ELECTRO-ORGANIC SYNTHESIS OF SOME NATURAL PRODUCT ANALOGUES

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Master of Science in Chemistry

by
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To all people who understand the deep
interest for education and make
it possible

ACKNOWLEDGEMENTS

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Abstract

Electro-organic Synthesis of Some Natural Products Analogues

By

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In this project an attempt was made to prepare lignans by oxidative and reductive coupling of the α-enolates and α-bromo derivatives of substituted propiophenones respectively. Propiophenone derivatives were prepared by the addition of ethylmagnesium iodide to substituted benzaldehydes followed by oxidation of the intermediate alcohols with Jones' reagent. The α-bromo propiophenone derivatives were prepared by treating the ketones obtained with bromine in chloroform solution.

Prior to preparative electrolysis of the α-enolates and α-bromo derivatives, the working potentials were determined by cyclic voltammetry and DC polarography. It was found out that the carbonyl functional group was reduced at a potential greater than -1.9V and C-Br bond it was cleaved to the corresponding free radical or carbanion in the potential range of -0.2V to -1.4V.

Preparative electrolysis of 3,4-methylenedioxypropiophenone in methanol containing sodium methoxide and potassium iodide at 1.05V (divided cell) gave the α-hydroxy

propiophenone derivatives. The methyl ether propiophenone derivatives were also obtained when the ketones were electrolyzed at various working potentials in qqueous-methanol medium containing the electrolytes sodium hydroxide and potassium iodide. Exhaustive preparative electrolysis of the α-bromo-3,4-dimethoxypropiophenone derivative at -1.7V vs SCE using platinum electrode (divided cell) gave a lignan of the 1,4-diaroylbutane derivatives.

I. INTRODUCTION

Organic electrochemistry was among the first general techniques to be employed at a time when organic chemistry itself was in its infancy. Organic electrochemists of the late nineteenth and early twentieth centuries very well recognized the basic principles of electrochemistry laid by Faraday and Nernest. The importance of the electrode potential in controlling the course of an electrolytic reaction was also understood by Haber in 1898.[1] The early twentieth century saw a flurry of activity in organic synthesis using electrochemical techniques by such individuals as Haber, Fichter, Thatcher, Kolbe and many others who recognized the promise of electrolysis as an important synthetic tool for both laboratory and industrial reactions.[2,3]

Interest and activity in organic electrochemistry declined in the 1930's and 1940's at a period when organic chemistry was flourishing and expanding in many directions.[4] This was due to inadequecies in the theory and in their instrumentation to stimulate growth of electro-organic research and achieve the still largely unexploited potential of electrochemistry in organic synthesis.

The development of electrochemical techniques and instrumentation, initially developed for analytical uses provided much information concerning the electrode process itself, and also gave the organic electrochemist the "eyes" to examine properly the electrode reaction he is dealing with.[5]

Nowadays, an extremely wide variety of electrochemical conversion can be carried out using relatively simple and inexpensive equipment, usually with the further advantages of speed, good yields and simplicity of work-up. It is possible to carry out many redox processes, that is, reductions and oxidations, far more efficiently electrochemically than with the aid of conventional reducing or oxidizing agnets. Furthermore, there are many reactions that can be carried out electrochemically which are not possible chemically.

In this project an attempt was made to electrochemically synthesize the various classes of lignans (1-5), natural products with a broad-range of therapeutic values, by oxidative (anodic) and reductive (cathodic) coupling of the α-enolates and α-bromo derivatives of substituted propiophenones. (6).

Synthesis of these compounds by this method has the unique advantage of low cost and simplicity of work-up. It also avoids the use of some hazardous and toxic chemical oxidants.

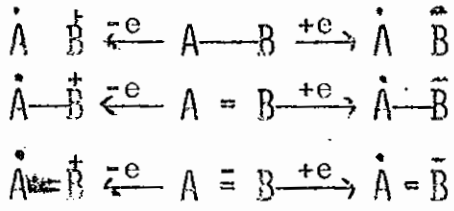
II. B A C K G R O U N D

Among all the elementary particles that matter is made up of, the electrons are the ones which are exploited by the chemist in synthesis and mechanism elucidation.

The transformation of a compound into another compound requires sufficient energy to overcome the activation energy. This could be provided thermally, photochemically or electrochemically. Thermal energy increases the random motion of the molecules. Hence, collision could take place at any point in space since movement is random. This collision between molecules causes electron transfer. Light irradiated reactants give high energy species which would react further to get rid of the excess energy. In electrically induced reactions, a rather direct route is followed. In this case, electrons are either torn away or given to the substrate. The activation energy in electrochemical reaction is in some cases lower than the corresponding simple chemical reaction due to the catalytic effect of the electrode. The first step in electrochemical reaction is an electron exchange between the electrode and the compound in solution. The exchange gives rise to a cation-radical or an anion-radical intermediate. The intermediates formed then under-

go chemical reaction which will be followed by further electron exchange or dimerization of the radicals.

Consider two atoms A and B which are sp, sp^2 or sp^3 hybridized. Electron removal or addition to these systems gives rise to the following intermediates:

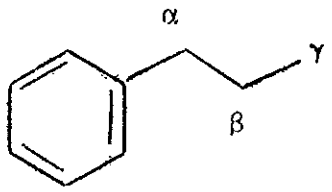


Different functional groups in a molecule are oxidized or reduced at different potentials. Hence, an electron addition or removal occurs only when that particular potential is reached. This allows to selectively conduct a certain chemical transformation in the presence of other functional groups. Electrode potential regions of some functional groups are given in Appendix I.

1. Lignans

Lignans constitute a class of natural products which frequently occur in wood[6,7] and characterized by the bonding of two phenylpropyl (C_6C_3 precursurs) groups at the

β-carbon atoms.

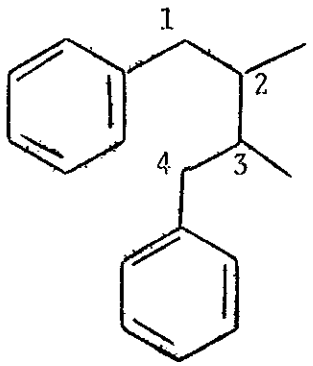


Lignans can be subdivided into several structural groups of which over 200 naturally occurring compounds are currently known. Some of the subclasses of lignans are given in Table 1.

TABLE 1

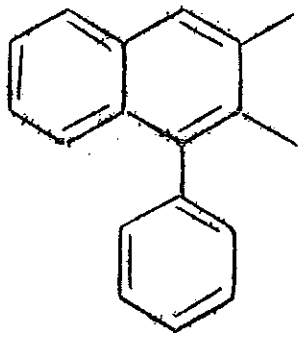
Subclassification of Lignans

1,4-Diarylbutane:



1

1-Arylnaphthalene



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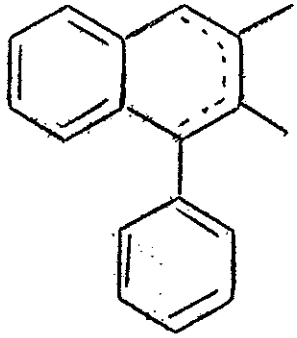
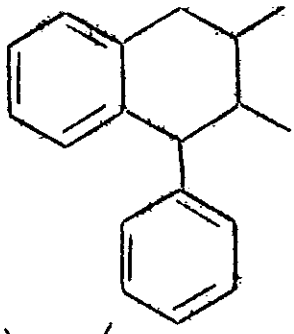
1-Aryldihydronapthalene



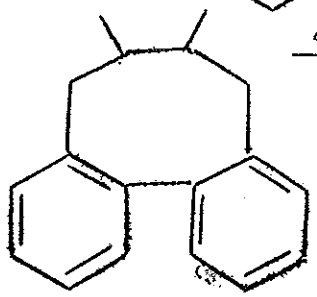
3

1-Aryltetrahydronapthalene



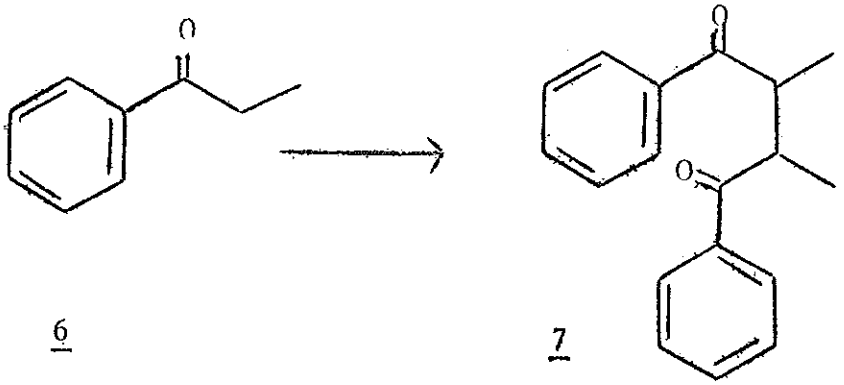
4

Dibenzocyclooctene:



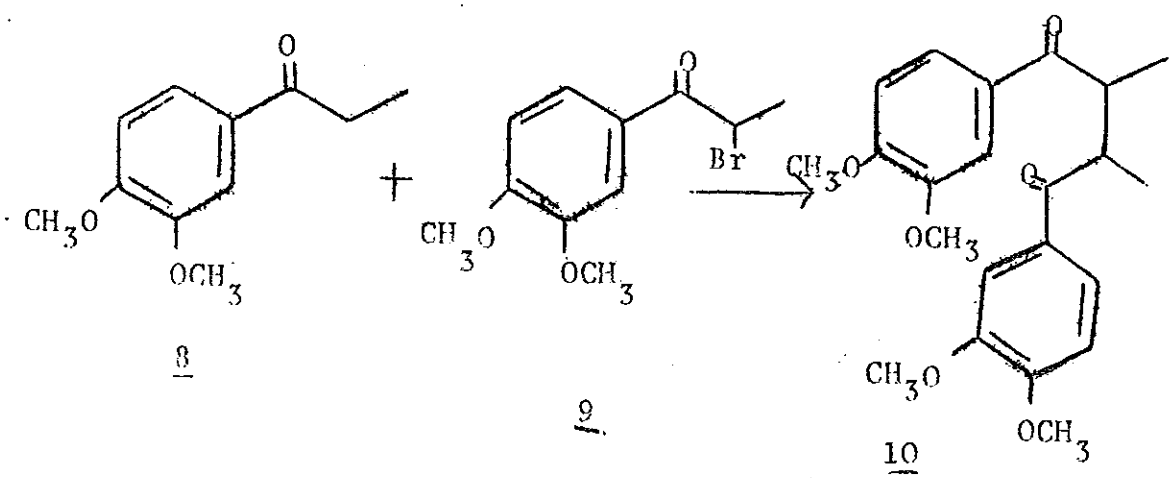
5

The different subclasses of lignans have been synthesized chemically by enolate oxidation and by α-bromoketone alkylation reactions. 2,3-diaroylbutane[8,9] (7) could be prepared by the oxidative coupling of a ketone enolate (6) with cupric chloride[10] or cupric trifluoromethanesulphonate[11]



6 7

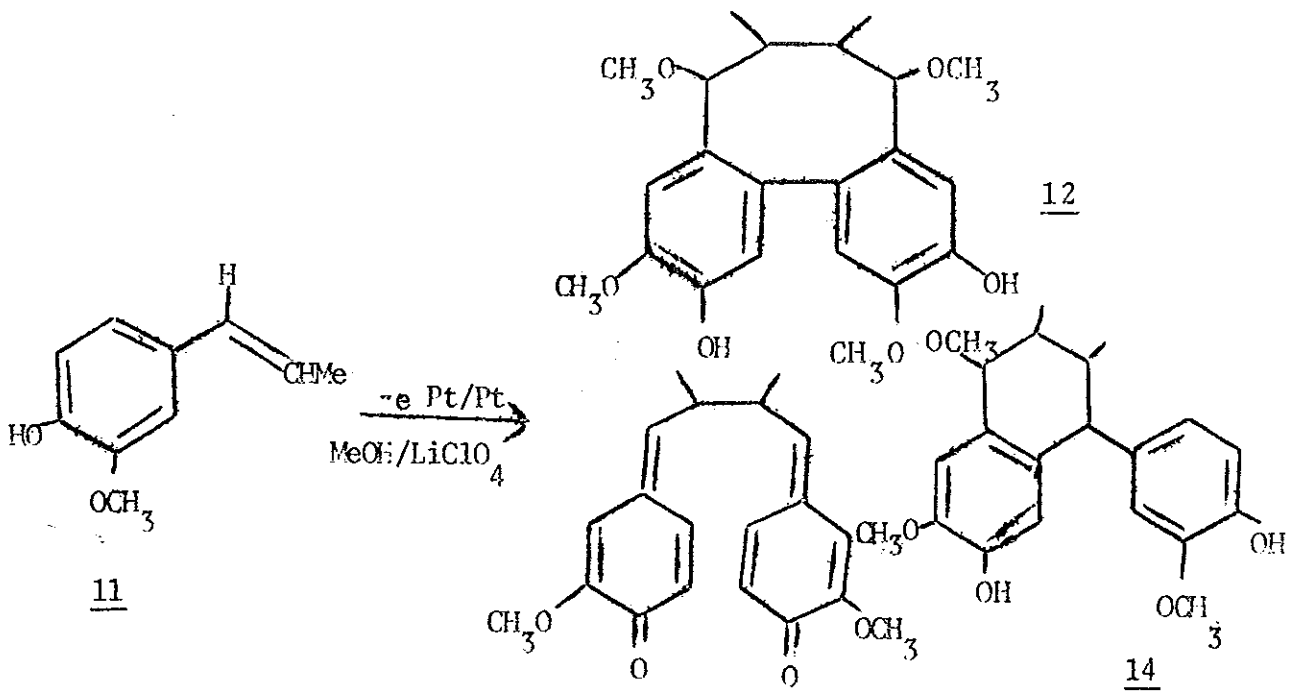
When 3,4-dimethoxypropiophenone (8) was alkylated with the corresponding α-bromoketone (9) in liquid ammonia with sodamide as the base, the racemic diketone (10) was isolated in good yield.



8 9 10

The various structural groups of lignans can be derived from 1,4-diketones by treatment of (10) with appropriate reagents[12-21]

Some structural groups of lignans were also electrochemically synthesized. Controlled potential electrolysis of E-isoeugenol (11) using undivided cell with platinum electrodes at 800mV vs SCE(r,t,7.5 hr) gave the



1,4-diaroylbutane (12,13) and 1-aryltetrahydronapthalene (14) subclasses of lignans as anodic oxidation products[22,23]

2. Constituents of an Electrochemical Cell and Methods of Electrolysis[24]

A schematic diagram of an electrochemical cell is shown in Figure 1. Each terminal of a source of direct current B is connected to an inert electrode, and both electrodes are immersed in a conducting solution (electrolyte dissolved in a given solvent). In this way an electrical circuit is completed: Current flows as positive ions of the electrolyte migrate to the negative electrode (cathode) and reduced or while negative ions migrate to the positive electrode (anode) and oxidized. Thus, every cell must contain both an anode and a cathode. The anode and the cathode are usually placed in the same or separate compartments separated by a porous barrier inorder to prevent further electrochemical destruction of products. The solution in the cathode compartment is known as the catholyte and that in the anode compartment is known as the anolyte. The substance whose electrochemical behaviour is to be investigated is known as the electroactive substance or substrate.

The working electrode is the electrode at which the electrochemical reaction of interest is carried out. When reductions are being studied, the cathode is the working

electrode. The counter electrode (auxilary electrode) is the other current - carrying electrode whose presence is necessary to complete the circuit. However, the design of an electrolysis cell can be extremely simple or quite complex, depending on the requirements of the actual system under investigation.

