SYNTHESIS OF
STERICALLY HINDERED DIESTERS

by

Richard Alexander Bankowitz UC 1979

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Approved by _____
Thesis advisor

Approved by _____

Approved by _____

Date _____

DEDICATION

To William B. Martin, Jr., whose steadfast patience, guidance, and scientific curiosity shall serve as an example for many years to come.

ACKNOWLEDGEMENT

I wish to gratefully acknowledge the aid received by Professor William B. Martin, Jr., in various portions of this work, and to thank him for his assistance in the interpretation of some of the spectroscopic data.

I also wish to thank Professors Martin and Hull for their aid in gathering the Mass Spectroscopic data.

By Richard A. Bankowitz 5-22-79

Richard A. Bankowitz Date

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ABSTRACT

BANKOWITZ, RICHARD A. Synthesis of Sterically Hindered Diesters Department of Chemistry, March, 1979

This thesis examines the synthesis of two sterically hindered diesters, neopentyl glycol dipivaloate and ditert-butyl 2,2-diethylmalonate. The implications of this hinderance for hydrolysis in basic medium are discussed.

The neopentyl glycol diester of 2,2-dimethylpropanoic acid is prepared with little difficulty by reaction of the glycol with the acid chloride in the presence of pyridine. The process gives the desired ester in approximately 66% yield.

The preparation of the ditert-butyl ester of diethylmalonic acid is also attempted by means of the acid chloride in the presence of pyridine. Preparation of the diethylmalonyl dichloride using acetonitrile as a solvent in most cases resulted in a drastically reduced yield due to what we attribute to the formation of substituted pyrimidines. By using cyclohexane, the desired acid chloride was able to be isolated in appreciable amounts. In both solvents, 2-ethylbutanoyl chloride is also obtained.

Reaction of the 2-ethylbutanoyl chloride with tert-butanol in the presence of pyridine gives tert-butyl 2-ethylbutanoate in 44% yield.

Ditert-butyl 2,2-diethylmalonate is not isolated after a similar reaction of diethylmalonyl dichloride with tert-butanol. However, spectroscopic evidence suggests that a small amount of the acid chloride of tert-butyl hydrogen 2,2-diethylmalonate is

isolated from the product mixture. The reactivity of this particular acid chloride appears atypically low for an aliphatic acid chloride, and this is explained by its large steric hindrance.

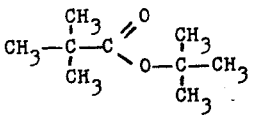
Preparation of the two hindered esters of this study by methods which utilize both the dicarboxylic acid chloride and the glycol would immediately suggest a feasible synthetic method for the preparation of the mixed polyester. On the basis of others' work, such a product would be suspected of being particularly resistant to basic hydrolysis.

INTRODUCTION

General methods for the synthesis of esters and mechanisms of their hydrolysis have been well studied. This thesis concerns itself chiefly with the synthesis of "sterically hindered" diesters, and the implications of this hindrance to their basic hydrolysis. The wealth of literature dealing with acid catalyzed hydrolysis has been purposely ignored.

Because the term "sterically hindered" is meaningless unless applied in a specific context, this term will be defined for the purposes of this thesis as follows. Those alcohols and carboxylic acids which possess alkyl groups α or β to the oxygen of the alcohol or to the carbonyl carbon of the acid, shall be considered as being "sterically hindered" with respect to the esterification reaction. Those esters which possess alkyl groups α to the carbonyl carbon, or α or β to the ether oxygen shall be considered as being "sterically hindered" with respect to saponification.

Work of others [15,24,26] suggests that acids which possess alkyl groups α or β to the acyl carbon are markedly reduced in their susceptibility to esterification. Even so, such a severely hindered ester as the t-butyl pivaloate (I) was prepared in appreciable yields by several techniques. [8,9,34]

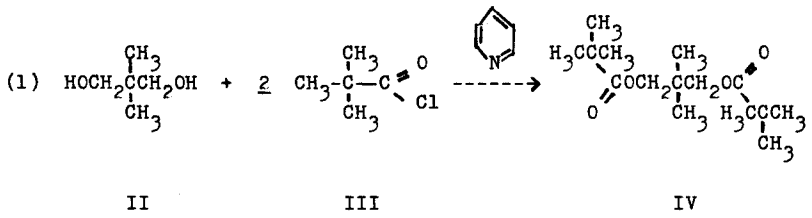


I

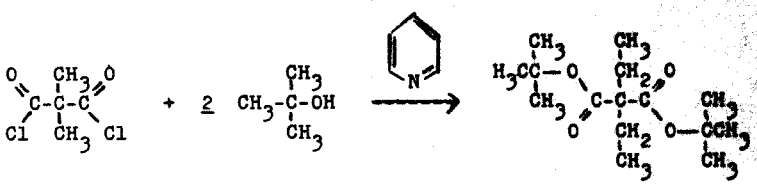
The sterically hindered neopentyl glycol has also been esterified with severely hindered acids.[3]

Once formed, esters such as (I) have been shown to be relatively resistant to basic hydrolysis.[8,15,24] In view of the fact that the saponification of these esters is severely limited, it seems reasonable that the same would be true of polyesters possessing similar characteristics. The obvious precursors of such polyesters would be sterically hindered dicarboxylic acids and sterically hindered glycols. To that end this study undertakes to examine the feasibility of esterification of each of these hindered difunctional compounds using an already familiar method.

Specifically, esterification of neopentyl glycol (II) is attempted in the presence of pyridine using the acid chloride of pivalic acid, (2,2-dimethylpropanoyl chloride) (III). The reaction, (1), yields neopentyl glycol dipivaloate (IV). The synthesis (2) of ditert-butyl 2,2-diethylmalonate (VII) is also attempted by reacting the diacid chloride of diethylmalonic acid (V) with tert-butanol in the presence of pyridine.

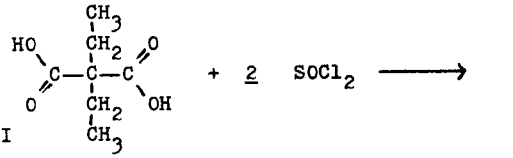


II III IV

(2) 

V VI VII

Though (III) was commercially available,* it was first necessary to prepare (V) by reaction of diethylmalonic acid (VIII) with thionyl chloride, $SOCl_2$ in the following manner.

(3) 

VIII

Both (IV) and (VII) are interesting materials for hydrolysis studies. Each possesses considerable steric hindrance about the acyl as well as the alkyl carbon, and thus would be limited in the rate of $B_{ac}2$ as well as $B_{al}2$ attack (see below). Also, since neither possesses enolizable protons, they could not hydrolyze via the recently observed ElcB mechanism, as do some malonate esters (see below).

*White Chemical Corp., Bayonne, N.J.

HISTORICAL PERSPECTIVE

I SYNTHESIS OF STERICALLY HINDERED ESTERS

The reversible, acid catalyzed reaction (4) of alcohols and carboxylic acids to yield esters has been extensively reviewed.[11]

(4) $R^1COOH + R^2OH \underset{\longleftarrow}{\overset{H^+}{\longrightarrow}} R^1COOR^2 + H_2O$

It is, however, difficult to prepare esters of trialkyl carboxylic acids in this manner, and such difficulty has been pointed out.[8,15,24]

Newman tried to improve yields of esters of hindered acids by employing a mixture of acid and alcohol in 100% H_2SO_4, however no tert-butyl ester could be prepared in this way.[23]

In the Fisher modification of Coopersmith, et. al., sulphuric acid or p-toluenesulphuric acid was used as the catalyst, along with an entrainer of toluene or heptane. Additionally, molecular sieves were used to remove the water of esterification. Using this method, these authors were able to prepare tert-butyl pivaloate in 99.5 % yields.[8] Walrath's preparation, however, was not as successful in terms of yield.[34]

The preparation of the esters via the acid chloride is a fairly general reaction. Branch and Nixon prepared the acid chlorides of a number of acids through the use of thionyl chloride and studied the relative rates of reaction

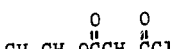
with ethanol.[4] None of their acids could be considered sterically hindered, however.

The same method was used successfully by Bender and Chen to prepare esters of the somewhat hindered 2,6-dimethylbenzoyl chlorides.[1] Walrath also reported good yields for the hindered tert-butyl pivaloate using the acid chloride in the presence of pyridine.[34]

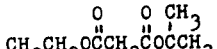
Ethyl nitrophenyl malonates of various types were prepared in a more recent study by the same technique. The most hindered ester produced in this study was ethyl o-nitrophenyl 2,2-dimethylmalonate.[16]

In a study particularly germane to ours, various esters of neopentyl glycol (II) were synthesized using acid chlorides of the "neo" variety. The dipivaloyl ester of neopentyl glycol (IV) was prepared in 81.5 % yield.[3]

In a variation of the method, the acid chloride of ethyl hydrogen malonate (IX) was prepared using phthalyl chloride ($C_6H_4(COCl)_2$). The 75 % yield of acid chloride is claimed by these authors as being superior to that obtained when thionyl chloride was used. Ethyl tert-butyl malonate (X) was obtained in 91 % yield by use of the half-acid chloride (IX) in the presence of dimethylaniline and t-butanol.[5]



IX

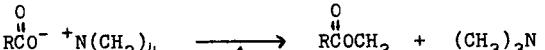


X

Another variation of the standard acid chloride technique was proposed by Crowther, et. al.[9] In this method the

the acid chloride was reacted at room temperature with the lithium salt of an alcohol. In this fashion preparation of tert-butyl pivaloate (I) was accomplished in 64 % yield.

In addition to the use of acid chlorides, several other methods have been proposed for the preparation of hindered esters. Fuson, et. al. were able to prepare methyl esters of 2,4,6-trimethylbenzoic acid in 63 % to 90 % yield by decomposition of tetramethylammonium salts (XI).[12] Such salts were prepared from tetramethylammonium hydroxide and the desired acid. The overall reaction (5) leading to the formation of the ester is the pyrolysis of (XI).



(5) $RC(=O)O^- {}^+N(CH_3)_4 \xrightarrow{\Delta} RC(=O)OCH_3 + (CH_3)_3N$

XI

The esterification method of Parish and Stock involved the in situ preparation of the mixed anhydride of trifluoroacetic acid and a desired carboxylic acid, followed by its subsequent reaction, with an alcohol. The reaction yielded sterically hindered esters such as pivaloyl naphthalate in 93 % yield; 2,4,6-trimethylbenzoic acid was methylated in 89 % yield.[26]

Esterification of 2,4,6-trimethylbenzoic acid was also accomplished by Grundy, et. al. using dimethylsulphate.[14] However, the utility of this method was limited to the preparation of the methyl ester.

Trialkyloxonium salts of type (XII) were used by Raber and Gariano to produce the desired ethyl ester by reaction with a carboxylic acid.[30]

(6) $RCO^- + CH_3CH_2-O^{\oplus}(CH_2CH_3)(CH_2CH_3) \ominus BF_3 \xrightarrow{\Delta} RCOCH_2CH_3$

XII

Their study was limited to the preparation of the ethyl ester.

A method specific for the esterification of hindered carboxylic acids, which was not limited to production of the methyl or ethyl ester, was described by Pfeffer, et. al.[27] This method achieved esterification of a given acid by use of alkyl halides in a basic solution of ethanol and hexamethylphosphoramide (HMPA). Acids of type (XIII) were esterified quantitatively (98 %) in 30 minutes using iodomethane. Also 2,4,6-trimethylbenzoic acid was methylated in 96 % yield after 20 minutes.

(7) $CH_3(CH_2)_2\overset{CH_3}{\underset{(CH_2)_2CH_3}{C}}CO_2H + CH_3I \xrightarrow{EtOH/HMPA} CH_3(CH_2)_2\overset{CH_3}{\underset{(CH_2)_2CH_3}{C}}CO_2CH_3$

XIII

Synthesis of highly hindered esters was also accomplished by Rothman through the use of isopropenyl ester intermediates.[31] The author's test compound of 2-butyl-2-heptyldecanoic acid (XIV) was converted to its isopropenyl ester (XV) by reaction (8).

(8) $n\text{-}C_8H_{17}\overset{n\text{-}C_4H_6}{\underset{n\text{-}C_7H_{15}}{C}}COOH \xrightarrow[Zn^{2+}\ 175\ C]{CH_3C\equiv CH} n\text{-}C_8H_{17}\overset{n\text{-}C_4H_9}{\underset{n\text{-}C_7H_{15}}{C}}COOC(=CH_2)CH_3$

XIV XV

Though (XIV) was totally inert to esterification using ethanol and HCl, both normal and hindered alcohols could be

esterified in good yield (> 75 %) using (XV). The reaction (9) was carried out at 175°C for 5-10 minutes with a trace of acid present.

$$(9)\quad XV + ROH \xrightarrow[H^+]{175\ C} n\text{-}C_8H_{17}\overset{\displaystyle n\text{-}C_4H_9}{\underset{\displaystyle n\text{-}C_7H_{15}}{C}}COOR + CH_3COCH_3$$

The method seemed remarkably effective for the production of sterically hindered esters, and even when the severely hindered 2-butyl-2-heptyldecanol was used in (9), the ester was obtained in 95 % yield.

II BASIC HYDROLYSIS: MECHANISMS

An assumption regarding the sterically hindered esters discussed in this thesis is that their rates of basic hydrolysis will be relatively reduced. The work presented in the experimental section does not involve ester hydrolysis. However, the effects of steric hindrance on the synthesis of these esters is so closely related to the effects of this same hindrance on their basic hydrolysis that some historical background in this area is deemed important for presentation. To that end, the literature dealing with base catalyzed ester hydrolysis will be reviewed briefly, and the effect of steric hindrance will be discussed.

The general mechanisms of ester hydrolysis have been categorized by Ingold.[17] By far the most common [11,22] mechanism of base catalyzed hydrolysis is bimolecular acyl-oxygen fission, or the Bac2 mechanism (10).[17]

$$R'\overset{O}{\overset{\|}{C}}OR + {}^{-}OH \underset{}{\overset{\text{slow}}{\rightleftharpoons}} \left[R'\overset{O^{-\delta}}{\overset{|}{C}}OR \right]_{OH^{-\delta}} \underset{\text{slow}}{\rightleftharpoons} R'\overset{O}{\overset{\|}{C}}OH + RO^{-}$$

(10) XVI

$$R'\overset{O}{\overset{\|}{C}}OH + {}^{-}OR \xrightarrow[\text{fast}]{} R'\overset{O}{\overset{\|}{C}}O^{-} + ROH$$

It should be noted that the corresponding unimolecular reaction ($B_{ac}1$) has never been observed.[22]

It can be readily seen that in reaction (10), the base is not really a catalyst because it is consumed.

Evidence for the attack on the acyl oxygen derives from the fact that optically active esters react with retention of configuration. Also when the ether oxygen is labeled as O^{18}, it almost invariably appears in the alcohol upon hydrolysis.[15]

The fact that the reaction proceeds via the tetrahedral intermediate (XVI) is demonstrated by simultaneous hydrolysis and carbonyl oxygen exchange with solvent.[15]

In addition to the almost universal $B_{ac}2$ mechanism, additional mechanisms of basic hydrolysis are possible. In some cases, when the acyl carbon is sufficiently hindered, attack on the alkyl carbon is observed. The unimolecular reaction, $B_{al}1$ (11),[17] will occur in acid with various esters in which R' is a tert-alkyl, allyl or benzyl group.[22] In basic solution the mechanism will occur only if the solution is almost neutral.[22]

(11)

$$R\overset{O}{\overset{\|}{C}}OR' \underset{\text{fast}}{\overset{\text{slow}}{\rightleftharpoons}} R\overset{O}{\overset{\|}{C}}O^{-} + R'^{+}$$

$$R'^{+} + OH_2 \underset{\text{slow}}{\overset{\text{fast}}{\rightleftharpoons}} R'\overset{+}{O}H_2$$

$$R'\overset{+}{O}H_2 + {}^{-}OH \xrightarrow{\text{fast}} R'OH$$

The bimolecular reaction, $B_{al}2$ (12),[17] is very rare. It is observed in cases of certain lactones such as Malolactone, and β butyrolactone. These two lactones are observed to hydrolyze with inversion of configuration.[15]

(12) $$R\overset{O}{\overset{\|}{C}}OR' + {}^{-}OH \underset{\text{fast}}{\overset{\text{slow}}{\rightleftharpoons}} R\overset{O}{\overset{\|}{C}}O^{-} + R'\overset{+}{O}H_2$$

The mechanism is also observed for 2,4,6-tritert-butyl benzoate, and in other reactions of type (13).[15]

(13) $$ArCOOMe + R'O^{-} \longrightarrow ArCOO^{-} + R'OMe$$

In a study of malonate esters specifically, it was found that the rarely observed ElcB mechanism (14) may take place during basic hydrolysis.[16]

(14) $$R''O\overset{O}{\overset{\|}{C}}\underset{H}{C}\overset{O}{\overset{\|}{C}}OR' \underset{H_2O}{\overset{{}^{-}OH}{\rightleftharpoons}} R''O\overset{O^{\ominus}}{\overset{\|}{C}}\underset{}{C}\overset{O}{\overset{\|}{C}}OR \longrightarrow \underset{\text{XVII}}{R''O\overset{O}{\overset{\|}{C}}CR=C=O} + {}^{-}OR$$

It was observed that malonate esters which satisfied certain requirements could be converted via a general base mechanism to an intermediate which would decay spontaneously to the products of hydrolysis. These requirements were that the ester possess enolizable protons and also a good leaving aroxide group such as the o- or p- nitrophenolate ion. Though the authors were unable to isolate the intermediate species, they maintained that (XVII) was strongly indicated.

III BASIC HYDROLYSIS: STERIC EFFECTS

Both electronic and steric effects are important in the

base catalyzed hydrolysis of esters. Due to the charged nature of the intermediate (XVI) of the $B_{ac}2$ reaction, hydrolysis proceeds faster as electron withdrawing groups are present.[11]

By assuming that steric and resonance effects are the same in esterification, and in basic and acidic hydrolysis, Taft [32] has provided a means of separating polar effects from the steric ones. Though the assumption has recently been challenged, the theory still achieves excellent internal consistancy. Taft has assigned a parameter, E_s, to incorporate the steric effect of a group during hydrolysis. Those groups which possess the most negative E_s values exert the strongest steric effects.

From the data derived from acidic hydrolysis of esters of type RCO_2R', it is apparent that R groups such as $(CH_3)_3C$, (E_s= -1.54) and $(CH_3CH_2)_3C$, (E_s= -3.8) contribute a large amount of steric hindrance.[33]

The effect of steric hindrance on hydrolysis has also been pointed out by Coopersmith. He noted that neo acid esters were 170 - 1300 times more unreactive in basic hydrolysis than were unhindered esters.[8]

This data correlates with Newman's observations of the esterification reaction. He found that in carboxylic acids, groups substituted α and especially β to the acyl carbon exerted strong steric effects. In his study, $(CH_3)_3CCOOH$ underwent esterification with methanol 26.8 times more slowly than acetic acid at 40 C°, and $(CH_3CH_2)_3CCOOH$ underwent the reaction 6170 times more slowly than did acetic acid under

the same conditions.[24]

Generally speaking, hydrolysis studies of esters of the type (IV) and (VII) are rare. Though esters of type (IV) were synthesized by Bochkova, et. al.,[3] their interest was chiefly in lubricative properties, and their work did not include hydrolysis studies. Only one article could be found in the literature which dealt specifically with the effect of screening groups on the basic hydrolysis of malonate esters.[19] Unfortunately it could not be obtained in time for a review to be included here.

EXPERIMENTAL

I SYNTHESIS OF NEOPENTYL GLYCOL DIPIVALOATE

A 500 ml three neck flask is equipped with a dropping funnel and a water cooled condenser which is closed by a $CaCl_2$ drying tube. The flask is charged with pivaloyl chloride (120.6 g, 1.00 mole). In the dropping funnel is placed neopentyl glycol (52.0 g, 0.496 mole) which has been previously dissolved in 100 ml pyridine*. The glycol/pyridine solution is added to the acid chloride over three hours with constant stirring. After addition is complete, the mixture is refluxed with continued stirring for approximately 24 hours.

The reaction yields a solid and a liquid layer. The solid is demonstrated to be pyridine HCl, (IR 0045). The liquid is distilled and a fraction is collected at 178°C with the aid of vacuum. This fraction totals 89.74 g, and is indicated by IR and NMR to be the neopentylglycol dipivaloate (IR 0046, NMR 020). The yield is 66 % of theory.

Approximately 50 g are washed with 50 ml of 0.10 N HCl. After equilibration and separation, the ester layer is washed with 50 ml of a solution of $NaHCO_3$. The ester layer is again separated, and then dried over molecular sieves. The VPC of this fraction shows approximately 95 % purity (VPC 01).

II PREPARATION OF THE DIETHYLMALONYL DICHLORIDE

A) Using Cyclohexane as the Solvent

*Dried previously over molecular sieves.

A 250 ml three neck flask is equipped with a water cooled condenser which is closed with a $CaCl_2$ drying tube. Into the flask is charged $SOCl_2$ (50.0 g, 0.420 mole) in 150 ml cyclohexane. Diethylmalonic acid (30.05 g, 0.190 mole) is added slowly with constant stirring (NMR 011). The mixture is refluxed for 18 hours with continued stirring.

The excess $SOCl_2$ and solvent are separated by distillation at approximately 78-85 C°. The resulting product is fractionally distilled using a column packed with glass beads and insulated with glass wool and foil. The following fractions are collected.

(1-001) At 124-135 C°: 10.99 g of a pale yellow liquid which is later identified as 2-ethylbutanoyl chloride (VPC02, NMR 001), which results from the decarboxylation of the diethylmalonic acid.

(1-002) At 190 C°: 12.43 g of a clear liquid which fumes in air and which is identified by IR and NMR to be the diethylmalonyl dichloride (IR 009,NMR 002).

