95°) under N_2 for 34 h, removal of t-butanol by azeotroping with benzene and restoration of original volume with fresh benzene produced a mixture showing IV and VIII substantially unreacted, per tlc and glc. The mixture was heated at reflux under N_2 for an additional 50 h and a basic precipitate (4.7 g dry weight) filtered off. The filtrate was washed with ice water (3 vol + 2 x 1 vol) and with aqueous KCl (3 x 1 vol). Crown ether could not be reclaimed from combined aqueous washes. The organic phase was dried over Na_2SO_4 and solvent (220 ml) was removed by distillation through a column (vapor temp 80°). Refrigeration of the residual liquid produced crystals which when filtered off cold and dried proved to be dibenzo-18-crown-6-ether (0.50 g; mp 162-163°). Hexane additions to the filtrate (2 x 5 ml) each followed by overnight refrigeration, produced, respectively, a solid and an oil from which the mother liquor was decanted. Distillation of the mother liquor, the last 1 ml through a column at reduced pressure (bp 70-92°; 1mm Hg), produced a heterogeneous liquid with one component chromatographically identical to IX (two tlc systems: THF/hexane (1:3) and dry benzene). The solid and the viscous oil (total 3.65 g) were dissolved in benzene (150 ml) and fractionated by column chromatography ("Baker Analyzed" silica gel, 60-200 mesh; 42 mm x 60 cm). One hundred millimeter fractions were collected. The column solvent was gradually changed from benzene to diisopropyl ether. Fractions 19 and 20, collected as diisopropyl ether/benzene (1:9) cleared the column, were crystallized by setting under hexane for 1 week. The air dried, chromatographically homogeneous substance, X (0.69 g) liquified in the presence of $CaCl_2$ and P_2O_5 but recrystallized in air. The procedure was repeated three times with a decrease in weight upon dessication and restoration to the original weight upon crystallization. Compound X (mp 67-70°); ir (KBr) 3000-3400 (H-bonding) and 3490, 3570 cm^{-1} (OH). Anal. found: C, 66.56; H, 7.00, may be an isomer of dibenzo-18-crown-6-ether.

Anal. Calcd. for $C_{20}H_{24}O_6$: C, 66.65; H, 6.71.

SUMMARY

Synthetic and naturally occuring substituted furans and tetrahydrofurans, especially fused tetrahydrofurans such as the 1,4:3,6-dianhydrohexitols, exhibit a variety of physiological activities and have industrial applications. However, fully unsaturated furo[3,2-b]furans are not known. An attempt to synthesize the parent fused ring compound was made.

Chloroacetaldehyde dimethyl acetal (I), by trans-acetalation with ethylene glycol, was used to prepare 2-(chloromethyl)1,3-dioxolane (II) which gave 2-(acetoxymethyl)1,3-dioxolane (III), with NaOAc and Li I. De-O-acetylation of III with methanolic methoxide resulted in 2-(hydroxymethyl)1,3-dioxolane (IV). Compounds II, III and IV were characterized by physical constants and IV was further characterized by its crystalline 2-nitrobenzenesulfenyl and 2,4-dinitrobenzenesulfenyl derivatives.

2-Chloromercuryfuran (VII) and 3-iodofuran (VIII) were prepared by a modification of the method of Gronowitz and Sorlin, starting from furoic acid.

In an attempt to form 2-(3-furyloxymethyl)1,3-dioxolane (IX) in benzene from IV and VIII, in the presence of dibenzo-18-crown-6-ether, an unknown compound (X), thought to be

a rearrangement product of the crown ether, was formed.

Compound IX, unstable in air at room temperature, was formed from IV and VIII in dimethoxyethane with NaH as base and a specially prepared Cu°/Cu_2O/CuO catalyst. In two attempts to form the furo[3,2-b]furan from IX in the presence of acid, the ether linkage was cleaved preferentially to the intended cleavage of the acetal function. Mechanisms for various steps in the synthetic sequence are discussed.

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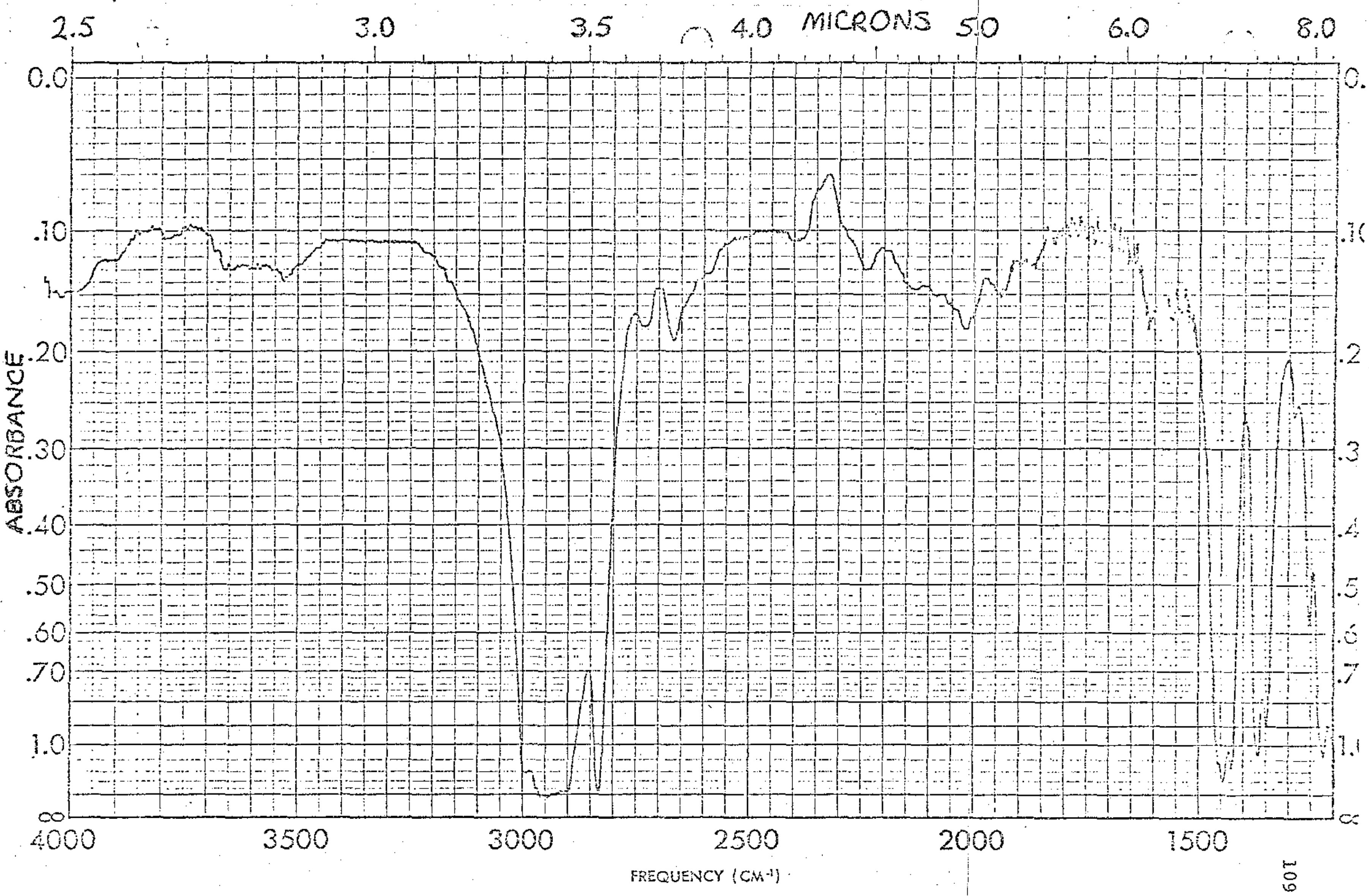
APPENDICES.



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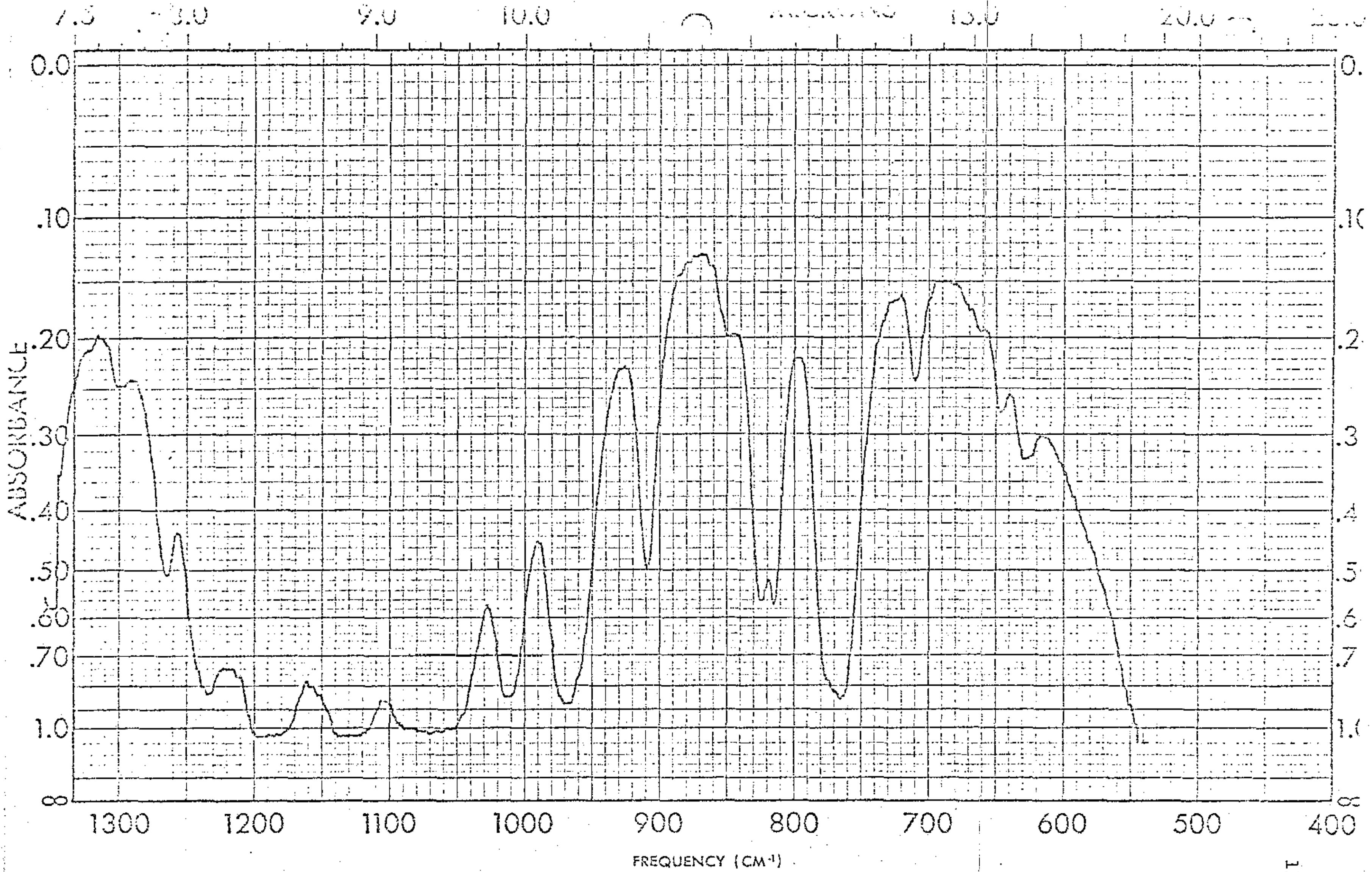