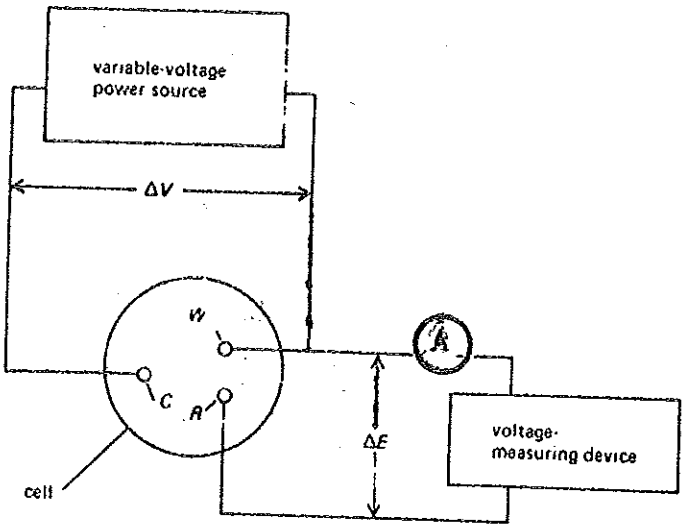


Figure 1 Schematic representation of a controlled potential electrolysis experiment.

C: Counter electrode

W: Working electrode

R: Reference electrode

A: Ammeter

Electrochemical oxidations or reductions may be carried-out at constant current or at constant potential of the working electrodes.[25-28] Of the general methods, controlled potential electrolysis (cpe) carried out with a potentiostat is by far the most suitable. Controlled potential electrolysis consists simply of an experiment in which an electrochemical reaction is allowed to proceed to completion at an electrode whose potential is held constant. It allows one to use a single agent (the electrode) whose potency is continuously variable over a wide range. The potentiostat controls the potential of the working electrode and maintains at a pre-set value against the reference electrode. In order to follow the course of the electrochemical reaction of interest, provision is made for recording the potential of the working electrode (or rather the change in potential) by using a reference electrode (e.g. a calomel electrode) the tip of which is placed as near as possible to the working electrode. The potential difference between the working and the reference electrodes is measured by a voltmeter with a very high internal resistance. The circuit connecting the electrolytic cell is also provided with an ammeter to measure the current flowing through the electrolyte.

In addition to the potential setting, however, there are a number of operating conditions governing a cpe which may be described by equations I-III for electrode processes controlled by the rate of mass transport to the electrode.

$$i_t = i_i 10^{-Kt} \quad \text{..... (I)}$$

$$K = 0.43 \frac{DA}{V\delta} \quad \text{..... (II)}$$

$$\frac{C_i}{C_t} = \frac{i_i}{i_t} \quad \text{..... (III)}$$

where i_t is the instantaneous current, i_i is the initial current, K is a constant, V is the solution volume (ml), C_i is the initial concentration of reactant (mole cm^{-3}), A is the area of the anode or cathode (cm^2), t is the time (min), D is the diffussion coefficient ($cm^2 sec^{-1}$) and δ is the Nernst diffussion layer thickness. Equations I and II signify that a short electrolysis time is achieved by using large electrode surface area, a small solution volume, and a small diffussion layer thickness attained by efficient stirring.

3. Determination of the Working Potential[24,29-31]

In electro-organic synthesis, one should be continually aware of the nature of the reaction he is conducting in terms of both the chemical and electrochemical pathways which may be possible for a given system. Information such as working potential, formation of unstable intermediates, multistep electron transfer, potential dependent adsorption, competing electrolytic reactions and so forth, can only be made "visible" by proper application of suitable electrochemical methods. The most widely used techniques are cyclic voltammetry (cv) and polarography which are unmatched in their ability to provide qualitative information about the steps in redox reactions with only a modest expenditure of time and effort in the acquisition and interpretation of data.

In the voltammetric experiment, the electrode has two interrelated roles: (a) by controlling the electrode potential, a variable and precisely known amount of oxidation or reduction is caused to occur in a small volume of solution within about 0.1 mm of the surface. (b) the current-potential data obtained during or after step (a) give information about the intermediates

and products formed in the electrode reaction, i.e. the electrode monitors the solution reactions. Thus, information concerning both the standard (formal) potentials and rates of reaction of intermediates and products can be obtained.

In cyclic voltammetry one scans the potential of the working electrode in an unstirred electrolyte solution in the anodic (cathodic) direction and records one or several peaks due to oxidation (reduction) of the subsrate. At some suitable potential, the direction of the scan is reversed and peaks due to reduction (oxidation) of intermediates and/or products formed during the forward scan are observed. In the simplest case a linear increase (decrease) of the potential with time is employed with scan rates in the range 0.01-1000 V sec^{-1}.

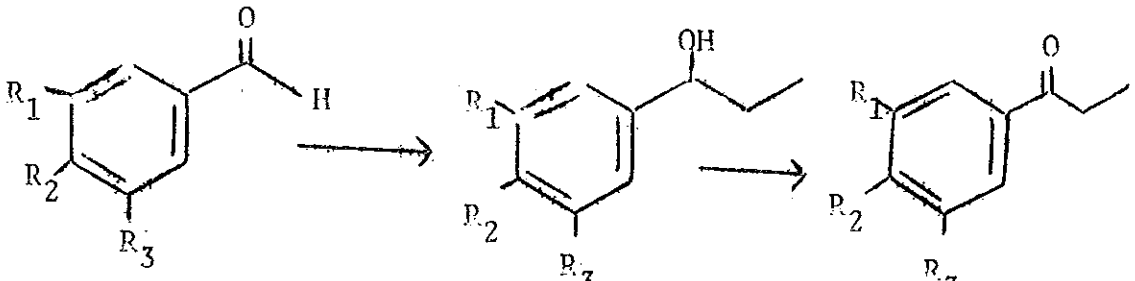
Polarography, one of the most widely used electrochemical techniques, can also provide a considerable amount of useful information with little experimental effort. Its basic component is its unique working electrode, the dropping mercury electrode (D.M.E.), which is a long thin (internal diameter 0.05-0.10 mm) capillary tube attached to a mercury reservoir of adjustable height. The

capillary is immersed in a solution containing the electroactive substance. Circuitry is provided such that (1) the mercury drop serves as a working electrode, (2) its potential may be scanned gradually (ca. 5mV/sec) to more negative potentials, and (3) the current flowing between the drop and the counter electrode is recorded as a function of the working electrode potential (relative to a nearby reference electrode). The number of polarographic waves indicate immediately the number of discrete electrode processes undergone by the substance, and the wave heights and shapes indicate the number of electrons involved in the overall and rate-determining steps. respectively, for each wave.

III. D I S C U S S I O N

1. Preparation of Substituted Propiophenone Derivatives

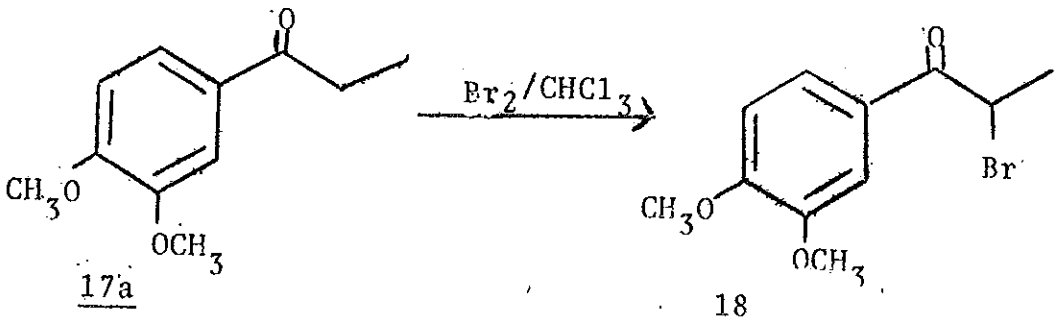
Propiophenone (17a and 17b) derivatives were prepared[32] by addition of ethylmagnesium iodide to substituted benzaldehydes 15 followed by Jones' oxidation of the intermediate alcohols 16. The ketones were found in 80% yield by this procedure.



15 16 17

	R_1	R_2	R_3
a	$-OCH_3$	$-OCH_3$	H
b	$-OCH_2O$		H

α-bromo-3,4-dimethoxypropiophenone 18 was prepared[32] in 38% yield by treating 17a with bromine in chloroform.



17a 18

2. Electrochemical Behavior of Propiophenone Derivatives

Before preparative electrolysis of the α-enolate and α-bromo derivatives were attempted, the electrochemical behaviour of these compounds were studied. The electrochemical behavior of both the ketones and the α-bromo derivatives were studied using DC polarography and cyclic voltammetry. For these studies various electrode materials such as dropping mercury (DME), hanging mercury (HME), platinum and glassy carbon were used. Acetonitrile was used as a solvent and tetrabutyl ammonium perchlorate (Bu_4NClO_4) as supporting electrolyte because of the stability of these compounds (-2.70 to 2.60V).

DC polarogram of the ketone 17b in acetonitrile, using Bu_4 $NClO_4$ as the supporting electrolyte, and a

$Ag/AgCl/Cl^-$ satd' as the reference electrode, and Pt auxiliary electrode shown in Figure 2. A well defined reduction wave at $E_{\frac{1}{2}}$ = -2.07V is displayed due to the carbonyl group. A similar pattern was also observed for the ketone 17a.

The polarogram of 18 under the same conditions gave three reduction waves with $E_{\frac{1}{2}}$ = -0.24V, -0.61V and -2.04V (Figure 3). It was concluded that the new reduction waves were due to the reduction of 18 to the corresponding free radical and/or carbanion intermediates.

Cyclic voltammetry of potassium iodide (supporting electrolyte) in methanol (Figure 4) exhibited a reversible redox couple at a peak potential of 0.2V which is due to the oxidation of the iodide to iodine. The pattern of the voltammogram was not changed when a solution of sodium methoxide was added.

The voltammogram of the strong base potassium t-butoxide ($KOC(CH_3)_3$) and Bu_4NClO_4 as supporting electrolyte in acetontrile (Figure 5) was complex in the potential range of -1.0V to +2.0V. As a result, it was not possible to study the electrochemical behaviour of the ketone enolates within this potential range.

The cyclic voltammograms (0-+2.0V) of 17a and 17b (Figure 6) in acetonitrile containing Bu_4NClO_4 as supporting electrolyte at platinum electrode and glassy carbon electrode showed two irreversible oxidation peaks at 1.75V and 1.92V. Since both ketones showed the same oxidation peaks at the same potentials, it was concluded that these potentials are associated with the acidic protons α to the carbonyl group.

The electrochemical behaviour of the ketones 17a and 17b were also studied in the cathodic region (0 to -2V) by cyclic voltammetry (Figure 7). The voltammogram of the ketones showed a single well defined irreversible peak at -1.92V due to the reduction of the carbonyl group.

The Voltammogram of 18 (Figure 8) in acetonitrile containing Bu_4NClO_4 as supporting electrolyte using glassy carbon electrode displayed a weak reduction peak at -1.10V and two well developed irreversible reduction peaks at -1.36V and -1.92V. It was observed that the peak at -1.36V diminished in height as the cycles were repeated. By comparison of the voltammogram of 17a and 18, it was concluded that the reduction peaks at -1.10V and -1.36V are due to the reduction of C - Br bond to

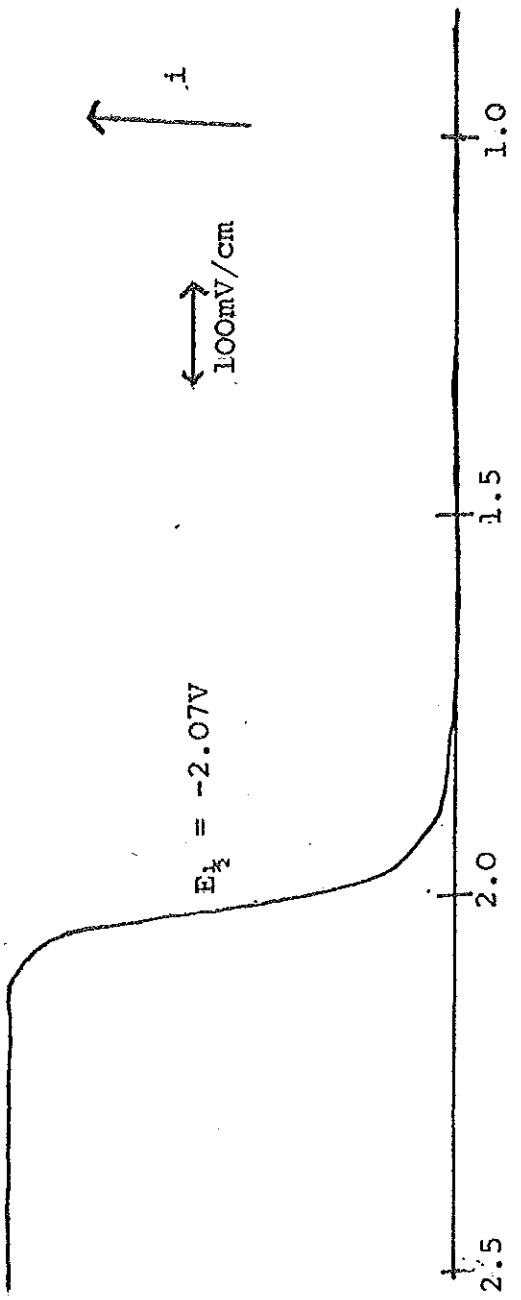


Figure 2: Polarogram of 17b at DME

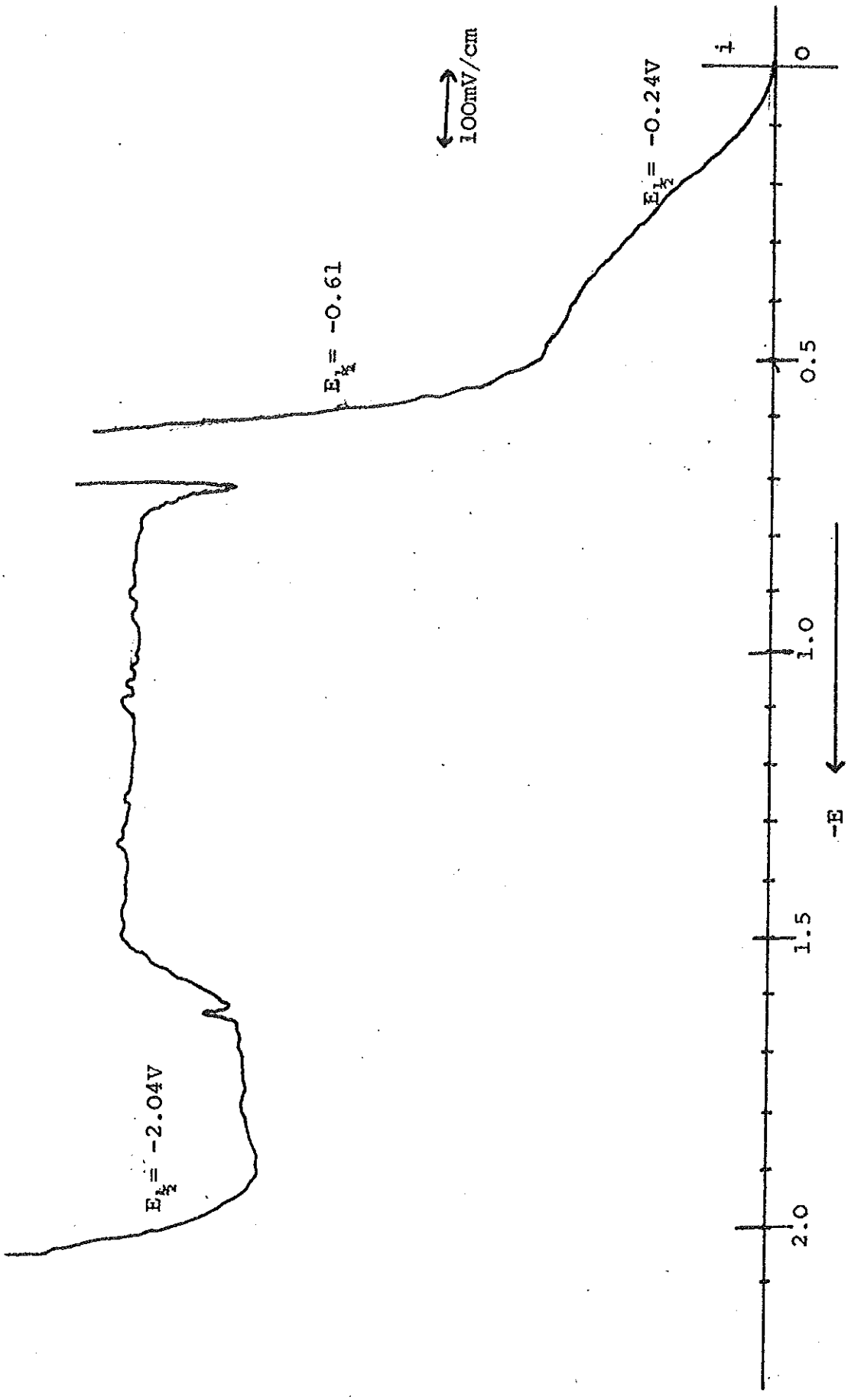


Figure 3: Rapid DC polarogram of 18 at DME.