The residue is a dark brown liquid which is left uncharacterized.

B) Using Acetonitrile as the Solvent

Diethylmalonic acid (33.0 g, 0.208 mole) is dissolved in 150 ml acetonitrile* with heat and stirring. The solution is placed in a dropping funnel. A 500 ml three neck flask is equipped with a water cooled condenser closed by a $CaCl_2$ drying tube. The flask is

*Dried previously over molecular sieves

charged with $SOCl_2$ (24.8 g, 0.208 mole) in approximately 50 ml acetonitrile. The acid is slowly dripped into the flask with stirring over the course of one hour. The solution is boiled at reflux for four hours at which time evolution of HCl is no longer noted.

After removal of the solvent at approximately 80 C°, the following fractions are collected:

(2-001) At 134 C: A clear liquid (IR 011, NMR 005)

(2-002) a At 140-154 C: A clear liquid (IR0012)

b At 154-170 C: A clear liquid (IR0013)

c At 190 C: A clear liquid (IR0014)

Each of the components of (2-002) gave similar IR data, and all are combined to give a total yield of 14.37 g of material. The resulting yield of acid chloride is 0.0729 mole, which is 70 % of theory.

This yield is atypical however, and when the experiment is repeated with similar molar ratios of $SOCl_2$ and diethylmalonic acid, but with greater amounts of acetonitrile, the yields are drastically reduced. All subsequent yields are below 13 % of theory. The apparent reason for these reduced yields will be addressed in the discussion.

III SYNTHESIS OF TERT-BUTYL 2-ETHYLBUTANOATE

A 250 ml 3 neck flask is equipped with a dropping funnel and a water cooled condenser which has been closed by a $CaCl_2$ drying tube. The flask is charged with the previously prepared and distilled product (1-001), (16.84 g,

0.125 mole). Into the dropping funnel are placed tert-butanol* (15.20 g, 0.205 mole) and pyridine* (16.0 g, 0.202 moles). The alcohol/pyridine solution is added to the flask with constant stirring. When the addition is complete the mixture is boiled at reflux for four hours and allowed to stand overnight.

The reaction yields solid white crystals of pyridine HCl and a liquid layer. After removal of excess pyridine and tert-butanol by distillation, the following fractions are collected:

(3-01) At 130 C°: 9.02 g of a clear liquid in which a white solid condenses. The liquid is indicated by IR and NMR to be tert-butyl 2-ethylbutanoate (VPC 03, IR0008, NMR 006). The yield is 42 % of theory. The presence of the white solid is attributed to the degradation and reformation of pyridine HCl.

(3-02) At 175 C° : A yellow liquid which appears to be a mixture of the above ester and 2-ethylbutanoic acid (IR 0016).

(3-03) At 190 C°: A yellow liquid which is indicated by IR and NMR to be 2-ethylbutanoic acid (IR 0006, NMR 007).

(4-01), the esterification product obtained using (2-01), is identical to product (3-01) and is isolated in similar yield (VPC 04, IR 0018, NMR 010). No acid was isolated in this case.

IV SYNTHESIS OF DITERT-BUTYL DIETHYLMALONATE

A 250 ml three neck flask is equipped with a dropping

*Dried previously over molecular sieves

funnel and a water cooled condenser which has been closed by a $CaCl_2$ drying tube. The flask is charged with product (1-02), which is indicated as being diethylmalonyl dichloride (15.21 g, 0.0772 mole). Into the dropping funnel are placed tert-butanol* (19.05 g, 0.257 mole), and pyridine* (16.93 g, 0.214 mole).

The alcohol/pyridine solution is added to the flask with constant stirring. When the addition is complete the mixture is boiled at reflux for five hours and allowed to stand overnight.

The reaction yields solid white crystals of pyridine HCl and a dark brown liquid. After removal of the pyridine HCl by filtration, and removal of the excess pyridine and tert-butanol at 115 C^{o}, the following fractions are collected:

(5-01) At 155-170 C^{o}: Approximately 2.0 g of a clear liquid (IR 0015). Some solid white material also began to crystalize in the collection flask which is attributable to the degradation and subsequent reformation of pyridine HCl.

(5-02) At 220 C^{o}: Less than 1.0 g of a dark brown, viscous liquid. No IR was run on this fraction.

This particular synthesis is repeated in order to clarify the nature of product (5-01), whose IR spectrum

15) is interesting in the carbonyl region.

A 500 ml three neck flask is equipped with a dropping funnel and a $CaCl_2$ drying tube. The flask is charged with product (2-02), which is indicated as being 2,2-diethyl-

*Dried previously over molecular sieves

malonyl dichloride (14.00 g, 0.0710 mole). To the acid chloride is added tert-butanol* (78.9 g, 1.06 moles) as one unit. To this mixture is added pyridine* (98.2 g, 1.24 moles) over the space of one hour, with constant stirring. The flask is left undisturbed for two weeks.

After that time the reaction mixture is scanned in the infrared region from 1800 to 1700 cm^{-1}. The presence of a large peak at 1800 cm^{-1} is interpreted as meaning a significant amount of the acid chloride had not reacted. Therefore the mixture is refluxed for four hours and again scanned in the same region. A significant peak at 1800 cm^{-1} is still present and refluxing is allowed to continue for three additional hours. At that time a significant peak is still present at 1800 cm^{-1}; however, the reaction is terminated at that point.

After removal of the excess solvents using a roto-evaporator, the resulting material consists of a considerable amount of white crystals of pyridine HCl, and a small amount of a red, viscous liquid. The pyridine HCl is washed several times with anhydrous ether in order to extract the liquid. The ether layer is washed with 50 ml 5 % NaOH and then washed twice with 50 ml of distilled water. The ether layer is then dried over molecular sieves. After evaporation of the ether using a roto-evaporator, 3.5 g of a light orange liquid remained (IR0047, NMR 026).

*Dried previously over molecular sieves

A VPC (VPC 06) of the material demonstrates it to consist of two major components.

By the use of TLC, it is found that an eluent of 7:3 benzene/ethyl acetate is able to give a good separation of the two components on silica. The R_f values are similar, but distinct enough such that an unambiguous separation could be achieved.

High Pressure Liquid Chromatography, employing a silica column and an eluent of 7:3 benzene/ethyl acetate, is able to isolate one of the components of the mixture. The differential refractometer indicated the passage of three closely spaced fractions which eluted in the following order.

(6-01) Approximately 0.25 g of an orange liquid (IR0049, NMR 027).

(6-02) 0.24 g of an orange liquid (IR 0050, NMR 028).

(6-03) 0.074 g of an orange liquid (IR 0051, NMR 029).

The resulting IR spectra are extremely similar, and (6-01) to (6-03) are interpreted as being identical materials.

During the separation some material was lost due to a leak in the system in the distil end of the scrubber column. It is not clear whether this accounts for the fact that the second component was not isolated.

DISCUSSION

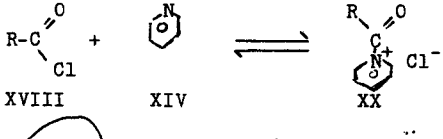
I THE ESTERIFICATION REACTIONS

The synthesis of esters (IV) and (VII) via the acid chloride technique was chosen based upon the previous success of others in preparing similarly hindered esters. Walrath[34] found this technique superior to that of Coopersmith[8] in preparing (I). Because of his success in the esterification of the pivaloyl chloride with the hindered tert-butanol, we anticipated no problems in each of the approaches employed.

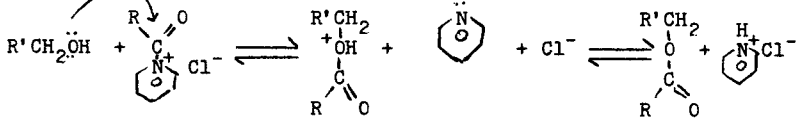
Esterification reactions involving acyl chlorides call for the presence of some type of base to neutralize the HCl formed. Pyridine (XIV) served this function in this study.

In addition to its neutralization function, there is some evidence that the pyridine may serve a catalytic purpose, by reacting to form the intermediate (XX).[22]

(15)



XVIII XIV XX



It is known that a mixture of (XVIII) and (XIV) will liberate heat, presumably by the formation of (XX).

A) Neopentyl Glycol Dipivaloate

Based upon the relatively successful esterification of

pivaloyl chloride using tert-butanol by Walrath[34], we had every reason to suspect the preparation of neopentyl glycol dipivaloate (IV) would present no difficulty. Indeed (IV) was obtained in 66 % yield with no complications. Our yield was comparable to that of Bochkova, et. al. who used the same technique.[3]

Examination of the Vapor Phase Chromatogram (VPC) obtained after purification of the ester shows that it is quite pure (VPC 01). We estimate the purity from the VPC to be approximately 95 %.

Spectroscopic evidence for the existance of this ester is found in the Infrared (IR) and Nuclear Magnetic Resonance (NMR) spectra obtained (IR 0046, NMR 020).

The large absorption present at 1715 cm^{-1} in(IR 0046)is indicative of the carbonyl group, and its position is consistent with that of the carbonyl absorption of an ester. The large absorption at 1145 cm^{-1} is characteristic of the C-O stretch, and its presence, together with the lack of an O-H absorption, indicates the material to be an ester with a fair amount of certainty. The smaller absorptions at 1476 cm^{-1}, 1360 cm^{-1}, and 1275 cm^{-1} are consistent with presence of a tert-butyl group[32].

The NMR spectrum (NMR 020) of three singlets is also consistent with (IV). The large singlet at 1.25 δ is no doubt due to the protons of the tert-butyl group. The absorption has been shifted downfield relative to where the tert-butyl protons would normally absorb, due to their close

proximity to the ether and/or carbonyl oxygens. The small singlet at 1.0δ is consistent with the absorption expected for the methyl hydrogens. The smallest singlet at 3.8δ is caused by the methylene protons. This absorption is shifted downfield relative to the normal absorption of the methylene group, and this is no doubt due to the proximity of the ether oxygen. The ratio of the integration (37:15:8) is also consistent with that expected for (IV), namely (36:12:8).

The fact that a white crystalline solid appeared in the distillate of the ester was at first puzzling. The IR spectra of this material (IR0045) was interesting because of the presence of absorption bands in the region of 2000 cm^{-1}, an area in which very few organic compounds absorb. A literature search of IR spectra revealed that this phenomenon occurs in some, but not all pyridine HCl - like salts.[28] This indicated the material to be pyridine HCl. What had indubitably happened was that pyridine HCl decomposed to pyridine and HCl vapor upon heating, and then recombined in the distillate.

B) Ditert-butyl 2,2-Diethylmalonate

Once again, based upon Walrath's[34] esterification of (III) using tert-butanol, we suspected that diethylmalonyl chloride, which possessed similar steric hindrance, would also esterify well with the hindered alcohol. Additionally, the literature contains preparations of similar type. Breslow[5] reported 75 % yield for the similar, though not as

hindered ester (IX). Holmquist and Bruice[16] reported preparation of the ethyl o-nitrophenyl 2,2-dimethylmalonate using the same technique. Despite these facts, synthesis of ditert-butyl 2,2-diethylmalonate (VII) could not be achieved easily.

1) Acid Chloride Preparation

For the purposes of synthesis (2), it was first necessary to prepare the diacid chloride from the diethylmalonic acid (VIII). The synthesis (3) was not as straightforward as hoped.

Due to the solid nature of the acid, the preparation could not be run neat. Cyclohexane was first investigated as a solvent for this preparation. It is clear from IR and NMR data that the desired acid chloride was obtained through this method, though the yield was poor. The product distilled at 190 C^{o} and gave IR spectrum (IR 0009) and NMR spectrum (NMR 002).

Examining the NMR of this product (NMR 002) one can see it is exactly the same as that of the original acid (NMR 011), except that the absorption of the acidic protons is absent. This is consistent with the formation of the diacid chloride. The integration for the methyl and methylene protons is the expected 3:2.

The IR spectrum obtained (IR 0009) is also consistent with the production of the diacid chloride. There is a complete lack of any indication of an acidic O-H stretch at 3500 cm^{-1} to 3200 cm^{-1}. The absorption at 1775 cm^{-1} to 1800 cm^{-1} is consistent with the carbonyl

stretch of an acid chloride. Note this absorption is somewhat shifted from the usual position seen in esters, 1725 cm^{-1}.[32]

Note also that this absorption is actually split into three separate peaks. It is known that acid chlorides which are ∝ substituted will usually give a split carbonyl absorption.[28] It is possible that the carbonyl groups in (V) may be somewhat locked into certain conformations due to the tendency of the large chloride atoms to avoid an eclipsed conformation with each other and with the bulky ethyl groups. This may lead to the possibility of symmetrical and asymmetrical stretching of the carbonyl, which would account for the multiple peaks.

Though the desired acid chloride was isolated, its yield was reduced due to the production of the lower boiling product (1-01), which was later determined to come about due to decarboxylation of the diethylmalonic acid. The distillation range of 124-135 C^{o} is close to the literature value for 2-ethylbutanoyl chloride (XXI) of 140 C^{o}. This product was found to undergo a reaction with tert-butanol to yield an ester whose structure is consistent with the formation of tert-butyl 2-ethylbutanoate (XXVI), (see below).

XXI

The IR and NMR data are also consistent with the formation of product (XXI). (IR 0011) shows a complete lack of an acidic O-H absorption. The absorption at 1800 cm^{-1} is similar to that seen for (V), (IR 0009) except that the splitting is not as prominent. Its position is consistent with the carbonyl stretch of an acid chloride. In general this spectrum is very similar to that of the diacid chloride (IR0009), which might be expected for two compounds whose structures are as similar as those of (XXI) and (V).

Examining the splitting pattern of the NMR spectrum (NMR 001) obtained for this product, one can easily see that despite their very similar IR spectra, these two materials must possess different structures.

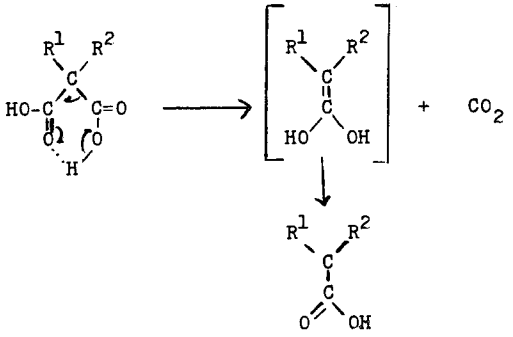
The ratio of the integration, 6:4:1, is consistent with the structure of (XXI). The appearance of the one proton pentet at 2.5$ is consistent with the presence of the methinyl proton. Furthermore, the presence of this proton in conjunction with the methyl protons, would be expected to cause the methylene protons to produce a multiplet, and this is the result obtained.

In addition to a good IR and NMR fit, the product, upon refluxing with tert-butanol, yielded an ester which was indicated as being tert-butyl 2-ethylbutanoate (XXVI), (see below).

The production of the decarboxylated acid and its

subsequent conversion to (XXI) should be expected. It is well known that diethylmalonic acid readily undergoes decarboxylation[7] and the delicate nature of the compound is one of the inherent problems in the synthesis of the desired ester.

The mechanism of this reaction is probably that proposed by King.[20]



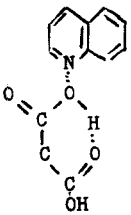
(16)

Because diethylmalonic acid (VIII) was insoluble in cyclohexane, and thus the acid chloride preparation was heterogeneous, the use of a more polar solvent was investigated. Acetonitrile was chosen, and it was found that (VIII) could be disolved in it with moderate heating. When the acid chloride preparation was repeated in this solvent, two products were isolated. Product (2-01), (IR 0011, NMR 005) was found spectroscopically to be identical to (1-01), (NMR 001). In this case the higher boiling product was collected over

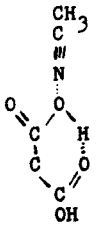
a broader range, 140° C - 190° C. Even though the range is quite broad, the fraction collected at 140° C (IR 0012), the fraction collected at 150° C, (IR 0013), and the fraction collected at 190° C, (IR 0014), were all shown spectroscopically to be identical.

The 70 % yield obtained in the first reaction using this solvent was encouraging, but unfortunately could not be repeated. It was not clear whether the reduced yield of (V) in subsequent reactions was due to increased heating or an increase in the amount of acetonitrile used. In any event, it seems acetonitrile is a poor choice of solvent for two reasons.

First, it was later noticed that small bubbles of what was presumed to be CO_2 were seen to evolve at a temperature as low as 60° C using the acetonitrile solvent. There is some evidence that the acetonitrile may accelerate the decarboxylation reaction. It was shown that the rate of decarboxylation of malonic acid is directly proportional to the concentration of quinoline present.[7] This has been proposed to be the result of the formation of the activated complex (XXII)[7], and a similar complex (XXIII) may be expected to form with acetonitrile.

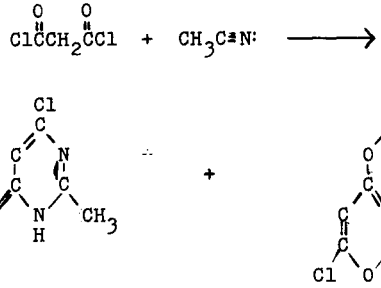


XXII



XXIII

The second reason that acetonitrile should be avoided as a solvent for the acid chloride preparation is that, as we later learned, acetonitrile will react with malonyl chlorides to yield substituted pyrimidines.[2,10] The following reaction was reported for acetonitrile and malonyl chloride.

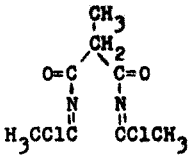


(17)

XXIV XXV

The authors demonstrated the reaction to be quite general and the decreased yield of (V), together with the production of highly colored products, would be consistent with the formation of these pyrimidines. However, the mechanism proposed by these authors calls for the presence of at least one ∝ hydrogen on the malonyl chloride, a characteristic which (V) does not possess. If (V) can not react to give products of type (XXIV) and (XXV), it is still possible for reaction (18) to occur. The reaction has been postulated as being the first step in the overall mechanism leading

to the production of (XXIV).

(18) V + 2 $CH_3C{\equiv}N$: ⟶ 

XXVI

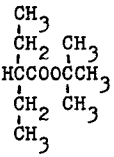
The intermediate (XXVI) would probably be a highly reactive species and could react to yield further addition products which could be responsible for the high colors obtained. It would be interesting from the standpoint of the reaction mechanism to isolate and identify these highly colored products.

2) Esterification of the Acid Chlorides

The synthesis of ditert-butyl 2,2-diethylmalonate was attempted by two separate methods. The first method utilized the separated fractions of the acid chloride preparations in a method identical to that used for the preparation of neopentyl glycol dipivaloate. A second method was employed to avoid the possible loss of acid chloride during handling. In this method, after solvent was removed, the crude, unseparated product of the acid chloride preparation was reacted with tert-butanol. The isolation of the diester was then attempted with no attempt to isolate the acid chloride. This latter method proved undesirable and yielded no esters, therefore it is not discussed further.

Tert-butyl 2-ethylbutanoate (XXVII) was obtained in 42 % yield when the decarboxylated acid chloride

prepared in cyclohexane (1-01) is esterified with tert-butanol. A similar yield is obtained using the acid chloride prepared in acetonitrile (2-01). The means by which 1-01 and 2-01 came about starting from diethylmalonic acid has already been discussed.



XXVII

Examination of the VPC (VPC 03) of this ester (3-01) obtained from the acid chloride prepared in cyclohexane, indicates it to be quite pure. The evidence for the existence of this ester can be seen in (IR 0008) and NMR 006).

The IR data clearly indicate the presence of an ester. The position of the large absorption at 1725 cm^{-1} is consistent with the carbonyl absorption of an ester. Also the rather large absorption at 1150 cm^{-1} to 1175 cm^{-1} is indicative of the presence of an ester. Additionally. the absorptions at 1250 cm^{-1}, 1370 cm^{-1}, and 1390 cm^{-1} are consistent with the presence of a tert-butyl group. [32]

An identical IR spectrum (IR 0018) is produced by the corresponding ester (4-01) obtained from the acid chloride prepared in acetonitrile. The NMR obtained for products (3-01) and (4-01),(NMR 006) and (NMR 010)

respectively, are quite similar and are consistent with the isolation of (XXVII). The structural assignment is more clearly made using (NMR 006).

In (NMR 006), the small, downfield absorption, which appears to be a multiplet, is consistent with the absorption expected for the methinyl proton. One would expect this proton to produce a pentet, and examining this multiplet one sees that the peak heights steadily increase on the left side. Such behavior would be expected if the peaks of the right side of the pentet were blended into the next absorption. The presence of this multiplet is not readily explainable in any other way. Its position is consistent with a proton which is adjacent to a carbonyl group, but at the same time is also adjacent to two electron-feeding ethyl groups.

The large singlet at approximately 1.5δ is what is expected for the tert-butyl protons and, as observed in (NMR 020), the absorption is shifted downfield due to their proximity to the ether oxygen. The absorption at 1.0δ is consistent with what is expected for the methyl protons of the ethyl group, but the observed triplet is somewhat distorted. The nature of the triplet is more clear in (NMR 010).

In order for this NMR to be consistent with the structure of ester (XXVII), one must assume that the

multiplet expected for the methylene protons is occuring in the area of 1.5δ, and that the tert-butyl absorption is superimposed upon it. This assumption is acceptable for two reasons. First it is known from previously observed NMR data (NMR 001, 005) that the analogous protons of the structurally similar 2-ethylbutanoyl chloride show a multiplet in this same area. Secondly, one can see evidence for some other type of absorption occurring under the large tert-butyl peak, which is asymmetrical. If this assumption is made, then the integration obtained is consistent with the proposed ester. One expects a ratio of 1:13:6 and the integration obtained is approximately 1:12 1/3:6.

