NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY. THE "ASYMMETRY EFFECT" AND ITS CONTRIBUTION TO MAGNETIC NONEQUIVALENCE

by

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THESIS

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ABSTRACT

Nuclear magnetic resonance spectroscopy. The "asymmetry effect" and its contribution to magnetic nonequivalence

D.R. Clarke

This thesis describes the syntheses of representative compounds of the series $ACH_2C{\equiv}CCXYZ$ and $4\text{-}XC_6H_4(4'\text{-}YC_6H_4)C_6H_5CCH_2R$ and discusses their ^1H nuclear magnetic resonance spectra. Contrary to expectation the protons of the methylene group in such compounds were found to be magnetically equivalent in a chemical shift sense. These results strongly suggest that if an asymmetry effect exists as a contributor to magnetic nonequivalence it must be extremely weak.

ACKNOWLEDGEMENTS

I wish to express my gratitude to Dr. T.J. Adley for his constant guidance and encouragement throughout the course of this work. I am pleased to acknowledge the financial support of the National Research Council of Canada and I am also indebted to Dr. R.T.B. Rye for CHN analyses.

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INTRODUCTION AND THEORY

In general the two criteria which can be conveniently applied to differentiate between magnetically differing nuclei are the chemical shift difference between the nuclei and the coupling constants of these nuclei with a third nucleus. In order to exhibit the chemical shift difference between the nuclei two conditions must be met:

(a) Atoms or groups which may exhibit nonequivalence cannot be related by any symmetry operation taking into consideration internal motions that are rapid compared to the time scale of a ^1H nuclear magnetic resonance (n.m.r.) experiment.

(b) There must exist a sufficient field gradient so that the non-equivalent atoms or groups of atoms exhibit chemical shifts resolvable on the instrument employed (1). In other words if the (average) environments are insufficiently dissimilar then magnetic equivalence will be observed. The effect satisfying this condition appears to be transmitted mainly through space (2).

When the protons of a methylene group are separated by one or more bonds from a centre of molecular asymmetry[1] they are frequently found to be magnetically nonequivalent. An AB-type n.m.r. spectrum is observed which may be further complicated by spin-spin coupling of the methylene group with protons attached to adjacent carbon atoms (3).

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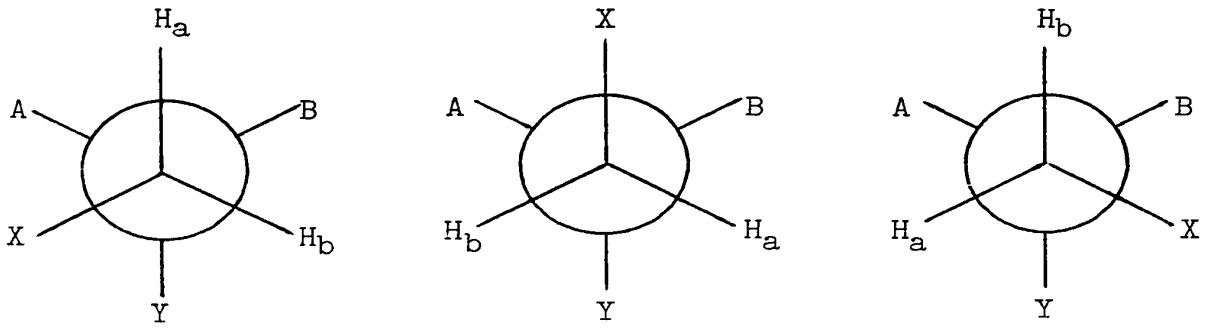
[1]The number of bonds between the interacting sites is in itself not significant. The interacting groups may be quite far apart and may be separated by atoms other than carbon. Nonequivalence of geminal nuclei can always be expected if there is present somewhere in the molecule a carbon atom with three different substituents (2).

It has been recognized for some time that rotational conformer preferences of the methylene group with respect to the adjacent asymmetric centre constitute an important factor responsible for magnetic non-equivalence in such molecules (4,5). However a number of workers have observed that the "intrinsic asymmetry" (3) of the protons of the methylene group, independent of conformer populations, presents a sufficient theoretical framework for nonequivalence to be observed (6-9). Consider a compound with three distinguishable rotational forms (1-3, Figure 1) of the general formula $ABYCCH_aH_bX$ in which energy barriers to rotation are sufficiently small at ordinary temperatures to permit free rotation. The eclipsed forms correspond to potential energy maxima and may be ignored (10).



(1) (2) (3)

Figure 1

In Figure 1, the environment of H_a in 1 is such that it is opposite to Y and has A and X to one side and B and H_b to the other. In 3, H_b is opposite to Y and has A and H_a to one side and B and X to the other. Since magnetic anisotropy in bonds can cause significant differences in magnetic shielding (2) and H_a does not have exactly the same environment in any of the conformers (1-3), the average environments

of H_a and H_b can never be exactly identical even if H_a and H_b spend equal times in each of the three possible conformations and a chemical shift can therefore be expected (i.e., the intrinsic asymmetry of the system ensures that H_a and H_b will be nonequivalent).

Magnetic nonequivalence has been ascribed to two factors: (a) differing conformer populations and (b) intrinsic asymmetry. The relative importance of these two effects as contributors to magnetic nonequivalence has been the subject of much investigation, although uncertainty on this subject still persists. One of the earliest observations of magnetic nonequivalence was the 30 MHz. room temperature ^{19}F spectrum of $CF_2BrCHBrC_6H_5$ (1) by Drysdale and Phillips (12). The fluorine atoms of 1 are magnetically nonequivalent on two counts; the coupling constant of each fluorine atom with the neighbouring hydrogen is different, and a chemical shift difference exists between the magnetically differing fluorine nuclei (2). Drysdale and Phillips interpreted the results as an indication that there is restricted rotation about the central C - C linkage in this substituted ethane. However Roberts and Nair (4) studied the fluorine spectrum of $CF_2BrCBrCl_2$ (2) and observed a single sharp line arising from equivalent geminal fluorines down to -30°, indicating that there is rapid rotation at room temperature about the central C - C bond in 2 and, by inference, in 1.

The solution to the apparent paradox is that in compounds like 1 (Figure 2) the geminal group does not have equivalent atoms in any of the conformers 1, 2 or 3; even if F_a and F_b spent equal times in each of the three possible conformations, their average environments can never be exactly identical and a chemical shift can therefore be expected.

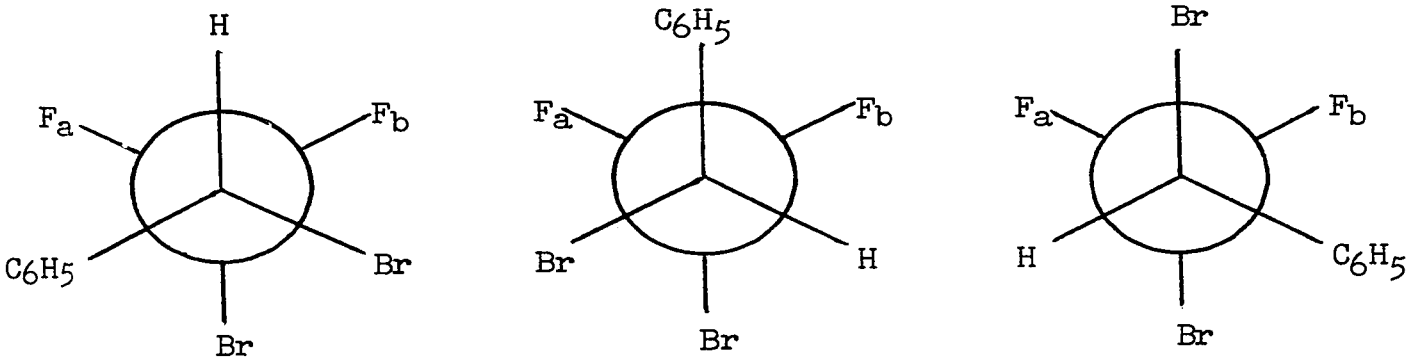


Figure 2

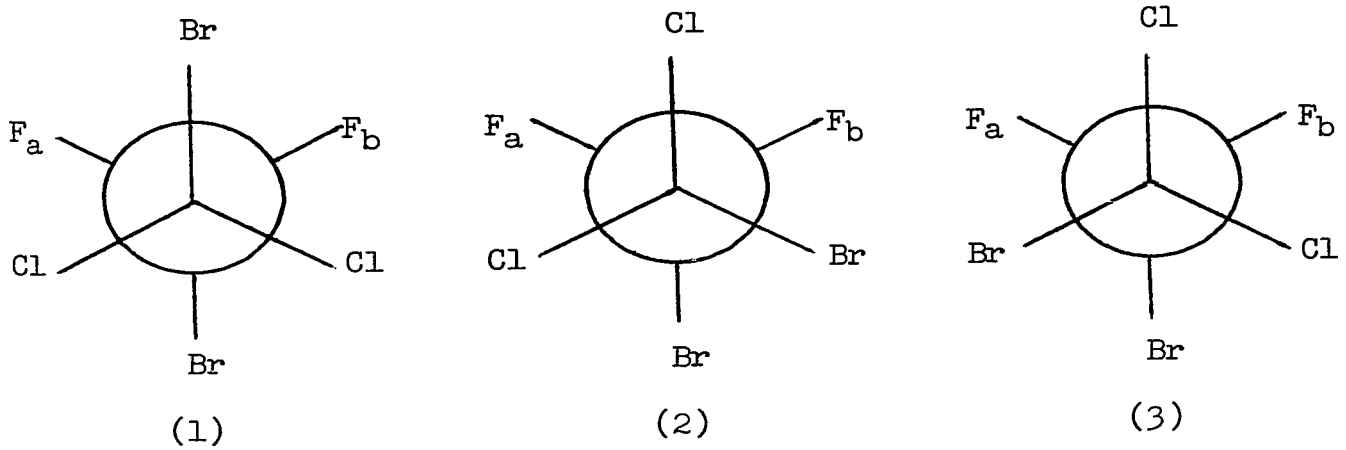


Figure 3

Compound 2 (Figure 3) of the type $CF_aF_bXCA_2B$ is more symmetrical than 1. There is the optically inactive meso form (conformer 1), in which X and B are trans, and the dl pair (conformers 2 and 3) in which X and B are gauche. The rotationally averaged fluorine shifts in 2 are given by (9):

$$\langle \nu_{F(a)} \rangle = \sum_n M_n \nu_n^a \quad \text{and} \quad \langle \nu_{F(b)} \rangle = \sum_n M_n \nu_n^b \qquad [1]$$

where M_n is the mole fraction of the rotamer n, and ν_n^i refers to the resonance frequency or chemical shift of the i^{th} nucleus in rotamer n.

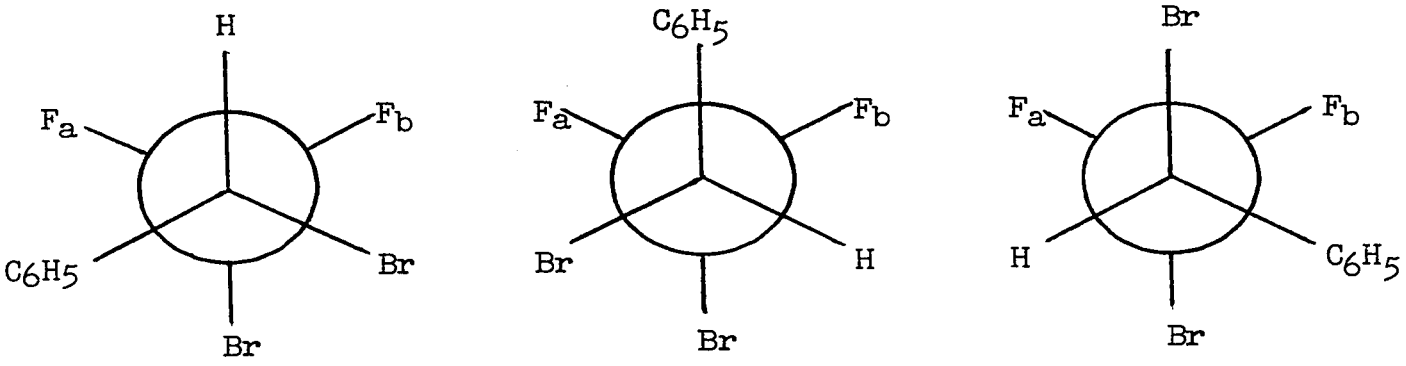
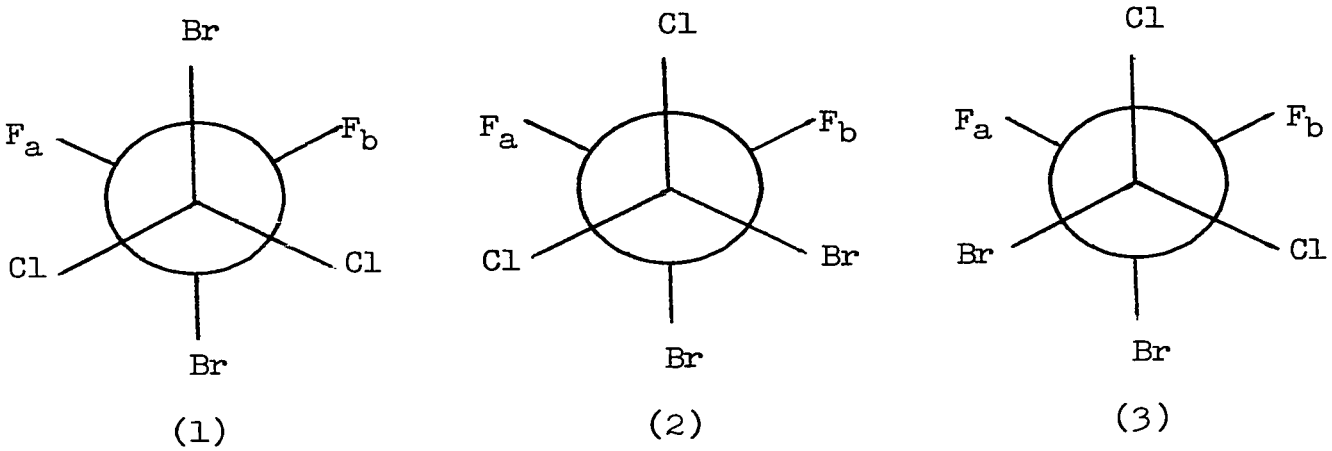


Figure 2



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where M_n is the mole fraction of the rotamer n, and $\nu_n{}^i$ refers to the resonance frequency or chemical shift of the i^{th} nucleus in rotamer n.

Therefore in compound 2:

$$\langle \nu_{F(a)} \rangle = M_1 \nu_1^{a} + M_d \nu_d^{a} + M_m \nu_m^{a} \qquad [2]$$

and $$\langle \nu_{F(b)} \rangle = M_1 \nu_1^{b} + M_d \nu_d^{b} + M_m \nu_m^{b} \qquad [3]$$

Since conformers 2 and 3 exist as a dl pair the residence times (and populations) for the two conformations with nonequivalent fluorines must be equal.

$$M_1 = M_d \quad \text{also} \quad \nu_d^{a} = \nu_1^{b} \quad \text{and} \quad \nu_1^{a} = \nu_d^{b}$$

Also conformer 1 may have a very different residence time from that of 2 or 3, but it has equivalent fluorines, therefore

$$\nu_m^{a} = \nu_m^{b}$$

Substitution of these relations in equation [3] leads to identical averaged fluorine shifts

$$\langle \nu_{F(a)} \rangle = \langle \nu_{F(b)} \rangle = M_1 \nu_1^{a} + M_d \nu_d^{a} + M_m \nu_m^{a}$$

Therefore down to -30° only a single sharp line will be observed in the n.m.r. spectrum of 2.

An example of magnetic nonequivalence of the methylene hydrogens was reported by Finegold (13) when he investigated the n.m.r. spectrum of diethyl sulphite (3). Instead of observing simple first order splitting of a 1:3:3:1 quartet for the methylene protons arising from coupling with the adjacent methyl groups, he observed two such quartets. One quartet was slightly displaced from the other showing somewhat different coupling constants with the adjacent methyl groups. Waugh and Cotton (6) observed that the two methylene protons of the same methylene group are not

stereochemically equivalent, because of the lack of symmetry of the tetrahedral sulphur atom. This presupposes that the barrier to rotation about the S-O bond is sufficiently high for nonequivalence to exist. Waugh and Cotton explicitly indicate that a symmetry argument alone completely independent of any facets of conformational isomerism could equally well account for such nonequivalence.

Since the prevalent theory indicates that magnetic nonequivalence may be largely ascribed to conformer population differences (3), the most favourable conformation for 3 might be as depicted in Figure 4. This would give rise to four methylene protons in differing environments which are further split into overlapping quartets by the adjacent methyl groups. When a time average is performed over all possible staggered and eclipsed conformers the nonequivalence still persists.

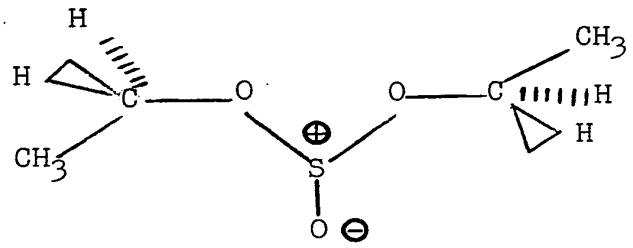

Figure 4

Waugh and Cotton (6) substantiated their conclusion for 3 based on a symmetry argument by investigating the n.m.r spectrum of $C_6H_5S(O)\text{-}OCH_2CH_3$ (4). This compound differs from 3 only in the replacement of one of the ethoxy groups with a phenyl group. Magnetic nonequivalence attributable to magnetically differing protons of the methylene group of 4 is shown in Figure 5.

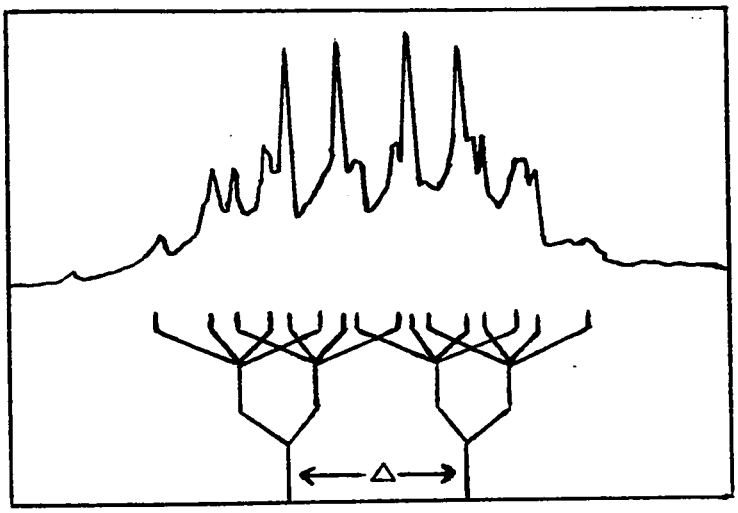

Figure 5

From J.S. Waugh and F.A. Cotton.

J. Phys. Chem. 65, 562(1961)

There exists a chemical shift difference between the nonequivalent methylene protons of 0.434 p.p.m., and geminal spin-spin coupling ($|J|$= 10 Hz.). Each methylene proton is also coupled, to almost exactly the same extent, with the methyl protons (J = 7.1 Hz.). The results were analogous to those obtained for 3 leading to similar conclusions.

It is significant that in the n.m.r. spectrum of diethoxy methane (5), the methylene protons exist as a simple quartet (6). This is in accord with the arguments presented, since 5 possesses too much symmetry to allow nonequivalence of the protons in the same methylene group to be observed.

It is known that in systems of the type ACX_2B, ACX_2OB and ACX_2SB, where A is an atom or group of atoms and B is a group which lacks a plane of symmetry, the X nuclei are sometimes magnetically nonequivalent (7).

Compounds of this type in which nonequivalence has been observed include the methylene hydrogens in the ethyl group of ethers (14), sulphites (13), sulphoxides (6, 15), diethyl sulphide-borane (15) and diethylmethyl ammonium iodide (15). Other compounds of this type in which the X nuclei are non-equivalent are the methylene hydrogens in various 1,1,1,2-tetra-substituted ethanes (14, 16), in the difluoromethylene group of appropriately substituted ethanes (4, 12, 14, 17) and for the methyls of various systems containing an isopropyl skeleton (18).

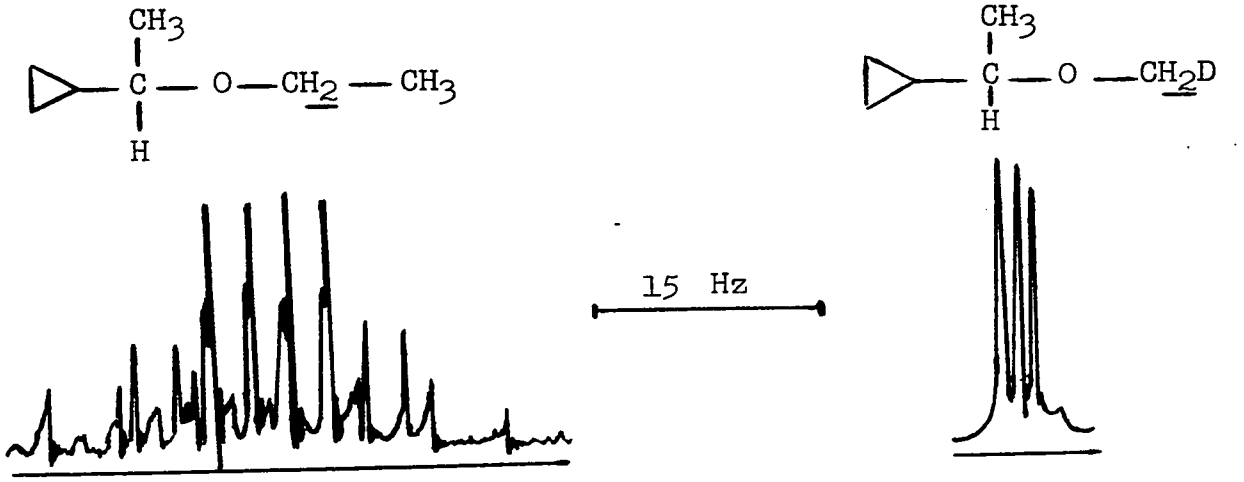

Figure 6

Nuclear magnetic resonance spectra of the methylene protons of cyclopropylmethylcarbinyl ethyl ether (6) and cyclopropylmethylcarbinyl methyl-d_1 ether (7) at 60 MHz.

From G.M. Whitesides, F. Kaplan, K. Nagarajan and J.D. Roberts. Proc. Natl. Acad. Sci. U.S. 48, 1112 (1962).

In 1962 Roberts and co-workers (3) studied the ^1H n.m.r. spectra of the $O-CH_2$ protons of cyclopropylmethylcarbinyl ethyl ether (6) and cyclopropylmethylcarbinyl methyl-d_1 ether (7) (Figure 6). Magnetic nonequivalence of the methylene group of 6 is observed, giving rise to an AB type spectrum which is further complicated by spin-spin coupling with the adjacent methyl group. It is to be noted that the group in question is removed from a centre of molecular asymmetry by two bonds. Substitution of a deuterium atom for the methyl moiety in 6 to give 7 will not give rise to any conformational preference of the methylene protons with respect to the asymmetric centre if the reasonable assumption is made that there are small differences between deuterium and hydrogen.[2] If a difference in chemical shift is observed for the methylene protons of 7 it should arise solely from an intrinsic asymmetry effect. The n.m.r. spectrum of 7 shown in Figure 6 clearly indicates, after account is taken of coupling between the protons and deuterium, that the methylene resonance is A_2. Roberts and co-workers have interpreted both the lack of nonequivalence in 7 versus the observed nonequivalence in the ethyl analog as strongly suggesting that conformational preference is the factor responsible for the magnetic nonequivalence of the methylene protons of 6.