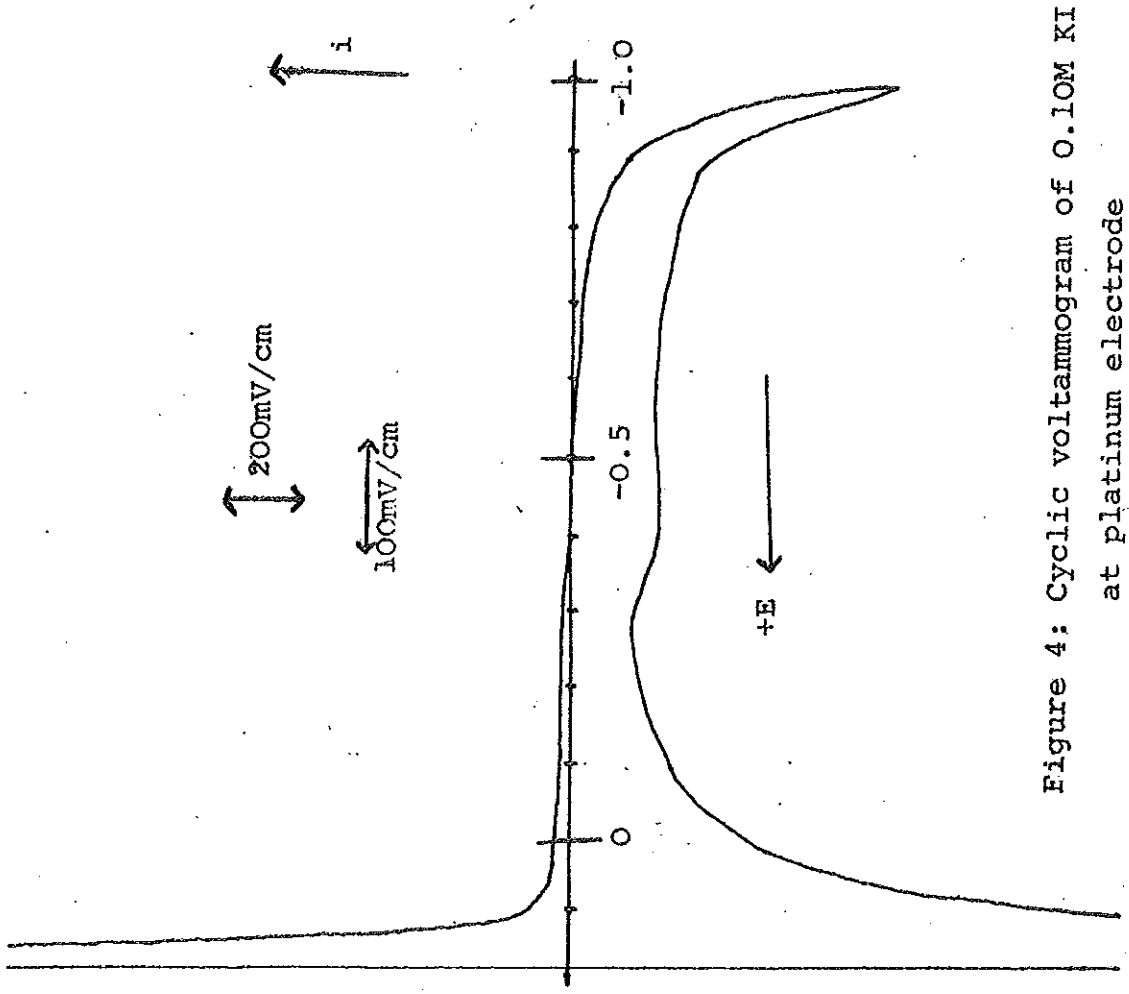


Figure 4: Cyclic voltammogram of 0.1OM KI in CH_3OH at platinum electrode

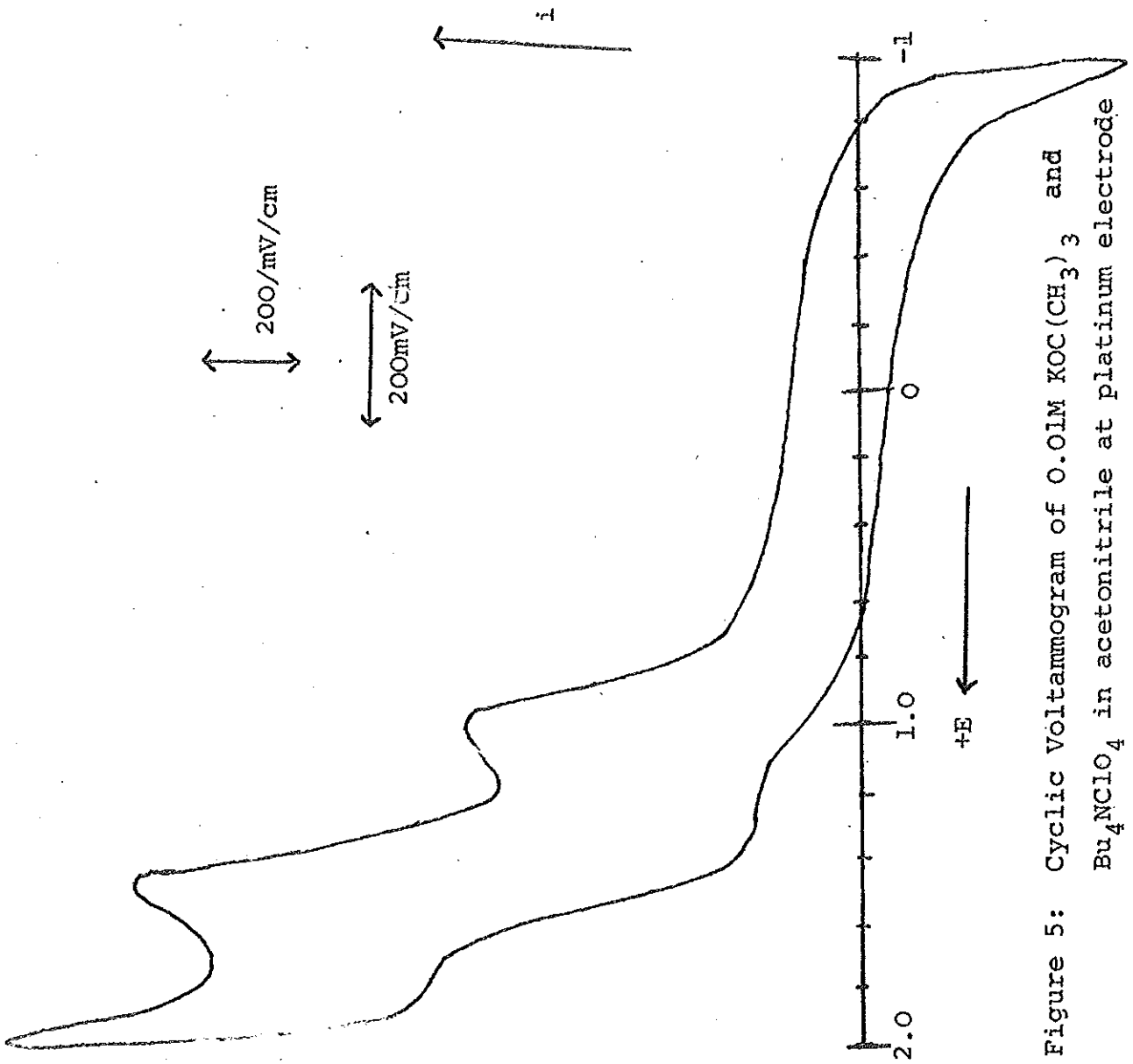


Figure 5: Cyclic Voltammogram of 0.01M $KOC(CH_3)_3$ and Bu_4NClO_4 in acetonitrile at platinum electrode