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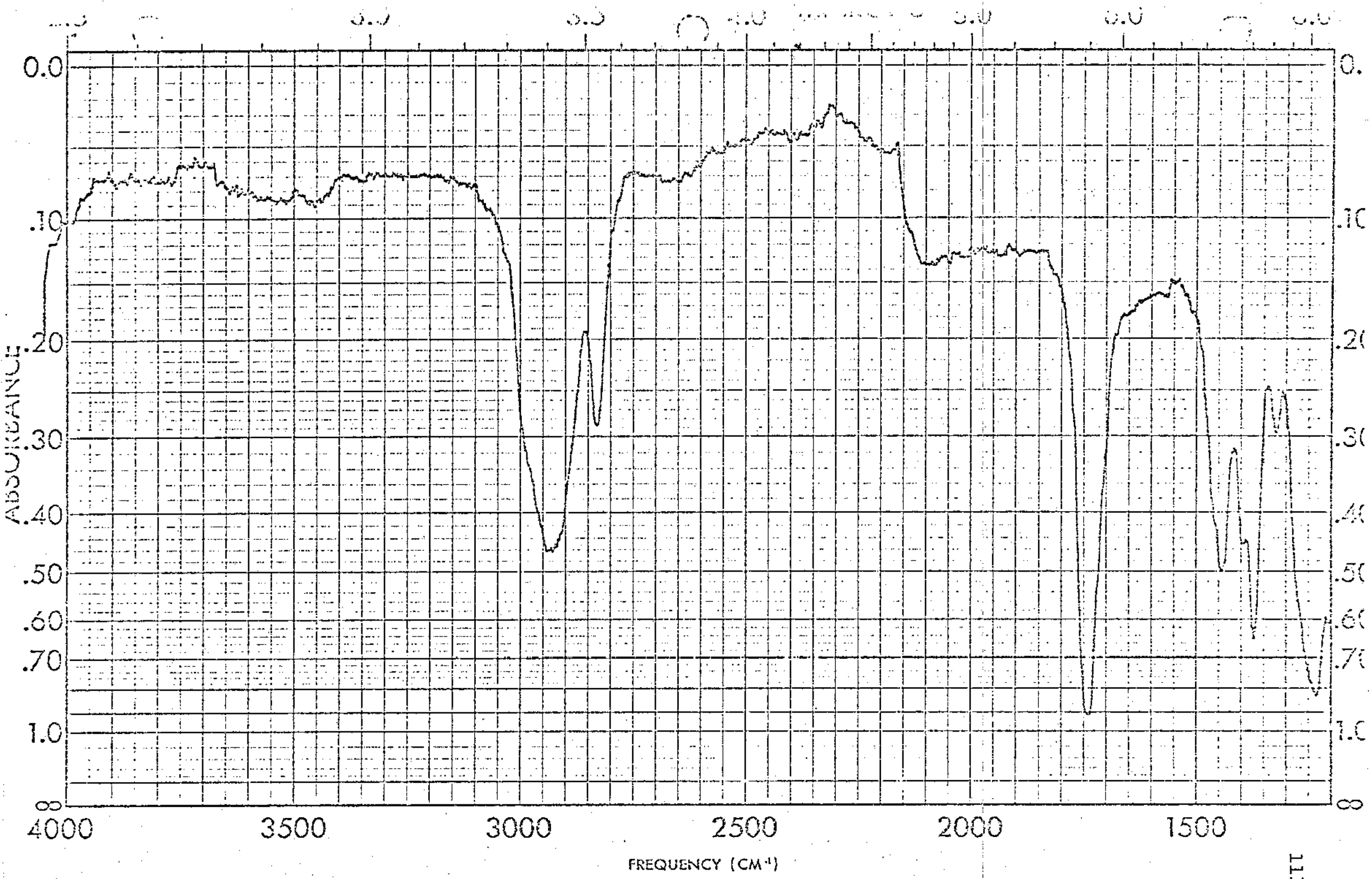

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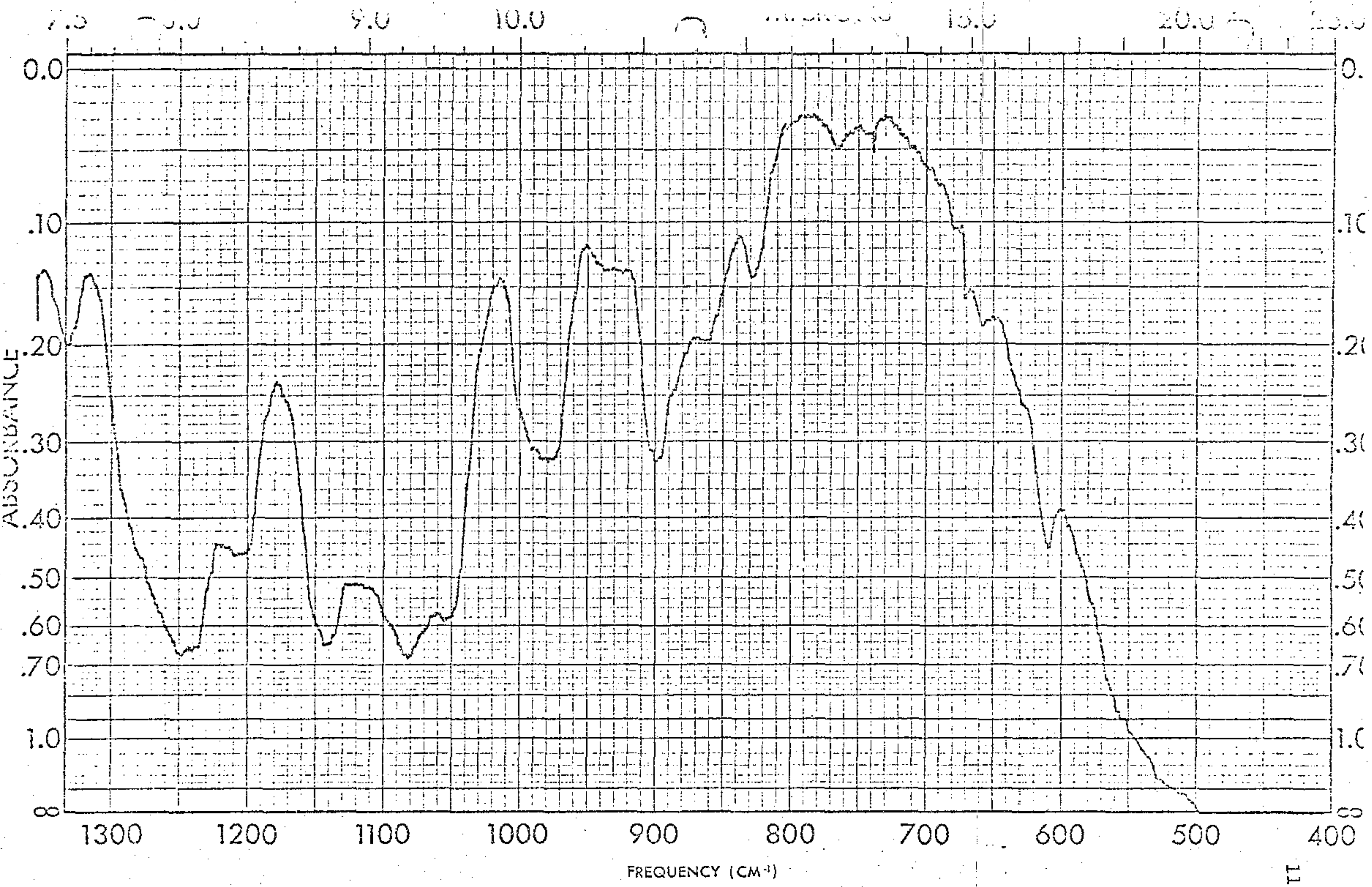

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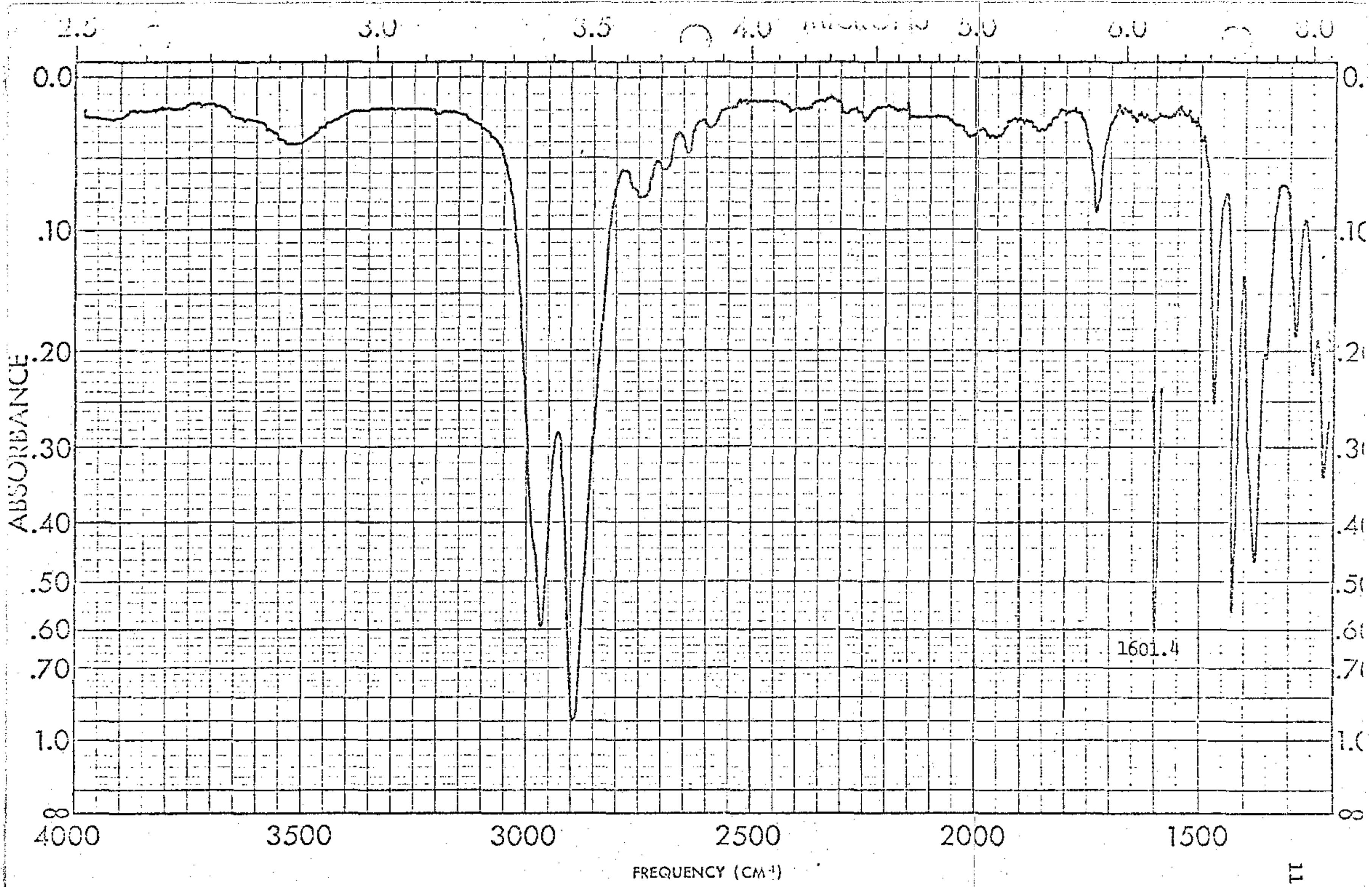

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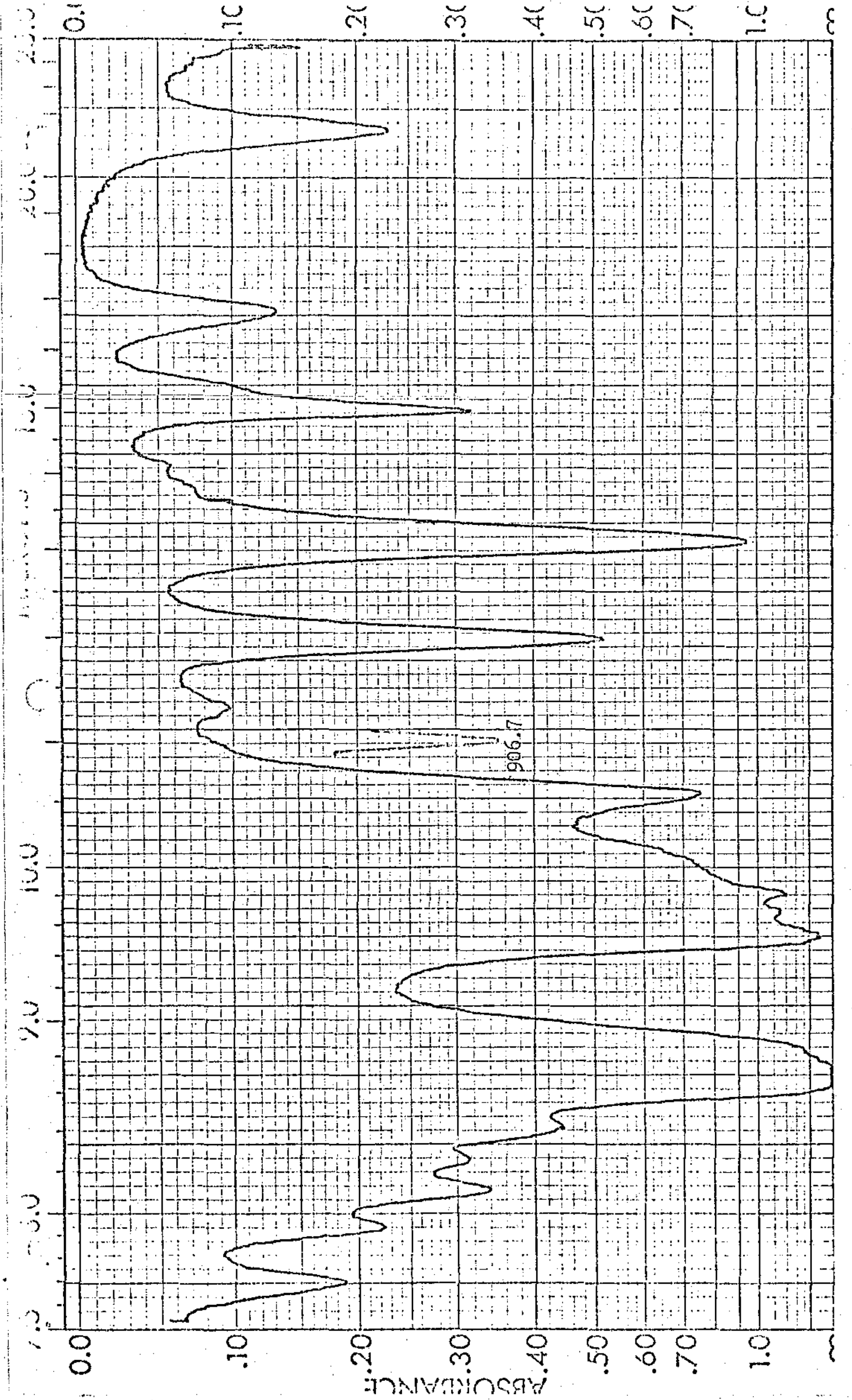