It is interesting that the triplet at 1.0δ should be split in a somewhat unusual fashion. Upon examination of the three dimensional structure of (XXVII), one will note that it is possible for the two sets of methyl protons of the ethyl groups to be magnetically inequivalent if there is a significant barrier to free rotation. A literature search revealed that the structurally similar 2-ethylbutaraldehyde gave a triplet at about 1.0δ whose appearance is almost identical to that observed in (NMR 010)[29]. Apparently the steric interactions of the carbonyl group are sufficient to limit rotation of the carbon to the extent where magnetic inequivalence is observed on the time scale of the NMR.

In addition to ester (XXVII), two other fractions

are obtained in this reaction. Fraction (3-03) is observed to be 2-ethylbutanoic acid. The IR obtained (IR 0006) clearly matches the literature spectrum for the acid. [28]

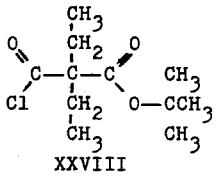
It is easy to see from examination of the IR spectrum (IR 0016) that fraction (3-02) is a mixture of (3-01) and (3-02).

The formation of the white crystaline solid of pyridine HCl in the distillate was seen here, as in the synthesis of the neopentyl glycol dipivaloate.

The synthesis of ditert-butyl diethylmalonate (VII) was attempted using diethylmalonyl dichloride (1-02). The resulting material obtained at 170 C^{o} gave IR spectrum (IR 0015), which is interesting in the area of the carbonyl region.

The absorption at 1150 cm^{-1}, which is similar in position to that seen in the spectrum of tert-butyl 2-ethylbutanoate (XXVII), is indicative of the presence of an ester. It is interesting that there are two large carbonyl absorptions present. The absorption at 1800 cm^{-1} is consistent with the carbonyl absorption of an acid chloride, and that of 1725 cm^{-1} is consistent with carbonyl absorption of an ester. Note that the carbonyl absorption at 1800 cm^{-1} is not identical to that observed for the diacid chloride (V), (IR 0009). Instead of the prominent splitting, only a small

shoulder is observed. The presence of the two carbonyl absorptions would indicate that either the fraction contained a mixture of ester and acid chloride, or that the half-acid chloride of tert-butyl hydrogen 2,2-diethylmalonate (XVIII) had been isolated. Since no VPC was taken, it is not clear which was the case.



XXVIII

After this particular esterification was repeated using diethylmalonyl dichloride (2-02), and a large excess of t-butanol, a similar fraction was isolated.

The VPC of the material clearly demonstrates it to consist of two major components (VPC 06).

On the basis of the IR data obtained, (IR 0047), it seems likely that one of these components is an ester and the other is either the diacid chloride or the half acid chloride. The spectrum is qualitatively very similar to that obtained previously for the previous esterification. However, the strength of the acid chloride carbonyl absorbance at 1800 cm^{-1} is markedly reduced in (IR 0047). Apparently, the large excess of tert-butanol and/or the longer reaction time allowed more acid chloride to be converted to the ester.

In view of the fact that the material is a mixture, the NMR obtained (NMR 026) is not particularly

useful. It does demonstrate that the structure of both components must be quite similar because apparently the absorptions of each proton overlap closely enough to give a spectrum which contains only three groups of peaks.

High Speed Liquid Chromatography was able to isolate one of the two components. Despite the fact that the differential refractometer indicated the passage of three closely spaced fractions, the resulting IR spectra, (0049-0051) and NMR spectra, (NMR 027-029) are similar enough for minor differences to be attributed to the presence of excess solvent. The NMR of the third fraction (NMR 029) which is the least clear, demonstrates the presence of a significant amount of excess solvent.

It is possible that the second component of the mixture was lost due to a leak which developed during the separation. It is also possible that this material may have been left on the column. Work is currently in progress to isolate this material.

Experimental evidence seems to be consistent with the conclusion that the material isolated is the half-acid chloride (XXVIII). Interestingly, though a VPC (MS 01) of this product demonstrates this fraction to be quite pure, the IR spectrum (IR 0049) shows two very distinct carbonyl absorptions. The absorption at 1815 cm^{-1}, which is indicative of the carbonyl of an acid chloride, is shifted slightly from the absorption seen in the

spectrum of (V), (IR 0009). The absorption at 1730 cm^{-1} is consistent with the presence of an ester. The absorption at 1140 cm^{-1} is also indicative of an ester.

The presence of the two carbonyl absorptions, though consistent with (XXVIII), is not consistent with the diester (VII). In no case in the literature could a diester be found which possessed such well separated carbonyl absorptions. Only in diethyl oxalate, $CH_3CH_2OOCCOOCH_2CH_3$, was the presence of two distinct peaks even detectable, and even here the difference in the location of their maxima is extremely small. [28]

The NMR data obtained (NMR 027) is qualitatively consistent with the structure of (XXVIII). The large singlet at 1.5δ is consistent with the expected absorption of the tert-butyl group, and its position is similar to that previously observed in the NMR of the tert-butyl 2-ethylbutanoate (NMR 006). The triplet at 1.0δ and the apparent quartet at 2.0δ are also consistent with the structure of (XXVIII). However, the integration obtained is in less than perfect agreement with the proposed product. The integration is close to 3:5:5, which is significantly different from the expected 4:9:6.

It should be noted that the presence of a TMS spinning side band may have distorted the integration in (NMR 027). In order to make sure that no TMS interfered with the integration, this spectrum was repeated with external TMS.

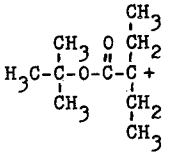
The integration of the resulting spectrum, (NMR 030), is 3:6:5, which does agree more closely with the expected value of 4:9:6, or 3 1/3: 7 1/2:5. In any event the integration is clearly more consistent with (XXVIII) than with the diester (VII) whose expected integration ratio would be 2:9:3.

The Mass Spectroscopic (MS) data obtained for this product (MS 01) was first interpreted as evidence for the isolation of the diester. The peak seen at 244 seemed inconsistent with the isolation of (XXVIII), whose molecular weight is only 234. Because of the compelling IR and NMR data however, and because the magnitude of the peak (0.4 % abundance) is only slightly above the cutoff level, we concluded that this peak must come about from the presence of a small amount of foreign material which was eluted through the Gas Chromatograph at the same time as the major fraction.

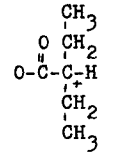
In assigning (MS 01) to (XXVIII)we note that there is a conspicuous lack of evidence for the presence of a chlorine atom. This is acceptable however, if one makes the assumption that all of the chlorine is lost initially. Such an assumption is consistent with what is known about the chemical behavior of acid chlorides.

All other peaks in the spectrum are quite readily assignable on the basis of (XXVIII). The base peak is obviously caused by the tert-butyl cation. The peak at 199 probably comes about due to a loss of the chlorine

atom. The peak at 172 is most likely due to the cleavage at -COCl to leave (XXIV). Cleavage of the tert-butyl group from (XXIV) to yield (XXX) would account for the formation of the peak at 116. The peak at 115 is probably due to (XXX) minus the methinyl proton.



XXIV



XXX

Thus the IR, NMR, and GC/MS data give good evidence for the isolation of (XXVIII). These data are not at all consistent, however, with the formation of the diester (VIII).

The lack of reactivity of this half-chloride (XXVIII) is truly remarkable inasmuch as it did not react with tert-butanol in the presence of a pyridine catalyst even after extensive refluxing. It also survived several washings with water, and this is highly atypical of an acid chloride.

It is unfortunate that the second component of the esterification reaction could not be isolated, but work is continuing in that direction. Such a material must be very structurally similar to (XXVIII) because the IR and the NMR of the mixture do not seem to indicate any blatantly extraneous peaks (IR 0047, NMR 026).

It would therefore not be inconsistent if this material were the diester, but further work is needed to verify this.

II IMPLICATIONS OF THIS STUDY

It is quite interesting and noteworthy that the esterification of neopentyl glycol dipivaloate (IV) should come about with such ease, whereas ditert-butyl 2,2-diethylmalonate (VII) could not be isolated. It should be noted that reactions (1) and (2) are quite similar inasmuch as the bulky groups on the homologous reactants (III) and (VI) are positioned from the reaction site. The bulky groups on the homologues (II) and (V) are positioned β and α respectively.

The fact that substitution in (II) is β rather than α would not alone account for the disparity in reactivities. Newman has shown that substitution at the β carbon exerts a stronger steric effect than substitution at the α carbon. [24]

Newman, however, has also presented data which illustrate that the ethyl group has a much greater steric effect than the methyl group.[24] The fact that (V) has two large ethyl groups α to the reaction site no doubt partially accounts for the difficulty in the esterification. From a study of models, we have seen that the two ethyl groups are large enough to partially block the p-z orbital of the carbonyl carbon. This is probably responsible for the inertness of (V) to esterification.

This fact alone, however, is insufficient to account

for the inability to isolate (VII) because 2-ethylbutanoyl chloride, which possesses two ethyl groups in an α position, esterifies in 44 % yield. Similarly it appears that (V) is not totally inert to esterification because the half-ester (XXVIII) has been formed.

In order for the two ethyl groups to effectively screen the p-z orbital, it appears that a third group must be present on the same carbon in order to buttress them. Newman notes that 2-ethyl 2-butanoic acid is 100 times slower than acetic acid in the esterification of methanol at 40 C^{o}; yet the trisubstituted $(CH_3CH_2)_3CCOOH$ is 6170 times slower than acetic acid under the same conditions. [24] The hindrance of the trisubstituted half-acid chloride (XXVIII) should be expected to be comparable, due to the effective blocking of the p-z orbital.

Apparently, this same hindrance is responsible for the stability of the half-acid chloride. It is clear from IR data that an acid chloride has been isolated, even after washing with water. This is truly remarkable in that most aliphatic acid chlorides react vigorously with any water present, and are usually fairly unstable even in normal humidity.

The implications of this steric hindrance to the formation of a mixed polyester of diethylmalonic acid and neopentyl glycol are clear. The same screening of the carbonyl carbon p-z orbital which accounts for the difficulty of esterification in (2), would also block attack of the carbonyl carbon by base in a $B_{ac}2$ reaction mechanism. Similarly

attack by base on the alkyl carbon in a $B_{al}2$ mechanism would be somewhat screened by the methyl groups of the neopentyl glycol. Thus we suspect this polyester, and others like it, would be particularly stable in basic medium.

However, in attempting to produce this polyester from diethylmalonic acid, the ease of esterification should be no greater than that observed using tert-butanol. It therefore seems that the acid chloride method would be impracticle for production of such a polyester.

Rothman's method, (see above), involving the use of isopropenyl ester intermediates, deserves to be investigated. Through this method he was able to prepare even the extremely hindered 2-heptyl-2propyl decyl 2'-heptyl-2'-propyl decanoate in 90 % yield. [31]

III SUGGESTIONS FOR FUTURE WORK

To accomplish the production of sterically hindered esters such as ditert-butyl 2,2-diethylmalonate, or to achieve a mixed polyester of sterically hindered glycols and sterically hindered dicarboxylic acids, the method of Rothman should be investigated.

In studying esterifications of dicarboxylic acids, the danger of decarboxylation should not be overlooked. Yields of the diester or polyester would be improved if acids were employed which were not as prone to decarboxylation as malonate derivitives.

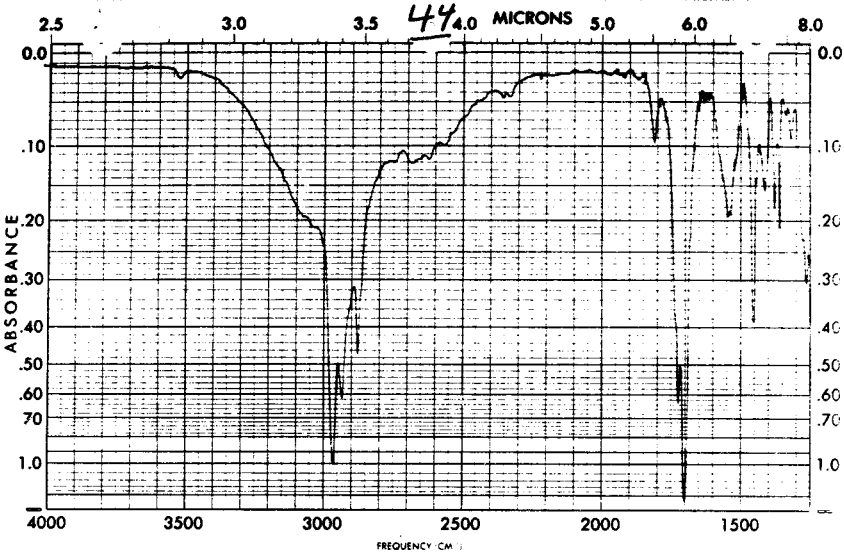
When preparing acid chlorides of hindered acids,

the substitution of thionyl chloride with phthalyl chloride as suggested by Breslow [5] should be investigated.

Both esters obtained in this study, (IV) and (XXVIII), are interesting for hydrolysis studies inasmuch as both are hindered to $B_{ac}2$ and $B_{al}2$ attack.

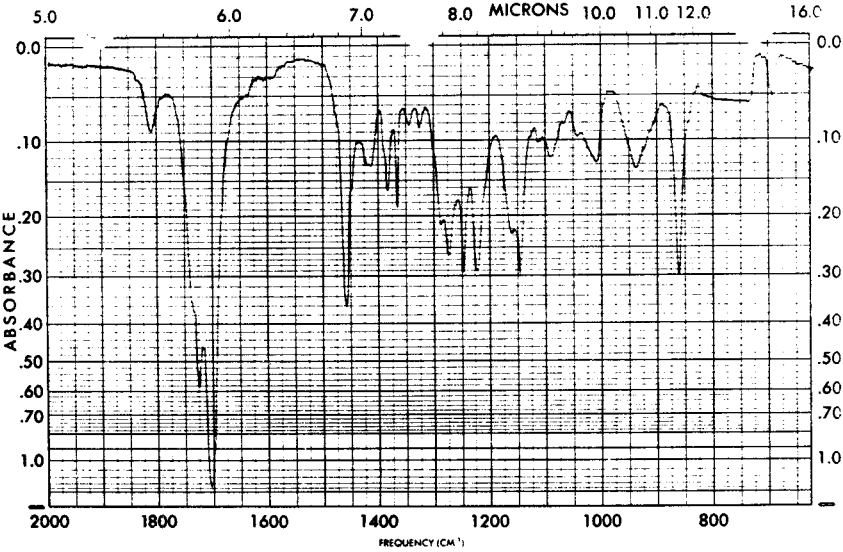
APPENDIX I:

Infra-red Spectra

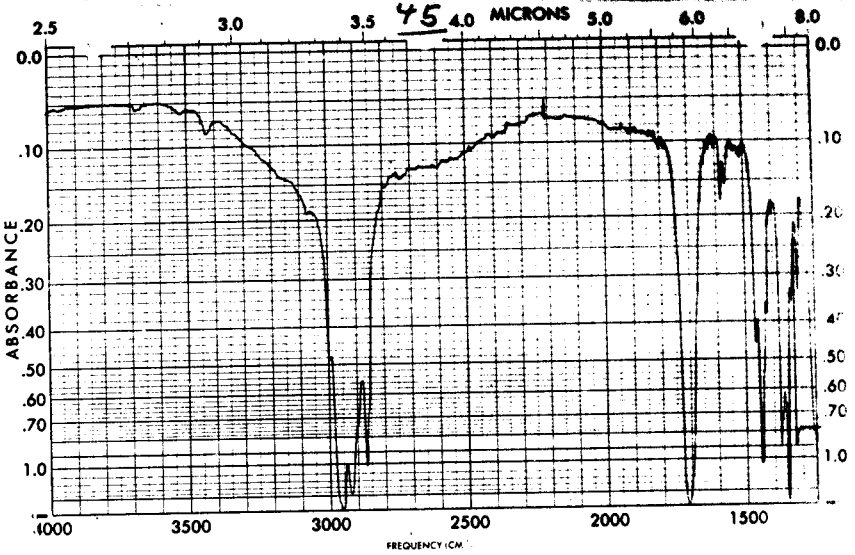


SAMPLE 3-003	CURVE NO. IR 0006A	SCAN SPEED Fast	OPERATOR
ORIGIN Run 2 product 3	CONC.	SLIT 2S	DATE 5/14/78
SOLVENT CCl4	CELL PATH	REMARKS	
	REFERENCE		

No. PR19R (237-1032) PRINTED IN U.S.A. RECORDING CHARTS GRAPHIC CONTROLS CORPORATION BUFFALO, NEW YORK

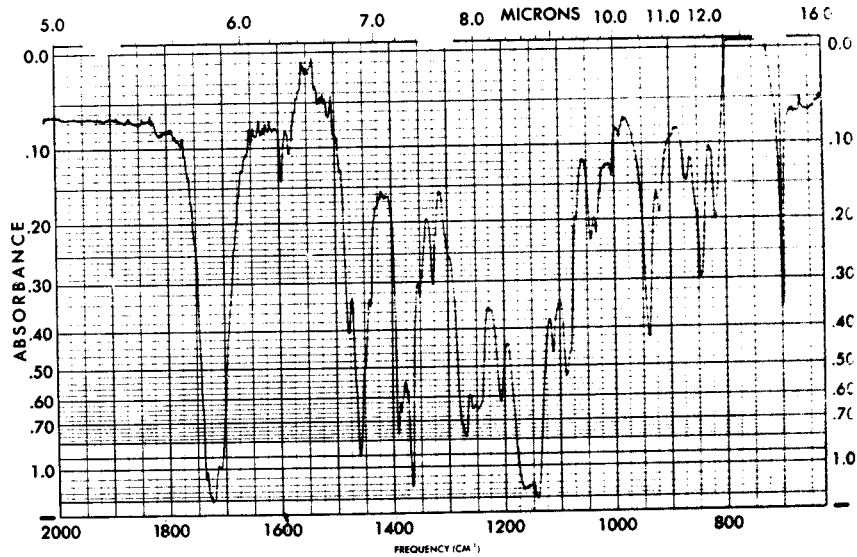


SAMPLE 3-003	CURVE NO. IR 0006B	SCAN SPEED Fast	OPERATOR
ORIGIN Run 2 product 3	CONC.	SLIT 2S	DATE 5/14/78
SOLVENT CCl4	CELL PATH	REMARKS	
	REFERENCE		

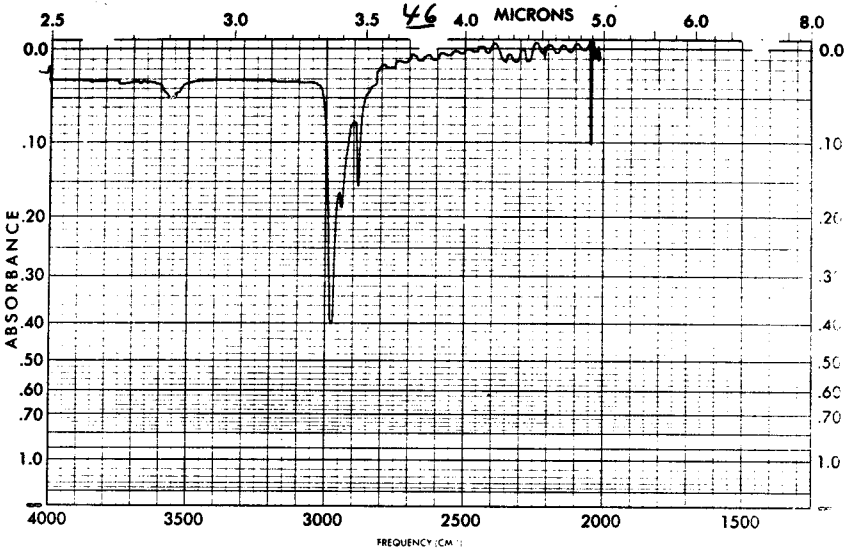


SAMPLE 2-BP130 (3-01)	CURVE NO. IR0008A	SCAN SPEED FST	OPERATOR
ORIGIN PRO 2 PRO 1	CONC.	SLIT 26	DATE 5/15/78
SOLVENT CCl4	CELL PATH	REMARKS	
	REFERENCE CCl4		

NO PR 19R (237-1032) RECORDING CHARTS

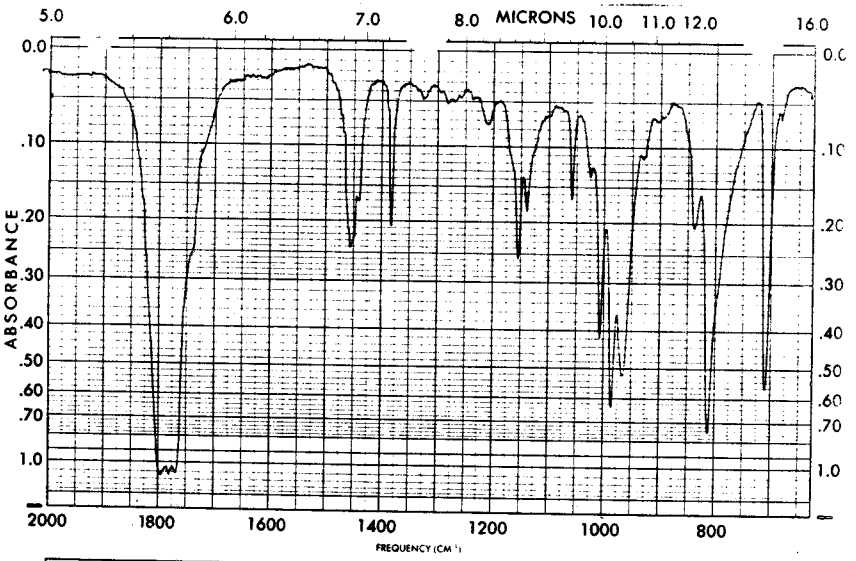


SAMPLE 2-BP130 (3-01)	CURVE NO. IR0008-B	SCAN SPEED FST	OPERATOR
ORIGIN PRO 2 PRODUCT 1	CONC.	SLIT 26	DATE 5/15/78
SOLVENT CCl4	CELL PATH	REMARKS	
	REFERENCE CCl4		