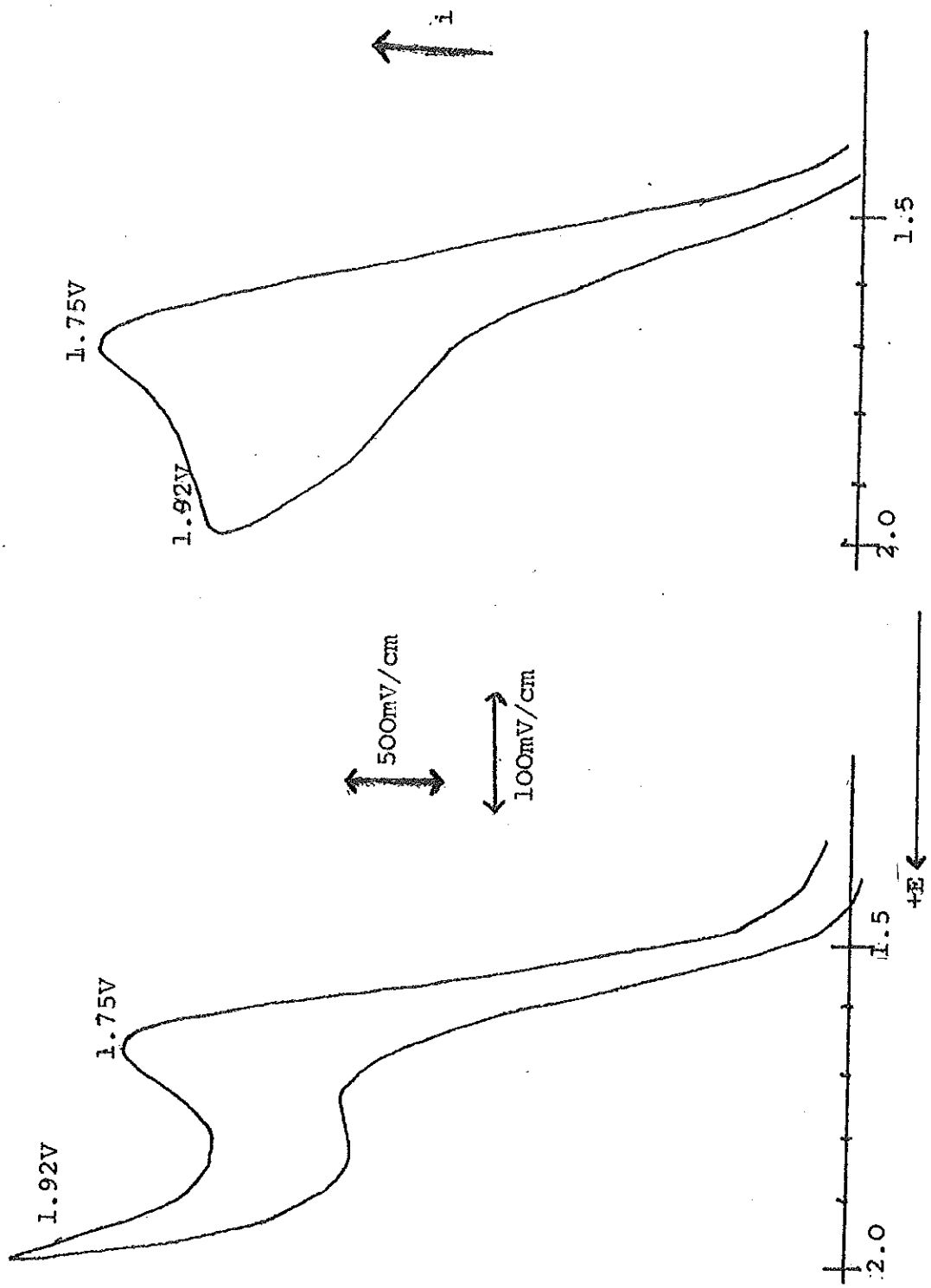


Figure 6: Cyclic Voltammogram of 17a and 17b at platinum electrode

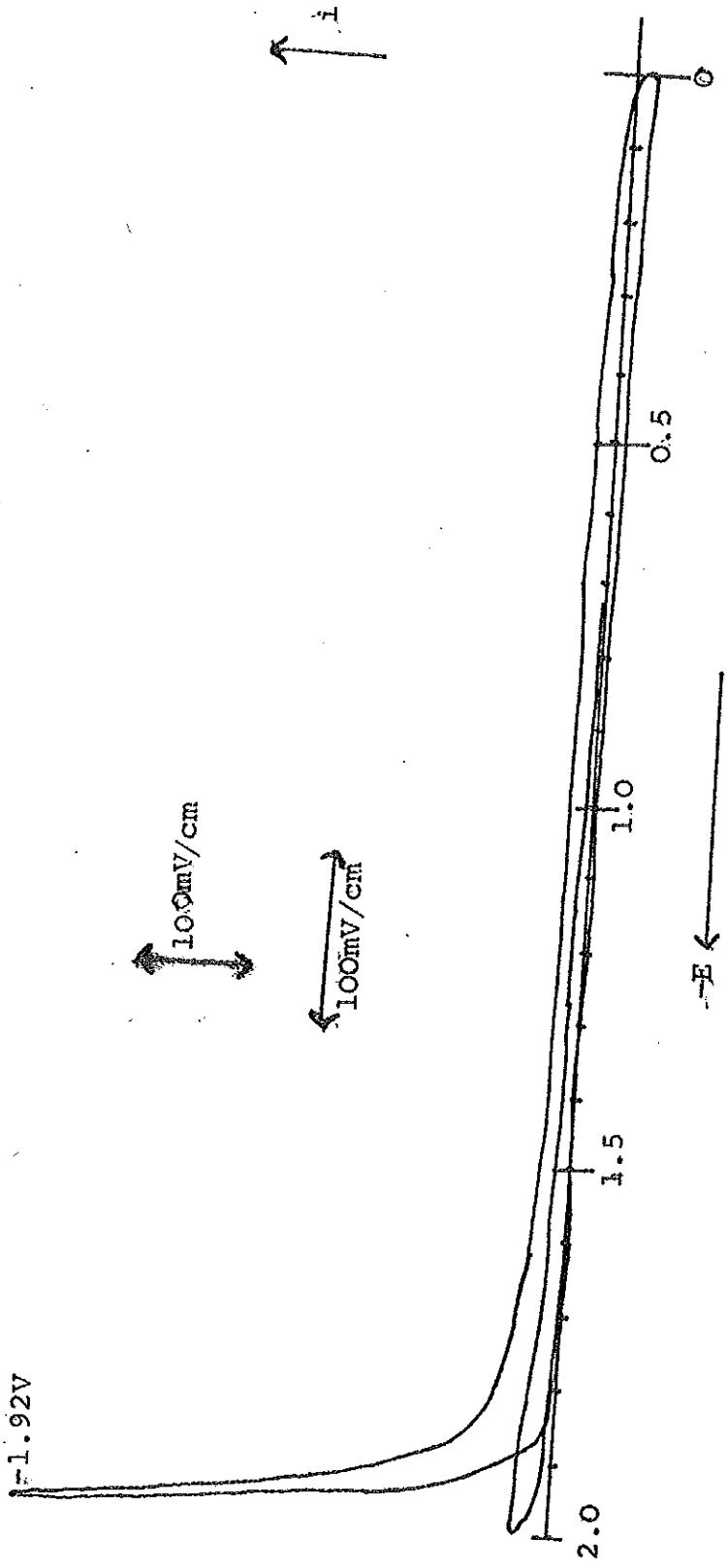


Figure 7 : Cyclic Voltammogram of 17b at platinum electrode

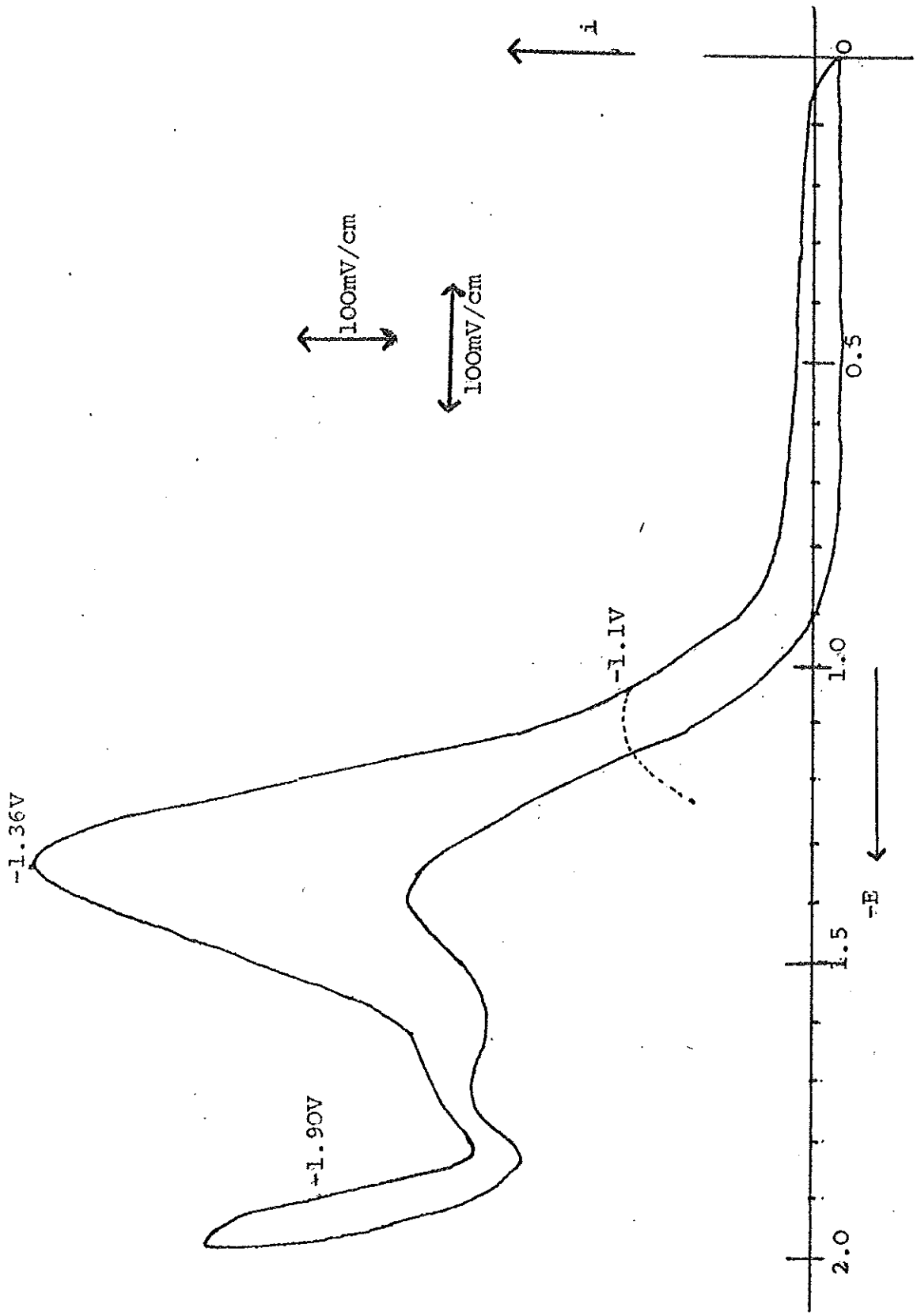


Figure 8: Cyclic voltammogram of 18 at carbon paste electrode

the corresponding free radical and/or carbonion intermediates. It was found out that the peak potentials for the reduction of C - Br shifted to -0.2V and -0.84V when hanging mercury electrode (HME) was used (Figure 9).

An attempt to study the electrochemical behaviour of the α-enolate generated was not successful due to the low stability of the bases used within the potential range of this experiment.

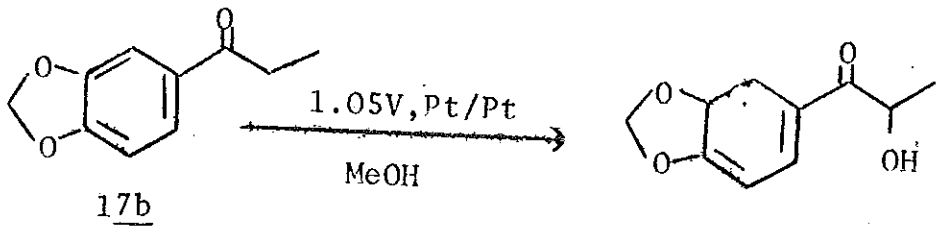
3. Preparative Electrolysis of Propiophenone Derivatives

The voltammograms of the ketones in basic media were complex. Hence the selection of the working potentials was not possible. The preparative electrolysis of 17a and 17b at various working potentials (0.55V, 1.05V, 0.50V, 1.75V, and 2.5V) in basic aqueous and non-aqueous media were conducted and gave products 19, 20a, 20b, 21b, and 22b. These oxidation products are natural product analogues.[7,8] A summary of the oxidation products and experimental conditions are given in Tables 2 and 3.

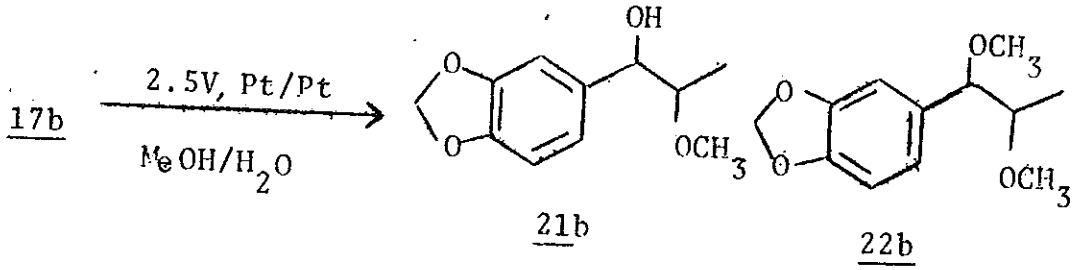
The structure of these oxidation products 19, 20a, 20b, 21b and 22b were determined on the basis of their spectral data (Appendix 2) as shown in the experimental section.

Table 2

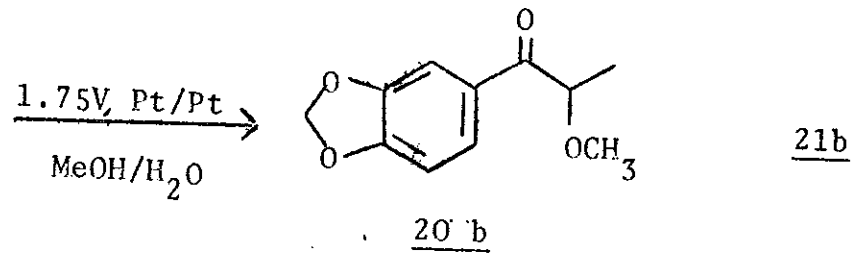
Summary of electrolysis product

1. 

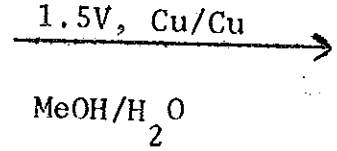
17b → 19

2. 

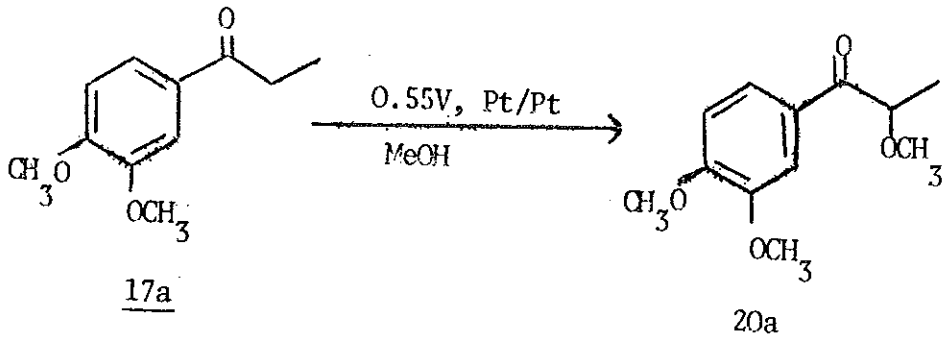
17b → 21b + 22b

3. 

17b → 20b + 21b

4. 

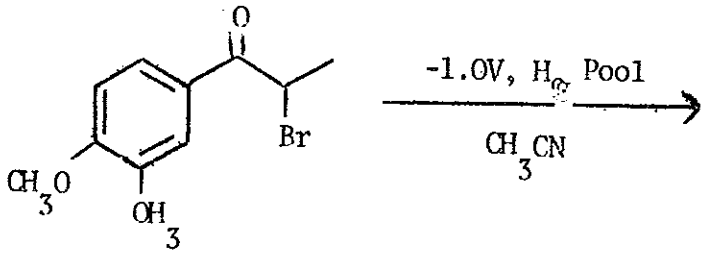
17b → 20b + 21b

5. 

17a 20a

6. 17a —(1.5V, Pt/Pt; MeOH/ H_2O)→ 20a

7. 17a —(1.84V, Pt/Pt; CH_3CN)→ I, J, K,

8. 

18 L

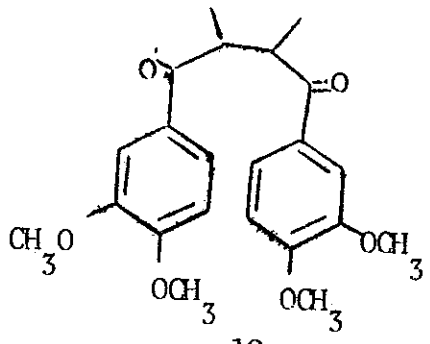
9. 18 —(-1.70V, Pt/Pt; CH_3CN)→ 

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TABLE 3

Summary of Electrolysis Experimental Conditions

	Ketone	base/supporting electrolyte	Solvent	Electrode	Working potential (V)/time	Product	Yield %
1.	17b	NaOMe/KI	MeOH	Pt	1.05, 18 hrs	19	70
2.	"	NaOH/KI	$MeOH/H_2O$	"	2.50, 24 hrs	21b,22b	20, 15
3.	"	NaOH/KI	$MeOH/H_2O$	"	1.75, 16 hrs	21b,20b	16, 30
4.	"	NaOH/KI	$MeOH/H_2O$	Cu	1.50, 24 hrs	21b,20b	10, 15
5.	17a	NaOH/KI	MeOH	Pt	0.55, 24 hrs	20a	30
6.	"	$NaOCH_3$	$MeOH/H_2O$	Pt	1.5 , 16 hrs	20a	30
7.	"	$/NaClO_4$	CH_3CN	"	1.84, 5 days	I,J,K	10, 15, 15
8.	18	$/Bu_4NClO_4$	CH_3CN	Hg pool	-1.0 , 3 days	L	10
9.	"	$/Bu_4NClO_4$	CH_3CN	Pt	-1.7V, 5 days	10	10

The molecular ion peak of compound 19 appeared at 194 which is consistent with the molecular formula $C_{10}H_{10}O_4$. The doublet at δ 3.73 disappeared when a drop of D_2O was added, indicating the presence of a hydroxyl group and this was further confirmed by its ir., ν_{max} 3450 cm^{-1}. There is also a characteristic peak at 1680 cm^{-1} for a carbonyl group.

The molecular ion peak of compound 20a appeared at 224 which is consistent with the molecular formula $C_{12}H_{16}O_4$. The doublet at δ 1.16 for the methyl group indicates the presence of only one proton adjacent to it. The singlet at δ 3.26 for three protons is due to a methoxy group.

The molecular ion peak of compound 20b appeared at 208 which is consistent with the molecular formula $C_{11}H_{12}O_4$. The doublet at δ 1.16 for the methyl group indicates there is only one proton adjacent to it. The singlet at δ 3.26 for three protons is for a methoxy group.

The molecular ion peak of compound 21b appeared at 210 which is consistent with the molecular formula $C_{11}H_{14}O_4$. The doublet at δ 1.20 for a methyl group indicates there is

one proton adjancent to it. The broak peak at δ 2.46 due to OH group disappeared when a drop of D_2O was added and this was further confirmed by its i.r, ν_{max} 3450 cm^{-1}. The singlet at δ 3.83 for three protons is due to the methoxy group.

The molecular ion peak of compound 22b appeared at 224 which is consistent with the molecular formula $C_{12}H_{16}O_4$. The doublet at δ 1.07 for a methyl group shows there is one proton adjacent to it. There is another doublet at δ 1.53 and multiplet and δ 4.16 with the same proton ratio (1H). The two singlets at δ 3.23 and δ 3.36 with the same proton ratio are for methoxy groups.

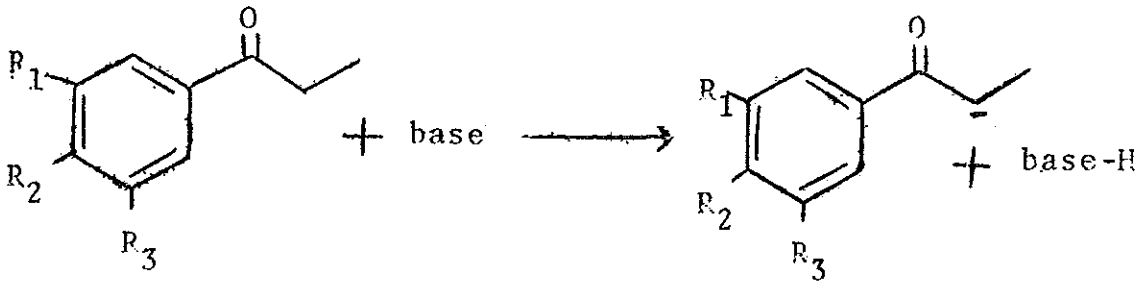
Exhaustive preparative electrolysis of 18 in acetonitrile containing Bu_4NClO_4 as supporting electrolyte at -1.0V vs SCE (r.t., 3 days) using Hg pool electrode gave unidentified reduction product in a 30% yield with mp 133-133°C and molecular ion peak of 374. However, electrolysis of 18 at -1.7V vs SCE (r.t., 5 days) using platinum cathode and the same solvent and electrolyte gave a reduction product in 10% yield as thick oil, which could not be crystallized from common solvents.

