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City University of New York PH.D. 1985

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STUDIES OF THE OPTICAL PURITY OF α-PHENYLNEOPENTYL CHLORIDE

Danielle Angrand Bright

A dissertation submitted to the Graduate Faculty in Chemistry in partial fulfillment of the requirements for the degree of Doctor of Chemistry, The City University of New York.

1985

This manuscript has been read and accepted for the Graduate Faculty in Chemistry in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

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Abstract

STUDIES OF THE OPTICAL PURITY OF α-PHENYLNEOPENTYL CHLORIDE

by

Danielle Angrand Bright

Several different approaches toward the determination of the specific rotation of optically pure α-phenylenopentyl chloride, 5, were studied. In the first of these procedures, S_Ni decomposition of optically pure α-phenylneopentyl chlorocarbonate gave samples of chiral 5 whose specific rotations were twice as high ($[\alpha]_D^{24} = -79°$) as literature values.

Application of the trialkylphosphine-carbon tetrachloride reaction to (R)-(+)-α-phenylneopentyl alcohol produced (S)-(-)-α-phenylneopentyl chloride whose specific rotation is (-)-112°. This is the highest rotation ever observed for this chloride. Thus, a greater degree of inversion stereospecificity was found in the R_3P /CCl_4 reaction than retention stereospecificity in the thermal rearrangement of the chlorocarbonate.

As a synthetic precursor to chiral α-phenylneopentyl chloride, racemic 1-chloro-(2,2-dimethylpropyl)-o-aminobenzene hydrochloride, V, was synthesized by a six-step sequence from anthranilic acid. It was converted to racemic 5 by diazotization-H_3PO_2 treatment successfully demonstrating the removal of the aryl amino group without loss of the benzylic chlorine.

The attempted resolution of the ortho substituted anilinium chloride, V, by means of anion exchange with (R)-(+)-d-10-camphorsulfonate was partially successful in that a sample of (R)-(+)-α-phenyl neopentyl chloride of specific rotation +81° (t = 25°C) was obtained

after diazotization-H_3PO_2 removal of the amino group of the less soluble camphor sulfonate anilinium salt.

A second effort to resolve V involved transformation of the amino group into an isocyanate function followed by reaction with optically pure (-) menthol to form levorotatory diastereoisomeric ℓ-menthyl carbamates. Fractional crystallization permitted separation of these isomers but all attempts to cleave them in acidic media frustrated resolution by yielding 4-t-butyl-3,1-benzoxazine-2-one.

The primary motivation for this work emerged from a mechanistic investigation of benzylic carbanion coupling processes. Reaction of diphenylmethyllithium with chiral α-phenylneopentyl chloride of rotation -106.5° at 25°C gave (R)-(-)-3,3-dimethyl-1,1,2-triphenylbutane of rotation -113°. The significance of this result is that coupling occurred with a minimum of 60% inversion of configuration. It also suggests that a polar nucleophilic displacement process is the predominant reaction pathway for the carbanion coupling process.

"If to do were as easy as to know what were good to do, chapels had been churches, and poor men's cottages prince's palaces."

Shakespeare

The Merchant of Venice

Acknowledgement

I wish to dedicate this thesis to my family, without whose love and support this work could never have happened.

I wish to express my gratitude to Professor H. E. Zieger for his guidance and encouragement.

I am grateful to Professors K. Grohman and R. Engel for their helpful suggestions.

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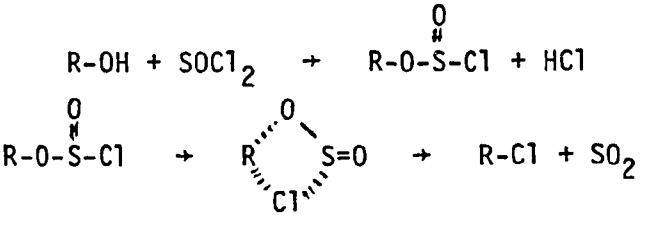
HISTORICAL PERSPECTIVE

Chiral α-phenylneopentyl chloride was synthesized by Winstein and Morse[1] from α-tert-butylbenzyl alcohol with thionyl chloride. Their purpose involved solvolytic studies of α-phenylneopentyl derivatives. This system provides a good model for evaluating steric hindrance to solvation of the benzylic cation. In fact, α-phenylneopentyl chloride is one of the slowest solvolyzing halides that they ever studied. Nair and Nair[2] give a value of 2.8×10^{-7} for its solvolysis rate constant in 80% acetone at 25°C. It slowly reacts with silver fluoride to produce α-phenylneopentyl fluoride[3]. On the other hand, all attempts to effect the S_N2 displacement of the chlorine atom with cyanide, hydroxide or amide ions have been fruitless (vide infra). Norris and Randles[4,5] also reported the stability of α-phenylneopentyl chloride towards S_N2 displacement with various nucleophiles.

The chloride obtained from (+)-α-phenylneopentyl alcohol's reaction with thionyl chloride is dextrorotatory and Winstein assumed that predominant retention of configuration was observed during the reaction due to the S_Ni mechanism.

I. Thionyl Chloride: The S_Ni Mechanism

The S_Ni mechanism proposed by Hughes, Ingold and coworkers[6] involves the intermediate formation of a chlorosulfite ester followed by loss of sulfur dioxide from the chlorosulfite and simultaneous formation of the carbon-chlorine bond.

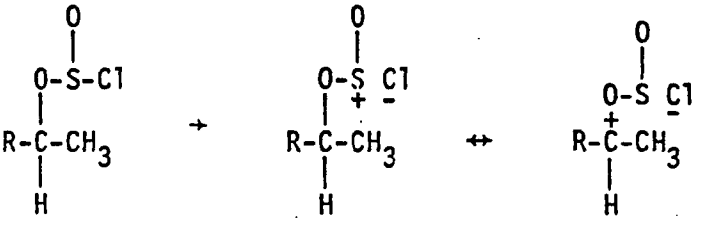


Two experimentally verifiable conditions are required by this mechanism: first, that a chlorosulfite results from the reaction of thionyl chloride and the alcohol and, second, that this chlorosulfite decomposes by a unimolecular reaction to give an alkyl chloride with retention of configuration.

Boozer and Lewis[7] synthesized various chlorosulfites purifying them by distillation in vacuo. They studied the thermal decomposition of these sulfite esters and found kinetic results consistent with a first-order rate law. They have also studied the effect of the solvent on the kinetics and stereochemistry of alkyl chloride production from secondary alkyl chlorosulfites[71]. They found that complete retention of configuration was obtained with dioxane whereas complete inversion was obtained in toluene.

For the reaction giving retention of configuration, a three-step process was written: (Scheme 1)

Scheme 1:



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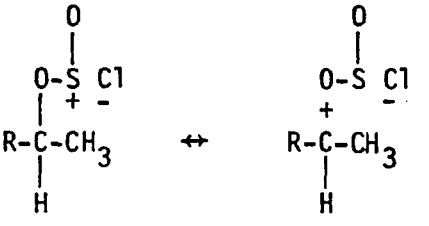

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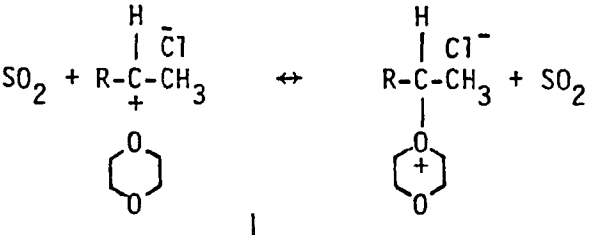
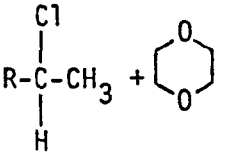




3

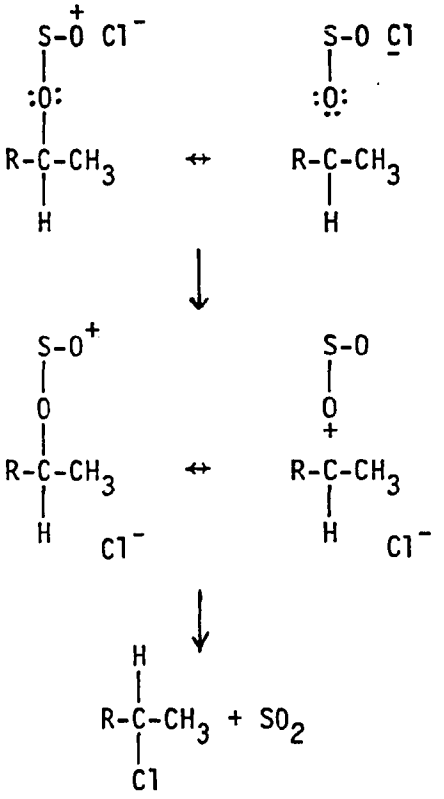
Step 1 involves the ionization of the chlorine-sulfur bond and consequent weakening of the carbon-oxygen bond. Step 2 represents the solvation by dioxane of the resulting carbonium ion and the loss of SO_2. These intermediatesdo not racemize because the solvation occurs from

the rear and introduces asymmetry. In step 3, the carbonium ion pair collapses to give a neutral molecule.

In toluene, there is a different mechanism. Step 1 is still present but toluene is neither nucleophilic nor a good solvating agent for carbonium ions. Step 2 cannot take place. Loss of sulfur dioxide from the carbonium ion cannot occur and attack on that side of the carbonium ion is difficult.

Under these conditions, a slower reaction can occur within the ion pair consisting of a relative motion of the ions. (Scheme 2)

Scheme 2:



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Those two mechanisms differ by the solvating power of the dioxane in the first case, which is able to displace sulfur dioxide from the carbonium ion. Toluene cannot solvate a carbocation as well as dioxane.

Wiberg and Shryne[8] obtained retention of configuration in both toluene and dioxane in the thermal decomposition of α-phenethyl chlorosulfite. The explanation given to this unexpected result is similar to the one proposed for the decomposition of α-phenethyl chlorocarbonate (see the next section: phosgene, the S_Ni mechanism).

Table 1: The Thermal Decomposition of α-Phenethyl Chlorosulfite Ester

% e.e. α-phenethyl alcohol	solvent	% e.e. chloride		% retention chloride	
		obs.	calc.	obs.	calc.
24.30	toluene	8.00	6.98	33	29
24.30	dioxane	11.25	12.75	46	52

The % enantiomeric excess (% e.e.) for the α-phenethyl alcohol was calculated based on the maximum rotation[9] (43.7°C, neat) known for this alcohol. The % e.e. for α-phenethyl chloride were obtained from the maximum calculated rotation[10] (125°C) and the maximum observed rotation[11] (109°C) known for this chloride.

The results of Wiberg and Shryne[8] show that decomposition is slightly more stereospecific in dioxane than it is in toluene.

II. Phosgene: The S_Ni Mechanism

Optically active alkyl chlorides also have been synthesized by the reaction of optically active alcohols with phosgene. The reaction of alcohols with phosgene to yield chloroformates (also named chloro-

carbonates) is a well-known reaction[12]:

$$R\text{-}OH + COCl_2 \rightarrow R\text{-}O\overset{O}{\overset{\|}{C}}Cl + HCl$$

The resulting chlorocarbonate decomposes to yield the corresponding chloride of retained configuration. The stereospecificity of this process varies with the starting alcohol.

In their study of the thermal rearrangement of α-phenylethyl chlorocarbonate, Wiberg and Shryne[8] showed that, either in toluene or dioxane solution, α-phenylethyl chloride was obtained with predominant retention of configuration. They suggested a mechanism similar to that of Boozer and Lewis[7] for the thermal decomposition with rearrangement of alkyl chlorosulfites. However, they suggested that α-phenylethyl chlorocarbonate possesses resonance stabilization that is not available in aliphatic systems.

The secondary alkyl chlorosulfites of Lewis and Boozer gave chloride of inverted configuration because of the difficulty of forming carbonium ions in toluene.

Table 2: The Thermal Decomposition of α-Phenethyl Chlorocarbonate

% e.e. α-phenethyl alcohol	solvent	% e.e. chloride		% retention chloride	
		calc.	obs.	calc.	obs.
18.63	toluene	13.6	15.6	73	84
22.77	dioxane	18.9	21.7	83	91

In this case, also, the decomposition is more stereospecific in dioxane than it is in toluene, probably due to the different solvating ability

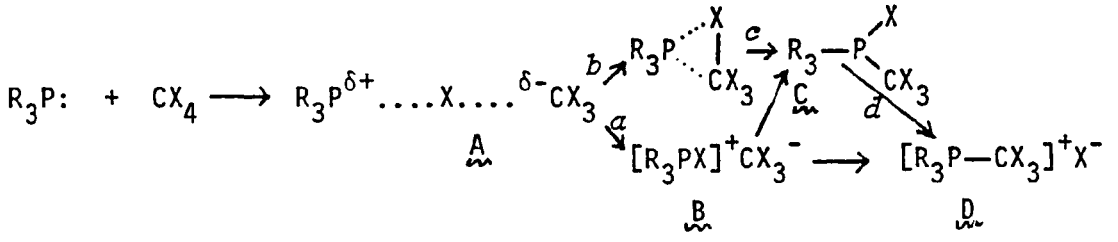
of those two solvents. The rearrangement of α-phenethylchlorocarbonate gives a higher percent retention of configuration than its corresponding chlorosulfite ester.

III. Carbon Tetrachloride-Triphenylphosphine Method

Recently, various methods have been described to prepare optically active chlorides from chiral alcohols [13,14,15,16,17].

The triphenylphosphine-carbon tetrachloride system attracted our attention because of the high stereospecificity claimed for its conversion of chiral alcohols into chlorides of inverted configuration[18].

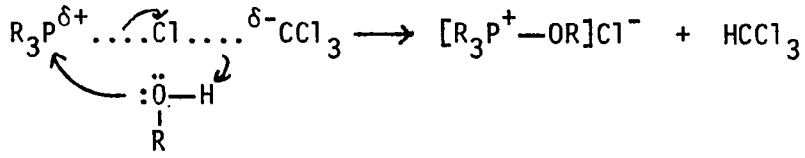
Trialkylphosphanes react with tetrachloromethane by an ionic mechanism[72] as shown below:



The existence of B has not been demonstrated, but the more stable trichloromethylphosphonium chloride D has been isolated[73]. Kinetic measurements based on the consumption of CCl_4 and the formation of $CHCl_3$, showed that D is formed by an intramolecular rearrangement of A via C.

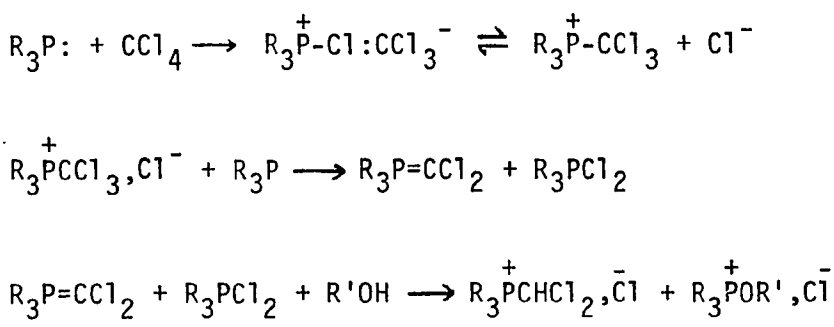
In the presence of alcohols, trialkyl or triphenylphosphine and carbon tetrachloride react to form an oxyphosphonium ion. Two different routes to the oxyphosphonium are possible:

1) the chloroform route:



The chloroform is formed by reaction of the alcohol with the dipolar associate (A). The fact that either A or B is involved in the formation of chloroform was demonstrated by Appel and his co-workers[73]; when a proton-active substrate, such as diethylamine, was mixed with the trichloromethylphosphonium chloride, D, no reaction occurred. No trace of chloroform could be detected.

2) the ylid route:



The phosphonium salt $R_3\overset{+}{P}CHCl_2,Cl^-$ can react with a fresh molecule of triphenylphosphine liberating a new oxyphosphonium moiety:

$$R_3\overset{+}{P}CHCl_2,Cl^- + PR_3 \longrightarrow R_3P{=}CHCl + R_3PCl_2$$

$$R_3P{=}CHCl + R_3PCl_2 + R'OH \longrightarrow R_3\overset{+}{P}CH_2Cl,Cl^- + R_3\overset{+}{P}OR',Cl^-$$

In the ylid route, there is little or no formation of chloroform. More triphenylphosphine is required to complete the reaction.

The polarity of the solvent used determines which pathway the reaction will follow. For instance, cyclohexanol in the moderately polar methylene chloride solvent follows the chloroform route for 46% (46% of the theoretical amount of chloroform has been measured), the balance being accounted for by the ylid route. The same reaction, when carried out in carbon tetrachloride gave 95% of the phosphonium salt ($R_3\overset{+}{P}CHCl_2,\overset{-}{Cl}$) indicating that the ylid pathway was the preferred one.

The oxyphosphonium intermediate ($R_3\overset{+}{P}OR,Cl^-$) was written in the ionic form[19] but other investigators suggest a covalent structure. Those intermediates have been isolated for hindered alcohols.

The formation of the oxyphosphonium intermediate is fast but its decomposition to product is sensitive to steric hindrance. Oxyphosphonium salts of primary alcohols decompose quickly at room temperature to give the alkyl chloride. For secondary and neopentylic alcohols, prolonged heating is necessary. The oxyphosphonium salt generally undergoes S_N2 displacement with inversion of configuration and neopentylic rearrangement does not take place. With secondary or hindered alcohols, inversion of configuration is often predominant or total.

Carbon tetrachloride is the most commonly used solvent for this reaction. However, acetonitrile[20] seems to be a far better solvent

because the reaction conditions are milder (room temperature) and the reaction time is shorter.

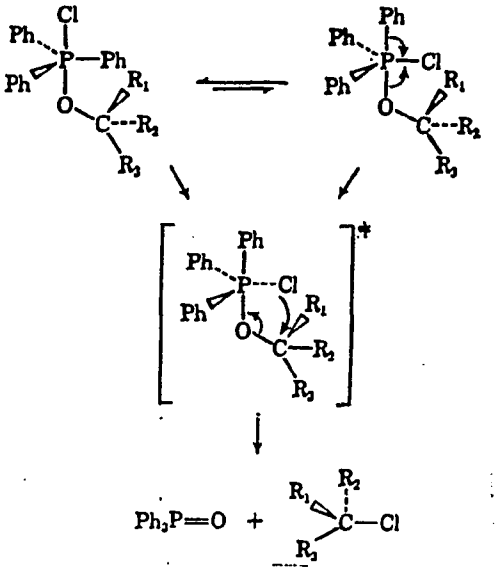
The neopentyl alcohol system:

Our interest in the neopentyl alcohol system arises from its similarity to α-phenylneopentyl alcohol. The two alcohols differ by one phenyl group. Franzus and his coworkers[21] have studied the decomposition of the oxyphosphonium intermediate in the reaction of neopentyl alcohol with triphenylphosphine carbon/tetrachloride. They demonstrated the existence of the oxyphosphonium intermediate $(CH_3)_3CCH_2OP(C_6H_5)_3Cl$ by means of ^{31}P-CH_2 coupling in NMR spectroscopy. Irradiation at the ^{31}P frequency collapsed the doublet. Also, they found that the rate of decomposition of the intermediate follows first-order kinetics. When optically active deuterated neopentyl alcohol was used, more than 85% inversion of configuration was observed. Observation of a very small isotope effect (k_H/k_D = 1.050) is consistent with a nearly balanced bond making, bond breaking process.

Several approaches to the mechanism of the oxyphosphonium intermediate decomposition have been considered:

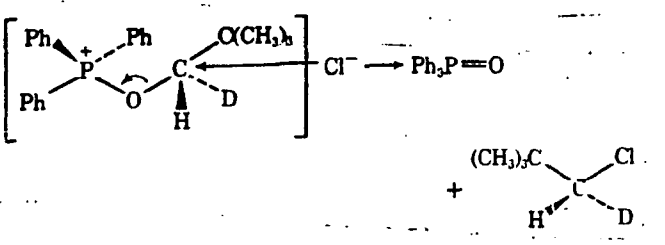
a) the four-center mechanism:

Weiss and Snyder[22] proposed a trigonal bipyramid for the intermediate where both oxygen and chlorine are apical. The apical oxygen or chlorine can be converted to the equatorial conformer by



pseudorotation. In this mechanism, P-Cl bond breaking precedes somewhat C-O bond cleavage in a very tight ion pair.