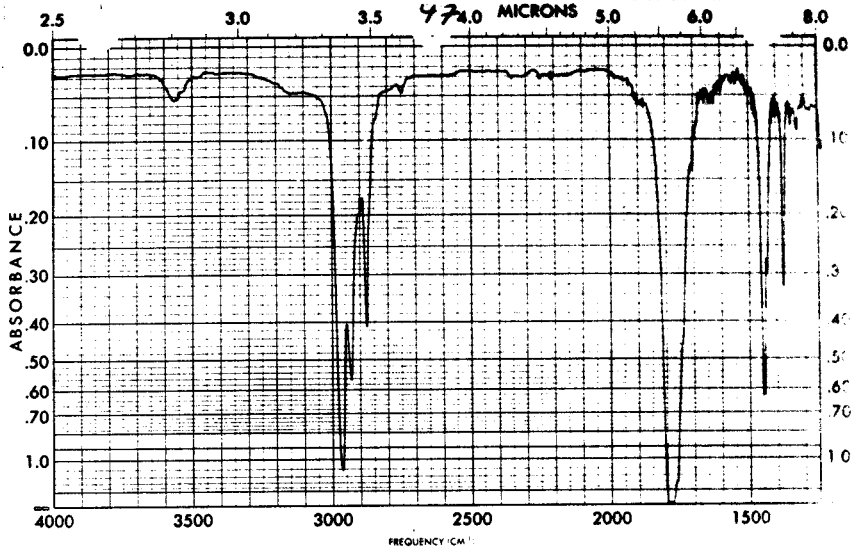
SAMPLE BP 190 (1-002)	CURVE NO. IR 00699A	SCAN SPEED Fst	OPERATOR
	CONC.	SLIT 25	DATE 6/29/78
ORIGIN Rxn (1)	CELL PATH	REMARKS Pyridine IR002	
SOLVENT CCl4	REFERENCE CCl4		

PR 19R (237-1032) RECORDING CHARTS



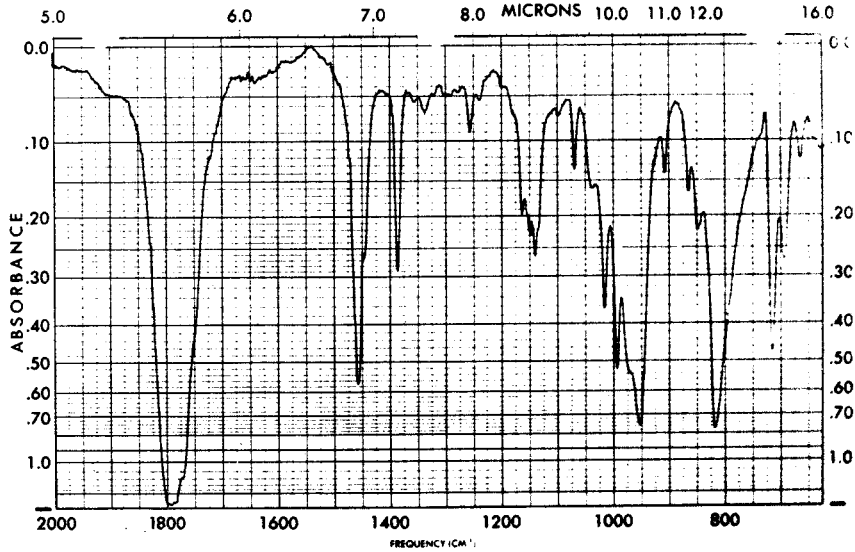
SAMPLE BP 190 (1-002)	CURVE NO. IR 00699B	SCAN SPEED Fst	OPERATOR
	CONC.	SLIT 25	DATE 5/29/78
ORIGIN Rxn (1)	CELL PATH	REMARKS Pyridine IR002	
SOLVENT CCl4	REFERENCE		

PR 19R (237-1032)



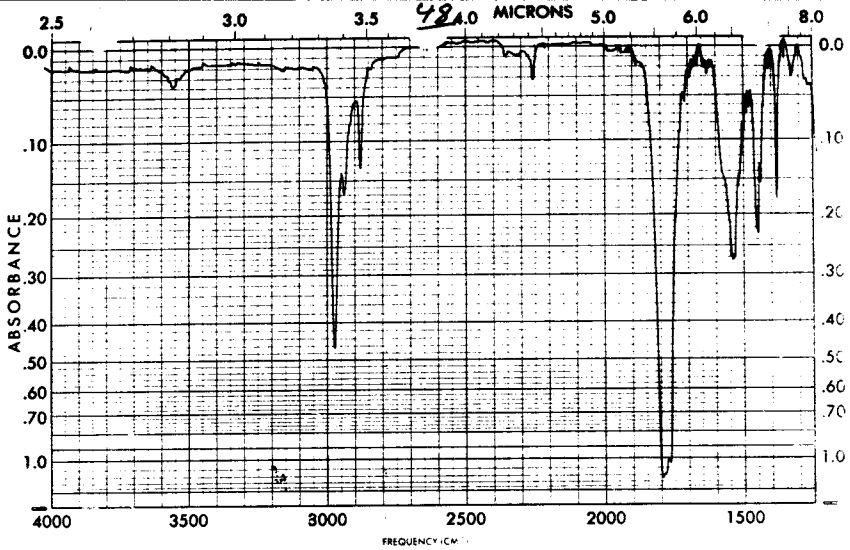
SAMPLE 2-001	CURVE NO. IR 0011A	SCAN SPEED	OPERATOR
ORIGIN Run 4 product BP 137	CONC	SLIT	DATE 9/1/72
SOLVENT CCl4	CELL PATH	REMARKS	
	REFERENCE CCl4		

PR 19R (237-1032) RECORDING CHARTS



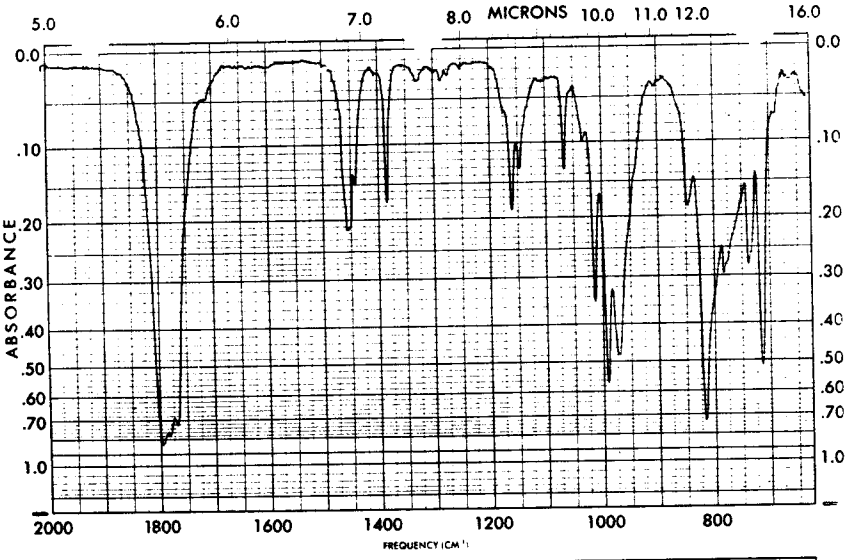
SAMPLE 2-001	CURVE NO. IR 001 #B	SCAN SPEED Fast	OPERATOR Carl
ORIGIN Run 4 Prod 1 BP 137	CONC	SLIT	DATE 8/31/72
SOLVENT CCl4	CELL PATH	REMARKS	
	REFERENCE CCl4		

PR 19R (237-1032)



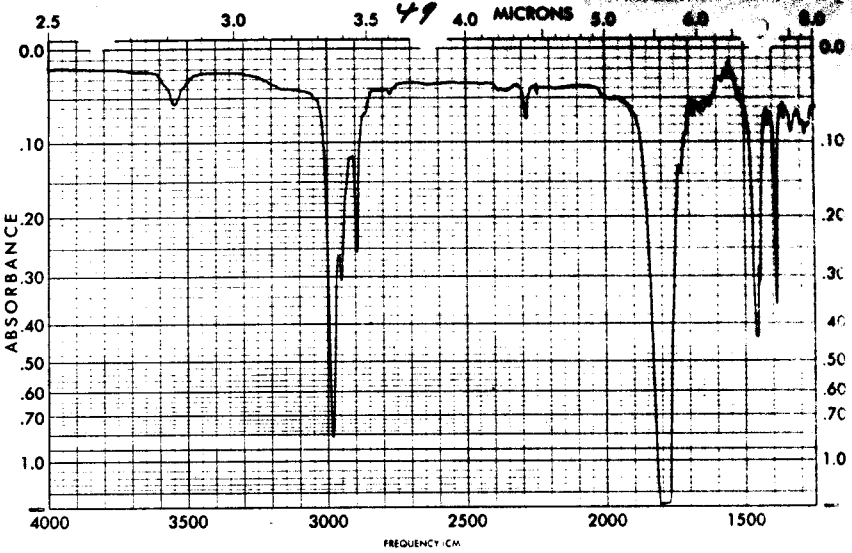
SAMPLE 2-002- (2-002 a) BP 104-106	CURVE NO. IR002A	SCAN SPEED Fast	OPERATOR
ORIGIN	CONC.	SLIT 25	DATE 6/5/78
SOLVENT CCl4	CELL PATH	REMARKS	
	REFERENCE CCl4		

PR 19R (237-1032) RECORDING CHARTS



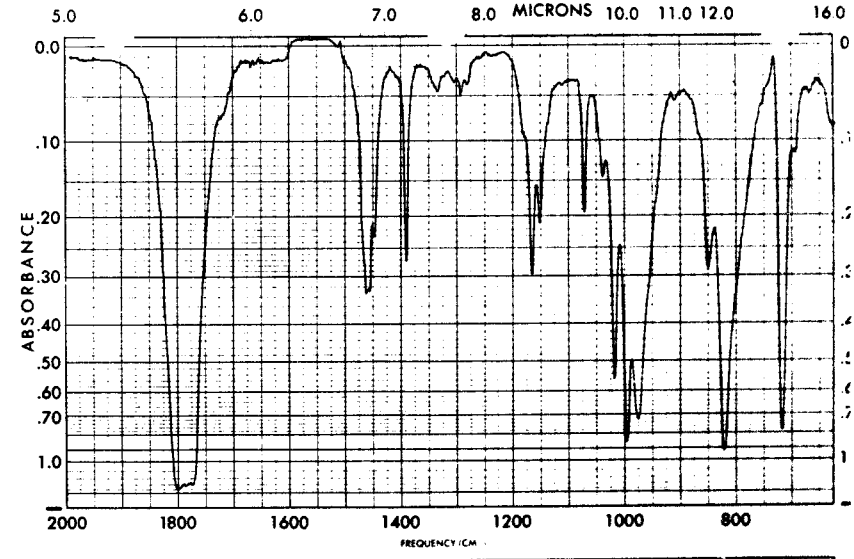
SAMPLE 2-002- (2-002a) BP = 170-174	CURVE NO. IR0012B	SCAN SPEED Fast	OPERATOR
ORIGIN	CONC.	SLIT 25	DATE 6/5/78
SOLVENT CCl4	CELL PATH	REMARKS	
	REFERENCE CCl4		

RECORDING CHARTS GRAPHIC CONTROLS CORPORATION BUFFALO, NEW YORK



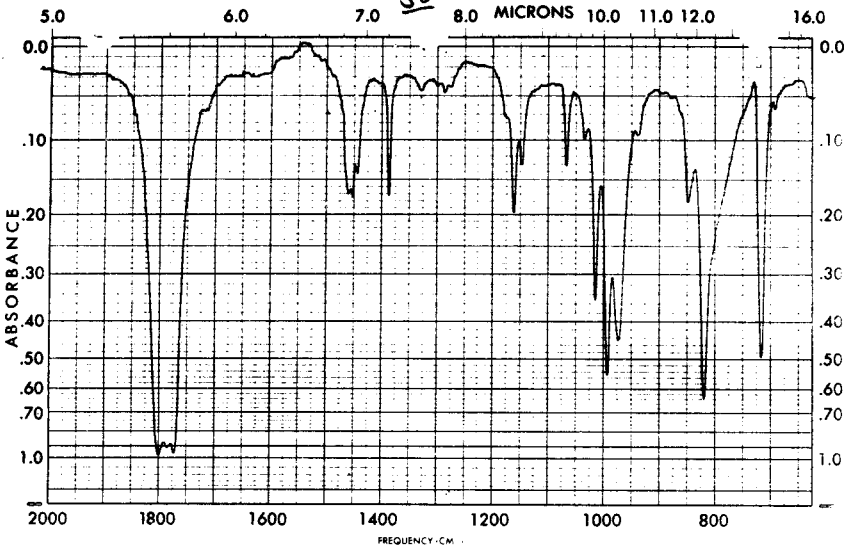
SAMPLE (2-002-b)	CURVE NO. IR 00131	SCAN SPEED 22	OPERATOR
	CONC.	SLIT 1.8	DATE 6/5/78
ORIGIN	CELL PATH	REMARKS	
SOLVENT CCl_4	REFERENCE CCl_4		

PR 19R (237-1032) RECORDING CHARTS



SAMPLE (2-002-b)	CURVE NO. IR 00138	SCAN SPEED Fast	OPERATOR
	CONC.	SLIT 25	DATE 6/8/78
ORIGIN	CELL PATH	REMARKS	
SOLVENT CCl_4	REFERENCE CCl_4		

PR 19R (237-1032)

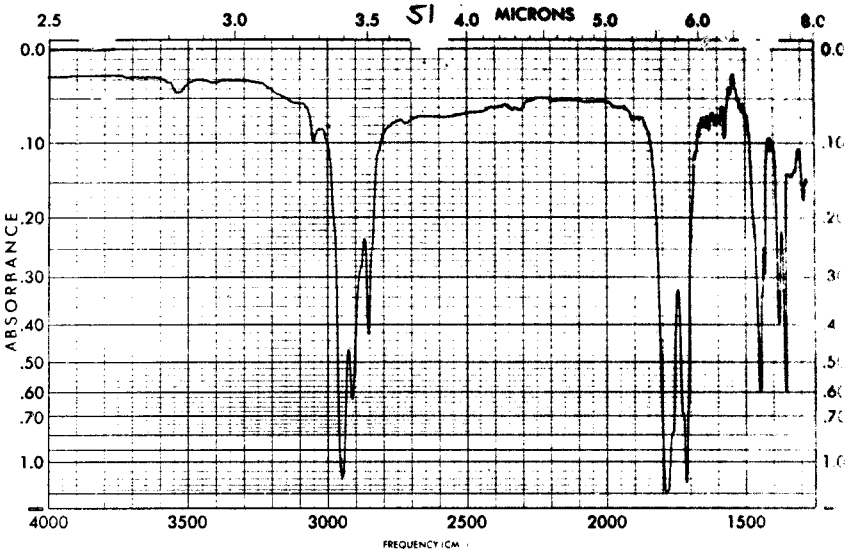


SAMPLE 2-002-C	CURVE NO. IR 0014 B	SCAN SPEED Pat	OPERATOR
	CONC	SLIT 25	DATE 6/5/78
ORIGIN Dr IPC	CELL PATH	REMARKS	
SOLVENT CCl4	REFERENCE CCl4		

PR 189 (237-1033)
RECORDING CHARTS

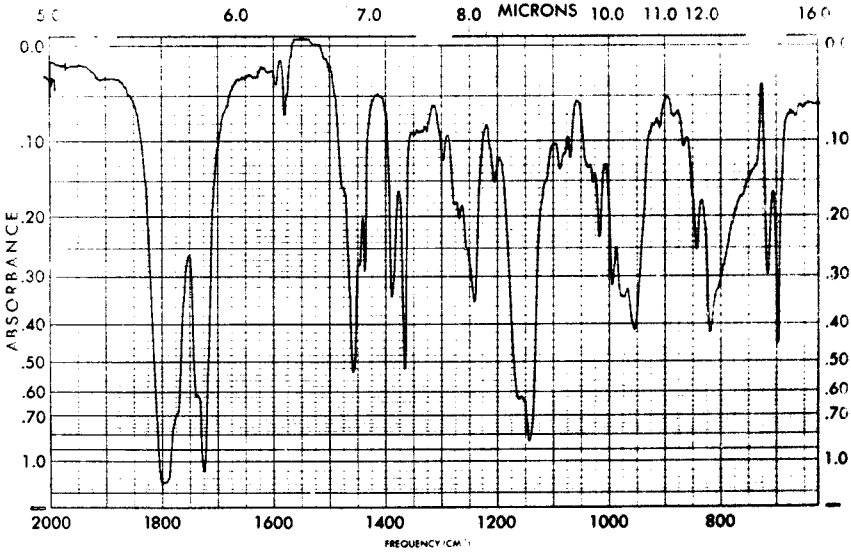
[redacted]

[redacted]



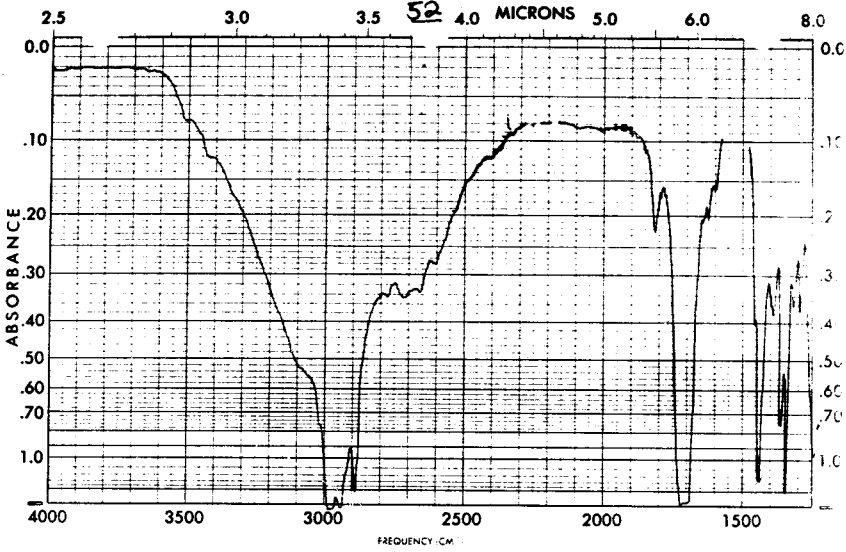
SAMPLE 5-01	CURVE NO IR0015A	SCAN SPEED P&T	OPERATOR
	CONC.	SLIT P-5	DATE 6/5/98
ORIGIN	CELL PATH	REMARKS	
SOLVENT	REFERENCE	Film @	

PR 19R (237-1032) Film D RECORDING CHARTS



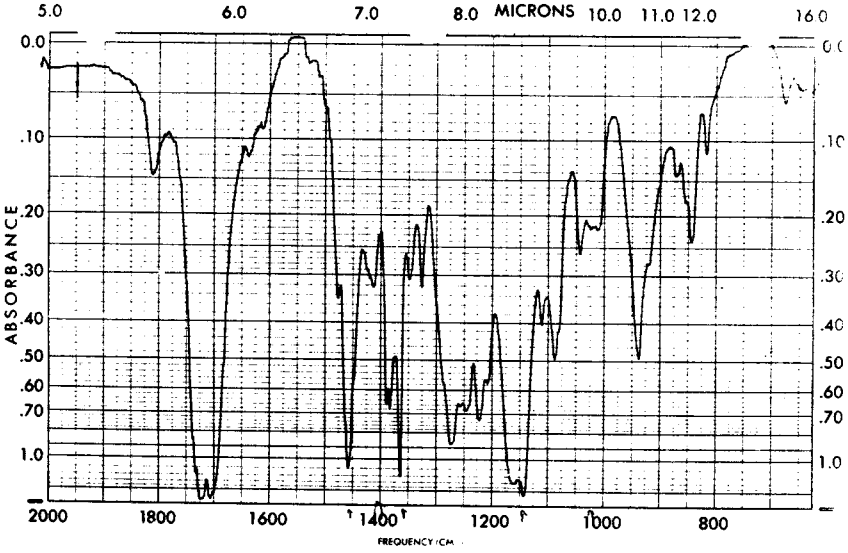
SAMPLE 5-02	CURVE NO IR0016B	SCAN SPEED P&T	OPERATOR
	CONC	SLIT P-5	DATE 6/5/98
ORIGIN	CELL PATH	REMARKS	
SOLVENT	REFERENCE	Film @	

PR 19R (237-1032) Film D



SAMPLE [illegible] BP 172 (3-02)	CURVE NO IR0016A	SCAN SPEED 15s	OPERATOR
ORIGIN	CONC	SLIT 2.5	DATE 6/19/78
SOLVENT CCl4	CELL PATH	REMARKS	
	REFERENCE CCl4		

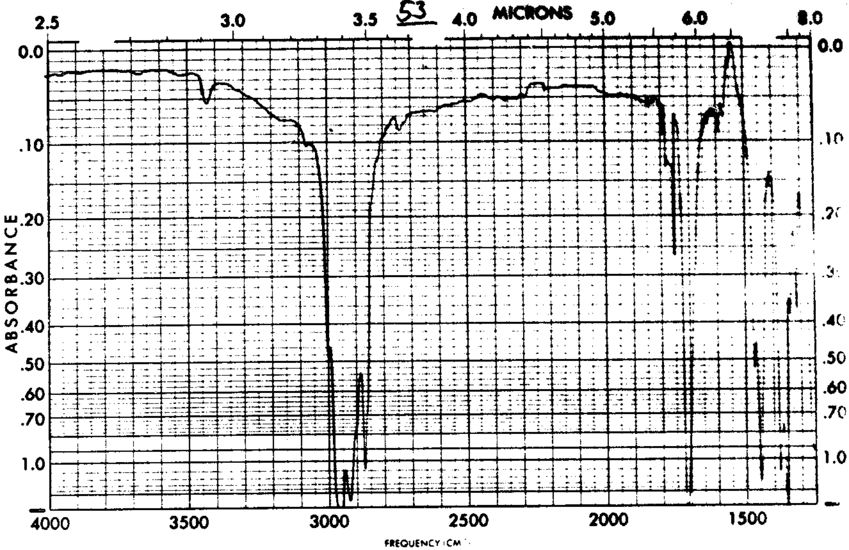
no. PR 19R (237-1032)