Gutowsky (9) failed to agree with the interpretation of Roberts and co-workers (3). He derived mathematical definitions for three distinct contributions to magnetic nonequivalence of nuclei in asymmetric molecules

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2"There is a very small isotope effect in the proton chemical shift of a CH_2D group versus a CH_3 group. It is due apparently to differences in vibrational amplitudes of C - D compared with C - H" (9).

in which an asymmetry effect is separated from two other terms, which involve differences in conformational populations. Gutowsky claimed that the asymmetry effect will make nuclei magnetically nonequivalent even though conformational populations are equal. He also cited the cases of compounds analogous to 2, as examples where conformer population differences do not lead to nonequivalence unless molecular asymmetry is high enough.

Consider the proton spectrum of a compound with three distinguishable rotational forms (1-3, Figure 1) each existing as a dl pair of general formula ABYCCH$_a$H$_b$X in which the CH$_2$-X group is in an asymmetric environment.

Rotationally averaged proton shifts $<\nu_H>$ are given by equation [4] i.e.,

$$<\nu_{H(a)}> = \sum_n M_n \nu_n^a \text{ and } <\nu_{H(b)}> = \sum_n M_n \nu_n^b \qquad [4]$$

If X = H, then the three rotamers and their population are identical and the compound is a single dl pair. Furthermore, because of the symmetry of the methyl group $\nu_1^a = \nu_3^b$, $\nu_2^a = \nu_1^b$ and $\nu_3^a = \nu_2^b$

Therefore one finds that

$$<\nu_{H(a)}> = <\nu_{H(b)}> = \Sigma\ 1/3\nu_n^a = \Sigma\ 1/3\nu_n^b \text{ and } <\nu_{H(a)} - \nu_{H(b)}> = 0 \qquad [5]$$

which means that all the protons are magnetically equivalent. However this fact tells us nothing about the relative values of the proton shifts ν_1^i, ν_2^i and ν_3^i which reflect the intrinsic asymmetry of the three nonequivalent sites. This asymmetry is present, even though the methyl group taken alone is symmetrical, but it is not observable in the high resolution proton spectrum unless the three distinguishable rotational forms can be frozen out.

If X ≠ H, the increased molecular asymmetry due to X converts the system from one dl pair to three. In general the presence of X causes the energies and populations of these three rotameric pairs to differ and it will change all six proton shifts ν_n^a and ν_n^b. This leads to a net chemical shift between the H_a and H_b protons of

$$<\Delta\nu_H> = <\nu_{H(a)} - \nu_{H(b)}> = \sum_n M_n(\nu_n^a - \nu_n^b) \quad [6]^3$$

which can be written more accurately as

$$<\Delta\nu_H> = \sum_n M_n(\Delta\nu_n^\circ + \delta\nu_n) \quad [7]$$

In equation [7] $\Delta\nu_n^\circ$ is defined as $(\nu_n^a - \nu_n^b)$ for the parent compound, with X = H, and $\delta\nu_n$ as the change in $\Delta\nu_n^\circ$ caused by the substitution of X for H (9). Rearrangement of equation[7]and introduction of the fact that $\sum_n 1/3\Delta\nu_n^\circ = 0$ gives the following terms:

$$<\Delta\nu_H> = \sum_n M_n\Delta\nu_n^\circ - \sum_n 1/3\ \Delta\nu_n^\circ + \sum_n M_n\delta\nu_n - \sum_n 1/3\ \delta\nu_n + \sum_n 1/3\ \delta\nu_n \quad [8]$$

Combining these terms we have:

$$<\Delta\nu_H> = \sum_n (M_n - 1/3)\Delta\nu_n^\circ + \sum_n (M_n - 1/3)\delta\nu_n + \sum_n 1/3\ \delta\nu_n \quad [9]$$

"The first term depends upon the shifts caused by the initial asymmetry of the parent compound when (X = H) and the population differences

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[3]Equation [6] accounts for conformational differences but does not account for changes in ν_n^a and ν_n^b when X is substituted for H <u>i.e.</u>, the additional asymmetry effect. Therefore the term $\delta\nu_n$ has to be added to equation [6]to describe the system fully.

introduced by having X ≠ H; the second term depends upon both the population differences and the shift changes $\delta\nu_n$ introduced by having X ≠ H; and the last term is the asymmetry effect, the net shift which would result from the shift changes produced by X if the rotamer populations were nonetheless equal" (9).

As previously indicated Roberts and co-workers (3) have interpreted the magnetic equivalence found for 7 as strongly suggesting that conformational preference is the factor responsible for the approximate 8 Hz. shift $<\nu_H>$ found between the methylene protons in 6. If however equation[9]is considered, in order for $(\Delta\nu_H)$ to be zero for the methylene protons of 7, substitution of D for H must not produce any asymmetry effect i.e., $\sum_n 1/3\delta\nu_n = 0$, and the populations of the three conformers must remain equal, which is not unexpected in view of the small differences between D and H. If deuterium substitution was more likely to cause a difference in chemical shift, arising from an asymmetry effect, greater than a shift because of conformational preferences, then the absence of any observable shift for the methylene protons would be evidence against the existence of the asymmetry effect. This requires however, that the asymmetry effect be more important than conformational preference effects. All accumulated evidence suggests that the asymmetry effect has the lesser significance (8,9). From these observations, Gutowsky (9) concluded that not only does the observed equivalence of the methylene protons of 7 tell us absolutely nothing about the relative importance of conformational preference and intrinsic asymmetry in 7, but also it has no bearing upon the nonequivalence found for the methylene protons in 6.

The intrinsic asymmetry effect is generally assumed to be temperature

independent (2), whereas the effect of differences in conformer population is temperature dependent. As the temperature is increased the chemical shift differences should approach a limiting value which may not be zero owing to the intrinsic asymmetry of the system. For the system described above $M_n \rightarrow 1/3$ and at the high temperature limit[4] $\langle \Delta \nu_H \rangle = \sum_n 1/3 \, \delta\nu_n$, which should be a direct measure of the contribution of the asymmetry effect to nonequivalence.

Gutowsky (9) analyzed the relative contribution of the asymmetry effect and differences in conformer population to magnetic nonequivalence in $BrCF_2CFBrCl$ (8). Differences in conformer population gave approximate values of $(\nu_a^F - \nu_b^F) = \Delta \nu_n$ for each of the three conformers, namely + 178, - 273 and + 75 Hz. at 40 MHz. At the high temperature limit $\langle \Delta \nu_F \rangle = \sum_n 1/3 \, \delta \nu_n = 6.7$ Hz., which is a measure of the asymmetry effect contribution to magnetic nonequivalence. It should be noted that the asymmetry effect is rather small when compared with the rotationally averaged shifts of 85 to 45 Hz. observed for temperatures ranging from 225° to 465°K.

Roberts and co-workers (8) cast some doubt on the relevance of 8 as a model for observing the asymmetry effect at high temperatures. They stated that "The problem of the possible importance of small contributors to magnetic nonequivalence arising from an intrinsic asymmetry, independent of rotational conformer populations, has not yet been completely

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[4]The temperature dependence of $\sum_n 1/3 \, \delta \nu_n$ would be extremely difficult to demonstrate in certain instances since it would involve working at temperatures where the differences in conformer population would contribute to magnetic nonequivalence.

resolved; however, no convincing experiment has so far been reported which has demonstrated significant contributions from intrinsic asymmetry to an observed chemical shift. However, it should be emphasized that in discussing the relative importance of conformational preference and intrinsic asymmetry, the question at issue is not whether the former or the latter is alone responsible for magnetic nonequivalence, but rather how much, if any, of an observed nonequivalence should be ascribed to intrinsic asymmetry. There seems little doubt that conformational preferences with respect to the asymmetric centre must in general be responsible for the major contributions to the magnetic nonequivalence"(8).

Snyder (7) studied the variation of the chemical shift between nonequivalent hydrogens of saturated systems employing different solvents. He observed that all of the chemical shifts values and differences can be interpreted as arising from properties of solvent related to local magnetic field anisotropy rather than any properties of solvent influencing conformational equilibria (i.e., solvents produce changes in chemical shift which override those caused by differences in rotational equilibria). Snyder suggests that anisotropy of the magnetic field about the carbon atom bearing the nonequivalent groups may well be the most important factor determining the chemical shift difference between nonequivalent nuclei. He substantiates these conclusions by providing examples of compounds in the series ACX_2B. When the B group is varied, profound differences in chemical shifts are observed, arising solely from changes in the magnetic

anisotropy of the B groups.[5]

Recently Snyder (19) pointed out that the significance of an asymmetry effect could be unambiguously assessed by examination of the n.m.r. spectra of compounds of the series $ACH_2C{\equiv}CCXYZ$. Since the barrier to rotation of the methyl group in methyl acetylenes is extremely low (less than 0.1 kcal $mole^{-1}$) (20), the energy difference between conformers would be very small. Therefore any magnetic nonequivalence observed should arise from an asymmetry effect. Another valid system suggested by Snyder lies in the substituted triphenylpropionic acids of the type $4\text{-}XC_6H_4(4'\text{-}YC_6H_4)C_6H_5CCH_2R$. Substituents X and Y should be chosen such that they impart large differences in magnetic properties to their respective rings. They should however be sufficiently small to guarantee equal conformer populations; hence any nonequivalence observed in the methylene protons should arise from the asymmetry effect.

The purpose of this work is to reduce the controversy surrounding the concept of magnetic nonequivalence of protons of methylene groups which are separated by one or more bonds from a centre of molecular asymmetry.

In accordance with the statement of Snyder it was considered that if an asymmetry effect makes a significant contribution to magnetic nonequivalence, then compounds of the series $ACH_2C{\equiv}CCXYZ$ and $4\text{-}XC_6H_4(4'\text{-}YC_6H_4)C_6H_5CCH_2R$ should be ideal for observing the effect. It was proposed to undertake a synthesis of these two classes of compounds and examine their ^1H nuclear magnetic resonance spectra.

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[5]Roberts and co-workers (8) suggest that the proximity of the asymmetric centre to the benzyl group in compounds related structurally to 1-phenylethyl benzyl ethers, results in a preferred conformation of the phenyl ring with respect to the methylene protons, and that the principal contribution to nonequivalence originates in the magnetic anisotropy of the phenyl group.

RESULTS AND DISCUSSION

A synthesis of compounds of the type $ACH_2C{\equiv}CCXYZ$ has been reported (21). The sequence of the reactions is described in Reaction Scheme 1. Acetylation of 1-Phenyl-2-propyne-1-ol with acetic anhydride followed by Mannich condensation of the ester with diethylamine and paraformaldehyde[6] gave 4-N,N-diethylamino-1-phenylbut-2-yn-1-acetate (9). An n.m.r. spectrum of 9 (Figure 7, p. 53) showed a doublet at 3.52 parts per million (p.p.m.) for the CH_2 group and a triplet at 6.61 p.p.m. for the acetylenic proton.

Hydrolysis with sodium methoxide yielded a second compound of the required type, 4-N,N-diethylamino-1-phenylbut-2-yn-1-ol (10). The n.m.r. spectrum of 10 (Figure 8, p. 54) was similar in some respects to 9 since the methylene group of 10 appeared as a doublet at 3.41 p.p.m. and the acetylenic proton appeared as a triplet at 5.49 p.p.m.

Spin decoupling experiments were carried out on compounds 9 and 10. In both cases the doublet for methylene groups and the triplet for the acetylenic protons collapsed to singlets. Therefore the doublet obtained for the CH_2 group in 9 and 10 was due to long range spin-spin coupling through the acetylenic bond, (J = 2.0 Hz.).

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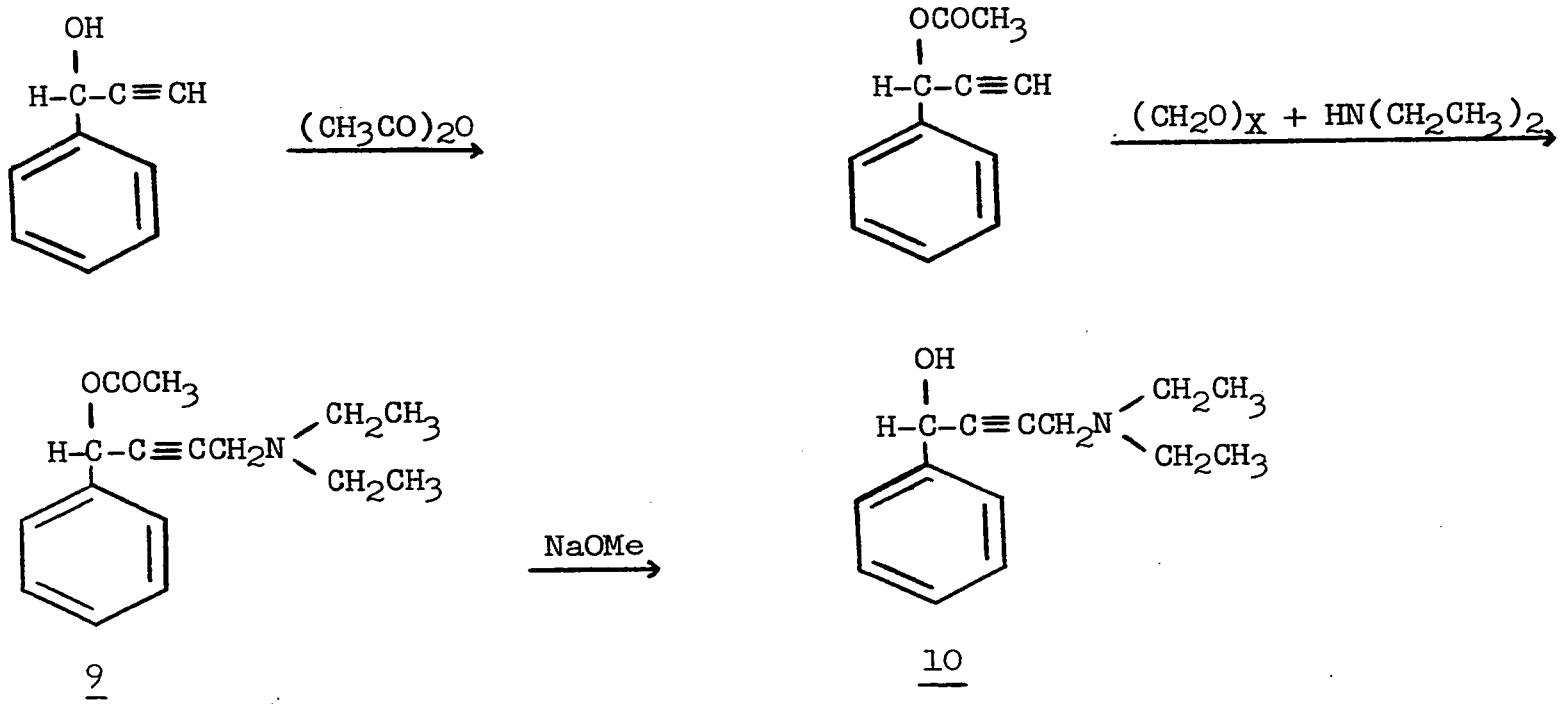
[6]There is a discrepancy between the original publication (21) and Chem. Abstr. 52 17270 (1958). The abstract indicates that $(CH_2O)_3$, trioxane was used, rather than $(CH_2O)_X$ in the synthesis of 9. However, trioxane is a crystalline cyclic trimer, sometimes named meta-formaldehyde. When the Mannich condensation was carried out with trioxane the required product was not obtained. The reaction was successful only when paraformaldehyde $(CH_2O)_X$ a straight chain linear polymer was used.



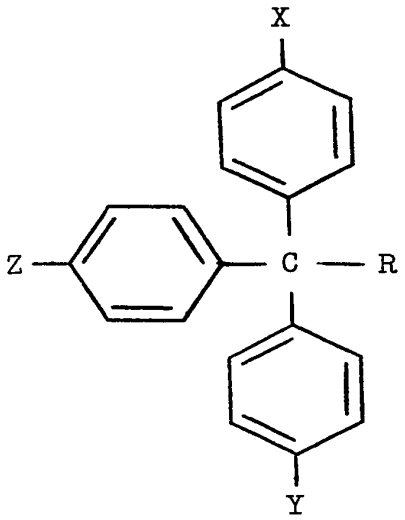
9 10

Reaction Scheme 1

Triphenylpropionic acids substituted in the required manner have not been reported. However condensation reactions of triphenylmethyl chloride and various triarylmethanols with active methylene compounds (CH_2XY) have been studied (22, 23). Triphenylpropionic acid derivatives and various by-products were obtained in the condensation reactions by Patai and co-workers. It was decided to synthesize compounds of the type $(4\text{-}XC_6H_4)(4'\text{-}YC_6H_4)(4''\text{-}ZC_6H_4)CR$ (Figure 9), which might then be condensed with malonic acid. Three different approaches were employed in an attempt to synthesize the desired compounds.

The first approach, essentially a Friedel-Crafts reaction,consisted of reacting appropriately substituted compounds with carbon tetrachloride or

α,α,α-trichlorotoluene in the presence of aluminum chloride.[7]



11a X = $NHCOCH_3$, Y = H, Z = H, R = Cl

11b X = $N(CH_3)_2$, Y = Cl, Z = H, R = Cl

11c X = $NHCOCH_3$, Y = CH_3, Z = OCH_3, R = Cl

11d X = OCH_3, Y = CH_3, Z = Br, R = Cl

11e X = OCH_3, Y = Cl, Z = H, R = OH

11f X = OCH_2CH_3, Y = Cl, Z = H, R = OH

Figure 9

The reactions attempted were (a) acetanilide with α,α,α-trichlorotoluene, (b) N,N-dimethylaniline and chlorobenzene with α,α,α-trichlorotoluene, (c) acetanilide, toluene and anisole with carbon tetrachloride, and (d) anisole, toluene and bromobenzene with carbon tetrachloride. The expected triarylmethyl chloride derivatives were not isolated after work-up of the reaction mixtures. In each experiment differing amounts of the starting materials were recovered unreacted. If the reaction occurred, it was only to a small extent. It was therefore decided to concentrate on a different procedure.

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[7] Triphenylmethyl chloride was produced in 69-75% yield from benzene and carbon tetrachloride in the presence of aluminum chloride, by the Friedel-Crafts reaction (24).

Grignard reagents add to carbonyl compounds to produce metal alkoxides which, on hydrolysis, give alcohols. Aldehydes with the exception of formaldehyde give secondary alcohols and ketones give tertiary alcohols.[8] The reaction of 4-methoxy-phenylmagnesiumbromide with 4-chlorobenzophenone was carried out a number of times under varying reaction conditions in an attempt to obtain (±)-4-chloro-4'-methoxy-triphenylmethanol (11e).

An infrared spectrum of the product obtained from each run indicated the presence of a substituted diaryl carbonyl stretching vibration band at 1665 cm^{-1} due to the starting material, 4-chlorobenzophenone.

In another attempt 4-chlorobenzophenone was added to a freshly prepared Grignard reagent formed by reacting 4-bromophenetole with magnesium metal in the presence of anhydrous diethyl ether. An infrared spectrum of the product obtained after work-up showed that the diaryl ketone stretching vibration band had disappeared; an n.m.r. spectrum indicated the presence of an alcohol proton at 3.09 p.p.m. The product (±)-4-chloro-4'-ethoxy-triphenylmethanol (11f) was isolated as an oil and could not be induced to crystallize from a variety of solvents. Column chromatography failed to yield a crystalline derivative although thin-layer chromatographic studies with three different solvent systems (petroleum ether, benzene and chloroform) indicated that the oil consisted of only one component. This approach was not investigated further because the

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[8]Triphenylmethanol was produced in 89-93% yield by the Grignard reaction (25); Kovache (26) has reported the reaction of 4-methoxy-phenylmagnesium bromide with benzophenone to give 4-methoxy-triphenyl-methanol in 60% yield.

triarylmethanol product could not be sufficiently purified for complete characterization.

