REACTIONS OF PARA-NITROANILINE WITH ACID CHLORIDES

BY

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FACULTY COMMITTEE

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ABSTRACT

Para-nitroaniline was reacted with acid chlorides forming amides. Their structures were elucidated by the performance of various spectral analyses.

PREFACE

I would like to express my sincere thanks and gratitude to Dr. David Kristol whose unselfish help made my work realizable and also to my wife, Susan.

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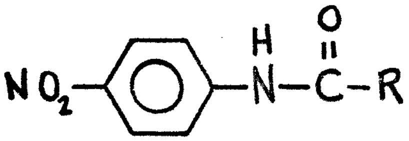
INTRODUCTION

The correlation of the structures of amides with their rates of hydrolysis with respect to enzymes is a relatively unexplored area of organic chemical research. Although it is well established that amides can hydrolyze under various conditions - that is under acidic and basic conditions and enzymatically - few works have been published with respect to correlating particular bulk sizes of molecules with their rates of hydrolysis. The purpose of my study was to synthesize a series of molecules in which the acid portion of the molecule became progressively larger, and ultimately to determine the rates of hydrolysis of these molecules both enzymatically and nonenzymatically.

My study was involved with the synthesis of these types of molecules, principally the synthesis of paranitroanilides of various saturated aliphatic carboxylic acids in which the size of the hydrocarbon portion of these acids was increased from compound to compound (see structure below).



The progression involved going from an aliphatic acid containing one methyl group (R = CH_3), to one containing three methyl groups (R = $C(CH_3)_3$), to one containing three ethyl groups (R = $C(C_2H_5)_3$), and finally to one containing an adamantyl group (R = adamantyl). There is some question as to whether in fact the adamantyl group should be considered larger than a trimethyl group or a triethyl group or somewhere in between both groups since, the adamantyl group, in effect is a triethyl compound which has a peculiar arrangement such that the three ethyls are tied back to each other.

Amides may be synthesized through a variety of reactions. Some of the more common methods of synthesis are employed by reacting amines with either acid chlorides, acid anhydrides or carboxylic acids. Following is a detailed analysis of these methods of synthesis.

Reactions of Amines with Acid Chlorides

The reaction of an aliphatic acid chloride with a primary amine is one of the fastest and most generally applicable methods of preparing amides in the laboratory.[1] A large variety of acid chlorides are available commercially, others are readily prepared from acids by treatment with such reagents as thionyl chloride or phosphorus pentachloride. Not only may halides of carboxylic acids but thoseof sulfonic and phosphonic acids, and of picric acid may be converted to amides by treatment with amines. Both aliphatic and

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[1] Solomon Marmor, Laboratory Guide for Organic Chemistry (Boston, 1964), p. 274.

aromatic amines may be subjected to acylation with acid chlorides.[2] The reaction

$$R^1\overset{O}{\overset{\|}{C}}\text{-Cl} + R^2R^3NH \longrightarrow R^1\overset{O}{\overset{\|}{C}}NR^2R^3 + HCl$$

(I)[3]

is, in general, a rapid exothermic reaction which proceeds well in organic solvents, in the liquid phase, in aqueous alkaline solutions (for the higher homologous members), and even, for isolated cases in the gaseous phase.[4] Presumably since the reaction often proceeds with vigour, this is why it has been so infrequently chosen for mechanistic investigation. Nevertheless, the rather scanty information available agrees with the predication that the acetyl chloride is more reactive than its higher homologues.[5] This is ascribed both to the increased +I effect stabilizing the carbonyl and to the greater steric interactions of higher alkyl groups causing a steric hindrance to the attacking amine nucleophile.

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[2] Wolf Karo and Stanley R. Sandler, *Organic Functional Group Preparations* (New York, 1970), p. 274.

[3] Jacob Zabicky, ed., *The Chemistry of Amides* (New York, 1970), p. 77.

[4] Norman O. V. Sonntag, "Reactions of Aliphatic Acid Chlorides," *Chemical Reviews*, 52 (1953), p. 269.

[5] Zabicky, *op. cit.*, pp. 77-78.

The reactivity of acyl halides is enhanced by electron-attracting substituents such as cyano (CN) and nitro (NO_2), whereas that of the crotonyl and benzoyl chlorides, in which there is conjugative stabilization of the carbonyl group by a localized double bond and a benzene ring, respectively, are less reactive than saturated acyl chlorides. A typical reactivity series is:

$$CH_3COCl > CH_3CH_2COCl > CH_3CH_2CH_2COCl > (CH_3)_2CHCOCl$$

$$ClCH_2COCl > PhCH_2COCl > CH_3COCl$$ [6]

Acid chlorides react with amines under a wide range of experimental conditions and the choice of the best procedure depends upon the nature and availability of the starting materials. Yields are usually in the 80-90% range, and purification of the product is rarely difficult;[7] however, the reaction conditions used do not always produce very high yields. For example, the acylation of 33 amines with 2-propylpentanoyl chloride (dipropylacetyl chloride) afforded yields ranging from 11% to 98%, of which half the amides were recovered in yields of 40% to 69% and one-third

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[6] Ibid., p. 78.

[7] Calvin A. Buehler and Donald E. Pearson, Survey of Organic Synthesis (New York, 1970), p. 899.

in yields of 80% to 90%.[8]

Since the reaction of an acid chloride with amines is highly exothermic, often quite violent, reaction conditions must be carefully controlled from the standpoint of safety. As a consequence, it is customary to carry this reaction out at ice temperatures. Even so, local over-heating may take place as acid chloride is being added to the amine, which may cause loss of amine content, particularly if large-scale laboratory reactions are attempted. Furthermore, the reaction rate is materially reduced by cooling. Therefore, adequate time for completion of the reaction must be allowed for isolation of the optimum yield.[9]

Acylation of the lower alkylamines is often conducted by adding the chloride to a cold, stirred, aqueous solution of the base, a method which has the advantages of technical simplicity and efficiency, although yields usually diminish as the homologous series is ascended. The lower yields encountered when amides are prepared from long-chain acyl chlorides probably arise from the difficulty of ensuring intimate contact between the hydrophobic acyl chloride and

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[8] Karo and Sandler, op. cit., p. 275.

[9] Ibid.

the water-soluble amine, and because the insoluble product tends to form a protective film around the unreacted chloride. These difficulties can be avoided by shaking a solution of the chloride in a suitable inert solvent with the aqueous amine. Ether is often employed, and the product amide is then obtained by evaporation of the organic layer.[10] Tetrahydrofuran has been employed in the preparation of adamantane-1-carboxamide.[11] Frequently, when a solvent immiscible with water is employed, the product, being insoluble in either phase, precipitates at the interface. Examples of this procedure, which often affords excellent yields, include the preparation of aromatic amides such as Figure A and steroid amides such as the one depicted in Figure B.[12]

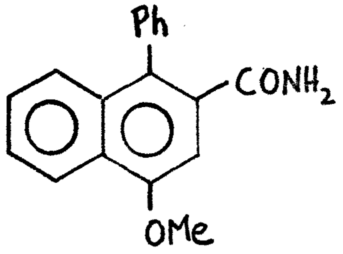

Figure A

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[10] Zabicky, op. cit., pp. 78-79.

[11] Ibid., p.79.

[12] Ibid.

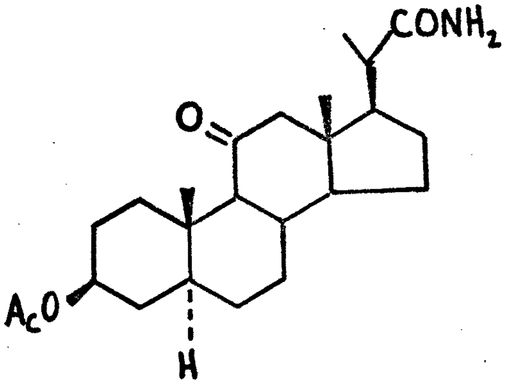

Figure B

As shown in equation I, the molecule of amine reacts with the acid chloride to also evolve hydrogen chloride which if not removed, combines with a second mole of amine to effectively reduce by one-half the amount of amine converted to a substituted amide. Therefore, two moles of amine are always consumed unless some other base is available to accept the hydrogen chloride which must be detached. When the reaction is performed in benzene or ether, it is the salt, $RNH_3^+Cl^-$ that precipitates, and the amide, RCONHR, is in the filtrate. In water perhaps the opposite situation is encountered. In order to conserve amine, the reaction is usually run in the presence of a hydrogen chloride acceptor, a suitable base which reacts preferentially with hydrogen chloride and much less rapidly, if at all, withthe aliphatic acid chloride than does the amine. The general conditions which are necessary to achieve this can be represented by expressions (a) and (b).[13]

$$\mathrm{RCOCl} + \mathrm{R'NH_2} \xrightarrow{k_1} \mathrm{RCONHR'} + \mathrm{HCl} \qquad \text{(II)}$$

$$:\mathrm{B} + \mathrm{HCl} \xrightarrow{k_2} \mathrm{H{-}B} + :\mathrm{Cl^-} \qquad \text{(III)}$$

$$\mathrm{R'NH_2} + \mathrm{HCl} \xrightarrow{k_3} \mathrm{R'NH_2HCl} \qquad \text{(IV)}$$

$$\mathrm{RCOCl} + :\mathrm{B} \xrightarrow{k_4} \mathrm{RCOB} + :\mathrm{Cl^-} \qquad \text{(V)}$$

(a) $k_2 > k_3$; (b) $k_4 << k_1$; preferably $k_4 = 0$.

Condition (a) can usually be maintained by employing as a hydrogen chloride acceptor a base which is stronger in the usual sense than the base $R'NH_2$. This effectively eliminates reaction IV from consideration. Thus, the acylation of an equimolar mixture of two amines usually gives the substituted amide of the weaker base and the hydrochloride of the stronger in many solvents. This is not true in all cases since in the case of ethylamine-ammonia, the stronger base is acylated. The second condition, (b), cannot always be achieved with aliphatic acid chlorides as readily as desired. Through the use of bases which do not undergo reaction V, such as the tertiary amine pyridine, which is preferably a stronger base than the amine being acylated, successful results are usually obtained.

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[13] Sonntag, op. cit. p. 269.

Effects observed in the acylation of two different amines with one acid chloride may be considered in the following way. Ionization of the acid chloride may be postulated first, followed by reversible addition of the carbonium ion to both amines (for example, with aniline and nitroaniline).

$$C_6H_5NH_2 + \overset{\oplus}{RCO} + \overset{\ominus}{Cl} \longrightarrow C_6H_5\overset{\oplus}{N}H_2COR + \overset{\ominus}{Cl} \qquad \text{(VI)}$$

$$O_2NC_6H_4NH_2 + \overset{\oplus}{RCO} + \overset{\ominus}{Cl} \longrightarrow O_2NC_6H_4\overset{\oplus}{N}H_2COR + \overset{\ominus}{Cl} \qquad \text{(VII)}$$

There will now be a reaction of the adduct with aniline, the stronger base, to pull a proton away.

$$O_2NC_6H_4\overset{\oplus}{N}H_2COR + \overset{\ominus}{Cl} + C_6H_5NH_2 \longrightarrow O_2NC_6H_4NHCOR + C_6H_5\overset{\oplus}{N}H_3 + \overset{\ominus}{Cl} \qquad \text{(VIII)}$$

Since equations VI and VII are equilibrium reactions, the aniline necessary in VI will be depleted by reaction VIII, making VII the favored reaction. If a still stronger base than aniline were available for reaction VIII, such as a hydroxide ion, then both reactions VI and VII should progress equally.[14]

In addition to pyridine, other organic bases which are suitable reagents for consuming the hydrogen chloride liberated

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[14] Ibid. p. 272.

during the acylation reaction are the tertiary amine dimethylaniline, triethylamine, tertiary alkylamines[15] and quinoline.[16] Another widely used procedure used for the consumption of the hydrogen chloride generated is the Schotten-Baumann method. This involves the reaction of the amine and the acyl chloride in the presence of aqueous alkali.[17] The bases most frequently employed are aqueous sodium hydroxide and potassium hydroxide; however aqueous sodium carbonate and sodium bicarbonate are also suitable inorganic bases.[18] This method has been widely used for the preparation of aromatic amides and anilides and is particularly suitable for the preparation of amino acids and peptides.

Although amide formation is favored in the Schotten-Baumann method, hydrolysis does take place to some extent,[19] especially with aliphatic acid chlorides since, in general they hydrolyze much more rapidly than aromatic types.

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[15] Zabicky, op. cit., p. 81.

[16] Karo and Sandler, op. cit., p. 275.

[17] Ibid., p. 279.

[18] Zabicky, op. cit., p. 80.

[19] Karo and Sandler, op. cit., p. 279.

Consequently, this results in substituted amides contaminated with acids; however somewhat better purity of product is obtained with the C_{10} to C_{18} aliphatic acid chlorides than with the C_2 to C_9 homologs.[20] However, hydrolysis in the Schotten-Baumann process is limited by the fact that the reaction is conducted in a two phase system in which the alkali is present in the aqueous phase and the acid chloride is present in the organic phase.