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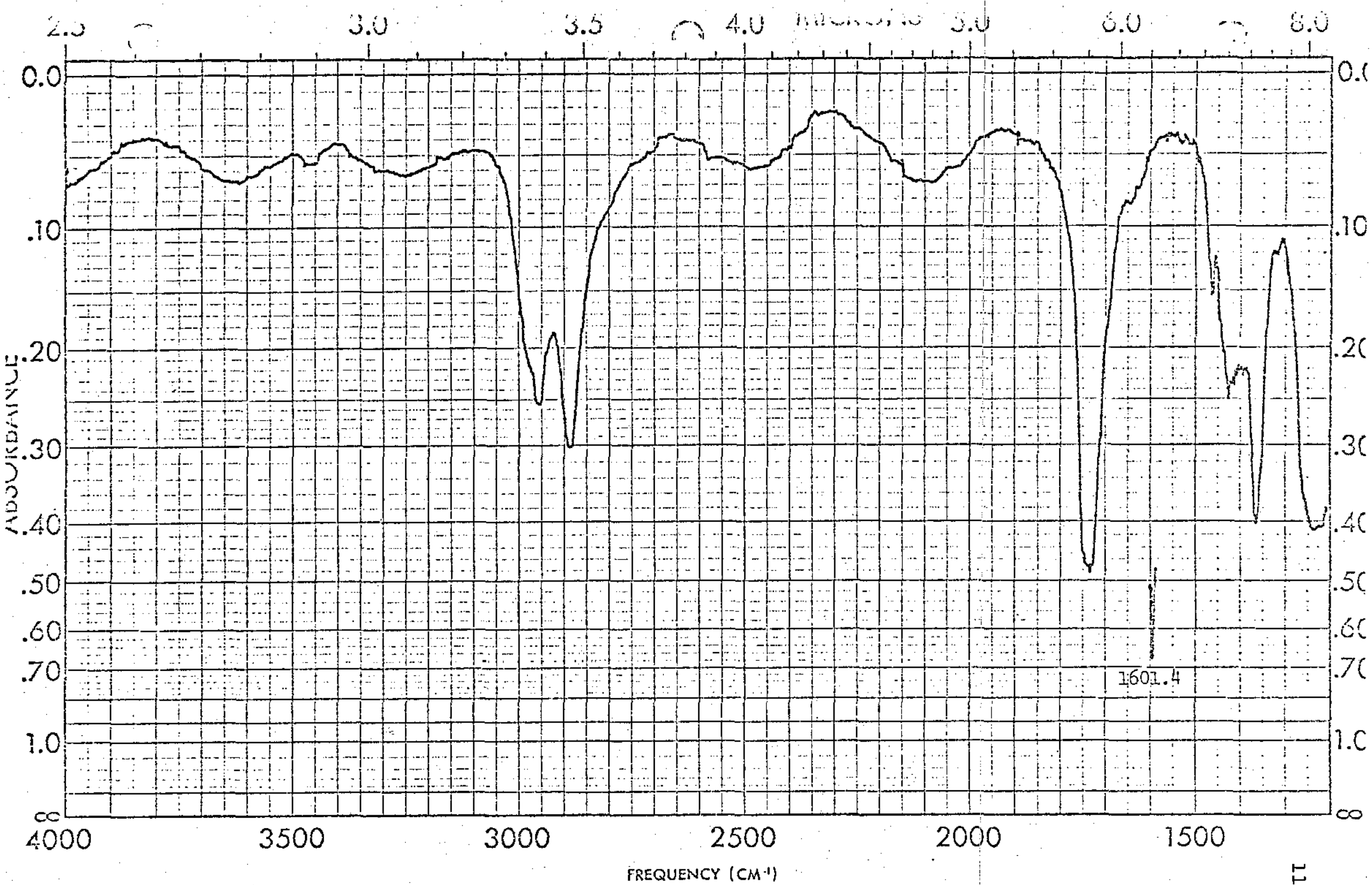

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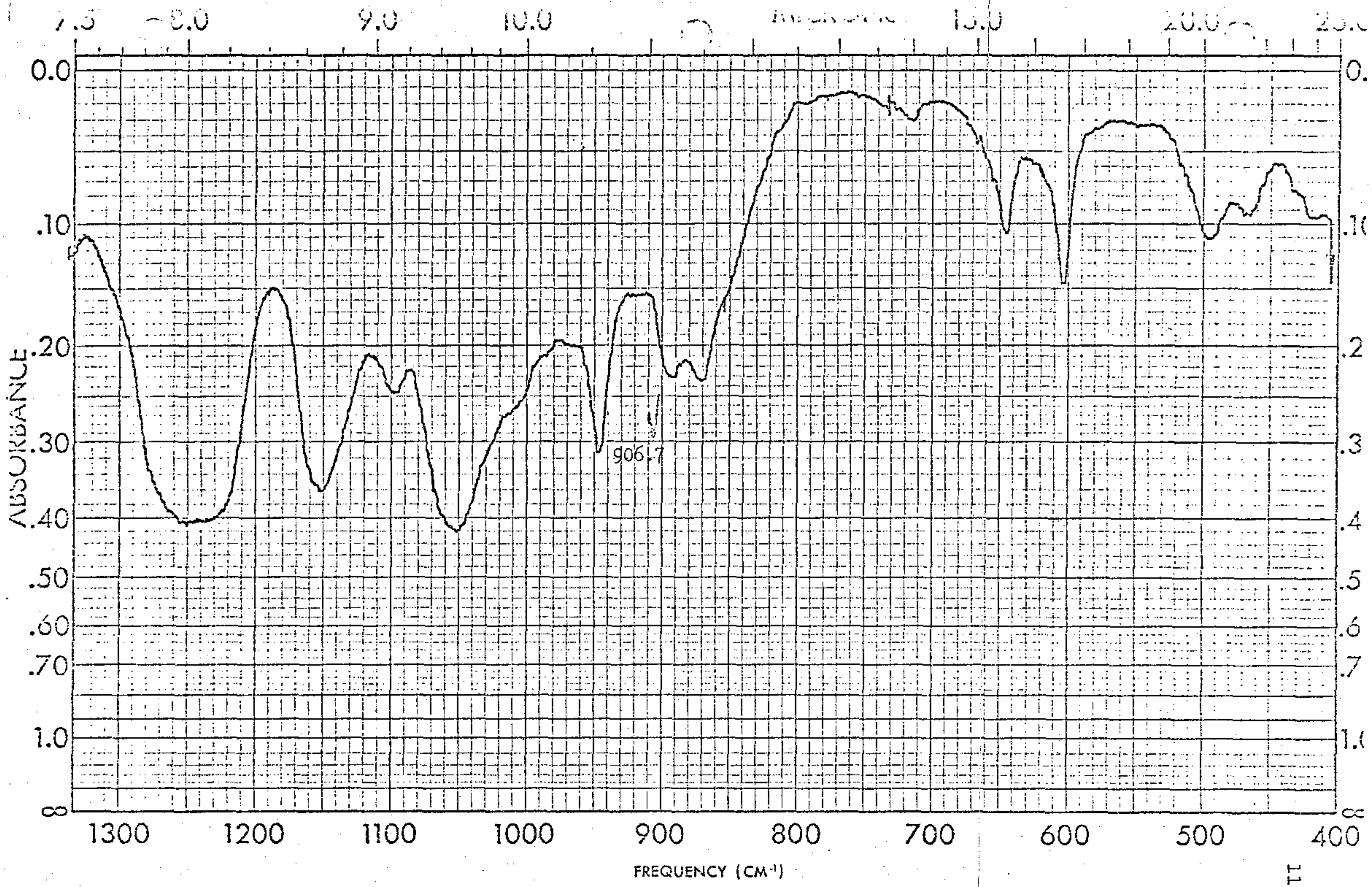

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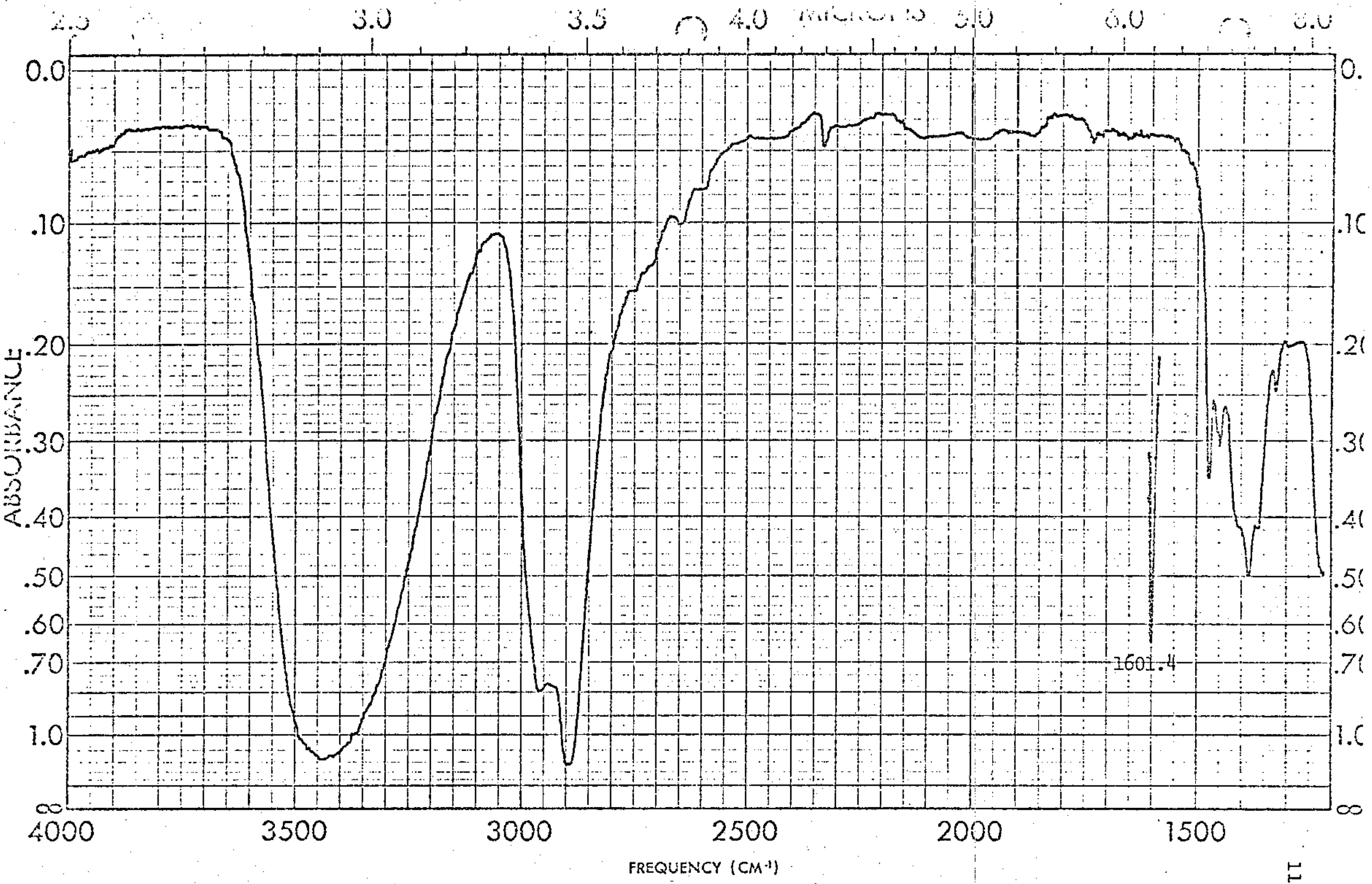