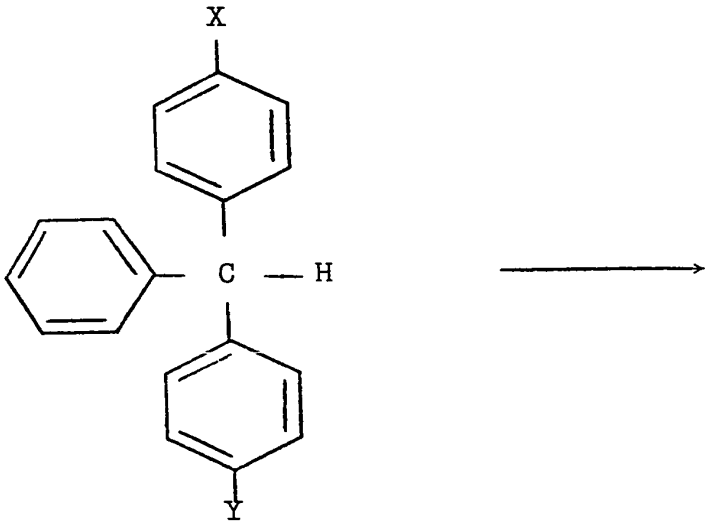
It was decided to synthesize compound 15b with X = NO_2 and Y = NH_2, the extremes of electron withdrawing and electron donating substituents, respectively. The Grignard reaction could not be applied in a direct synthesis of compounds when X = NO_2 and Y = NH_2, as most primary aromatic amines behave toward Grignard reagents as though they contain an active hydrogen and form so-called nitrogen Grignard reagents. Furthermore the initial reaction of an aryl nitro compound with arylmagnesium halide consists of an addition followed by a reduction to a diarylhydroxylamine derivative (27), outlined in Reaction Scheme 2. Therefore a third approach to the desired product was investigated. The sequence of reactions is described in Reaction Scheme 3.

$$RNO_2 \xrightarrow{R'MgX} RR'(XMgO)N\rightarrow O \xrightarrow{R'MgX} RR'NOMgX + R'CMgX$$

$$RR'NOMgX \xrightarrow{2R'MgX} RR'NMgX + R'_2 + (XMg)_2O \quad (27)$$

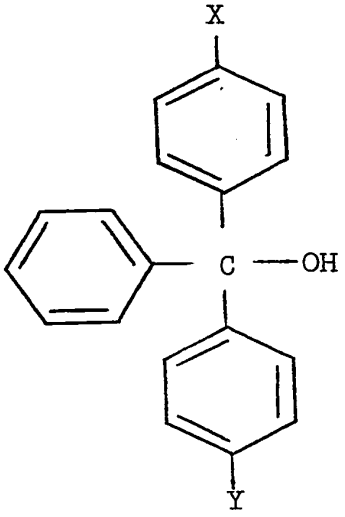
Reaction Scheme 2

4,4'-Diaminotriphenylmethane (12a) was prepared according to the procedure of Baeyer and Villiger (28). The compound 12a could be selectively oxidized with hydrogen peroxide (29) to the corresponding 4,4'-dinitro compound 12b. An n.m.r. spectrum (Figure 10, p. 55) of the product obtained in the oxidation reaction showed no resonance absorption arising from the amino protons of 12a. A singlet due to the methine proton was observed at 5.9 p.p.m., whereas a complex multiplet corresponding to the thirteen aromatic protons, in which an A_2X_2 pattern was discernible, occurred in the range 7.2 to 8.6 p.p.m. An infrared spectrum did not show any evidence of N-H stretching or bending vibrations; however, two large absorption bands



12a X = Y = NH_2

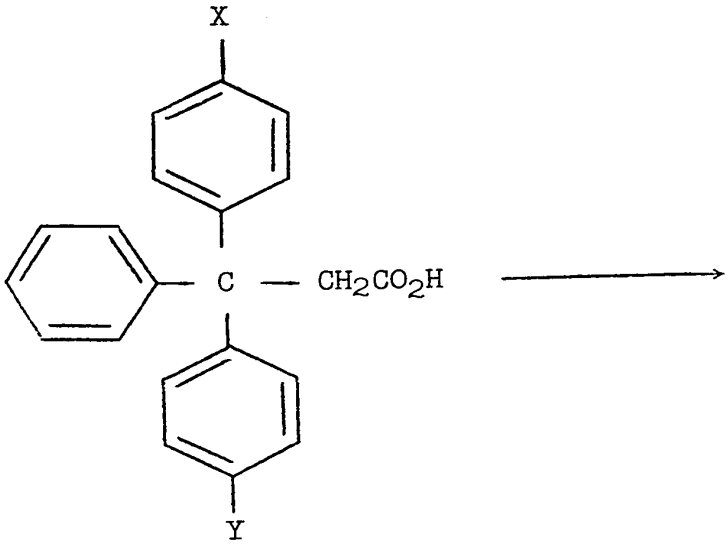
12b X = Y = NO_2



13a X = Y = NO_2

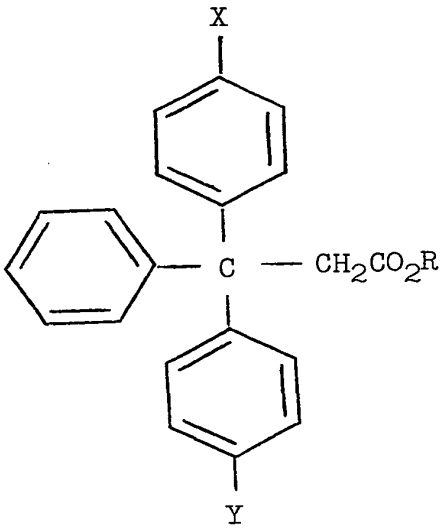
13b X = NH_2, Y = NO_2

13c X = $NHCOCH_3$, Y = NO_2



14a X = $NHCOCH_3$, Y = NO_2

14b X = NH_2, Y = NO_2



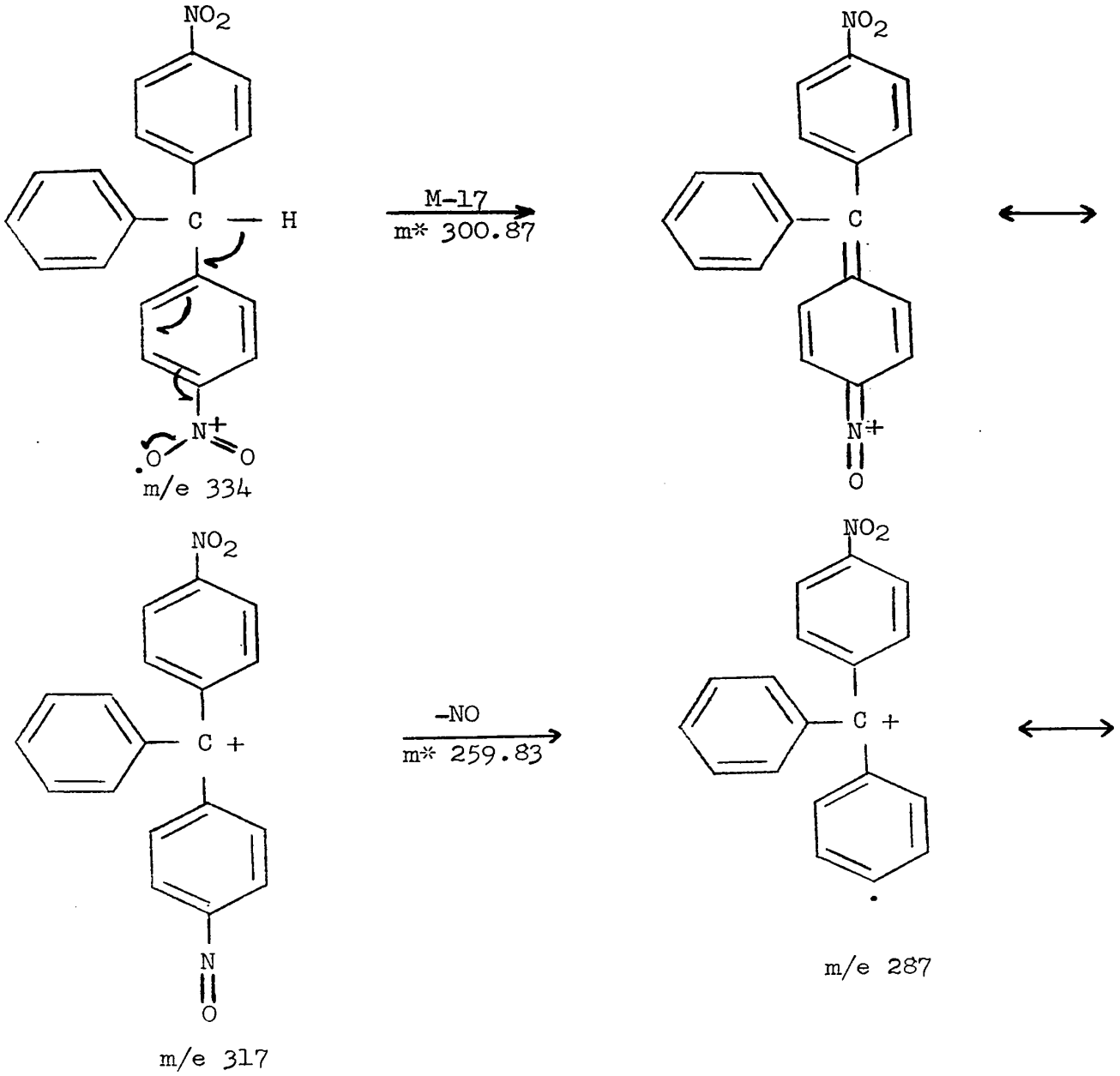
15a X = NH_2, Y = NO_2, R = CH_2CH_3

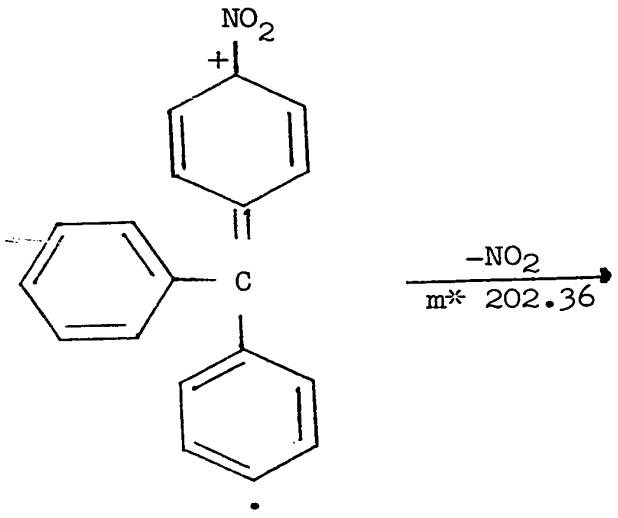
15b X = NH_2, Y = NO_2, R = CH_3

Reaction Scheme 3

were readily observed for aromatic C-NO_2 vibrations at 1515 and 1347 cm^{-1}.

A mass spectrum indicated the presence of a molecular ion at m/e 334 with fragments at m/e 317, 287 and 241. By considering the presence of metastable ions in the spectrum, the partial elucidation of the decomposition pathway is suggested in Fragmentation Scheme 1 (30).





Fragmentation Scheme 1

It can be seen that 12b loses a hydrogen and oxygen in a concerted process (M-17) rather than by successive loss of hydrogen (M-1) followed by oxygen (M-16). A mass spectrum of 4,4'-dinitrodiphenylmethane[9] also showed a metastable transition for the direct loss of hydrogen and oxygen.

Treatment of 12b with CrO_3 gave the alcohol 4,4'-dinitrotriphenylmethanol[10] (13a) (32) in 76% yield. The mechanism proposed for the chromic acid oxidation of a tertiary C-H group to a tertiary alcohol (33) may be represented by Reaction Scheme 4. The transition state for hydrogen transfer is a resonance hybrid, in which the carbon atom has both radical and carbonium ion character (33).

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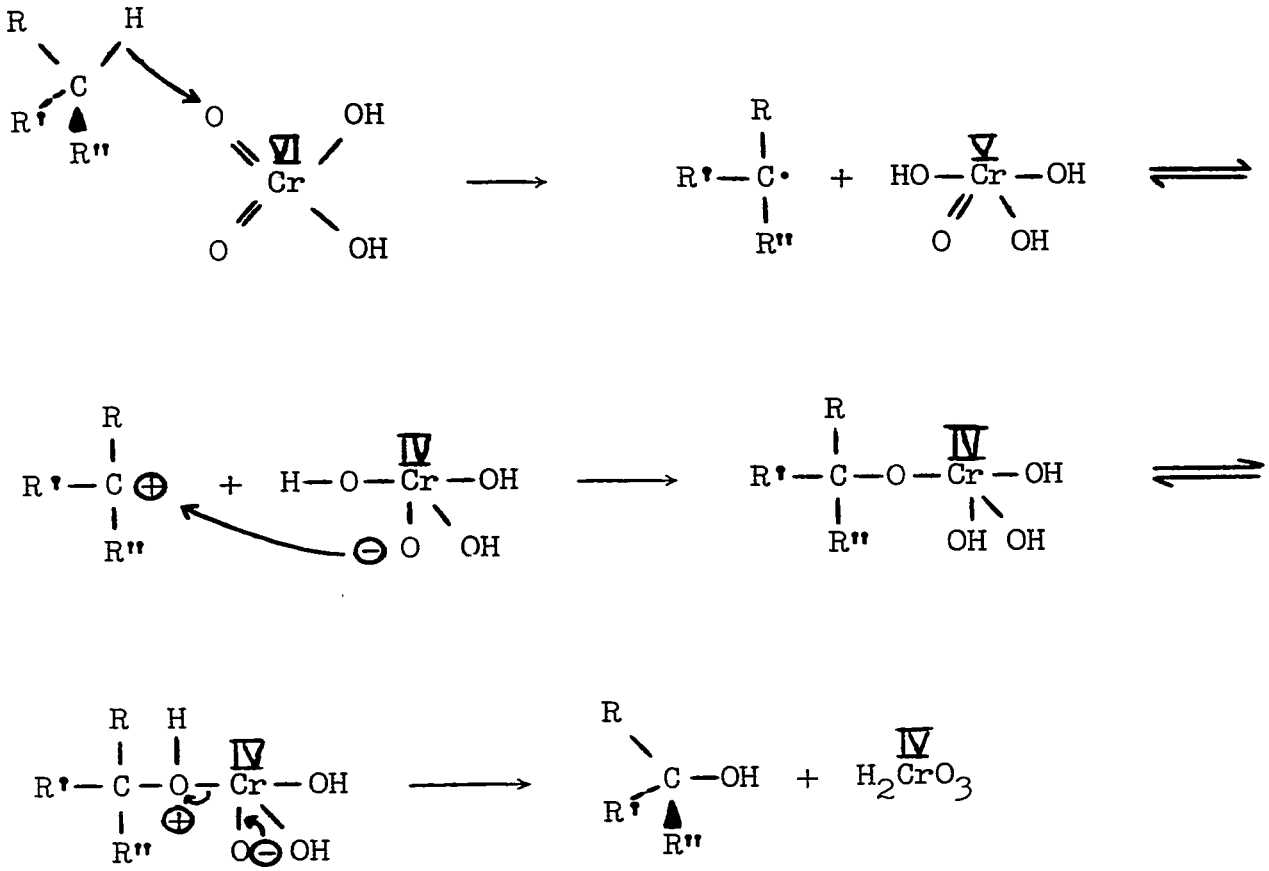
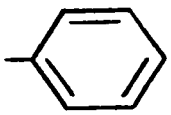
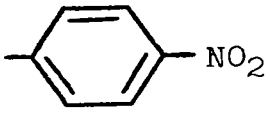
[9]4,4'-Dinitrodiphenylmethane was prepared according to the procedure of Staedel (31).

[10]This compound has been previously reported by N.C. Deno, J.J. Jaruzelski and A. Schriesheim. J. Am. Chem. Soc. 77, 3044 (1955). No experimental details on its preparation or physical properties were given.



13a

R = 

R' = R'' = 

Reaction Scheme 4

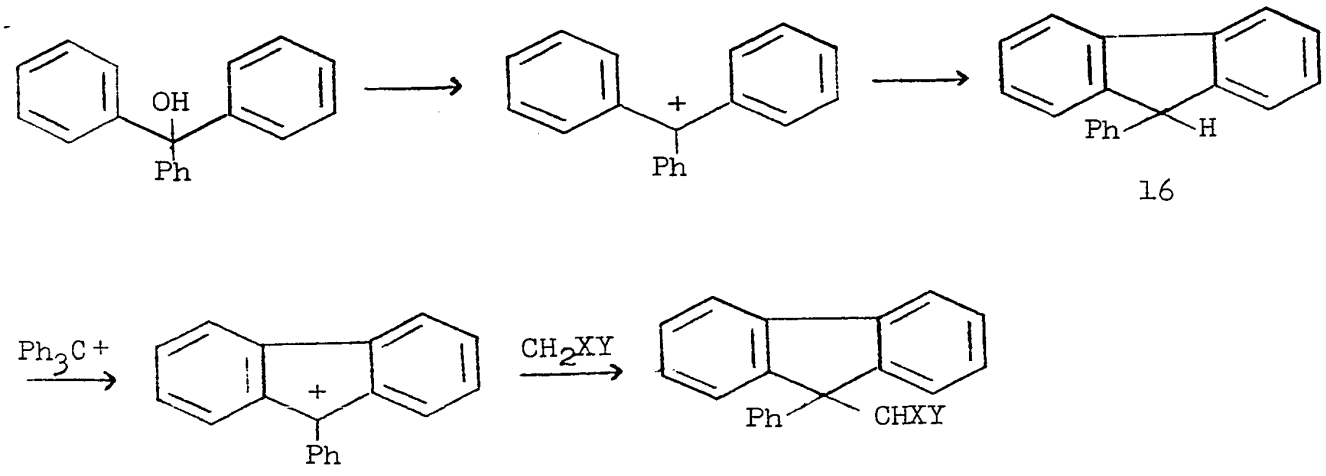
An infrared spectrum of 13a indicated the presence of a hydroxyl stretching vibration at 3560 cm^{-1}. The n.m.r. spectrum (Figure 11, p.56) showed a singlet arising from the hydroxyl proton at 3.68 p.p.m. The hydroxyl proton resonance peak disappeared when D_2O was added to the sample.

The partial reduction 13a → 13b was carried out in 64% yield by addition of sodium polysulphide and sulphur to a refluxing solution of the dinitro compound in aqueous ethanol (34). The n.m.r. spectrum of 13b (Figure 12, p.57) clearly indicated the presence of two A_2X_2 systems centered at 6.9 and 8.0 p.p.m. corresponding to the aromatic moieties with the NH_2 and NO_2 substituents, respectively, and a singlet at 3.6 p.p.m. arising from the accidental degeneracy of the hydroxyl and amino protons. The resonance peak attributed to the hydroxyl and amino protons disappeared when D_2O was added to the sample. An infrared spectrum showed two N-H stretching vibration bands at 3380 and 3306 cm^{-1}, an N-H bending vibration at 1615 cm^{-1} and aromatic C-NO_2 vibrations at 1503 and 1340 cm^{-1}. A mass spectrum indicated the presence of a molecular ion at m/e 320 with significant fragments at m/e 303, 243, 228 and 198 probably corresponding to the loss of OH (M-17), C_6H_5 (M-77), C_6H_6N (M-92) and $C_6H_4NO_2$ (M-122).

Treatment of (±)-4-amino-4'-nitro-triphenylmethanol (13b) with acetic anhydride gave an amide 13c which could not be induced to crystallize, but was readily identified by its n.m.r., infrared and mass spectra. The n.m.r. spectrum (Figure 13, p.58) showed a singlet (-NH-) at 8.20 p.p.m., a complex multiplet (benzenoid protons) from 6.80-8.00 p.p.m., a singlet (-OH) at 4.02 p.p.m., and a singlet ($-CH_3$) at 1.88 p.p.m. An i.r. spectrum showed an amide C=O stretching vibration at 1670 cm^{-1}. Mass spectrometry showed a molecular ion at m/e 362

and peaks at m/e 345, 303, 285, 240 and 288 probably corresponding to loss of OH (M-17), then loss of $CH_2{=}C{=}O$, C_6H_5 (M-77), $C_6H_4NO_2$ (M-122) and C_8H_8NO (M-134).

As earlier indicated Patai and Dayagi (23) carried out a number of reactions involving triarylmethanols. Their attempts to condense malonic acid with triphenylmethanol in basic or neutral media failed. The tendency of triarylmethanols to undergo the reaction appeared to depend on the nature of the aryl substituents. It was reported that nitro substituted triarylmethanols have little tendency to give carbonium ions and fail to react, whereas carbonium ions formed from more active alcohols[11] may undergo intramolecular cyclizations to form the corresponding fluorene derivatives. The reaction may stop at 16 or continue to form the ion 17, which itself may condense with the active methylene compounds. The sequence of reactions is described in Reaction Scheme 5.



Reaction Scheme 5

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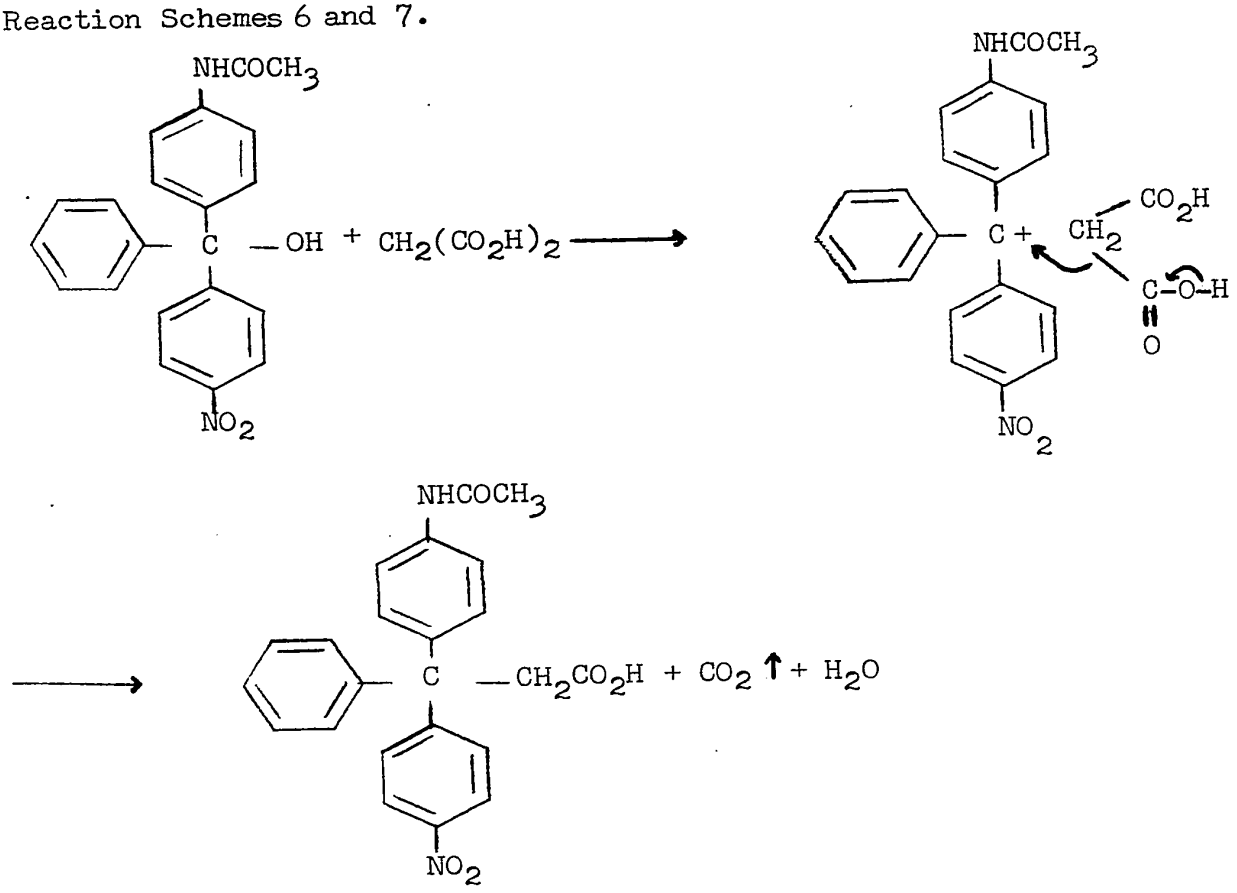
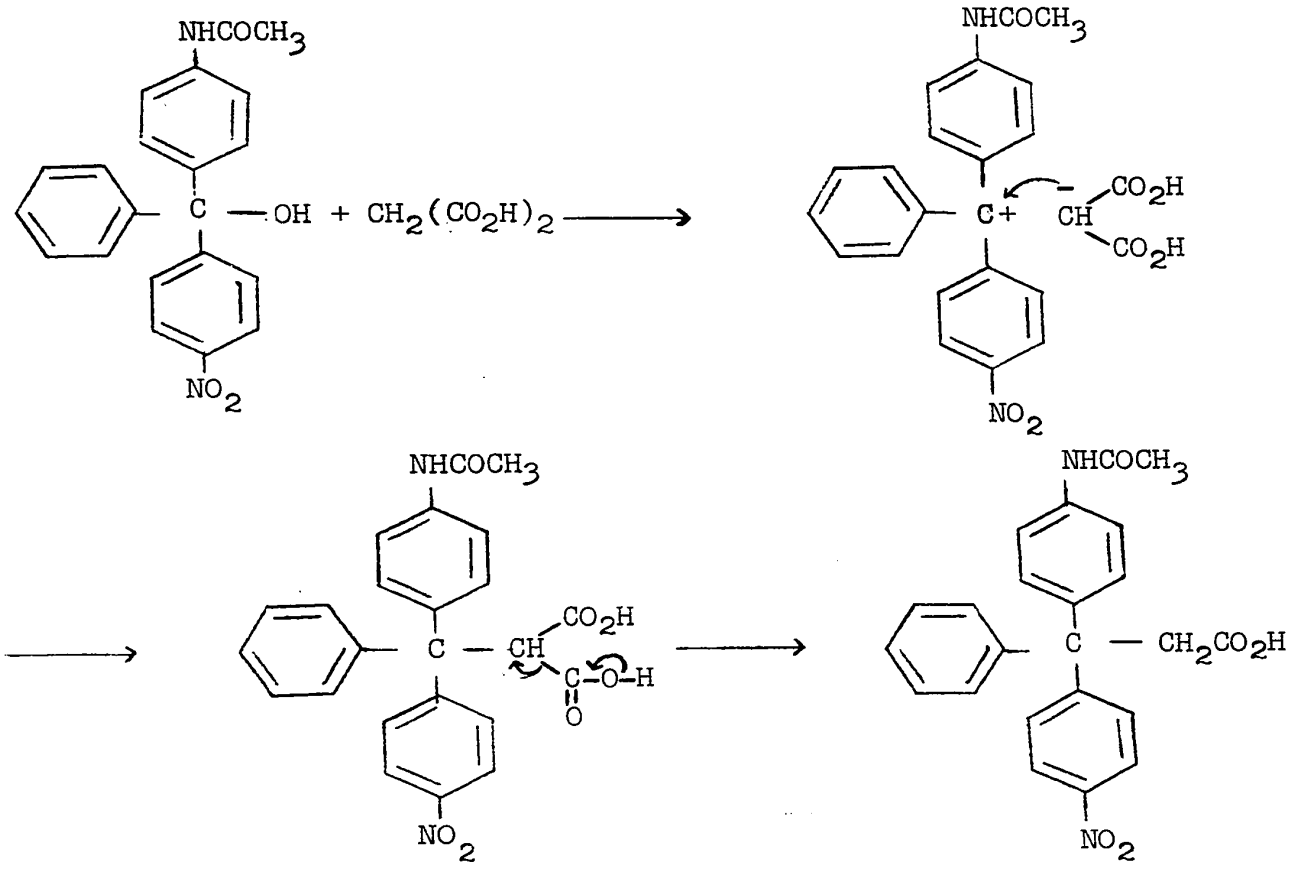
[11] i.e., compounds containing electron donating substitutents.