Franzus and coworkers[21] proposed an ion pair with the phosphorus tetrahedrally coordinated for the oxyphosphonium intermediate.



To make up for the unreasonable charge separation, they considered the ion pair as a cluster of ion pairs. In this case, a positive phosphorus in one ion pair can be in part electrically neutralized by a negative chloride from another ion pair. This interpretation is also incomplete since an external nucleophile such as cyanide ion was unable to compete with the chloride ion in the displacement reaction.

b) $\sigma_{2s} + \sigma_{2a}$ thermal pericyclic reaction:

Aneja, Davies, and Knaggs[23] proposed a $\sigma_{2s} + \sigma_{2a}$ thermal pericyclic reaction to account for the stereochemistry.

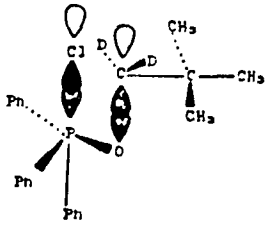


Figure 2. The decomposition of the intermediate $(CH_3)_3CCD_2OPCl(C_6H_5)_3$ in a $_s2_s + _s2_a$ pericyclic reaction.

This mechanism accounts for the inversion of configuration, the first-order kinetics and the small isotope effect. This model shows front side attack of the chlorine. In that case, the rate of decomposition of the intermediate should be faster since the neopentyl system is only slightly hindered by front side steric hindrance.

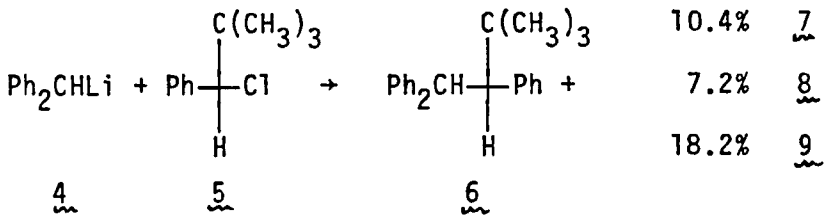
STATEMENT OF PROBLEM

In 1979, Zieger and Mathisen[24] reported that trityl lithium and benzhydryllithium couple with neopentyl halides by an S_N2 mechanism:

$$\underset{\underline{1}}{Ph_3CLi} + \underset{\underline{2}}{X\text{-}CH_2\text{-}C(CH_3)_3} \rightarrow \underset{\underline{3}}{Ph_3C\text{-}CH_2\text{-}C(CH_3)_3}$$

$$\underset{\underline{4}}{Ph_2CHLi} + \underset{\underline{2}}{X\text{-}CH_2\text{-}C(CH_3)_3} \rightarrow Ph_2CH\text{-}CH_2\text{-}C(CH_3)_3$$

Mathisen[25] reported that the coupling reaction of diphenylmethyllithium with chiral α-phenylneopentyl chloride ($[\alpha]_D^{21}$ = +41.1° in THF) gave a sample of (+)-3,3-dimethyl-1,2,2-triphenylbutane of rotation +39.2° in 50.5% yield along with meso-α,α'-ditert-butylbibenzyl (7), (+)-α,α'-ditert-butylbibenzyl (8) and 1,1,2,2-tetraphenylethane (9).



4 5 6

In order to study the mechanism of the coupling reaction that produced 6, a knowledge of the specific rotations of optically pure 5 and 6 were required. A sample of R-(-)-6 was synthesized[26] from the known R-(-)-α-tert-butylphenylacetic acid by Scheme 4 described below. The results of that work cast substantial doubt on the optical purities of (+)-5 used in the coupling reaction. It motivated several different approaches to determining the specific rotation of optically pure 5.

One effort involved exhaustive displacement studies of chloride ion from samples of 5 by various nucleophiles to form the alcohol, amine, and acid derivatives of 5. The idea was to compare the rotations of α-phenylneopentyl alcohol, amine, or α-t-butylphenylacetic acid obtained by this method with the known literature values.

The second approach involved synthesis of optically active samples of 5 from R-(+)-α-phenylneopentyl alcohol, a compound whose optical purity was well established. The work in this area concerned the S_Ni conversion of chiral α-phenylneopentylchlorocarbonate into chiral chloride 5 and the application of the tri-n-butylphosphine-carbon tetrachloride reaction to R-(+)-alcohol to afford S-(-)-5.

In addition, the synthesis of a racemic precursor to α-phenylneopentyl chloride which possesses a reactive functional group remote from the chiral center, which is easily removable and by means of which resolution can be achieved, was undertaken.

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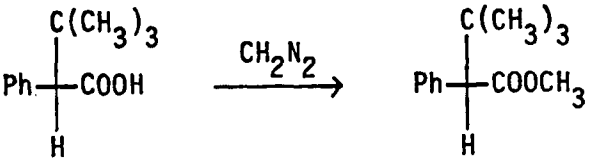
RESULTS AND DISCUSSION

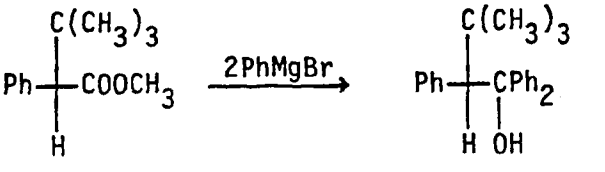
I. The Synthesis of (R)-(-)-1,1,2-Triphenyl-3,3-dimethyl Butane 6.

A sample of (R)-(-)-6 was synthesized[26] from the known R-(-)-α-tert-butylphenylacetic acid[27,28,29] according to the reactions shown in Scheme 3.

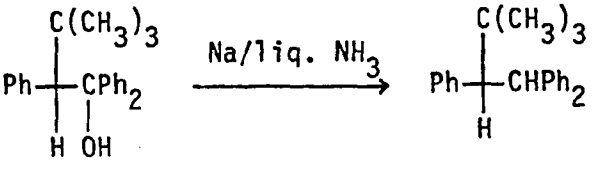
Scheme 3:



(R)-(-)10 $[\alpha]_D^{21} = -61.5°$ (R)-(-)11 $[\alpha]_D^{22} = -50.1°$



(R)-(-)11 $[\alpha]_D^{22} = -50.1°$ (R)-(-)12 $[\alpha]_D^{22} = -32.8°$



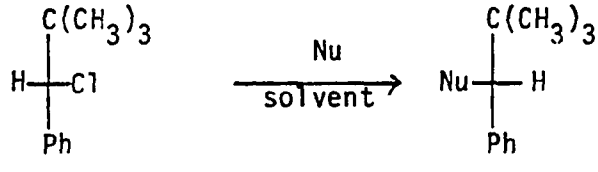
(R)-(-)12 $[\alpha]_D^{22} = -32.8°$ (R)-(-)-6 $[\alpha]_D^{22} = -188.6°$

Comparison of the sample of (+)-6 ($[\alpha]_D$ = +39.2°) obtained in the coupling reaction of benzhydryllithium with R-(+)-α-phenylneopentyl chloride with the sample synthesized by Scheme 3 ($[\alpha]_D^{22}$ = -188.6) showed that +6 has the S configuration and that coupling had occurred with a minimum of 20% inversion of configuration.

The samples of (+)-5 which were used in the coupling reaction were obtained by treatment of optically pure[1,74] (R)-(+)-α-phenylneopentyl alcohol 13 with thionyl chloride in carbon tetrachloride following the literature directions[1]. Slightly higher rotations than those reported by the literature were obtained for (+)-5. This fact convinced us that the optical purity of (+)-5 could be as low as 20%.

II. Displacement Reactions

To establish the absolute rotation of α-phenylneopentyl chloride, nucleophilic displacements on chlorocompound 5 under S_N2 conditions were studied.



The specific rotations of optically pure α-phenylneopentyl alcohol[1], α-t-butylphenylacetic acid[27-29] and α-phenylneopentyl amine[30] are known. Displacement of chloride ion from optically active samples of 5 by cyanide, hydroxide or amide ions will give a measure of the optical purity of α-phenylneopentyl chloride if one assumes 100% inversion of configuration. Unfortunately, 5 gave no VPC detectable quantity of α-phenylneopentyl alcohol after stirring for 3 days with

potassium hydroxide at 70°C in HMPA. α-Phenylneopentyl amine was not obtained from the reaction of 5 with sodium amide after refluxing in THF for 19 hours with or without a catalytic amount of 18-crown-6. In the case of cyanide displacement, after 7 days at 110°C in HMPA, a small amount of a new compound, presumably the cyanide (< 10%) was detected by VPC. These results confirm the findings of Norris and Randles[4,5] who tried without success displacement reactions on α-phenylneopentyl chloride with various nucleophiles (lithium nitroethamide, nitrite ion, sodium benzene thiolate) and concluded that due to steric hindrance, this particular chloride was very inert towards S_N2 reactions.

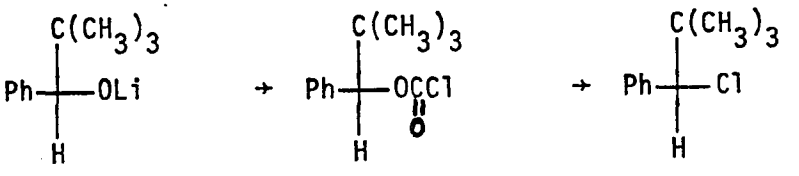
However, as mentioned earlier, Mathisen[25] reported that benzhydryllithium couples with chiral α-phenylneopentyl chloride ($[\alpha]_D^{21}$ = +41°) with a minimum of 20% inversion of configuration. When a sample of (S)-(-)-α-phenylneopentyl chloride of rotation -106.5° at 25°C prepared by the carbon tetrachloride/tri-n-butyl phosphine method (vide infra) was reacted with diphenylmethyllithium, there was obtained (R)-(-)-3,3-dimethyl-1,1,2-triphenylbutane 6 of rotation -113° at 25°C. Considering the specific rotation of optically pure (R)-(-)-6 to be 188°, the % enantiomeric purity of the sample of hydrocarbon of rotation -113° is 60% and the coupling occurred with a minimum of 60% inversion of configuration. The formation of cross coupling products[25] (meso-α,α'-ditert-butylbibenzyl, (+)-α,α'-ditertbutylbibenzyl and symmetrical tetraphenylethane) and the uncertainty on the absolute rotation of α-phenylneopentyl chloride prevent conclusion on the exact degree of inversion.

The coupling of benzhydryllithium with chiral chloride 5 is slow at room temperature. It requires 13 hours for completion. On the

other hand, it has been reported that diphenylmethyllithium (^{13}C NMR[31], UV[32]) in THF exists primarily as contact ion pairs. Since the proportion of solvent separated ion pairs increases with decreasing temperature[31,33,34,35,36], it could be of interest to study the reaction at lower temperature (0°C) and observe the change in rate. Increasing the speed of the coupling reaction might minimize side reactions such as electron-transfer processes.

III. Chiral α-Phenylneopentyl Chloride from Chiral α-Phenylneopentyl Alcohol: the Chlorocarbonate Route:

Samples of R-(+)-α-phenylneopentyl chloride having rotations of +67° and +72° were synthesized by reaction of the lithium salt of optically pure (+)-α-phenylneopentyl alcohol with phosgene followed by decomposition at 90° of the chlorocarbonate (see Table 2).



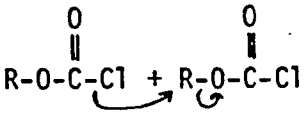
(+) 13a → (+) 14 → (+) 5

Table 3: Specific Rotations of α-Phenylneopentyl Chlorocarbonates and α-Phenylneopentyl Chloride.

run	$[\alpha]_D$ 13[a]	% e.e. 13	$[\alpha]_D$ 14[b]	Solvent	$[\alpha]_D$ 5[c]
1	+31.1	100	+31.6	neat	+67 (at 22°)
2	+31.6	100	+32.3	neat	+72 (at 22°)
3	-20.1	66	-24.2	dioxane	-51.1 (at 25°)
4	-20.1	66	-24.2	dioxane	-52.4 (at 24°)
5	-20.1	66	-24.2	toluene	-35.7 (at 24°)

[a] in acetone, [b] in CCl_4, [c] in THF.

The specific rotations of the two samples of optically active 5 from runs 1 and 2 prepared by this route were higher than the values obtained when thionyl chloride was the chlorinating agent. Since in runs 1 and 2, the decomposition was carried out neat, the possibility of chlorocompound formation by intermolecular displacement might result in a decrease of the stereospecificity of the reaction:



A. Solvent Effect

To investigate further the mechanism of the chlorocarbonate rearrangement, samples of α-phenylneopentyl chlorocarbonates of 66% optical purity were decomposed in dioxane and in toluene.

1) Decomposition in Dioxane

It was found that, in 0.53 and 0.57 M dioxane solution, the reaction occurred with predominant retention of configuration (runs 3 and 4, Table 3). The samples of (-)-α-phenylneopentyl chloride obtained exhibited rotations of -51.1° and -52.4°.

The optical purity of the starting alcohol was 66%. By extrapolation, we can calculate values that should be obtained if the starting alcohol were 100% optically pure. The calculated rotations for the chlorocompound are 77° and 79°.

Table 4: Solvent Effect on the Stereospecificity of the Decomposition: the Dioxane Case.

run	% e.e. 14a	$[\alpha]_D$ 5	calc. $[\alpha]_D$ if e.e. = 100
3	66	-51.1°	-77°
4	66	-52.4°	-79°

The calculated values in Table 4 are slightly higher than those obtained when the decomposition was carried out neat (+67°, +72° in runs 1 and 2), showing that the rearrangement is slightly more stereospecific when dioxane is used.

2) Decomposition in Toluene

In contrast, the decomposition of chiral α-phenylneopentyl chlorocarbonate (run 5) in toluene is less stereospecific:

Table 5: Solvent Effect on the Stereospecificity of the Decomposition: the Toluene Case.

run	% e.e. 14a	$[\alpha]_D$ 5	calc. $[\alpha]_D$ if e.e. = 100
5	66	-35.7°	-54.1°

A rotation of -35.7° was obtained for the resulting chloride. The decrease in the stereospecificity of the rearrangement can be accounted for by the fact that toluene does not solvate carbocations as well as dioxane.

B. Salt Effect

Optically active α-phenylneopentyl chlorocarbonate used in the thermal decomposition was not distilled prior to use since it decomposed partially to give the chlorocompound 5 upon distillation.

To be certain that dissolved lithium chloride was not present in the crude chlorocarbonate and was not responsible for S_N2 displacement of the chlorocarbonate instead of the S_Ni mechanism claimed, the following changes were made in the experimental conditions.

In run 3, the chlorocarbonate solution was filtered at room temperature to eliminate lithium chloride and decomposed in dioxane. The rotation of the resulting chiral α-phenylneopentyl chloride was -51.1° at 24°C (see Tables 2 and 3).

In run 4, the chlorocarbonate solution was cooled to -60°C prior to filtration and decomposed in dioxane. The resulting chloride exhibited a rotation of -52.4° at 25°, indicating a slight change in rotation. In order to be able to draw a stronger conclusion concerning

the salt effect, sodium or potassium α-phenylneopentyl alkoxide should be reacted with phosgene. The sodium or potassium chloride by-product is less soluble than lithium chloride in the ether solution of the chlorocarbonate. Because lithium chloride has more covalent character than sodium or potassium chloride, S_N2 displacement of dissolved chloride ion on the chlorocarbonate should be minimized.

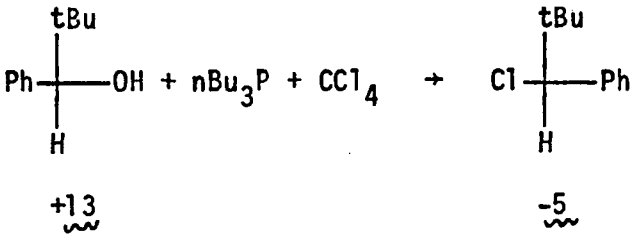
It has been reported that secondary alcohols react sluggishly with sodium hydride to give sodium alkoxides[37]. On the other hand, potassium hydride has been shown to exhibit remarkable activity towards weak organic acids such as amines, sulfoxides, and hindered tertiary carbinols. Potassium hydride should react smoothly with chiral α-phenylneopentyl alcohol to yield the potassium alkoxide which, upon reaction with phosgene, will give the expected chlorocarbonate along with potassium chloride. Filtration at -60°C, followed by decomposition in dioxane will yield α-phenylneopentyl chloride of higher rotation if there is a solubility effect of the salt.

Due to the higher stereospecificity observed in the carbon tetrachloride-tri-n-butylphosphine system, (see next section), this experiment was not attempted.

IV. S-(-)-α-Phenylneopentylchloride from R-(+)-α-Phenylneopentyl Alcohol: the tri-n-Butyl Phosphine-Carbon Tetrachloride Route:

Samples of S-(-)-α-phenylneopentyl chloride having rotations of -107.7° and -106.8° at 25°C were secured by reacting R-(+)-α-phenylneopentyl alcohol[1] with tri-n-butyl phosphine and carbon tetrachloride. These values are the highest rotations by far ever observed for the system.

Upon mixing the carbon tetrachloride solution of (+)-13 with an equimolar amount of tri-n-butyl phosphine, an exothermic reaction resulted. After stirring at room temperature for two days, the reaction mixture was mainly composed of unreacted alcohol (NMR). An excess of tri-n-butyl phosphine and prolonged heating were necessary to complete the reaction.



+13 -5

Table 6: α-Phenylneopentyl Chloride from nBu_3P/CCl_4

run	$[\alpha]_D$ 13	e.e. 13	$[\alpha]_D^{25}$ 5
1	+31.6	100	-107.7
2	+30.1	95	-106.5

In the second run, the alcohol is 95% optically pure which gives a calculated rotation of 112° for the chloride 5 based on enantiomerically pure α-phenylneopentyl alcohol. Small variations with temperature were observed in the specific rotation of the sample obtained in run 2 (see Table 7).

Table 7: Specific Rotations of S-(-)-α-Phenylneopentyl Chloride: Variations with Temperature:

t°	α°	$[\alpha]_D^\circ$
20°	-21.65	-107.2
21	-21.61	-107.0
22	-21.53	-106.6
24	-21.51	-106.5
25	-21.50	-106.5
26	-21.45	-106.2
30	-21.30	-105.5

V. Stereospecificity

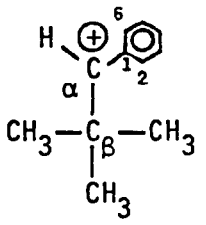
A. The Chlorocarbonate Decomposition

Synthesis of chiral α-phenylneopentyl chloride from the corresponding chlorocarbonate ester shows a higher S_Ni stereospecificity (+79°) than its formation from the chlorosulfite ester (+41°). S_N1 ionization is more likely to occur in thionyl chloride than it is in phosgene, decreasing the stereospecifity of the chlorosulfite rearrangement.

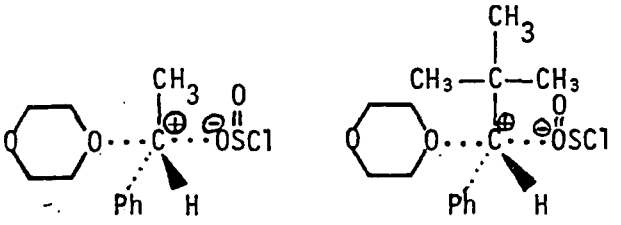
The thermal decomposition of α-phenethylchlorocarbonate in dioxane gave between 83% and 91% retention of configuration[8] in the formation of α-phenethylchloride.

Based on the higher rotation observed (+112°) for α-phenylneopentyl chloride, a maximum of 70% retention of configuration can be calculated for the thermal decomposition of α-phenylneopentyl chlorocarbonate in dioxane. This value (70%) is a maximum since the optical purity of the sample of rotation 112° is not established as yet. The

decomposition of α-phenylneopentylchlorocarbonate occurs with a lower degree of S_Ni stereospecificity than that of α-phenethyl chlorocarbonate. α-Phenethylchlorocarbonate and α-phenylneopentylchlorocarbonate differ from each other by a steric factor. Winstein and Morse[1] showed that the rate of solvolysis of α-phenylneopentyl chloride compared to α-phenethyl chloride is in the ratio of 1 to 490. They attributed the slowness of the α-phenylneopentyl system predominantly to retarding steric effects, i.e., steric hindrance to solvation and steric strain associated with the planar arrangement of the C_β-$C_\alpha HC_1C_2C_6$ skeleton in the carbocation.