SAMPLE Rxn 2 product 2 (recrystallized) BP 172 (3-02)	CURVE NO. IR0016B	SCAN SPEED 15s	OPERATOR
ORIGIN	CONC	SLIT 2.5	DATE 6/19/78
SOLVENT CCl4	CELL PATH	REMARKS	
	REFERENCE CCl4		

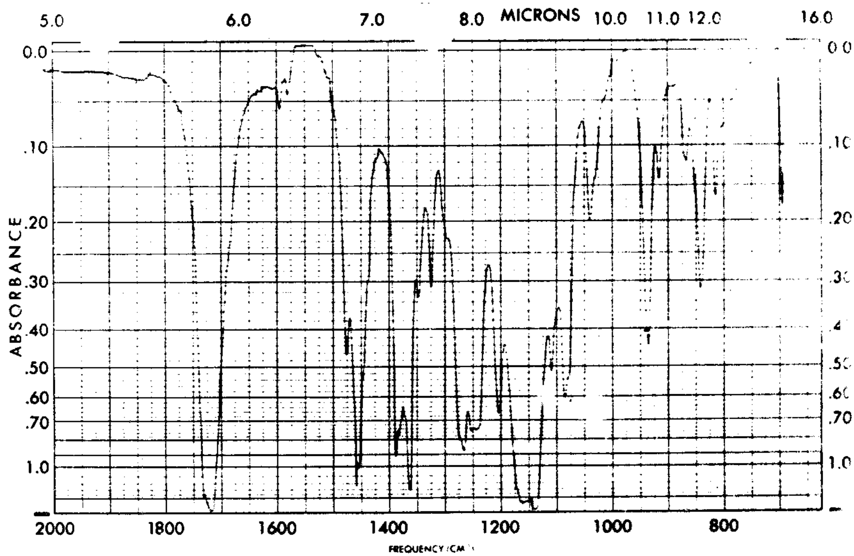
no. PR 18R (237-1033)

53



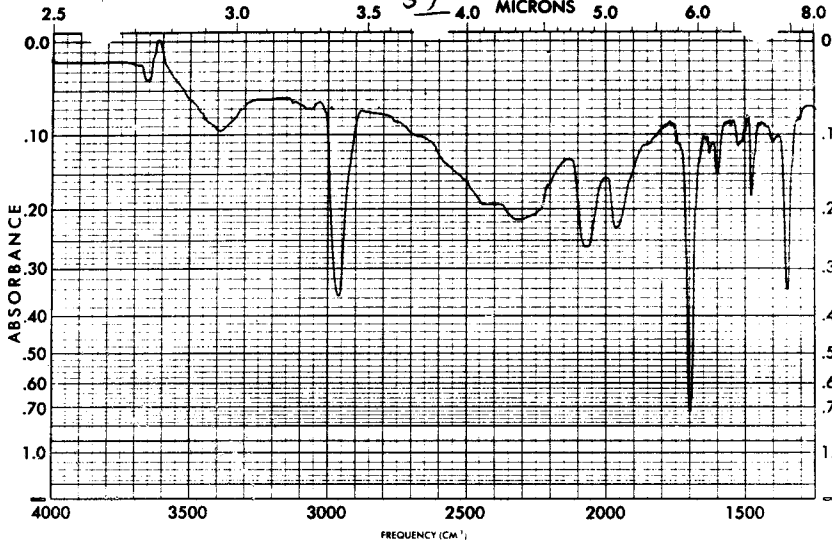
SAMPLE Ester (4-01)	CURVE NO. IR 0018 A	SCAN SPEED Fst	OPERATOR Ms
	CONC.	SLIT 25	DATE 11/19/83
ORIGIN Est Run II acetonitrile acid	CELL PATH	REMARKS	
SOLVENT CCl_4	REFERENCE		

No PR 19R (237-1032) RECORDING CHARTS



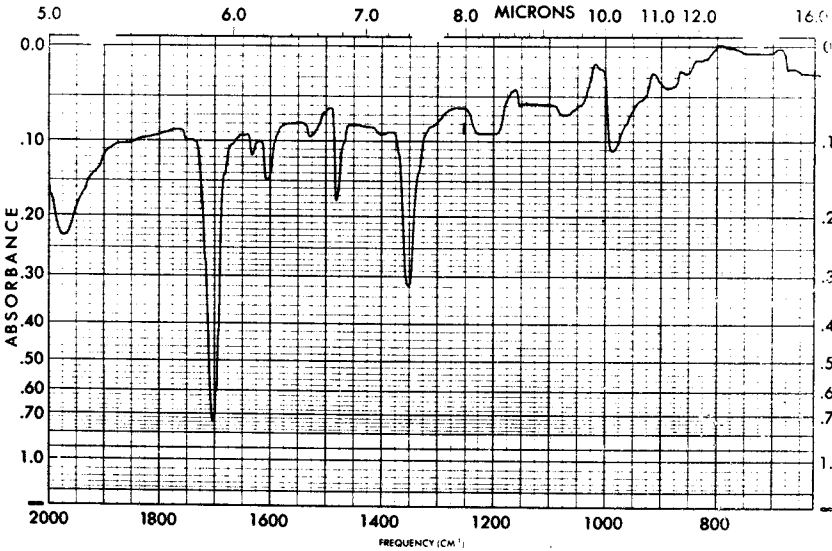
SAMPLE Ester (4-01)	CURVE NO IR 0018 - B	SCAN SPEED Fst	OPERATOR MP
	CONC	SLIT 25	DATE 11/19/83
ORIGIN Est. run II acetonitrile acid	CELL PATH	REMARKS Product of decanoic	
SOLVENT CCl_4	REFERENCE	acid 4 (reaction no 130)	

No PR 18R (237-1033) GRAPHIC CONTROLS CORPORATION BUFFALO NEW YORK

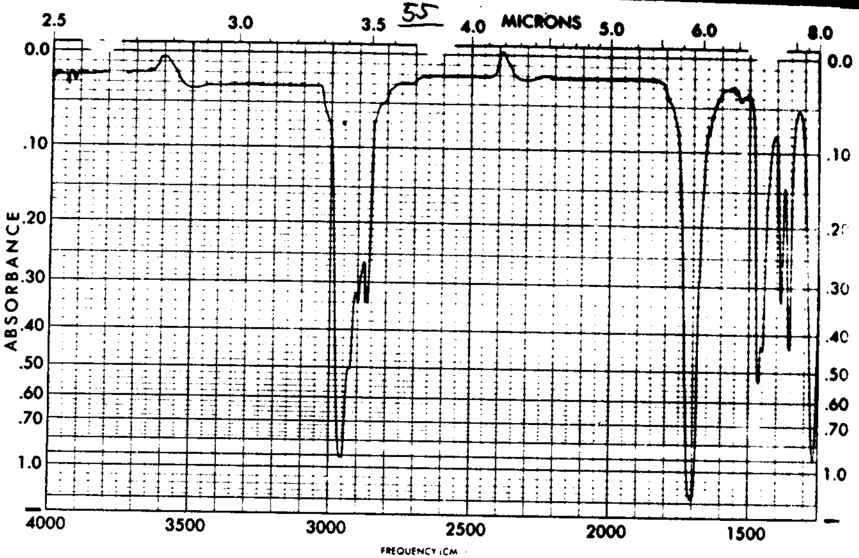


SAMPLE Perkin Chrystal of Solid Component (4-4)	CURVE NO. IR 0045 A	SCAN SPEED Fast	OPERATOR
ORIGIN	CONC.	SLIT 25	DATE 3/24/78
SOLVENT CCl4	CELL PATH	REMARKS Spectrum of Pyridine HCl	
	REFERENCE CCl4		

No PR19R (237-1032) RECORDING CHART GRAPHIC CONTROLS CORPORATION

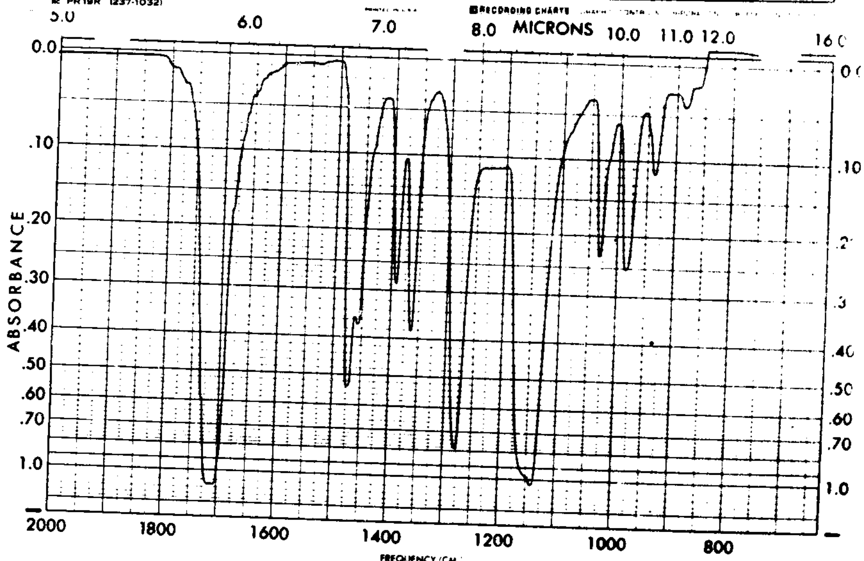


SAMPLE Perkin Chrystal of Solid Component (4-4)	CURVE NO. IR 0045 B	SCAN SPEED Fast	OPERATOR
ORIGIN	CONC.	SLIT 25	DATE 3/24/78
SOLVENT CCl4	CELL PATH	REMARKS Spec of Pyridine HCl	
	REFERENCE CCl4		



SAMPLE Heptyl Ester (Distilled 170-180)	CURVE NO IR 0046 A	SCAN SPEED Fst	OPERATOR
ORIGIN	CONC	SLIT 25	DATE 3/24/77
SOLVENT CCl4	CELL PATH	REMARKS	
	REFERENCE CCl4		

PR 19R (237-1032)



SAMPLE Heptyl Ester	CURVE NO IR 0046 B	SCAN SPEED Fst	OPERATOR
ORIGIN	CONC	SLIT 25	DATE 3/24/77
SOLVENT CCl4	CELL PATH	REMARKS	
	REFERENCE CCl4		

PR 18R (237-1033)

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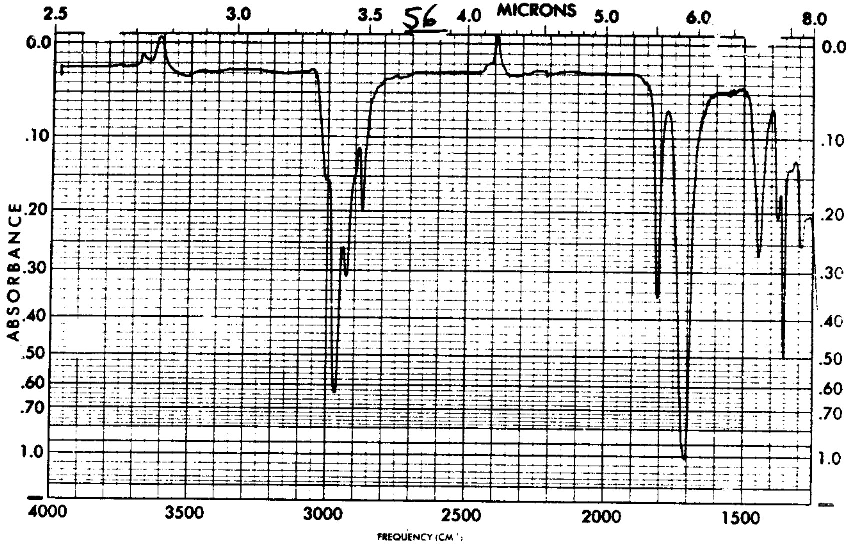
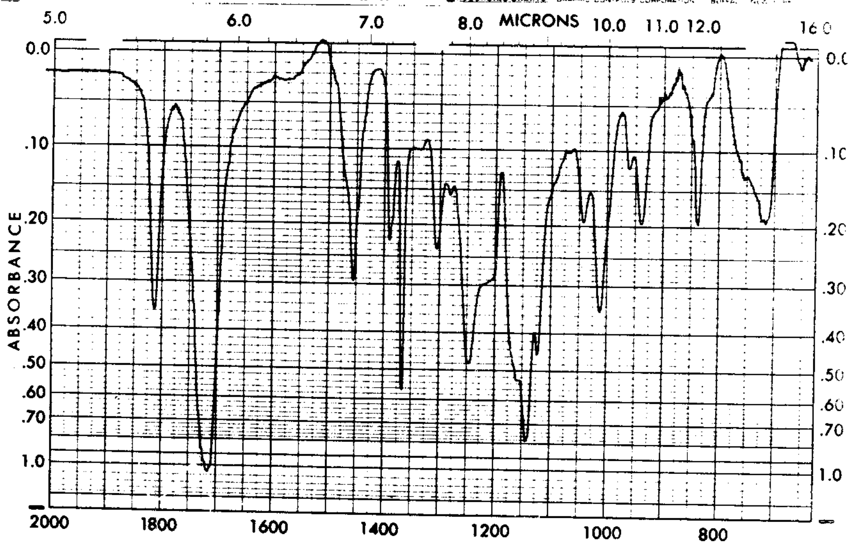


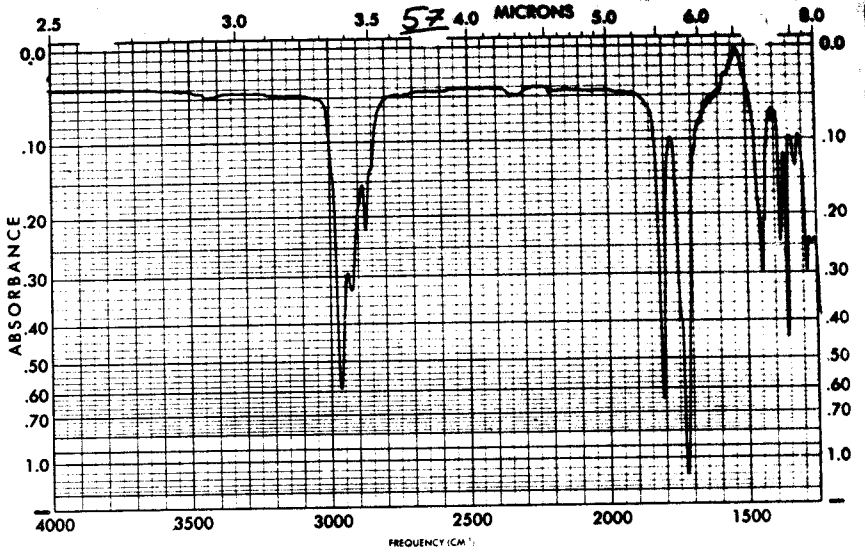
SAMPLE [illegible]	CURVE NO. IR 0047 A	SCAN SPEED Fst	OPERATOR
	CONC.	SLIT 25	DATE 4/18/79
ORIGIN	CELL PATH	REMARKS	
SOLVENT CHCl3	REFERENCE CHCl3		

No. PR19R (237-1032) PRINTED IN U.S.A. RECORDING CHARTS GRAPHIC CONTROLS CORPORATION BUFFALO, N.Y.



SAMPLE [illegible] acid	CURVE NO. IR 0047 B	SCAN SPEED Fst	OPERATOR
	CONC.	SLIT 25	DATE 4/17/79
ORIGIN	CELL PATH	REMARKS	
SOLVENT CHCl3	REFERENCE CHCl3		

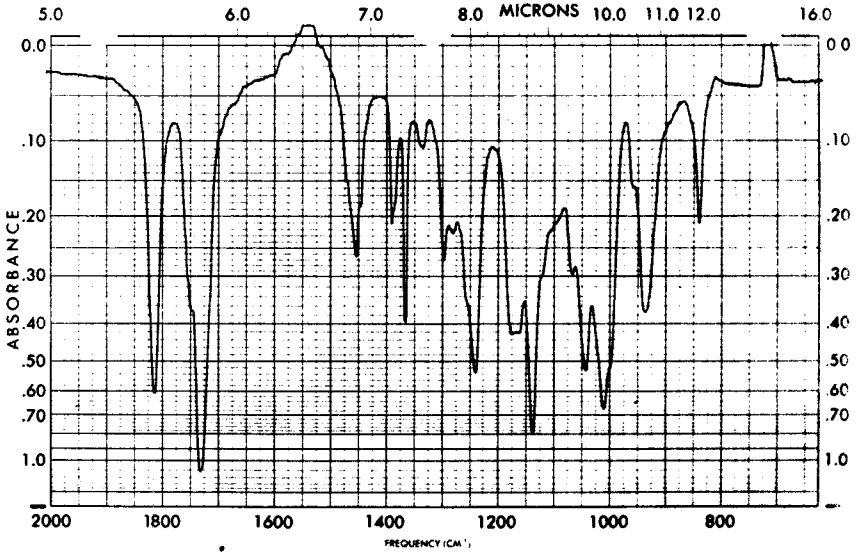
No. PR 19R (237-1033) PRINTED IN U.S.A. RECORDING CHARTS GRAPHIC CONTROLS CORPORATION



SAMPLE Lc #1 (6-01)	CURVE NO IR 00494A	SCAN SPEED Fst	OPERATOR
	CONC	SLIT 8-6	DATE 5-2-72
ORIGIN	CELL PATH	REMARKS	
SOLVENT CCl4	REFERENCE CCl4		

no PR 19R (237-1032)

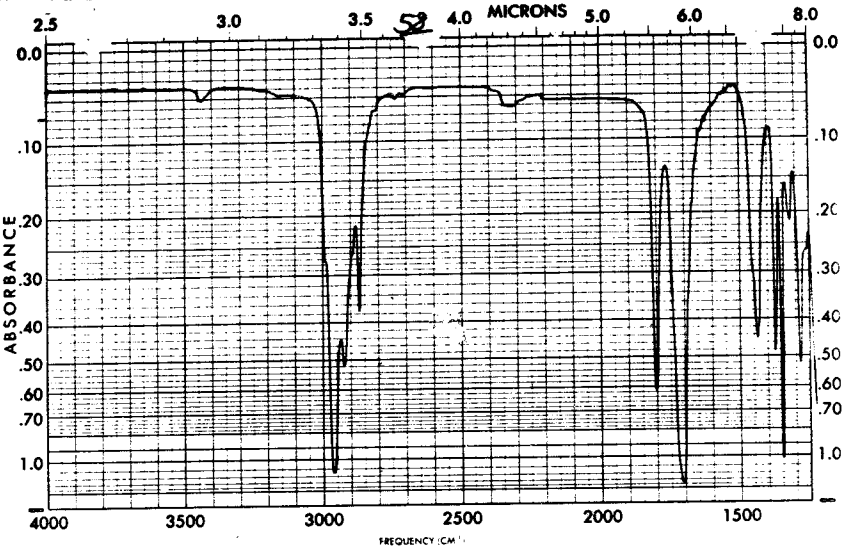
RECORDING CHARTS GRAPHIC CONTROLS CORPORATION



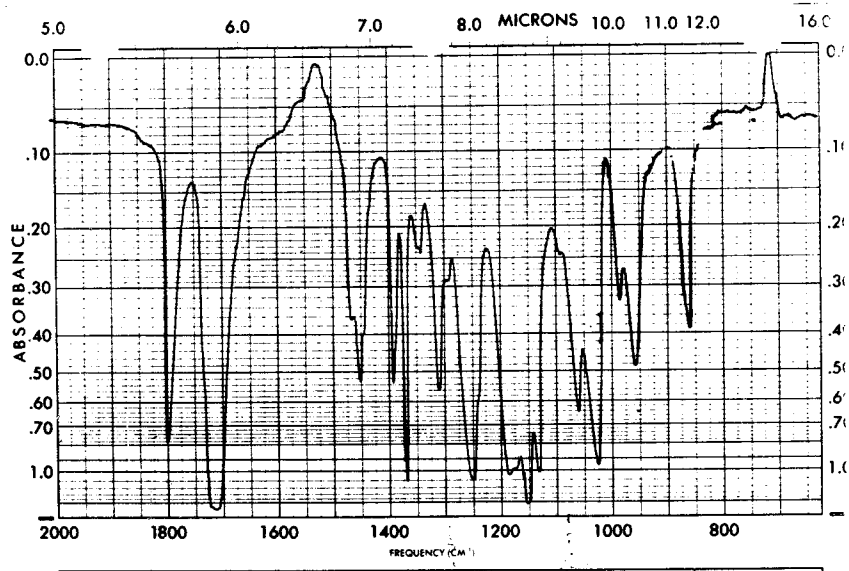
SAMPLE Lc #1 (6-01)	CURVE NO. IR 00498	SCAN SPEED Fst	OPERATOR
	CONC.	SLIT 8-6	DATE 5-2-72
ORIGIN	CELL PATH	REMARKS	
SOLVENT CCl4	REFERENCE CCl4		

no PR 19R (237-1033)