In the acylation of certain primary amines in anhydrous solvents, a part of the acid chloride may add to the base to produce a salt-like material, either the hydrochloride of the amide or the acid chloride salt of the amine.[21] The separation of the amide from the inorganic salt is made easy by the fact that the inorganic salt is soluble in water whereas the amide is soluble in organic solvents. This is the advantage of performing these reactions in organic solvents since not only does the solvent facilitate the separation of product, but the solvent serves as a heat absorber during the reaction as well.[22] Some organic solvents which have been used to mitigate the exothermicity of amidation

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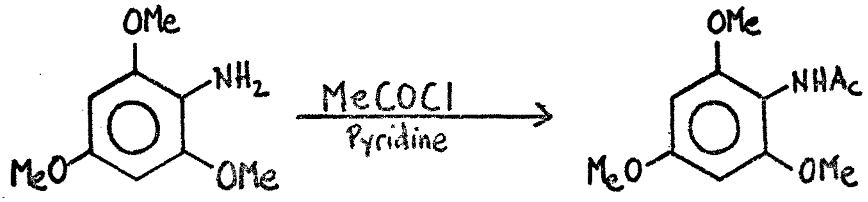
[20] Sonntag, op. cit., pp. 272-273.

[21] Ibid., p. 274.

[22] Marmor, op. cit., p. 275.

are ethylene dichloride, ether, benzene, carbon tetrachloride, chloroform and toluene.[23]

The formation of amides by acylation of amines with acid chlorides is applicable to a wide range of structural types. Some typical examples are:[24] (equation X)



(X)

The crude 2,4,6-trimethoxyacetanilide was filtered and purified by recrystallization from water. The yield was 80%.

Acetone and sodium carbonate were used in equation XI, whereas cold water was used in equation XII.[25]

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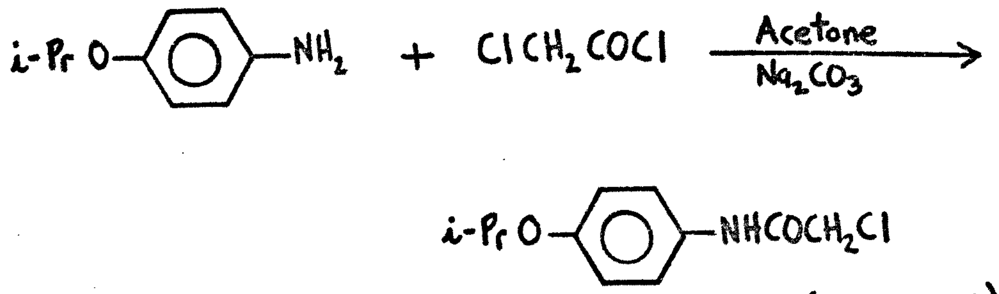
[23] Buehler and Pearson, op. cit., p. 899.

[24] J. S. Bradshaw, R. D. Knudsen, and E. L. Loveridge, "The Photoreactions of 2,4-Dimethoxyacetanilide," The Journal of Organic Chemistry, 35, (1970), p. 1220.

[25] Zabicky, op. cit., p. 82.



(XI)

(86% yield)

$$Cl(CH_2)_4COCl + EtNH_2 \xrightarrow{H_2O\ (Cold)} Cl(CH_2)_4CONHEt \qquad (XII)$$

(71% yield)

Reactions of Amines with Acid Anhydrides

The acylation of amines by acid anhydrides is very similar to the acylation with acyl halides. The reactivity of the anhydrides may be somewhat lower than that of the corresponding acyl halides, consequently a longer reaction period is usually desirable.[26]

The general availability of anhydrides is limited. Their preparation is often more difficult than the preparation of the corresponding acyl halide. Furthermore, if an unusual acid has to be converted, in effect, two moles of acid are required to prepare one mole of amide. Ocasionally use of an anhydride may be indicated, if the product or intermediate

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[26] Karo and Sandler, op. cit., p. 281.

reagents are sensitive to hydrogen chloride or if the course of the reaction must be modified.[27]

For acyclic anhydrides, amides are produced while cyclic anhydrides give imides, acid amides, or diamides depending on the reagent and the experimental conditions. Recently, superior yields of amides have been obtained by the use of mixed anhydrides produced from the free acid, diethylamine, and ethyl chloroformate. In most cases, mixed anhydrides give acid derivatives derived from the weaker acid portion of anhydrides with the exception of those from trifluoroacetic acid. Here mixtures of amides are obtained.[28]

The mechanism of the reaction (equation XIII)

$$R'CO_2COR^2 + R^3R^4NH \longrightarrow R'CONR^3R^4 + R^2CO_2H \quad [29] \qquad \text{(XIII)}$$

is usually discussed in terms of nucleophlilic addition to to a carbonyl group affording a tertrahedral intermediate (Figure I), although Satchell has obtained evidence for a

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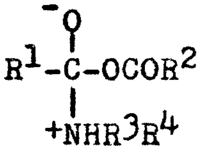
[27] *Ibid*.

[28] Buehler and Pearson, *op. cit*., p. 900.

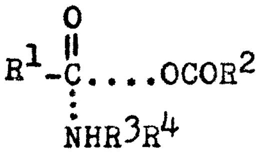
[29] Zabicky, *op. cit*. p. 86.

synchronous displacement process proceeding through the transition state (Figure II).[30]



$$R^1-\overset{{}^{-}O}{\underset{{}^{+}NHR^3R^4}{C}}-OCOR^2$$

(Figure I)



$$R^1-\overset{\overset{O}{\|}}{\underset{\vdots\atop NHR^3R^4}{C}}\cdots\cdot OCOR^2$$

(Figure II)

Both hypotheses lead to the same generalizations concerning the effects of the structure of the reactants on the rate of reaction. Increase in the electron-attracting power of R in the anhydride $(RCO)_2O$ will increase the reaction rate by enhancing the electrophilic character of the carbonyl carbon atom and by stabilizing the leaving group, RCO_2^-. Thus anhydrides containing strongly electronegative substituents, e.g. trifluoroacetic anhydride, are highly effective acylating agents while conversely, increase in the electron-attracting power of the groups R^3 and R^4 in the amine, by lowering its nucleophilicity, will decrease the rate of acylation. Very weakly basic amines, such as nitroanilines react very slowly with most anhydrides and special conditions are needed for the efficient preparation of their acyl derivatives. Acylation with anhydrides appears to be catalyzed by acid; in the absence of an excess of added acid the process is usually autocatalytic.[31]

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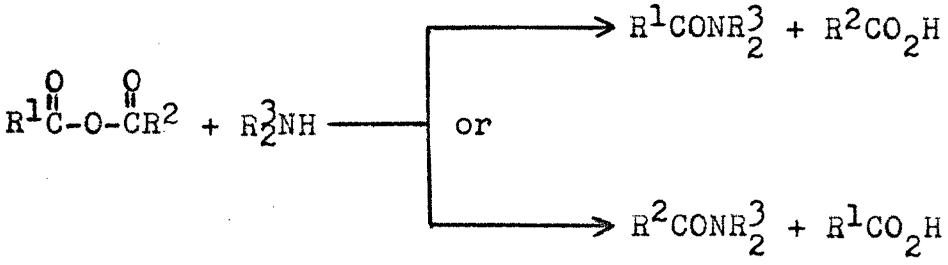
[30] *Ibid*.

[31] *Ibid*.

If the carboxylic anhydrides are unsymmetrical, then two possible sites for attack by amines are available leading to formation of two different acylated products (equation XIV).



$$R^1\overset{O}{\overset{\|}{C}}\text{-}O\text{-}\overset{O}{\overset{\|}{C}}R^2 + R^3_2NH \longrightarrow \begin{cases} R^1CONR^3_2 + R^2CO_2H \\ \text{or} \\ R^2CONR^3_2 + R^1CO_2H \end{cases} \qquad (XIV)$$

The course of this reaction is controlled by steric and electronic effects of R^1 and R^2. Steric effects are readily predicted; attack by the amine will occur preferentially at the carbonyl group adjacent to the less bulky substituent. Electronic effects are more complex.[32]

The anhydrides most widely used for acylation of amines and amides are the easily obtainable symmetrical compounds such as the lower aliphatic carboxylic anhydrides, benzoic anhydrides and cyclic anhydrides; although, recently developed methods for the simple preparation of carboxylic acid anhydrides will help widen the scope of this reaction.[33]

A wide variety of experimental methods is available for

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[32] Ibid., p. 87.

[33] Ibid., p. 88.

acylation of amines by anhydrides. Frequently, the two reagents are mixed together without a solvent and heated; however, inert solvents such as ether, acetone, toluene and petroleum ether are often employed. Acetic acid is a particularly useful solvent for acylation with acetic anhydride. Pyridine and tertiary amine bases catalyze acylation by anhydrides and often provide convenient solvents.[34]

A useful method developed by Chattaway for the acylation of aromatic amino acids and amino phenols involves addition of acetic anhydride to a solution or suspension of the amine in ice-cold aqueous caustic soda. As in the Schotten-Baumann method, hydrolysis of the acylating agent is usually unimportant. For acylation of weakly basic amines, sulphuric acid is an effective catalyst. It functions, presumably, by protonation of the anhydride thus facilitating attack by the amine.[35]

Under suitable experimental conditions, selective partial acylation of diamines, amino alcohols and amino phenols can be accomplished.[36] A typical example is illustrated

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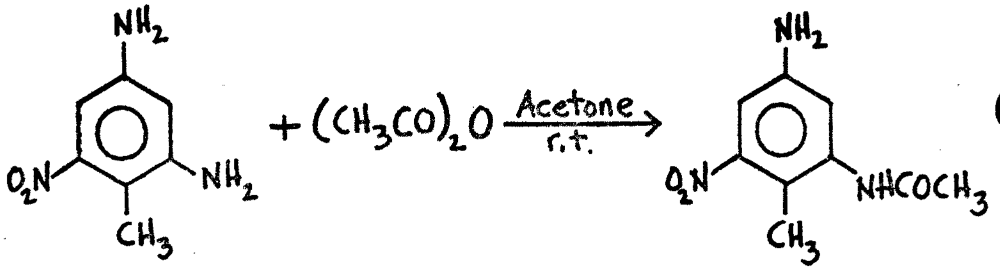
[34] _Ibid._

[35] _Ibid._

[36] _Ibid._

below (equation XV).



(XV)

This was purified after one recrystallization from 80% alcohol or toluene to give a yield of 92%.[37]

The formation of amides by acylation of amines prepared in situ by reduction of suitable precursors is a well-known reaction. Aromatic nitro compounds, for example, readily afford acetanilides when treated with reducing agents in acetic anhydride. Under suitable conditions, selective acylation can be achieved. Thus o-hydroxyacetanilide is obtained from o-nitrophenol in acetic acid-acetic anhydride

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[37] A. C. Farthing and G. D. Parkes, "Derivatives of 2:4:6-Trinitrotoluene: Monoreductions of Polynitrocompounds," <u>Journal of the Chemical Society,</u> (1948), pp. 1275-1277.

by reduction with stannous chloride or by hydrogenation.[38]

Acyclic unsymmetrical anhydrides of simple carboxylic acids offer two different points of attack for nucleophilic reagents. With amines, mixtures of both possible amides are frequently obtained and the course of such reactions is often altered dramatically by small changes in experimental conditions. Thus aniline when treated with acetic chloroacetic anhydride in benzene yields mainly the chloroacetyl derivative, but in aqueous acetone the same reaction affords a mixture of which acetanilide is the major component.[39] Similar results were obtained with other mixed carboxylic anhydrides leading Emery and Gold[40] to suggest that in non-polar media reaction usually occurs at the carbonyl group adjacent to the more powerfully electron-attracting substituent.

Acetic formic anhydride, reacts with amines selectively at the formyl carbonyl group and thus provides an excellent method for the preparation of formamides. It also has found considerable use for protecting amino groups in the synthesis

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[38] Zabicky, op. cit., p. 90.

[39] Ibid., pp. 90-91.

[40] A. R. Emery and V. Gold, "Quantitative Studies of the Reactivities of Mixed Carboxylic Anhydrides," Journal of the Chemical Society, (1950), p. 1443.

of peptides and other natural products.[41]

Reactions of Amines with Carboxylic Acids

The mechanism for the reaction of a carboxylic acid with an amine is as follows:

$$RCOOH + R'NH_2 \rightleftarrows RCOONH_3R' \longrightarrow RCONHR' + H_2O \quad ^{42} \qquad (XVI)$$

Since an equilibrium is involved in this reaction, an excess of either amine or acid is desirable, the choice depending on which component is less costly. Furthermore, the reaction is not general in that it succeeds well with straightchain, aliphatic acids, but poorly with aromatic or hindered acids or with less basic amines.[43]

Since the reaction is formally the reverse of amide hydrolysis, it is reasonable to assume that it follows the normal route proceeding through a tetrahedral intermediate with displacement of the OH^- as depicted in more depth in equation XVII.[44]

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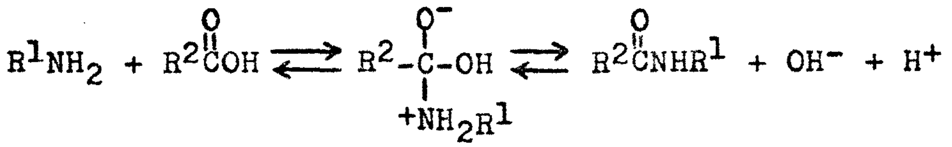
[41] Zabicky, op. cit., p. 91.

[42] Buehler and Pearson, op. cit., p. 895.

[43] Ibid.

[44] Zabicky, op. cit., p. 106.