In the chlorocarbonate decomposition, a carbocation solvated by dioxane is involved. Because of steric hindrance, dioxane will solvate the α-phenethyl carbocation better than the α-phenylneopentyl cation. As a consequence, attack by chloride ion on the same side from which



$^-$OSOCl departed, i.e., with retention of configuration will be favored in the α-phenethyl system. In the α-phenylneopentyl case, a larger amount of racemization can be expected because of poorer solvation.

B. The Oxyphosphonium Decomposition

The specific rotation of 112° obtained for α-phenylneopentyl chloride in the carbon tetrachloride/tri-n-butyl phosphine experiment indicates a higher degree of inversion stereospecificity than the amount of retention observed in the thermal rearrangement of the chlorocarbonate.

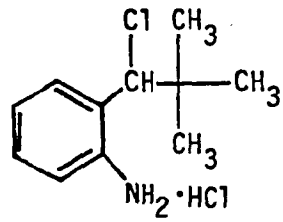
Because an excess of tri-n-butyl phosphine was needed to complete the reaction[18], the ylid route was probably the preferred pathway to the formation of the oxyphosphonium intermediate. This intermediate undergoes S_N2 displacement with inversion of configuration.

This result is to be contrasted with the apparent stability of α-phenylneopentyl tosylate, which is comparable to the oxyphosphonium intermediate with regard to steric hindrance, towards S_N2 displacement. α-Phenylneopentyl tosylate upon reaction with lithium chloride in HMPA at 90°C was recovered unchanged. Failure of chloride ion to displace the tosylate group can be accounted for by steric hindrance to back side attack. To be consistent with this result, the decomposition of the oxyphosphonium intermediate to α-phenylneopentyl chloride must occur by an internal S_N2 displacement.

Although the tri-n-butyl phosphine/carbon tetrachloride system gives a maximum rotation of 112° for α-phenylneopentyl chloride, which represents the largest specific rotation ever observed for this compound, the stereospecificity of this process is not known. And, because of the bulky t-butyl group attached to the chiral center, it is reasonable to assume that the reaction is not 100% stereospecific.

VI. Synthetic Efforts Towards Chiral α-Phenylneopentyl Chloride: the 1-Chloro-(2,2-dimethylpropyl)-o-aminobenzene Hydrochloride Approach:

A more rigorous approach to the question of the optical purity of α-phenylneopentyl chloride is to synthesize a precursor to this molecule, which contains a reactive functional group that is remote from the chiral center, which is easily removable, and by means of which resolution can be achieved. 1-Chloro-(2,2-dimethylpropyl)-o-aminobenzene hydrochloride is such a structure.



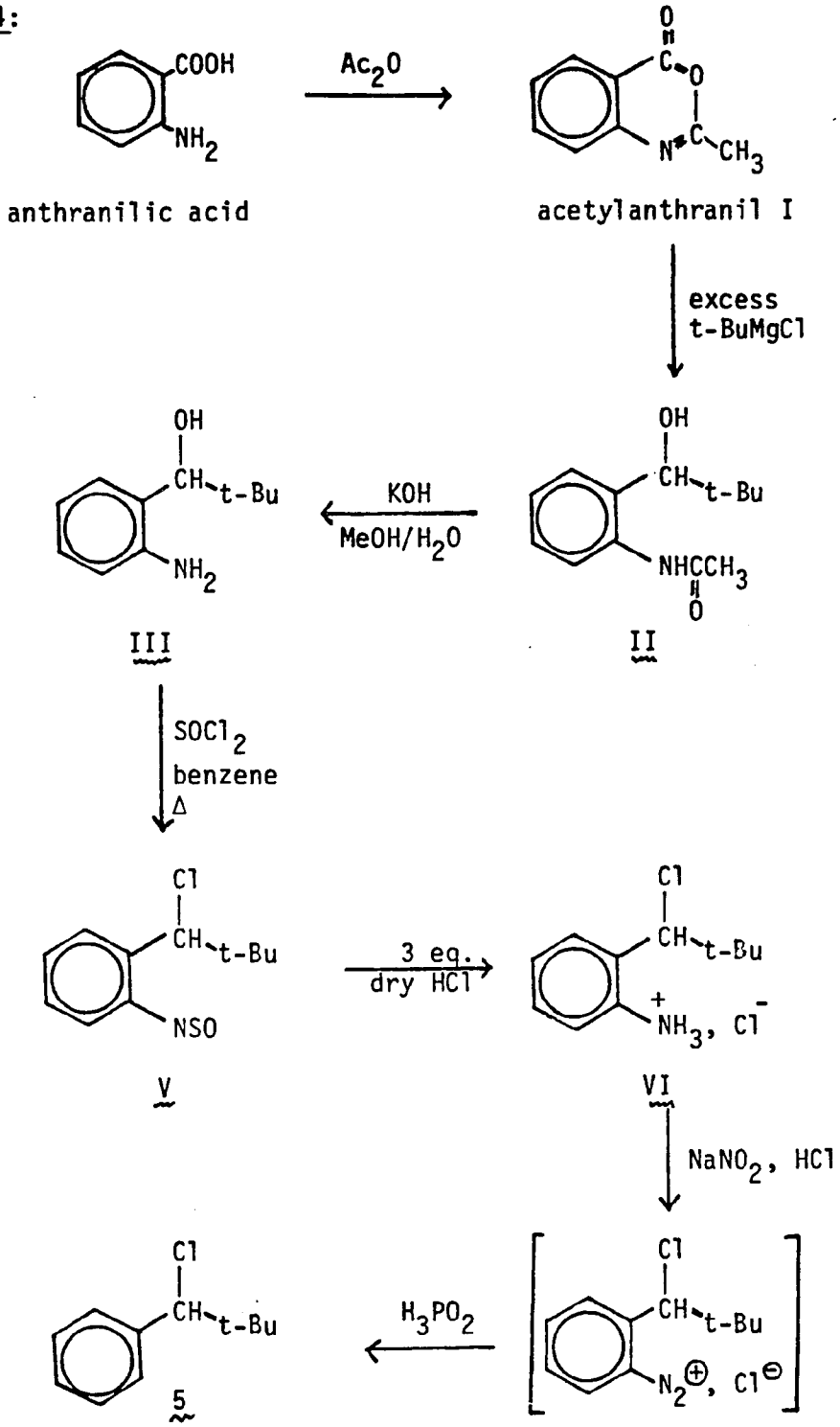
The amino group can be removed from the aromatic ring by diazotization followed by treatment with hypophosphorous acid.

Although the ortho amino group will increase the reactivity at the benzylic chlorine, this problem can be circumvented by avoiding alkaline conditions. On the other hand, the ortho amino compound was selected over the meta or para derivatives because, in the first case, the amine function is closer to the chiral center, thereby increasing the chances of a good resolution.

A. Synthesis of Racemic α-Phenylneopentyl Chloride

Racemic α-phenylneopentyl chloride has been synthesized by the sequence of reactions showed in Scheme 4:

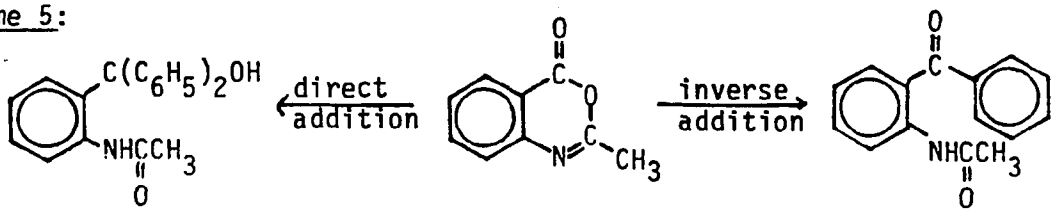
Scheme 4:


COOH
NH2
Ac2O
O
C
O
N
C
CH3
anthranilic acid
acetylanthranil I
excess
t-BuMgCl
OH
CH
t-Bu
NH2
KOH
MeOH/H2O
NHCCH3
O
III
II
SOCl2
benzene
Δ
Cl
NSO
3 eq.
dry HCl
+
NH3, Cl-
V
VI
NaNO2, HCl
H3PO2
N2⊕, Cl⊖
5

1) Synthesis of Alcohol Amide II

Addition of Grignard reagent to acetylanthranil to give keto amide or tertiary alcohol amide is a well studied reaction[38,39,40]. It has been reported that addition of one mole of phenylmagnesium bromide (inverse addition) to one mole of acetylanthranil gives N-acetyl-2-amino-benzophenone, whereas addition of acetylanthranil to the Grignard solution yields α-(2-benzamidophenyl)-benzhydrol (see Scheme 5). With two moles of the reagent per mole of acetylanthranil, the only product obtained is the tertiary alcohol.

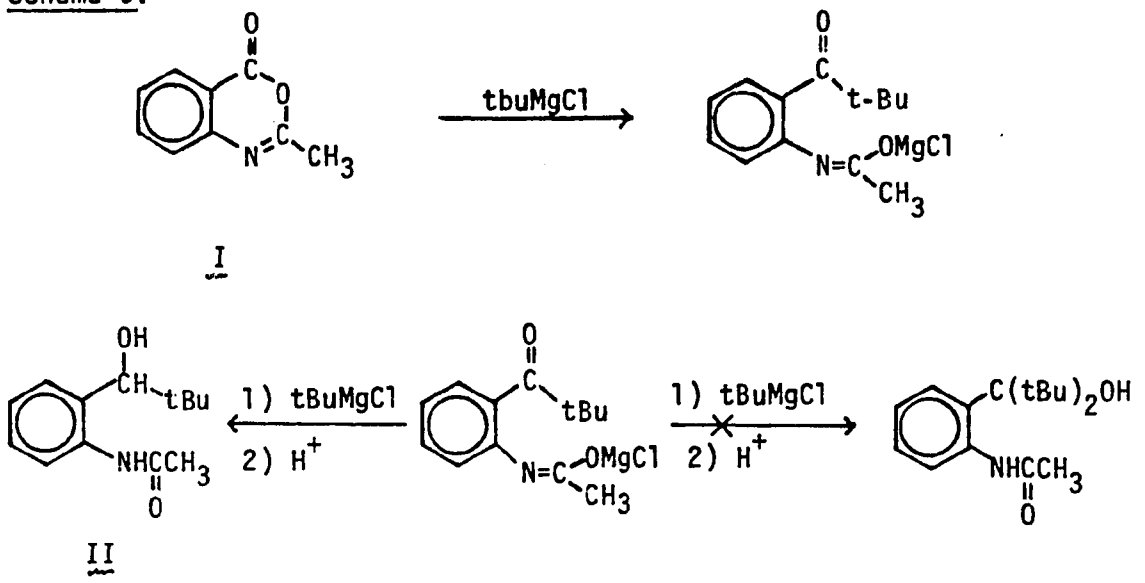
Scheme 5:



I

To synthesize alcohol amide II, acetylanthranil solution was added directly to an excess of t-butylmagnesium chloride. The first step of the reaction is the formation of N-acetyl-2-aminopivalophenone. But, because of steric hindrance, addition of a second mole of t-butylmagnesium chloride is difficult and Grignard reduction outweighs Grignard addition (see Scheme 6).

Scheme 6:

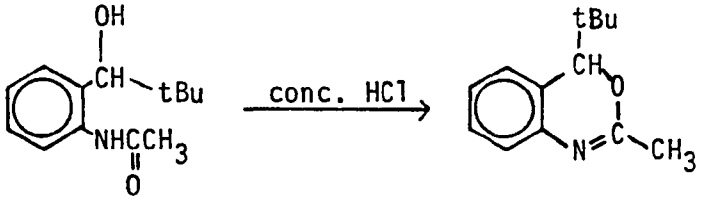


I

II

II was obtained in good yield and its structure was confirmed by its IR and NMR spectra as well as its microanalysis. Alcohol amide II was easily dehydrated by concentrated hydrochloric acid at room temperature to give 4-t-butyl-2-methyl-3,1-benzoxazine VII (see Scheme 7). After two months exposure to air, II was regenerated from benzoxazine VII.

Scheme 7:

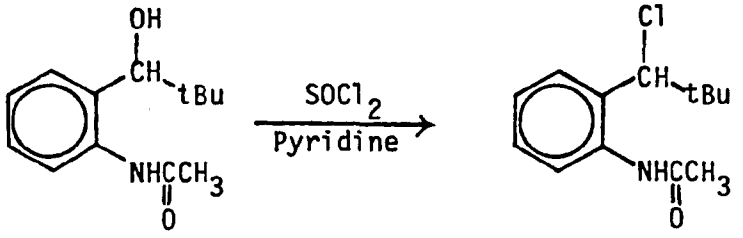


II VII

2) Synthesis of 1-Chloro-(2,2-dimethylpropyl)-o-aminobenzene Hydrochloride:

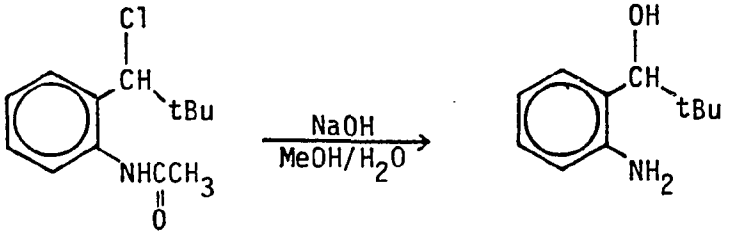
a) The Chloroamide Approach:

Chloroamide VIII was prepared by reacting alcohol amide II with thionyl chloride in the presence of pyridine:



II VIII

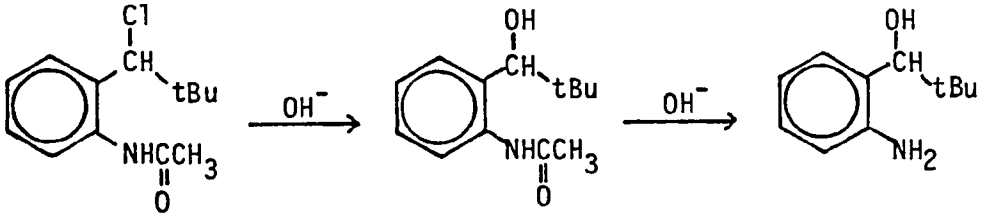
Upon treatment of VIII with sodium hydroxide in methanol-water, the aminoalcohol III was obtained (see Scheme 8).



Three possible mechanisms can be written for the conversion of chloroamide VIII to alcohol amine III:

Hypothesis 1: Hydroxide ion displaces chloride ion before hydrolysis of the amide function as shown in Scheme 9.

Scheme 9:

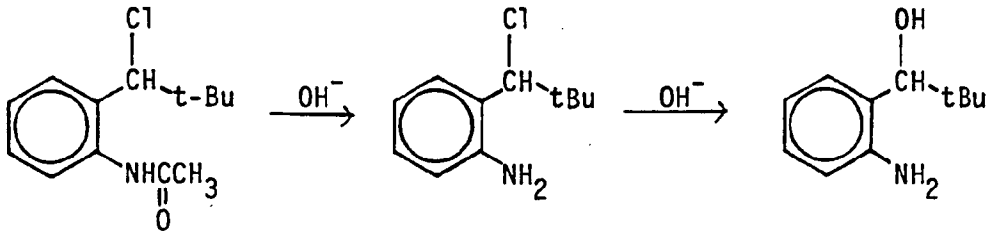


VIII II III

The fact that, under the same reaction conditions, α-phenylneopentyl chloride failed to give the corresponding alcohol because of steric hindrance is against this mechanism. The benzylic chlorine in VIII being more sterically hindered than its α-phenylneopentyl analog, substitution will be more difficult.

Hypothesis 2: Hydrolysis of the amide group precedes substitution of the chlorine as shown in Scheme 10.

Scheme 10:

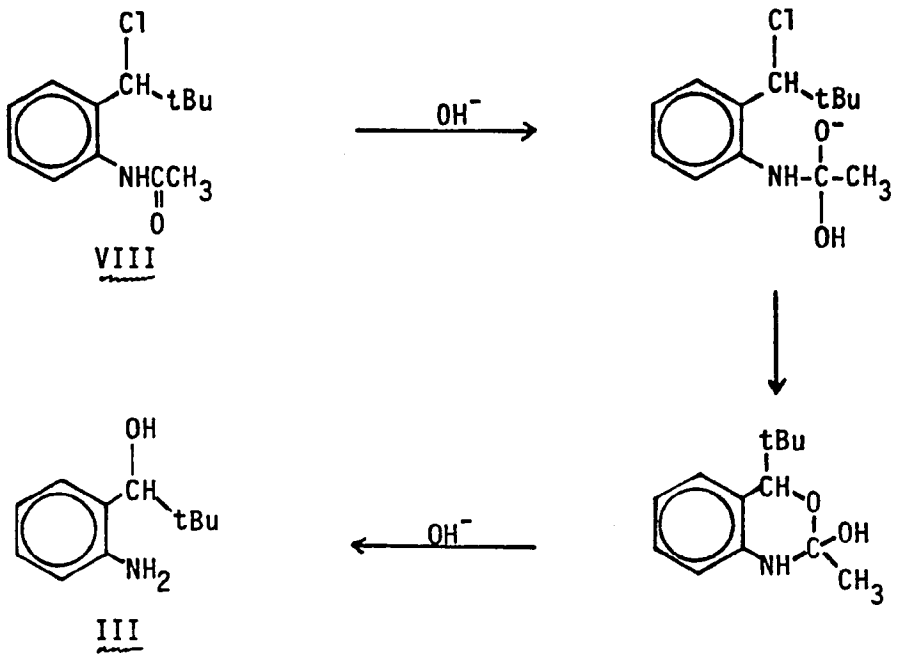


VIII III

This possibility is easily ruled out. Since the intermediate chloroaniline is unstable at room temperature, it cannot resist the harsh reaction conditions (reflux). It is also known to polymerize under basic conditions (see next section).

Hypothesis 3: Hydroxide ion attack on the carbonyl, followed by displacement of chloride ion, results in the formation of the intermediate hemiketal which, upon further reaction with OH^-, yields alcohol amine III (Scheme 11).

Scheme 11:



The driving force of the reaction is the formation of the intermediate six-membered ring. Neighboring group participation changes drastically the reactivity of the benzylic chlorine. This mechanism seems to be the more reasonable of the three proposed.

Hydrolysis of amide VIII, under acidic conditions, gave complex mixtures and made us turn our attention to the sulfinyl amine route.

b) The Sulfinylamine Approach:

N-sulfinylamines were first synthesized by Bottinger[41] in 1878, but their structure was established by Michaelis and Herz[42] twelve years later. More recently, various groups[43,44,45,46] have made renewed studies of the structure and the behavior of the organic N-sulfinyl compounds.

Upon reaction of III or its hydrochloride with thionyl chloride in benzene, there was obtained an orange liquid identified as

α-(o-N-sulfinylaminophenyl)neopentyl chloride V (see Scheme 4). This compound exhibits a band at 1170 cm^{-1} in its IR spectrum characteristic of an aromatic NSO group[43].

Addition of three moles of hydrogen chloride to the sulfinylamine yielded the chloro anilinium chloride VI pictured in Scheme 4.

3) Stability of Chloroanilinium Chloride VI:

Chloroanilinium chloride VI is reasonably stable at room temperature. Under basic conditions, it fails to yield α-(o-aminophenyl)-neopentyl chloride. Instead, complex mixtures are obtained. It is also unstable in water, probably because of acid-base equilibrium leading to the reactive free amine. The NMR spectrum of VI in d-6-DMSO shows the existence of an equilibrium between VI and the free aniline in a 4:1 ratio. These properties will dictate the choice of reaction conditions when it comes to the resolution of VI.

4) Racemic α-Phenylneopentyl Chloride from VI:

Diazotization of VI followed by treatment with hypophosphorus acid gave a sample of racemic α-phenylneopentyl chloride whose IR and NMR spectra were superimposable with those of an authentic sample of (±)-α-phenylneopentyl chloride (see Scheme 4). This result is of significance because it demonstrates that diazotization followed by reduction occurs without any apparent effect on the benzylic chlorine. The success of this approach depends now on the resolution step.

B. Studies in the Resolution of 1-Chloro-(2,2-dimethylpropyl)-o-aminobenzene Hydrochloride VI

In planning a resolution, one has to consider various factors[47]. It is crucial to select a good resolving agent that will form

diastereomers sufficiently different in solubility to make their separation possible. The choice of solvent is also important. A good solvent for resolution should dissolve selectively one of the diasteromers. In our studies of the resolution of VI, two different routes have been explored.