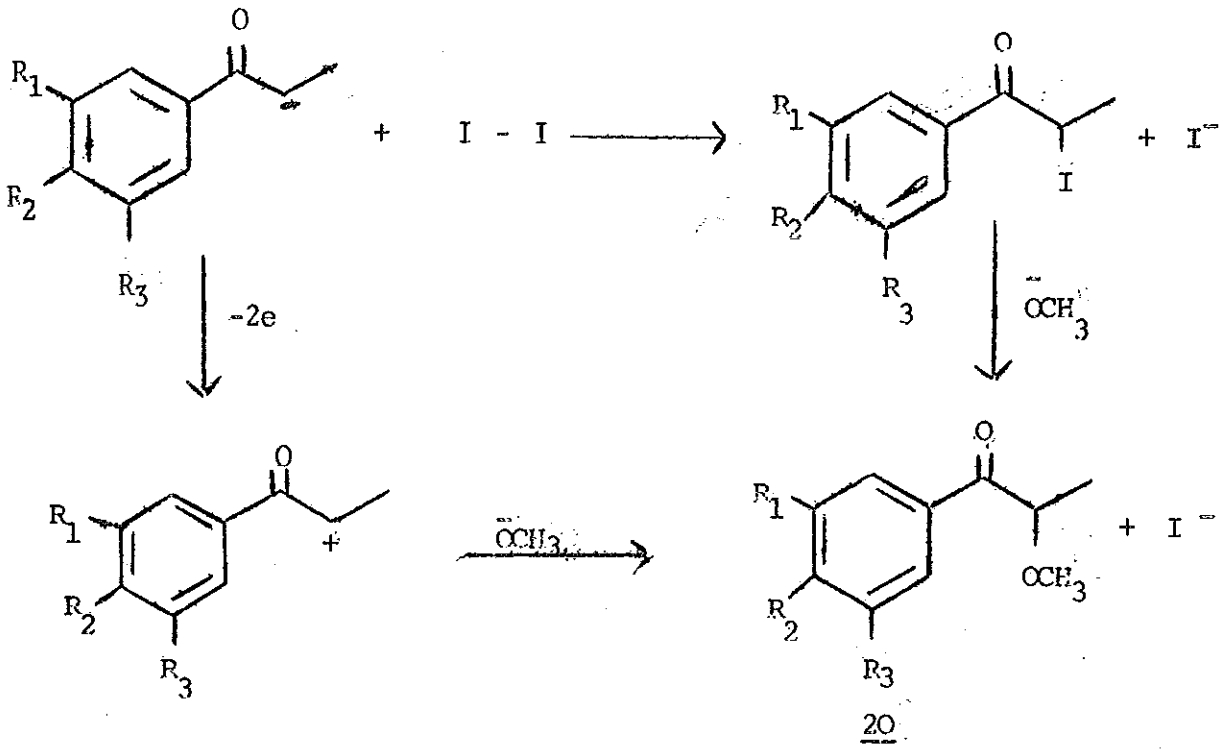
Its NMR gave a doublet at δ 1.43 for methyl groups, a singlet at δ 3.90 for methoxy groups and aromatic protons at δ 6.70-7.53. Mass spectrum of the product showed a molecular ion peak of 386. This mass spectral data is consistent with the molecular formula $C_{22}H_{26}O_6$ and the NMR spectra further confirms the structure of a symmetrical compound where coupling of two phenylpropanoides has taken place at the β-carbon to give compound 10.

4. Mechanisms

Possible mechanistic explanation was sought for these electrolysis products by examining both the identified products formed and the electrochemical behaviour of the bases, solvents and electrolytes within the potential range of 0 to 2.5V as shown below.

$$2I^- \longrightarrow I_2 + 2e$$

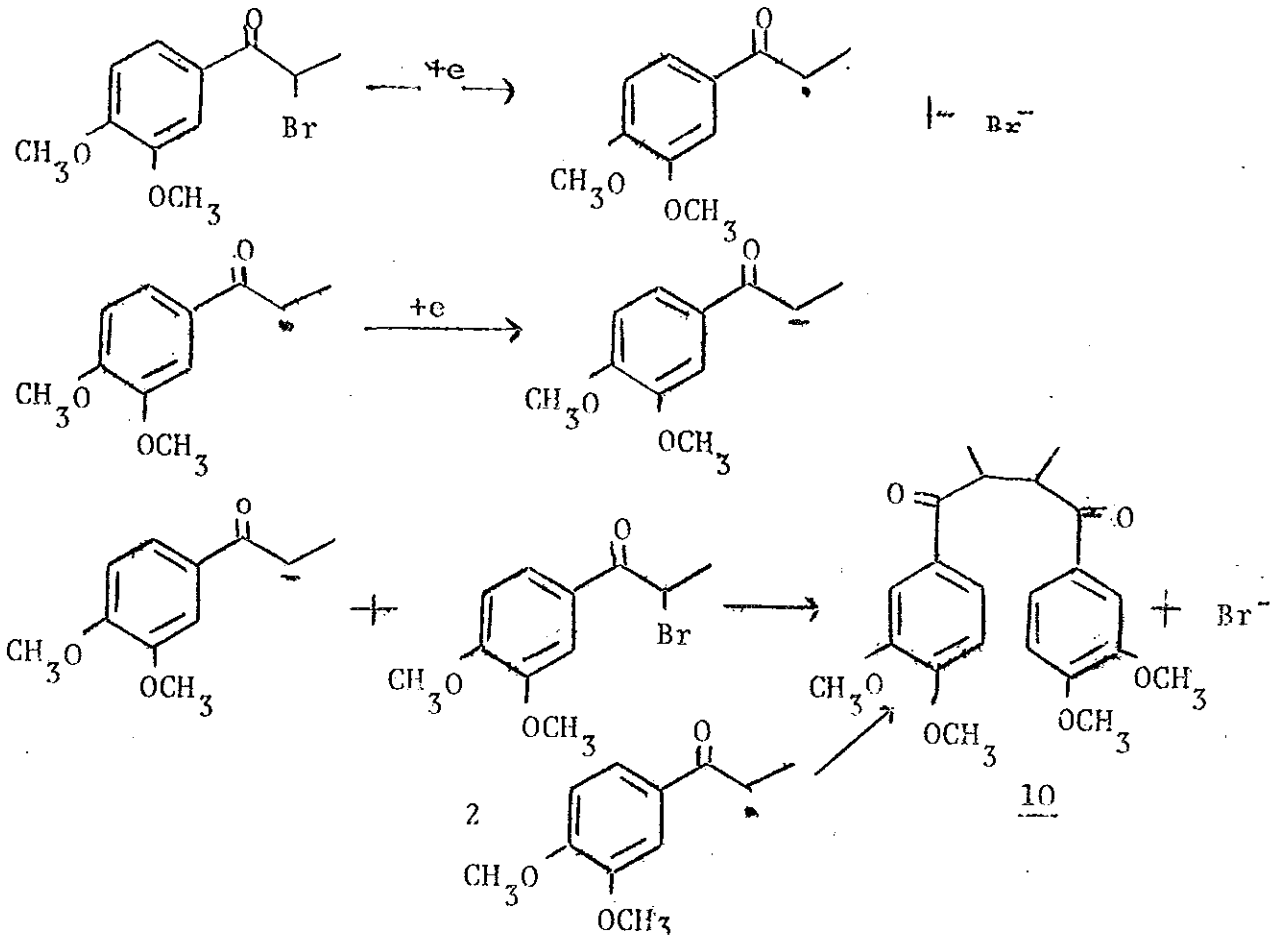




Treatment of propiophenone derivatives[8,9] with a base are known to give carbonions which could enolize and react with halides. The halo group alpha to the carbonyl could easily be displaced with a nucleophile to yield the corresponding α-methoxy ketone(20)[32].

Product 21 could arise as a result of reduction of the carbonyl group at the cathode due to the permeability of the fritted glass cell divider. A plausable mechanism that accounts for the formation of products 19 and 22b interms of electrochemical reaction is not suggested.

The possible mechanism for the formation of the coupled product 10, is given below:



Thus, as can be seen from the above mechanism the coupled product, 10, could arise by an electron transfer followed by a chemical reaction (ECE) process or by a radical-radical coupling reaction.

In this project, attempted synthesis of lignans by the anodic oxidation of the α-enolate derivatives

was not possible. However, some unexpected and yet useful natural product analogues were prepared. It has been discovered that α-hydroxy ketones of 19 type which were isolated from spruce wood lignin[33] could be prepared cleanly in high yield from the corresponding propiophenone derivatives by electrolysis (divided cell, Pt electrode) of the ketone in absolute methanol as a solvent, sodium methoxide as a base and potassium iodide as the supporting electrolyte. In general, it was found out that quite similar oxidation products were isolated and similar oxidation pathways could also be operative in all cases.

On the other hand, it was possible to obtain the coupled product, 10, which is one of the subclasses of lignans electrochemically from the α-bromo derivative. The yield of this reaction could be maximized by determining the optimum conditions for generation of the radical or carbanion intermediates by the proper choice of electrode material, reaction temperature, stirring rate and the working potential.

IV. E X P E R I M E N T A L

Melting points were determined on Thomas-Hoover capillary melting point apparatus. All melting points are uncorrected. Infra-red spectra were determined in nujol or in KBr pellets using Perkin-Elmer Model 727B spectrophotometer. Proton Magnetic Resonance spectra were recorded on a Varian Associates T-60A instrument with tetramethylsilane (TMS) as internal standard. The solvent was deutrochloroform unless otherwise specified. Chemical shifts are expressed in ppm relative to the TMS internal standards. Mass spectra were recorded on Finnigan 3200 GC/MS instrument.

Analytical thin layer chromatography (tlc) were run on 0.25 mm thick layer of silica gel GF_{254} (Merck), solvents used were CCl_4: Et_2O (5:1) unless otherwise specified. Spots were detected by their ultraviolet fluorescence. Preparative thin layer chromatography were run on 1.00 mm thick layer of silica gel $PF_{254+366}$ (Merck) and solvent systems were the same as indicated in tlc. Spots were detected by their ultraviolet fluroscence.

A 0-50V dc power supply (Cenco) was used. Standard calomel electrode was used as a reference electrode. Simple 0-10A and 0-500 mA ammeters were used to measure the current. Platinum, copper and mercury pool electrodes and fritted glass cell divider were also used for preparative electrolysis.

The instrument used for the cyclic voltammogram studies was a standard operational amplifier based potentiostat electroanalyzer model Mp-1502A (Philips) employing a three electrode configuration. The different working electrodes used for these studies were hanging mercury prepared by coating a commercial silver electrode with mercury and hanging on it mercury drops, platinum and glassy carbon. The auxilary electrode was a platinum wire while a Ag/AgCl/KCl (satd) aq. electrode was used as reference electrode. The voltammograms were recorded on PM 8041 x-y recorder (Philips) with a sweep rate of 4V/min.

D.C. polarographic studies were obtained using an E 505 - 506 Metrohm polarorecord. The potentials were refered to a Ag/AgCl/KCl (satd') aqueous electrode. A 1mM solution of compound in acetonitrite containing Bu_4NClO_4(0.1M) at r.t. was used.

Acetonitrile was purified by drying over calcium hydride (CaH_2) for several days followed by fractional distillation and stored over molecular sieve (4A).

Ether and tetrahydrofuran were purified by refluxing with $LiAlH_4$ for two days followed by fractional distillation for fresh use.

Drying of methanol was accomplished by distilling, after refluxing over magnesium with a small amount of iodine for two hours.

Supporting electrolytes used for the different electrolysis were commercial tetrabutyl ammonium perchlorate, sodium hydroxide, sodium methoxide (sodium in dry methanol) potassium iodide and sodium-perchlorate without recrystallization.

1. Preparation of Ethylmagnesiumiodide (Grignard Reagent)

8 g of magnesium turnings for Grignard synthesis was washed with dry ether and dried in an oven at 100-110°C and allowed to cool in a desicator. A solution of 35 ml of iodoethane in dry ether (100 ml) was poured in a pressure equalizing separatory funnel. 3-4 ml of the iodide solution was introduced in the flask which contained 8 g of magnesium and a crystal of iodine. It was warmed in a water bath to start the reaction. The ether refluxed when the reaction commenced. The water bath was removed and the etheral iodide solution was added dropwise with stirring. When the reaction became vigorous, the flask was cooled in an ice bath. The reaction was completed in about 2 hours.

2. Preparation of Ethylpiperonyl Carbinol (16b)

A solution of piperonal (30 g) in dry ether (75 ml) was added during 20 min to a solution of ethylmagnesium iodide (Grignard reagent) with stirring. The mixture was stirred for an additional 20 min. The stirred solution was treated with saturated ammonium chloride and the oily product was recovered from the ether layer by distillation under reduced pressure. The oily product

obtained was 34 g (87% yield). δ 0.83 (t, 3H(Me)), 1.63 (q, 2H($-CH_2-$)), 2.73 (s, 1H(OH)), 4.37 (t, 1H), 5.83 (s, 2H ($-OCH_2O-$)), 6.70-7.50(m,3ArH).

3. Preparation of Jones Reagent[34]

A solution was prepared from 27 g of chromium trioxide in 25 ml of conc. H_2SO_4 and was diluted to a volume of 100 ml with distilled water.

4. Preparation of 3,4-methylenedioxypropiophenone (17b)

30 g of the alcohol (17b) was dissolved in distilled acetone (100 ml) and poured in a 1-L three necked round bottomed flask fitted with a pressure equalizing separatory funnel, a therometer and mechanical stirrer. The stirred solution was cooled to 20°C in an ice bath and the chromic acid oxidizing solution (Jones reagent) was added from the separatory funnel slowly so that the temperature did not exceed 35°C. The addition was continued until the orange colour of the reagent persisted for sometime.

The mixture was filtered and the residual green salt was washed with 20 ml portions of acetone and the washings were added to the main acetone solution. The

filtrate was concentrated under vacuum and it was extracted with ether (3 x 50 ml). The ether extracts were combined and washed with saturated sodium bicarbonate solution (2 x 50 ml) and then with distilled water (3 x 50 ml). The ether extract was dried over anhydrous sodium sulfate, filtered and evaporated (under vacuum). The light brown semisolid product thus obtained was distilled at 137-140°C/20 mm of Hg to yield 24.0 g of a colourless oil which solidified upon standing, mp 38-39° (lit [45] 38-39°), δ 1.20 (t, 3H(Me)), 2.87 (q, 2H($-CH_2-$)), 5.93 (s, 2H($-OCH_2O-$)), 6.63-7.63 (m, 3ArH).