If we now consider that the electron withdrawing effect of the nitro substituent in (±)-4-Acetanilidyl-4'-nitrophenyl-phenyl-methanol (13c), could be compensated by the presence of an electron donating substituent, the carbonium ion should form and condensation occur. The amide substituent is moderately activating and only partially compensates for the electron withdrawing effect of the nitro substituent. Nevertheless it was found that the fusion of 13c with malonic acid at 170° furnished the condensation product 14a in 76% yield. The mechanism for the condensation reaction with malonic acid has not been clearly established. Two possible alternatives which may describe the reaction are outlined in Reaction Schemes 6 and 7.



Reaction Scheme 6



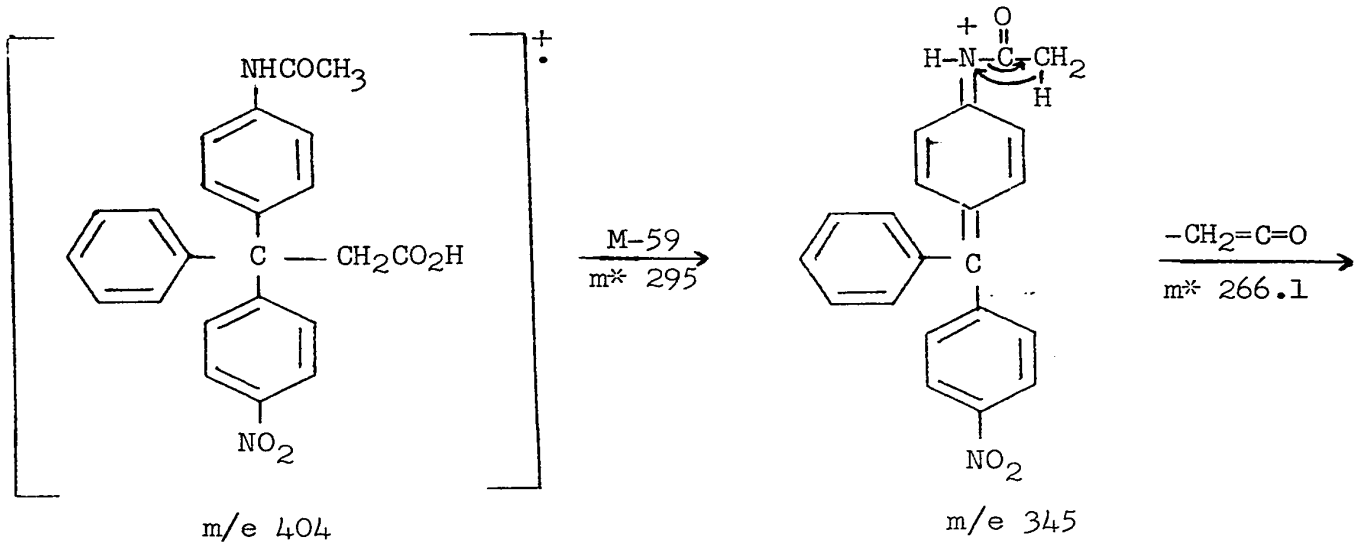
Reaction Scheme 7

Patai and Dayagi (23) have carried out other condensation reactions with various active methylene compounds (CH_2XY) where neither X nor Y corresponded to carboxyl groups. In these cases decarboxylation could not occur and the compounds isolated were usually identified as the normal products of tritylation, Ar_3CHXY. Also in one instance where X and Y corresponded to carboxyl groups, tritylmalonic acid was isolated. This experimental evidence gives some credence to the superficially less plausible mechanism suggested by Reaction Scheme 7.

The infrared spectrum of 14a (Figure 14, p. 59) indicated the presence of acid and amide carbonyl stretching vibrations at 1715 and 1665 cm^{-1}, respectively. An n.m.r. spectrum (Figure 15, p. 60) showed a

singlet (acid proton) at 9.84 p.p.m., a complex multiplet (benzenoid protons overlapping with N-H) from 8.80-7.40 p.p.m., a singlet ($-CH_2-$) at 4.22 p.p.m., and another singlet ($-CH_3$) at 2.70 p.p.m.

The mass spectrum indicated the presence of a molecular ion at m/e 404 with significant fragments at m/e 345, 303,[12] and 257 probably corresponding to loss of CH_2CO_2H (M-59) followed by the loss of $CH_2{=}C{=}O$ then loss of NO_2. The partial elucidation of the decomposition pathway is suggested in Fragmentation Scheme 2.



m/e 404 m/e 345

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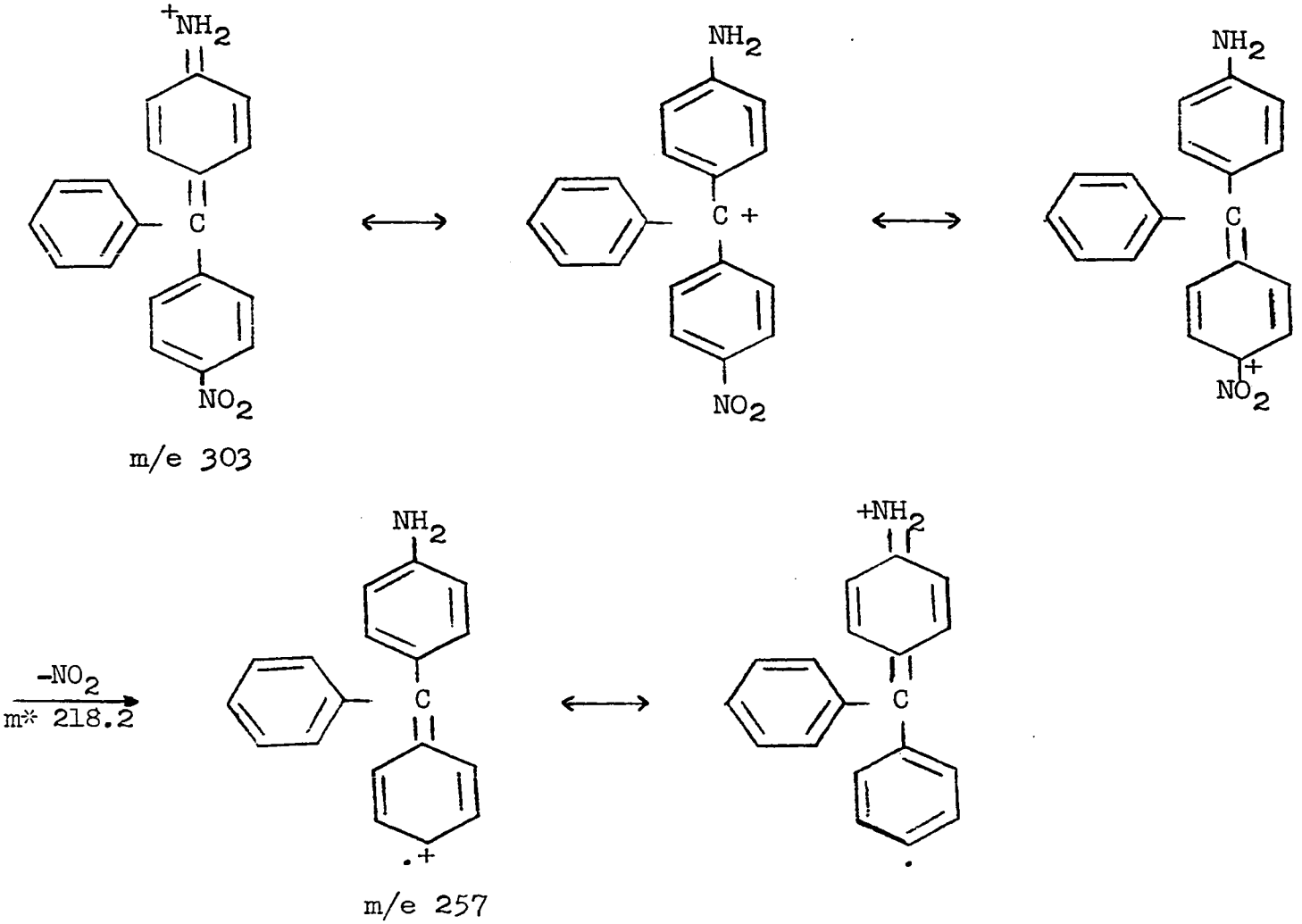
[12]The existence of the fragment ion at m/e 303 was confirmed when mass spectral studies were carried out on acetanilide. The first important fragment peak was observed at M-42 (i.e., m/e 93) indicating that migration of a hydrogen from the methyl group to the nitrogen atom had occurred with the subsequent loss of ketene (35). The mass spectrum of 13c also indicated this type of rearrangement.



Fragmentation Scheme 2

As indicated earlier, Patai and co-workers (22) carried out a number of reactions involving triphenylmethyl chloride and active methylene compounds. Much milder conditions were required for condensations with triphenylmethyl chloride than with the corresponding alcohol, so that the extent of side reactions and the amount of by-products were reduced considerably. It was decided to attempt to synthesize 4,4'-dinitrotri-

phenylmethyl chloride[13] (18) from 13a and to carry out the subsequent condensation with malonic acid on 18. The product obtained from the reaction of 4,4'-dinitrotriphenylmethanol and acetyl chloride[14] however, was not the desired product. An n.m.r. spectrum of the product indicated only the presence of an A_2X_2 system centered at 8.1 p.p.m. arising from the aryl moieties substituted with nitro substituents. An infrared spectrum (Figure 16, p.61) showed that a diaryl ketone had been formed as exhibited by the presence of a carbonyl stretching vibration at 1660 cm^{-1}. From the melting point (189°) of the product and the above data, the ketone formed was identified as 4,4'-dinitrobenzophenone.

W.H. Starnes (37) has postulated a mechanism for the oxidation of triarylmethanol derivatives with lead tetraacetate. If an analogy can be made between the alcohols used by Starnes[15] and the alcohol used in the attempt to prepare 18 an explanation for the formation of 4,4'-dinitrobenzophenone can readily be given. The reaction proceeds via

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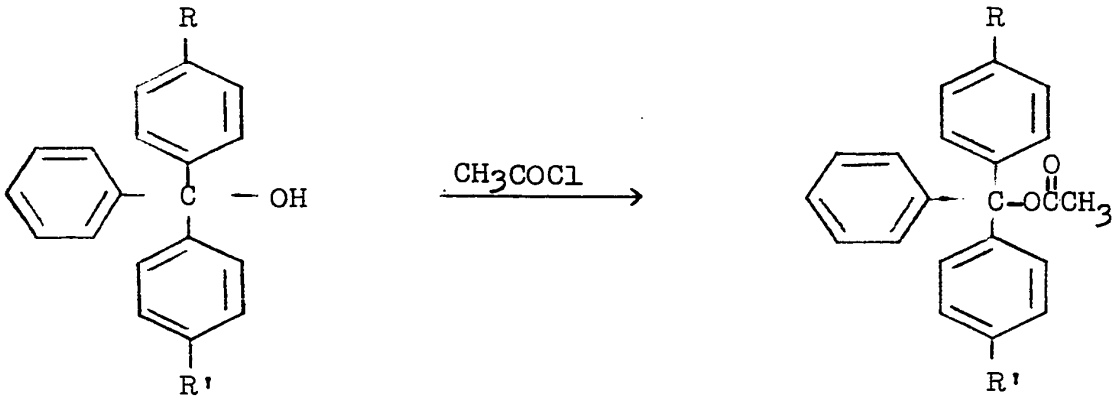
[13] 4,4'-dinitrotriphenylmethyl chloride (18) has been produced in a four step synthesis by K. Ziegler and W. Mathes. Ann. 479, 188 (1930). Since 13a was produced in a three step synthesis in the laboratory and was available, it was decided to use the dinitro alcohol as the starting material in an attempt to synthesize 18.

[14] Triphenylmethyl chloride was produced in 93-95% yield from the reaction of triphenylmethanol and acetyl chloride (36).

[15] The alcohols investigated by Starnes were 4-methoxytriphenylmethanol, 4-nitrotriphenylmethanol and triphenylmethanol.

a radical process to form a hemiketal ester,[16] followed by hydrolysis to give a benzophenone derivative. The probable mechanism for the formation of 4,4'-dinitrobenzophenone is outlined in Reaction Scheme 8.



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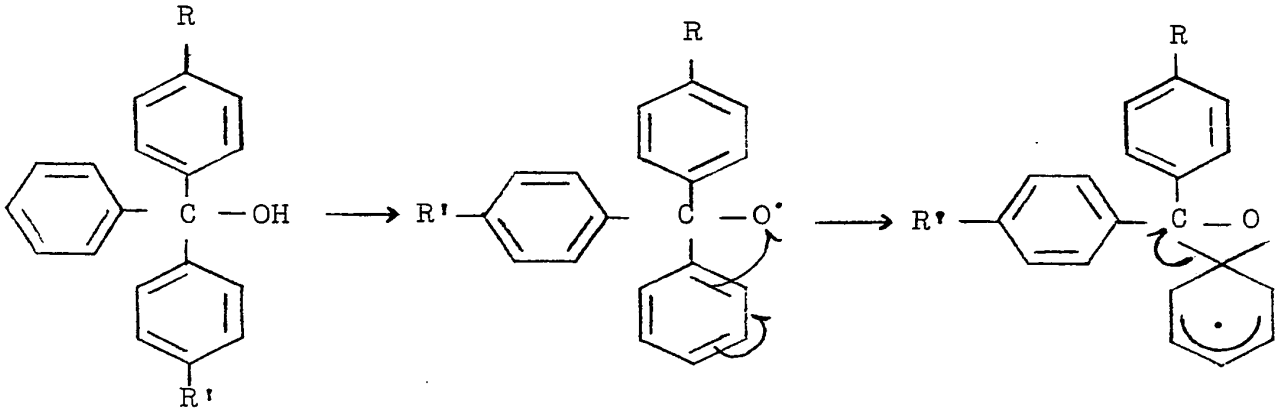

R = R' = $-NO_2$

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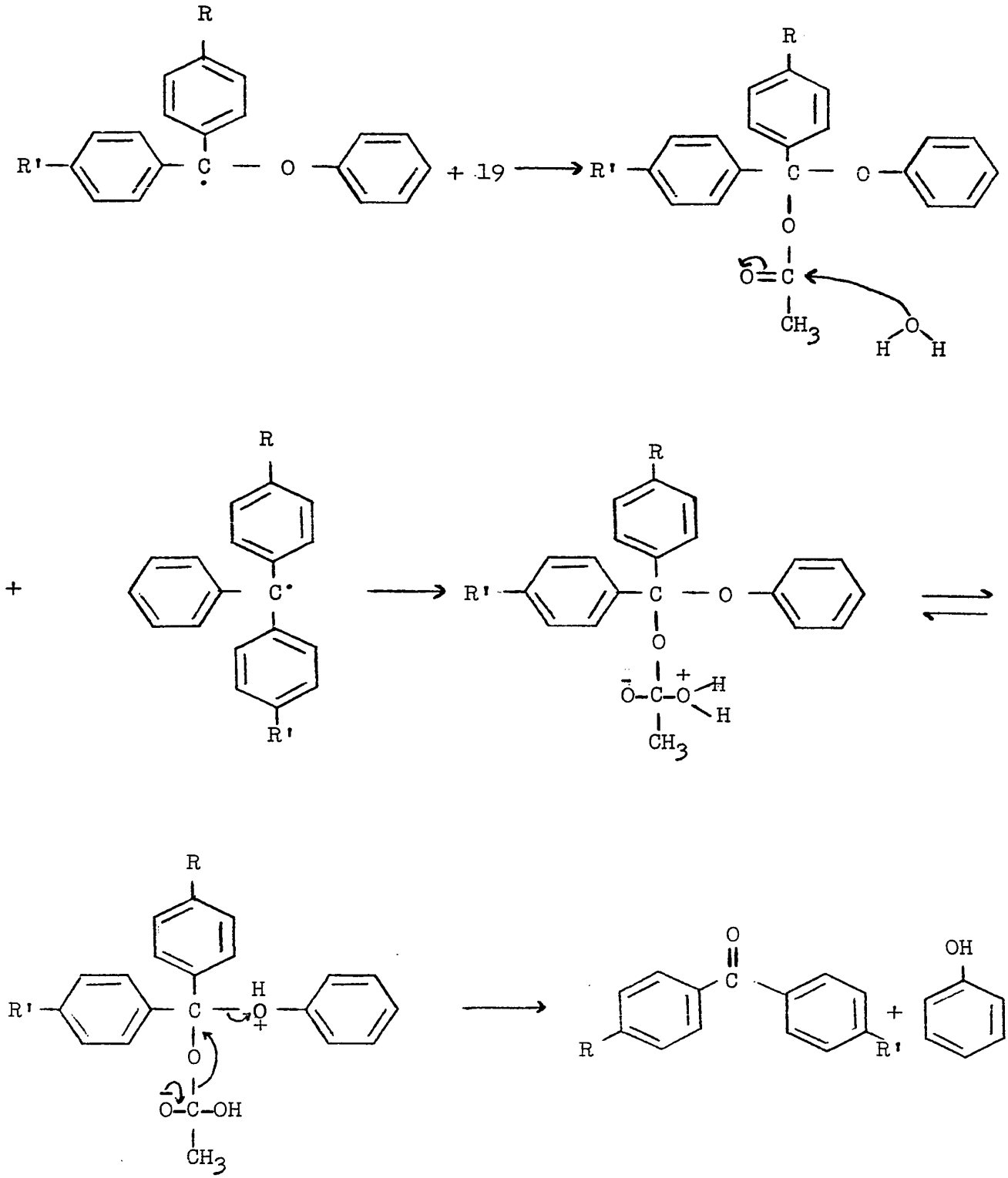
[16]The hemiketal ester formation arises from the intramolecular migration of a phenyl group proceeding via a bridged transition state (38).



Reaction Scheme 8

This approach was not investigated further and it was decided to concentrate on the hydrolysis of 14a → 14b. Of the methods attempted, hydrolysis of 14a to the amino acid 14b was found to proceed most smoothly with a solution of 10% aqueous hydrochloric acid in ethanol, although some of the ethyl ester 15a[17] was formed in the process. Although 14b was not sufficiently purified for complete characterization, it was sufficiently pure to use in subsequent reactions. An infrared spectrum of 14b (Figure 17, p. 62) showed that the amide carbonyl stretching vibration had disappeared. It indicated the presence of N-H stretching vibrations at 3460 and 3390 cm^{-1} and N-H bending vibrations at 1620 and 1590 cm^{-1} arising from the primary NH_2 group of the amino acid.

Esterification of the amino acid 14b with dimethyl sulphite after the method of Cruickshank and Sheehan (38) produced the methyl ester in nearly quantitative yield. After column chromatography, a yellow glass was obtained which could not be induced to crystallize from a variety of solvents. Thin layer chromatographic studies with three different solvent

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[17]An infrared spectrum of 15a showed the presence of an ester carbonyl stretching vibration at 1731 cm^{-1}. The n.m.r. spectrum of 15a (Figure 18, p. 63) showed a complex multiplet (benzenoid protons) from 8.39-6.52 p.p.m. in which two A_2X_2 patterns centered at 7.92 and 6.85 p.p.m. were clearly discernible. The spectrum indicated the presence of a singlet, superimposed on a quartet and broad peak at 3.73 p.p.m. arising, respectively, from the methylene protons, the methylene protons in the ethyl group of the ester and the amino protons. A triplet was also observed at 0.92 p.p.m. corresponding to the methyl protons of the ethyl group. The broad peak attributed to the amino protons disappeared when D_2O was added to the sample (Figure 19, p. 64).

systems (petroleum ether, benzene and chloroform) indicated that the glass consisted of only one component.

An infrared spectrum of 15b (Figure 20, p. 65) indicated the acid carbonyl stretching vibration had disappeared and showed the presence of an ester carbonyl stretching vibration at 1735 cm^{-1}. The n.m.r. spectrum of 15b (Figure 21, p. 66) clearly indicated the presence of two A_2X_2 systems centered at 8.0 and 6.9 p.p.m. corresponding, respectively,[18] to the aromatic moieties with NO_2 ($|J_{XX}|$ = 5.1, J_{AX} = 9.18 and J'_{AX} = 0.52 Hz.), and NH_2 ($|J_{XX}|$ = 4.90, J_{AX} = 8.95 and J'_{AX} = 0.35 Hz.), substituents. A singlet superimposed on a broad peak at 3.80 p.p.m. arising, respectively, from the methylene and amino protons, and a singlet ($-CH_3$) at 3.46 p.p.m. were observed. The resonance peak for the amino protons disappeared (Figure 22, p. 67) when D_2O was added to the sample.

Since conformational effects are greatest at low temperatures an examination of the low temperature (-40°) n.m.r. spectrum of 15b was carried out to ascertain whether conformers were equally populated. It was observed that the n.m.r. spectrum at low temperature was analogous to the room temperature spectrum of 15b.

The mass spectrum indicated the presence of a molecular ion at m/e 376 with fragments at 303 and 257 corresponding to the loss of $CH_2CO_2CH_3$ (m-73) followed by loss of NO_2. The partial elucidation of the decomposition pathway is suggested in Fragmentation Scheme 3.