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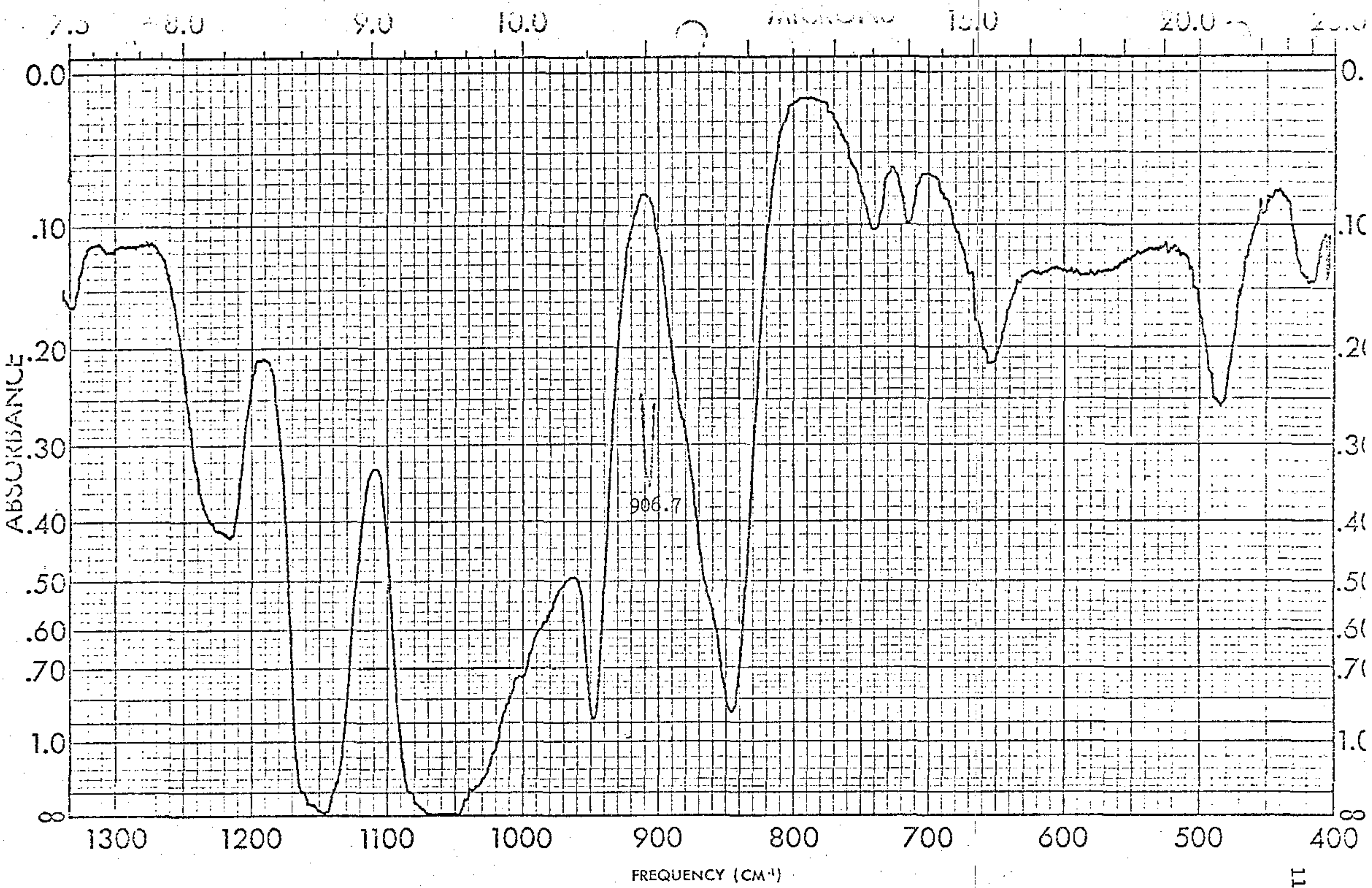

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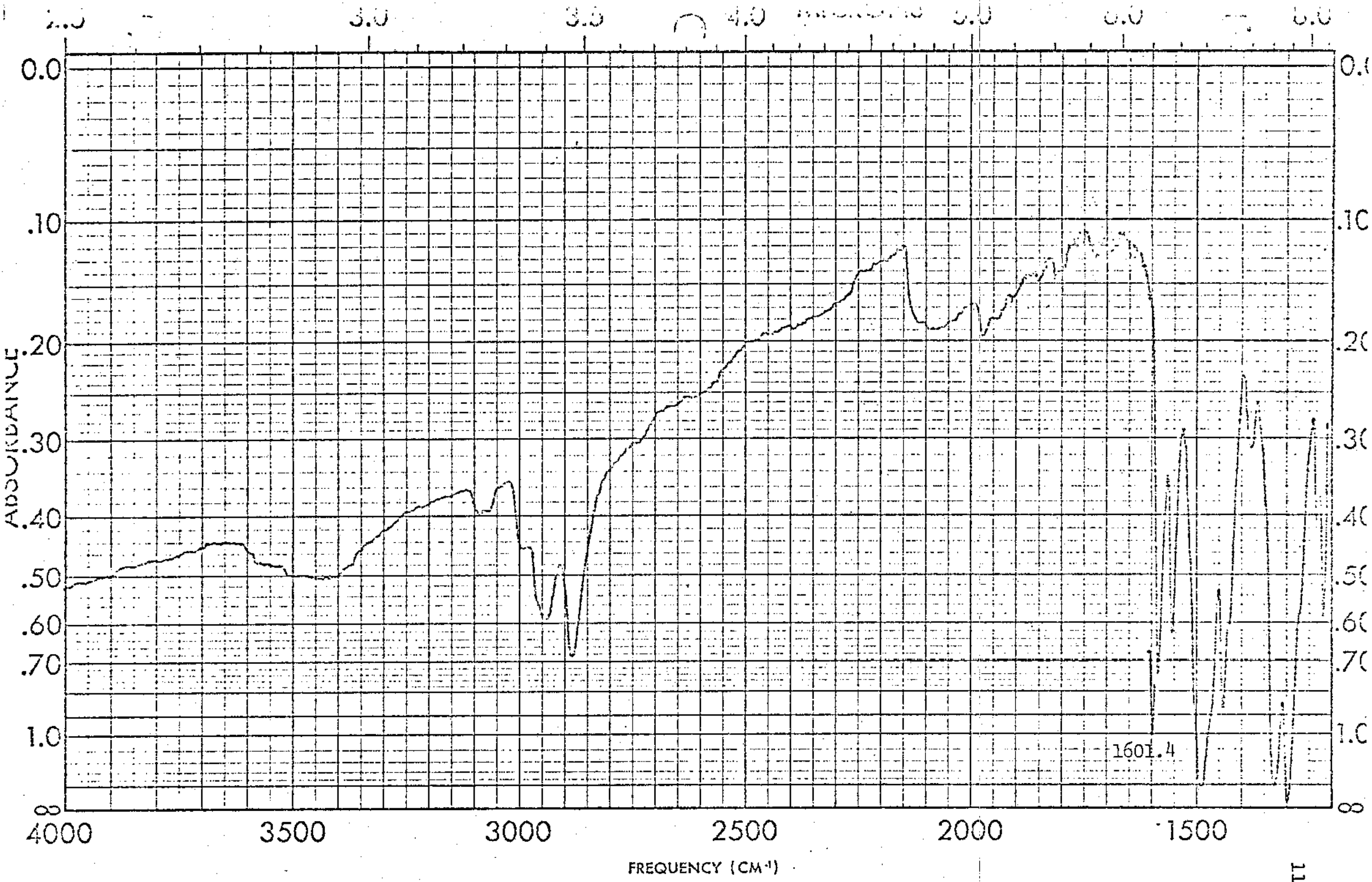

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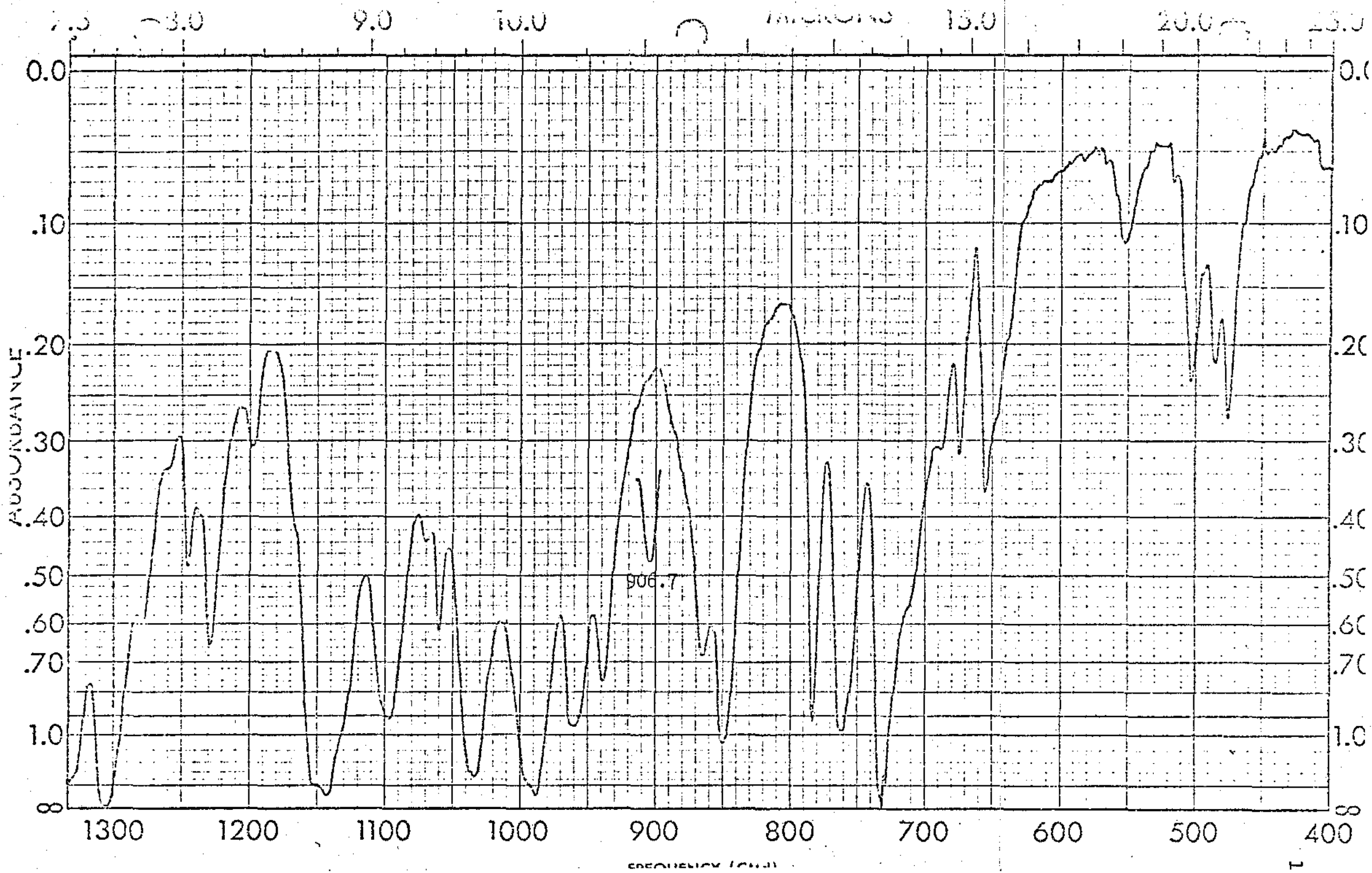