5. Preparation of 3,4-dimethoxypropiophenone (17a)

A solution of veratrole (20.0 g) in dry ether (120 ml) was added with stirring during 20 min. to a solution of ethylmagnesium iodide prepared from magnesium (8.0 g) and ethyliodide (35 ml) in ether (100 ml). The mixture was stirred (motor) for an additional 20 min. and worked up in the usual way to give 20.0 g (83%) of ethylveratrole carbinol (16a) which was subsequently dissolved in acetone (150 ml) and oxidized with excess Jones reagent. The dark brown oily product was distilled at 150°/35 mm of Hg to give the ketone as a white solid (16.0 g, 84% yield),

mp 57-58°C (lit[34] 58-59). δ 1.20 (t, 3H(Me)), 2.90 (q, 2H(-CH_2-)), 3.90(s, 6H(2 OMe), 6.70-7.50(m, 3ArH).

6. Preparation of α-bromo-3,4-dimethoxypropiophenone (18)

3.2 g of the ketone was dissolved in 20 ml of chloroform and a solution of bromine (2.5 g) in chloroform (10 ml) was added slowly with stirring at room temperature for 2 hrs. with stirring. It was washed with water and then with bicarbonate solution. The chloroform layer was dried with anhydrous calcium chloride. It was concentrated under reduced pressure and the brown semi-liquid residue was recrystallized from methanol (15 cc) to give 1.75 g (38% yield) of the α-brominated ketone, mp 85-87°. δ 1.83 (d, 3H(Me)), 3.83 (s, 6H(2OMe), 5.16 (q, 1H, (-CHBr), 6.80-7.60 (m, 3 ArH).

7. Electrolysis of 3,4-Methylenedioxypropiophenone in methanol

A solution of 17b (2.0 g) in dry methanol (100 ml) containing sodium hydroxide (4.0 g) and potassium iodide (2.0 g) as a base and supporting electrolyte respectively was deareated by bubbling with nitrogen for 10 min. and was electrolyzed (divided cell) with stirring at 1.05 V

vs SCE (r.t., 18 hrs.). The solution was quenched with an equal volume of water and extracted with ether (3 x 25 ml). The solvent was dried (Na_2SO_4) and evaporated under reduced pressure. The oily product (1.6 g) crystallized upon standing. It was recrystallized from low boiling petroleum ether to yield 1.4 g (70%) of white flakes, mp 81-82°C. δ 1.40 (d, 3H(Me)), 3.73 (d, 1H(OH)), 6.00 (s, 2H(-OCH_2O-), 6.70-7.53 (m, ArH); m/e 194(M^+); ν_{max}(KBr pellets) 3450 cm^{-1}, 1680 cm^{-1}.

8. Electrolysis of 3,4-Methylenedioxypropiophenone (17b) in Aqueous Methanol

A solution of 17b (2.0 g) in methanol (120 ml) containing sodium hydroxide (4.0 g) and potassium iodide (2.0 g) in water (40 ml) as a base and supporting electrolyte respectively was deareated by bubbling with nitrogen for 10 min. and electrolyzed (divided cell) with stirring at 2.5V vs SCE (r.t., 24 hrs.). Work-up was done as above and 2.0 g of oily product was obtained. Tlc showed four spots. Ptlc was done on 1.0 g of the oil yielding 500 mg of the starting material. Two major oxidation products were isolated from Ptlc:

Compound A

Yield 200 mg (20%), thick oil, δ 1.20 (d, 3H(Me)), 2.46 (s, broad peak(OH)), 3.83 (s, 3H(OMe)), 6.06 (s, 2H(-OCH_2O-), 6.70-7.70 (m, ArH); m/e 210(M^+); ν_{max}(film), 3450 cm^{-1}, 1050 cm^{-1}.

Compound B

Yield 150 mg (15%), thick oil, δ 1.07 (d, 3H(Me)), 1.53 (d, 1H), 3.23 (s, 3H(OMe)), 3.34 (s, 3H(OMe)), 4.16 (q, 1H), 6.00 (s, 2H(-OCH_2O-) 6.70-7.70 (m, ArH; m/e 224(M^+).

9. Electrolysis of 3,4-Methylenedioxypropiophenone (17b) in Aqueous Methanol

A solution of 17b (500 mg) in methanol (100 ml) containing sodium hydroxide (4.0 g) and potassium iodide (2.0 g) in water (40 ml) as a base and supporting electrolyte respectively was deareated by bubbling with nitrogen for 10 min. and was electrolyzed (divided cell) with stirring at 1.75V vs SCE (r.t., 16 hrs.). Work-up was done as usual. From Ptlc two major products were isolated.

Compound C

Yield 80 mg (16%), thick oil, δ 1.20 (d, 3H(Me)), 2.46 (s, broad peak (OH)), 3.83 (s, 3H(OMe)), 6.06 (s, 2H($-OCH_2O-$), 6.70-7.70 (m, ArH) m/e 210(M^+), ν_{max}(film), 3450 cm^{-1}, 1050 cm^{-1}. (This compound was found to be identical to compound A indicated previously).

Compound D

Yield 150 mg (30%), thick oil; δ 1.16 (d, 3H(Me)), 3.26 (s, 3H(OMe)), 5.90 (s, 2H($-OCH_2O-$), 6.68-7.49 (m, ArH); m/e 208(M^+).

10. Electrolysis of 3,4-Methylenedioxypropiophenone (17b) using Copper Electrode

Electrolysis of 17b (2.0 g) in methanol (100 ml) using sodium hydroxide (4.0 g) and potassium iodide (2.0 g) in water (40 ml) as a base and supporting electrolyte respectively was done at 1.5V vs SCE (r.t., 24 hrs.) with stirring. The electrode was oxidized at the end of electrolysis. Work-up was done as usual and two oxidation products and 400 mg of the starting material were isolated from Ptlc of 1.0 g of the compound.

Compound E

100 mg (10% yield), thick oil, δ 1.20 (d, 3H(Me)), 2.46 broad peak (s, 1H(OH), 3.83 (s, 3H(OMe)), 6.06 (s, 2H(-OCH_2O-), V_{max}(film), 3450cm^{-1}, 1030 cm^{-1}. (This compound was found to be identical with compound A).

Compound F

150 mg (15% yield), thick oil, δ 1.16 (d, 3H(Me)), 3.26 (s, 3H(OMe)), 5.92 (s, 2H(-OCH_2O-), 6.68-7.50 (m, ArH); m/e 208(M^+). (This compound was found to be identical with compound D).

11. Electrolysis of 3,4-Methylenedioxypropiophenone (17b)

A solution of 17b (2.0g) in THF (100 ml) containing 0.01 moles of potassium t-butoxide and Bu_4NClO_4 (1.0 g) as a base and supporting electrolyte respectively was electrolyzed (divided cell) with stirring at 1.2V vs SCE (r.t. 24 hrs.). Work-up was done in the usual way. Tlc showed the starting material with no oxidation product.

12. Electrolysis of 3,4-Dimethoxypropiophenone (17a)

A solution of 17a (2.0 g) in methanol (120 ml) containing sodium hydroxide (4.0 g) and potassium iodide

(2.0 g) was deareated by bubbling with nitrogen for 10 min. and was electrolyzed (divided cell) with stirring at 0.55V vs SCE (r.t., 24 hrs.). The work-up was done in the usual way. The oily product (1.8 g) thus obtained showed three spots on tlc. Ptlc on 500 mg of the sample gave 300 mg of the starting material and 150 mg of an oxidation product.

Compound G

Yield 150 mg (30%), thick oil, δ 1.16 (d, 3H(Me)), 3.26 (s, 3H(OMe), 3.86 (s, 6H(OMe)), 6.66-7.60 (m, ArH); m/e 224(M^+).

13. Electrolysis of 3,4-Dimethoxypropiophenone (17a)

A solution of 17a (500 mg) in 100 ml of methanol containing a solution of sodium methoxide (0.5 g of sodium in 60 ml methanol) was deaerated by bubbling with nitrogen for 10 min. and was electrolyzed (divided cell) with stirring at 1.5V vs SCE (r.t., 16 hrs.). Work-up was done in the usual way. One oxidation product (150 mg) was isolated from Ptlc with 200 mg of the starting material.

Compound H

Yield 150 mg (30%), thick oil δ 1.16 (d, 3H(Me)), 3.26 (s, 3H(OMe)), 3.86 (s, 6H(2OMe)), 6.66-7.60 (m, ArH); m/e 224(M^+).

14. Electrolysis of 3,4-Dimethoxypropiophenone using A Standard Potentiostat

A solution of 17a (500 mg) in acetonitrile (100 ml) containing sodiumperchlorate (1.0 g) as supporting electrolyte was deaerated by bubbling with nitrogen for 10 min. and was electrolyzed (divided cell) with stirring at 1.80V vs SCE (r.t., 5 days). During electrolysis the colour of the solution was changing and became brown on the third day. Cyclic voltammogram of the solution was taken daily and a decrease in current peak height($I_{p,a}$) was observed. Work-up was done in the usual way. The resulting oily product was filtered through a short column containing 50 g of silica using CCl_4 and ether gradient eluent. A dark-brown crystal (300 mg) mp > 230° with no aromatic proton (NMR) was recovered by eluting the column with methanol/ether (1:1). The other fractions were combined and Ptlc gave 100 mg of the starting material and three other oxidation products.

Compound I

Thick oil (10 mg), δ 1.20 (s), 6.33 (s), m/e 279(M^+), ν_{max}(neat), 2929 cm^{-1}, 1740 cm^{-1}, 1460 cm^{-1}.

Compound J

Thick oil (15 mg), δ 1.20 (s), 4.06 (d), 7.02-7.50 (ArH), m/e 391(M^+).

Compound K

Brown solid (15 mg), mp 126-130°, δ1.26 (s), 3.36 (s, broad), 7.1 (s), m/e 302(M^+).

15. Electrolysis of α-bromo-3,4-dimethoxypropiophenone (18)

A solution of 18 (200 mg) in acetonitrile (50 ml) containing Bu_4NClO_4 (250 mg) as supporting electrolyte was deaerated by bubbling with nitrogen for 10 min. and was electrolyzed (divided cell, Hg pool electrode) using a standard potentiostat employing a three electrode configuration at -1V (r.t., 3 days). Work-up was done in the usual way. From Ptlc 100 mg of the starting material was recovered with one major reduction product (60 mg)

Compound L

mp 133-135°C, δ 1.30-1.90 (m), 4.00 (s), 6.70-7.0 (ArH); m/e 374(M^+).

16. Electrolysis of α-bromo-3,4-dimethoxypropiophenone

A solution of 18 (500 mg) in acetonitrile (150 ml) containing Bu_4NClO_4 (1.0 gm) as supporting electrolyte was deaerated by bubbling with nitrogen for 10 min. and was electrolyzed (divided cell) with stirring at-1.7V (r.t., 5 days). Work-up was done as usual yielding 450 mg of thick oil. Tlc showed three spots which were separated by Ptlc to give 300 mg of the starting material and a reduction product (50 mg).

Compound M·

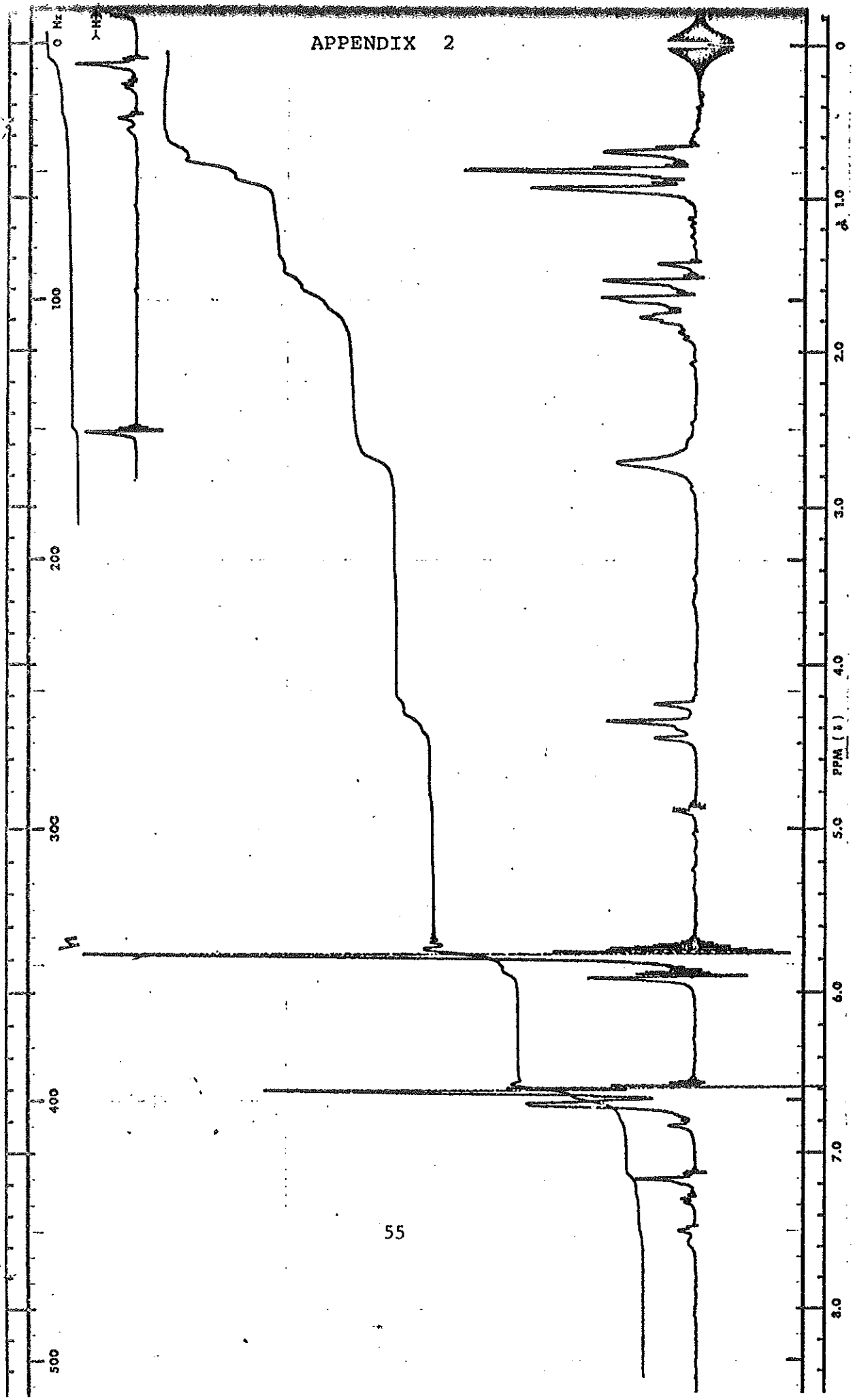
Thick oil which showed white floating crystals in methanol. δ 1.43 (d, 6H(2 Me), 3.90 (s, 12H(4(OMe)), 6.70-7.50 (m, ArH); m/e 386(M^+).