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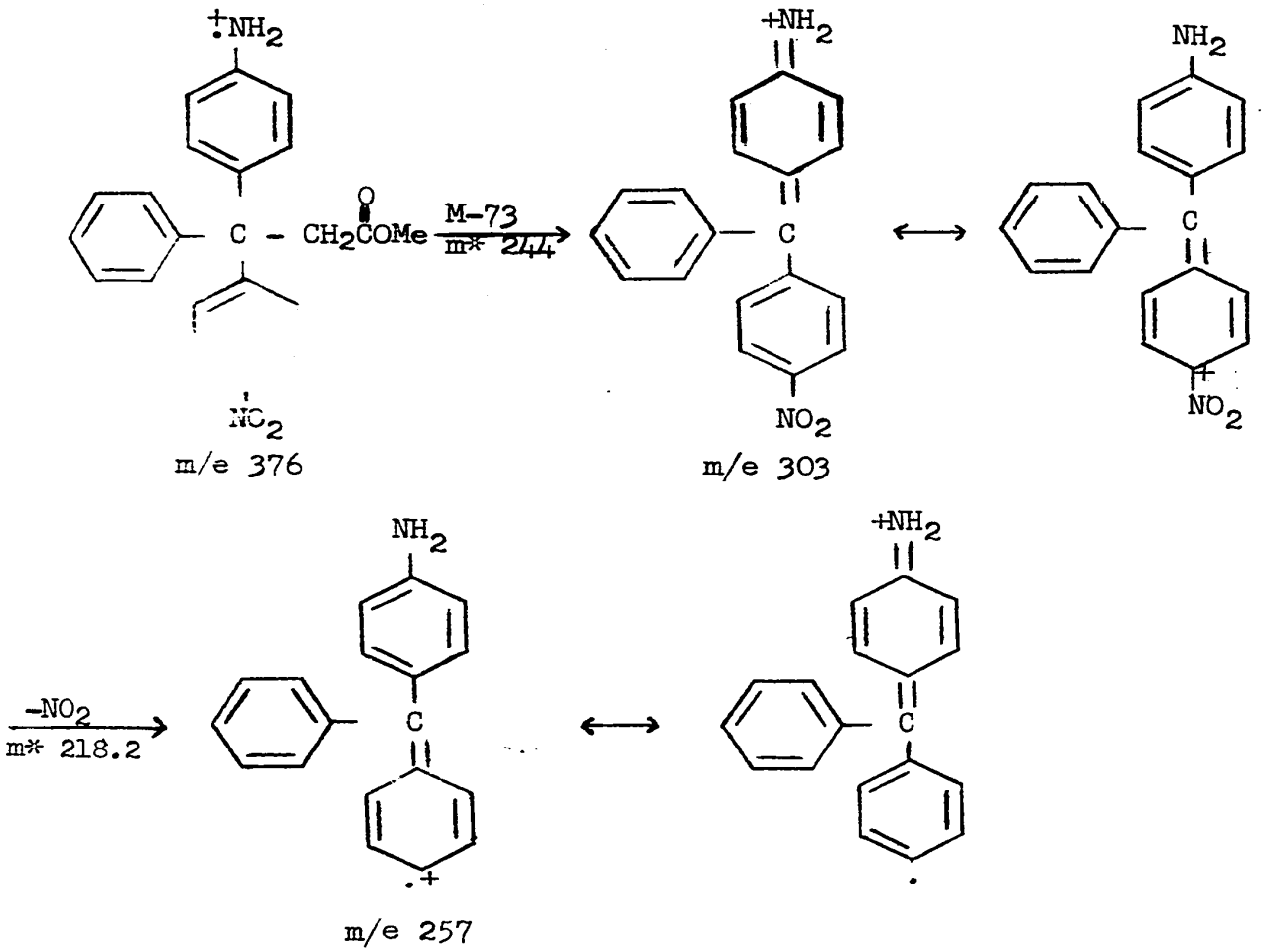
[18]The coupling constants were calculated following the methods outlined by Pople, Schneider and Bernstein (39a), and J.D. Roberts (39b).



Fragmentation Scheme 3

SUMMARY

The 60 and 100 MHz. n.m.r. spectra of compounds 9, 10, 14a, 14b, 15a and 15b were examined.[19] Compounds 14a, 14b, 15a and 15b showed only a singlet for the CH_2 group, while the doublet obtained for the CH_2 group in 9 and 10 was due to spin coupling through the acetylenic bond.

No case was observed in which any multiplicity of the methylene group was attributable to magnetic nonequivalence. The well established dependence of the magnitude of magnetic nonequivalence on solvent was considered; however a variety of solvents (acetone-d_6, carbon tetrachloride, chloroform-d_1 and dimethyl sulfoxide-d_6) failed to demonstrate any significant effect. These experiments strongly suggest that if an asymmetry effect exists as a contributor to magnetic nonequivalence it must be extremely weak.

Nevertheless on the basis of an examination of these compounds it would not be valid to assume that an asymmetry effect makes no contribution whatsoever to magnetic nonequivalence. If we assume that the equally populated conformers 1,2 and 3 (Figure 1) are rapidly interconverting, then because of lack of symmetry the two protons of the methylene group are never stereochemically equivalent. However, if the electronic screening of H_A and H_B does not significantly differ for each of the rotational isomers, then magnetic nonequivalence may not be observed.

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[19]The n.m.r. spectra of the methylene protons were studied at sweep widths of 250, 100 and 50 Hz. Figures 23, (p.68) and 24, (p. 69) represent the 100 MHz. n.m.r. spectra of the CH_2 group of compounds 9 and 15b at sweep widths of 100 and 250 Hz., respectively.

This could arise if the asymmetric magnetic field is too far removed in compounds 9 and 10 and too weak in compounds 14a, 14b, 15a and 15b to exert any appreciable influence on H_A and H_B.

Of all the compounds studied in this or in the numerous publications preceeding this thesis, there is no definite evidence available of an asymmetry effect which has been isolated from conformational effects.

EXPERIMENTAL

Melting points were determined on a Mettler FP1 Melting and Boiling Point Apparatus and are uncorrected. Elemental analyses were performed using an F and M Model 185 CHN analyzer.

Thin layer chromatographic determinations were on Eastman Chromatogram Sheets 6060 coated with silica gel containing fluorescent indicator.

Infrared spectra were recorded on a Perkin-Elmer 225 Grating Spectrophotometer and Beckman IR-8 Spectrophotometer.

Mass spectra were determined on a Hitachi RMU-6E single focussing mass spectrometer using an ionizing voltage of 70 e.v. and a source temperature of 250°.

The ^{1}H nuclear magnetic resonance spectra were recorded on Varian A-60A and HA-100 spectrometers operating at 60 and 100 MHz., respectively. The A-60A can distinguish lines 0.3 Hz. apart, which at an applied field of 14,092 gauss or frequency of 60 MHz.represents a resolving power of some 2 in 10^{8}. The chemical shifts are in parts per million from tetramethylsilane as internal reference and are recorded on the δ scale. Decoupling experiments were carried out using a model V-6058A spin decoupler.

4-N,N-Diethylamino-1-phenylbut-2-yn-1-acetate (9) and 4-N,N-Diethylamino-1-phenylbut-2-yn-1-ol (10)

These compounds were prepared according to the procedure described by Clarke and Pinder (21).

Reaction of α,α,α-trichlorotoluene with N,N-dimethyl aniline and chlorobenzene

α,α,α-Trichlorotoluene (29.32 g, 0.15 mole) was added to a mixture of N,N-dimethyl aniline (18.18 g, 0.15 mole) and chlorobenzene (16.88 g, 0.15 mole) which had been cooled in an ice bath. By slow addition of

$AlCl_3$ (16.33 g, 0.13 mole) the temperature of the reaction mixture, which had turned green, was controlled so that it did not increase above 20°. After addition of $AlCl_3$, three 5-ml aliquots were removed from the reaction mixture and were treated in the following manner:

The first aliquot was heated in an attempt to bring it to reflux, however polymerization occurred at 70°.

Benzene (100 ml) and 6N HCl (50 ml saturated with NaCl) were added to the second aliquot. The aqueous layer was extracted with three 10-ml portions of benzene. The benzene extracts were combined and dried over anhydrous sodium sulphate. Concentration under reduced pressure yielded a liquid which had a boiling point of 192° and was identified as N,N-dimethyl aniline.

Ten percent NaOH was added to the third aliquot, the aqueous layer was once again extracted with three 10-ml portions of benzene. After combining the extracts, drying over anhydrous sodium sulphate and removing the solvent under reduced pressure a liquid was obtained which was identified as N,N-dimethyl aniline.

Reaction of acetanilide, toluene, anisole and carbon tetrachloride

Aluminum chloride (16.33 g, 0.13 mole) was slowly added to a mixture of acetanilide (20.27 g, 0.15 mole), toluene (13.82 g, 0.15 mole), anisole (16.22 g, 0.15 mole) and carbon tetrachloride (23.08 g, 0.15 mole) which had been cooled in an ice bath. After adding a few grams of $AlCl_3$ the reaction mixture, which was yellow became viscous. Addition of $AlCl_3$ was continued and a solid precipitated from solution. The solid was removed by filtration, dried and recrystallized from carbon tetrachloride - chloroform (1:1) to give crystals m.p. 113°C. An infrared spectrum indicated the

presence of an amide carbonyl stretching band ν_{max} (KBr) 1665 cm^{-1} and was identical to the spectrum of acetanilide. To the liquid portion of the reaction mixture, benzene (100 ml) and 6N HCl (50 ml saturated with NaCl) were added. The aqueous layer was extracted with three 10-ml quantities of benzene. The benzene extracts were combined and dried over anhydrous sodium sulphate. Concentration under reduced pressure yielded a solid which was identified as acetanilide.

(±)-4-Chloro-4'-ethoxy-triphenylmethanol (11f)

To a mixture of magnesium metal (2.43 g, 0.10 mole), a small crystal of iodine, and anhydrous ether (50 ml), some 4-bromophenetole was added neat, dropwise, until the brown coloration arising from iodine disappeared. The remaining 4-bromophenetole was diluted with anhydrous ether (100 ml) and addition was continued. When addition was complete 30.17 g (0.15 mole) of 4-bromophenetole had been added. The reaction mixture was refluxed for 30 min and then 4-chlorobenzophenone (7.1 g, 0.033 mole) was added dropwise at a rate sufficient to keep the mixture under gentle reflux. After addition was complete the reaction mixture was refluxed for 24 h. A saturated aqueous solution of NH_4Cl (100 ml) was then added dropwise followed by addition of 10% HCl (10 ml). The ether layer was washed with saturated aqueous solutions of NaCl (100 ml) and $NaHCO_3$ (100 ml), respectively, and dried over anhydrous sodium sulphate. Concentration under reduced pressure yielded an oil. Chromatography of 11f on neutral alumina (Brockman Activity 1, 80-200 mesh) and eluting with benzene, yielded a brown glass which could not be induced to crystallize; ν max (neat) 3500 cm^{-1} (OH); δ ($CDCl_3$) 6.82-7.57 (13 proton multiplet, benzenoid protons, in which an A_2X_2 system centered at 7.11 p.p.m. was clearly observed), 4.09 (2 proton quartet, CH_2, J = 7.2 Hz.), 3.09 (1 proton

singlet, OH) and 1.39 (3 proton triplet, CH_3, J = 7.2 Hz.).

4,4'-Diaminotriphenylmethane (12a)

This compound was prepared in 45% yield according to the procedure of Baeyer and Villegar (28). The solid obtained had a m.p. of 110° in agreement with the value quoted, if benzene of crystallization were present.

4,4'-Dinitrotriphenylmethane (12b)

4,4'-Diaminotriphenylmethane (12a) (15g, 0.055 mole) was added to a mixture of 180 ml H_2O_2 (30%), concentrated H_2SO_4 (12 ml) and acetic acid (400 ml) (29). The reaction mixture, which immediately turned light brown, was slowly heated to 70° at which point heating was discontinued. After approximately 30 minutes a solid precipitated from solution and heat was reapplied. The reaction mixture was then maintained between 70-80° overnight. After cooling a yellow-brown product was removed by filtration, washed with water and dried. A small additional quantity of crude material could also be obtained by the addition of water to the filtrate. Recrystallization from n-propyl alcohol-benzene (1:1) gave the required product m.p. 169-170° (9.3 g, 51%). An analytical sample was prepared by sublimation at 3mm, 160° (bath) to give yellow prisms, m.p. 169-170°; ν_{max} (KBr) 1605, 1595, 1515 (C-NO_2) and 1347 cm^{-1} (C-NO_2); δ ($CDCl_3$) 7.2-8.6 (13 proton multiplet, in which an A_2X_2 pattern could be discerned), 5.9 (one proton singlet, CH); mass spectrometry indicated the presence of a molecular ion at 334. Anal. Calcd. for $C_{19}H_{14}N_2O_4$: C,68.26; H,4.22; N,8.38. Found for 12b: C,68.57; H,3.97; N,8.56.

4,4'-Dinitrophenylmethanol (13a)

4,4'-Dinitrotriphenylmethane (12b), (10 g, 0.03 mole) was added to a previously cooled solution (0°) of chromium trioxide (6 g, 0.06 mole) and water (6 ml) in acetic acid (40 ml) (32). The reaction mixture was slowly brought to reflux temperature and the disappearance of the methine proton was monitored by removing 5-ml aliquots and examining the n.m.r. spectrum of the product after work-up. The reaction was generally complete after 12 hours. Upon cooling a solid precipitated which was removed by filtration, washed with water and dried. The solid was recrystallized from CCl_4-Benzene (1:1). Subsequent recrystallization from n-propanol gave white crystals of 4a m.p. 133°, (7.96 g, 76%); ν_{max} (KBr) 3565 cm^{-1} (O-H); δ ($CDCl_3$) 7.1-8.6 (13 proton multiplet, benzenoid protons), 3.68 (1 proton singlet, O-H).

Anal. Calcd. for $C_{19}H_{14}N_2O_5$: C,65.14; H,4.03; N,8.00. Found for 13a: C,65.26; H,4.33; N,7.86.

(±)-4-Amino-4'-nitro-triphenylmethanol (13b)

4,4'-Dinitrotriphenylmethanol (13a) (5.0 g, 0.14 mole) was dissolved in 5 ml of ethanol and heated to reflux. To this was added dropwise a solution of sodium polysulphide (2.5 g) and sulphur (0.7 g) in aqueous ethanol. Refluxing was continued for 15 min. The solution was then cooled and poured into ten times its volume of ice-water. The yellow solid obtained was removed by filtration and dried in vacuo. Recrystallization from n-propanol gave a yellow solid which was sufficiently pure to use in subsequent reactions, (2.92 g, 64%). In order to prepare an analytical sample the product was chromatographed on neutral alumina (Brockman Activity 1, 80-200 mesh), eluting with benzene followed by benzene-chloroform (1:1). The syrupy

product was crystallized from n-propanol. Repeated recrystallization from the same solvent gave crystals of 4b m.p. 122.5-123°; ν_{max} (KBr) 3458 (OH), 3380 and 3306 (NH), 1615 (NH bending), 1503 and 1340 cm^{-1} (C-NO_2); δ ($CDCl_3$) 6.56-8.42 (13 proton multiplet, benzenoid; two A_2X_2 systems, centered at 6.91 and 8.0 p.p.m. were clearly observed), 3.6 (singlet, 3 protons, OH and NH_2 overlapping). Mass spectrometry showed the presence of a molecular ion at m/e 320.

Anal. Calcd. for $C_{19}H_{16}N_2O_3$: C,71.24; H,5.03; N,8.75. Found for 13b: C,71.16; H,4.98; N,8.59.

(±)-4-Acetanilidyl-4'-nitrophenyl-phenyl-methanol (13c)

(±)-4-Amino-4'-nitro-triphenylmethanol (13b) (20 g, 0.063 mole) was acetylated at room temperature with acetic anhydride (19.1 g, 0.12 mole) in the presence of a few drops of pyridine. After pouring the reaction mixture into water, the product was extracted with chloroform. The solution was washed first with a saturated aqueous $NaHCO_3$ solution, then with water, and dried over anhydrous sodium sulphate. Concentration under reduced pressure yielded a glass which when heated with ligroin gave an amorphous solid. Chromatography of 13c on neutral alumina (Brockman Activity 1, 80-200 mesh) eluting with benzene-diethylether (3:1) gave a brown glass which could not be induced to crystallize (18.8 g, 83%); ν_{max} (KBr) 1670 cm^{-1} (C=O); δ ($CDCl_3$) 8.2 (1 proton singlet, NH), 6.8-8.0 (13 proton multiplet, benzenoid protons), 4.02 (1 proton singlet, OH) and 1.88 (3 proton singlet, CH_3); mass spectrometry indicated the presence of a molecular ion at m/e 362.

(±)-3-[4-Acetanilidyl-4'-nitrophenyl-phenyl]-propionic acid (14a)

To (±)-4-acetanilidyl-4'-nitrophenyl-phenyl-methanol (13c) (2 g, 0.006 mole) was added malonic acid (8 g, 0.08 mole) (23). The solids were fused at 170° for 36 min. After cooling, the product was extracted with a saturated aqueous solution of $NaHCO_3$ and precipitated by the addition of dilute HCl. After filtration the product was dried and recrystallized from benzene. Subsequent recrystallization from ethanol-benzene (1:1) and ethanol, gave a white amorphous solid 5a m.p. 174°, 1.7 g (76%); ν_{max} (KBr) 1715 (C=O, acid), 1665 cm^{-1} (C=O, amide); δ (CF_3CO_2H) 9.84 (1 proton singlet, acid proton), 8.80-7.40 (14 proton multiplet, benzenoid protons overlapping with N-H), 4.22 (2 proton singlet, CH_2), 2.70 (3 proton singlet, CH_3). Mass spectrometry indicated the presence of a molecular ion at m/e 404.

Anal. Calcd. for $C_{23}H_{20}N_2O_5$: C,68.31; H,4.99; N,6.93. Found for 14a C,68.45; H,5.17; N,7.01.

Hydrolysis of the Amide 14a and esterification of the product to (±) Methyl 3-[4-anilino-4'-nitrophenyl-phenyl]-propionate (15b)

(±)-3-[4-Acetanalidyl-4'-nitrophenyl-phenyl]-propionic acid (14a) (4 g, 0.01 mole) was dissolved in 100 ml of hot aqueous ethanol. An aqueous solution of 10% HCl (40 ml) was then added dropwise. Refluxing was continued until thin layer chromatography showed complete disappearance of 14a. After cooling, ammonium hydroxide (sp. gr. 0.90) was added until pH 5.9, whereupon a yellow solid precipitated. This solid was chromatographed on partially deactivated alumina (Brockman, Neutral Activity 1 (100 g) to which had been added 5 g water); elution with chloroform yielded (±) ethyl 3-[4-anilino-4'-nitrophenyl-phenyl]-propionate (15a), identified by its ^1H n.m.r. and

infrared spectrum. The amino acid could be removed from the column by the addition of ammonium hydroxide (sp. gr. 0.90). Careful addition of HCl (36.5%) to the ammoniacal solution caused precipitation of the amino acid at pH 5.9. After drying in vacuo the solid had a m.p. (120-125°). It was identified as (±)-3-[4-anilino-4'-nitrophenyl-phenyl]-propionic acid (14b) from its infrared and n.m.r. spectra. The hydrochloride of 14b (2 g, 0.005 mole) was esterified with dimethylsulphite (5 g, 0.045 mole) (16) to give the methyl ester hydrochloride as a glass in quantiative yield. The free amine 15b was obtained by treatment of an aqueous ethanolic solution of the hydrochloride of 15b with ammonium hydroxide (sp. gr. 0.90). The compound failed to recrystallize from any of the usual solvents. Chromatography of 15b on neutral alumina (Brockman Activity 1, 80-200 mesh) gave after elution with carbon tetrachloride followed by benzene a yellow glass, which could not be induced to crystallize. Its infrared spectrum showed ν_{max} 3490 (N-H), 3395 (N-H), 1735 (C=O), 1620 (N-H bending), 1512 ($C-NO_2$), 1348 cm^{-1} ($C-NO_2$); δ ($CDCl_3$) 6.50-8.38 (13 proton multiplet, benzenoid; two A_2X_2 systems were clearly discerned), 3.80 (4 protons, a sharp spike for CH_2 superimposed on a broad peak, NH_2), 3.46 (3 proton singlet, CH_3). A mass spectrum indicated the presence of a molecular ion at m/e 376.

Anal. Calcd. for $C_{22}H_{20}N_2O_4$: C,70.20; H,5.36; N,7.44. Found for 15b C,70.14; H,5.64; N,7.58.

4,4'-Dinitrobenzophenone

To a refluxing solution of 13a (1.25 g, 0.0036 mole dissolved in 70 ml of benzene) was added dropwise acetyl chloride (0.62 g, 0.0079 mole).

The homogeneous mixture was refluxed for 24 h. Upon cooling the solution, a solid precipitated. The solid was removed by filtration and dried. Recrystallization from benzene gave crystals m.p. 188-189°; ν_{max} (KBr) 1660 cm^{-1} (diaryl C=O); δ ($CDCl_3$) 8.40-7.22 (benzenoid protons, in which an A_2X_2 system centered at 8.1 p.p.m. was clearly discernible). The solid was identified as 4,4'-dinitrobenzophenone.

BIBLIOGRAPHY

1. V.J. Morlino and R.B. Martin. J. Am. Chem. Soc. 89, 3107 (1967).
2. M. van Gorkom and G.E. Hall. Quart. Rev. 22, 14 (1968).
3. G.M. Whitesides, F. Kaplan, K. Nagarajan, and J.D. Roberts. Proc. Natl. Acad. Sci. U.S. 48, 1112 (1962), and references therein.
4. P.M. Nair and J.D. Roberts. J. Am. Chem. Soc. 79, 4565 (1957).
5. J.A. Pople. Mol. Phys. 1, 3 (1958).
6. J.S. Waugh and F.A. Cotton. J. Phys. Chem. 65, 562 (1961).
7. E.I. Snyder. J. Am. Chem. Soc. 85, 2624 (1963).
8. G.M. Whitesides, D. Holtz, and J.D. Roberts. J. Am. Chem. Soc. 86, 2628 (1964).
9. H.S. Gutowsky. J. Chem. Phys. 37, 2196 (1962).
10. D.H.R. Barton and R.C. Cookson. Quart. Rev. 10, 44 (1956).
11. L.M. Jackman and N.S. Bowman. J. Am. Chem. Soc. 88, 5565 (1966).
12. J.J. Drysdale and W.D. Phillips. J. Am. Chem. Soc. 79, 319 (1957).
13. H. Finegold. Proc. Chem. Soc. 283 (1960).
14. P.R. Schafer, D.R. Davis, M. Vogel, K. Nagarajan, and J.D. Roberts. Proc. Natl. Acad. Sci. U.S. 47, 49 (1961).
15. T.D. Coyle and F.G.A. Stone. J. Am. Chem. Soc. 83, 4138 (1961).
16. D.R. Davis and J.D. Roberts. J. Am. Chem. Soc. 84, 2252 (1962). D.R. Davis, R.P. Lutz, and J.D. Roberts. J. Am. Chem. Soc. 83, 246 (1961).
17. J.N. Shoolery and B. Crawford, Jr. J. Mol. Spectroscopy, 1, 270 (1957).
18. S. Goodwin, J.N. Shoolery, and L.F. Johnson. J. Am. Chem. Soc. 81, 3065 (1959); H.O. House and W.F. Gilmore. J. Am. Chem. Soc. 83, 3980 (1961); T.H. Suddall III and C.H. Prohaska. J. Am. Chem. Soc. 84, 2502 (1962).

19. E.I. Snyder. J. Am. Chem. Soc. 88, 1165 (1966).

20. V.W. Laurie and D.R. Lide. J. Chem. Phys. 31, 939 (1959).

21. C.B. Clarke and A.R. Pinder. J. Chem. Soc. 1967 (1958)

22. S. Patai, S. Dayagi and R. Friedlander. J. Chem. Soc. 723 (1962).

23. S. Patai and S. Dayagi. J. Chem. Soc. 716 (1962).

24. M. Gomberg. Ber. 33, 3147 (1900); C.R. Hauser and B.E. Hudson, Jr. Organic syntheses. Collective Vol. III. John Wiley and Sons, Inc., New York. 1955. p. 842.

25. W.E. Bachmann and H.P. Hertzner. Organic syntheses. Collective Vol. III. John Wiley and Sons, Inc., New York. 1955. p. 839.