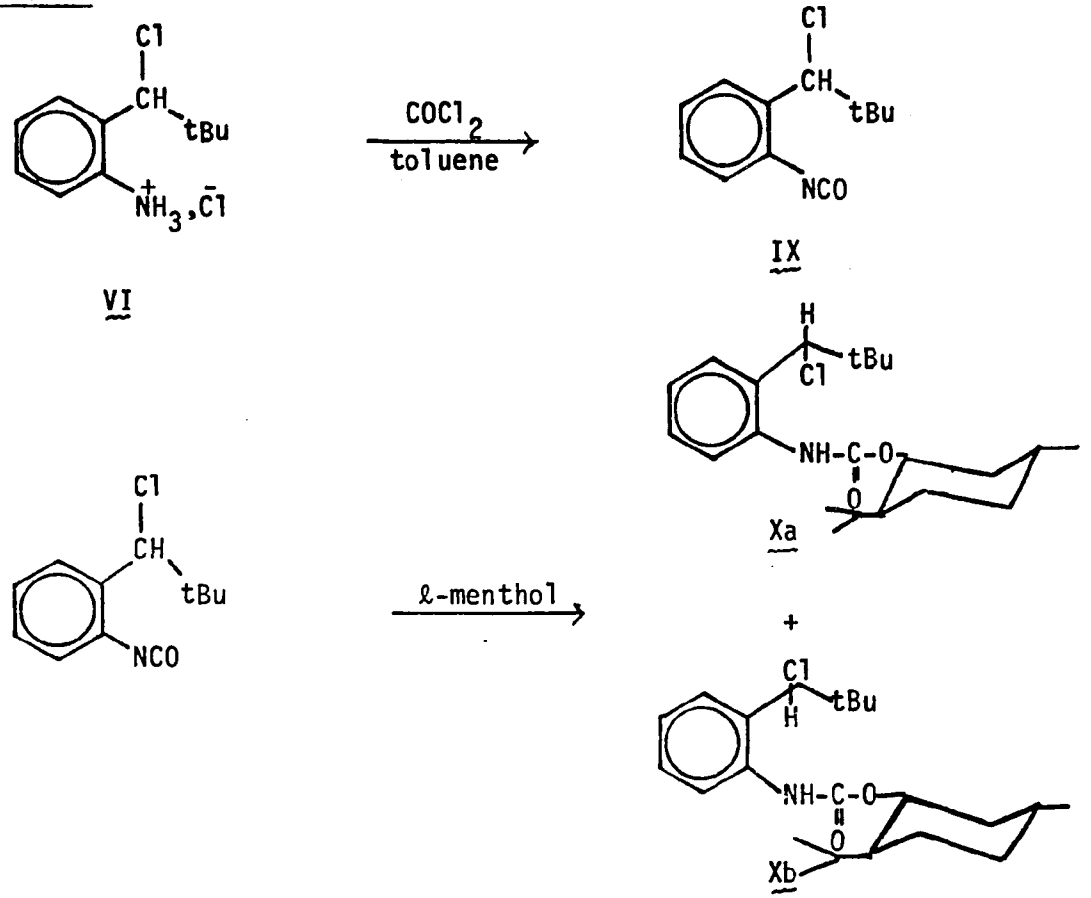
1) The Carbamate Route:

The carbamate approach seems attractive because it involves the formation of covalent diastereomers which will be easier than the diastereomeric salts to handle because of possible acid-base equilibria in the latter. Moreover, mild methods have recently been described[48] for their cleavage.

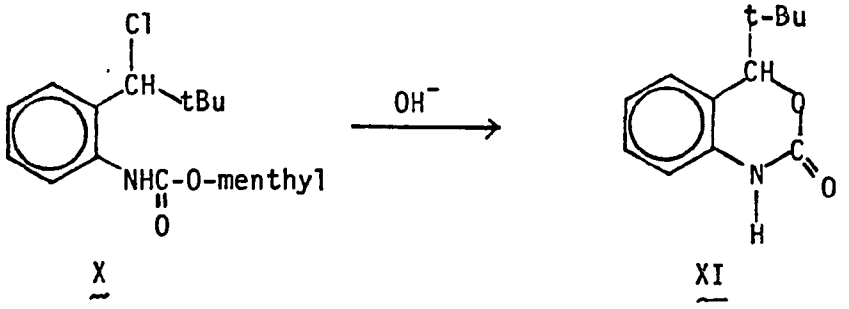
Pirkle and Hockstra[49] reported the resolution of a variety of alcohols via the formation of diastereomeric carbamates derived from racemic alcohol and chiral 1-(1-naphthyl)-ethylisocyanate.

By reacting the racemic isocyanate derivative of VI with a chiral alcohol (ℓ-menthol), diastereomeric carbamates of VI are obtained and separated by fractional crystallization (see Scheme 12).

Scheme 12:

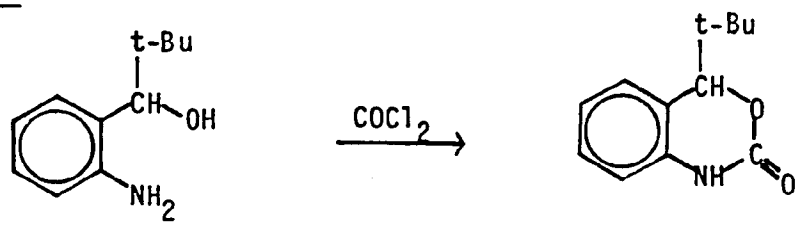


Cleavage of diasteromeric carbamates X under the proper reaction conditions should yield optically active chloroanilinum chloride XI. Basic conditions have been avoided because of the tendency of the chloroaniline of VI to polymerize. Also, bases such as hydroxide ion would yield the cyclic product XI:



Various acidic conditions have been explored and led to the formation of benzoxazine-2-one XI. In acidic medium, protonation of X can occur on the nitrogen, on the oxygen of the carbonyl or on the oxygen attached to the menthyl group. In all three cases, there is always the possibility of forming a six-membered ring upon attack of the carbonyl group by the nucleophile and this seems to be the preferred pathway. Compound XI was also prepared by the known reaction[50] of alcoholamines with phosgene for comparison (see Scheme 13).

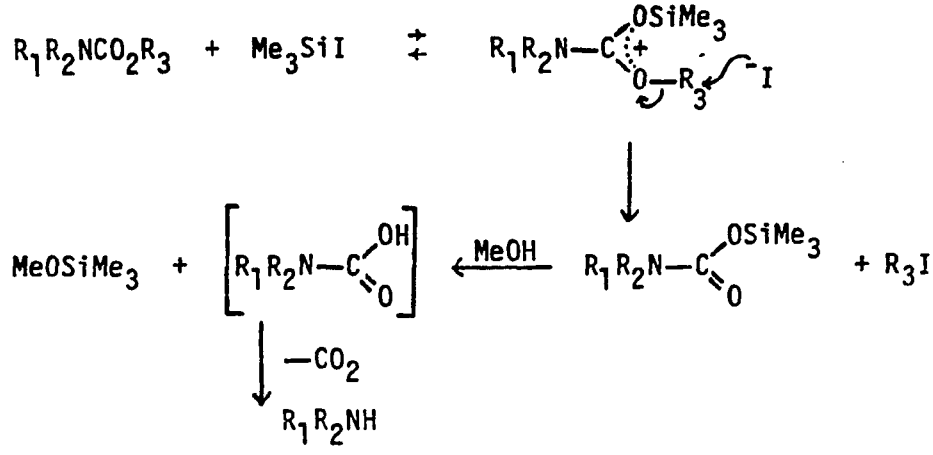
Scheme 13:



III XI

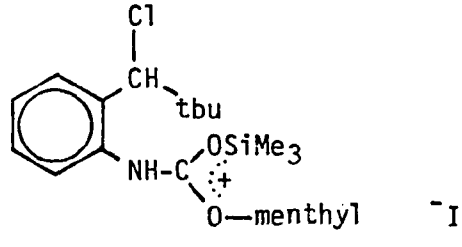
The structure of XI was confirmed by its IR, NMR spectra as well as its microanalysis.

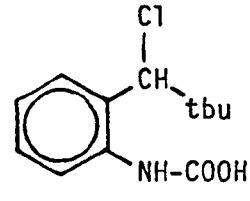
Jung and Lyster[51] described the cleavage of alkyl carbamates by reaction with trimethylsilyl iodide followed by methanolysis of the resulting trimethylsilyl carbamates in high yields. They proposed the following mechanism for the reaction:



In the case of nucleophilic amines, methanol pretreated with gaseous HCl was used to quench the reaction so that the amine was protonated as formed.

The success of the trimethylsilyliodide method when applied to carbamate X depends on two factors.





The first factor is that the nucleophile, I^-, will preferentially attack the menthyl group instead of displacing chloride ion. The second one is that decomposition of the intermediate carbamic acid to the amine will be faster than cyclization.

When the reaction was carried out at low temperature (5°C), a thick oil which polymerizes was obtained. At higher temperature ($CHCl_3$, reflux) cyclic compound XI was isolated.

Because cleavage of the diastereomeric carbamates X yielded preferentially the cyclic product XI, resolution of VI via formation of diastereomeric salts was undertaken.

2) The Diastereomeric Salts Approach:

Direct resolution of chloroanilinium chloride VI by anion exchange was studied.

a) The Resolving Agent:

In choosing a good resolving agent for VI, several factors have to be considered. As we mentioned earlier, the free aniline of VI is unstable at room temperature. This fact implies that VI should be used in the resolution instead of its corresponding chloroaniline. A possible resolution method could involve the reaction of VI with the salt of the resolving agent resulting in the precipitation of an inorganic salt which will be insoluble in the solvent chosen.

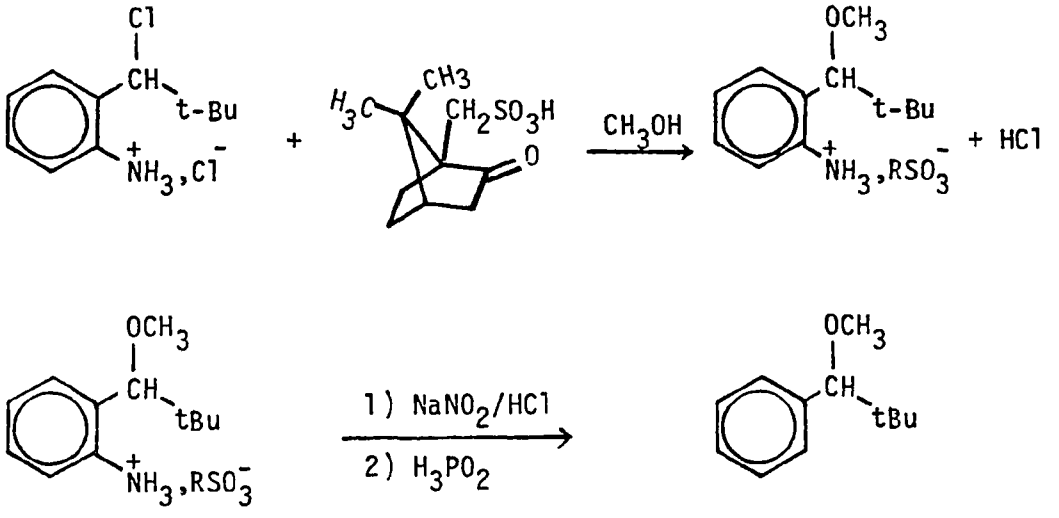
On the other hand, VI is the salt of a strong acid and a weak base. The use of a resolving acid stronger than HCl that will avoid acid-base equilibrium is another possibility. d-10-Camphorsulfonic acid was the resolving agent that we elected to study. The sodium camphorsulfonate salt approach was not attempted because of solubility problems. Instead, the acid was directly reacted with VI taking advantage of the fact that d-10-camphorsulfonic acid is stronger than HCl and of the gaseous nature of hydrogen chloride. By sweeping away the HCl formed, the equilibrium can be driven to the formation of diastereomeric camphorsulfonate salts.

b) The Solvent:

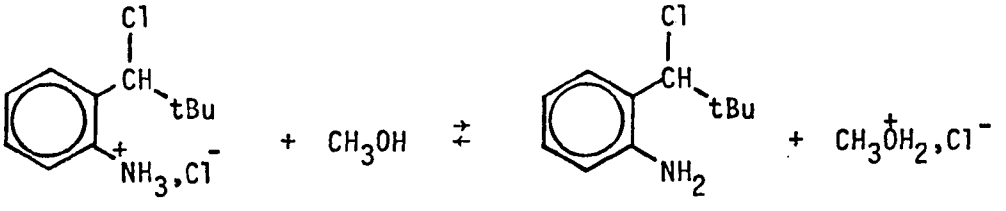
To avoid acid-base equilibrium, non-basic solvent should be used in the resolution. This point was illustrated by the mixing of a

methanolic solution of VI with a methanolic solution of d-10-camphorsulfonic acid followed by isolation and recrystallization of the resulting camphorsulfonate salt. Upon diazotization and treatment with hypophosphorous acid, there was obtained a racemic liquid. Its IR spectrum displays a strong band at 1085 cm^{-1} consistent with a C-O stretching vibration. Its NMR spectrum shows a methoxy peak at 3.17 ppm. This substance was identified as 1-methoxy-2,2-dimethyl-1-phenylpropane (see Scheme 14).

Scheme 14:



Upon dissolution of VI in methanol, an equilibrium was established:



VI

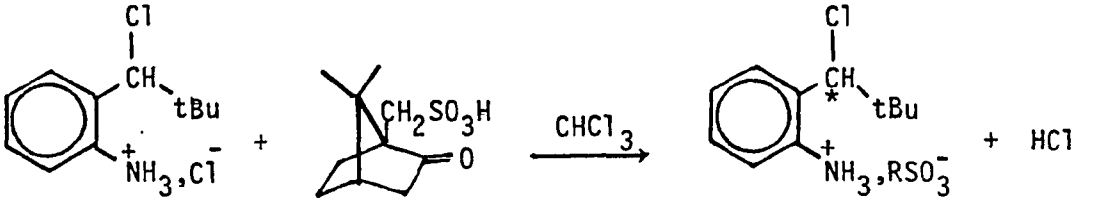
With the generation of a small amount of free aniline, the benzylic position is activated and the formation of a benzylic carbocation is favored. Solvolysis of this carbocation by methanol gives the methoxy derivative.

Chloroform was chosen to be the solvent of resolution because of its non-basicity and because chloranilinium chloride and d-10-camphorsulfonic acid are reasonably soluble in it.

c) Results:

Upon mixing a chloroform solution of VI with a chloroform solution of the resolving acid and chasing the hydrogen chloride with argon, a slowly formed precipitate melting at 170-172°C is obtained. Its IR and NMR spectra are consistent with the structure of the chloroanilinium camphorsulfonate salt XII (see Scheme 15 below). The yield is 47% indicating that one diastereoisomer is preferentially crystallized. Camphorsulfonate salt XII is barely soluble in chloroform, methylene chloride (6.76 mg/ml) and nitromethane (1.3 mg/ml). Because the use of "basic" solvents is prohibited, the finding of a suitable recrystallization solvent is still under study.

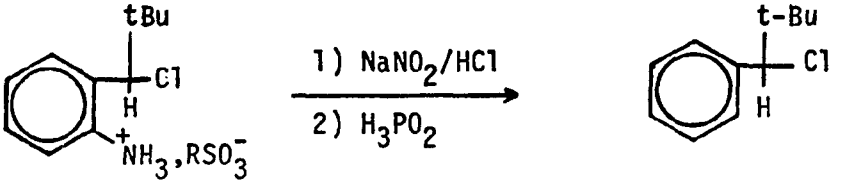
Scheme 15:



VI

XII a & b

Upon diazotization of a sample of XII followed by treatment with hypophosphorous acid, (+)-α-phenyl neopentyl chloride of rotation 81° was obtained. Since (+)-α-phenylneopentyl chloride has the R configuration, diastereomeric camphorsulfonate salt from which a sample of (+)-5 was obtained has also the R configuration at the benzylic carbon:



R-(+)-XIIa R-(+)-5

The specific rotation observed (+81°) for 5 is lower than the 107° value of the carbon tetrachloride/tri-n-butyl phosphine experiment, showing that partial resolution of XII was achieved. However, this result demonstrates the validity of the remote resolving handle approach to the question of the optical purity of α-phenylneopentyl chloride. The finding of a good recrystallization solvent will undoubtedly increase the specific rotation of 5 obtained by this method.

VII. A Suggested Extension for the Synthesis of Chiral α-Phenylneopentyl Chloride.

In our previous study, the o-chloroanilinium chloride VI was preferred over the meta or para isomers because of the proximity of the amino group to the chiral center, increasing the chances of a good resolution. But, the ortho amino group activates greatly the benzylic chlorine (see previous studies) causing difficulties in the resolution

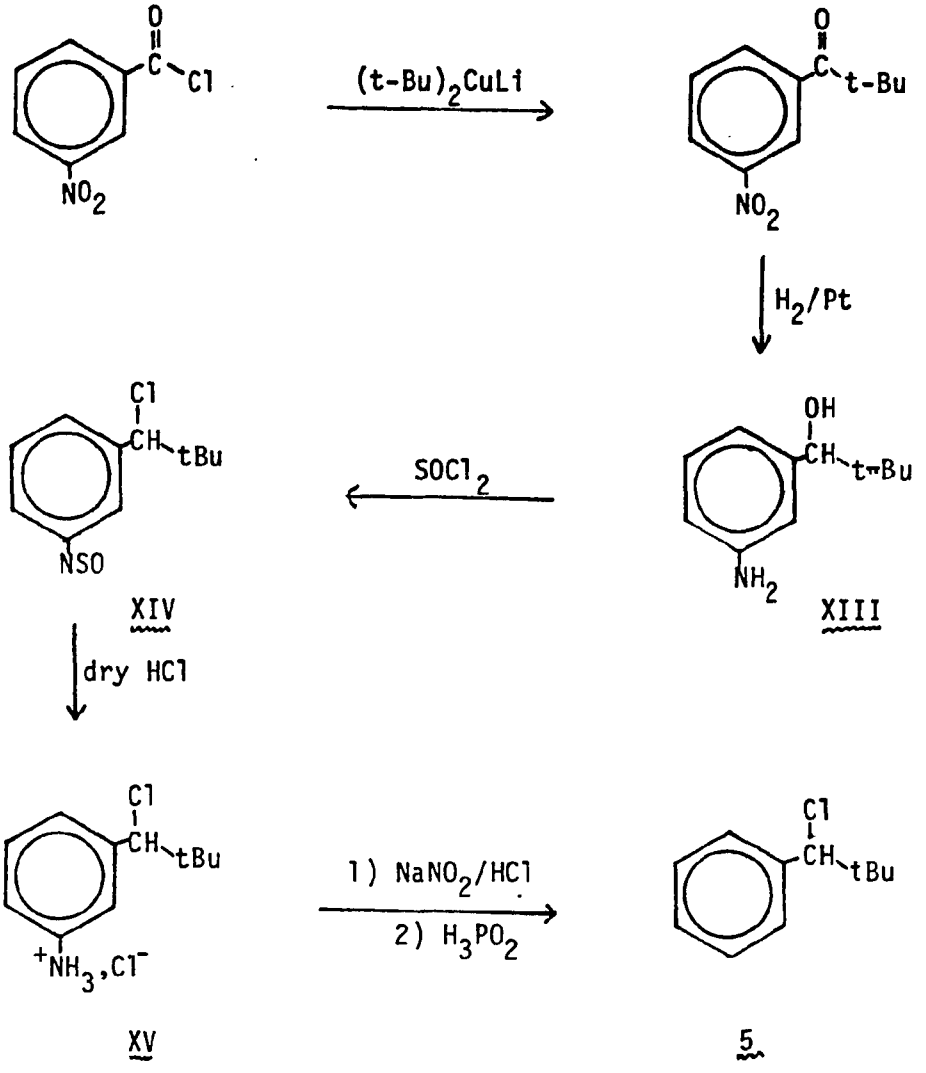
step or in the cleavage of the carbamates. In the meta isomer, the amino function is three carbons away from the chiral center. This situation is not as good as the previous one (ortho isomer) with regard to asymetric induction but resolution can probably be achieved.

The main advantage of the meta isomer over the ortho is that the electronic effects of the amino group on the benzylic chlorine are decreased in the former case. The benzylic chlorine being less activated, this will result in a greater stability of the meta chloro aniline. Also, solvolysis of the benzylic chloride in solvents such as methanol should be minimized.