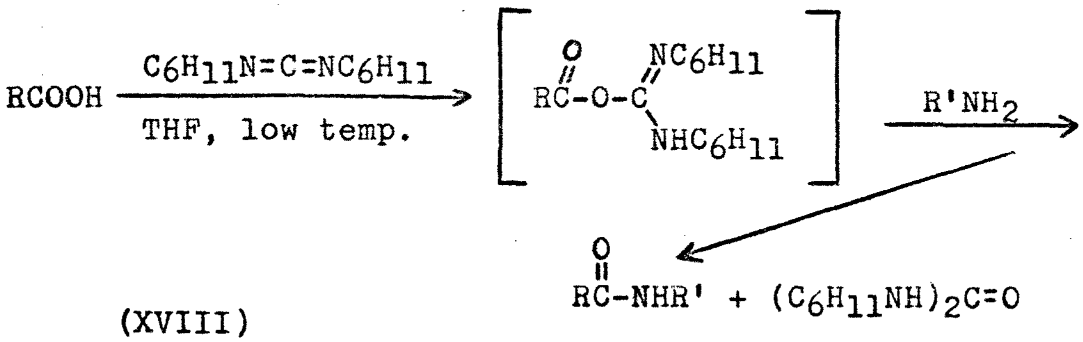
$$R^1NH_2 + R^2\overset{O}{\overset{\|}{C}}OH \rightleftharpoons R^2\text{-}\underset{+NH_2R^1}{\overset{O^-}{C}}\text{-}OH \rightleftharpoons R^2\overset{O}{\overset{\|}{C}}NHR^1 + OH^- + H^+$$

(XVII)

There is evidence in support of this mechanism for reactions of amines with monocarboxylic acids in aqueous solution, but with dicarboxylic acids the reaction appears to proceed by initial formation of anhydrides.[45]

A good general procedure involves heating a mixture of acid and amine at about 200°C. Examples of its use include the preparation of benzanilide, substituted N-β-(phenylethyl) phenylacetamides, and N-phenyloleiamide.[46]

The most elegant synthesis of amides from acids and amines is the carbodiimide method as depicted in equation XVIII.[47]



(XVIII)

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[45] Ibid.

[46] Ibid.

[47] Buehler and Pearson, op. cit., p. 896.

Yields of amides are almost quantitative. The method is particularly useful for the preparation of peptides and suffers only from the expense of the reagent. Water soluble or dispersed acids, including peptides, may be converted into amides in water by means of water-soluble carbodiimides, such as N-ethyl-N'-3-dimethylamine-propylcarbodiimide at ca. pH 4.7.[48]

It has also been possible to prepare amides by subjection of acid and amine vapors to a silica gel surface at 280°C and by azeotroping the water with xylene after using catalytic amounts of Amberlite IR 120 (H^+). But even in aqueous solution, some tendency exists for the amide to form an equilibrium mixture with the amine and acid, particularly in the case of dibasic acids.[49]

Phosphoramide and its N-alkyl and N-aryl derivatives are excellent reagents for the direct conversion of acids into their amides. For example, N,N-dimethylamides may be prepared from a wide range of acids by heating them with hexamethylphosphoramide. Other phosphoramides for use in this type of reaction are readily prepared in situ from amines and suitable phosphoryl halides. Thus heating of a carboxylic acid with an amine and phosphoryl chloride in benzene affords

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[48] *Ibid.*, p. 898.

[49] *Ibid.*

the appropriate amide in excellent yield. Also in this group of "activated amine" derivatives incorporating phosphorous, mention must be made of phosphazo compounds which are readily prepared in situ from an amine and phosphorous trichloride, and which yield, the appropriate amide when treated with a carboxylic acid (equation XIX).

$$R'NH_2 + PCl_3 \longrightarrow R'N{=}P{-}NHR^1 \xrightarrow{R^2CO_2H} R^2CONHR^1 + (PHO_2)_x \qquad (XIX)$$

The method has been mainly used for peptide synthesis, but can be applied generally to the preparation of amides from amines and carboxylic acids by warming them in benzene with phosphorous trichloride.[50]

I chose to react an amine with various acid chlorides because of the fact that the acid chlorides were commercially available, and that their reactions go to completion and involve simply the removal of hydrogen chloride which is an easy process to perform. Pyridine was chosen in all reactions as the hydrogen chloride acceptor not only because it is a strong base but because it is also a good reaction solvent. In order to moderate the exothermic reaction, tetrahydrofuran was used as the solvent medium in each synthesis.

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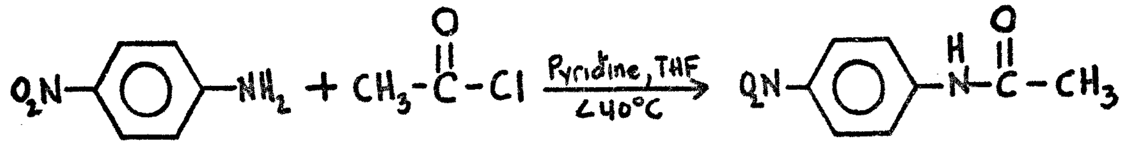
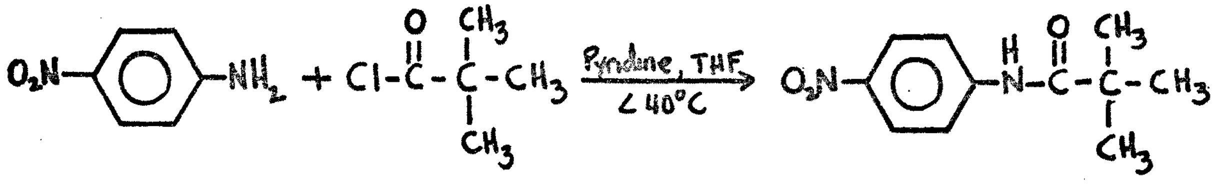
[50] Zabicky, <u>op</u>. <u>cit</u>., p. 108.

The equations of the four syntheses performed are listed below.

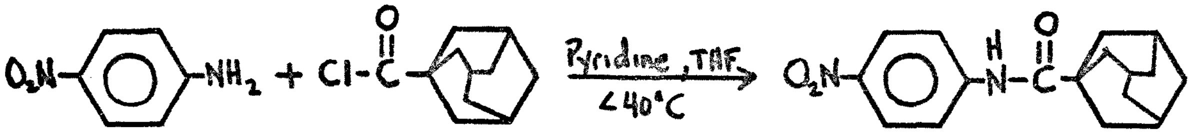
I. The Reaction of Acetyl Chloride and p-Nitroaniline



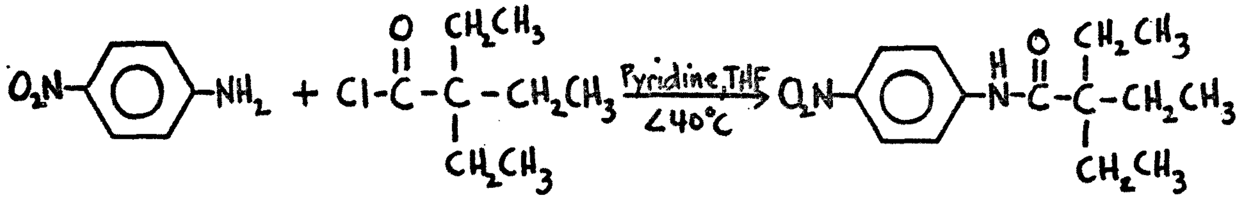
II. The Reaction of Pivaloyl Chloride and p-Nitroaniline



III. The Reaction of Adamantane Carboxylic Acid Chloride and p-Nitroaniline



IV. The Reaction of 2,2-Diethylbutyryl Chloride and p-Nitroaniline



In each reaction, ten percent excesses of the acid chloride were used since acid chloride can easily decompose in the presence of moist air.

EXPERIMENTAL PROCEDURE

Ten percent excesses of acetyl chloride, pivaloyl chloride, 1-adamantane carboxylic acid chloride, and 2,2-diethylbutyryl chloride were separately reacted with p-nitroaniline. An experimental method and a statement of results are fully outlined in the following discussion for each of the above reactions.

The Reaction of Acetyl Chloride and p-Nitroaniline

In the reaction of acetyl chloride and p-nitroaniline, a ten percent excess of acetyl chloride (0.055 moles, 4.1 g) was placed in a stoppered graduated dropping funnel. Similarly, 0.05 moles (6.9 g) of p-nitroaniline was placed in a 500 ml round bottom flask. To the p-nitroaniline was added 5 ml of pyridine and 25 ml of tetrahydrofuran. The magnetically stirred p-nitroaniline went into solution in about five minutes. While continuing to magnetically stir the contents in the round bottom flask, the acetyl chloride in the graduated funnel were added dropwise at first. After five minutes, the temperature in the flask had risen to 38°C. The addition was stopped and the flask was placed in an ice bath until the temperature of the flask dropped to 30°C. At this point a deep yellow colored precipitate was evident. The addition of the remainder of the acetyl chloride in the graduated funnel was continued while maintaining the reaction and at a quickened pace. After about five minutes all of the acetyl chloride had been added. The final batch temperature rose to 35°C. At this point the contents in the flask were kept stirred overnight.

To the yellow precipitate in the flask which was separated by suction filtration were added equal portions of water and ethanol in 25 ml increments each up to a total of 100 ml each. At this point the discovery of the error of adding ethanol instead of ethyl ether was made and the water and alcohol were removed by suction filtration. To the solids remaining were added equal portions of water and ethyl ether in 25 ml increments each up to a total of 150 ml each. This procedure was performed since the amide formed is soluble in ether while the amine salt formed (p-nitroaniline hydrochloride) is soluble in water. The contents in the flask were transferred to a 500 ml separatory funnel where the lower water layer was removed. The ether layer (batch) was then washed per the following procedure: (1) Two, 200 ml washes of 1 M sodium carbonate (to remove the hydrochloride), (2) one 200 ml water wash (to remove the carbonate), (3) two 200 ml washes of 0.1N hydrochloric acid (to remove the p-nitroaniline), and (4) one 200 ml water wash (to remove the hydrochloric acid). For each wash, the lower layer (water layer) was discarded after settling times of approximately 5-10 minutes for each wash.

Due to solids that were continually present in the water layer of each wash, plugging of the bottom outlet of the separatory funnel occurred resulting in a loss of product on the first Sodium Carbonate wash due to excessive pressure buildup. Due to solids still present in the ether layer, the batch was not dried with magnesium sulfate, instead the batch was transferred to a 500 ml round bottom flask and rotary evaporated at about a temperature of 40°C. A bright yellow solid formed on the walls of the flask weighing 1.32 g. This solid was recrystallized from ethanol by adding small amounts of ethanol at reflux until the solids were dissolved. A total of 35 ml of ethanol was necessary. At this point heating was stopped and the flask was allowed to cool to room temperature. When cool the crystals were suction filtered and washed with cold ethanol to yield a creamy-yellow solid weighing 0.45 g. The solid was identified as p-nitroacetanilide. The melting point range was 212-218°C.

The mother liquors were saved and the solution had evaporated after several days leaving a solid weighing 0.77 g. This second crop was also recrystallized from ethanol. A total of 32 ml of ethanol added at reflux was needed to dissolve the solids. The flask was cooled to room temperature and then placed in an ice bath for one hour. The crystals were suction filtered and washed with cold ethanol to yield a creamy-yellow solid weighing 0.19 g.

The Reaction of Pivaloyl Chloride and p-Nitroaniline

In the reaction of pivaloyl chloride and p-nitroaniline, a ten percent excess of pivaloyl chloride (0.055 moles, 6.63 g) was placed in a stoppered graduated dropping funnel. Similarly, 0.05 moles (6.9 g) of p-nitroaniline was placed in a 500 ml round bottom flask. To the p-nitroaniline was added 3 ml of pyridine and 25 ml tetrahydrofuran. The p-nitroaniline went into solution almost immediately upon stirring magnetically. While continuing to stir the contents in the round bottom flask, the contents in the graduated funnel were added dropwise for several minutes. At this time the batch temperature had risen to 37°C and the addition of the pivaloyl chloride was stopped until the batch temperature dropped to 30°C by placing the flask in an ice bath. The addition of the pivaloyl chloride was continued at a slightly faster pace and was completed in about five more minutes. Only near the end of the pivaloyl chloride addition did the contents in the flask become cloudy and then finally a deep yellow precipitate was evident. This slurry was kept stirred for two days. Upon sitting for two more days, most of the liquid in the flask had evaporated and a deep yellow solid was present.

Since the above reation results in the formation of an amide and an amine hydrochloride, the following procedure was used to isolate the product. The amide formed is soluble in ether and the amine hydrochloride formed is soluble in water; therefore, to the solids in the round bottom flask were added equal portions of ethyl ether and water in 25 ml increments. A total of 200 ml of both ethyl ether and water were added before it appeared the majority of the solids were in solution. Since some solids were still evident in the water layer, and due to the difficulty in washing the products in the first reaction due to these solids, it was decided to filter the entire solution of ether and water by suction filtration. The solids were then saved for later use. The ether/water filtrate was then transferred to a 500 ml separatory funnel and a wash of the filter flask of 60 ml each ether and water was then added to the filtrate. The lower water layer was then discarded. The ether layer (batch) was then washed per the following procedure: (1) Two 200 ml washes of 1M sodium carbonate (extreme care was needed due to the gas evolution that resulted and small buildup of solids near the bottom outlet of the separatory funnel), (2) one 200 ml wash of water, (3) two 200 ml washes of 0.1N hydrochloric acid, and (4) one 250 ml wash of water. For each wash, the lower layer (water) was discarded. Also evident during each wash was an emulsion layer which at all times was kept with the ether layer (batch).

In order to dry the batch, both the ether layer and emulsion layer were added to a 400 ml beaker containing approximately a quarter inch layer of magnesium sulfate. The mixture was stirred by hand for several minutes and then the magnesium sulfate was filtered off via suction filtration. The magnesium sulfate cake was washed with fresh ether until no yellow batch color was visible. The filtrate (containing ether and emulsion layers) was transferred to a 500 ml round bottom flask. A wash of several ml ether was added to the filter flask and then transferred to the round bottom flask. The filtrate was then concentrated by rotary evaporation at about a temperature of 40°C using a water bath. A bright yellow solid formed on the walls of the flask in about 1½ hours. Its weight was 3.9 g.