26. A. Kovache. Ann. Chim. 10, 184 (1918).

27. M.S. Kharasch and O. Reinmuth. Grignard reactions of nonmetallic substances. Prentice-Hall Inc., New York. 1954. Chap. 19. p. 1199.

28. A. Baeyer and V. Villiger. Ber. 37, 2848 (1904).

29. R.R. Holmes and R.P. Bayer. J. Am. Chem. Soc. 82, 3454 (1960).

30. F.W. McLafferty. Interpretation of mass spectra. W.A. Benjamin Inc., New York. 1967. p. 64.

31. W. Staedel. Ann. 283, 153 (1894).

32. K.B. Wiberg and R.J. Evans. Tetrahedron, 8, 313 (1960).

33. J. Rocek. Tetrahedron Letters, 4, 135 (1962).

34. L.M. Litvinenko and N.F. Levchenko. Zhur. Obshchei Khim. 31, 562 (1961).

35. K. Biemann. Mass spectrometry. Organic chemical applications. McGraw-Hill Book Co. Inc., New York. 1962. p. 112.

36. W.E. Bachmann. Organic syntheses. Collective Vol. III. John Wiley and Sons, Inc., New York. 1955. p. 841.

37. W.H. Starnes, Jr. J. Am. Chem. Soc. 90, 1807 (1968).
W.H. Starnes, Jr. J. Am. Chem. Soc. 89, 3368 (1967).

38. P.A. Cruickshank and J.C. Sheehan. Anal. Chem. 36, 1191 (1964).

39. (a) J.A. Pople, W.G. Schneider and H.J. Bernstein. High resolution nuclear magnetic resonance. McGraw-Hill Book Co. Inc., New York. 1959. p. 138. (b) J.D. Roberts. An introduction to the analysis of spin-spin splitting in high resolution nuclear magnetic resonance spectra. W.A. Benjamin, Inc., New York. 1961. p. 89.

APPENDIX

Figure 7 ^{1}H nuclear magnetic resonance spectrum of (a), 4-N,N-diethylamino-1-phenylbut-2-yn-1-acetate (9), 60 MHz., 500 Hz. sweep width; (b) Decoupling experiment (p. 16).*

Figure 8 ^{1}H nuclear magnetic resonance spectrum of 4-N,N-diethylamino-1-phenylbut-2-yn-1-ol (10), 60 MHz., 500 Hz. sweep width (p. 16).

Figure 10 ^{1}H nuclear magnetic resonance spectrum of 4,4'-Dinitrotriphenylmethane (12b), 60 MHz., 500 Hz. sweep width (p. 20).

Figure 11 ^{1}H nuclear magnetic resonance spectrum of (a) 4,4'-Dinitrotriphenylmethanol (13a), 60 MHz., 500 Hz. sweep width; (b) after addition of deuterium oxide (p. 25).

Figure 12 ^{1}H nuclear magnetic resonance spectrum of (a) (±)-4-Amino-4'-nitro-triphenylmethanol (13b), 60 MHz., 500 Hz. sweep width; (b) after addition of deuterium oxide (p. 25).

Figure 13 ^{1}H nuclear magnetic resonance spectrum of (±)-4-Acetanilidyl-4'-nitrophenyl-phenyl-methanol (13c), 60 MHz., 500 Hz. sweep width; (b) after addition of deuterium oxide (p. 25).

Figure 14 Infrared spectrum (KBr); (±)-3-[4-Acetanilidyl-4'-nitrophenyl-phenyl]-propionic acid (14a), (p. 28).

Figure 15 ^{1}H nuclear magnetic resonance spectrum of (±)-3-[4-Acetanilidyl-4'-nitrophenyl-phenyl]-propionic acid (14a), 60 MHz., 500 Hz. sweep width (p. 28).

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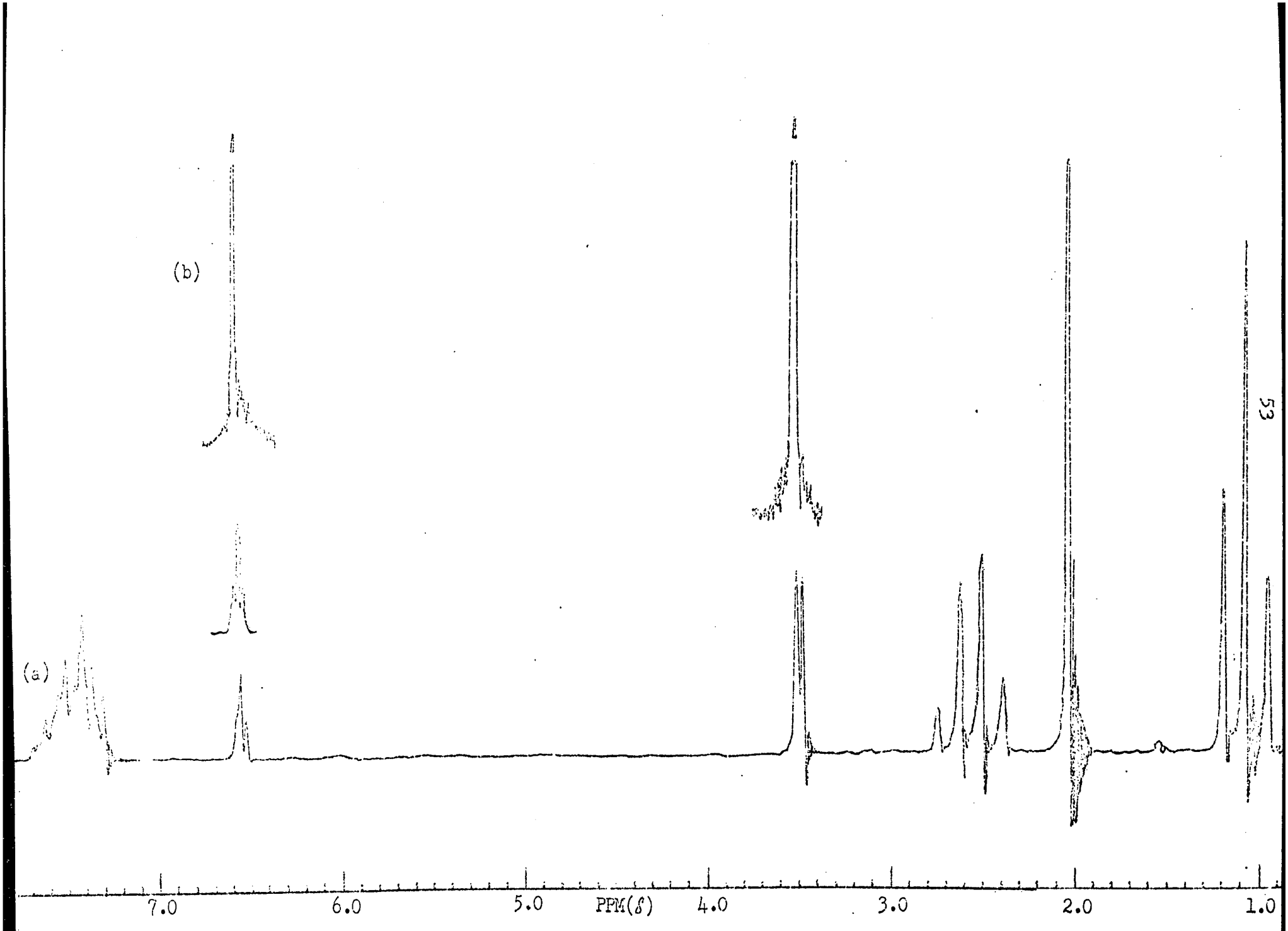
*Cross references with text are given in brackets after spectrum identification.



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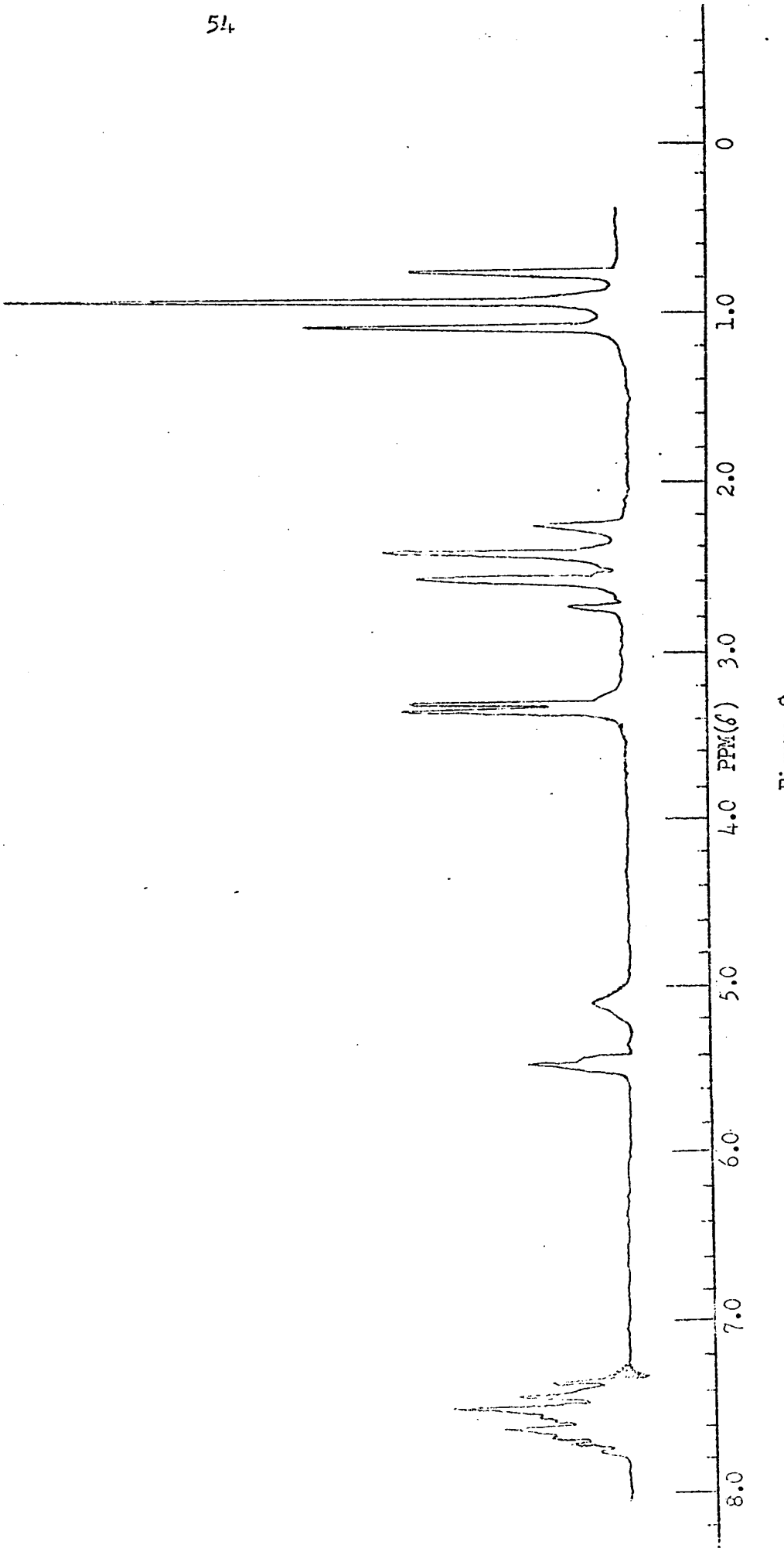

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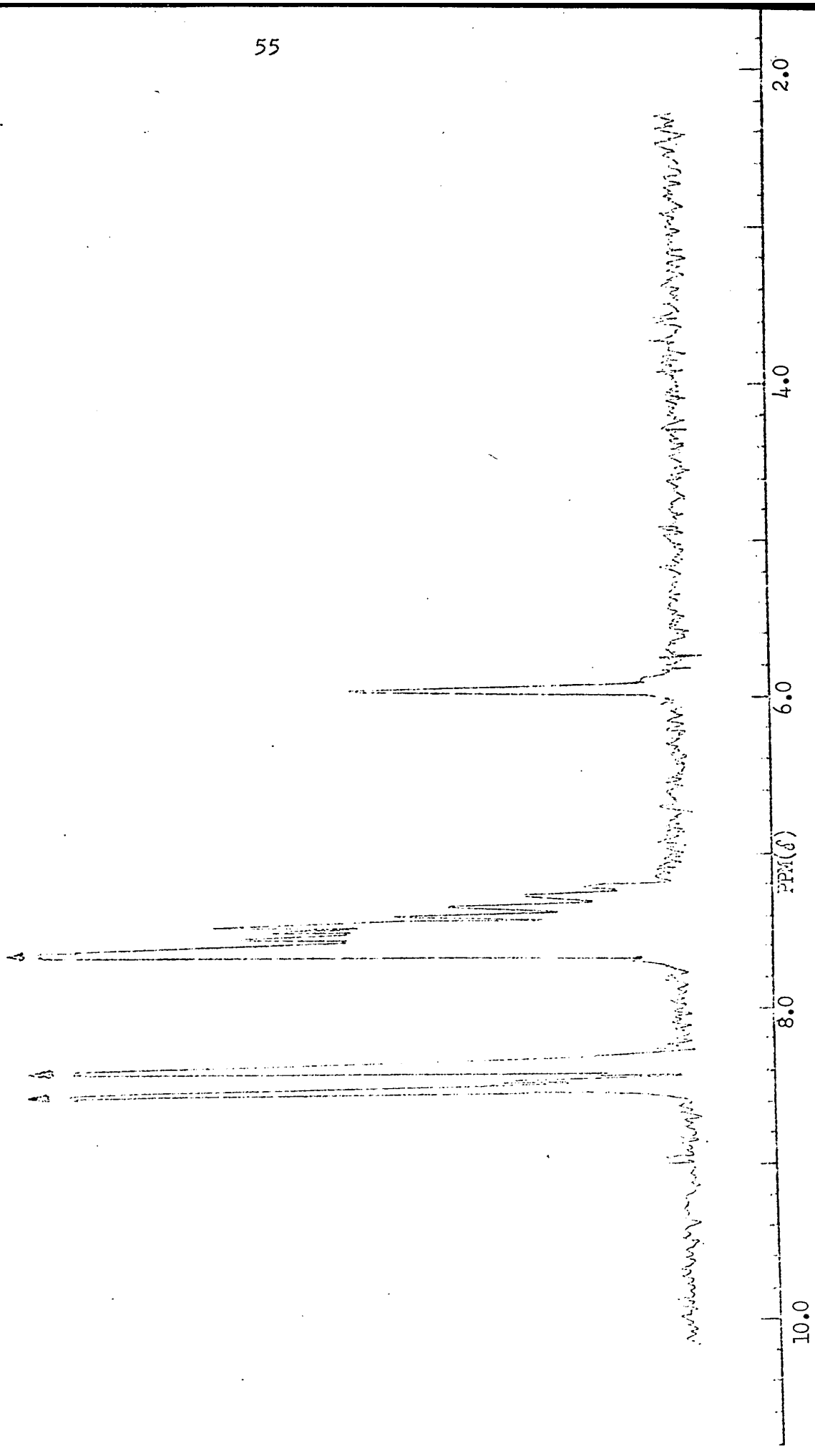

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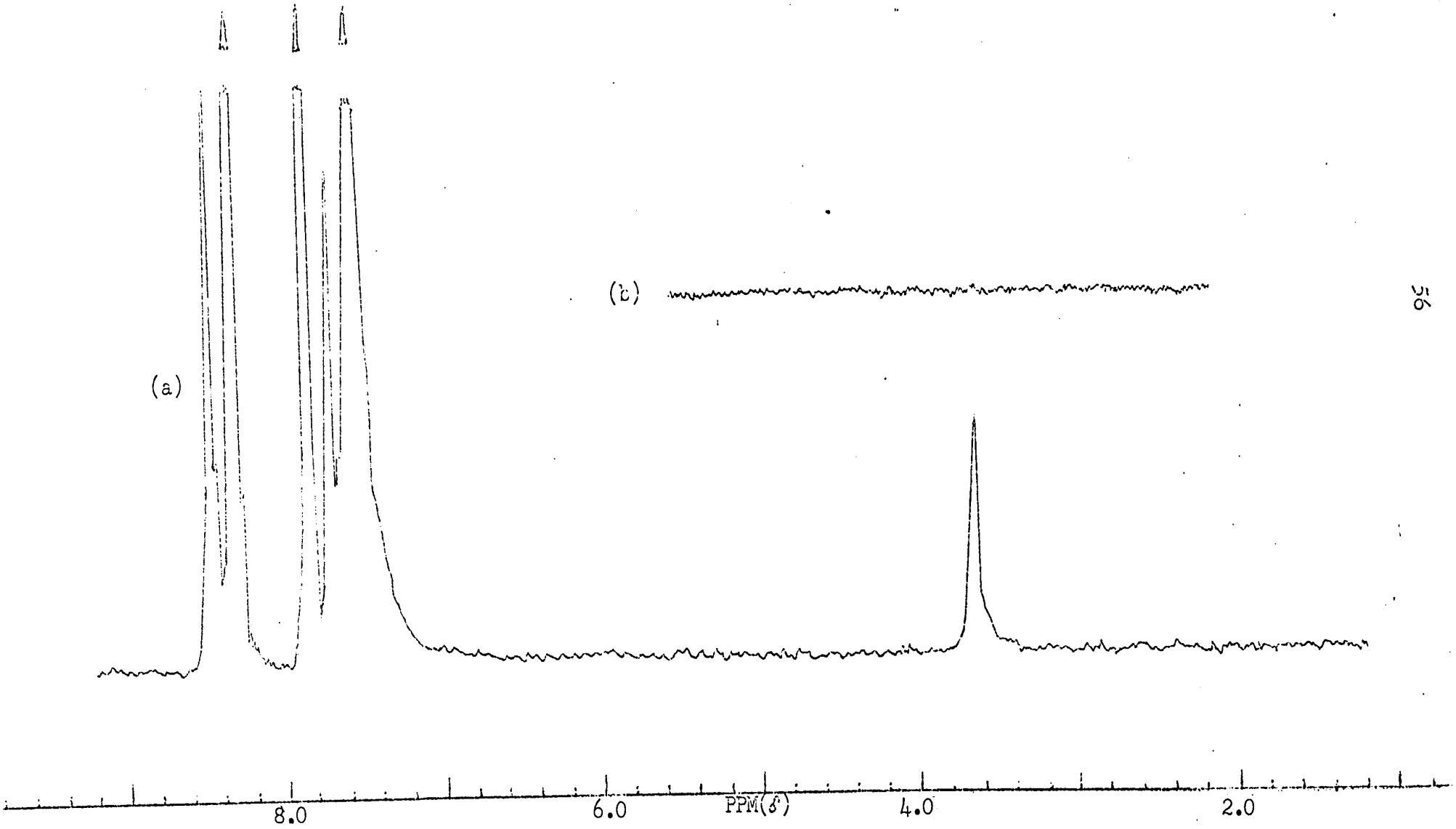

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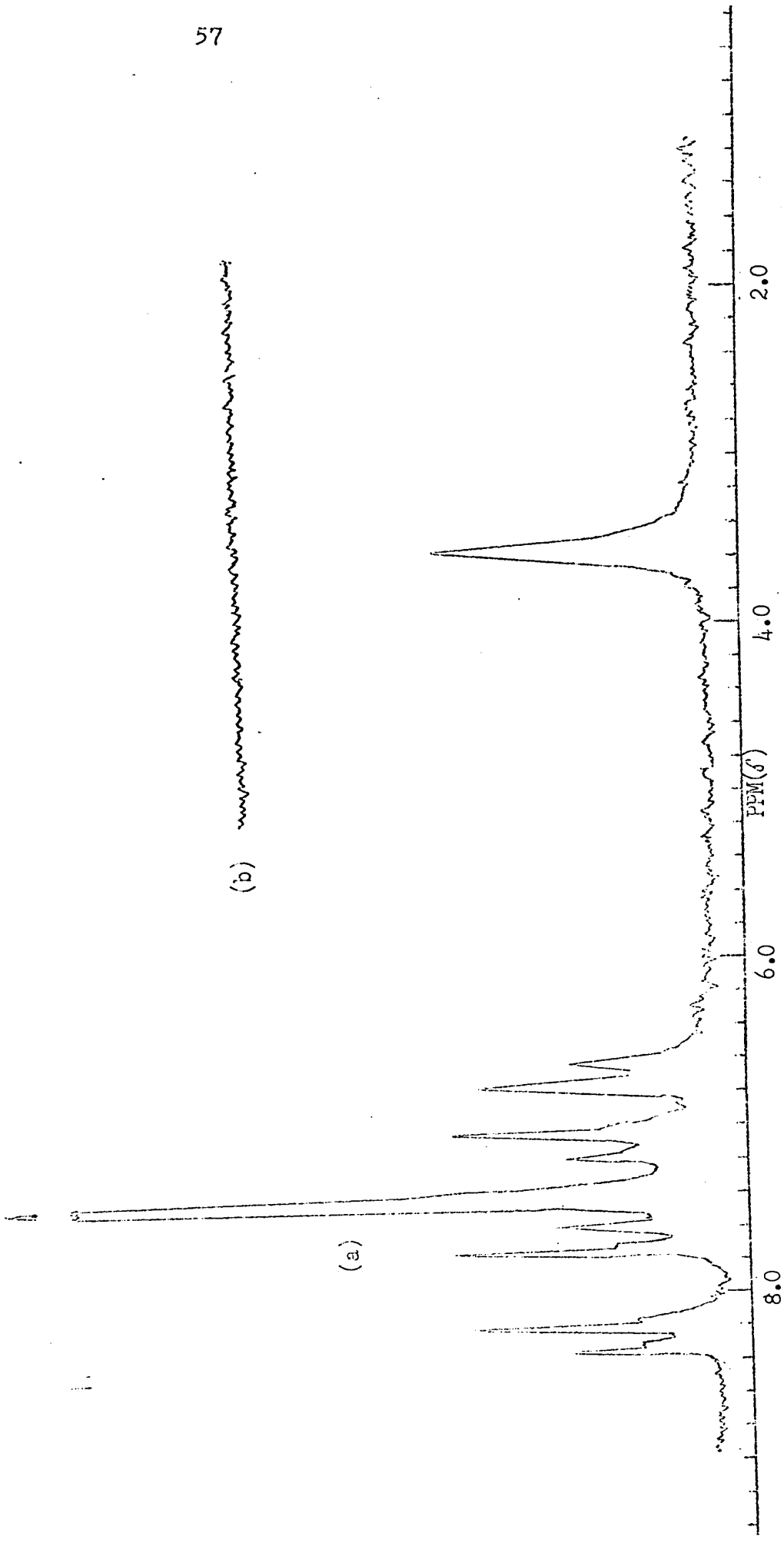