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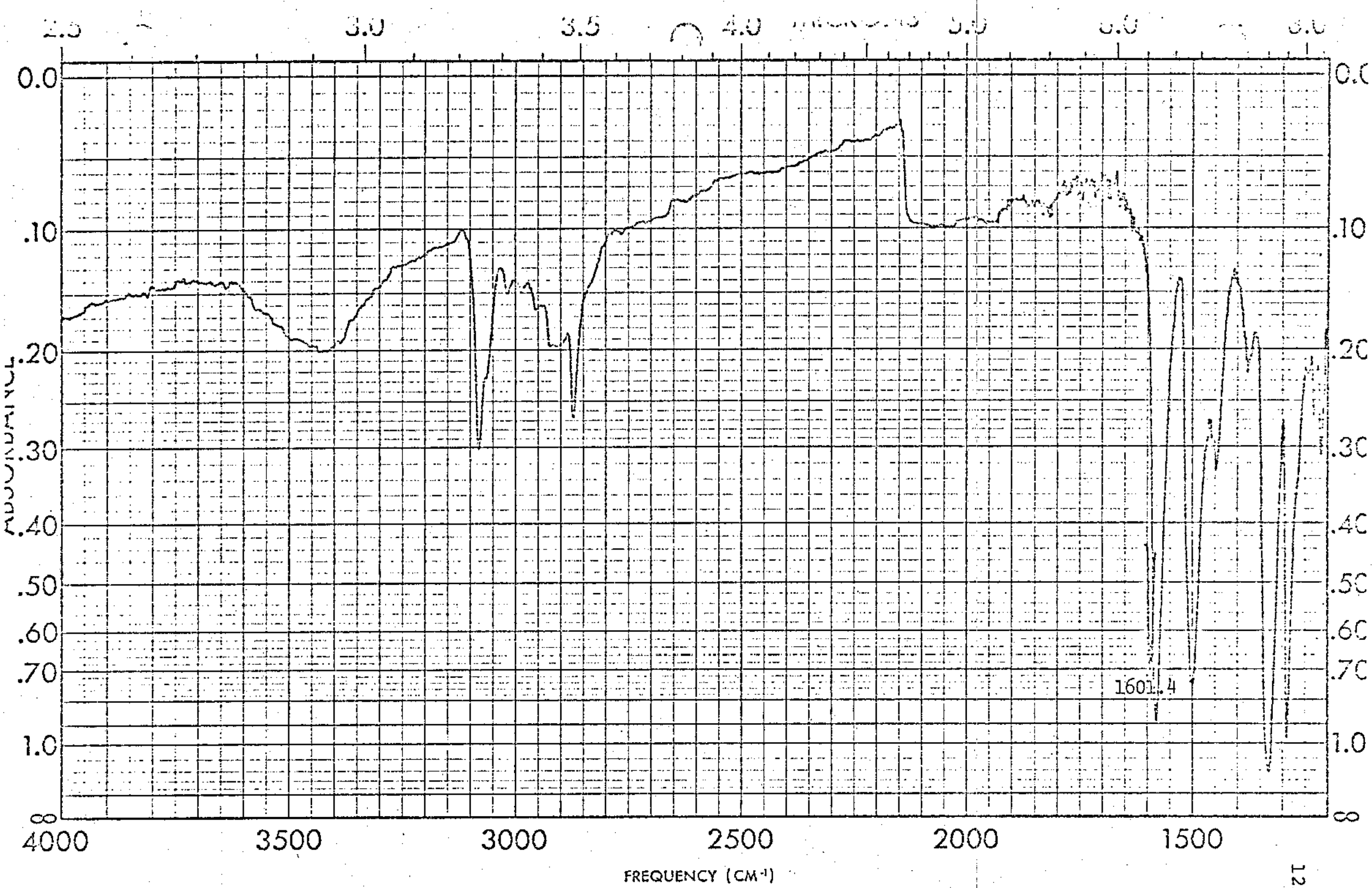

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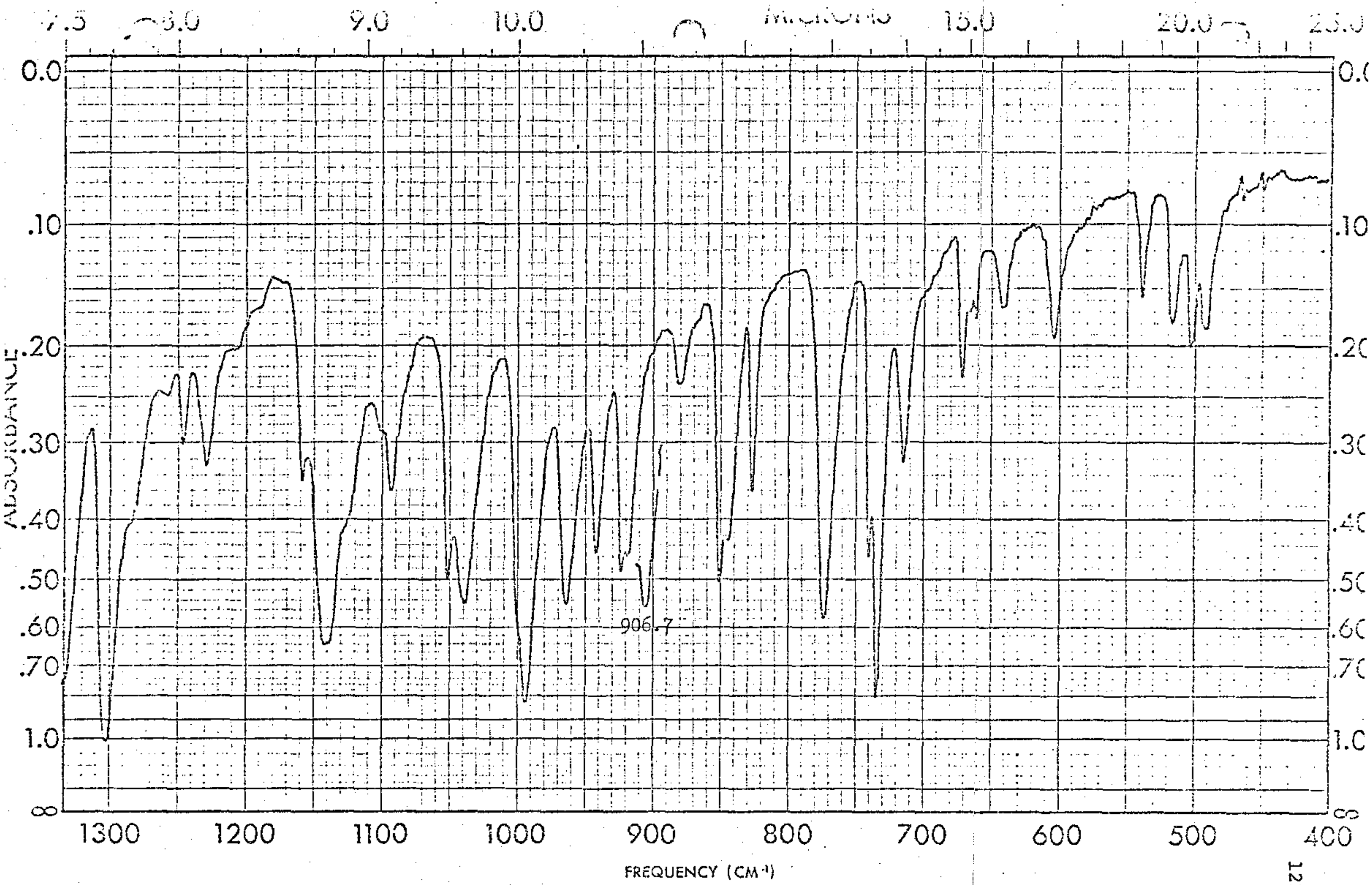

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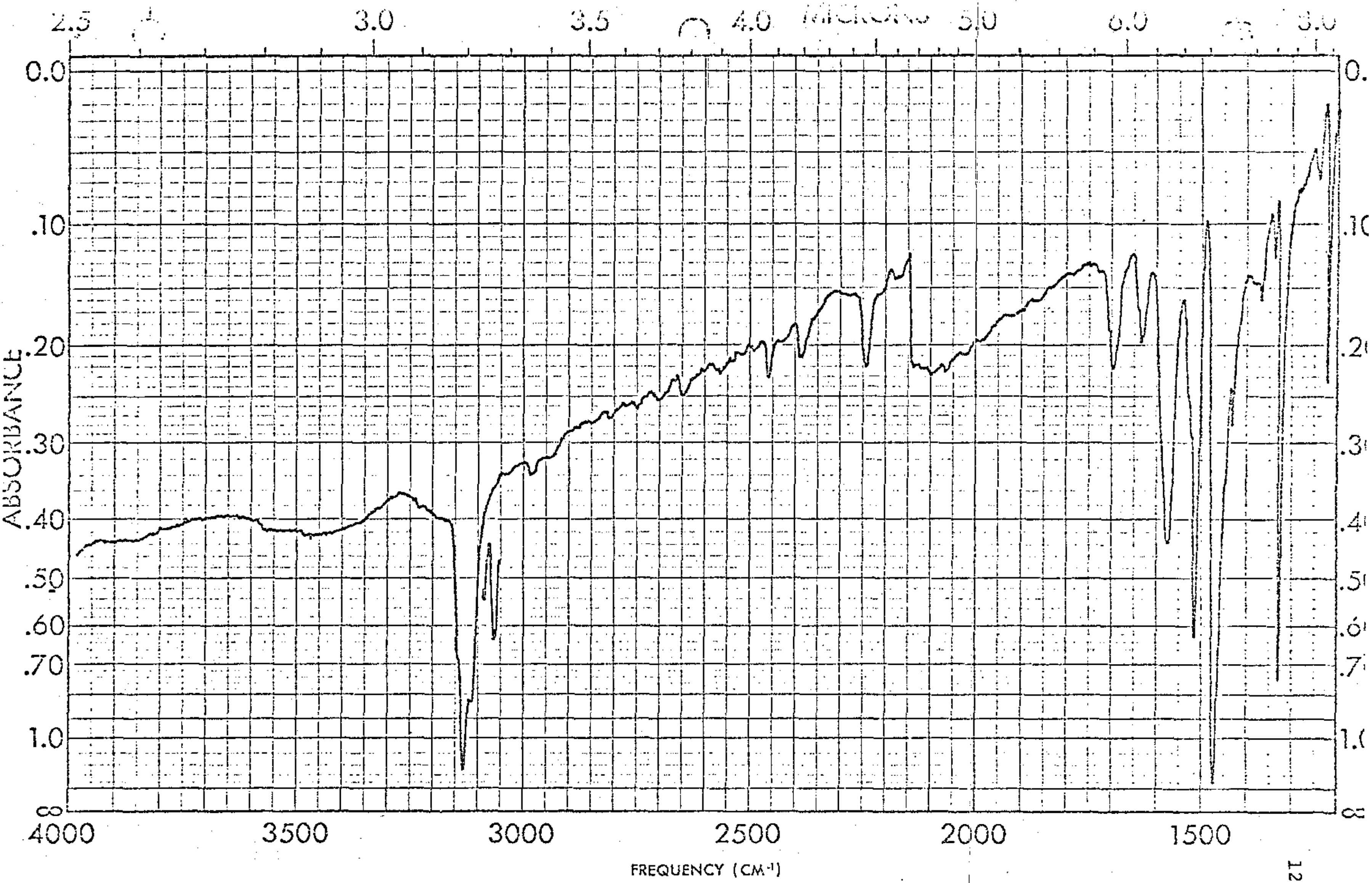