This solid was recrystallized from ethanol in two parts as follows: Part one - 2 g of solid were added to a 250 ml round bottom flask. About 30 ml of warm ethanol were added while stirring magnetically. A cloudy solution resulted and two more ml of ethanol were added to dissolve all the solids. At this point the flask was placed in a water bath and cooled to 35°C. Ice was then added to the bath to cool the contents in the flask to 20-25°C. The batch was aged for one-half hour and then was suction filtered and washed with a small amount of cold ethanol to yield an off-white crystalline solid weighing 1 gm. Its melting point was 156-158°C.

The mother liquors were than transferred from the filtrate flask to a 250 ml round bottom flask. A small wash of ethanol was used to rinse the filtrate flask of solids that had formed. This was added to the filtrate in the round bottom flask. The mother liquors were then concentrated via rotary evaporation using 50°C heat. The solids recovered (wet) weighed 1.78 g. The color was dark yellow-brown.

Part two - The remaining 1.90 g of yellow solid was also added to a 250 ml round bottom flask. A total of only 7 ml ethanol was needed to dissolve the contents while stirring magnetically at reflux. The flask was cooled gradually at room temperature, then placed in a water bath and finally in an ice-water mixture and allowed to stand for one-half hour. The contents were then suction filtered and washed with a small amount of cold ethanol to yield a pale yellow solid weighing 1.06 g.

These mother liquors were also concentrated via rotary evaporation using 50°C heat and a round bottom flask. The solids recovered (wet) weighed 0.74 g and were dark yellow-mustard in color.

Finally, the solids filtered off during the initial ether/water wash were also recrystallized from ethanol. The solids were not weighed; however, 14 ml of hot ethanol were needed to dissolve solids at reflux using a 250 ml round bottom flask with magnetic stirring. The contents were cooled at room temperature for one hour. Crystallization occurred rapidly. The contents were then suction filtered and washed with small amounts of cold ethanol. A total of 1.19 g of crystalline material was recovered. Their color was off-white.

These mother liquors were also concentrated via rotary evaporation using 50°C heat and 250 ml round bottom flask. The solids recovered (wet) weighed 0.57 g and were light yellow-tan in color.

The Reaction of 1-Adamantane Carboxylic Acid Chloride and p-Nitroaniline

In the reaction of 1-adamantane carboxylic acid (solid) and p-nitroaniline, a ten percent excess of adamantane carboxylic acid chloride (0.00756 moles, 1.5 g) was weighed out. Similarly 0.00687 moles (0.949 g) of p-nitroaniline was placed in a 250 ml round bottom flask. To the p-nitroaniline was added 1 ml pyridine and 20 ml tetrahydrofuran. The p-nitroaniline went into solution almost immediately after magnetic stirring had begun. While continuing to stir the contents in the round bottom flask, the adamantane carboxylic acid chloride was added slowly with a spatula. Since very little heat of reaction occurred (batch temperature only rose to 26°C), the total addition time took only several minutes. About five minutes after the addition, the contents in the flask became a little cloudy until after several more minutes, a deep yellow precipitate became visible. The contents in the flask were stirred over night. By the next day, the precipitate that had formed was less concentrated than that which was observed in the previous two reactions.

Since this reaction also results in the formation of an amide and an amine hydrochloride, the following procedure was used to isolate the product (amide). The amide formed is soluble in ether (organic layer) and the amine hydrochloride formed is soluble in water; therefore, to the slurry-solution in the round bottom flask were added equal portions of ethyl ether and water in 25 ml increments. A total of 100 ml of both ethyl ether and water were added before both layers appeared to be in solution. This solution was then transferred to a 500 ml separatory funnel. A wash of 10 ml of both ether and water was used to rinse the round bottom flask and this wash was added to the separatory funnel. Very few solids were evident in the water layer as compared with the previous two reactions of acetyl chloride and pivaloyl chloride with p-nitroaniline. However, a large emulsion layer (of solid form) had formed which was evidently product also. The lower water layer cut was made and the ether/emulsion layers were washed per the following procedure: (1) Two 200 ml washes of 1M sodium carbonate (extreme care was needed due to the gas evolution that resulted), (2) one 100 ml water wash, (3) two 100 ml washes of 0.1N hydrochloric acid and, (4) one 100 ml water wash. For each wash, the lower layer (water) was discarded after settling times of approximately 5-10 minutes

Since solids were present and it was desirable to dry the product layer, it was decided to filter off the emulsion solids via suction filtration and then the filtrate (ether layer) could be dried with magnesium sulfate. Therefore the ether layer was added to a 250 ml beaker containing approximately a quarter inch layer of magnesium sulfate. The mixture was stirred by hand for several minutes and then the magnesium sulfate was filtered off via suction filtration. The magnesium sulfate cake was washed with fresh ether until no yellow batch color was visible. The ether filtrate was transferred to a 250 ml round bottom flask followed by a wash of several ml ether to rinse the filtrate flask out. The filtrate was then concentrated by rotary evaporation at about a temperature of 40°C using a water bath. A bright yellow solid formed on the walls of the flask in about one hour. Its weight was 0.36 g.. The emulsion layer solids were also weighed equaling 1.18 g. These were light-tan to cream colored.

Both the ether layer solids and emulsion layer solids were recrystallized from ethanol as follows: (1) ether layer solid - the 0.36 g of solid were added to a 250 ml round bottom flask. About 7 ml of boiling ethanol were needed to dissolve all the solids to a clear solution. Magnetic stirring was employed. At this point the flask was allowed to cool at room temperature for one hour. Crystallization took place almost immediately after removal from the hot water bath which was used during the ethanol addition. The contents in the flask were suction filtered and washed with small amounts of chilled ethanol. An off-white crystalline solid weighing 0.11 g was recovered. The melting point range of this crystalline off-white solid was 197.5 - 201.5°C.

The mother liquors were then transferred from the filtrate flask to a 250 ml round bottom flask. A small wash of ethanol was used to rinse the filtrate flask of solids that had formed. This was added to the filtrate in the round bottom flask. The mother liquors were then concentrated via rotary evaporation using 50°C heat. The solids recovered (wet) weighed 0.23 g and were dark brown in color. No melting point was taken.
(2) emulsion layer solid - the 1.10 g of solid were added to a 250 ml round bottom flask. About 27 ml of boiling ethanol were needed to dissolve all the solids to a clear solution. The contents in the flask were magnetically stirred while in a hot water bath to keep the ethanol at reflux. At this point the flask was allowed to cool at room temperature for about one hour. Crystallization took place almost immediately. The contents in the flask were suction filtered and washed with small amounts of chilled ethanol. An off-white crystalline solid weighing 0.88 g was recovered. The melting point of this crystalline off-white solid was

199 - 200.5°C.

The mother liquors were then transferred from the filtrate flask to a 250 ml round bottom flask. A small wash of ethanol was used to rinse the filtrate flask of solids that had formed. This was added to the filtrate in the round bottom flask. The mother liquors were then concentrated via rotary evaporation using 50°C heat. The solids recovered (wet) weighed 0.17 g and were light tan-light yellow in color. No melting point was taken.

The Reaction of 2,2-Diethylbutyryl Chloride and p-Nitroaniline

In the reaction of 2,2-diethylbutyryl chloride (liquid) and p-nitroaniline, a ten percent excess of 2,2-diethylbutyryl chloride (0.01046 moles, 1.7 g) was placed in a stoppered graduated dropping funnel. Similarly 0.00951 moles (1.31 g) of p-nitroaniline was placed in a 250 ml round bottom flask. To the p-nitroaniline was added 2 ml pyridine and 25 ml tetrahydrofuran. Stirring magnetically the p-nitroaniline went into solution almost immediately. While continuing to stir the contents in the round bottom flask, the contents in the graduated funnel were added dropwise. Since only a small heat of reaction occurred - temperature rose from 25°C to 29°C - the entire addition time took only several minutes. The solution in the round bottom flask turned cloudy immediately and in several minutes a deep yellow precipitate was evident. The contents in the flask were kept stirred for two days. At that time a very heavy yellowish slurry was present.

In order to separate the amide formed (product) and the amine hydrochloride formed, the following procedure was used to isolate the product. To the slurry in the round bottom flask were added equal portions of ethyl ether and water in 25 ml increments. A total of 50 ml of both ethyl ether and water were added before both layers appeared to be in solution. This solution was then transferred to a 500 ml separatory funnel. A wash of 16 ml of both ether and water was used to rinse the round bottom flask and this wash was added to the separatory funnel. No solids or emulsion layer were present. The lower water layer (amine hydrochloride) cut was made and the ether layer was washed per the following procedure: (1) two 66 ml washes of 1M sodium carbonate (extreme care was needed due to the gas evolution that resulted), (2) one 66 ml water wash, (3) two 66 ml washes of 0.1N hydrochloric acid, and (4) one 66 ml water wash. For each wash, the lower layer (water) was discarded after settling times of approximately five minutes. All the washes proceded very smoothly due to the lack of solids present in either the water or organic layers.

In order to dry the batch, the ether layer was placed in a 250 ml beaker containing approximately a quarter inch layer of magnesium sulfate. The mixture was stirred by hand for several minutes and then the magnesium sulfate was filtered off via suction filtration. The magnesium sulfate cake was washed with small amounts of fresh ether until no yellow batch color was visible. The ether filtrate was transferred to a 250 ml round bottom flask followed by a wash of several ml ether to rinse the filtrate flask of all visible yellow color. The filtrate was then concentrated by rotary evaporation at about a temperature of 40°C using a water bath. A bright yellow solid formed on the walls of the flask in about forty minutes. Its weight was 1.5 g.

This solid was then recrystallized from ethanol using the following procedure. The 1.5 g of solid was placed in a 250 ml round bottom flask. The flask was then placed in a water bath, hot enough to boil ethanol. To the solid, ethanol was added dropwise until the product completely dissolved. Only 3 ml of ethanol were needed. The contents of the flask were stirred magnetically. The flask was then removed from the water bath where it was allowed to cool gradually at room temperature. However, crystallization was slow and it was decided to immerse the flask in an ice bath where the batch aged for 15-20 minutes. Solids were then visible. The crystals in the flask were suction filtered and washed with small amounts of chilled ethanol. Only 0.30 g of a light yellow crystalline solid were recovered. The melting point of this crystalline solid was 134.5-138.5°C. A larger ethanol wash would have been used; however, very little product was in evidence and even the cold wash seemed to be dissolving the product. A white solid was evident when the wash was originally applied.

The mother liquors were then transferred from the filtrate flask to a 250 ml round bottom flask. A small wash of ethanol was used to rinse the filtrate flask of solids that had formed and this wash was added to the round bottom flask. The mother liquors were then concentrated via rotary evaporation using 50°C heat. The solids recovered (wet) weighed 1.62 g and were orange-yellow to brown in color. No melting point was taken.

DISCUSSION OF RESULTS

The infrared spectrum, nmr spectrum and elemental analysis of the paranitroacetanilide, paranitropivalanilide, paranitro-1-adamantanecarboxanilide, and paranitro-2,2-diethylbutyranilide were performed by Merck & Co., Inc., Rahway, New Jersey. The infrared spectra were obtained by use of a Beckman Acculab #4 Spectrophotometer. Potassium bromide dispersion pellets were used. The concentration of product was about 0.6%. The nmr spectra were obtained by use of a Varian A-60A Spectrometer. The solvents used were hexadeuterodimethylsulfoxide for the paranitroacetanilide, paranitro-1-adamantanecarboxanilide, and paranitro-2,2-diethylbutyranilide, and deuterochloroform for the paranitropivalanilide. The elemental analyses, consisting of carbon, hydrogen, and nitrogen determinations, were performed on a Perkin-Elmer C-H-N Elemental Analyzer. The melting points were performed on a Thomas Hoover Capillary Melting Point Apparatus.

All samples prior to submission for testing were dried at room temperature for twenty-four hours at a pressure of 0.5 mm. Hg. Their analyses will be discussed in detail.

Paranitroacetanilide

Figure I shows the infrared spectrum for paranitroacetanilide. The intense peak at 3300 cm^{-1} is indicative of a N-H absorption which appears in the amide function. The three peaks at 3250 cm^{-1}, 3190 cm^{-1}, and 3120 cm^{-1} are indicative of the C-H absorption which are inthe methyl group and benzene ring. This identification is typical of aliphatic and aromatic compounds. The very sharp, intense peak at 1700 cm^{-1} is due to the C=O bonding of the amide. This position on the spectrum is that expected for an amide. The series of peaks found between 1500-1650 cm^{-1} are due to the benzene ring and the N-H group. The two very strong peaks at 1520 cm^{-1} and 1350 cm^{-1} are due to the nitro group (NO_2) on the benzene ring. This is verified by the fact that generally nitro groups appear between 1300-1370 cm^{-1} and 1500-1570 cm^{-1}. Another very sharp, intense peak can be seen at 860 cm^{-1}. This is due to two adjacent hydrogen atoms which is indicative of a para substituted molecule. In the case of paranitroacetanilide, the benzene ring is a para substituted ring.

For the elemental analysis, the calculated percentages were: carbon 53.33%, hydrogen 4.48%, nitrogen 15.55%. The actual percentages found were carbon 50.66%, hydrogen 4.36%, nitrogen 14.85%. The carbon result is off slightly; however, the hydrogen is in excellent agreement. The nitrogen result, although slightly off, is generally more difficult to pinpoint and thus appears to be in close agreement. The degree of error on the carbon analysis indicates some small impurity present which can be seen on the nmr spectrum (Figure II), and will be explained later in further detail.