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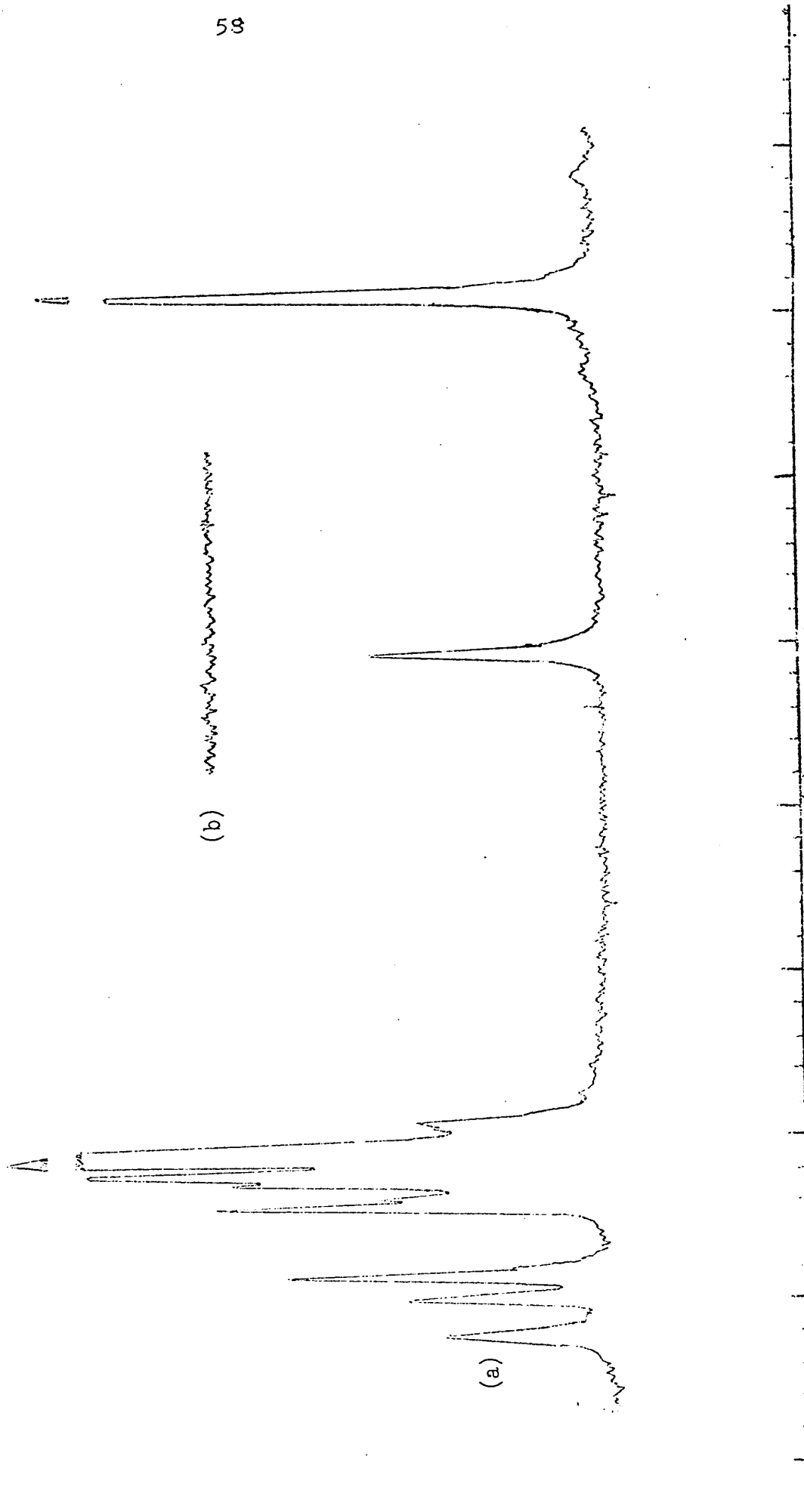

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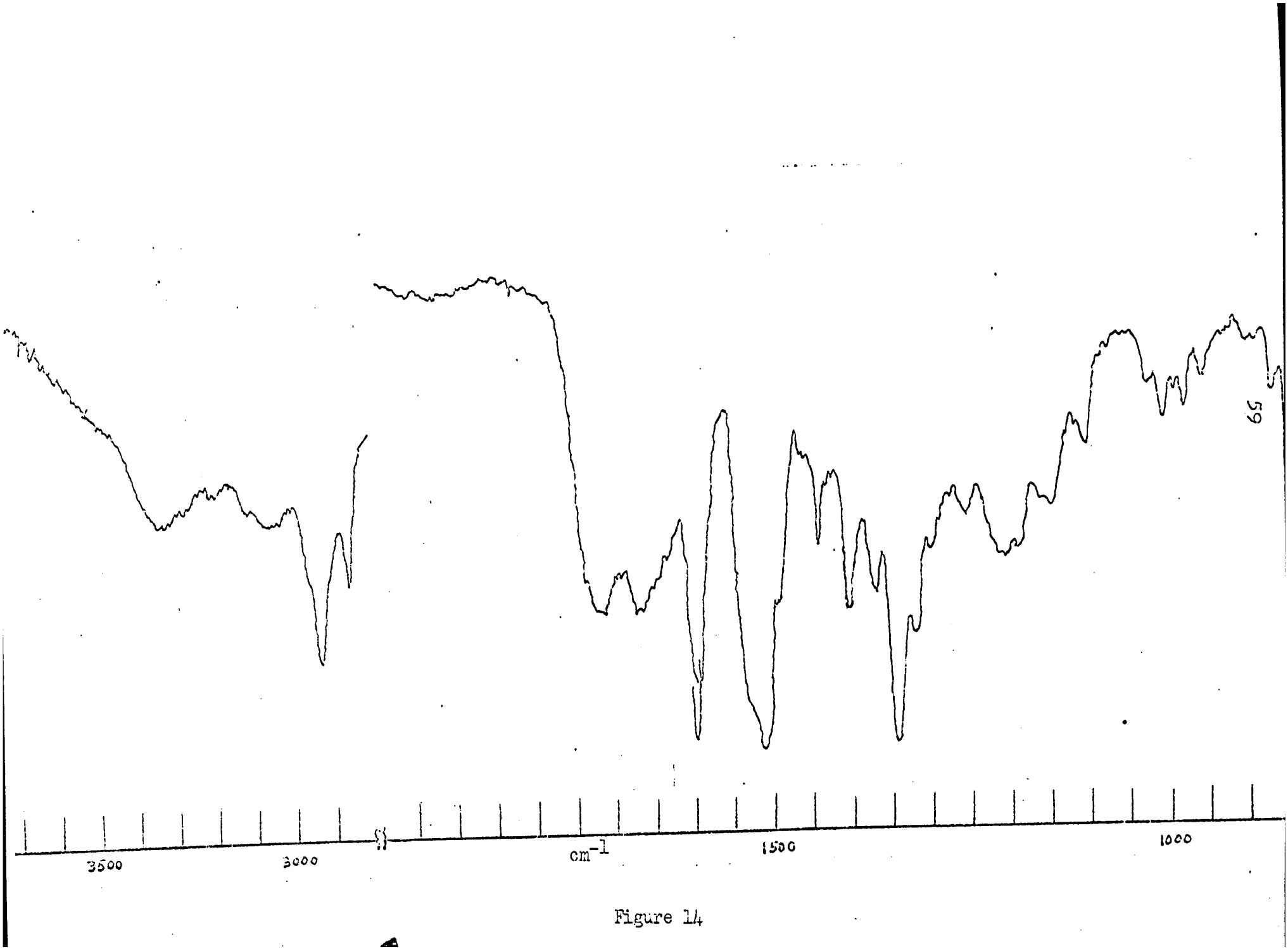

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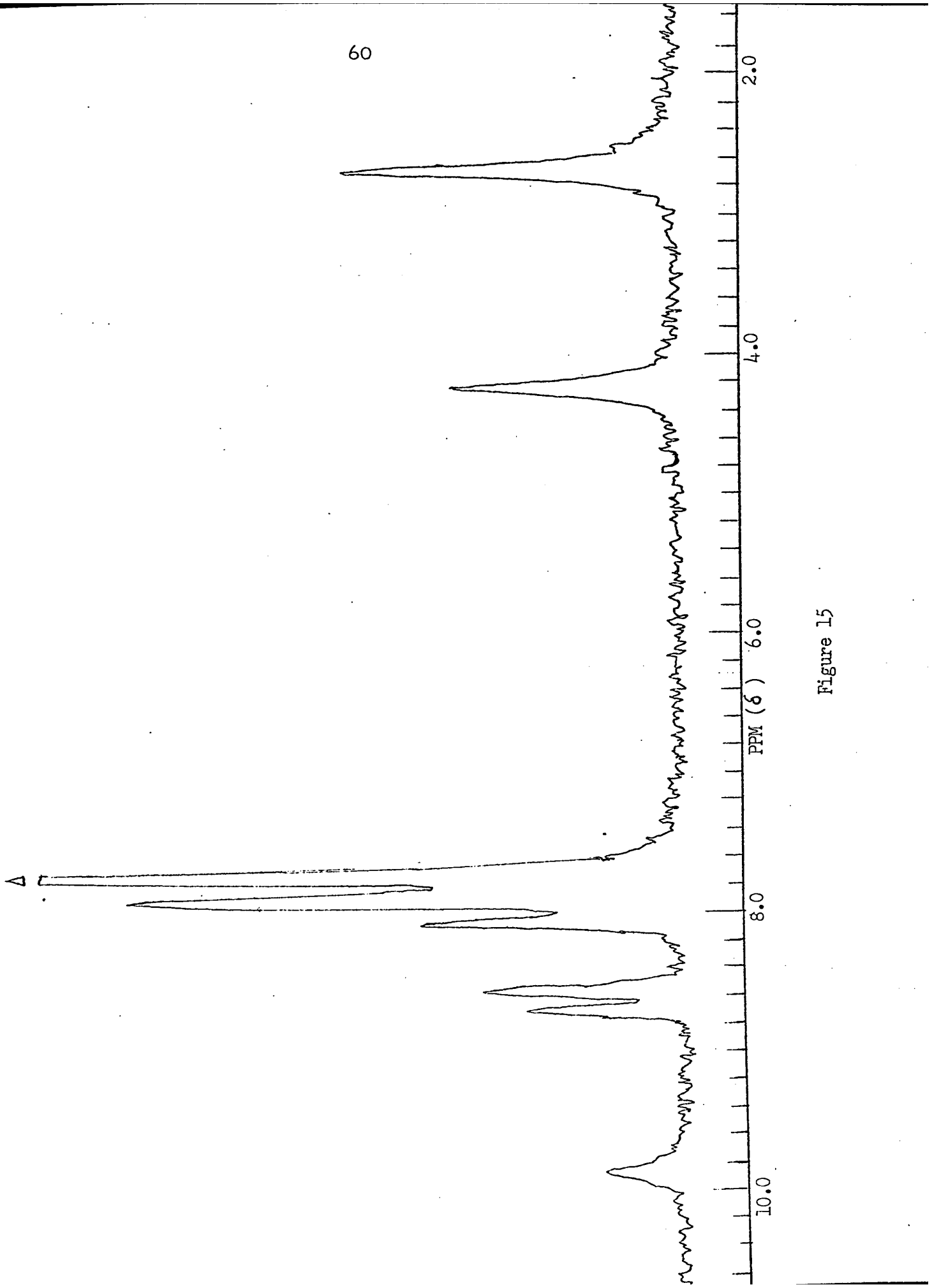

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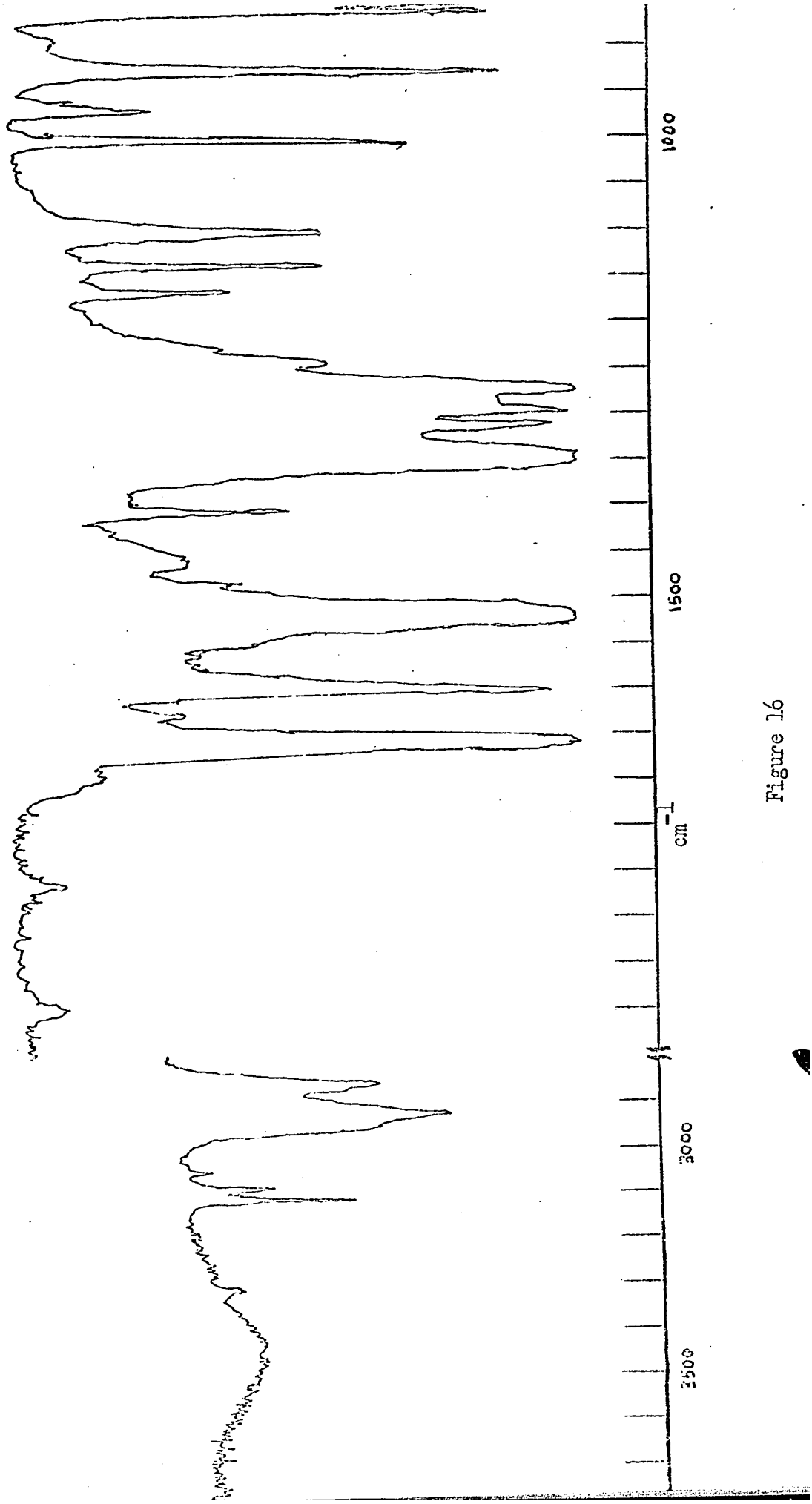

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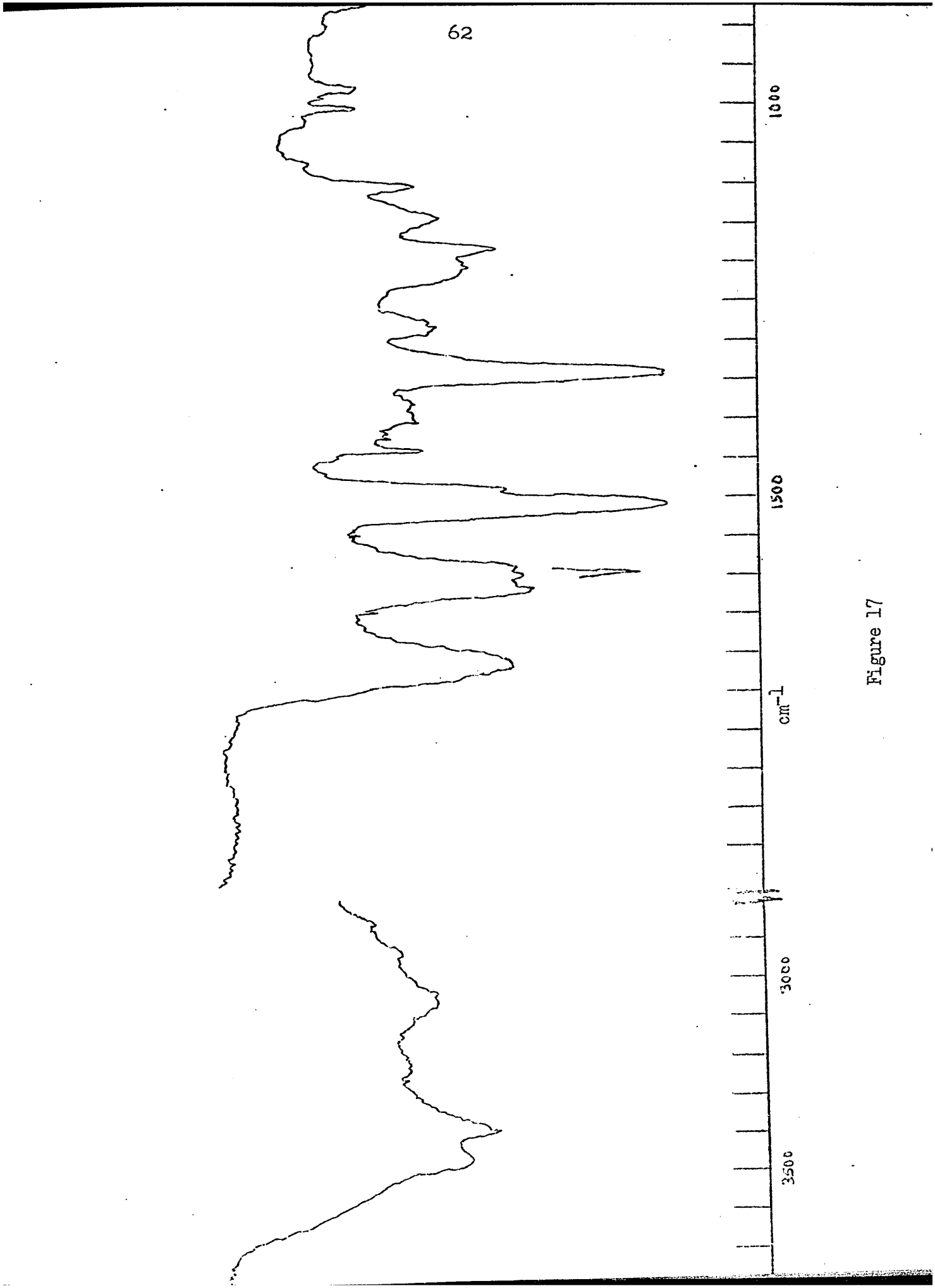

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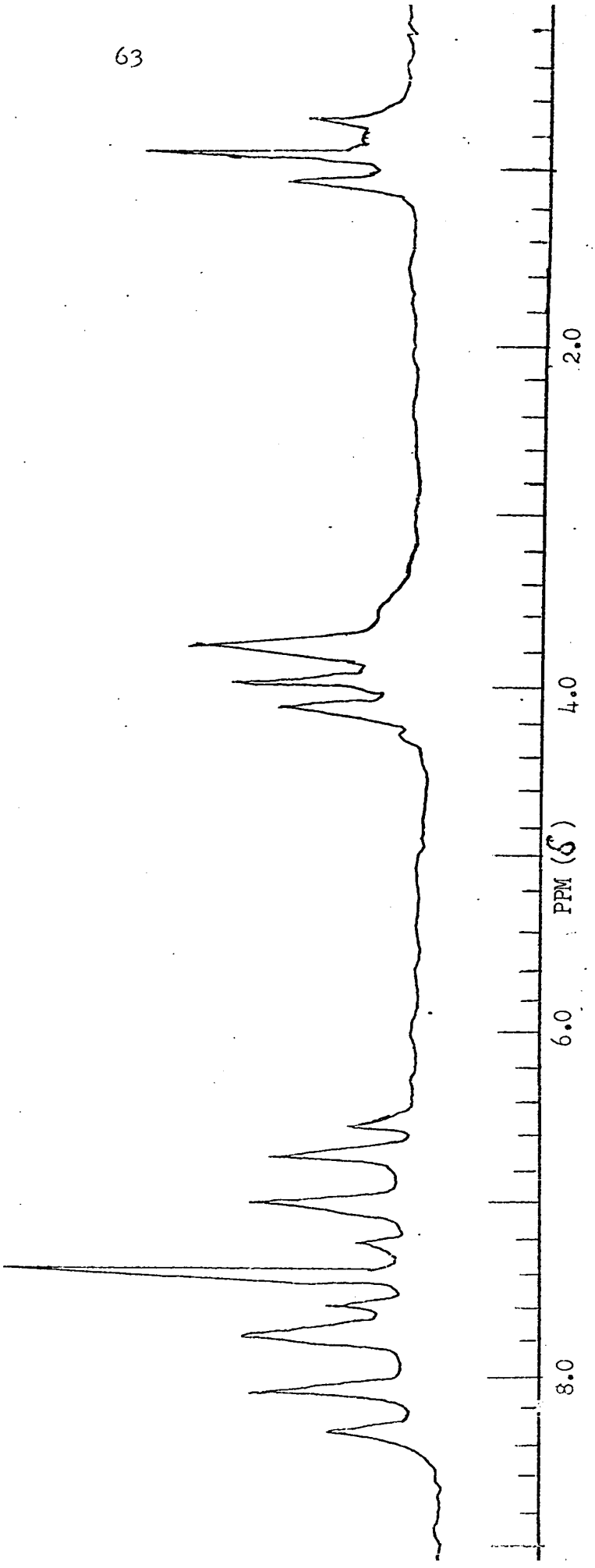

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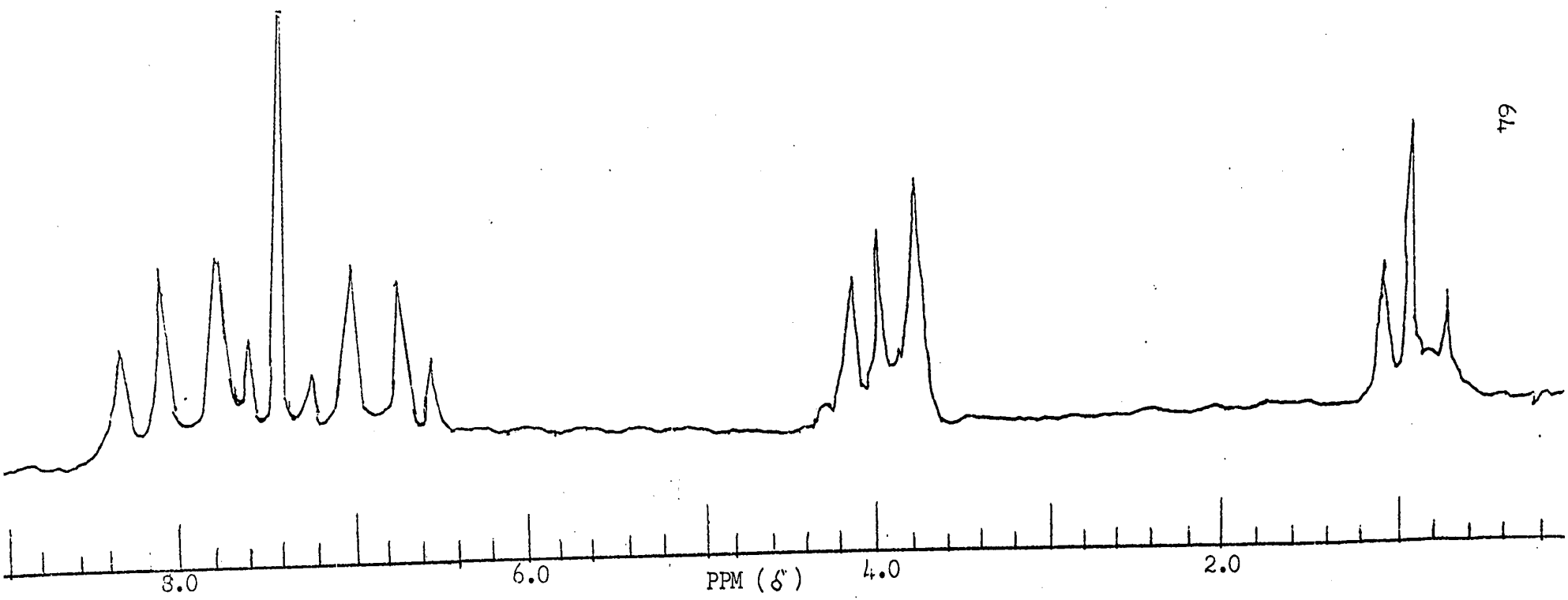