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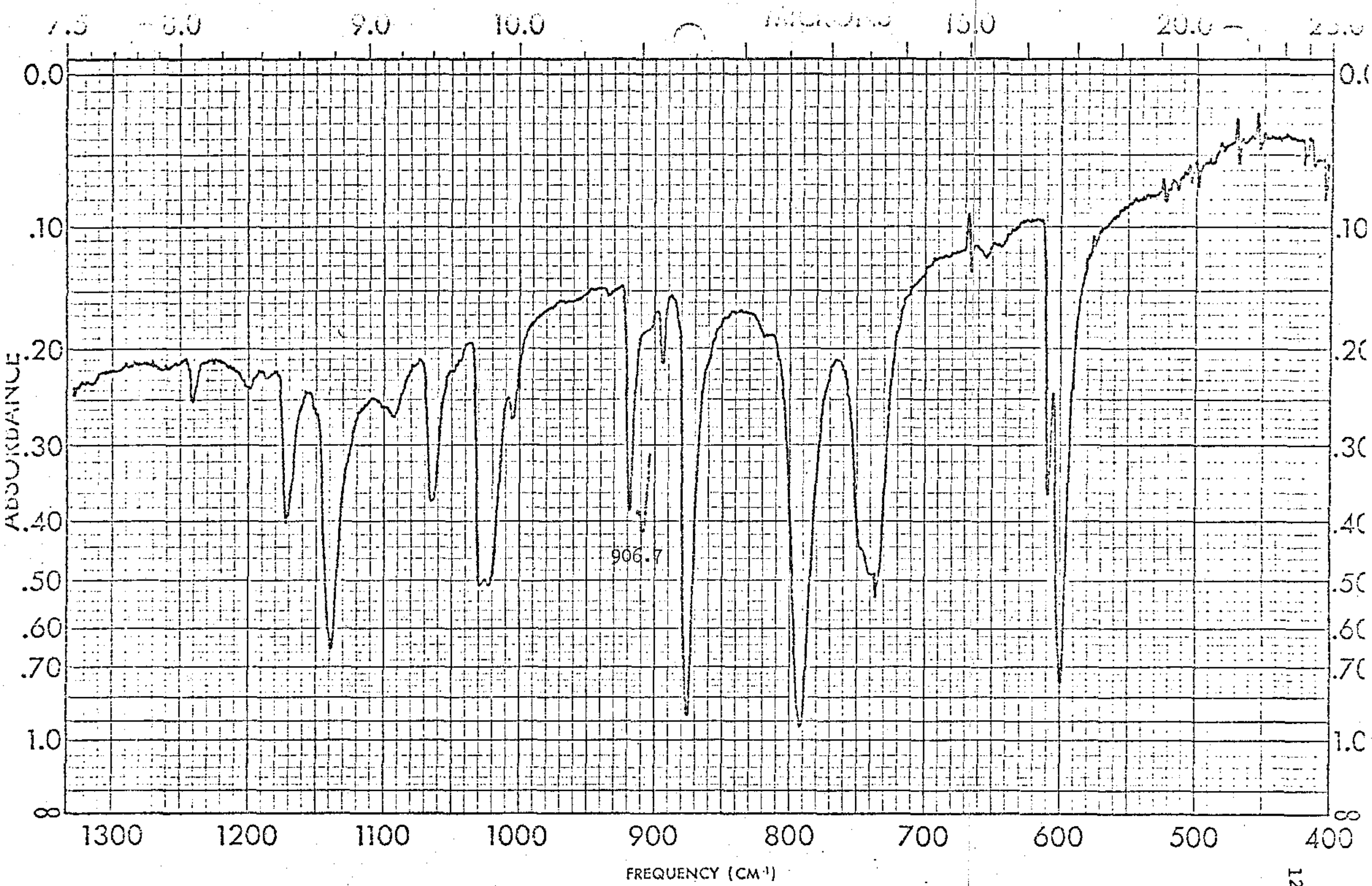

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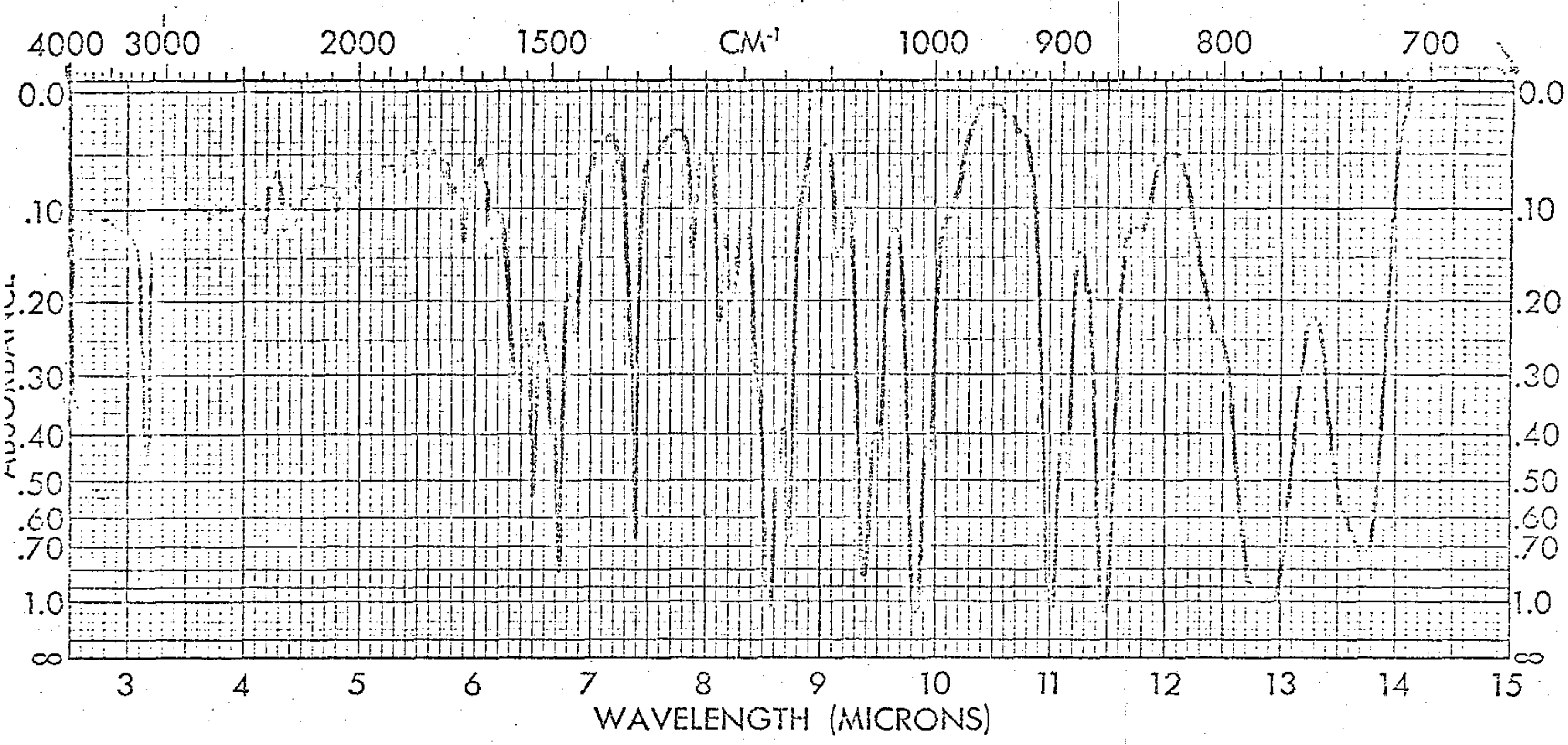

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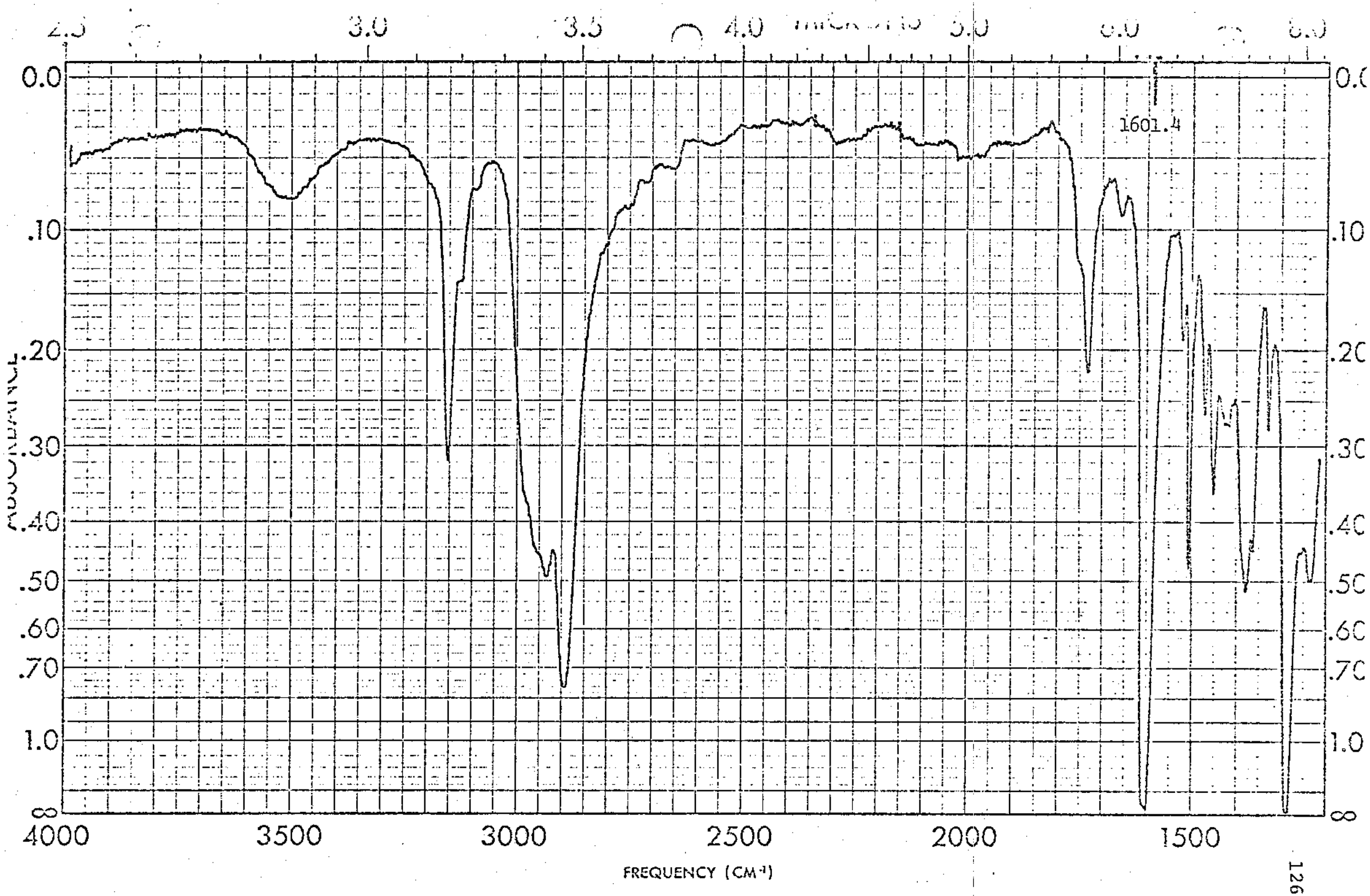
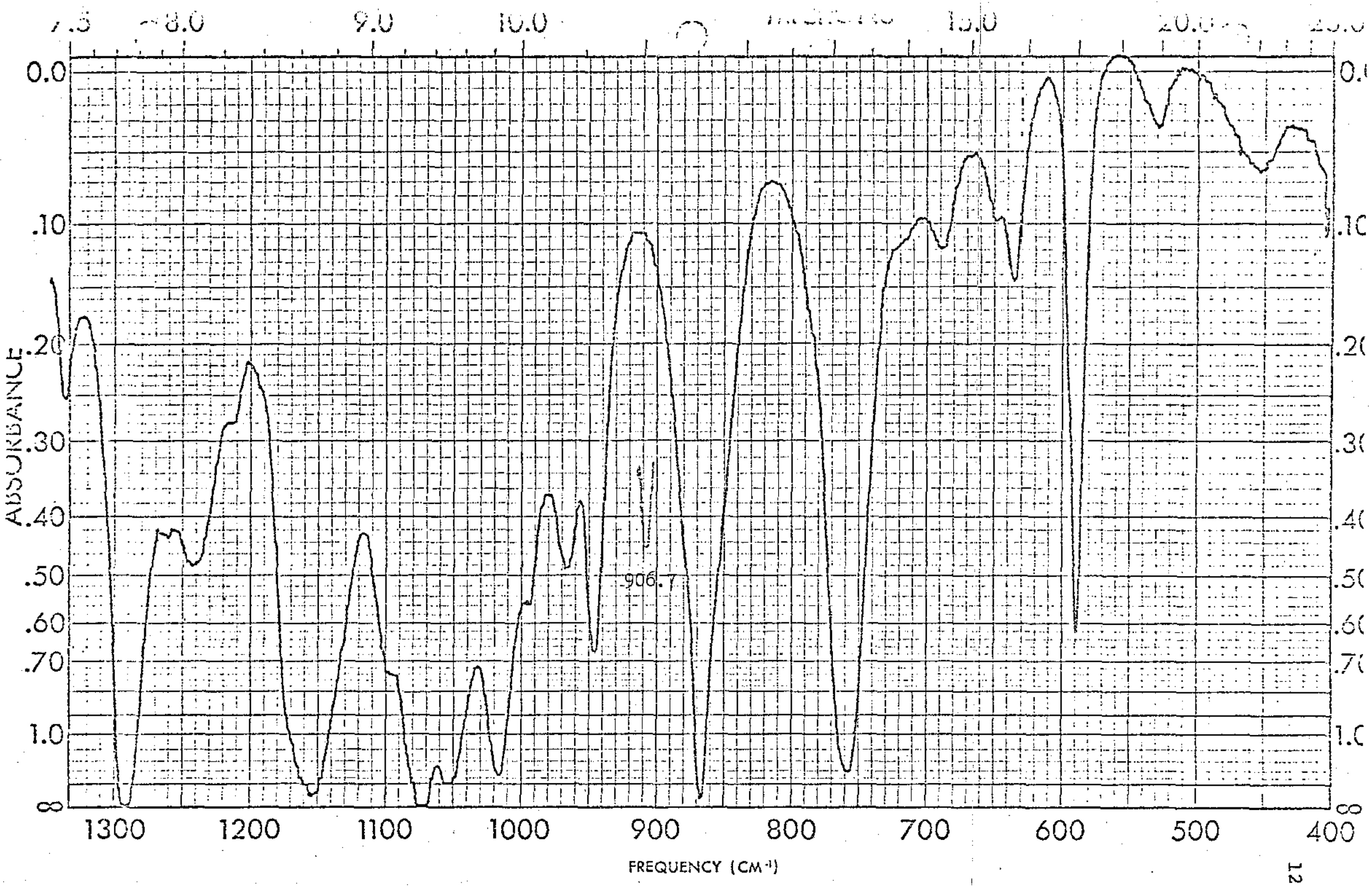
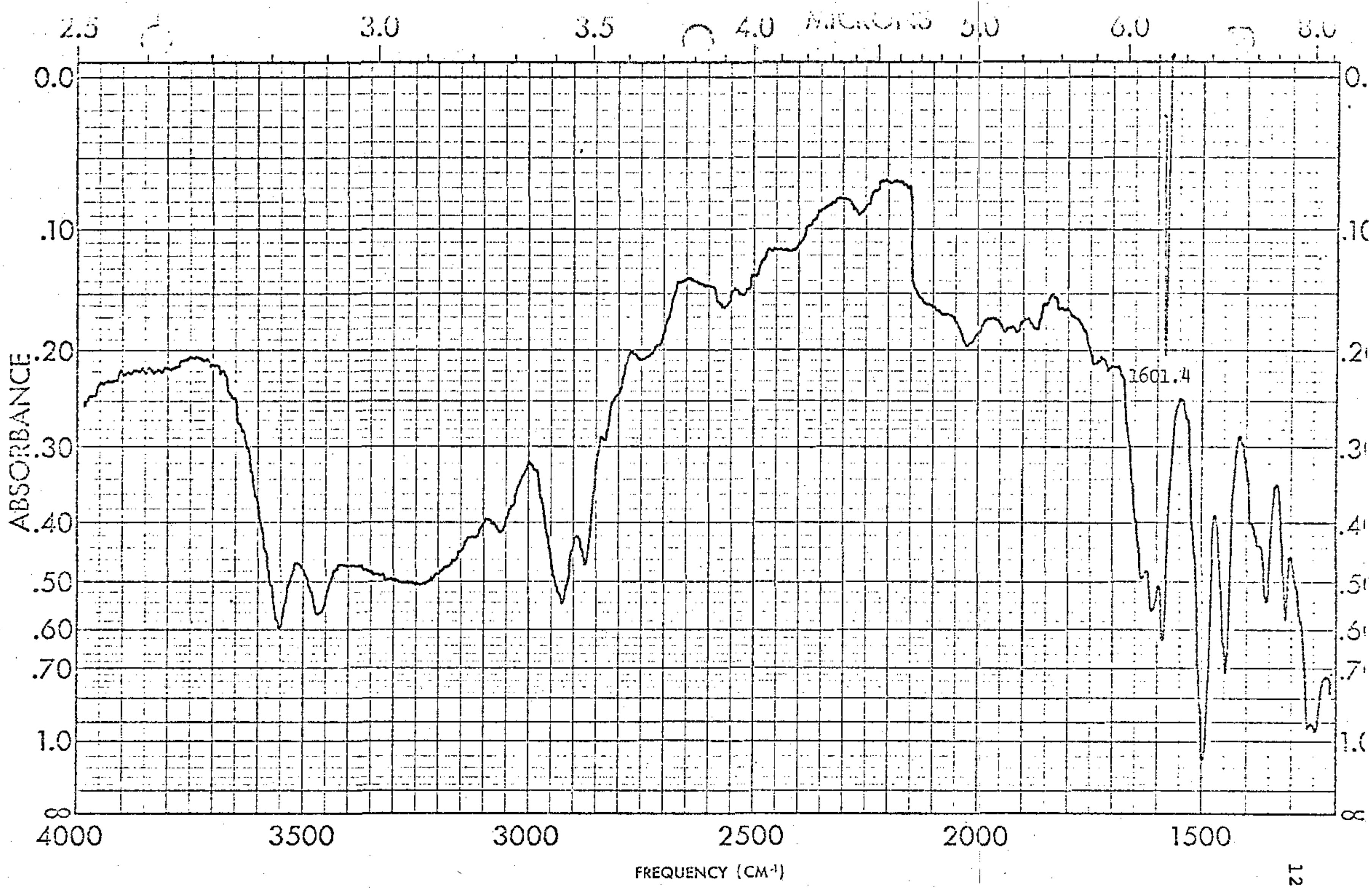