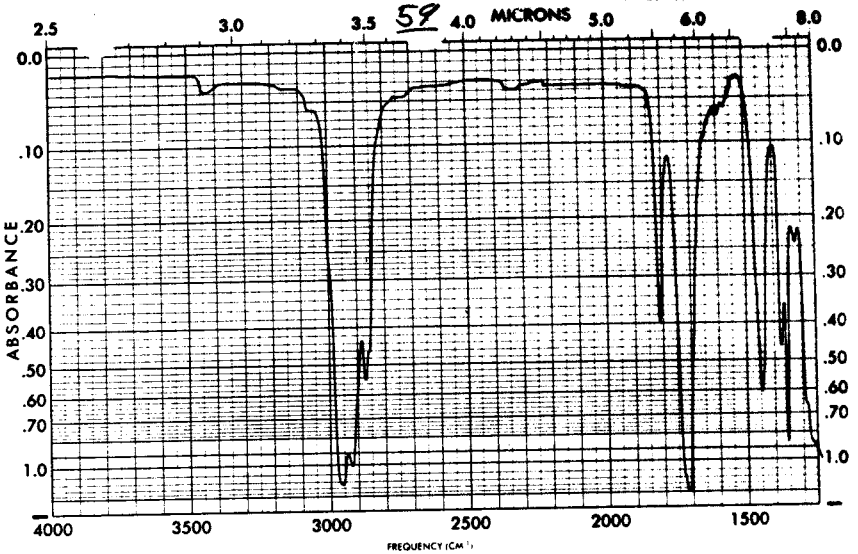
GRAPHIC CONTROLS CORPORATION



SAMPLE LC #2 (6-02)	CURVE NO. IR 0050-A	SCAN SPEED Fst	OPERATOR
ORIGIN	CONC.	SLIT 25	DATE 5/2/72
SOLVENT CCl4	CELL PATH	REMARKS	
	REFERENCE CCl4		

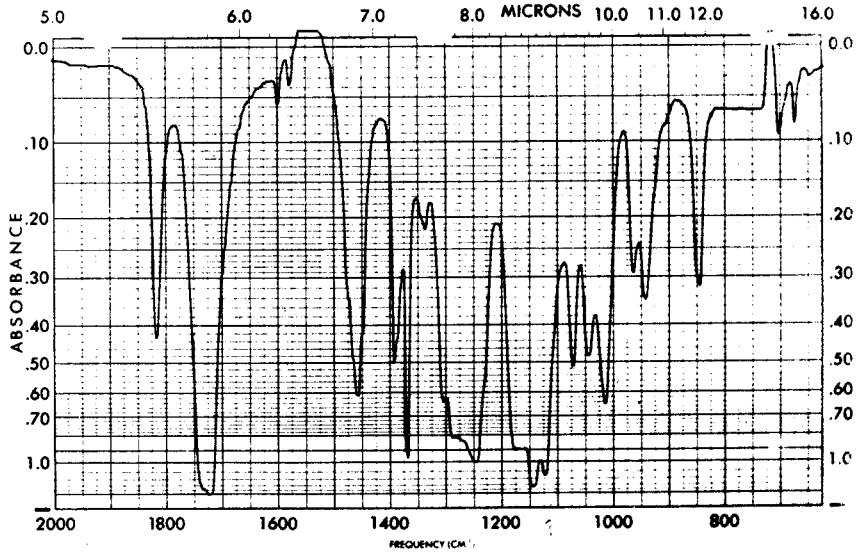


SAMPLE LC #2 (6-02)	CURVE NO. IR 0050-B	SCAN SPEED Fst	OPERATOR
ORIGIN	CONC.	SLIT 25	DATE 5/2/72
SOLVENT CCl4	CELL PATH	REMARKS	
	REFERENCE CCl4		



SAMPLE LC product 3 (6-03)	CURVE NO. IR 00 51 - A	SCAN SPEED Fast	OPERATOR
ORIGIN	CONC.	SLIT 2.5	DATE 5/2/00
SOLVENT CCl4	CELL PATH	REMARKS	
	REFERENCE CCl4		

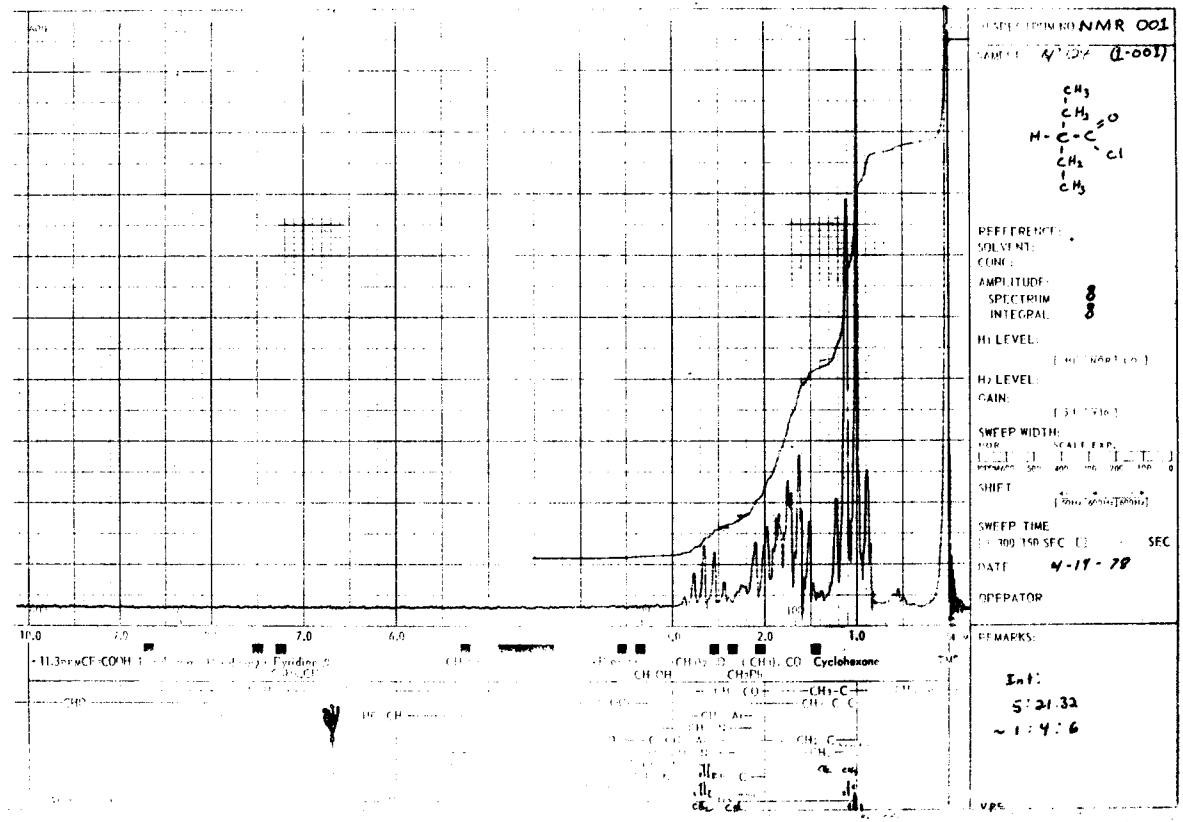
PR 16R (237-1032) RECORDING CHARTS GRAPHIC CONTROLS CORPORATION

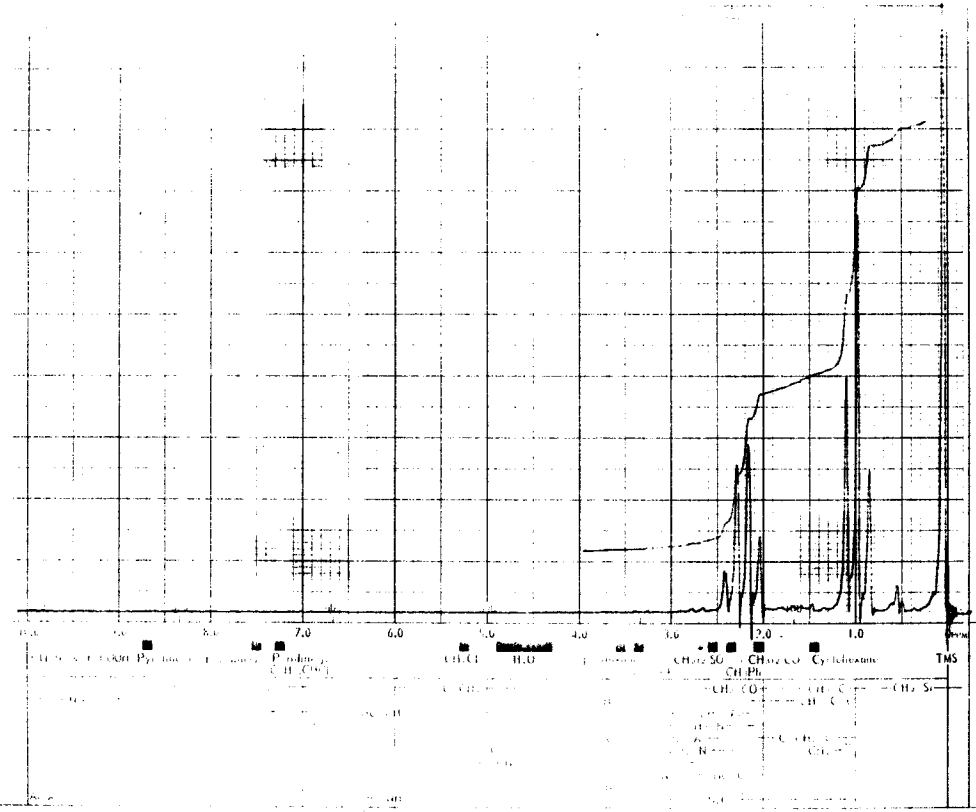


SAMPLE LC product 3	CURVE NO. IR 00 61-B	SCAN SPEED Fast	OPERATOR
ORIGIN	CONC.	SLIT 2.5	DATE 5/2/00
SOLVENT CCl4	CELL PATH	REMARKS	
	REFERENCE CCl4		

APPENDIX II:

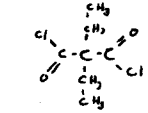
NMR Spectra


NMR 001
(1-001)
PREFERENCE:
SOLVENT:
CONC:
AMPLITUDE:
SPECTRUM 8
INTEGRAL 8
RF LEVEL:
H2 LEVEL:
GAIN:
SWEEP WIDTH:
SHIFT
SWEEP TIME
SEC
DATE 4-19-79
OPERATOR
REMARKS:
Int:
5:21.32
~1:4:6
10.0
7.0
6.0
2.0
1.0
Cyclohexone



SPECTRUM NO. NMR 002

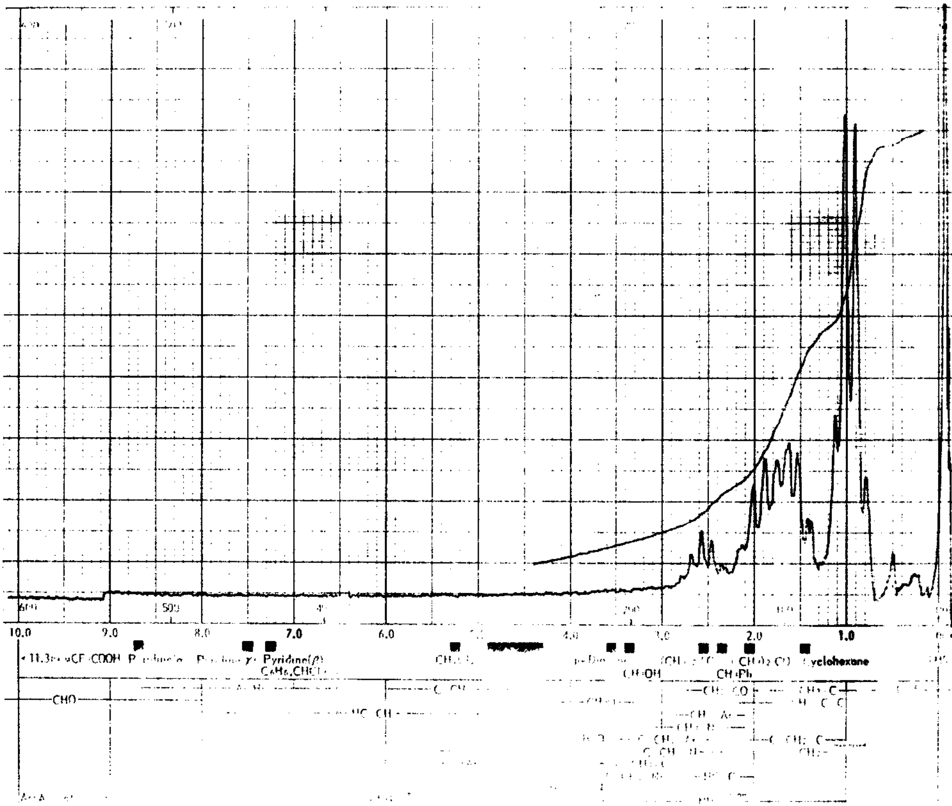
SAMPLE: 4-hydroxy-3,3,4-trimethyl-2-pentanone acid chloride 1-002



REFERENCE: TMS
SOLVENT: CCl_4
CONC:
AMPLITUDE:
SPECTRUM 6
INTEGRAL 8
H1 LEVEL:
[ ] [ ] NOR [ ] [ ]
H2 LEVEL:
GAIN:
[ ] [ ] x10 [ ]
SWEEP WIDTH:
NOR SCALE EXP.
1200 1000 800 600 500 400 300 200 100 0
SHIFT
[ ] [ ] [500Hz] [600Hz] [ ]
SWEEP TIME
[ ] 300 150 SEC [ ] SEC
DATE: 4-14-78
OPERATOR
REMARKS:

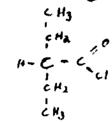
CHART NO. 435-7204 PRINTED IN U.S.A.

6.2



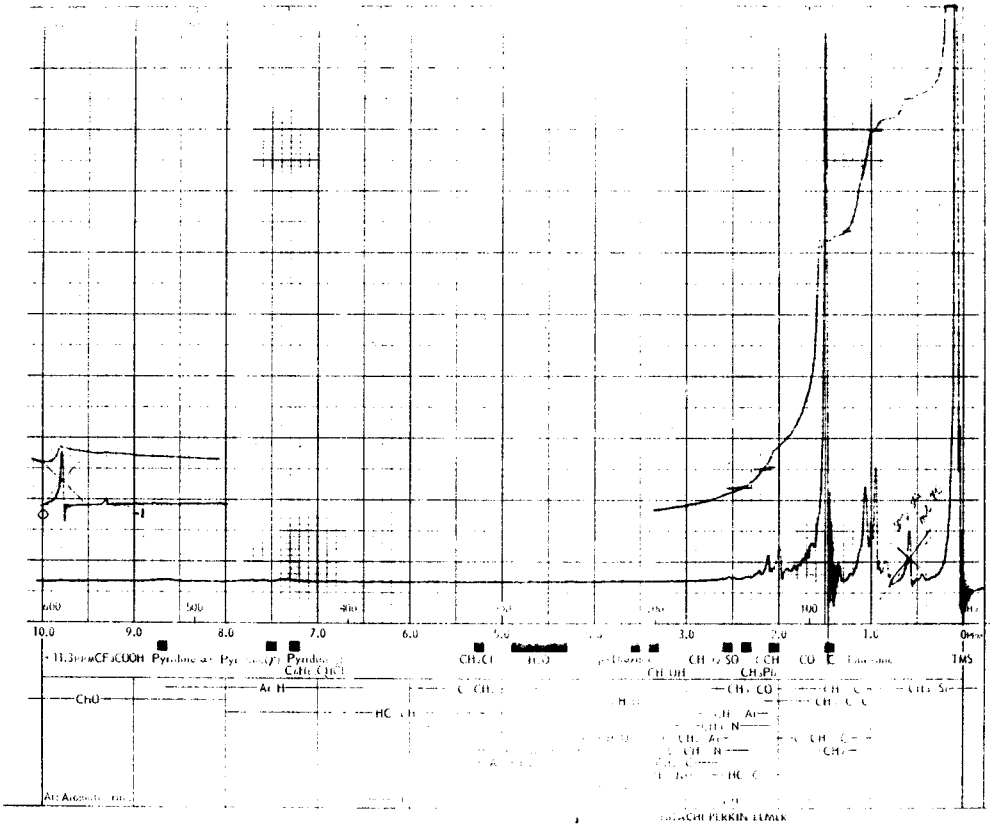
NMR 005

SAMPLE: BPZY — Good this run (2-001)



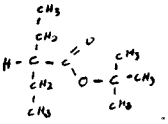
REFERENCE: TMS
SOLVENT: CCl_4
CONC:
AMPLITUDE
SPECTRUM 9
INTEGRAL 7
H₁ LEVEL:
H₂ LEVEL:
GAIN:
SWEEP WIDTH:
SWEEP TIME
SEC
DATE: 5-29-78
OPERATOR
REMARKS:

63



INSPECTION NO. MR006

SAMPLE: 2-BP130 (3-02)



REFERENCE: TMS

SOLVENT: CCl_4

CONC:

AMPLITUDE:

SPECTRUM 5

INTEGRAL 7

H1 LEVEL:

H2 LEVEL:

GAIN:

SWEEP WIDTH:

SCALE EXP:

SHIFT

SWEEP TIME

SEC

DATE: 5-8-78

OPERATOR

REMARKS:

Int

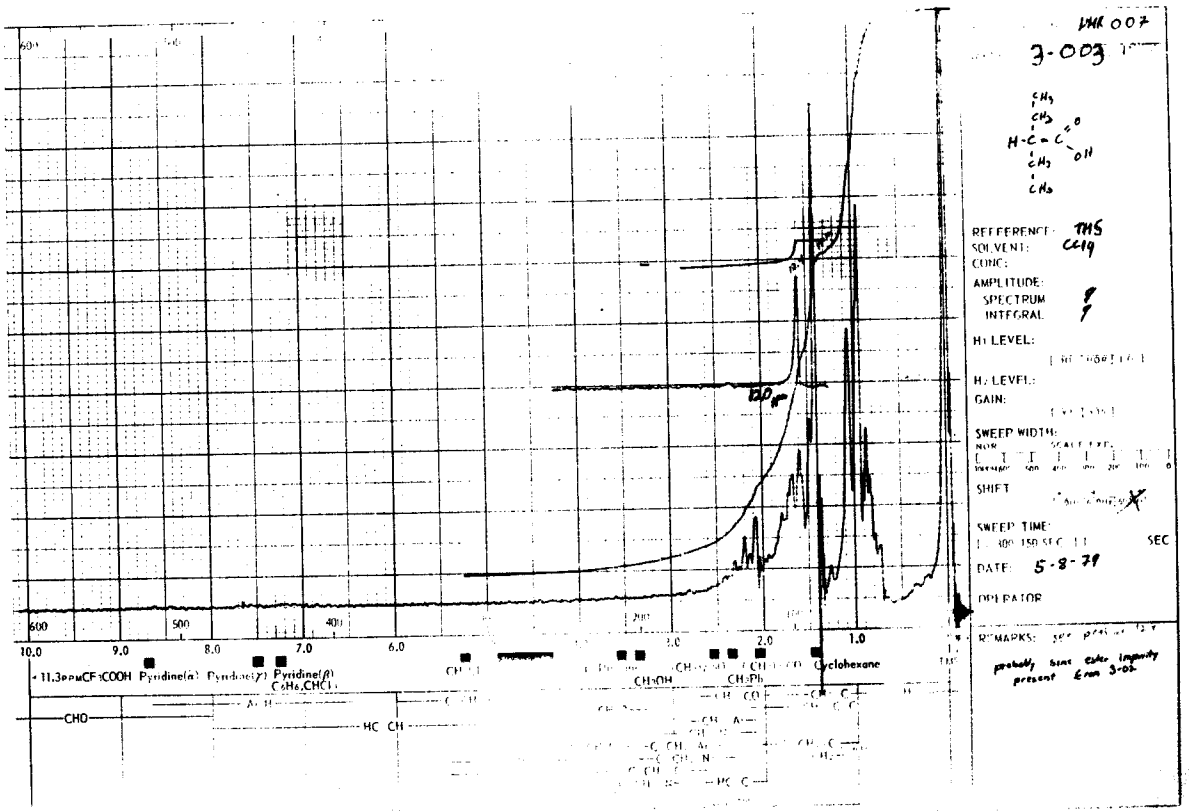
expected : 1:13:6

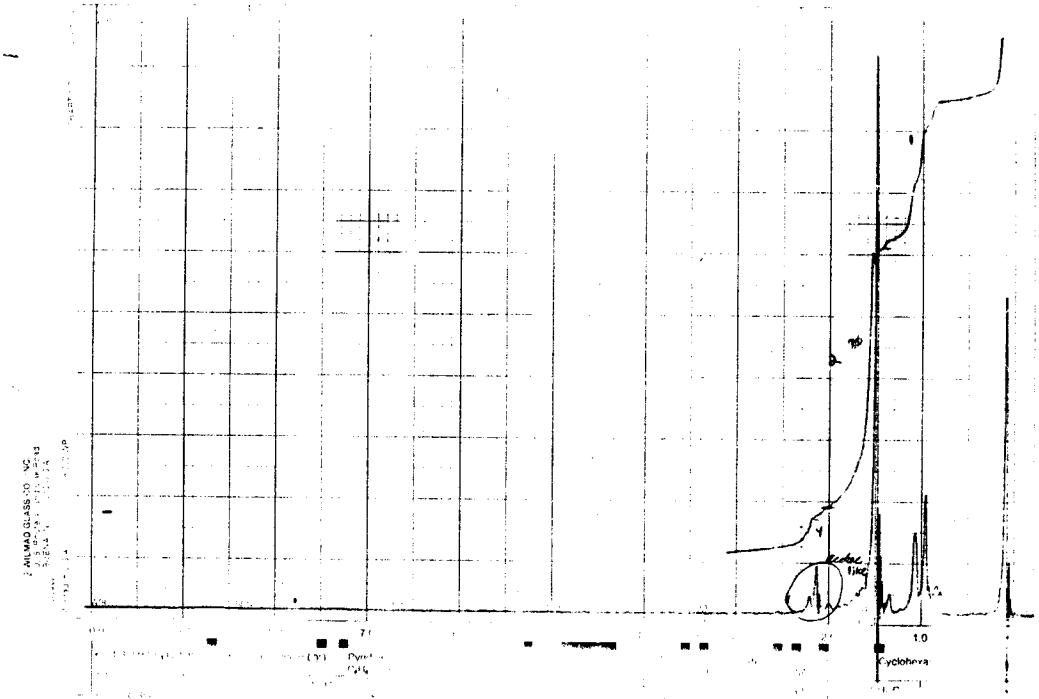
obtained: 3:37 : 17

≈ 1 : 12½ : 6

CHART NO. 435-7204 PRINTED IN U.S.A.