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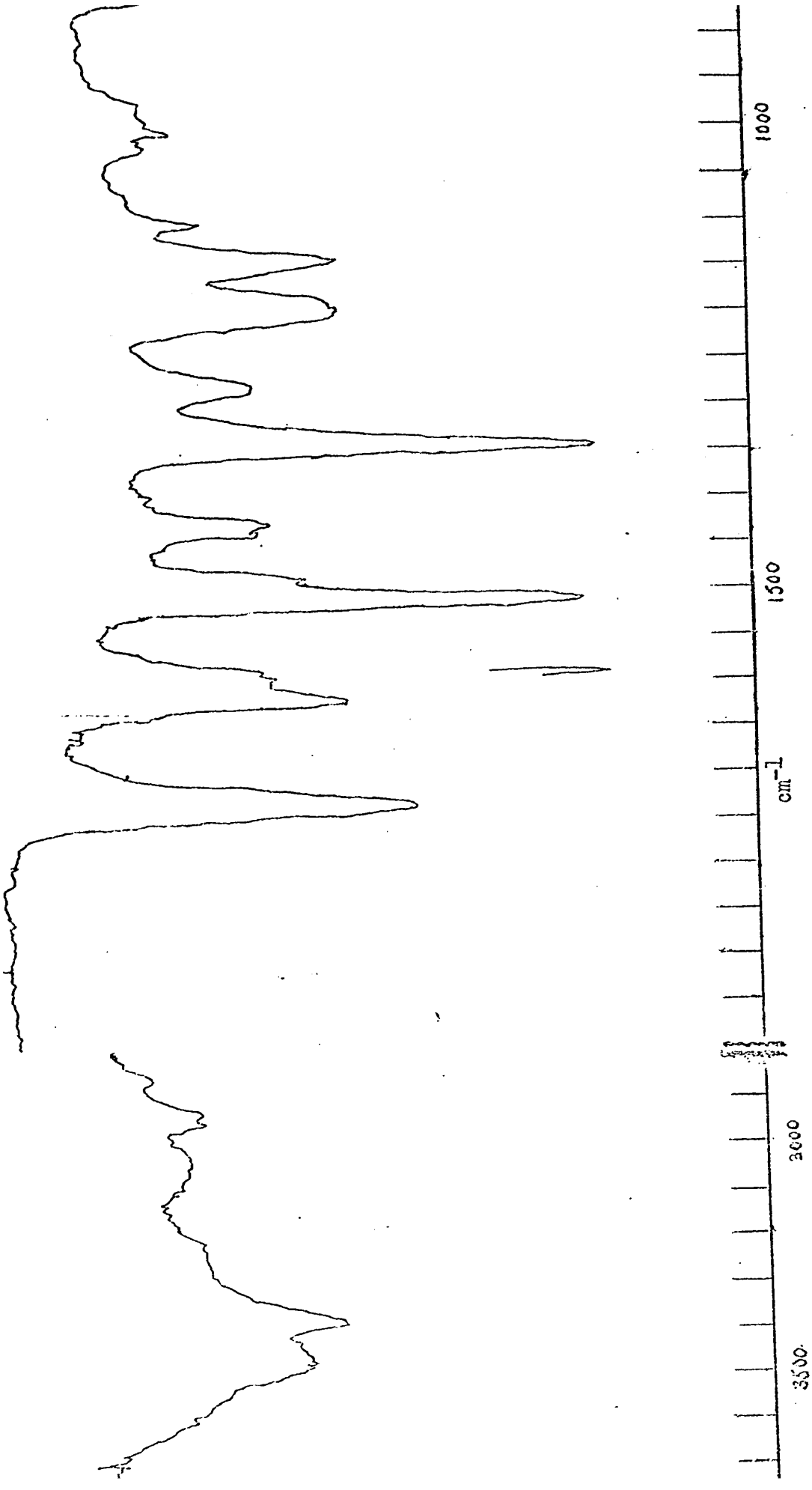

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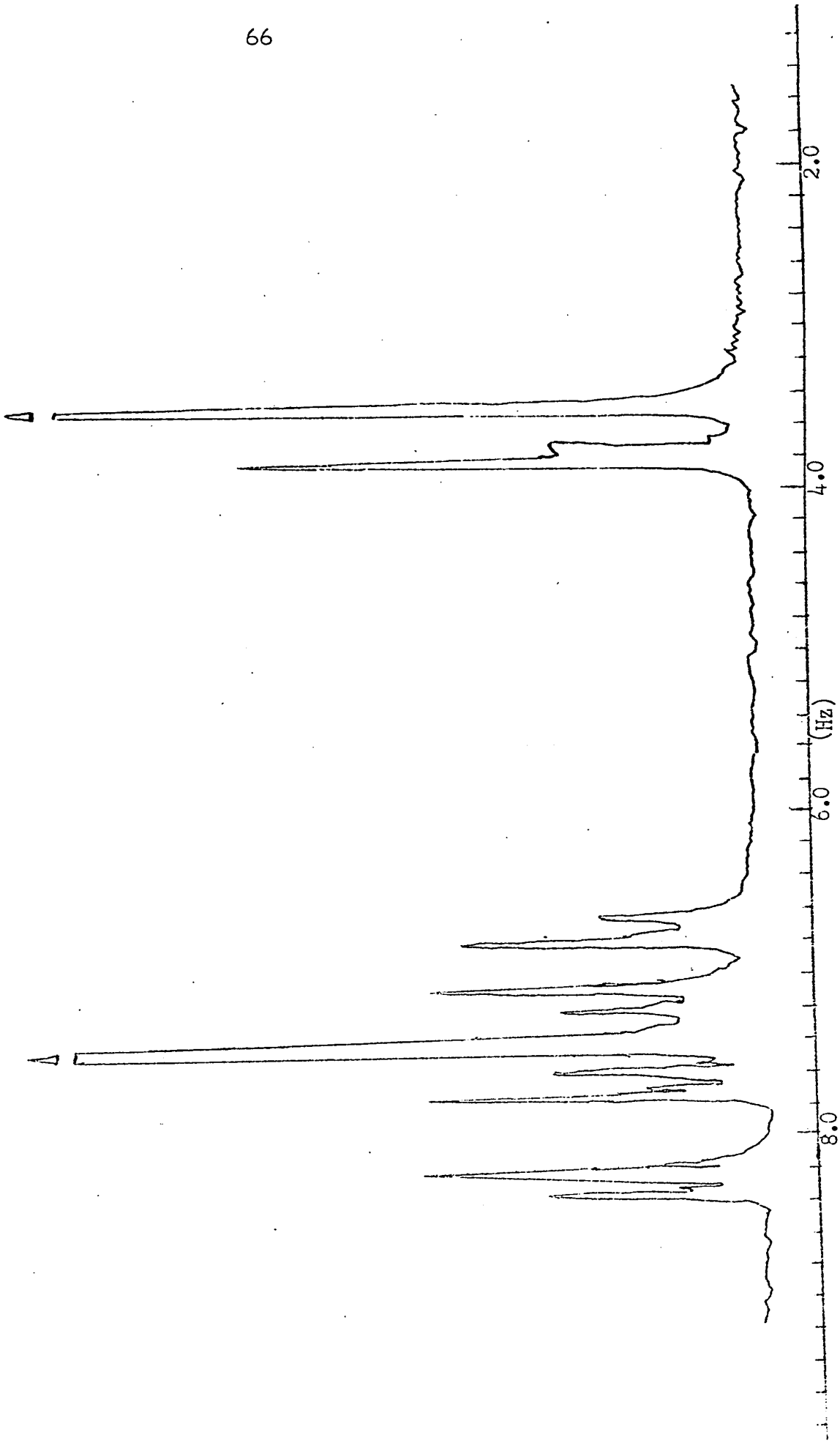

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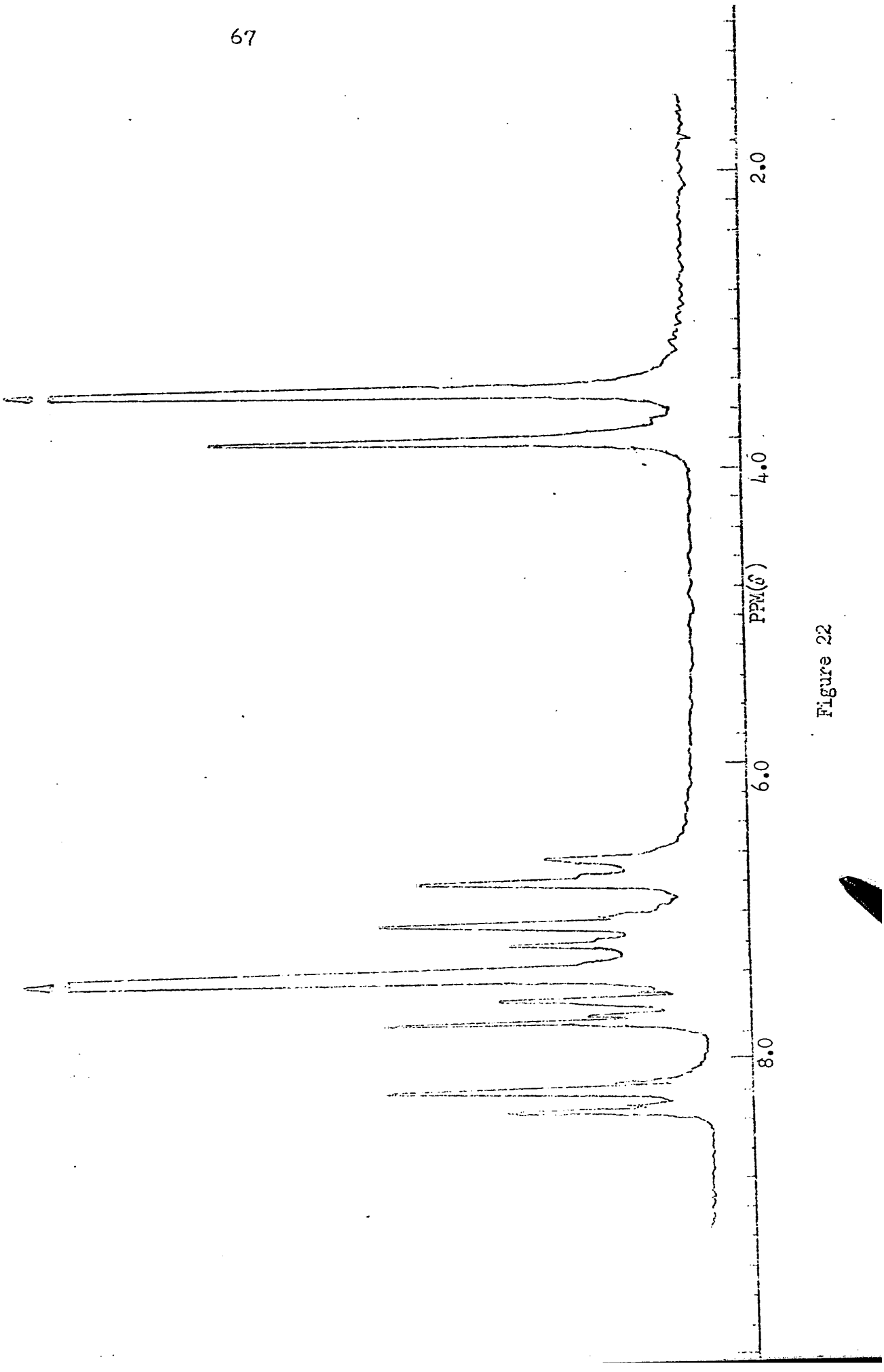

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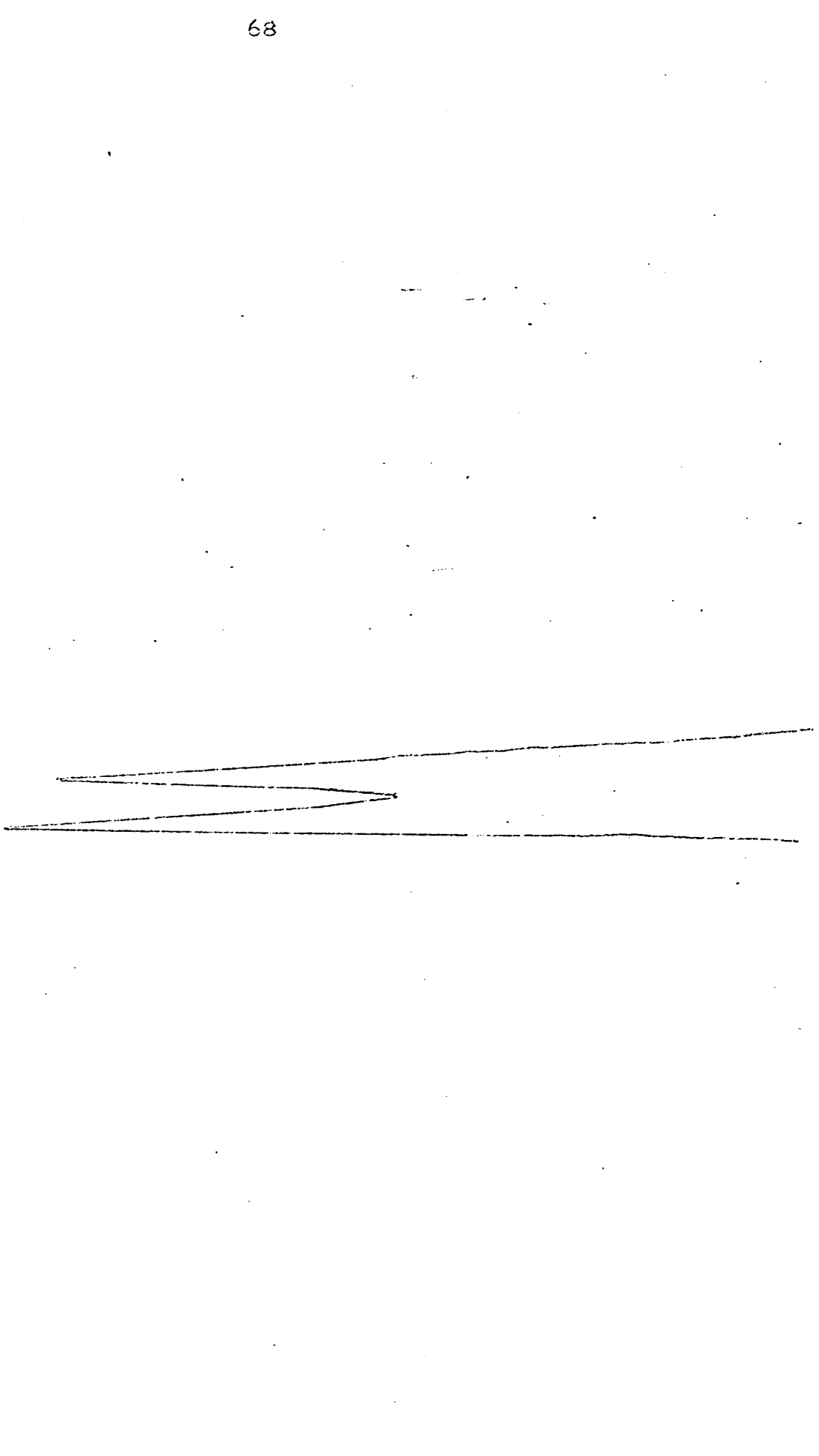

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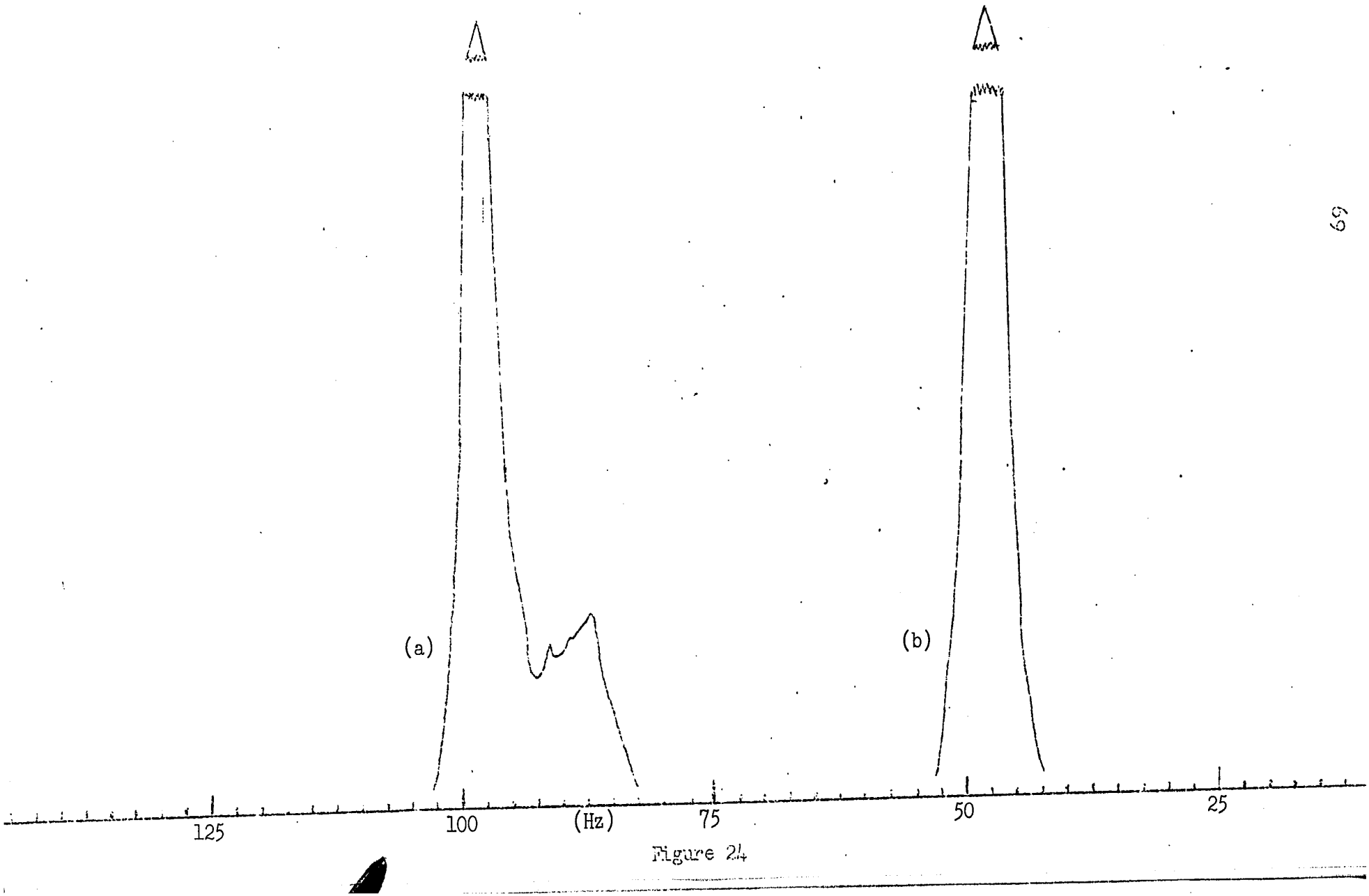

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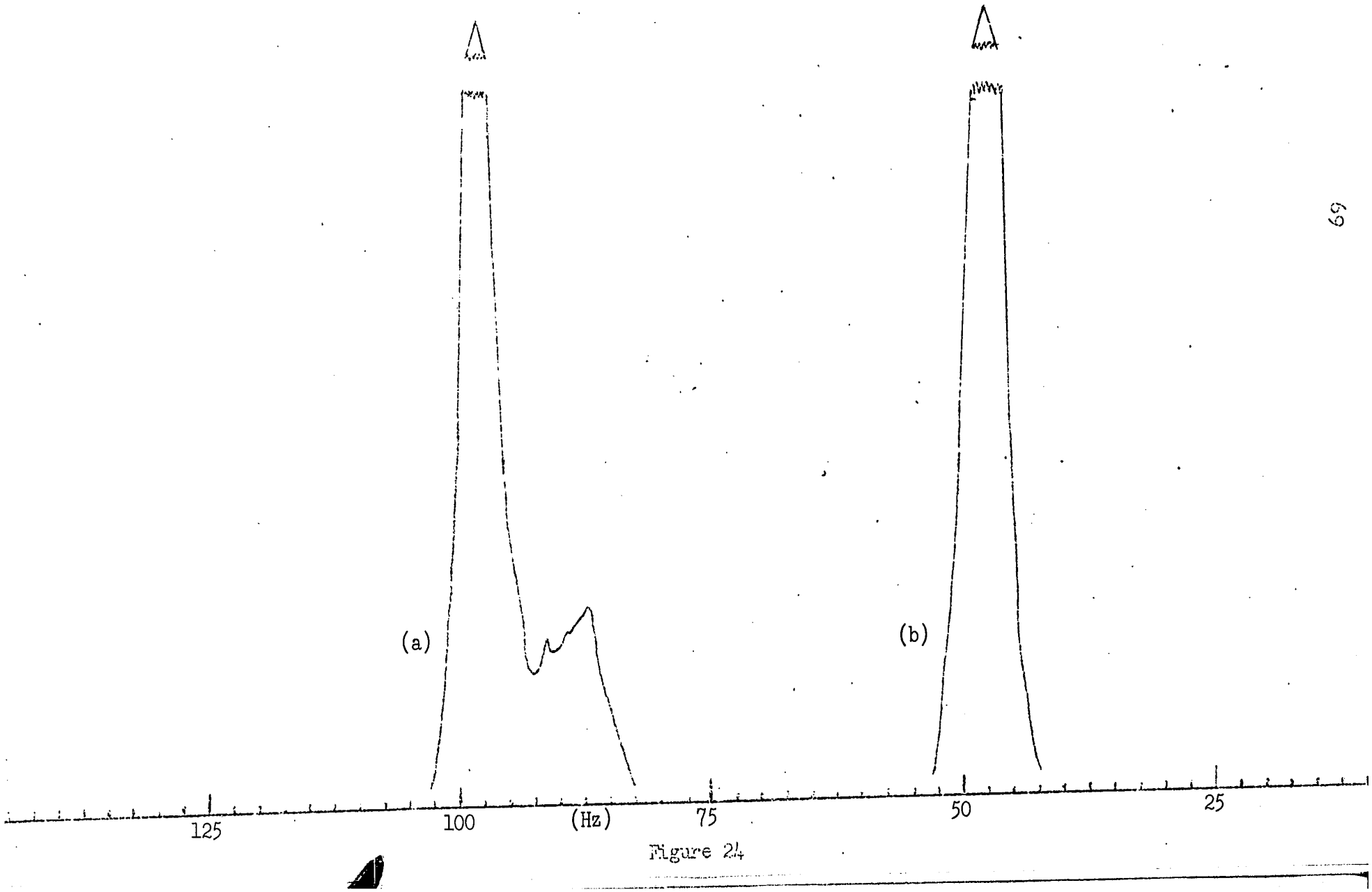

Figure 24