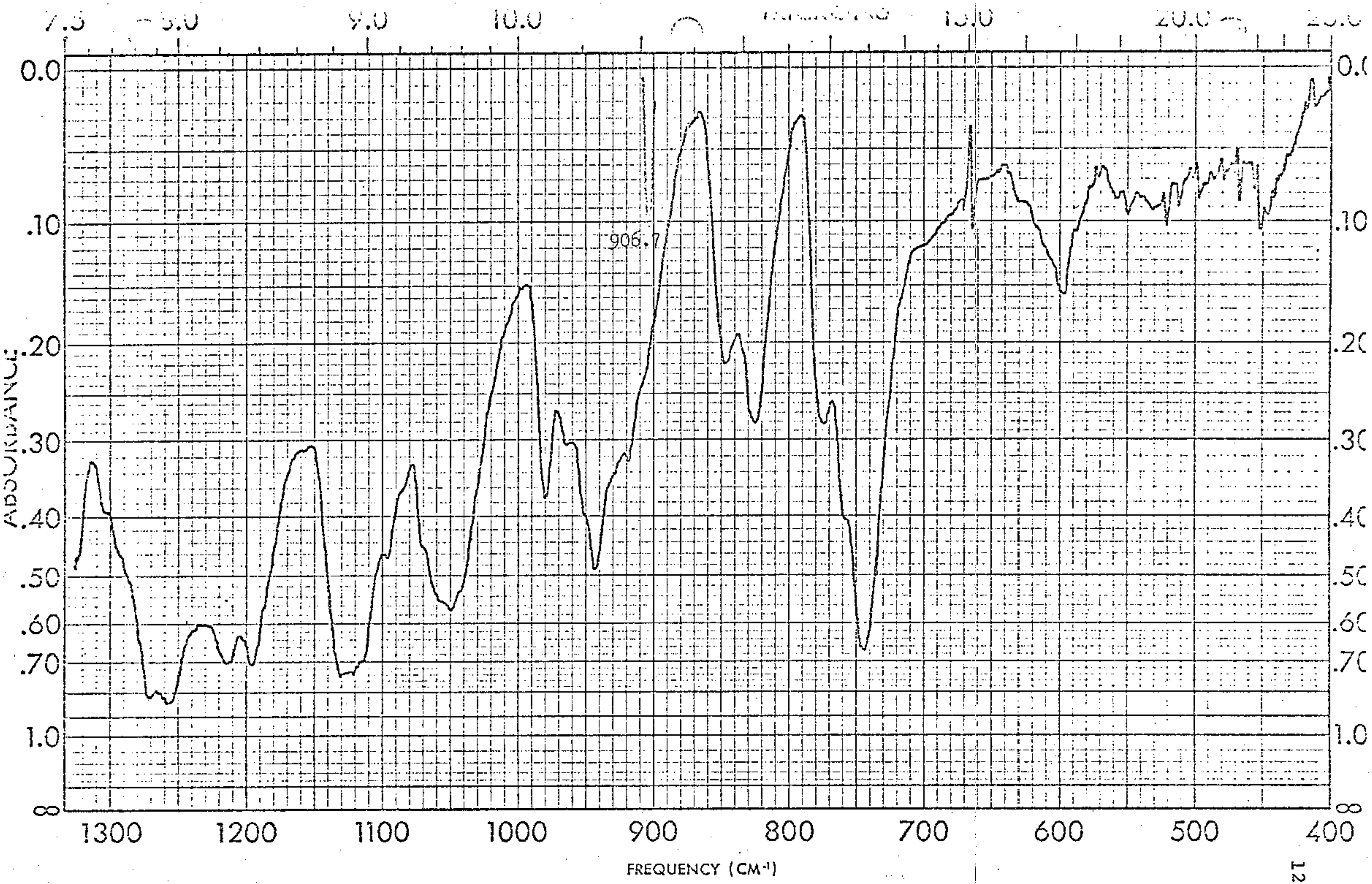
2-(3-furyloxymethyl)1,3-dioxolane (IX)



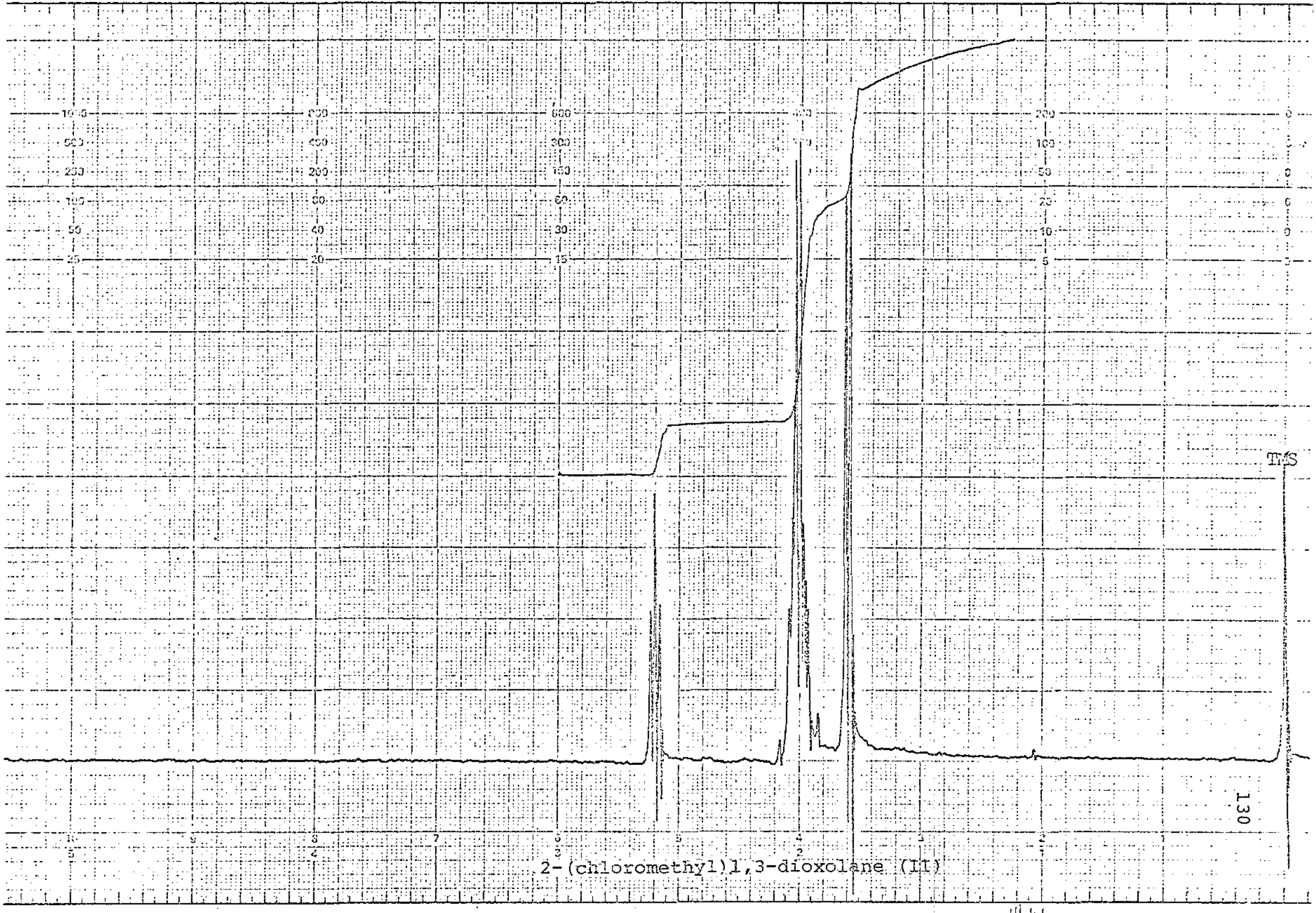
2-(3-furyloxymethyl)1,3-dioxolane (IX)