APPENDIX 1

Electrode potentials regions of some functional groups [24,28,30]

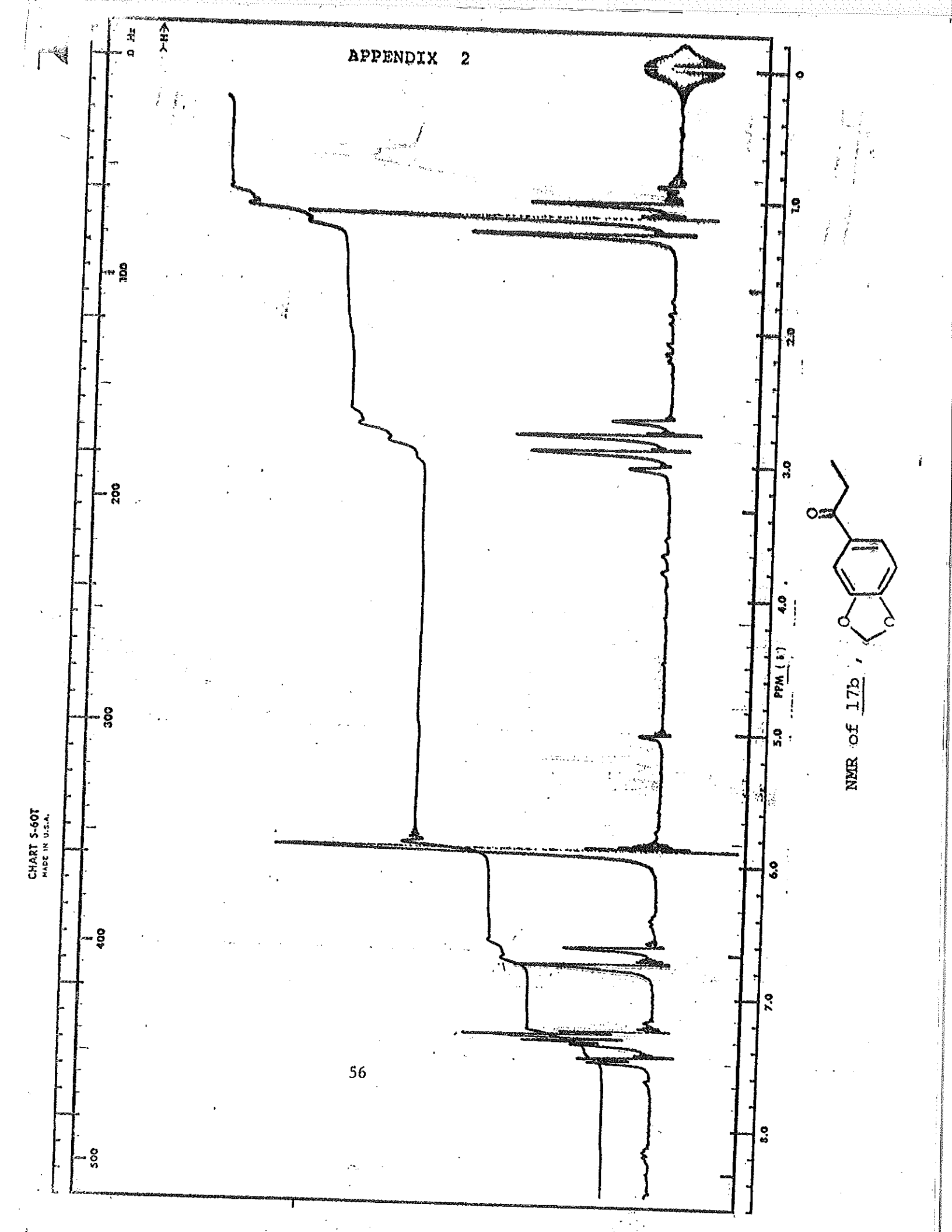
Functional group	Volts
RCO_2^-	2.2
Benzene	2.08
Alcohols	> 2.5
Allyl alcohol	>2.0
Amides	2.0
Ar-x	1.9
Allyl bromide	-1.29
Acetophenone	-1.99
Monobromide	+ 2.2
Activated olefins	-2.3