A. Synthesis of m-Chloroanilinium Chloride XV:

The meta chloroanilinium chloride XV can be synthesized by the sequence of reactions shown in Scheme 16.

Scheme 16:

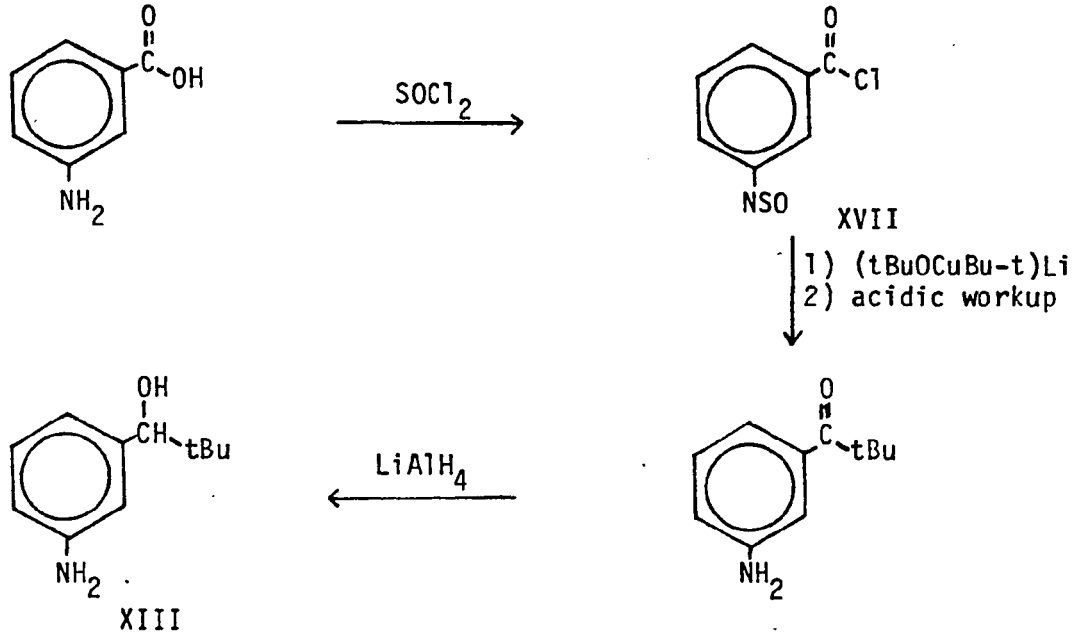


m-Nitrobenzoyl chloride is easily obtained from the corresponding acid. Organocuprates have been used at -78° for selective reaction with the acid chloride portion of molecules containing halo, cyano, acyl, alkoxy, carbonyl groups[52], and nitro groups[53,54]. A significant limitation on the broad utility of these reagents has often been the difficulty in using thermally unstable t-alkyl cuprate. Posner and Whitten[55] proposed the use of mixed cuprates $(ZCuR)^{-}Li^{+}$ in which Z would stabilize the reagent containing a tertiary alkyl group. t-Butyl group has been

transferred using the alkoxy[56] and thioalkoxy[57] t-butyl cuprate. Selective addition of the t-butylmoiety to m-nitrobenzoyl chloride to give m-nitropivalophenone can be achieved by the use of any of these reagents. Catalytic hydrogenation[58] will yield the meta amino alcohol.

An alternate approach to the meta amino alcohol involves selective addition of alkoxy t-butylcuprate to meta-N-sulfinylamino-benzoyl chloride. Acidic workup, followed by neutralization, will give the corresponding m-aminopivalophenone which can be further reduced to

Scheme 17:



the meta amino alcohol. The success of this synthetic scheme depends on the electrophilicity of the sulfur in the NSO group compared to the carbonyl of the acid chloride. N-sulfinyl amines have been shown to react at 0-5°C with organomagnesium and organolithium compounds to yield sulfinamides[44] but the addition of organocuprate to the NSO function has not been studied yet. Because of electronic factors, one can expect the

N-sulfinylamine function to be less reactive than the acid chloride towards organocuprate reagents, specifically if mild reaction conditions are used.

m-Chlorosulfinylamine XIV and m-Chloroanilinium Chloride XV can be easily obtained by the same reactions described in Section VI for the ortho isomer.

B. Resolution of m-Chloroanilinum Chloride XV:

1) The Diasteromeric Salt Approach:

If the free aniline is stable at room temperature, it should be used in the resolution step instead of its salt to eliminate the HCl by-product. In the event of the instability of the free aniline, the HCl by-product can be chased by bubbling argon through the solution or by evaporating the solvent to dryness and recrystallizing the diastereomeric salts. Because of the lower reactivity of the benzylic chlorine, a wider range of solvents is available for resolution. For instance, solvolysis is not expected to occur in methanol as was the case with the ortho isomer. d-10-Camphorsulfonic acid has proven to be a suitable resolving agent for the ortho isomer. It can also be applied to the meta compound.

If resolution cannot be achieved by the above method, binaphthyl phosphoric acid is another possibility. This reagent is known to permit the resolution of a variety of weakly basic amines[59].

2) The Carbamate Route:

Diasteromeric ℓ-menthyl carbamates of XV can also be obtained as described for the ortho isomer. Acidic cleavage will yield the resolved quaternary anilinium chloride enantiomers, because formation of a six-membered ring is not a possiblity anymore.

SUMMARY AND CONCLUSIONS

Several different approaches were applied to the problem of determining the specific rotation of α-phenylneopentyl chloride 5.

Displacement studies of chloride ion from 5 by various nucleophiles (cyanide, hydroxide, amide ions) were unsuccessful. On the other hand, diphenylmethyllithium coupled with a sample of chiral α-t-butylbenzyl chloride 5 of rotation -106.5° at 25°C to yield (R)-(-)-3,3-dimethyl-1,1,2-triphenyl butane of rotation -113°. The significance of this result is that coupling occurred with a minimum of 60% inversion of configuration. It also suggests that a polar nucleophilic displacement process is the predominant reaction pathway.

Production of chiral α-phenylenopentyl chloride by the S_Ni decomposition of a chlorocarbonate obtained by the action of phosgene on optically pure α-phenylneopentyl alcohol under various reaction conditions gave samples of chiral 5 whose specific rotations were substantially higher (+67°, +72°, -77°, -79°) than the literature values obtained with the chlorosulfite ester (+41°).

Application of the trialkylphosphine:carbon tetrachloride reaction to (R)-(+)-α-phenylneopentyl alcohol gave (S)-(-)-α-phenylneopentyl chloride whose specific rotation is 112°. This is the highest rotation ever obtained for 5. Although a greater degree of inversion stereospecificity is observed in the $R_3P:CCl_4$ reaction than retention stereospecificity in the thermal rearrangement of the chlorocarbonate, the exact percentages of optical purities for 5 are still unknown. As a precursor to 5, racemic 1-chloro-(2,2-dimethylpropyl)-o-aminobenzene hydrochloride V has been synthesized by a six-step sequence from anthranilic acid. It was successfully converted to racemic 5 by diazotization followed by treatment with H_3PO_2.

Resolution work on V was carried out by two different pathways. In one of these attempts, diastereoisomeric &-menthyl carbamates were obtained and separated by fractional crystallization. Attempts to cleave them under acidic conditions frustrated resolution by yielding 4-t-butyl-3,1-benzoxazine-2-one XI. The second approach involved the formation of diastereomeric d-10 camphorsulfonate salts XII a & b. Partial resolution was achieved and a sample of (R)-(+)-α-phenylneopentyl chloride of rotation +81° was obtained by diazotization of XIIa followed by reduction with H_3PO_2.

Suggestions have been made for the synthesis of optically pure α-phenylneopentyl chloride from 1-chloro-(2,2-dimethylpropyl)-m-aminobenzene.

EXPERIMENTAL

Solvents:

Benzene (Baker Analyzed Reagent) was dried over sodium and distilled prior to use.

Diethyl ether (Anhydrous, Baker Analyzed Reagent) was refluxed for 24 hours over sodium metal. A small amount of benzophenone was added and the diethyl ether was distilled from the resulting benzophenone ketyl immediately before use.

1,4-Dioxane (Baker Analyzed Reagent) was first dried over calcium hydride for several days and filtered. The dioxane was then refluxed over sodium metal for 24 hours and was distilled prior to use.

Tetrahydrofuran (Baker Analyzed Reagent) was first dried over CaH_2 for several days and filtered. After reflux for 24 hours over sodium metal, a small amount of benzophenone was added. The THF was distilled from the resulting benzophenone ketyl immediately before use.

Toluene (Baker Analyzed Reagent) was dried over sodium and distilled prior to use.

Hexamethylphosphorictriamide (Aldrich Chemical Co.) was predried over molecular sieves (4 Å) for several days, distilled under vacuo, and stored over molecular sieves under argon.

Resolving Agents:

Brucine dihydrate (Aldrich Chemical Co.) m.p. 176-178°C, $[\alpha]_D^{20}$ -79.3° (C = 1.3, C_2H_5OH).

Cinchonine (Aldrich Chemical Co.) m.p. 258-260°C, $[\alpha]_D^{23}$ +228° (C = 0.5, C_2H_5OH).

Cinchonidine (Aldrich Chemical Co.) $[\alpha]_D^{23}$ -106.6° (C = 5.10, C_2H_5OH) m.p. 210-211°C.

d-10-Camphorsulfonic acid, 99% (Aldrich Chemical Co.) m.p. 194°C (dec) $[\alpha]_D^{20}$ +19.9 (C = 2, H_2O).

ℓ-menthol (Aldrich Chemical Co.) m.p. 43-45°C, b.p. 212 $[\alpha]_D^{20}$ = -50°C (C = 10, C_2H_5OH).

Other Reagents:

Aluminum Oxide - 90, 70-230 mesh, neutral, activity stage 1 (Merck) was used in column chromatography.

n-Butyllithium (Alfa Inorganics) was analyzed before use by the double titration method designed by Gilman and Cartlege[60].

tri-n-Butylphosphine (Aldrich Chemical) was used as obtained.

Phosgene gas (Union Carbide Corporation) was used as obtained.

Silica gel - 60, 230-400 mesh (Merck) was used for column chromatography.

Thionyl Chloride (Aldrich Chemical Co.) was used as obtained.

Trimethylsilyliodide (Aldrich Chemical Co.) was used without further purification.

Instruments:

Gas chromatographic analyses were performed using a Hewlett Packard model 5880 instrument equipped with a hydrogen flame ionization detector. Column diameters were 1/8 inch and the lengths were 6 feet. 10% SE-30 on chromosorb W was used for the packing.

NMR spectra were obtained using a Varian T-60 spectrometer. Spectra were obtained as solutions in deuterochloroform.

Infrared spectra were taken using a Perkin-Elmer, model 1320,

spectrophotometer. The infrared spectra of liquids were obtained from the neat liquid between sodium chloride plates. Solid samples were pulverized with KBr using a Wig-L-Bug amagalmater and pressed into discs.

Rotations were observed with a O. E. Rudolph & Sons, Model No. 70, polarimeter.

Elemental analyses were done by Schwarzkopf Laboratories, Woodside, New York.

Thin Layer Chromatographies were performed using F1500 silica gel sheets from Schleicher & Schuell and precoated TLC sheets (silica gel 60 F_{254}, layer thickness 0.2 mm) from E. M. Reagents.

All melting points were obtained using a Mel-Temp Melting Point Apparatus and are uncorrected.

Experimental Conditions:

All reactions involving alkyllithium or Grignard reagents were carried out in flame-dried, argon-filled reaction flasks. Introduction or removal of solvents, alkyl lithium, etc., was accomplished by syringe techniques[61].

Solvents were removed *in vacuo* using a Buchler Rotary Evaporator.

Argon was dried using a Normag Gas Purification Apparatus[62].

The Synthesis of Pivalophenone

A. Reaction of benzonitrile with t-butylmagnesium chloride.

To the Grignard solution, prepared from 1.5 mole of magnesium (36 g) and 1.25 mole of t-butyl chloride (116 g, 138 ml) in 250 ml of anhydrous ether, was added dropwise 1.13 mole of freshly distilled benzonitrile in 100 ml of dry ether. At the end of the addition, the mixture was red. It was poured over cracked ice and hydrolyzed with concentrated sulfuric acid. The solution was extracted with ether, washed with saturated sodium bicarbonate and saturated sodium chloride solutions. The organic layer was dried over sodium sulfate. Evaporation of the ether followed by fractional distillation gave 24.3 g of pure pivalophenone, b.p. 65° (2 mm).

IR: carbonyl band 1675 cm^{-1}

NMR: (neat) δ 1.26 (9H, S), 7.20-7.83 (5H, m)

B. Reaction of phenyllithium with the lithium salt of pivalic acid.

a) Synthesis of phenyl lithium.

20 g of a 30% suspension of lithium in petroleum (~ 0.8 mole) were placed in a flask with 100 ml of dry ether under an argon atmosphere. To this suspension was added 47.1 g (0.3 mole) of bromobenzene in 70 ml of dry ether. After the addition was completed, the mixture was refluxed for two hours.

b) Synthesis of the acid salt.

To a solution of 0.3 mole (30.6 g) of neopentanoic acid dissolved in 100 ml of ether was added dropwise an hexane solution of butyl lithium (0.3 mole). A white precipitate was formed.

c) The phenyllithium prepared previously was added to the ether suspension of the acid salt. The mixture was refluxed for 24

hours, cooled, poured over a mixture of ice and sulfuric acid. After washing with 2 x 250 ml of 10% NaOH solution, the organic layer was dried over sodium sulfate. Removal of the ether followed by distillation in vacuo gave 16.3 g of ketone (b.p. 77-84°C (7 mm), 24% yield).

C. Reaction of phenylmagnesium bromide with pivalonitrile.

a) Synthesis of pivaloyl chloride[63].

102 g of neopentanoic acid (1.00 mole) were added portionwise to 143 g (88 ml, 1.2 mole) of thionyl chloride with stirring. After stirring overnight at room temperature followed by one hour refluxing, simple distillation gave 91.5 g of pivaloyl choride (b.p. 100-105°C, 75% yield) lit.[63] b.p. 103-104°C.

b) Synthesis of pivalacetamide.

In a 500-ml flask, fitted with a magnetic stirrer and cooled in an ice-salt bath, was placed 250 ml of concentrated ammonium hydroxide. The acid chloride (91.5 g, 0.76 mole) was added dropwise. After the addition was completed, stirring was continued overnight at room temperature. The crystals were filtered, washed with water. [55.1 g, m.p. 149-152°C, 72% yield.] Recrystallization from ethanol/water improved the melting point to 151-153°C. Lit.[64] m.p.: 154-157°C.

IR: NH_2 band: 3400, 3210 cm^{-1}, carbonyl band: 1655 cm^{-1}

c) Synthesis of pivalonitrile.

66.6 g of pivalacetamide (0.665 mole) were refluxed with 145 ml of thionyl chloride for 22 hours. After this time, the excess $SOCl_2$ was removed on the rotary evaporator, and the mixture was poured onto cracked ice and extracted with ether. The organic layer was washed with water and saturated sodium bicarbonate solution and dried over sodium sulfate. Distillation gave 28.7 g (55%) of

pivalonitrile, b.p. 104-105°C. Lit.[64] b.p.: 105-106°C.

IR: C≡N band: 2242 cm^{-1}

d) Synthesis of pivalophenone[65].

The Grignard reagent was prepared from 0.35 mole of magnesium (8.4 g), 0.36 mole of bromobenzene (56.5 g) and 150 ml of dry ether. Without cooling, pivalonitrile (28.7 g, 0.346 mole) in 40 ml of dry ether was added rapidly to the Grignard solution. A slight rise in temperature occurred. The mixture was refluxed for 3 days, during which time the crystalline imine complex separated. It was poured onto cracked ice and concentrated HCl and allowed to stand 4 hours for complete hydrolysis. The ketone was extracted twice with ether. The combined organic layers were washed with water and saturated sodium bicarbonate, then dried over sodium sulfate. Distillation in vacuo gave 43.5 g of pivalophenone (78% yield), b.p. 112-113°C (20.5 mm). Lit.[65] b.p.: 222-224°C (750 mm).

α-Phenyl Neopentyl Alcohol from Pivalophenone[66].

Pivalophenone (40 g, 0.245 mole) was added dropwise over a period of one hour to a stirred suspension of 0.246 mole of lithium aluminum hydride in 150 ml of dry ether. After the addition was completed, the reaction mixture was heated under gentle reflux for 3 hours 20 minutes. At the end of this time, the mixture was cooled and sufficient water was added to decompose the unreacted hydride. The reaction mixture was neutralized with hydrochloric acid. The ether layer was removed and the aqueous solution was extracted with 3 x 100 ml of ether. The ethereal solutions were combined and washed with a saturated solution of sodium bicarbonate, then with water, and dried over sodium sulfate. Distillation in vacuo gave 35.9 g of α-phenylneopentyl alcohol (90%

yield) b.p. 84-87°C (3 mm), m.p. 38-40°C. Lit.[66] m.p.: 45°C.

The Resolution of α-Phenylneopentyl Alcohol[1]

α-phenylneopentyl alcohol was resolved via its acid phtalate (115 g, 0.368 mole) with cinchonidine (107.5 g, 0.366 mole) according to the literature directions. There was obtained 17.0 g of (+)-α-phenylneopentyl alcohol (56% yield) m.p. 54-55°C, $[\alpha]_D^{24}$ = +30.1°C (0.0441 g/ml, acetone), e.e. 95%, and 24 g of (-)-α-phenylneopentyl alcohol, m.p. 40-42°C, $[\alpha]_D^{23}$ = -20.1°C (0.0409 g/ml, acetone), e.e. 66%.

The Synthesis of Racemic α-Phenylneopentyl Chloride with Thionyl Chloride from α-Phenylneopentyl Alcohol[1]

0.149 mole (24.4 g) of racemic α-phenylneopentyl alcohol and 0.372 mole (45 g) of thionyl chloride yielded 18.3 g of α-phenylneopentyl chloride, b.p. 75-76°C (6 mm), 75% yield. Lit.[1] b.p. 89.5-90.5°C (6.7 mm).

Synthesis of α-tert-Butylphenylacetic Acid

The title acid (2-Phenyl-3,3-dimethylbutanoic Acid) was synthesized from t-butylphenylcarbinyl chloride (α-phenylneopentyl chloride, 115 g, 0.63 mole) by reaction with magnesium (18 g, 0.75 mole) in THF followed by carbonation in a Parr apparatus according to the literature directions[67]. The yield of acid after a recrystallization from petroleum ether was 65 g (54%, m.p. 103-106°C).

Resolution of α-t-Butylphenylacetic Acid[27]

α-tert-Butylphenylacetic Acid (69.2 g, 0.36 mole) was mixed with 107.7 g of brucine dihydrate (.25 mole) in warm methanol (1.9 L). Methanol (1 L) was distilled and 115 g of a salt, m.p. 96-106°C was

obtained. Two recrystallizations from methanol gave 70.5 g of salt (m.p. 112-130°C, $[\alpha]_D^{21}$ = -56.52°C,[$CHCl_3$, 0.0559]).

The foregoing salt was decomposed with 2 N HCl and the resulting carboxylic acid was recrystallized from hexane to give 19.8 g of (-) acid, m.p. 141-142°C, $[\alpha]_D^{21}$ = -61.45°, ($CHCl_3$, 0.0309); lit.[27] m.p. 141-142°C, $[\alpha]_D^{25}$ = -62.9°, ($CHCl_3$, 5).

The mother liquor of the first crop of resolution was concentrated and acidified with HCl to give 35 g of (+) acid which was reacted with cinchonine (54 g, 0.18 mole) in 770 mL of warm methanol to which 250 ml of hot water was added. The salt, which deposited on cooling, was recrystallized twice from methanol/water (5:2) to give 29.4 g of solid, m.p. 194-200°C, $[\alpha]_D^{21}$ = +143.6°, ($CHCl_3$, 0.0424). Hydrolysis of this (+) salt by 2 N HCl, followed by recrystallization from hexane, gave 8.1 g of (+)-α-tert-butylphenylacetic acid, m.p. 140-141°, $[\alpha]_D^{28}$ = +62.6°, ($CHCl_3$, .0335 g/ml). The best lit. m.p. is 140.8-141.5°C .[27]

Preparation of (R)-(-)-Methyl-α-tert-Butylphenylacetate

Treatment of 18.7 g of (-)-α-tert-butylphenylacetic acid (0.097 mole, m.p. 141-142°C, $[\alpha]_D^{21}$ = -61.45°, $CHCl_3$, 0.0309) with 0.2 mole of diazomethane (from N-nitroso-N-methyl-p-toluene sulfonamide, Diazald) produced 16.7 g of (R)-(-)-methyl-α-t-butylphenylacetate (83%, m.p. 31-32°C). Recrystallization from hexane at -20°C gave 15.9 g of purified ester (m.p. 33-34°C, $[\alpha]_D^{21}$ = -50.12°, [$CHCl_3$, 0.0393]).