Unknown Compound (X)

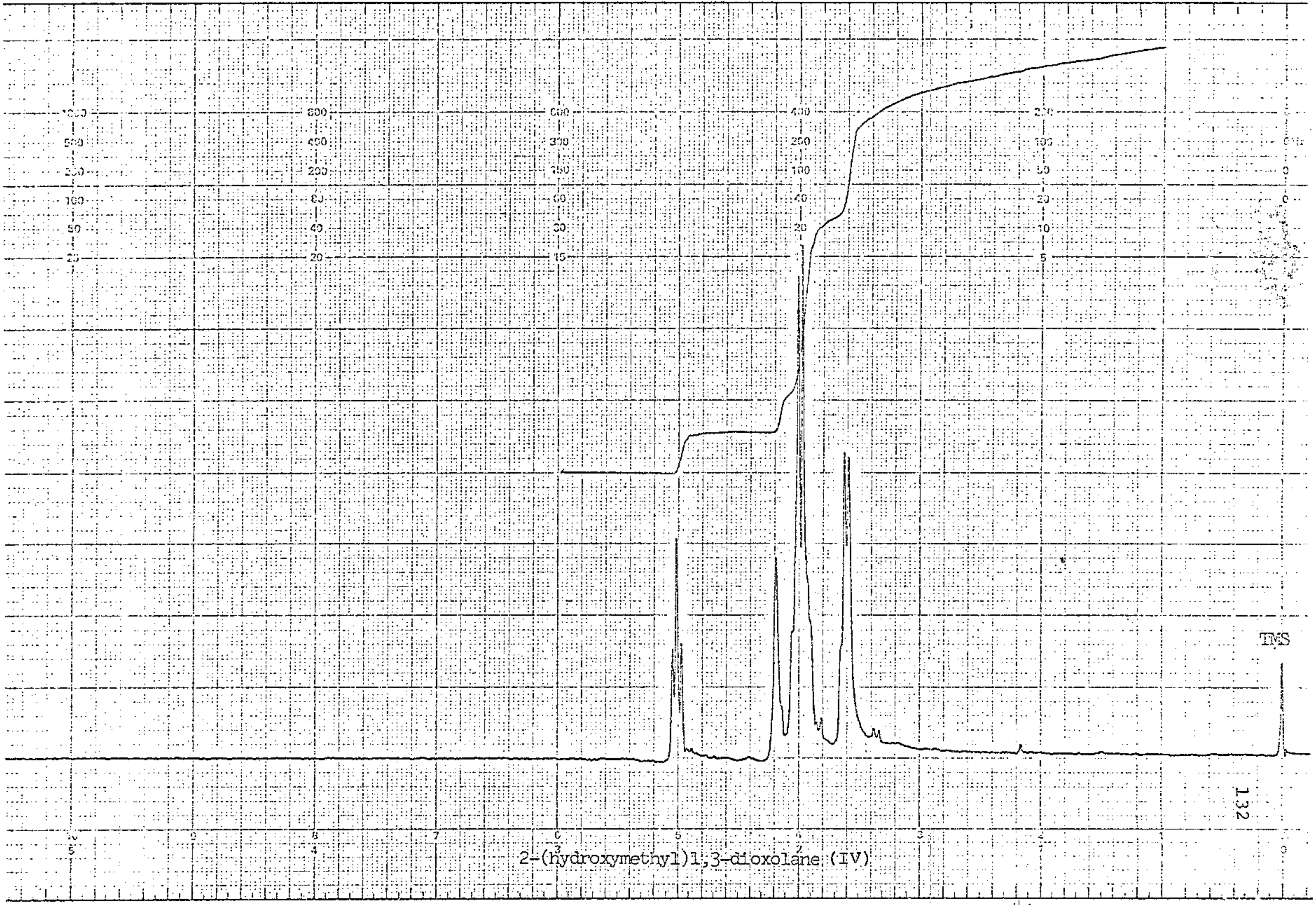


Unknown Compound (X)

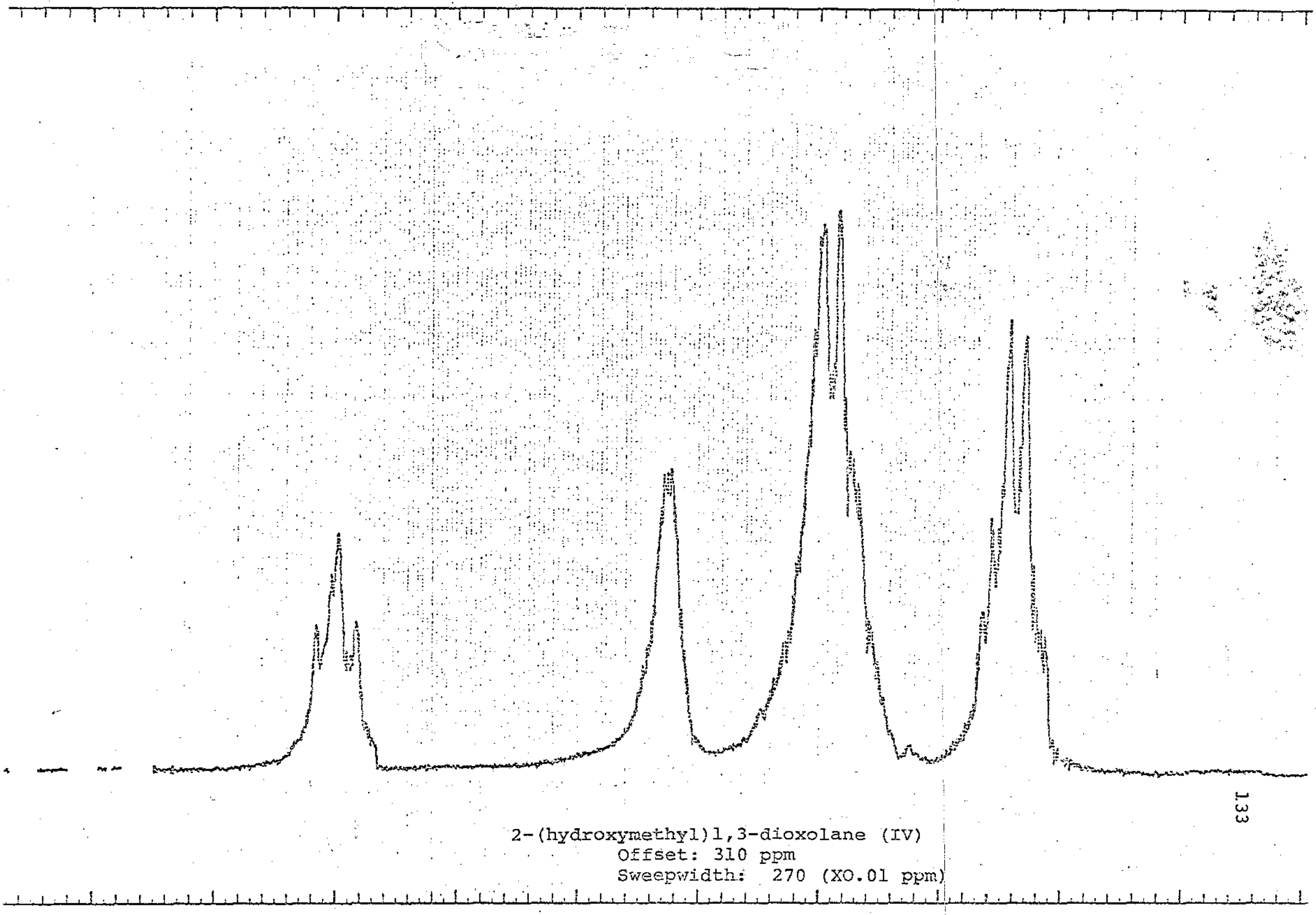


2-(chloromethyl)1,3-dioxolane (II)

2-(acetoxymethyl)1,3-dioxolane (III)



2-(hydroxymethyl)1,3-dioxolane (IV)



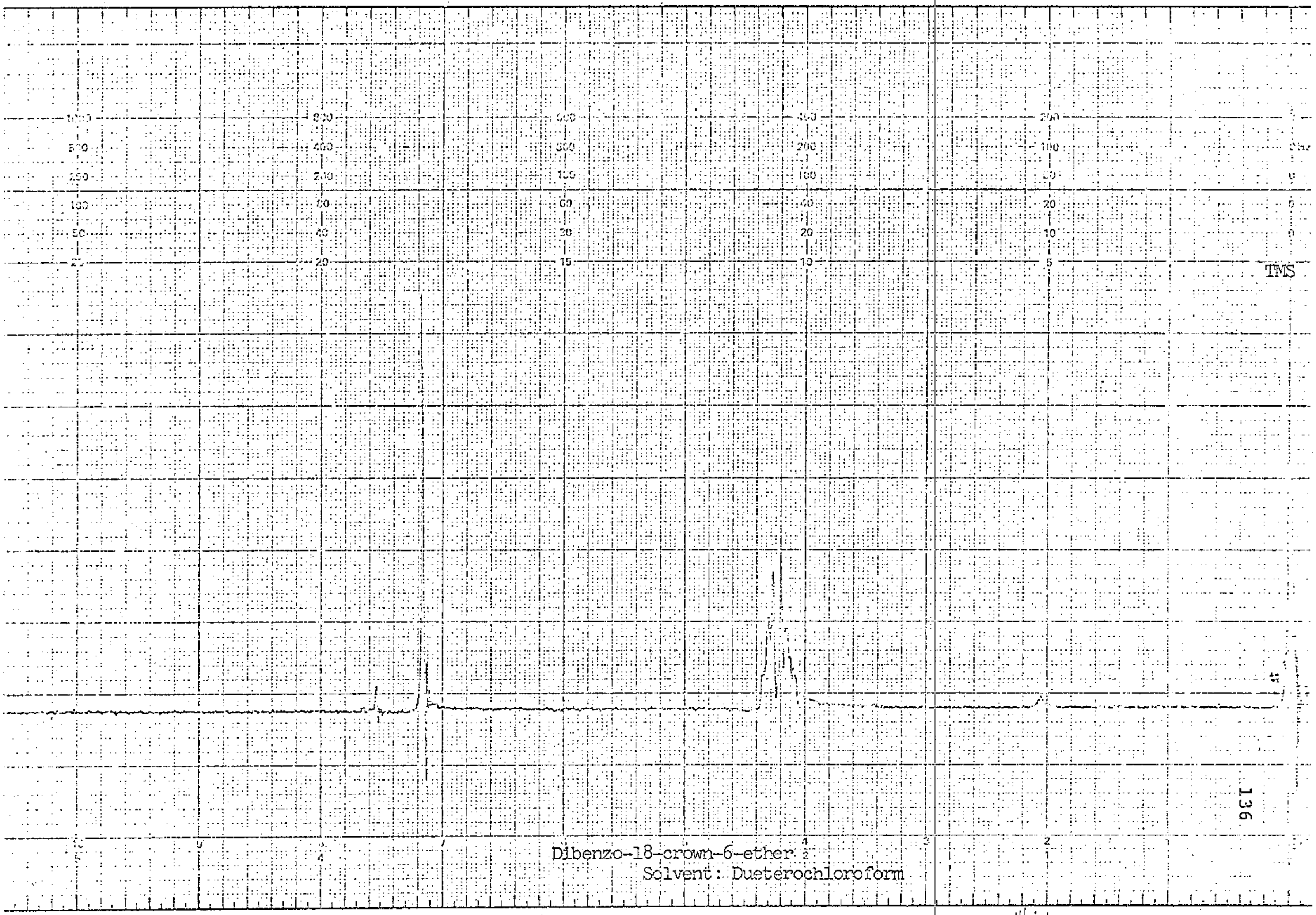
2-(hydroxymethyl)1,3-dioxolane (IV)
Offset: 310 ppm
Sweepwidth: 270 (X0.01 ppm)

2-(3-furyloxymethyl)1,3dioxolane (IX)

Unknown Compound (X)
Solvent: DMSO

CHART No. TPJ—4HC

THOMPSON PACKARD



Dibenzo-18-crown-6-ether
Solvent: Dueterochloroform

CHART No. TPJ–4HC