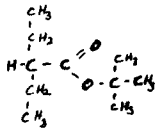
PERKIN ELMER


VMR 007
3-003
REFERENCE: TMS
SOLVENT: CCl4
CONC:
AMPLITUDE:
SPECTRUM
INTEGRAL
H1 LEVEL:
H2 LEVEL:
GAIN:
SWEEP WIDTH:
SHIFT
SWEEP TIME:
SEC
DATE: 5-8-79
OPERATOR
REMARKS:
probably some ester impurity present from 3-00
10.0
9.0
8.0
7.0
6.0
3.0
2.0
1.0
Cyclohexane
CHO
HC CH



NMR 010

(E4-01)



TMS
CCl_4

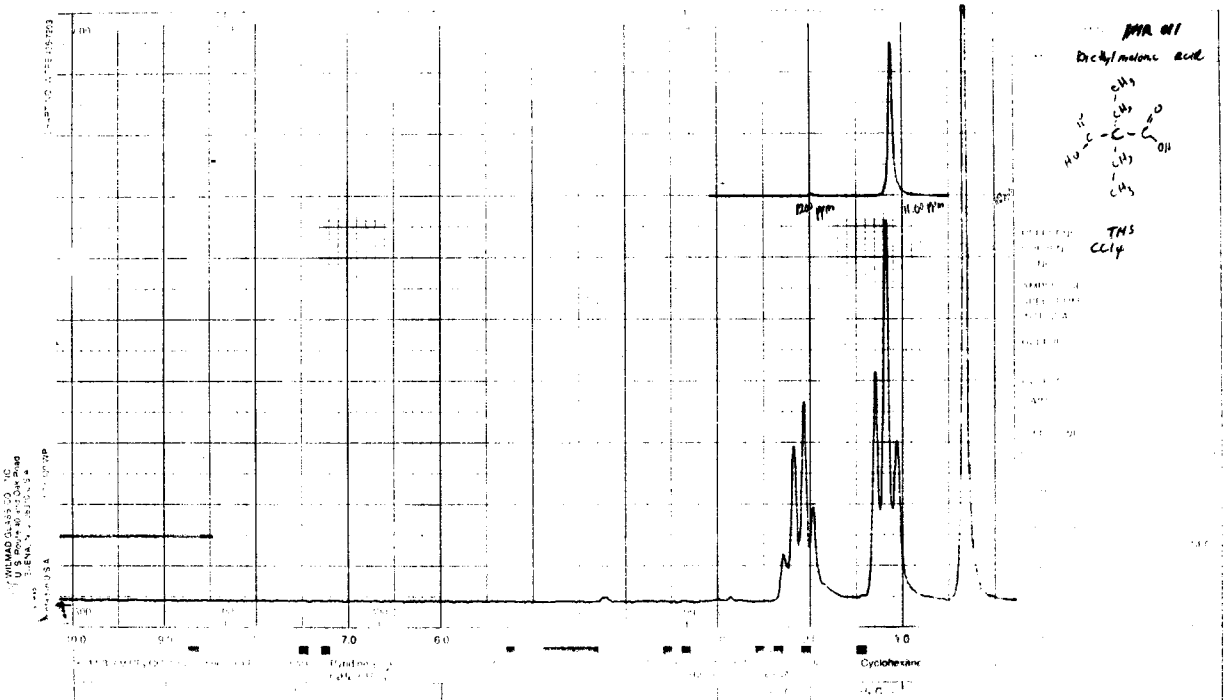
6

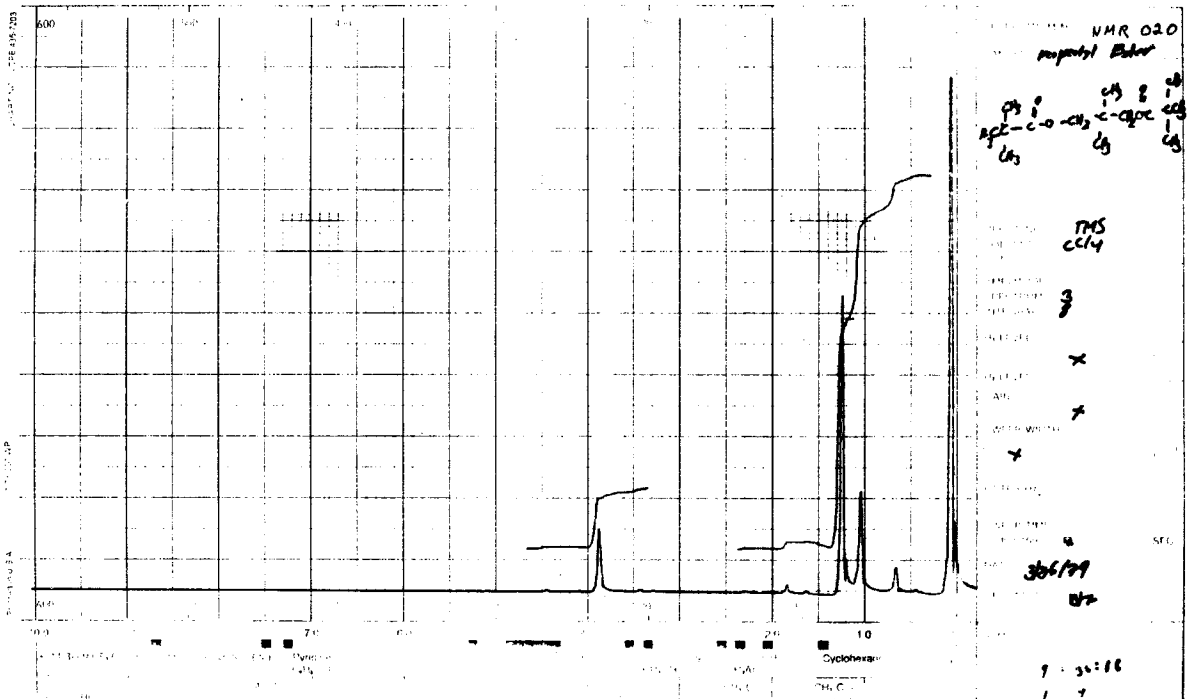
X

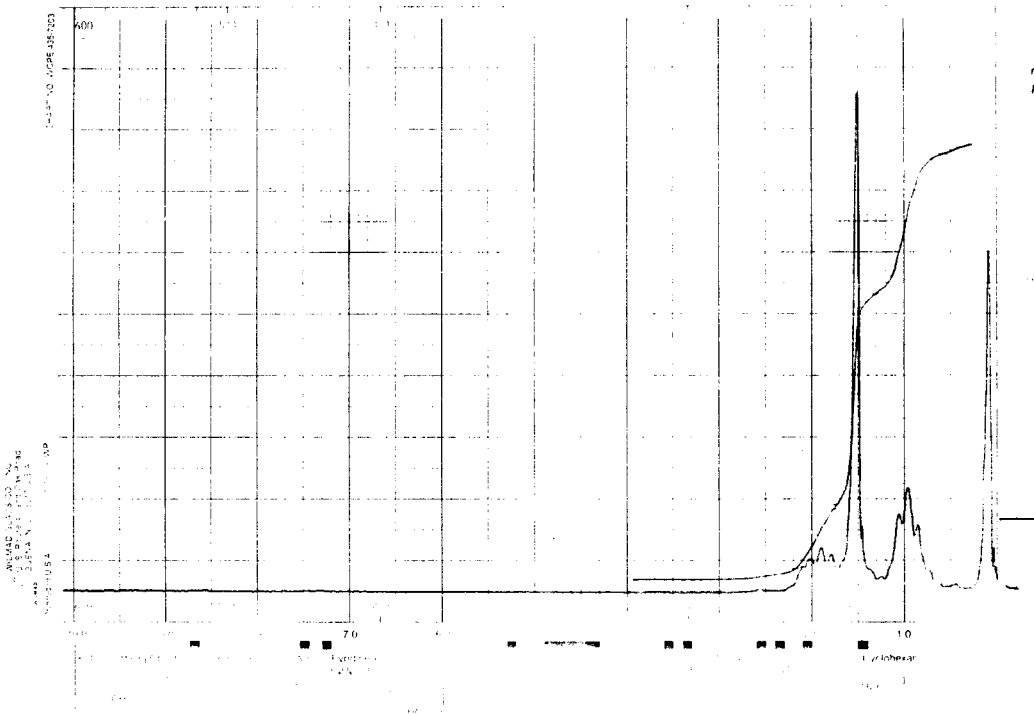
11-14-78

integ: 4 : 44 : 24
1 : 11 : 6

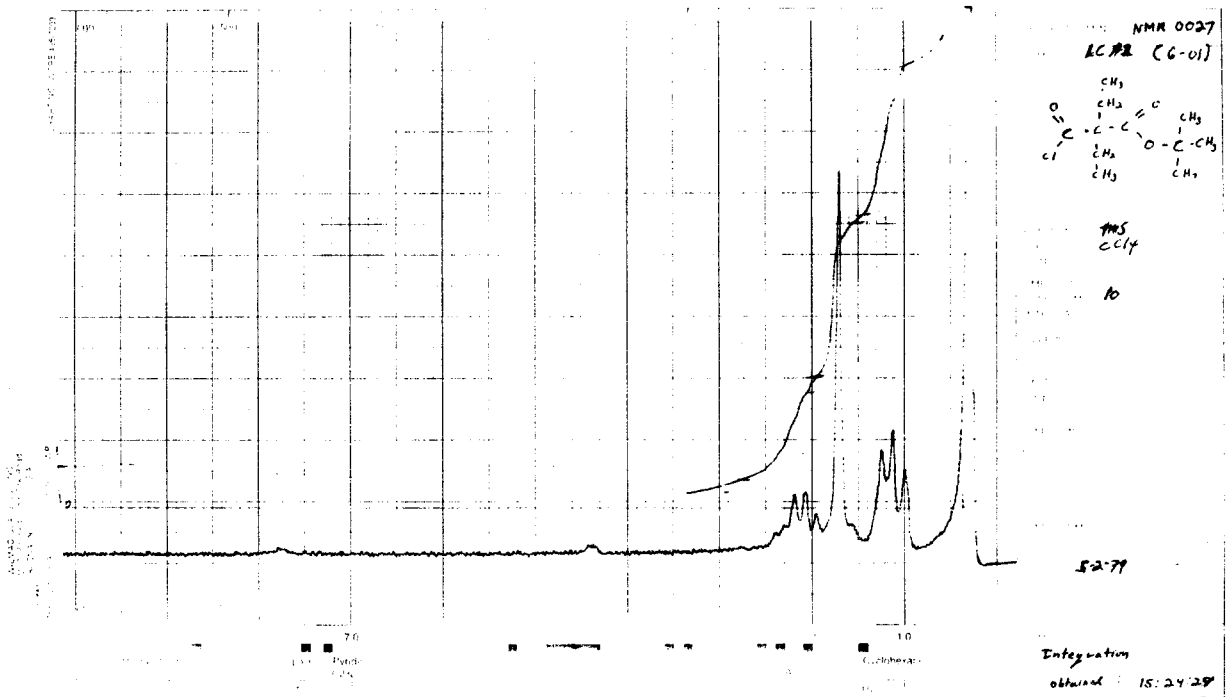
expected : 1 : 11 . 6


PMR 011
Diethylmalonic acid
TMS
CCl4
7.0
6.0
1.0
Cyclohexane


NMR 020
TMS
CCl4
Cyclohexane
Cyclohexane


NMR 026
Esterification of
Diethylmalonic acid.
Product mixture.
TMS
7
8
4/17/79
7.0
1.0
Integration
3:11 :9

69


NMR 0027
LC #2 (C-01)
CH3
CH2
C
CH3
O
C
C
C
CH3
Cl
CH2
O
C
CH3
CH3
CH3
TMS
CCl4
10
5-2-79
7.0
1.0
Integration
obtained : 15:24:29
~ 3 : 5 . 5
expected : 4 : 6

70

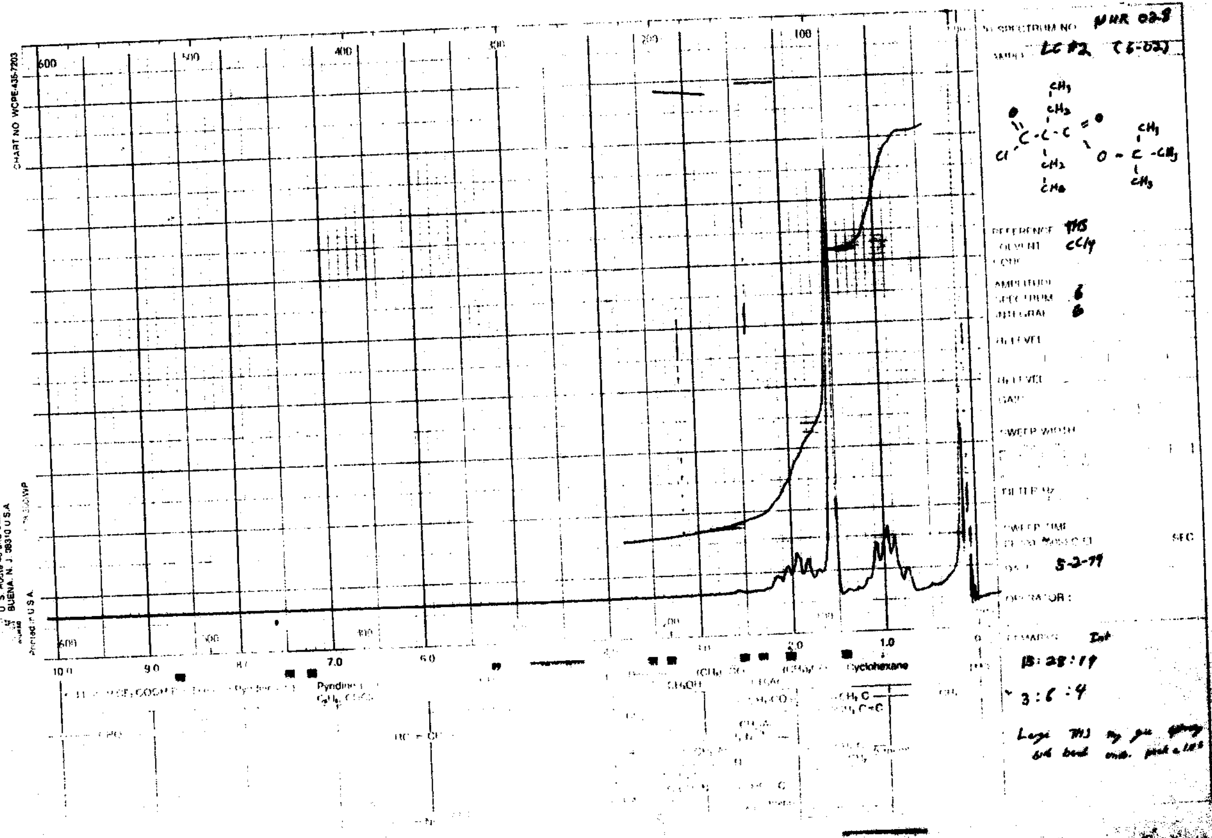
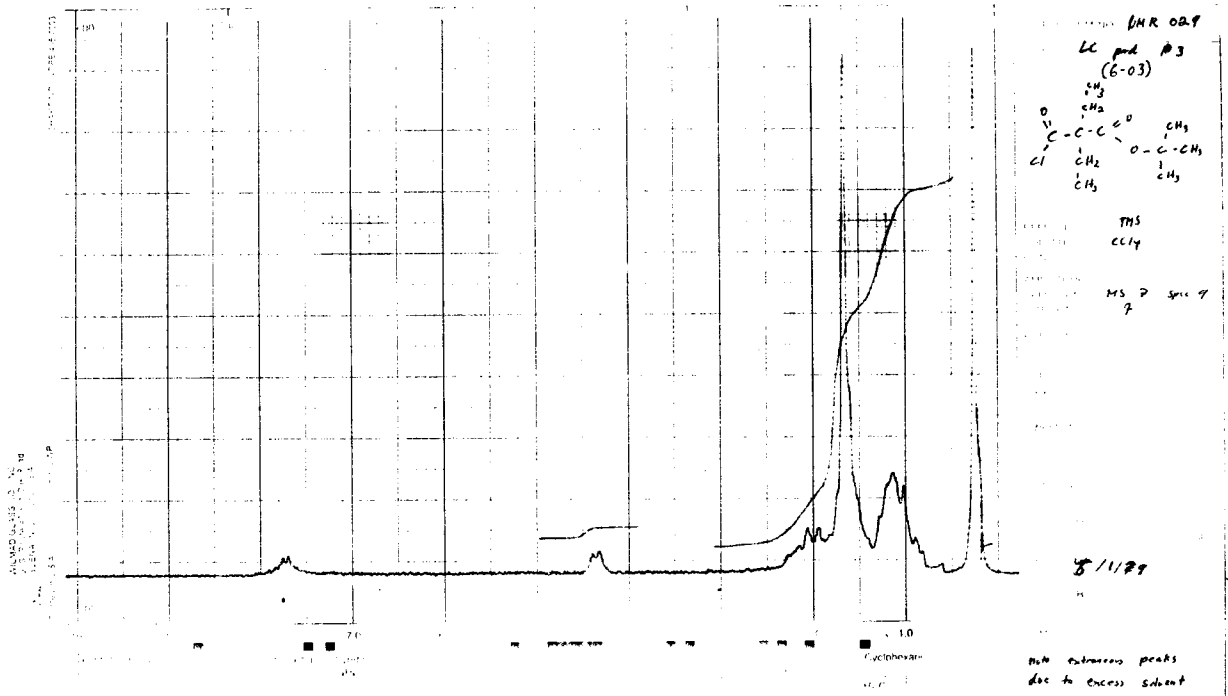
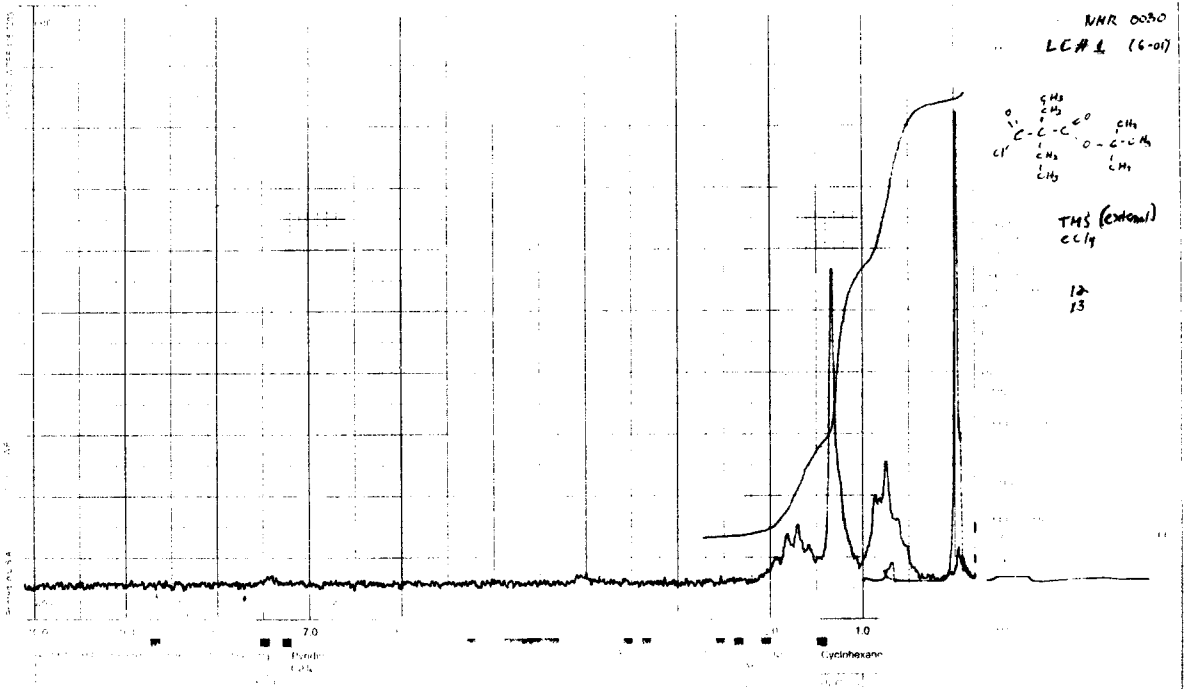


CHART NO. WCPE-435-7203
WILMAD GLASS CO. INC.
SPECTRUM NO. NMR 028
SAMPLE LC #2 (6-02)
REFERENCE TMS
SOLVENT CCl_4
SPECTRUM 6
INTEGRAL 6
SWEEP WIDTH
FILTER Hz
SWEEP TIME
DATE 5-2-79
OPERATOR:
REMARKS Int
13:28:19
3:6:4
Pyridine
Cyclohexane
10.0
9.0
7.0
6.0
2.0
1.0
600
500
400
300
200
100


PMR 029
LC peak #3
(6-03)
TMS
CCl4
MS ? spec ?
7.0
1.0
Cyclohexane
8/1/79
Note extraneous peaks
due to excess solvent


NMR 0030
LC# 1 (6-01)
THS (external)
CCl4
12
13
7.0
1.0
Cyclohexane

APPENDIX III:

Mass Spectra

Next Spectrum recorded will be 15 15

** ANALYSIS CONDITIONS FOR RUN # 3

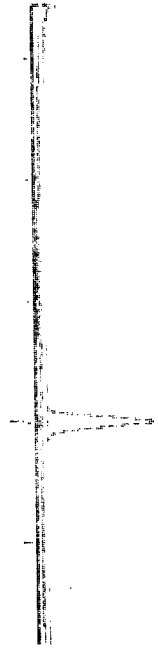
TEMP1	TIME1	RATE	TEMP2	TIME2	INJ.PORT	MAN.OVEN	SOLVENT	RUN TIME
100	2.0	16.0	180	10.0	250	250	0.5	15.0

FLOW RATE (ml./min.)	29
MS PEAK DETECT THRESHOLD	1000
SAMPLES PER .1 AMU	4
ELECTRON MULTIPLIER	1500
GC PEAK DETECT THRESHOLD	3000 TRIGGERED ON TOTAL ABUNDANCE

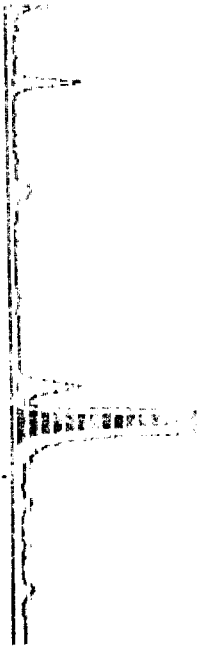
SAMPLE NAME di-t-butyl diethylmalonate MS/GC 01

OPERATOR Marton + Hull

TOTAL ABUNDANCE FROM 40 TO 300
Full Scale= 62000



ION 57.0
Full Scale= 300



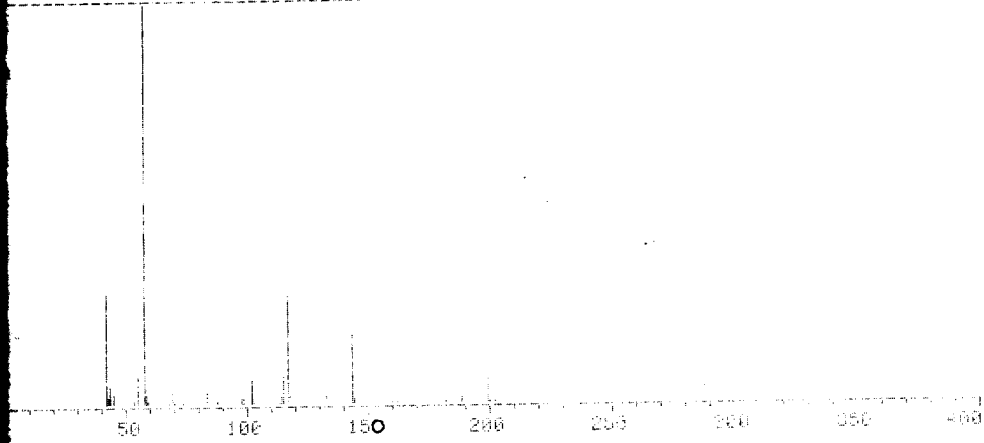
SPECTRA SAVED: Run # 3

Spectrum	Ret. Time
15	3.9

Spectro Plot/Tab Program: [05992-12006 Rev 3/9/77]

26

** Spectrum # 15 ** Sample # 3 Retention Time = 3.9
File type = 2 Number of peaks detected = 133
Scanned from 40 to 300
Base Peak = 57.1 Base Peak Abundance = 3638 Total Abundance = 9113



Lower Abundance Cutoff Level = 5.0

MASS	ABUNDANCE	MASS	ABUNDANCE	MASS	ABUNDANCE
41.2	27.7	101.1	6.6	143.1	16.8
55.1	7.1	115.2	7.2	158.2	6.2
57.1	100.0	116.1	26.9		

** Spectrum # 15 ** Sample # 3 Retention Time = 3.9
File type = 2 Number of peaks detected = 133
Scanned from 40 to 300
Base Peak = 57.1 Base Peak Abundance = 3638 Total Abundance = 9118

Lower Abundance Cutoff Level = 0.1

MASS	ABUNDANCE	MASS	ABUNDANCE	MASS	ABUNDANCE
41.2	27.7	81.1	0.1	110.1	0.2
42.2	2.1	83.1	3.5	111.2	0.4
43.1	4.3	84.2	0.1	129.1	1.9
44.1	0.2	85.1	0.2	138.1	0.1
45.1	2.5	86.2	0.2	143.1	16.8
50.1	0.1	87.1	1.0	144.1	1.3
51.1	0.2	88.1	0.1	145.1	0.2
53.1	1.1	95.1	0.1	160.2	0.4
55.1	7.1	97.2	1.5	161.1	0.8
57.1	100.0	98.1	1.6	172.2	1.2
58.1	4.7	99.1	0.7	173.2	0.2
59.1	4.5	101.1	6.6	181.1	0.7
60.2	0.1	102.1	0.3	188.1	1.4
67.1	0.3	113.1	0.3	189.2	0.1
69.1	3.2	114.1	1.9	199.2	6.2
70.1	0.4	115.2	7.2	200.2	1.0
71.1	0.4	116.1	26.9	201.1	0.6
73.1	0.5	117.1	2.0	244.2	0.4

UN82
B218S/1979

BANKOWITZ, R.A.
CHEMISTRY

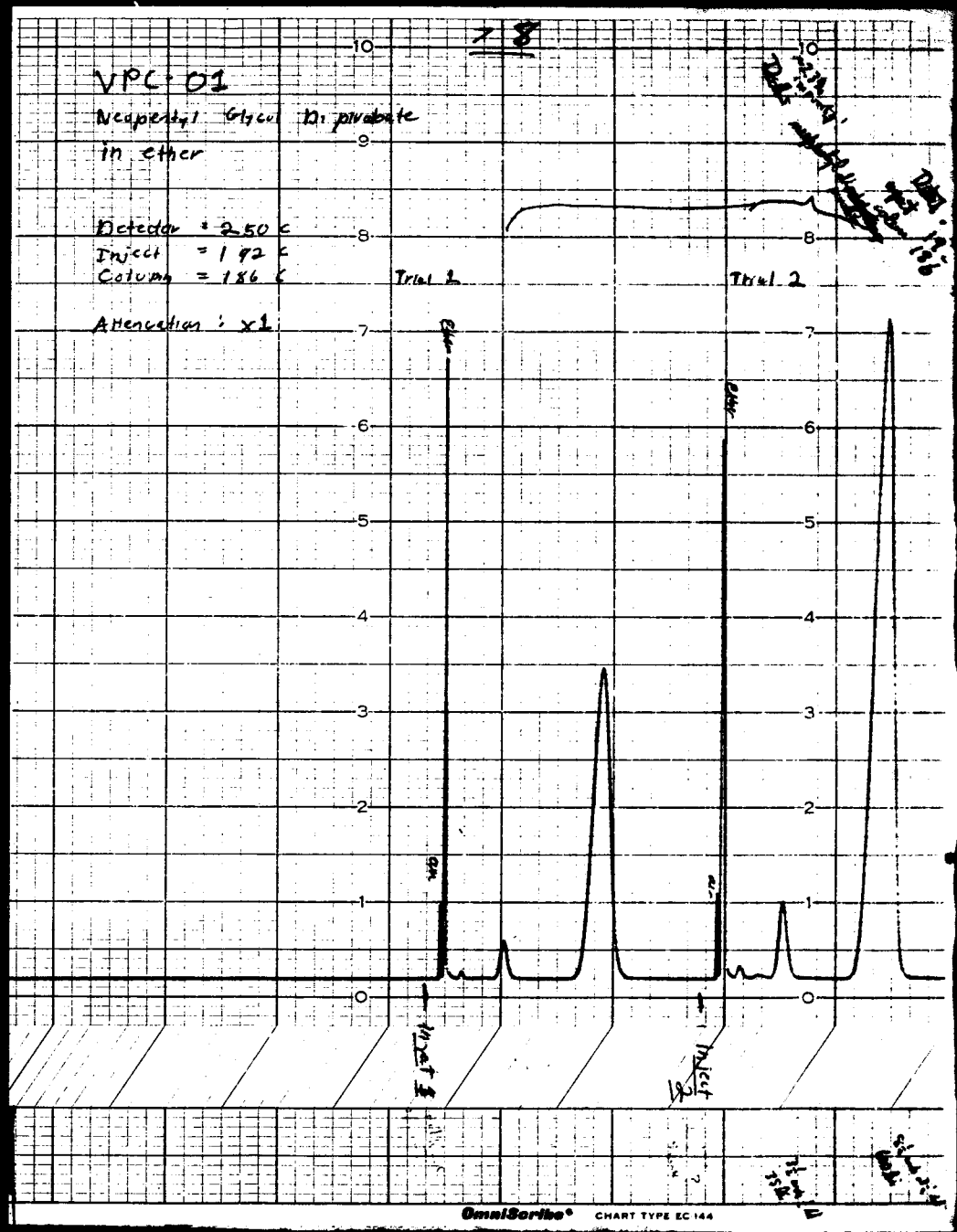
SYNTHESIS OF STERICALLY HINDERED DIESTERS

HRS. 5/79 SHT. 2 OF 2

END

APPENDIX IV:

Vapor Phase Chromatograms


VPC-01
Neopentyl Glycol Dipivalate
in ether
Detector = 250 C
Inject = 192 C
Column = 186 C
Attenuation : x1
Trial 1
Trial 2
Ether
Ether
Inject
Inject
OmniScribe
CHART TYPE EC-144

VPC 02

Product 1-01

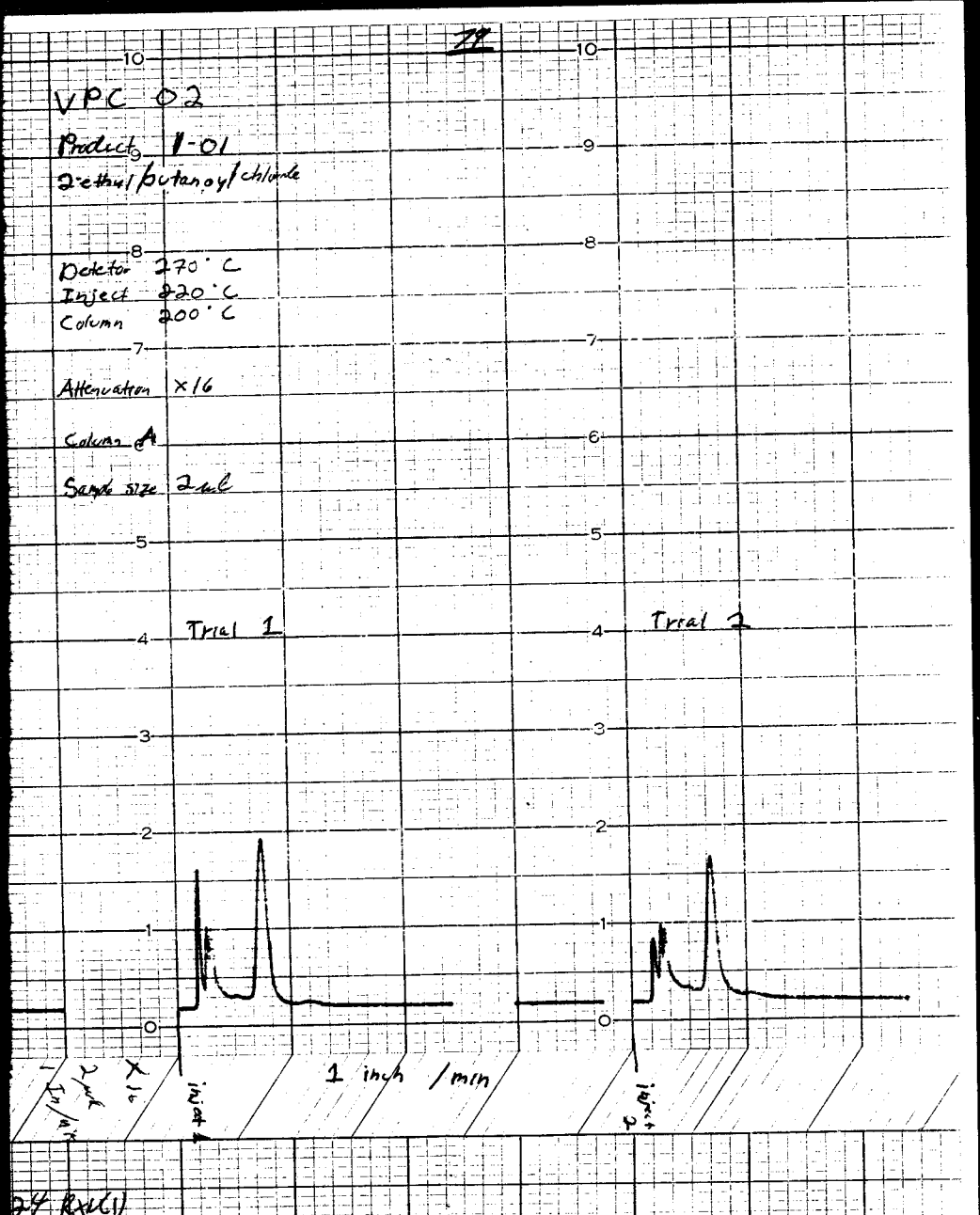
2-ethyl butanoyl chloride

Detector 270° C
Inject 220° C
Column 200° C

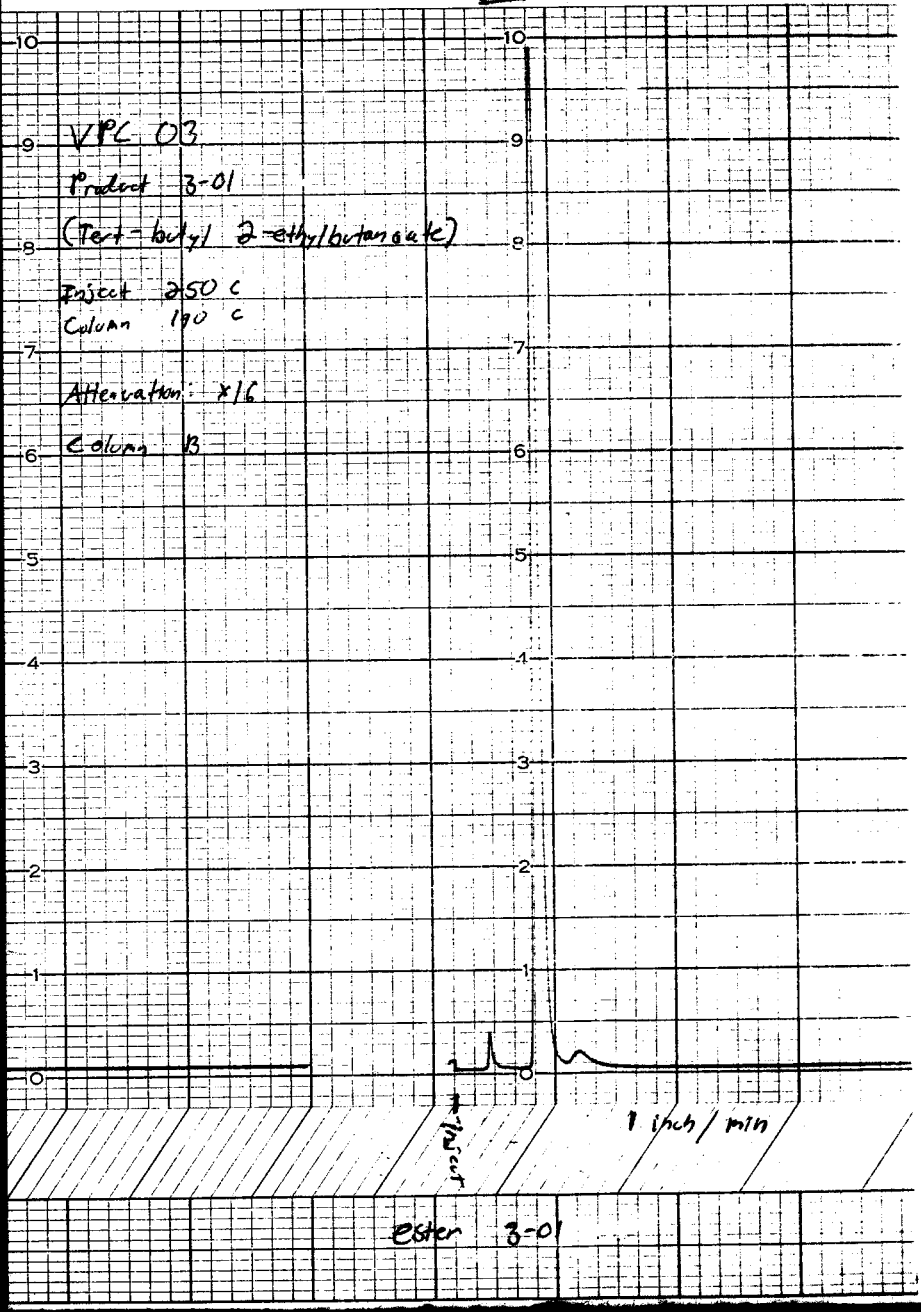
Attenuation ×16

Column A

Sample size 2 uL



24 RxL(1)


VPC 03
Product 3-01
(Tert-butyl 2-ethylbutanoate)
Inject 250 c
Column 190 c
Attenuation: x16
Column B
10
9
8
7
6
5
4
3
2
1
0
Inject
1 inch / min
ester 3-01

VPC 04

(4-01)

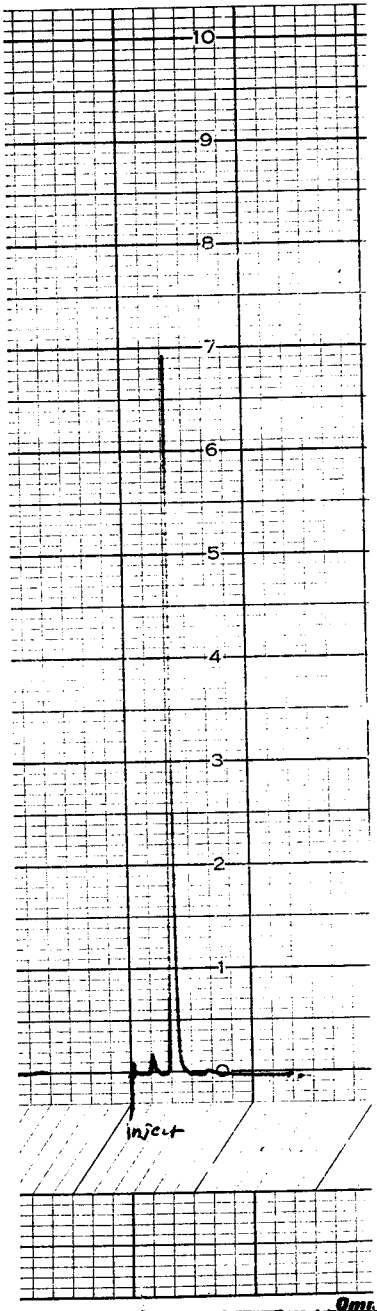
Tert-butyl 2-ethyl butanoate

Detector 250°C

Inject 200°C

Column 190°C

Column B



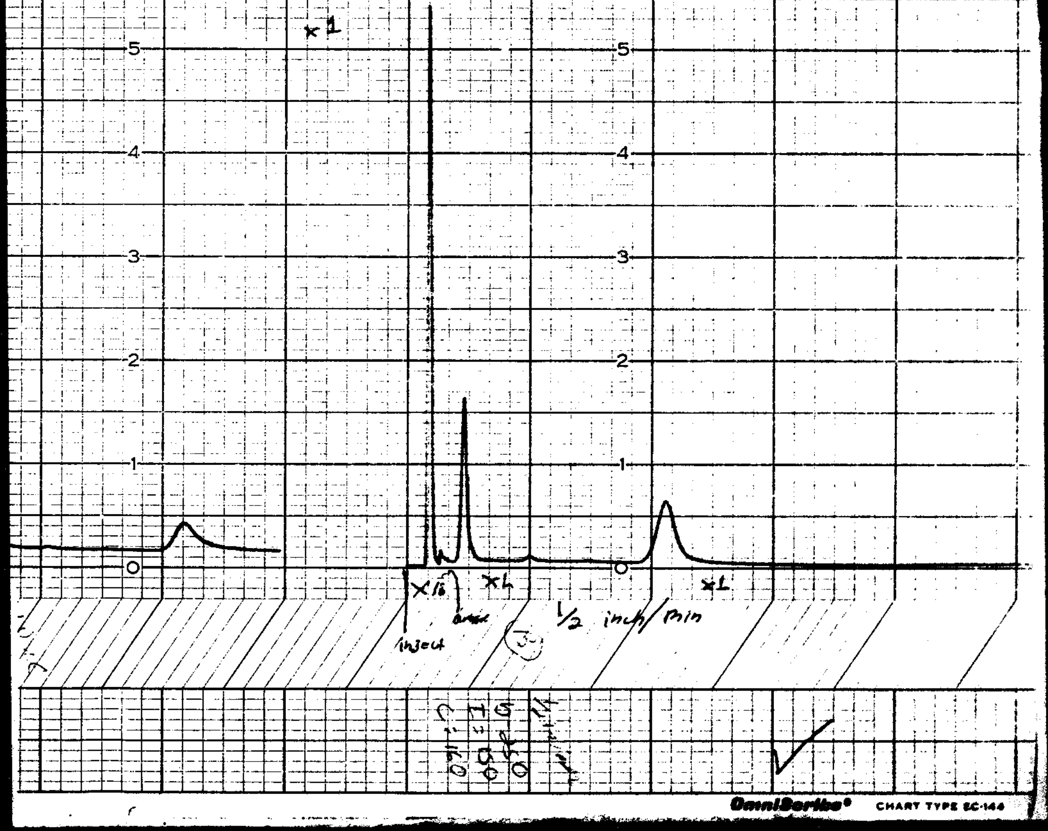
VPC 06

Esterification #2
of Diethylmalonic acid
with t-butanol

Detector = 250
Inject = 150
Column = 160

Column B

Attenuation ×16
×1



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END