H NMR: ($CDCl_3$) δ 1.0 (s, 9H), 3.5 (s, 1H), 3.6 (s, 3H), 7.26-7.6 (m, 5H).

IR: 1735 cm^{-1}

Analysis: $C_{13}H_{18}O_2$ Calcd: %C, 75.69; %H, 8.79

Found: %C, 75.83; %H, 8.76

75.56; %H, 8.77

Synthesis of (R)-(-)1,1,2-Triphenyl-3,3-Dimethylbutanol:

Phenylmagnesium bromide was prepared from triply sublimed magnesium (2.33 g, 0.097 mol) and 13.75 g of bromobenzene (.0875 mol) in THF. The R(-) ester (3 g, 0.0145 mol from the sample described above) in 30 ml of THF was added dropwise to the phenylmagnesium bromide, was refluxed for 3 hours, was stirred overnight, and was hydrolyzed with saturated NH_4Cl. Extraction into ether followed by drying ($MgSO_4$), filtration and distillation of the solvent gave 4.2 g of a solid which was recrystallized from methanol to give 1.7 g of the title alcohol (31.2%, m.p. 168-171°, $[\alpha]_D^{21}$ = -31.6,[$CHCl_3$, 0.0243]). Further purification by recrystallization improved the rotation to $[\alpha]_D^{21}$ = -32.8°, ($CHCl_3$, 0.0201).

NMR: ($CDCl_3$) δ, 0.85 (s, 9H), 2.81 (s, 1H), 4.00 (s, 1H), 6.8-8.13 (m, 5H).

IR: 3610 & 3440 cm^{-1}

Analysis: $C_{24}H_{26}O$ Calcd: %C, 87.23; %H, 7.93
Found: %C, 86.70; %H, 7.84

Synthesis of (S)-(-)1,1,2-Triphenyl-3,3-Dimethylbutane:

To 2.113 g (0.0064 mol) of the foregoing purified R(-) alcohol, 1.22 g of absolute ethanol, 20 ml of dry THF and approximately 40 ml of liquid ammonia were added 0.882 g of sodium (.0384 mol) in small pieces. The solution acquired a transient blue color; stirring was continued overnight at 25°C. The residue was treated with crushed ice, extracted into ether, dried over $MgSO_4$, and the ether was evaporated under reduced pressure. The crude solid was recrystallized from methanol to give 0.9 g of crystals (m.p. 136-140°C, $[\alpha]_D^{21}$ = -156.2°, CCl_4, 0.03067).

Two successive recrystallizations from methanol did not completely purify the product. Column chromatography on alumina using hexane: benzene, 99:1 gave 0.160 g of purified hydrocarbon, m.p. 149-150°, $[\alpha]_D^{21}$ = -188.6°, (CCl_4, 0.01613).

NMR: ($CDCl_3$) δ, 0.77 (s, 1H), 3.65, 4.6 (q, J_{AB} = 11 Hz), 6.8-7.7 (m, 15H).

Analysis: $C_{24}H_{26}$ Calcd: %C, 91.67; %H, 8.33
Found: %C, 91.13; %H, 8.44

Synthesis of Racemic 1,1,2-Triphenyl-3,3-Dimethylbutanol:

To 1.45 g of magnesium (0.06 mol) in 10 mL of THF was added 9.2 g of α-phenylneopentyl chloride (0.050 mol) in 10 mL THF. After the addition was completed, the mixture was refluxed for 30 minutes and 5.5 g of benzophenone (0.030 mol) was added. At the beginning of the addition, a red color appeared, followed by a blue color which slowly disappeared. The reaction was refluxed for 2 hours, stood at 25°C for 19 hours, and hydrolyzed. After the usual workup, 15.4 g of a liquid was obtained. Crystallization at -20°C from petroleum ether gave 5.3 g of crude racemic alcohol, m.p. 142-146°C (53.5%). Recrystallization from methanol improved the m.p. to 148-152°C. The NMR spectrum of this alcohol was indistinguishable from that for the R(-) alcohol.

The Synthesis of the Oxime of Pivalophenone:

55.6 g of hydroxylamine hydrochloride (0.8 mol) were dissolved in 100 ml of water. To that solution was added 150 ml of a 5 M sodium hydroxide solution followed by 95.3 g (0.59 mol) of pivalophenone. Enough ethanol was added to obtain a clear solution which was warmed on a steam bath for 30 minutes. Crystals deposited upon cooling. They

were filtered (100 g, m.p. 160-164°C) and recrystallized from ethanol/water (m.p. 162-166°C). Lit.[68] m.p. 165-166°C.

The Synthesis of (±)-α-Phenylneopentylamine[68]:

To a solution of 166.3 g (0.94 mol) of the oxime of pivalophenone in 900 ml of absolute ethanol was added, in small portions, 241 g (10.4 mol) of sodium. After the addition was completed, the mixture was cooled to room temperature, water was added, and the ethanol distilled. The residue was extracted with ether. The mother liquors were extracted twice with ether. The combined organic layers were washed with water, and dried over sodium sulfate. The ether was removed on the rotary evaporator. Distillation in vacuo of the residue gave 118.6 g of a colorless liquid (b.p. 84-85°C/4.5 mm, 77% yield). Lit.[68] b.p. 115-115.5°C, 122 mm, 95% yield.

IR (cm^{-1}): NH_2 bands 3320, 3390

NMR (ppm) neat: 0.85 (s, 9H), 3.55 (s, 1H), 7.18 (m, 5H)

The Synthesis of α-Phenylneopentyl Tosylate[1]:

To 16.4 g (0.100 mol) of α-phenylneopentyl alcohol in 100 ml of anhydrous pyridine at 0°C was added 19.1 g (0.100 mol) of tosyl chloride. The reaction mixture was kept at 4°C for 3 days. A solid, presumably pyridinium chloride, was filtered. The solution was extracted with CCl_4, washed with water. The organic layer was dried over potassium carbonate. Removal of CCl_4 on the rotary evaporator followed by addition of petroleum ether and storage at -15°C gave 5.2 g (16%) of α-phenylneopentyltosylate, m.p. 65-70°C.

NMR (ppm): 0.83 (s, 9H), 2.3 (s, 3H), 5.1 (s, 1H), 6.95-7.60 (m, 9H)

Lit.[1] m.p. 75-76°C.

The Attempted Synthesis of α-Phenylneopentyl Chloride from α-Phenyl Neopentyl Tosylate:

Run 1: 2.0 g (6.2 mmol) of tosylate, 265 mg (6.25 mmol) of lithium chloride in 20 ml of dry HMPA were heated at 90°C under an argon atmosphere. After 4 days at this temperature, the starting material was recovered unchanged.

Run 2: 1.2 g of α-phenylneopentyl tosylate (0.0038 mol), 0.30 g of sodium chloride (0.050 mol), a catalytic amount of 18-crown-6 (100 mg) in 15 ml of dry HMPA were heated at 60°C under an argon atmosphere for 24 hours. After extraction, the tosylate was recovered unchanged.

The Attempted Synthesis of α-Phenylneopentyl Cyanide From α-Phenylneopentyl Chloride:

4.0 g of α-phenylneopentyl chloride (0.022 mol), 1.62 g (0.033 mol) of sodium cyanide, 10 drops of water, and 20 ml of HMPA were heated at 110°C for 3 days. GC analysis showed the presence of a new compound (10%) presumably the cyanide. After 7 days, there was no improvement.

The Attempted Synthesis of α-Phenylneopentyl Alcohol From α-Phenylneopentyl Chloride:

4.0 g (0.022 mol) of α-phenylneopentyl chloride, 1.9 g (0.033 mol) of potassium hydroxide and 20 ml of HMPA were heated at 70°C for 3 days under an argon atmosphere. After extraction, the starting material was recovered unchanged.

The Attempted Synthesis of α-Phenylneopentyl Amine from α-Phenylneopentyl Chloride:

Run 1: To a suspension of sodium amide (1.9 g, 0.050 mol) in 15 ml of dry THF was added 5.0 g (0.027 mol) of α-phenylneopentyl chloride in

20 ml of anhydrous THF. The mixture was refluxed for 4 hours. Extraction gave the starting material.

Run 2: To a suspension of sodium amide (1.9 g, 0.050 mol), 1 g of 18-crown-6 in 15 ml of dry THF was added a solution of α-phenylneopentyl chloride (5.0 g, 0.027 mol) in 20 ml of dry THF. The reaction mixture was refluxed for 19 hours and then extracted. The starting material was recovered unchanged.

The Reaction of Diphenylmethyllithium with (-)-α-Phenylneopentyl Chloride

(-)-α-Phenylneopentyl Chloride (2.057 g, 0.0113 mole, $[\alpha]_D^{25}$ = -106.8° [THF, 0.1119 g/mol]) in 25 ml of THF was added dropwise over a period of 15 minutes to diphenylmethyllithium (0.0113 mole) in 20 ml of THF at room temperature. The mixture was allowed to stir overnight and 50 ml of ether was added. The solution was washed with 2 x 25 ml of saturated ammonium chloride solution and was dried over sodium sulfate. Evaporation of the solvent followed by addition of 10 ml of hexane did not give symmetrical tetraphenylethane. Removal of the hexane yielded 3.781 g of oil. VPC analysis of this oil indicated 27% of unreacted α-phenylneopentyl chloride, 33% of diphenylmethane, 2.1% and 3.7% of (dℓ) and meso-α,α'-ditert-butylbibenzyl and 30% of 1,1,2-triphenyl-3,3-dimethylbutane. Column chromatography of the mixture on alumina yielded 884 mg (34%) of (R)-(-)-1,1,2-triphenyl-3,3-dimethylbutane which was recrystallized from methanol.

m.p. 135-139°, $[\alpha]_D^{26}$ = -113.3° (0.0128 g/ml, CCl_4). The IR and NMR spectra of this sample were superimposable with those of an authentic sample of the same isomer prepared as shown in the three-step sequence of Scheme 3.

Synthesis and Thermal Decomposition of Optically Active α-Phenylneopentyl-chlorocarbonate:

To a solution of 6.9 g of R(+)-α-phenylneopentyl alcohol (0.0421 mol, $[\alpha]_D^{21}$ = +31.1°, [0.0241 g/ml, acetone]) in 80 ml of anhydrous ether was added 0.0429 mol of butyllithium in hexane. After stirring overnight at 25°C, the alkoxide solution was added to a solution of phosgene (9.1 g, 0.091 mol) in 100 ml of dry ether at -60°C. The mixture was warmed slowly to room temperature, became turbid, and was filtered to separate LiCl. Evaporation of the solvent left 8.8 g of a yellow liquid that was identified as α-phenylneopentylchlorocarbonate (92% yield):

NMR: (neat) 0.87 δ (s, 9H), 5.51 (s, 1H), 7.26 (s, 5H)

IR: $\nu_{c=o}$ = 1780 cm^{-1}. $[\alpha]_D^{21}$ = +31.6°, (0.0474 g/ml, CCl_4).

The attempt to distil the crude chlorocarbonate gave a colorless liquid, b.p. 39-41°C, 0.06 torr, and b.p. 47-50°C, 0.2 torr, which proved to be 46.5% chlorocarbonate and 53.5% (+)5 by NMR analysis. Warming of this sample of chlorocarbonate at 95°C completed the decomposition to yield crude (R)(+)-α-phenylneopentyl chloride (3.7 g, 48%, $[\alpha]_D^{22}$ = +67.0°, [0.0248 g/ml THF]). The NMR spectrum was identical to that of a racemic sample of α-phenylneopentyl chloride.

Run II: A comparably sized preparation produced 10.1 g of α-phenyl-neopentylchlorocarbonate, 90%, $[\alpha]_D^{20}$ = +32.3°, (.05965 g/ml CCl_4). Decomposition by heating in the absence of solvent at 100°C for 2 hours gave 4.7 g of R-(+)-α-phenylneopentyl chloride $[\alpha]_D^{22}$ = +72.0°, (0.08943 g/ml, THF) $[n]_D^{20}$ = 1.5130.

Analysis: $C_{11}H_{15}Cl$ Calcd: %C, 72.37 %H, 8.28

Found: %C, 71.92 %H, 8.07

Run III: 10.0 g of (S)-(-)-α-phenylneopentyl alcohol (0.0609 mol, $[\alpha]_D^{23}$ = -20.1°, [0.0409 g/ml, acetone], 66% optical purity) produced 12.9 g of (S)-(-)-α-phenylneopentyl chlorocarbonate (93% yield, $[\alpha]_D^{25}$ = -24.0°, [0.05079 g/ml, CCl_4]) as described in Run I. Decomposition in boiling dioxane (100 ml, one hour), followed by distillation of the dioxane and distillation in vacuo yielded 7.0 g of (R)-(-)-α-phenylneopentyl chloride (63% yield, $[\alpha]_D^{25}$ = -51.1°, [0.11925 g/ml, THF], b.p. 70-75°C at 3 mm). The NMR spectrum of this sample was identical with the NMR of an authentic sample of (±)-α-phenylneopentyl chloride.

Run IV: (-)-α-Phenylneopentyl chlorocarbonate was prepared as described in Run I. After standing at room temperature for 2 days, the reaction mixture was cooled to -60°C before filtration to separate lithium chloride. The cooling should minimize the amount of lithium chloride dissolved in the ether solution of chlorcarbonate. 6.0 g (0.0265 mol) of (-)-α-phenylneopentyl chlorocarbonate ($[\alpha]_D^{24}$ = -24.2°, [0.06482 g/ml, CCl_4], 66% e.e.) were dissolved in 50 ml of dry dioxane (0.53 M solution) and refluxed for one hour. Distillation of the dioxane at atmospheric pressure followed by distillation in vacuo of the residue yielded 3.1 g of (R)-(-)-α-phenylneopentyl chloride, b.p. 83-84°C/6 mm, 64% yield, $[\alpha]_D^{24}$ = -52.4°, (0.12432 g/ml, THF).

Run V: 6.5 g (0.0287 mol) of (-)-α-phenylneopentyl chlorocarbonate ($[\alpha]_D^{24}$ = -24.2°, [0.06482 g/ml, CCl_4], 66% e.e.) prepared in Run IV were dissolved in 50 ml of dry toluene (0.57 M solution) and refluxed for one hour. Distillation of the toluene at atmospheric pressure followed by distillation in vacuo of the residue yielded 3.3 g of (-)-α-phenylneopentyl chloride, b.p. 80-85°C (7 mm) 63% yield, $[\alpha]_D^{24}$ = -35.7°, (0.08478 g/ml, THF).

(S)-(-)-α-Phenylneopentyl Chloride from R-(+)-α-Phenylneopentyl Alcohol. Tributylphosphine Experiments.

Run I: To a magnetically stirred solution of R-(+)-α-phenylneopentyl alcohol (762.4 mg, 4.65 mmol, m.p. 55-56°C, $[\alpha]_D^{21} = \overset{+}{+}31.6°$, [acetone, 0.03757 g/ml]) in 9.3 ml of carbon tetrachloride was added 8.7 mmol of tributylphosphine (2.2 ml). An exothermic reaction resulted. The reaction mixture was refluxed overnight. The solvent was evaporated and the residual oil was passed through alumina with 80:20 petroleum ether/benzene as the eluent. There was obtained 416.9 mg (49%) of S-(-)-α-phenylneopentyl chloride $[\alpha]_D^{25} = -107.7°C$ (0.03565 g/ml, THF). The NMR of this compound was superimposable with that of an authentic sample of racemic α-phenylneopentyl chloride.

Run II: To a magnetically stirred solution of R-(+)-α-phenylneopentyl alcohol (5.0 g, 30.5 mmol, m.p. 54-55°C, $[\alpha]_D^{24} = +30.1°$, [0.0441 g/ml, acetone]) in 61 ml of carbon tetrachloride was added tri-n-butylphosphine (12.4 ml, 10.0 g, 49.3 mmol). An exothermic reaction resulted. The reaction mixture was refluxed for 49 hours. The benzene was evaporated and the residue passed through alumina (eluent: 80:20 petroleum ether/benzene). Evaporation of the solvent followed by distillation in vacuo yielded 3.02 g of liquid (54% yield), b.p. 84-85°C (7 mm), $[\alpha]_D^{25} = -106.8°$, (0.1119 g/ml, THF).

Synthesis of Acetylanthranil (I):

Acetylanthranil (244 g, b.p. 144-145°C at 12 mm, m.p. 78-80°C) was prepared from 2 mol of anthranilic acid (274 g) and 6 mol of acetic anhydride (618 g, 580 ml) according to the literature directions[69,70].

Synthesis of α-(o-Acetamidophenyl)-neopentyl Alcohol: II

To the Grignard reagent formed by the reaction of 1.65 mole of t-butylchloride (152.5 g, 180 ml) and 2.0 moles of magnesium (48 g) in 300 ml of dry ether was added dropwise a solution of 86.2 g (0.53 mol) of acetylanthranil in 350 ml of dry benzene. Stirring with a mechanical stirrer was continued for 36 hours. At the end of this time, the reaction mixture was hydrolyzed with ice/concentrated hydrochloric acid and extracted with 2 x 250 ml of ether. The ether layer was washed once with 250 ml of water, followed by 3 x 250 ml of 1 N NaOH and 500 ml of water and dried over magnesium sulfate. Evaporation of the solvent gave 82.4 g of crystals, m.p. 120-122°C, 70% yield. Recrystallization from benzene-petroleum ether brought the melting point to 121-123°C.

IR: cm^{-1} 3400; 3300; 1660

NMR: (ppm) 0.86 (s, 9H), 1.91 (s, 3H), 4.40 (1H, s),
4.73 (1H, s), 6.90-7.25 (m, 3H),
8.01 (1H, d, J - 7Hz), 9.91 (s, 1H)

Analysis: C & H: calcd: %C, 70.56 %H, 8.65 %N, 6.33
found: %C, 70.44 %H, 8.52 %N, 6.26

Synthesis of α-(o-Aminophenyl)-neopentyl Alcohol (III):

A mixture of 94.7 g of amide(II) (0.43 mol) and 150 ml of Claisen's alkali (50.7 g, 0.903 mol of KOH in 37 ml of H_2O completed to 150 ml with methanol) was refluxed for 23 hours. At the end of this time, the reaction mixture was cooled, extracted twice with ether. The ether extracts were washed with water and brine and dried over potassium carbonate. Removal of the solvent followed by recrystallization of the solid from benzene/petroleum ether gave 70.6 g of crystals, m.p. 74-75°C, 92% yield.

IR: cm^{-1} 3424; 3421; 3270 (OH and NH_2)

NMR: ppm 0.93 (s, 9H), 3.53 (broad, 3H), 4.38 (s, 1H), 6.50-7.33 (m, 4H)

Analysis: C & H: Calcd: %C, 73.70 %H, 9.56 %N, 7.81

Found: %C, 73.55 %H, 9.45 %N, 7.56

Synthesis of the Quaternary Ammonium Salt of α-(o-Aminophenyl)neopentyl Alcohol III. HCl:

5.3 g (0.0296 mol) of aminoalcohol(III) were dissolved in 20 ml of dry ether. Dry HCl was bubbled through the solution for one minute. A white precipitate (6.2 g, 97% yield, m.p. 159-160°C) was formed and filtered.

IR: cm^{-1} 3460; 3300; 3000; 1480

NMR: ppm (d_6 - DMSO) 0.88 (s, 9H), 4.68 (s, 1H), 7.36 (m, 4H)

Synthesis of α-(o-N-Sulfinylaminophenyl)-neopentyl Chloride V:

To a suspension of 10.8 g of quaternary ammonium salt V (0.050 mol) in 100 ml of dry benzene was added dropwise 20 ml of thionyl chloride (0.274 mol) in 60 ml of dry benzene. After the addition was completed, the mixture was refluxed for 23 hours. Benzene and excess thionyl chloride were evaporated. Distillation in vacuo of the residue gave 11.44 g of an orange liquid, b.p. 126-128°C (3 mm), 94% yield.