The nmr spectrum for the paranitroacetanilide is a classic spectrum for this amide. The four peaks that appear as a quartet centered around 8.0δ are hydrogens that appear on the benzene ring. Usually the region around 8.0δ is the region of absorption of a benzene ring; thus, this is a classic pattern for hydrogens on a benzene ring. The area under the curve is indicated by the integration curve which covers approximately five large boxes for the four peaks centered around 8.0δ (aromatic region). In the aliphatic region there is a very sharp, single peak at approximately 2.2δ which is indicative of an aliphatic hydrogen attached to carbon. The total area under this peak is approximately four large boxes. Consequently, the ratio of hydrogens calculated is approximately four aliphatic hydrogens to five aromatic hydrogens. This is in close agreement with the paranitroacetanilide molecule which contains three aliphatic hydrogens and four aromatic hydrogens; almost a 4:5 ratio. The appearance of a quartet at 8.0δ on the nmr spectrum is due to the fact that each hydrogen on the benzene ring is being split by a neighboring hydrogen. Instead of obtaining a single peak, a number of peaks will be realized depending on how many hydrogens appear on the neighboring carbon atom. If there is one hydrogen on a neighboring carbon, then two peaks will appear. If there are two hydrogens on a neighboring carbon, then three peaks appear, etc. This is in contrast to the methyl group that appears as a singlet at approximately 2.2δ since the neighboring carbon atom in this case has no hydrogen atoms. In the case of paranitroacetanilide, all four hydrogens on the benzene ring have a neighboring hydrogen which means that every peak will be split into two peaks. The structure of the paranitroacetanilide depicted below in Figure C will better explain this phenomenon. On the benzene ring can be seen two hydrogens which are labeled (a) and two hydrogens which are labeled (b). The hydrogens labeled (a) are close to the N-H group while the hydrogens labeled (b) are close to

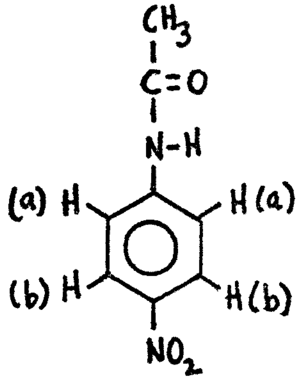


Figure C

the nitro group (NO_2). This means the (a) and (b) hydrogens are not in the identical electronic environment. Consequently, although both the (a) and (b) groups are hydrogens, they absorb in a different region in the spectrum. If there were no splitting, two peaks would be seen due to the benzene ring hydrogens; one due to the (a) hydrogens and one due to the (b) hydrogens. The (a) hydrogens are equivalent to each other while the (b) hydrogens are equivalent to each other; however, the (a) hydrogens are not equivalent to the (b) hydrogens since both groups are in a different relative position the the nitro (NO_2) and the NH group. However, each (a) hydrogen has one neighboring hydrogen causing its peak to be split into two and each (b) hydrogen has one neighboring hydrogen causing its peak to be split into two. Thus rather than seeing two single peaks, we see four peaks for these aromatic hydrogens. The fact that four peaks are present also confirms the fact that the nitro group is in the para position.

Also shown on the nmr spectrum is a broad peak located at approximately 2.6δ. The broadness of this peak is typical of a hydrogen attached to a nitrogen. The area under this peak as indicated by the integration curve covers approximately one large box; thus, there is approximately one hydrogen on the nitrogen compared to about four hydrogens on a saturated carbon which is an approximate agreement to the fact that there is one N-H and three C-H's in the molecule. This is a typical classic pattern which would be expected.

The upper line seen on the nmr spectrum indicated by offset is probably a trace of acid. The offset indicates that the spectrum continues past 9 or 10 δ and the only substances the absorb in this area are carboxylic acid hydrogens and perhaps aldehyde hydrogens. Since one of the starting materials was an acid chloride, hydrolysis of which is easy, a small amount of acid is thus probably present. This phenomenon might be reflected in the elemental analysis of the paranitroacetanilide which had a lower percent carbon than was expected since the acid impurity present is poorer in carbon. The percent carbon in acetic acid is 40%. The melting point for the paranitroacetanilide was 212-218^{0}C.

Paranitropivalanilide

Figure III shows a very clean infrared spectrum for this compound. The very sharp, intense peak at 3330 cm^{-1} is a typical peak for an N-H absorption. The next peak seen classically at 3000 cm^{-1} is for aliphatic hydrogens attached to carbon. The methyl (CH_3) absorption seen here is very dominant since there are three Methyl groups in this molecule and they all absorb in the same region. It is interesting to note the weaker relative absorption for the benzene ring hydrogens at approximately 3050 - 3070 cm^{-1}

as compared to the paranitroacetanilide which had a much stronger relative absorption in the region between the N-H and the C-H aliphatic. The reason for this is that in this molecule there are more aliphatic (CH_3) hydrogens (9) than there are aromatic hydrogens (4) whereas in the paranitroacetanilide the ratio of aliphatic to aromatic hydrogens was 3:4. The very sharp, intense peak at 1680 cm^{-1} is due to the C=O bonding of the amide. Its position has shifted by 20 cm^{-1} (1700 cm^{-1}) from the paranitroacetanilide, a possible indication of the inductive effect of the methyl groups because the molecule now has three methyl groups thus pushing their electron density into the carbonyl region, and stabilizing the carbonyl. The peaks found between 1610 - 1650 cm^{-1} are again indicative of the benzene ring. The two very strong peaks located at 1510 cm^{-1} and 1350 cm^{-1} are due to the nitro group (NO_2) on the benzene ring. This again is verified by the fact that generally nitro groups (NO_2) appear between 1300 - 1370 cm^{-1} and 1500 - 1570 cm^{-1}. Another very sharp, intense peak can be seen at 860 cm^{-1}. This peak is again indicative of the para substitution in the benzene ring, that is, the nitro and N-H are para to each other.

The nmr spectrum as depicted on Figure IV is again in total agreement with what was expected. The benzene region, centered at approximately 7.9δ, again has four peaks that appear as a quartet showing para substitution. The two hydrogens on each side of the benzene ring are thus splitting their neighboring hydrogens giving the classic pair of doublets. The total area under the curve in the aromatic region as indicated by the integration curve covers approximately 4½ large boxes; whereas, the aliphatic region centered around 1.3δ shows a very sharp singlet (denoting no impurities) which covers an area of approximately 10 large boxes. Therefore the ratio of aliphatic hydrogens to aromatic hydrogens is approximately 10:4.5 or slightly better than 2:1 ratio. In fact, in the paranitropivalanilide molecule there are nine aliphatic hydrogens and four aromatic hydrogens, again slightly better than a 2:1 ratio. Therefore the areas and positions are in agreement for aliphatic and aromatic hydrogens. Another comparison between the paranitroacetanilide and the paranitropivalanilide is that the aliphatic region has shifted to the right. The paranitroacetanilide absorption was approximately 2.1δ whereas the paranitropivalanilide absorption is at 1.3δ. This is an indication of the isolation taking place of the three methyl groups from the electron attracting carbonyl group.

For the elemental analysis, the calculated percentages were: carbon 59.45%, hydrogen 6.35%, nitrogen 12.61%. The actual percentages found were: carbon 59.44%, hydrogen 6.22%, nitrogen 12.28%. The carbon agrees extremely well, the hydrogen very well, and the nitrogen within experimental error. Overall, this was an excellent agreement for this compound. The melting point for this compound was determined to be 156-158°C.

Paranitro-1-adamantanecarboxanilide

Figure V shows a very clear infrared spectrum for this compound. The very sharp peak located at 3360 cm^{-1} is a typical N-H absorption. In all three cases thus far (p-nitroacetanilide, p-nitropivalanilide, p-nitro-1-adamantanecarboxanilide), the N-H absorption has been a single peak which is indicative of a single hydrogen on the nitrogen. In contrast, a double peak would have been evident if there had been two hydrogens attached to the nitrogen. The interesting fact just discussed in the previous spectrum (p-nitropivalanilide) that there were more aliphatic hydrogens than aromatic hydrogens and therefore the absorption in the aliphatic region was greater than the aromatic region, is even more pronounced in the case of the paranitro-1-adamantanecarboxanilide compound. Here there are fifteen aliphatic hydrogens on the adamantyl portion of the molecule and only four hydrogens on the aromatic (benzene) portion of the molecule. This phenomenon is reflected in the spectrum since in the region between 2850-2950 cm^{-1}, can be seen a very intense aliphatic absorption while in the region around 3050 cm^{-1}, the aromatic absorption is very weak. Thus far the ratio of absorption of aliphatic hydrogens to aromatic hydrogens has increased from the paranitroacetanilide to the paranitropivalanilide to the paranitro-1-adamantanecarboxanilide which is what should be expected. The sharp, intense peak at 1675 cm^{-1} is due to the C=O bonding (carbonyl group) which again is typical of the amide. The aromatic (benzene ring) absorption is evident at 1620 cm^{-1}. And again the two very strong peaks at 1340 cm^{-1} and 1530 cm^{-1} are due to the nitro group on the benzene ring. Finally the very intense peak at 860 cm^{-1} is characteristic of the para absorption which was also present in the previous two derivatives. This infrared spectrum was in agreement with the structure postulated.

The nmr spectrum, as depicted on Figure VI, is another classic case in the aromatic region centered around 8.1 δ in which four peaks that appear as a pair of doublets depict para substitution. The two hydrogens on each side of the benzene ring are thus splitting each other giving the classic doublet once again. The area under these doublets can be seen to be about 3½ large boxes on the integration curve. In the aliphatic region, two large singlets (not a doublet) can be seen. The first singlet which is rather broad and centered at 2.0δ has an area of almost eight large boxes, while the second singlet, centered at approximately 1.75δ has an area of almost 4½ boxes. Thus in the aliphatic region, these two singlets are in a ratio of almost 2:1, a phenomenon caused by the fact that the adamantyl derivative, which is essentially an aliphatic unit, has two distinct regions on it.

The area under the aliphatic peaks thus total 12½ boxes as compared to the aromatic region of 3½ boxes which is very close agreement to the fact that the actual ratio of aliphatic hydrogens to aromatic hydrogens is 15:4. In addition to these peaks, there is a complex peak centered roughly at 2.5 δ which is indicative of the N-H structure in the amide functional group. The extraneous peak at the offset is probably due to a trace of impurity, perhaps 1-adamantane carboxylic acid. Thus, the nmr spectrum is in agreement with the structure expected.

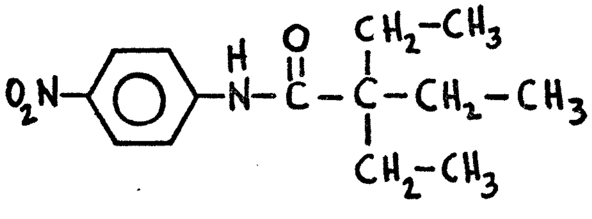
For the elemental analysis, the calculated percentages were: carbon 67.98%, hydrogen 6.71%, nitrogen 9.33%, The actual percentages found were: carbon 67.93%, hydrogen 6.50%, nitrogen 9.07%. Thus all results were very close to those expected and within experimental error. The melting point for this compound was found to be 199-200°C. The sharp melting point is indicative of a pure sample.

Paranitro-2,2-diethylbutyranilide

The infrared spectrum as displayed on Figur VII, shows two peaks at 3350 cm^{-1} where the N-H absorption is expected. This is indicative of two different amides that are present; each one has an N-H group and each one is absorbing in a slightly different position in the infrared spectrum. The aliphatic region at 2980 cm^{-1} and lower is very strong, indicative of a large number of C-H absorptions as would be expected from the ethyl groups present which have a total of fifteen aliphatic hydrogens. The aromatic region at 3060 - 3090 cm^{-1} is very weak in comparison because there are only four aromatic hydrogens. The sharp intense peak at 1685 cm^{-1} is due to the C=O bonding (carbonyl group). In comparison, the paranitroacetanilide compound, which contains three hydrogens had C=O absorption at 1700 cm^{-1}, while the paranitropivalanilide, which contains three methyl groups had C=O absorption at 1680 cm^{-1}. In other words, there is no consistent progression on the IR spectrum shown in going from a compound containing three hydrogens to one containing three methyls to one containing three ethyl groups. Again the two very pronounced peaks at 1350 cm^{-1} and 1520 cm^{-1} are due to the nitro group on the benzene ring. Finally the peak at 855 cm^{-1} is again powerful indication of the para substituted benzene.