APPENDIX 2



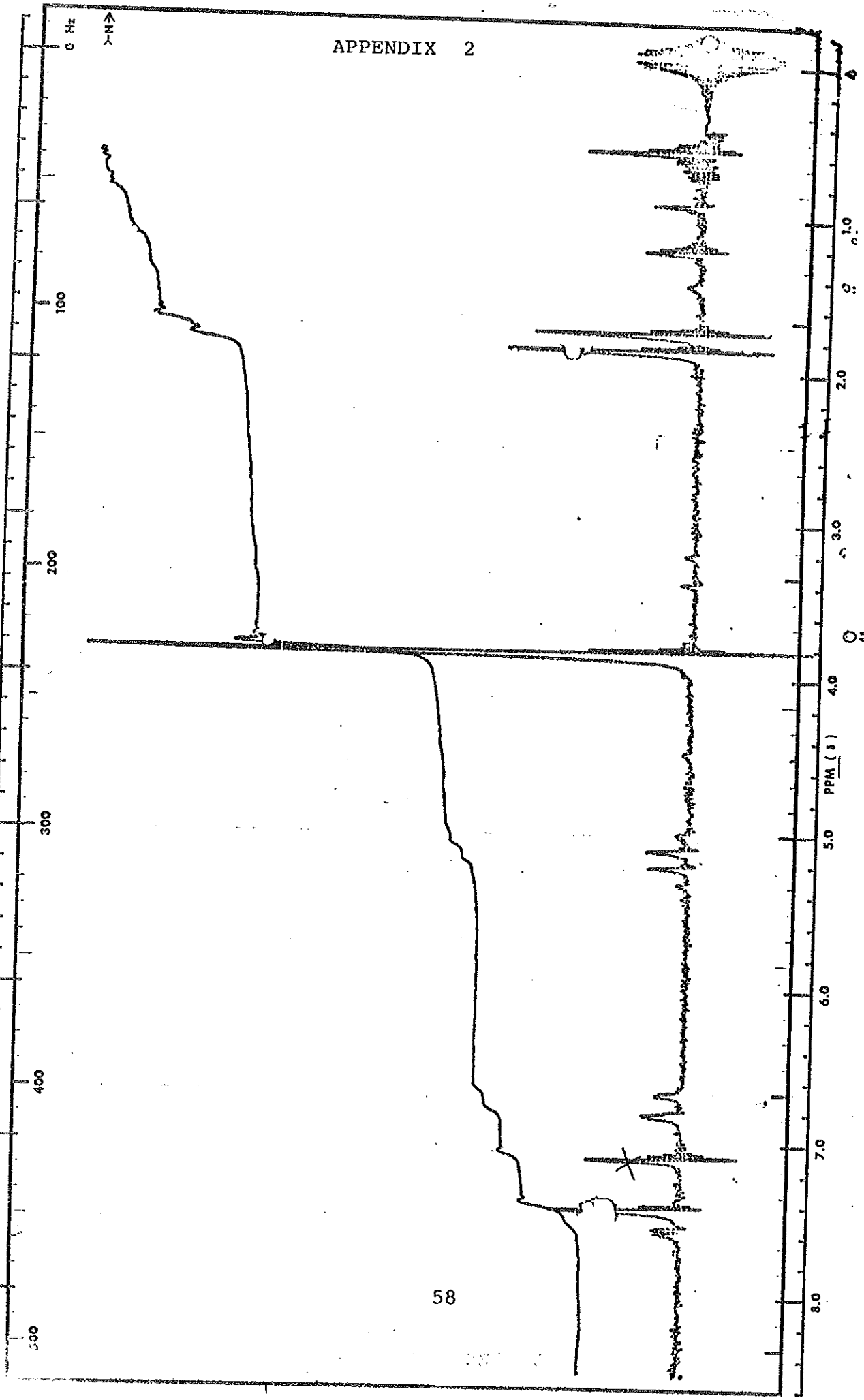
NMR of 16b,

APPENDIX 2

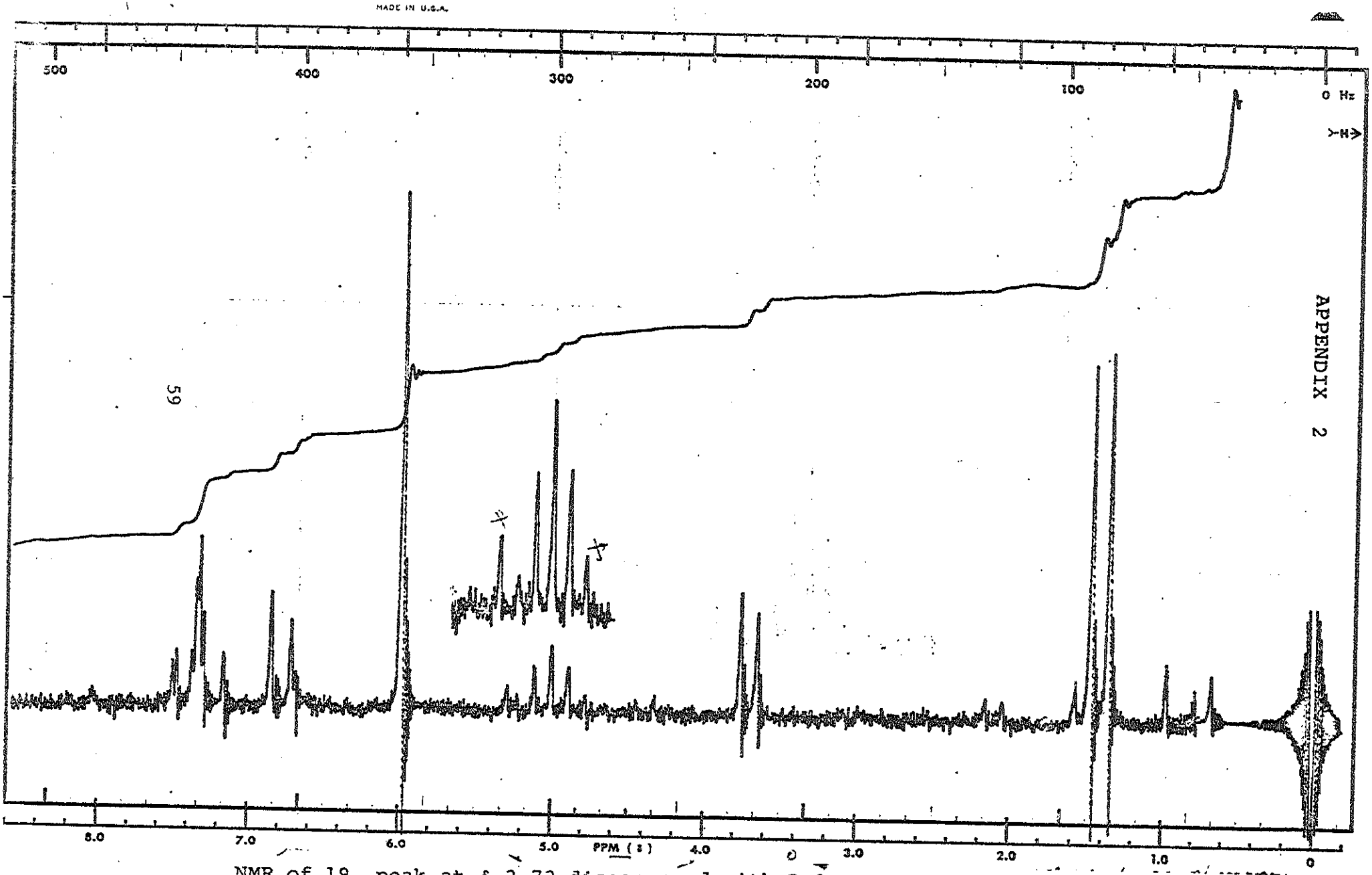


NMR of 17b ,

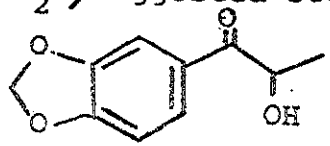
APPENDIX 2

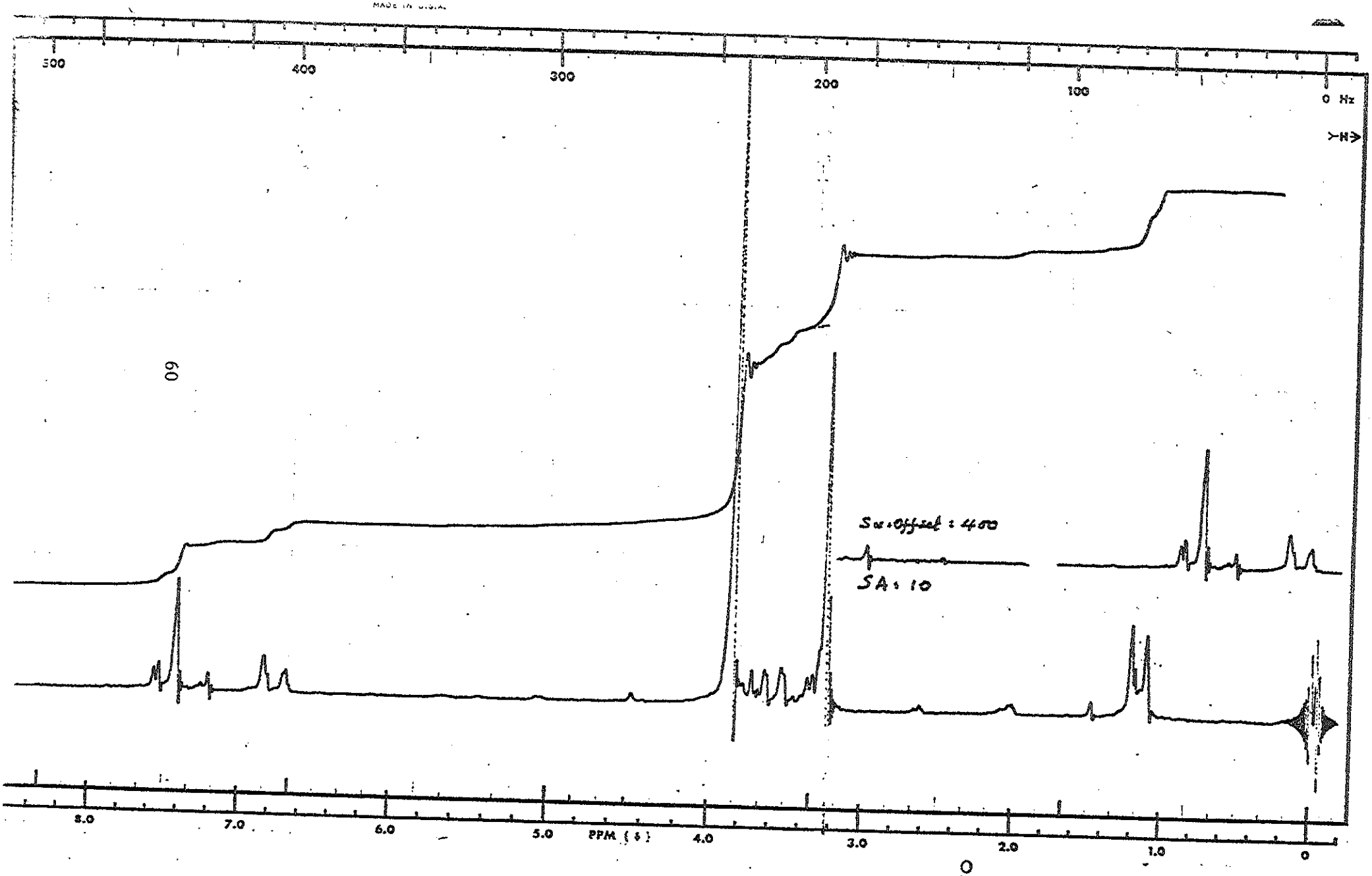


NMR of 18,

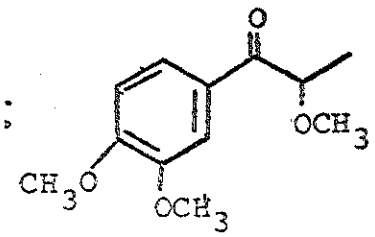


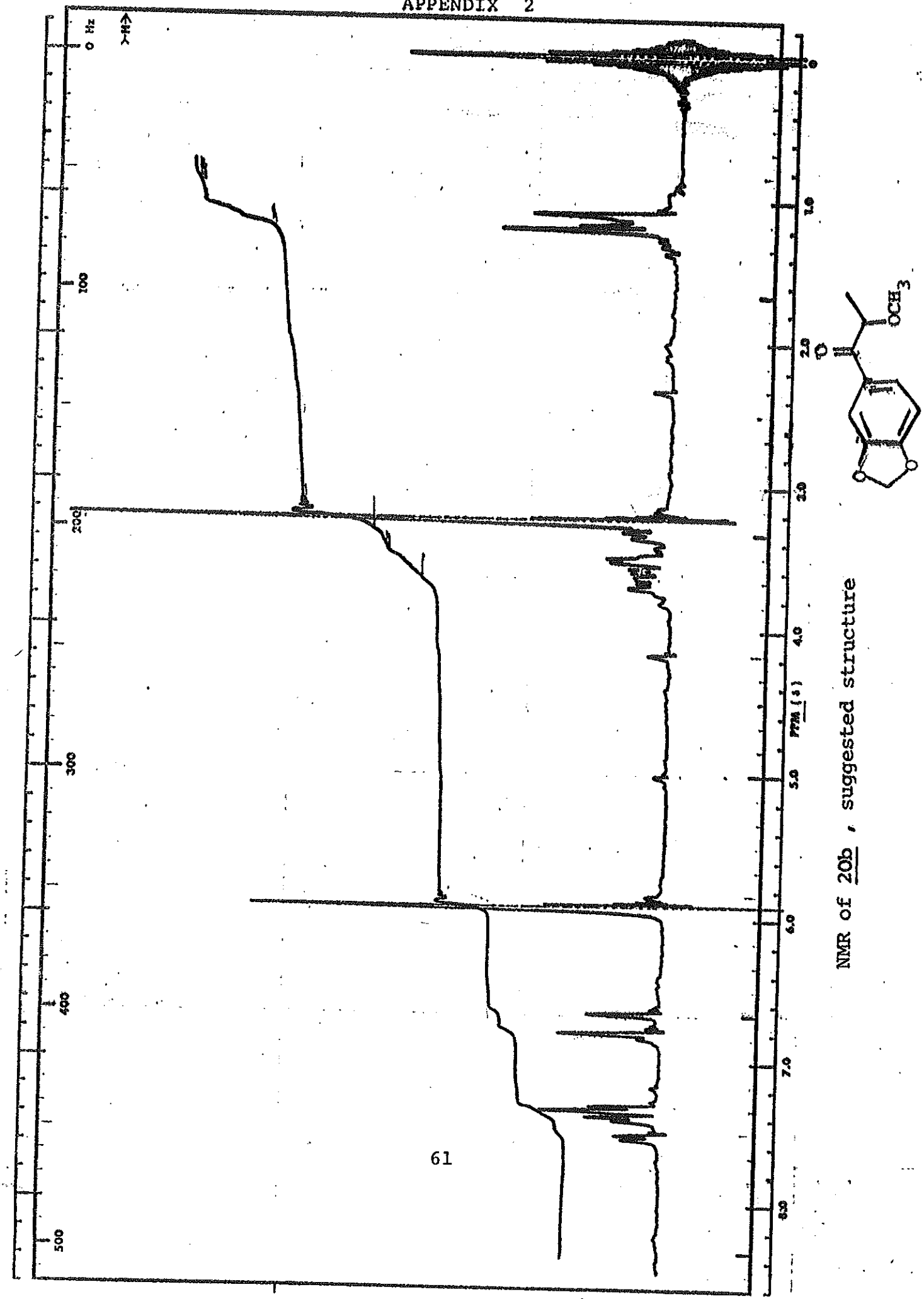
NMR of 19, peak at δ 3.73 dissapeared with D_2O, suggested sturucture



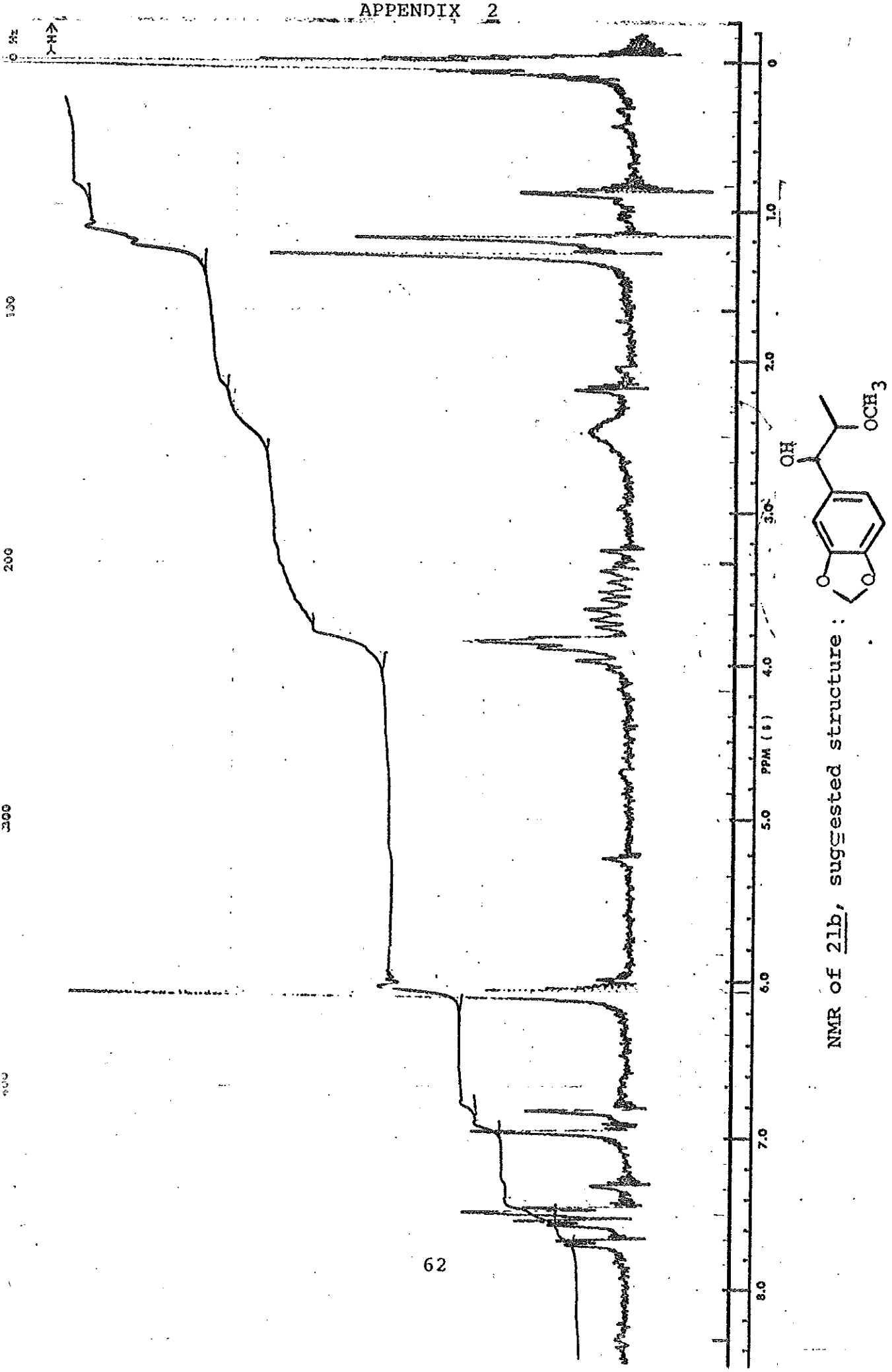


NMR of 20a, suggested structure;

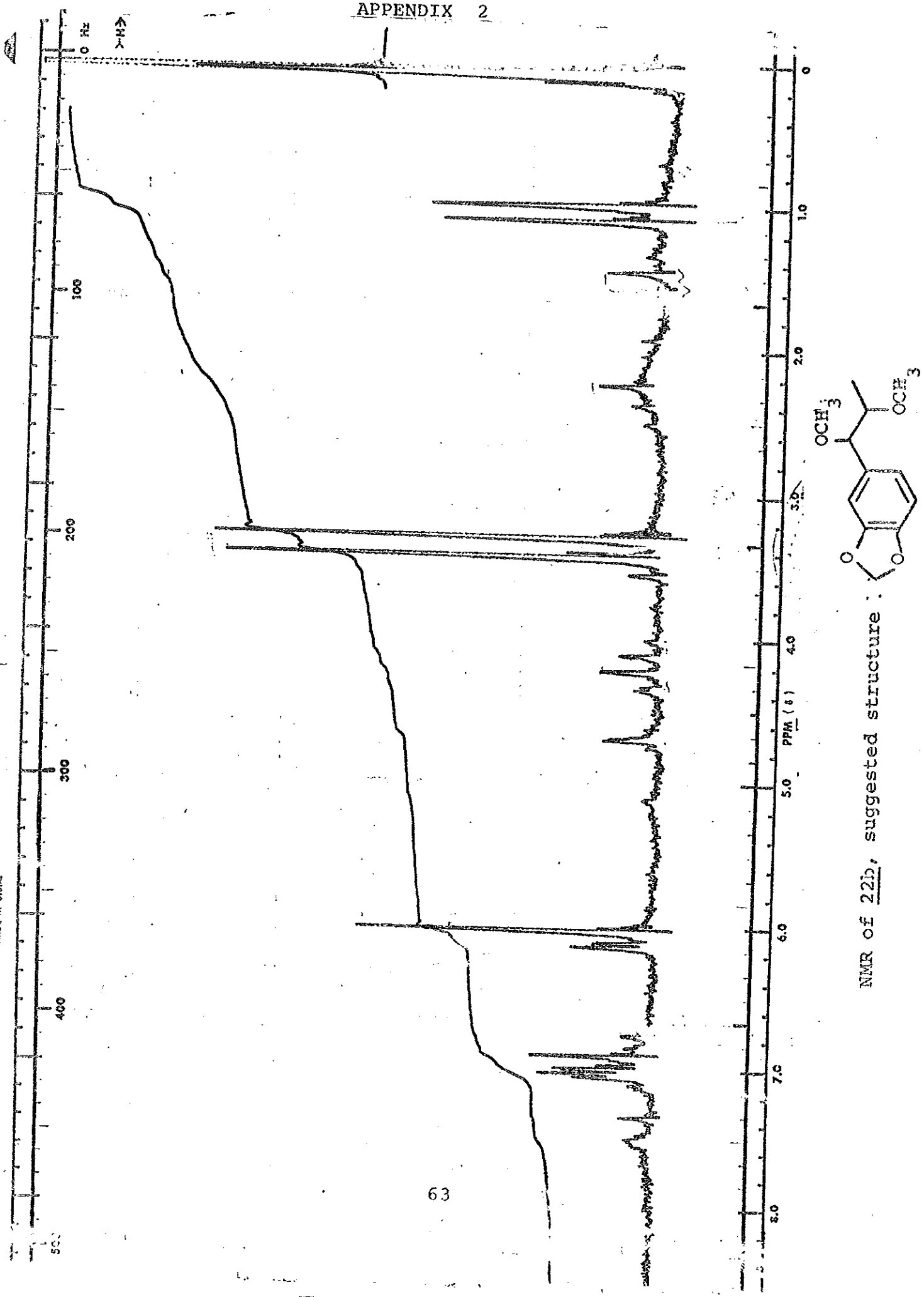




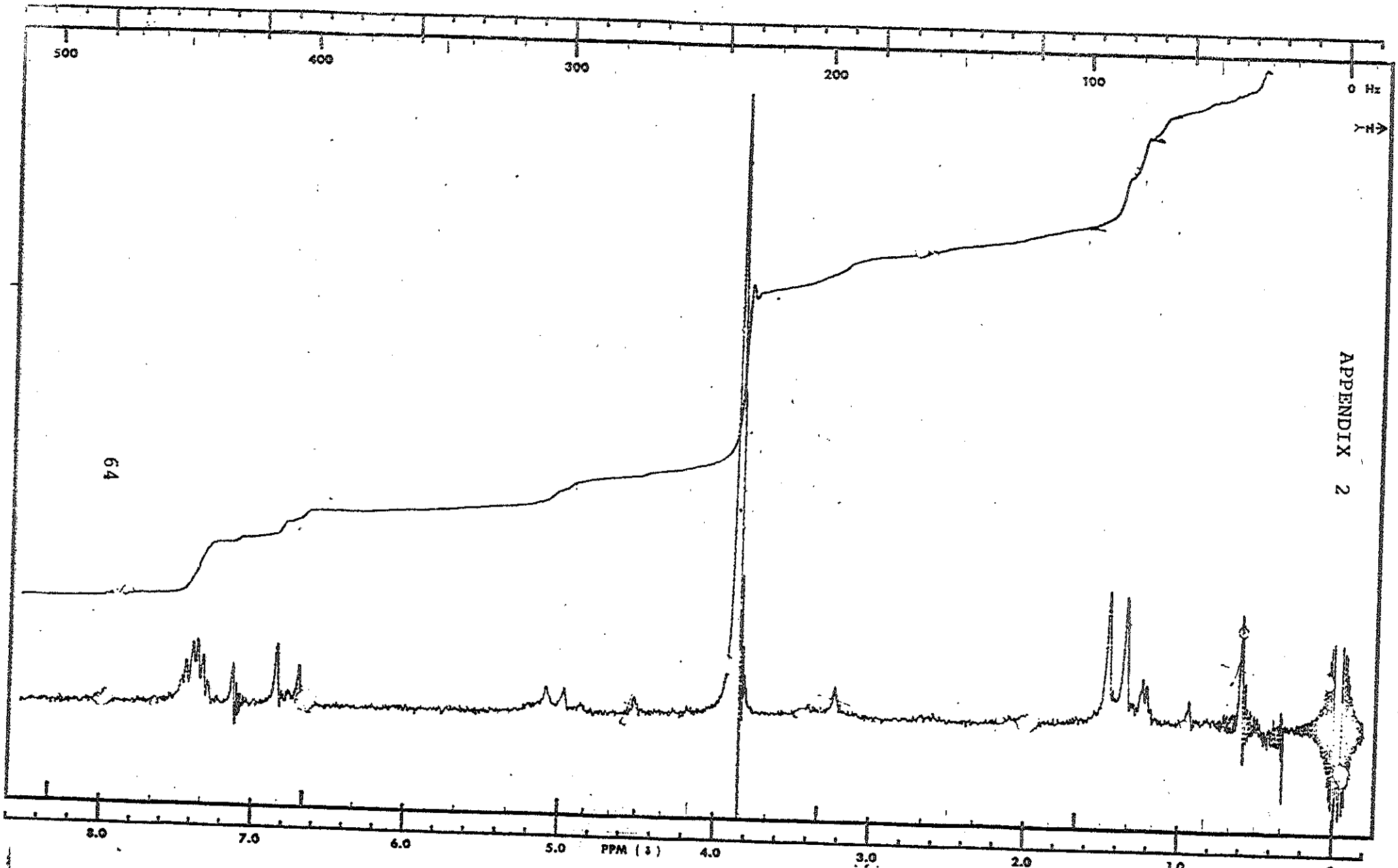
NMR of 20b , suggested structure



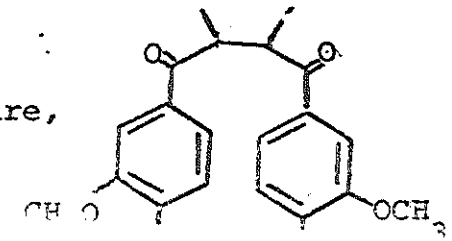
NMR of 21b, suggested structure :



NMR of 22b, suggested structure :



NMR of 10, suggested structure,



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