IR: cm^{-1} 1170 NSO band

NMR: ppm 1.05 (s, 9H), 5.90 (s, 1H), 7.43-8.17 (m, 3H), 8.77-8.97 (m, 1H)

Chlorosulfinyl amine V can also be made directly from amino alcohol III in comparable yield.

Synthesis of the Quaternary Ammonium Salt of α-[o-Aminophenyl]neopentyl Chloride VI from Sulfinylamine V:

Dry HCl was passed for 4 hours through a solution of chlorosulfinylamine V (48.1 g, 0.197 mol) in 250 ml of dry ether. The precipitate was washed with dry ether and 43.5 g of solid (m.p. 158-160°C, 94% yield) were collected.

IR: cm^{-1} 2900 broad NH_3^+

NMR: ppm 1.13 (s, 9H), 5.48 (s, 1H), 7.27-7.87 (m, 4H), 10.8 (broad, 3H)

Synthesis of (±)-α-Phenylneopentyl Chloride from the Racemic Quaternary Ammonium Chloride Salt of α-(o-Aminophenyl)-neopentyl Chloride:

To a suspension of 661 mg (2.82 mmol) of chloroanilinium chloride in 4 ml of concentrated HCl and 2 ml of water at -5°C were added 758 mg of sodium nitrite in 8 ml of water. The reaction mixture turned orange. To the solution were added 18 ml of 50% hypophosphorous acid. Stirring was continued at 0°C for 3 hours. The reaction mixture was extracted with ether, washed with sodium bicarbonate, dried over sodium sulfate, and evaporated to give 429 mg of an oil (83%) whose IR and NMR spectra were superimposable with those of an authentic sample of racemic α-phenylneopentyl chloride.

Synthesis of α-(o-Isocyanatophenyl)-neopentyl Chloride VII:

Run I: Through a suspension of quaternary ammonium salt VI (9.9 g, 0.042 mol) in 200 ml of spectroscopic grade toluene, was bubbled phosgene (20.6 g, 0.21 mol). The reaction mixture was refluxed until all solid had disappeared (1 hour). The toluene was distilled and the residue distilled in vacuo to yield 8.33 g of isocyanate [b.p.

98-104°C (1.5 mm), 89% yield].

IR: cm^{-1} 2270 NCO band

NMR: ppm 1.02 (s, 9H), 4.98 (s, 1H), 6.72-7.08 (m, 3H), 7.33-7.55 (m, 1H).

Run II: 0.356 mole (83.3 g) of quaternary ammonium salt VII in 1 liter of spectroscopic grade toluene and 0.66 mole of phosgene yielded 71.5 g of the isocyanate, b.p. 130-132°C (5 mm), 90% yield.

Synthesis and Resolution of Diastereomeric ℓ-Menthylcarbamates of VII:

Run I: 5.6 g (0.037 mol) of ℓ-menthol and 8.3 g (0.037 mol) of isocyanate VII in 80 ml of benzene were refluxed for 46 hours. At the end of that time, the benzene was evaporated and the residual viscous oil was crystallized from 80 ml of hexane at 0°C. There was obtained 8.2 g of solid, m.p. 118-140°C. Two successive recrystallizations from hexane afforded 1.7 g of crystals melting at 145-147°C, $[\alpha]_D^{29}$ = -16.1° (benzene, 0.06764 g/ml).

The mother liquors of the first crystallization were evaporated and recrystallized from hexane to yield 2.0 g of crystals, m.p. 123-127°C, $[\alpha]_D^{27}$ = -71.0° (benzene, 0.0545 g/ml).

Run II: 50 g of ℓ-menthol (0.320 mole) and 71.5 g of isocyanate VII (0.320 mole) in 500 ml of benzene were refluxed for 39 hours. Crystallization from benzene/hexane followed by recrystallization gave 17.1 g of solid (28% yield, m.p. 143-145°C, $[\alpha]_D^{26}$ = -12.8° [0.05642 g/ml, benzene]).

IR: (cm^{-1}): NH band 3290 cm^{-1}; C=O band: 1690 cm^{-1}

NMR: 0.67 (3H, d J $4H_3$), 0.83 (6H, d J $6H_3$), 0.93 (9H, s), 4.67 (1H, m), 5.03 (1H, s), 6.43 (1H, broad), 6.93-7.76 (4H, m)

The mother liquors of the first crystallization were evaporated and recrystallized twice from hexane to yield 10.521 g of crystals (17% yield, m.p. 121-124°C, $[\alpha]_D^{25}$ = -72.2° [0.0324 g/ml, benzene]).

IR: NH band: 3300 cm^{-1}; C=O band: 1690 cm^{-1}

NMR: 0.78 (3H, d, J 4Hz), 0.95 (6H, d, J $5H_3$), 1.02 (9H, s), 4.67 (1H, m), 5.05 (1H, s), 6.38 (1H, broad), 6.88-7.68 (4H, m)

Synthesis of α-(o-Acetamidophenyl)-neopentyl Chloride VIII:

5.0 g of α-(o-Acetamidophenyl)-neopentyl alcohol (0.0226 mole) were dissolved in 20 ml of methylene chloride. To the solution was slowly added 0.0230 mole of pyridine (1.82 g, 1.86 ml) followed by 0.0230 mole of thionyl chloride (2.74 g, 1.62 ml). The reaction mixture was refluxed for 3½ hours. After cooling, it was extracted with CH_2Cl_2, washed with water, dried over magnesium sulfate. The solvent was evaporated to give a solid which, upon recrystallization from benzene/petroleum ether, yielded 3.4 g of crystals (63%), m.p. 144-146°.

IR: amide function 1660 cm^{-1} (C=O)

NMR: (ppm) 0.98 (9H,s), 2.06 (3H,s), 5.11 (1H,s), 7.0-7.6 (4H,m), 8.20 (1H,s)

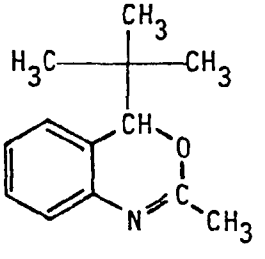
Analysis:	calcd.	%C 65.13	%H 7.57	%Cl 14.79	%N 5.84
	found	64.89	7.68	14.81	5.73

Reaction of α-(o-Acetamidophenyl)-neopentyl Alcohol with Concentrated Hydrochloric Acid at Room Temperature:

5.0 g (0.0226 mole) of the alcohol amide II were dissolved in 20 ml of concentrated hydrochloric acid and left at room temperature for 1½ hours. After that time, 25 ml of water was added and the solution was made basic with sodium hydroxide. It was extracted twice with ether, washed with water, dried over sodium sulfate. The ether was removed on the rotary evaporator. The resulting liquid was distilled in vacuo to give 3.2 g of an oil, b.p. 123-125° (7 mm), 65% yield-IR and NMR spectra of this compound are consistent with the structure of 4-t-butyl-2-methyl-3,1-benzoxazine. Sodium fusion test on a sample indicates loss of the chlorine.

IR: C=N 1640 cm^{-1}

NMR: (ppm) 0.83 (9H,s), 2.01 (3H,s), 4.76 (1H,s), 6.70-7.10 (4H,m)



4-t-butyl-2-methyl-3,1-benzoxazine

VII

Reaction of α-(o-Acetamidophenyl)-neopentyl Chloride VIII with Sodium Hydroxide in Methanol:

1.0 g of the amidochloro compound IX (4.17 mmole) was dissolved in 10 ml of methanol. To the solution was added 2 g of NaOH (50 mmoles) in 5 ml of water. The reaction mixture was refluxed for 19 hours, poured into water, extracted with ether, washed with water and dried over

potassium carbonate. Evaporation of the solvent gave an oil which crystallized upon addition of petroleum ether. 486 mg of solid, m.p. 72-73°, were obtained (53% yield). The NMR and IR spectra of this sample were superimposable with those of an authentic sample of α-(2-aminophenyl)-neopentyl alcohol III.

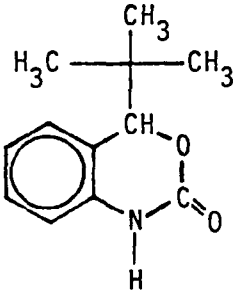
The Synthesis of 4-t-Butyl-3,1-benzoxazine-2-one XI

To a suspension of 3.7 g of the quaternary ammonium salt of α-(o-aminophenyl)-neopentyl alcohol (0.0172 mole) in 100 ml of dry dioxane was added 16 g (0.16 mole) of phosgene. After stirring overnight at room temperature, a clear yellow solution was obtained. Removal of the solvent yielded 3.4 g of a solid melting at 160-164°C. Recrystallization from benzene gave 2.88 g of solid (81% yield) melting at 163-165°C.

IR: (cm^{-1}) 3260, 3200, 3160, 3150, 3100, 1735, 1690, 1600, 1040, 1035

NMR: (ppm) 0.95 (1H,s), 4.83 (1H,s), 6.7-7.1 (4H,m), 9.73 (1H,s)

Analysis:			
calcd.	%C 70.25	%H 7.36	%N 6.82
found	69.94	7.42	6.55



4-t-butyl-3,1-benzoxazine-2-one XI

Cleavage of Diastereoisomeric Carbamates X a & b

Run 1: 2.9 g of a mixture of diastereoisomeric ℓ-menthyl carbamate (7.7 mmoles) were dissolved in 50 ml of dry ether. The solution was saturated with dry HCl and 10 ml of CH_3OH pretreated with dry HCl were added to it. The reaction mixture was refluxed for 2 days. Evaporation of the methanol, followed by addition of petroleum ether gave 1.2 g of a compound melting at 164-165° and identified via its IR and NMR spectra as 4-t-butyl-3,1-benzoxazine-2-one XI.

Run 2: 915 mg of carbamate (2.43 mmole), 8 ml of acetic acid and 2 ml of concentrated hydrochloric acid were refluxed for 4½ hours. After removal of the acetic acid, a solid melting at 160-164°C was recovered and identified via its IR and NMR spectra and melting point as 4-t-butyl-3,1-benzoxazine-2-one XI.

Run 3: 952 mg of carbamate (2.53 mmoles) and 5 ml of thionyl chloride were refluxed for 3½ hours. The excess thionyl chloride was evaporated and chased with CCl_4. The carbamate was recovered unchanged.

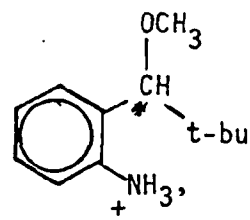
Run 4: 1.590 g of carbamate (4.22 mole) in 100 ml of toluene and 7 g of phosgene (70 mmoles) were refluxed for 1 hour. Removal of the toluene and excess phosgene gave the starting material.

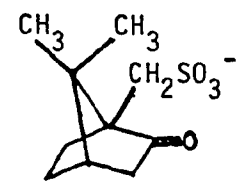
Run 5: 3.84 g of carbamate were dissolved in 10 ml of chloroform (1 M solution) and cooled to 4°C. 1.7 ml (2.4 g, 0.012 mole) of trimethylsilyl iodide were added to the solution. The reaction mixture turned brown and the temperature rose to 7°C. After 40 minutes at 5°C, 1.2 ml of methanol pretreated with gaseous HCl was added and the temperature rose to 11°C. Evaporation of the chloroform yielded a thick oil that polymerizes.

Run 6: To a solution of 2.933 g (7.73 mmole) of carbamate in 8 ml of dry chloroform, under an argon atmosphere was added 1.5 ml of trimethylsilyl iodide (10.5 mmoles). The reaction mixture turned greenish. It was refluxed for 23 hours. At this time, 2 ml of methanol pretreated with dry HCl were added. The solvent was removed on the rotary evaporator and addition of 10 ml of hexane yielded 400 mg of a solid melting at 165-166° and identified via its IR and NMR spectra as 4-t-butyl-3,1-benzoxazine-2-one XI.

Reaction of VI with d-10-Camphorsulfonic Acid in Methanol

10.0 g of chloroanilinium chloride VI (0.0427 mole) and 9.90 g (0.0427 mole) of d-10-camphorsulfonic acid were dissolved in 50 ml of methanol. Upon addition of 300 ml of ethyl acetate, a precipitate was formed. It was recrystallized three times from ethyl acetate/methanol 5:1 to give 1.3659 g of solid, m.p. 156-160°, $[\alpha]_D^{25}$ = +21.7° (0.05875 g/ml, methanol) identified via its IR and NMR spectra as





The free methoxy aniline was regenerated from its salt by treatment with base. It did not display any optical activity.

Free methoxy aniline:

IR: NH_2 bands: 3380, 3480 cm^{-1}; C-O band: 1085 cm^{-1}

NMR: 0.97 (9H,s), 3.23 (3H,s), 3.83 (1H,s), 4.33 (2H, broads)
6.47-7.27 (4H,m)

Diazotization of the methoxy camphorsulfonate salt: 450 mg of the salt (1.04 mmole) was stirred at 0-5°C with 4 ml of concentrated HCl and 2 ml of water. A solution of 887 mg sodium nitrite in 8 ml of water was added to the reaction mixture with stirring. After 20 minutes at that temperature, 18 ml of precooled H_3PO_2 was added and stirring was continued for an additional 2 hours. The mixture was extracted with ether, washed twice with saturated sodium bicarbonate, and dried over K_2CO_3. Evaporation of the solvent gave 130 mg (70%) of racemic 1-methoxy-2,2-dimethyl-1-phenylpropane.

IR: C-O stretching band: 1085 cm^{-1}

NMR: 0.87 (9H,s), 3.17 (3H,s), 3.75 (1H,s), 7.23 (5H,s)

Resolution of VI with d-10-Camphorsulfonic Acid in $CHCl_3$

Run 1: A solution of 1.975 g (0.010 mole) of chloroanilinium chloride in 30 ml of $CHCl_3$ was mixed with a solution of 2.323 g (0.010 mole) of d-10-camphorsulfonic acid in 50 ml of $CHCl_3$. Argon was bubbled through the solution to eliminate the HCl by-product. After 4 hours, 1.73 g of solid, m.p. 170-172°C, was deposited (XII a).

IR: carbonyl band: 1745 cm^{-1}; aromatic C=C: 1620 cm^{-1}

NMR: (d_6-DMSO) 0.80 (3H,s), 0.92 (3H,s), 1.07 (9H,s)

Run 2: A solution of 23.4 g of chloroanilinium chloride V (0.100 mole) in 200 ml of $CHCl_3$ was mixed to a solution of 25.0 g (0.1 mole) of d-10-camphorsulfonic acid monohydrate in 1 ℓ of $CHCl_3$. After passing argon through the solution for 5 days to remove HCl, there was no formation of a precipitate. The chloroform was removed under vacuum and 600 ml of a 50:50 mixture of benzene/petroleum ether were added to the residual oil. After one month at 4°C, 13.3 g of

solid, m.p. 168-171°, were obtained (29% yield, based on both diasteroisomers).

The IR and NMR spectra of this sample were superimposable with those from Run 1. $[\alpha]_D^{24}$ = +21.5° (0.0571 g/ml, DMSO)

Synthesis of (R)-(+)-α-Phenylneopentyl Chloride from XII a

Run 1: 965 mg of XII a (2.25 mmoles) were added to 10 ml of concentrated HCl and 5 ml of water at 0°C. 2.4 g of sodium nitrite in 16 ml of water was added to the reaction mixture. After 5 minutes, 15 ml of precooled H_3PO_2 was added to the orange solution. Stirring was continued for 2 hours at that temperature. The solution was extracted twice with ether and washed 3 times with saturated $NaHCO_3$ solution and dried over sodium sulfate. Evaporation of the solvent gave an oil which was chromatographed on silica gel (eluent: petroleum ether). 327 mg (80%) of (+)-α-phenylneopentyl chloride, $[\alpha]_D^{25}$ = +81° (0.03269 g/ml, THF) were obtained. The IR and NMR spectra of this sample were superimposable with those of an authentic sample of racemic α-phenylneopentyl chloride.

Run 2: 11.952 g of XII a (0.0278 mole, $[\alpha]_D^{24}$ = +21.5°) were mixed with 100 ml of concentrated HCl and 50 ml of water at 0°C. 10 g of sodium nitrite (0.144 mole) in 50 ml of water were slowly added to the reaction mixture. After stirring for 30 minutes at 0°C, 150 ml of a precooled solution (50%) of H_3PO_2 were added to the orange solution. The reaction mixture was kept at 4°C for 12 hours. It was then extracted with 3 x 100 ml of ether. The combined organic layers were washed twice with 100 ml of water followed by 3 x 100 ml of a saturated $NaHCO_3$ solution and dried over $MgSO_4$. Removal of the solvent gave 4.49 g of an oil (88%). Distillation in vacuo yielded 3.839 g of

(+)-α-phenylneopentyl chloride, b.p. 72° (3 mm), 76% yield, $[\alpha]_D^{22}$ = +68° (0.23652 g/ml, THF). The IR and NMR spectra of this sample were superimposable with those of an authentic sample of racemic α-phenylneopentyl chloride.

REFERENCES

1. Winstein, S.; Morse, B. K.; J. Org. Chem. (1952) *17*, 113.

2. Nair, M.R.; Nair, S. V.; Indian J. Chem, Sect. B (1979), *18*B(4), 341.

3. Anderson, S.; Drakenberg, T.; Organic Magentic Resonance (1983), *21*, 730.

4. Norris, R. K.; Randles, D.; Aust. J. Chem. (1979) *32*, 1487.

5. Norris, R. K.; Randles, D.; Aust. J. Chem. (1976) *29*, 2621.

6. Cowdrey, W. A.; Hughes, E. D.; Ingold, C. K.; Masterman, S.; Scott, A.D.; J. Chem. Soc. (1937), 1252.

7. Lewis, E. S.; Boozer, C. E.; J. Am. Chem. Soc. (1952), *74*, 308.

8. Wiberg, K. B.; Shryne, T. M.; J. Am. Chem. Soc. (1955) *77*, 2774.

9. Burwell, R. L.; Shields, A. D.; Hart, H.; J. Am. Chem. Soc. (1954) *76*, 908.

10. Hoffmann, H.M.R.; Hughes, E. D.; J. Chem. Soc. (1964), 1244.

11. Gerrard, W.; J. Chem. Soc. (1945), 106.

12. Matzner, M.; Kurkjy, R. P.; Cotter, R. J.; Chem. Rev. (1964) *64*, 645.

13. Gloede, J.; Z. Chem. (1982) *22*, 126.

14. Carman, R. M.; Shaw, I. M.; Aust. J. Chem. (1976) *29*, 133.

15. Hepburn, D. R.; Hudson, H. R.; J. Chem. Soc. Perkin I, (1976), 754.

16. Bose, A. K.; Lak, B.; Tet. Lett. (1973), 3927.

17. Mukaiyama, T.; Shoda, S.; Watanabe, Y.; Chem. Lett. (1977) 383.

18. Castro, B.R.; Organic Reactions (1983) *29*, 1.

19. Downie, I. M.; Holmes, J. B.; Lee, J. B.; Chem. Ind. (London) (1966) *28*, 900.

20. Cristol, S. J.; Strom, M. R.; Stall, D.P.; J. Org. Chem. (1978) *43*, 1150.

21. Jones, L. A.; Sumer, C. E., Jr.; Franzus, B.; Huang, T.T.S.; Snyder, E. I.; J. Org. Chem. (1978) *43*, 2821.

22. Weiss, R.G.; Snyder, E.I.; J. Org. Chem. (1970) *35*, 1627.

23. Aneja, R.; Davies, A.P.; Knaggs, J.A.; Tet. Lett. (1974) 67.

24. Zieger, H.E.; Mathisen, D.E.: J. Am. Chem. Soc. (1979), *101*, 2207.

25. Mathisen, D.E.: Ph.D. Thesis, City University of New York (1980).

26. Bright, D.A.; Mathisen, D.E.; Zieger, H.E.; J. Org. Chem (1982), *47*, 3521.

27. Imajo, S.; Kuritani, H.; Shingee, K.; Nakagawa, M.; J. Org. Chem. (1979) *44*, 3587.

28. Aaron, C.; Dull, D.; Schmiegel, J.L.; Jaeger, D.; Ohashi, Y.; Mosher, H.S.; J. Org. Chem (1967) *32*, 2897.

29. Cervinka, O.; Hub, L.; Collect. Czech. Chem. Comm. (1970) *35*, 721.

30. Warren, M. E.; Smith, H.E.; J. Am. Chem. Soc. (1965) *87*, 1757.

31. O'Brian, D.H.; Russell, C.R.: Hart, A.J.; J. Am. Chem. Soc. (1976) *98*, 7427.

32. Menon, B.; Buncel, E.; J. Organometallic Chem. (1978) *15*, 257.

33. Hogen-Esch, T.E.; Smid, J.; J. Am. Chem. Soc. (1966) *88*, 307.

34. Buncel, E.; Menon, B.; J. Org. Chem. (1979) *44*, 317.

35. Grutzner, J.B.; Lawlor, J.M.; Jackman, L.M.; J. Am. Chem. Soc. (1972) *94*, 2306.

36. Buncel, E.; Menon, B.; J. Chem. Soc., Chem. Comm. (1978) 758.

37. Brown, A.C.; J. Am. Chem. Soc. (1973) *95*, 982.

38. Misra, B.K.; Rao, Y.R.; Mahapatra, S.N.; Indian J. Chem. Sec. B (1980) *19*, 908.

39. Mustafa, A.; Askar, W.; Kamel, M.; Shalaby, A.F.A.; Hassen, A.E.A.E.; J. Am. Chem. Soc. (1955) *77*, 1612.

40. Lothrup, W. E.; Goodwin, P.A.; J. Am. Chem. Soc. (1943) *65*, 363.

41. Bottinger, C.; Ber. dtsch. Chem. Ges. (1878) *11*, 1407.

42. Michaelis, A.; Herz, R.; Ber. dtsch. Chem. Ges. (1890) *23*, 3480.

43. Kresze, G.; Maschke, A.; Albrecht, R.; Bederke, K.; Patzschke, H.P.; Smalla, H.; Trede, A.; Angew. Chem. Int. Ed. (1962) *1*, 89.