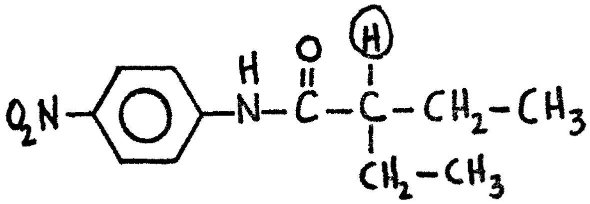
The nmr spectrum, as depicted on Figure VIII, is again a classic case in the aromatic region centered around 8.0δ in which four peaks that appear as a quartet depict para substitution. The two hydrogens on each side of the benzene ring are thus splitting each other giving the doublet once again. The area under these doublets can be seen to be about 3½ large boxes on the integration curve. Centered at approximately 3.3δ is a water peak indicating either a slightly wet compound or solvent. At about 2.6δ is a complex peak due to the N-H absorption of the amide. There are then two striking absorptions, one located at approximately 0.9δ and the other at approximately 1.5 - 1.6δ. The absorption at 0.9δ is very noteworthy since it is farther to the right on the spectrum than any previous compound. In fact a progression can be seen, for as the amount of hydrogens are increased, they absorb more and more to the right on the spectrum, the farther removed from the carbonyl they are. For example, the paranitroacetanilide which has one methyl group absorbed at 2.1δ while the paranitropivalanilide which has three methyl groups absorbed at approximately 1.3 - 1.4δ. Finally the paranitro-2,2-diethylbutyranilide has three ethyl groups, consequently, the methyl groups are separated from the carbonyl by two carbon atoms and the absorption is down at 0.9δ. This absorption center at 0.90δ is a triplet which signifies that these hydrogens absorbing in this region are split by two neighboring hydrogens as would be expected from an ethyl group. The region around 1.5 - 1.6δ where we would expect the CH_2 absorption to exhibit a quartet because there are three neighboring hydrogens on the methyl group, is however, more complex than expected. This phenomenon is probably due to an impurity of the analogous diethyl amide where there is one lone hydrogen on a carbon adjacent to the carbonyl group. The structures exhibited below will better explain this reasoning.

A.) Triethylamide expected



The ratio of aliphatic hydrogens would thus be 1:0:6:9.

B.) Diethylamide impurity

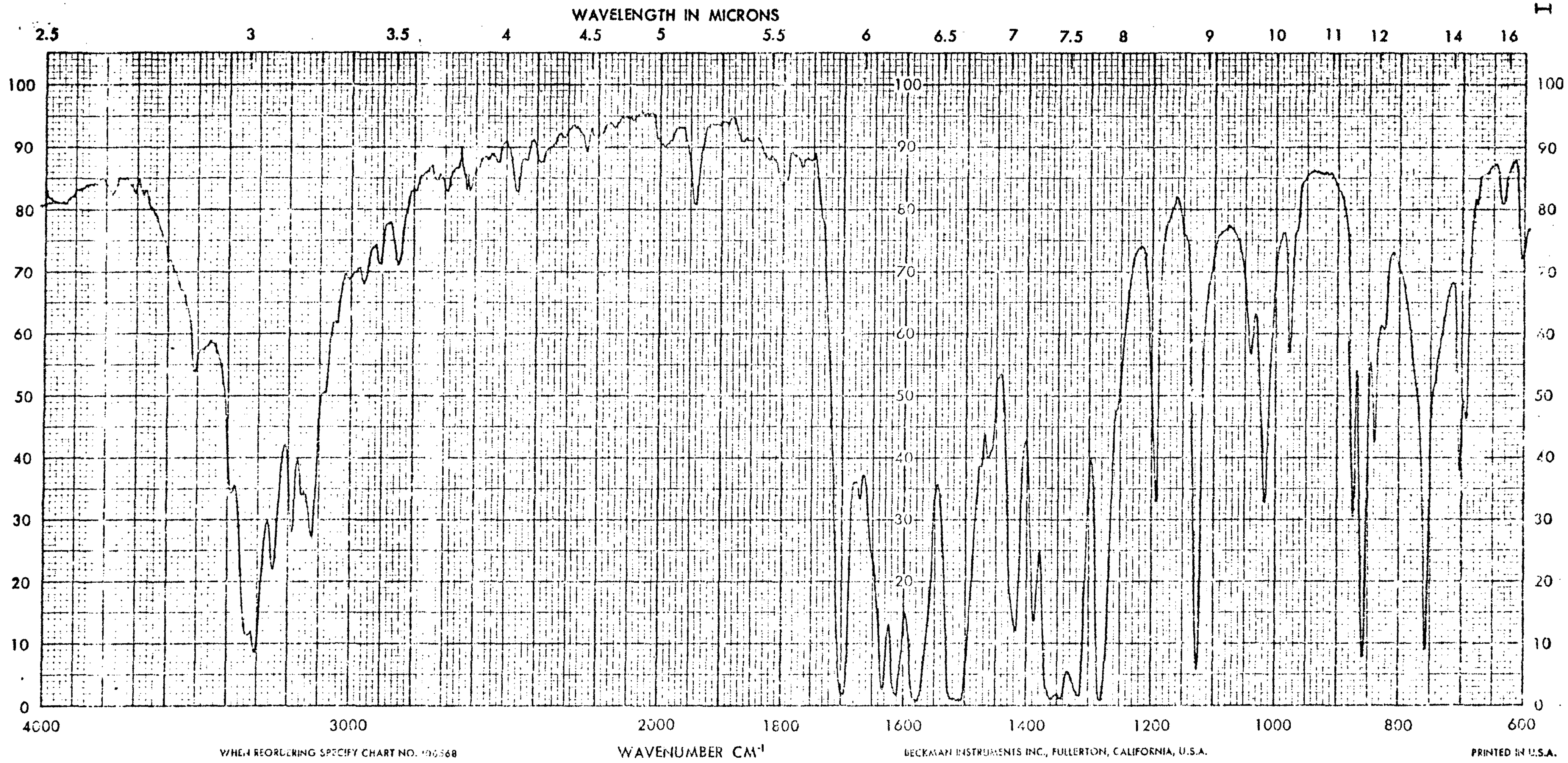


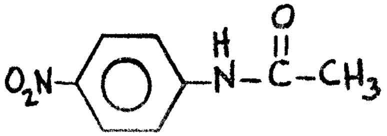
Note the ratio of aliphatic hydrogens changes to 1:1:4:6. This one lone hydrogen (circled) is splitting the methylene (CH_2) groups so that they become more complex than the quartet expected from an ideal ethyl group. This diethylamide hydrogen was introduced because the reagent used in this reaction was impure itself, unbeknownst to us beforehand. The reagent contained both the desired triethylacetylchloride and a significant amount (about one-third) of the diethylacetychloride. The C-H that is present in the diethylamide impurity apparently absorbs in the region centered around 2.3 - 2.4 δ where two new peaks can be seen. This hydrogen is probably being split by two neighboring hydrogens and therefore, the splitting can be seen. Estimating the curve in the area is difficult but an approximation of seven small boxes for the hydrogen attached to the N-H, five small boxes for the lone hydrogen on the carbon, forty small boxes for the CH_2 groups and fifty-nine small boxes for the CH_3 groups come between the expected 1:0:6:9 ratio and the 1:1:4:6 ratio of the impurity group.

In addition to these peaks, on the offset line, two hydrogens can be seen. These are undoubtedly due to carboxylic acid hydrogens. The peaks are separated from each other and absorb relative to each other at a 7:3 ratio. These two peaks were caused by two different carboxylic acid impurities which resulted from the hydrolysis of two different acid chlorides which were present in the original reactant. These hydrogen ratios of 7:3 in the acid are probably a reflection of the 7:3 ratio which appears to be present in the amides absorbing in the region between 0.90-2.3δ. The benzene ring has not been affected because the absorption due to the hydrogens on the benzene ring would appear in the same place regardless of whether there were three ethyl groups or two ethyl groups on those positions far removed from the benzene ring.

For the elemental analysis, the calculated percentages were: carbon 64.60%, hydrogen 6.20%, nitrogen 10.76%. The actual percentages found were: carbon 61.12%, hydrogen 6.52%, nitrogen 11.43%. The elemental analysis is thus deviated from the calculated values; probably due to the fact that there are two different amides present. The carbon is lower than the calculated value which would be expected if there were a significant amount of the diethyl compound present which of course contains less carbon. The hydrogen and nitrogen are slightly higher probably due to the fact there is a relatively higher percent hydrogen and nitrogen in the diethyl compound. Again the same reasoning can be used for the higher percentage of oxygen present also. The melting point of this compound was 134.5 - 138.5°C. This is a narrow range for an impure compound, however, the similarity in structures between the diethyl and triethyl compounds probably results in a small depression in the melting point.

FIGURE I





KBr Dispersion

Concentration - Abt. 0.6%

Date: 2-18-75

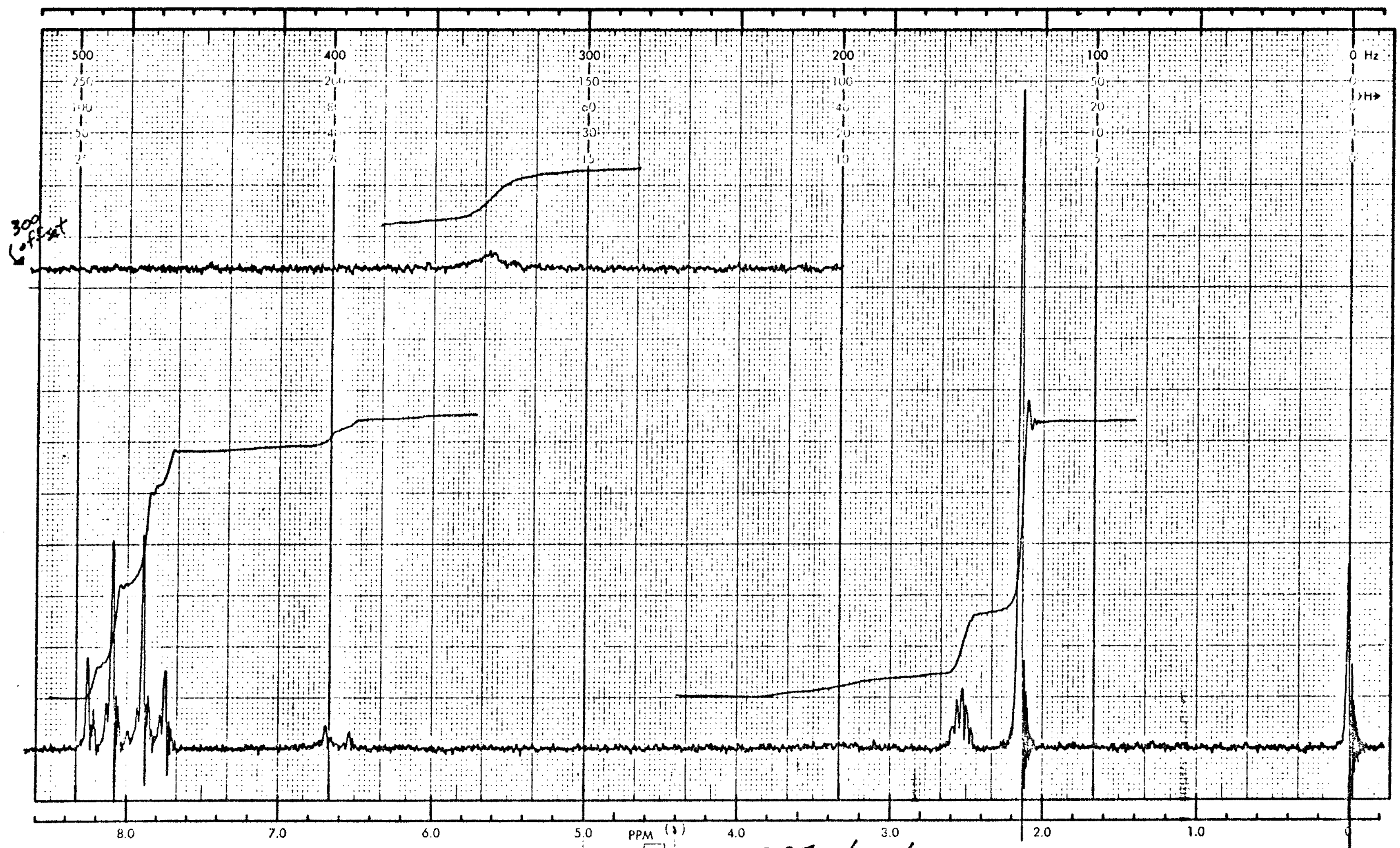


FIGURE II

MANUAL

SWEEP OFFSET (Hz): 0-300
SPECTRUM AMPLITUDE: 10.
INTEGRAL AMPLITUDE: 80+10.
SPINNING RATE (RPS): —

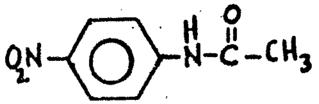
SWEEP TIME (SEC): 50 [✓ 250]
SWEEP WIDTH (Hz): 25 50 100 250 [✓ 500]
FILTER: [✓ 1] 2 3 4 5 6 7 8
RF POWER LEVEL: .05

AUTO ☐
(250)
(500)
(2)
(.05)

SAMPLE: P. 27 m/L 2/3

SOLVENT: DMSO-d6

REMARKS:



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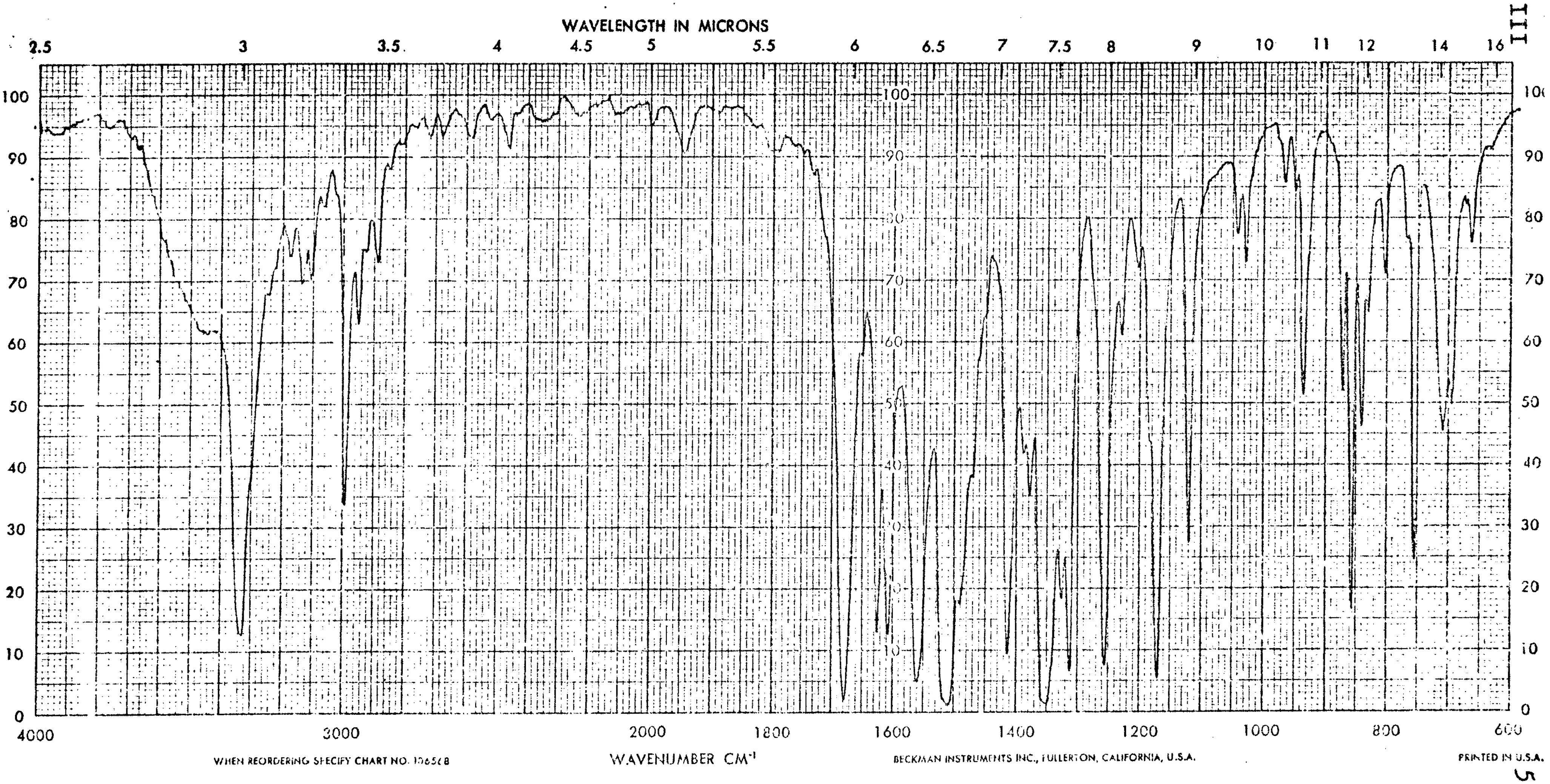
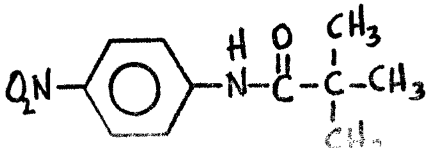
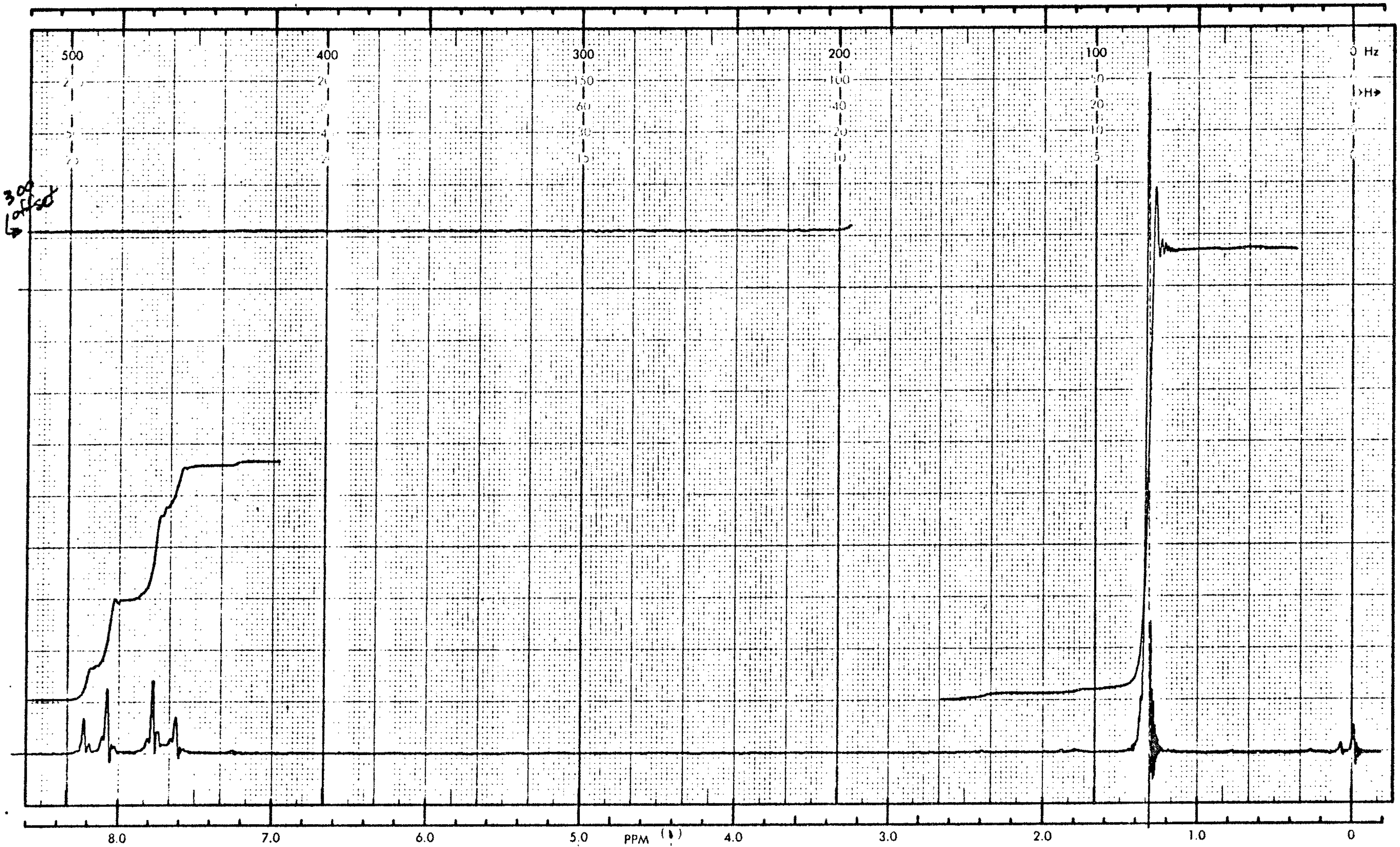
60 MHz NMR SPECTRUM NO. A-0164

FIGURE III





KBr Dispersion
Concentration - Abt. 0.6%
Date: 2-18-75



MANUAL

SWEEP OFFSET (Hz): 0-300
SPECTRUM AMPLITUDE: 3.2×1
INTEGRAL AMPLITUDE: 80+3.2
SPINNING RATE (RPS): —

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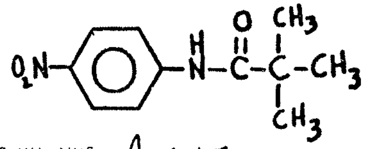
SWEEP TIME (SEC): 50 [✓ 250]
SWEEP WIDTH (Hz): 25 50 100 250 [✓ 500]
FILTER: [✓ 1] 2 3 4 5 6 7 8
RF POWER LEVEL: .05

AUTO ☐
(250)
(500)
(2)
(.05)

SAMPLE: Page 33 Step 9

SOLVENT: $CDCl_3$

REMARKS:



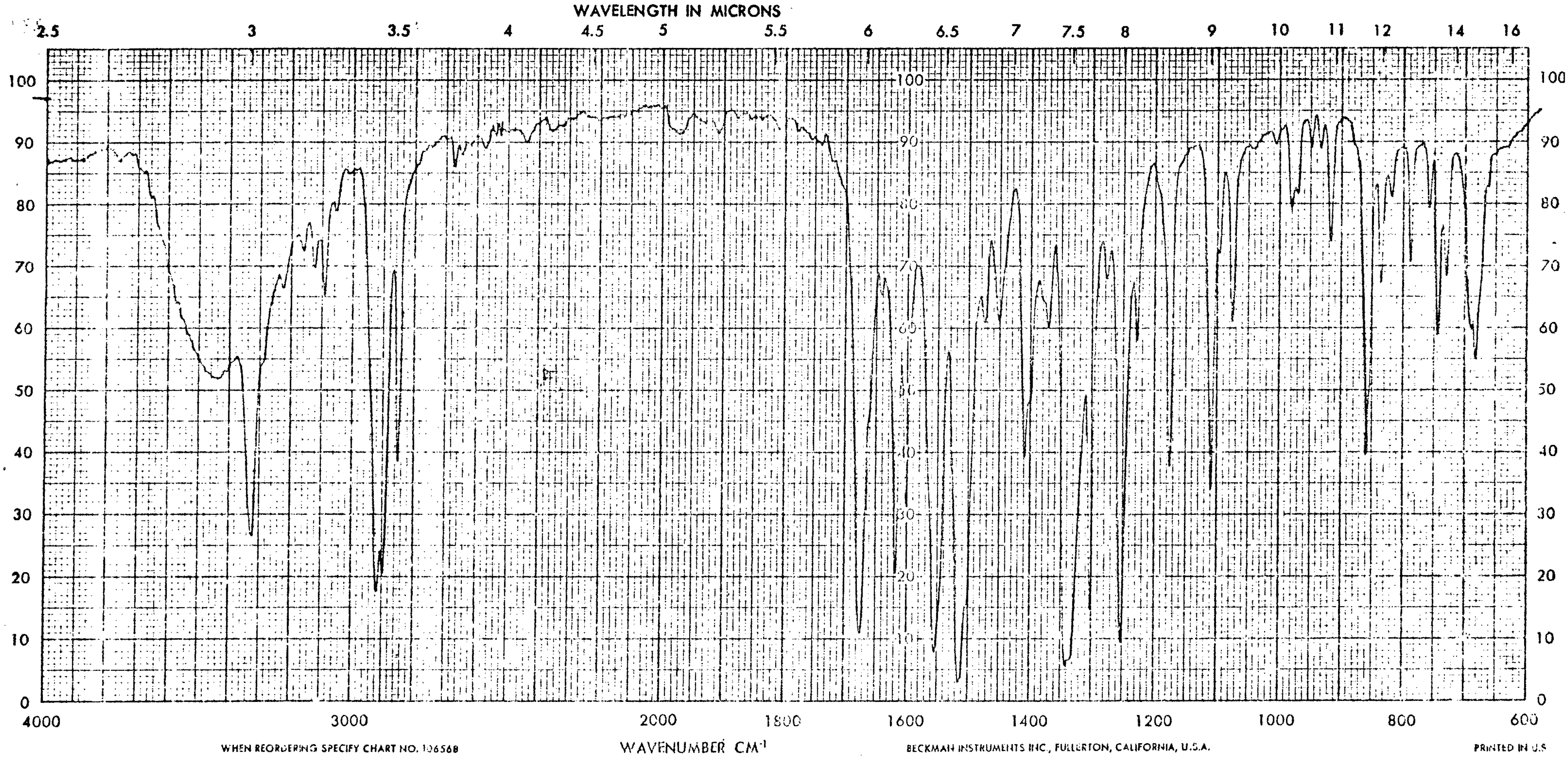
60 MHz NMR SPECTRUM NO A-0165

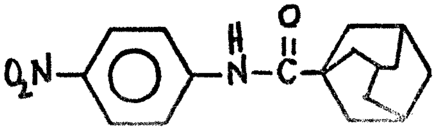
DATE: 2/14/75

OPERATOR: R.R.

FIGURE IV

FIGURE V





KBr Dispersion
Concentration - Abt. 0.6%
Date: 2-19-75

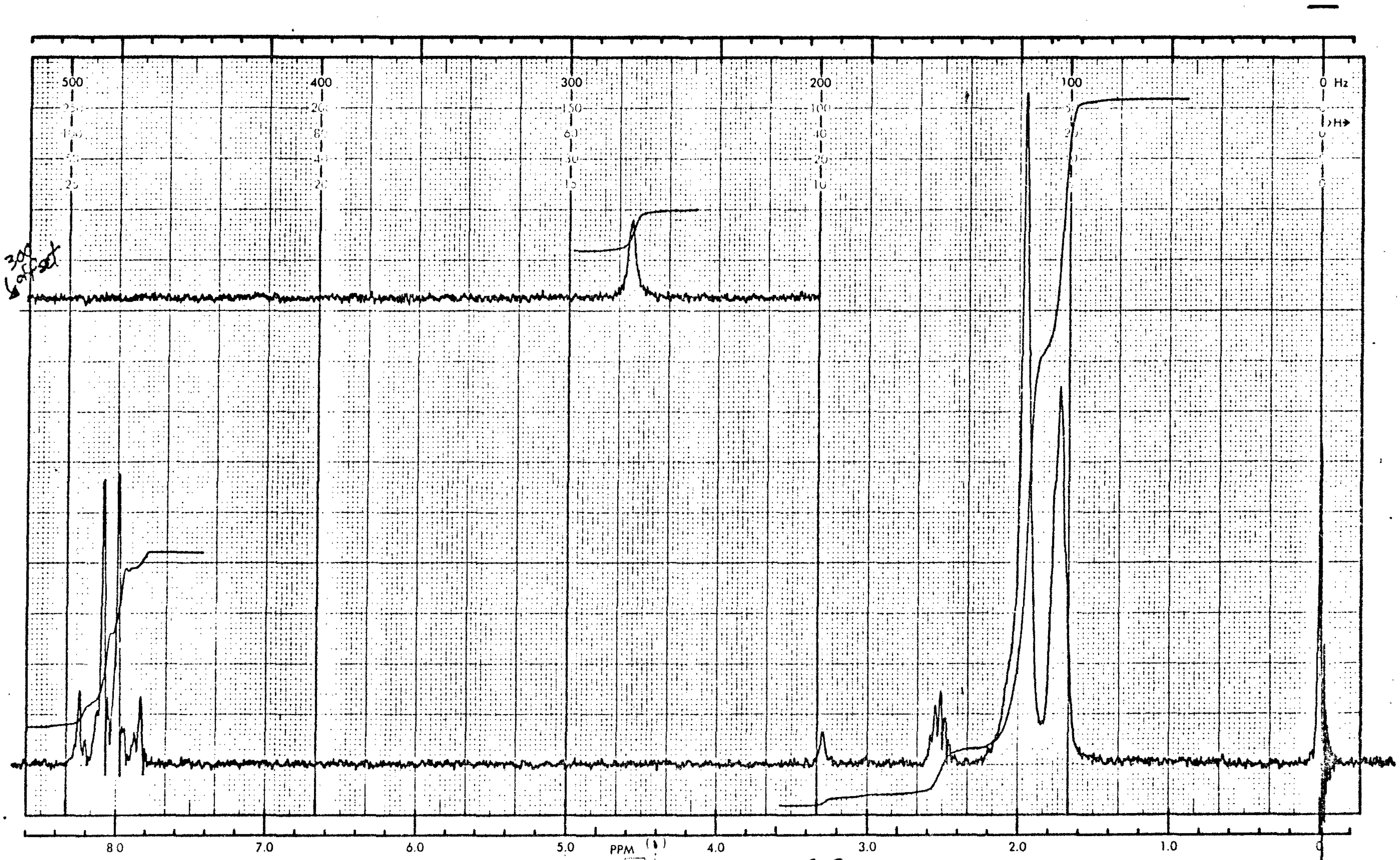


FIGURE VI

MANUAL

SWEEP OFFSET (Hz): 0-300
SPECTRUM AMPLITUDE: 12.5
INTEGRAL AMPLITUDE: 80+6.3
SPINNING RATE (RPS): —

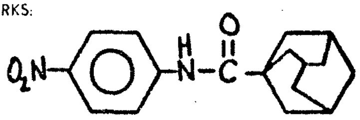
SWEEP TIME (SEC): 50 [✓ 250]
SWEEP WIDTH (Hz): 25 50 100 250 [✓ 500]
FILTER: [✓ 1] 2 3 4 5 6 7 8
RF POWER LEVEL: .05

AUTO ☐
(250)
(500)
(2)
(.05)

SAMPLE: page 39 Step 6B

SOLVENT: DMSO-d6

REMARKS:



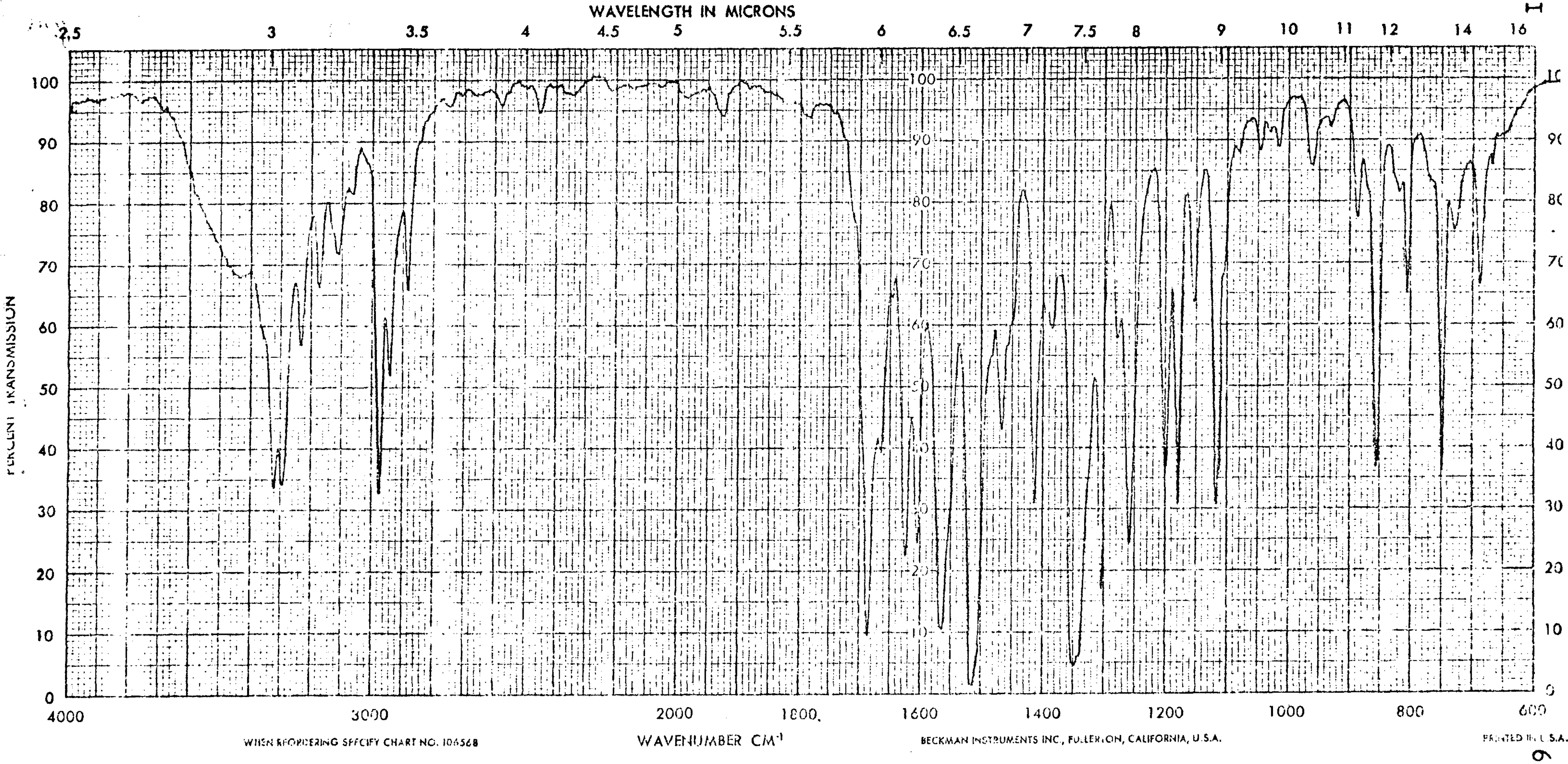
No. VN 1009 (S-60T)

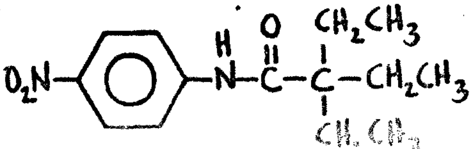
DATE: 3/5/75

OPERATOR: R.R.

60 MHz NMR SPECTRUM NO. A-0166

FIGURE VII

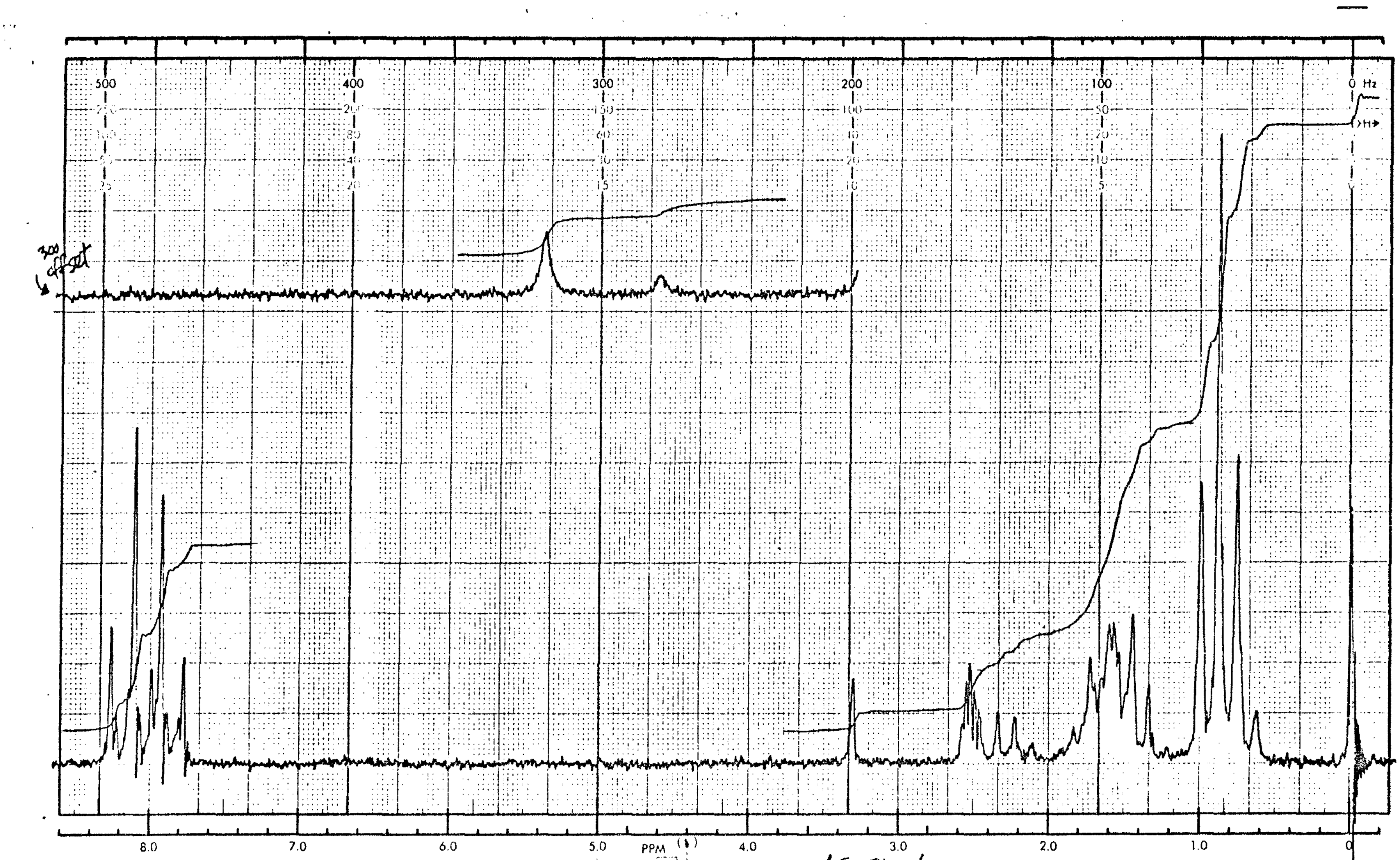




KBr Dispersion

Concentration - Abt. 0.6%

Date: 2-18-75



MANUAL

SWEEP OFFSET (Hz): 0-300
SPECTRUM AMPLITUDE: 16.
INTEGRAL AMPLITUDE: 80 + 6.3
SPINNING RATE (RPS): —

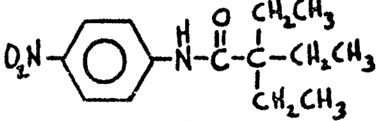
SWEEP TIME (SEC): 50 [✓ 250]
SWEEP WIDTH (Hz): 25 50 100 250 [✓ 500]
FILTER: [✓ 1] 2 3 4 5 6 7 8
RF POWER LEVEL: .05

AUTO ☐
(250)
(500)
(2)
(.05)

SAMPLE: page 45 Step 6

SOLVENT: DMSO-d_6

REMARKS:



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OPERATOR: R.R.

60 MHz NMR SPECTRUM NO. A-0167

FIGURE VIII

CONCLUSION

This thesis helped to further advance the findings of many researchers who reacted acetyl chlorides with amines to form various amides. Even though no progressions were seen on the infrared spectrum in respect to larger aliphatic hydrogen groups, the nmr spectrum did show progression to the right in this respect. In addition, the formation of these compounds should lead to further enhancement in the knowledge of the size of the alkyl side chains by determining the rates of hydrolysis of these amides.

REFERENCES

Buehler, C.A. and Pearson, D.E., Survey of Organic Synthesis. New York: Wiley Interscience, 1970, pp. 895-900.

Bradshaw, J.S., et. al.,"The Photoreactions of 2,4-Dimethoxyacetanilide," The Journal of Organic Chemistry, 35, 1970, p. 1220.

Emery, A.R. and Gold, V., "Quantitative Studies of the Reactivities of Mixed Carboxylic Anhydrides," Journal of the Chemical Society, 1950, p.1443.

Farthing, A.C. and Parkes, G.D., "Derivatives of 2:4:6-Trinitrotoluene:Monoreduction of Polynitro-compounds," Journal of the Chemical Society, 1948, pp. 1275-1277.

Karo, W. and Sandler, S.R., Organic Functional Group Preparations. New York: Academic Press, 1970, pp. 274-285.

Marmor, S., Laboratory Guide for Organic Chemistry. Boston: D.C. Heath and Company, 1964, pp. 274-275.

Sonntag, N.O.V., "Reactions of Aliphatic Acid Chlorides," Chemical Reviews, 52, 1953, pp. 269-277.

Zabicky, Jacob, The Chemistry of Amides. New York: Interscience Publishers, 1970, pp. 74-96,105-109.