44. Kresze, G.; Wucherpfennig; Angew, Chem. Int. Ed. (1967) *6*, 149.

45. Smith, W. T., Jr.; King, G. G.; J. Org. Chem (1959) *24*, 976.

46. Davis, M.; White, A.W.; J. Org. Chem (1969) *34*, 2985.

47. Wilen, S.H.; Collet, A.; Jacques, J.; Tetrahedron (1977) *33*, 2725.

48. Greene, T.W.; Protective Groups in Organic Synthesis, John Wiley & Sons (1981) p. 222.

49. Pirkle, W.H.; Hockstra, M.A.; J. Org. Chem (1974) *26*, 3904.

50. Kricheldorf, H.R.; Chem. Ber. (1970) *103*, 3353.

51. Jung, M.R.; Lyster, M.A.; J.C.S. Chem. Comm. (1978) 315.

52. Posner, G.H.; Whitten, C.E.; McFarland, P.E.; J. Am. Chem. Soc. (1972) *94*, 5106.

53. Posner, G.H.; Whitten, C.E.; Tetrahedron Lett. (1970) 4647.

54. Dubois, J.E.; Boussu, M.; Lion, C.; Tetrahedron Lett (1971) 829.

55. Posner, G.H.; Whitten, C.E.; Tetrahedron Lett. (1973) 1815.

56. Posner, G.H.; Org. Reactions (1975) *22*, 253.

57. Posner, G.H.; Whitten, C.E.; Org. Synth. (1976) *55*, 122.

58. House, H.O.; Modern Synthetic Reactions, W. A. Benjamin, Inc., New York (1965) p. 9.

59. Jacques, J.; Fouguey, C.; Viterbo, R.; Tetrahedron Lett. (1971) 4617.

60. Gilman, H.; Cartledge, F.K.; J. Organometallic Chem. (1964) *2*, 447.

61. Shriver, D.F.; The Manipulation of Air-Sensitive Compounds, McGraw-Hill, New York (1969).

62. Otto Fritz, BmbH, Feldstraße, 6238 Hofheim am Taunus, West Germany sells an apparatus for the ultra high purification of permanent gases. The apparatus has been described in detail in *Chemie fur Labor und Betrieb* (1975) *8*, 305-310. One of its principal advantages is a safety device for over and under atmospheric pressures.

63. Brown, H.C.; J. Am. Chem. Soc. (1938) *60*, 1325.

64. Beilstein, *2*, 320.

65. Pearson, D.E.; J. Am. Chem. Soc. (1950) *72*, 4169.

66. Brewster, J.H.; Patterson, J.; Fidler, D.A.; J. Am. Chem. Soc. (1954) *76*, 6368.

67. Aaron, C.; Dull, D. Schmiegel, J.L.; Jaeger, D.; Ohashi, Y.; Mosher, H.S.; J. Org. Chem. (1967) *32*, 2797.

68. Brodhag, A.; Hauser, C.R.; J. Am. Chem. Soc. (1955) *77*, 3024.

69. Bogert, M.T.; Seil, H.A.; J. Am. Chem. Soc. (1907) *29*, 529.

70. Bogert, M.T.; Gortner, R.A.; Amend, C.G.; J. Am. Chem. Soc. (1911) *33*, 949.

71. Lewis, E.S.; Boozer, C.E.; J. Am. Chem. Soc. (1953) *75*, 3182.

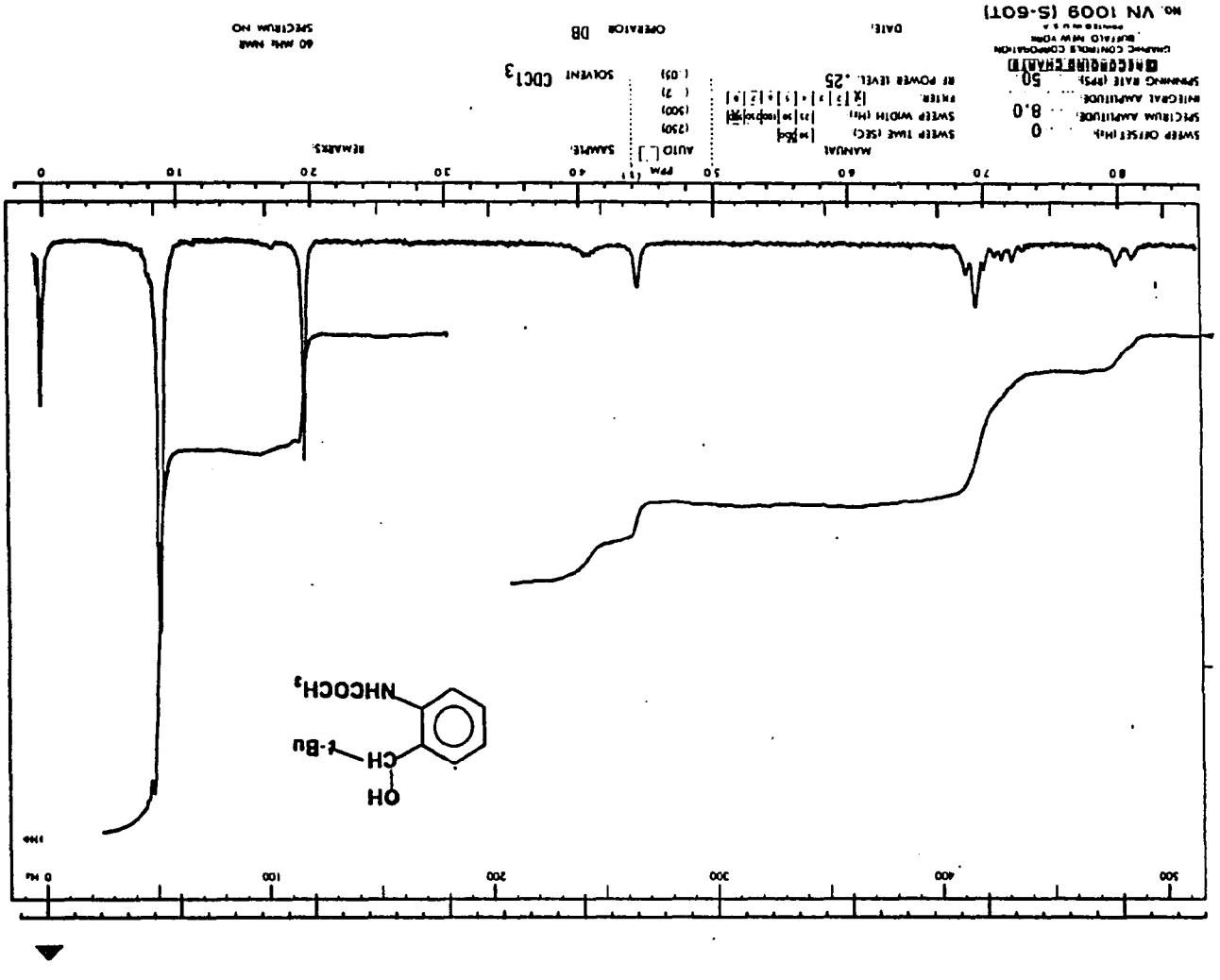
72. Appel, R.; Angew. Chem. Int. Ed. (1975) *14*, 801.

73. Appel, R.; Knoll, R.; Michel, W.; Morbach, W.; Wihler, H.D.; Veltmann, H.; Chem. Ber. (1976) *109*, 58.

74. Clark, D.R.; Mosher, H.S.; J. Org. Chem. (1970) *35*, 1114. (b) MacLeod, R.; Welch, F.J.; and Mosher, H.S.; J. Am. Chem. Soc. (1960) *82*, 876. (c) Vavon, G.; Angelo, C.; C. R. Hebd. Seances Acad. Sci. (1947) *224*, 1435.

APPENDIX A

NMR Spectra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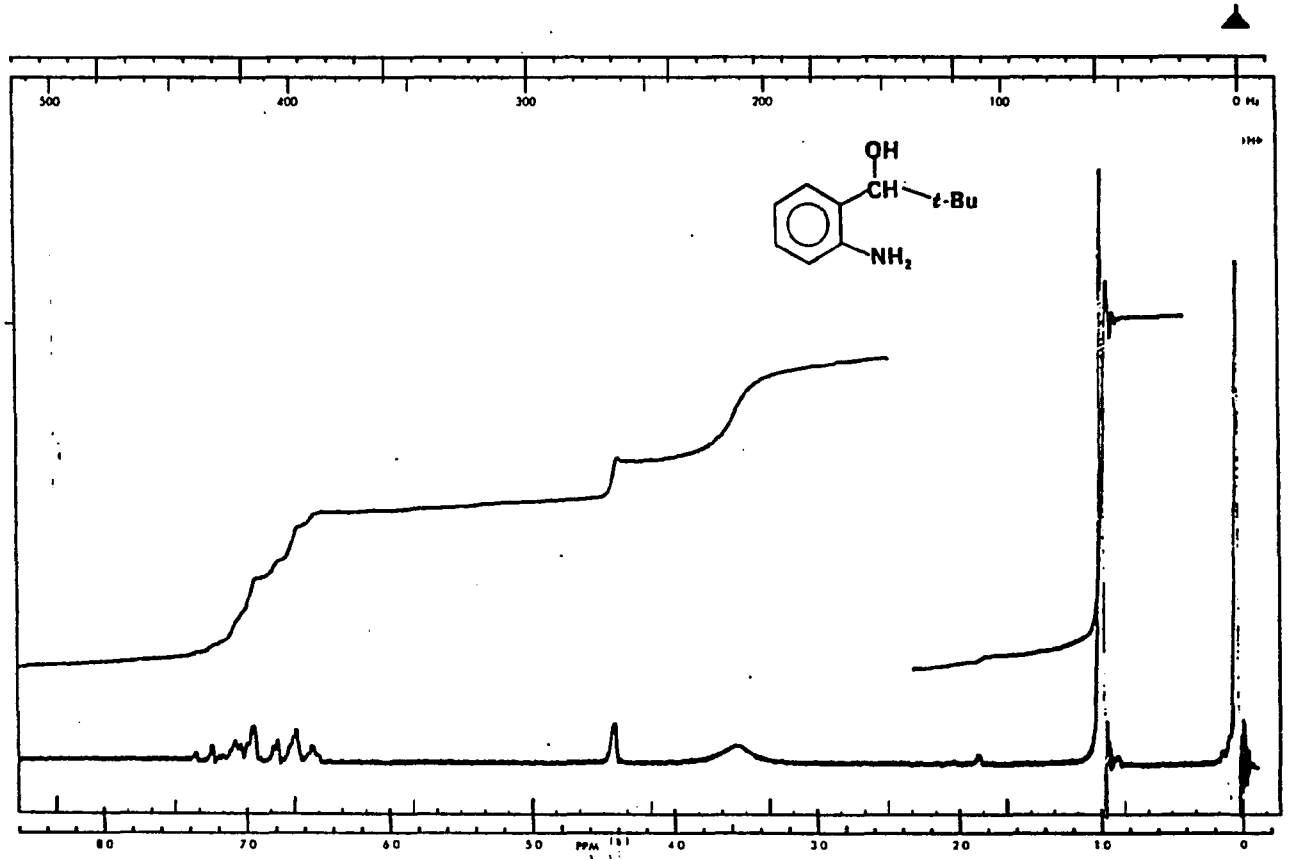

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REMARKS

DATE
OPERATOR
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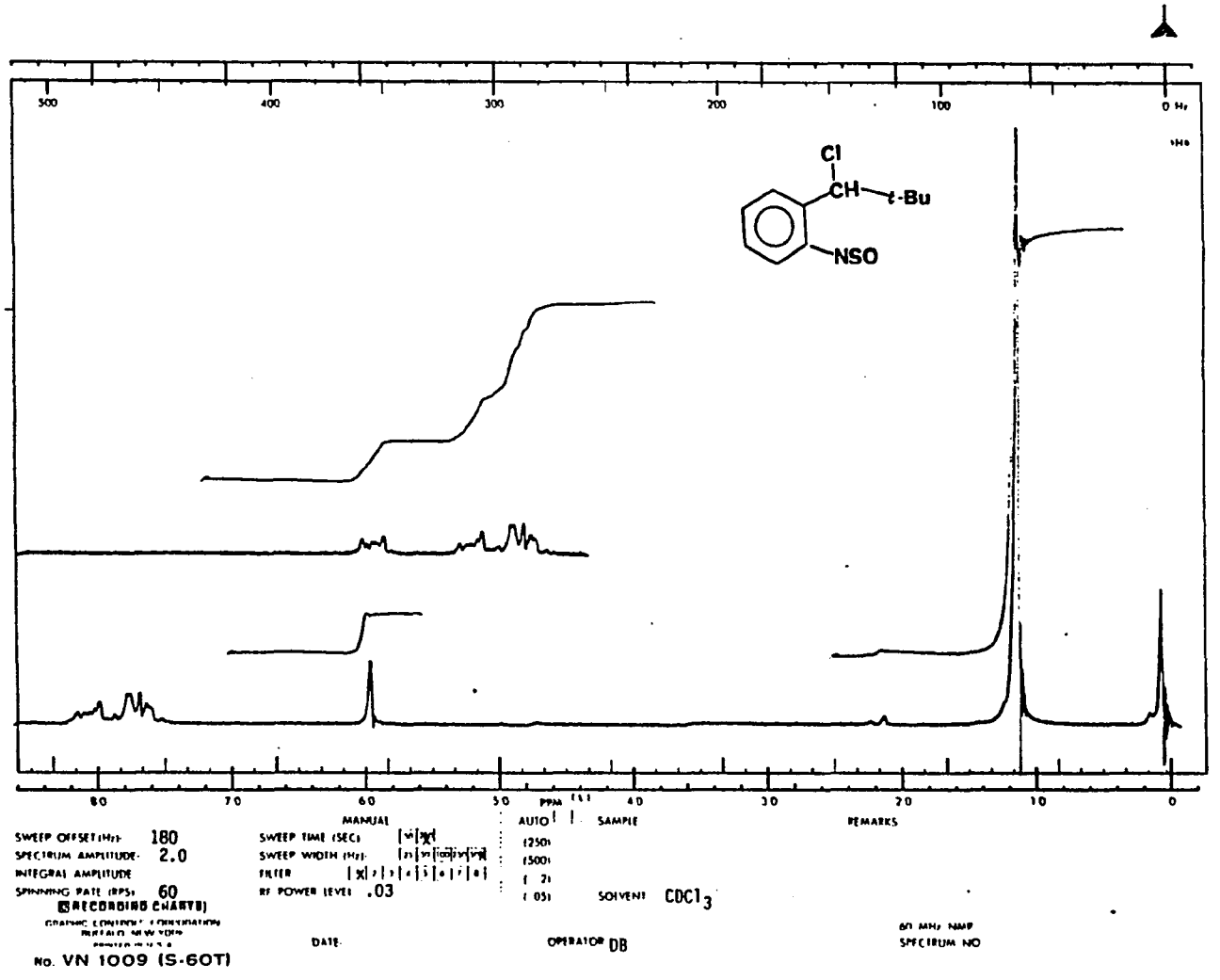
SPECTRUM NO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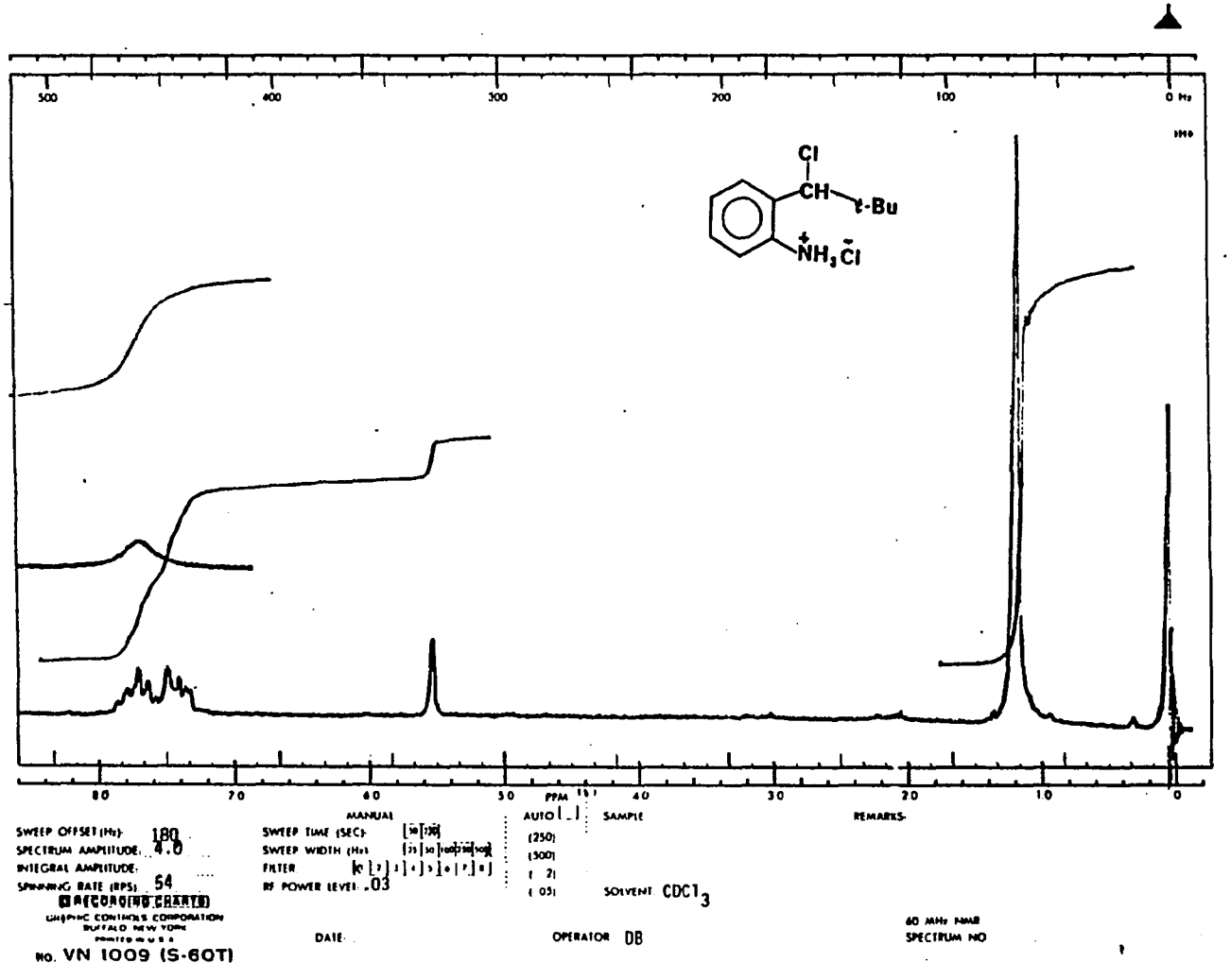
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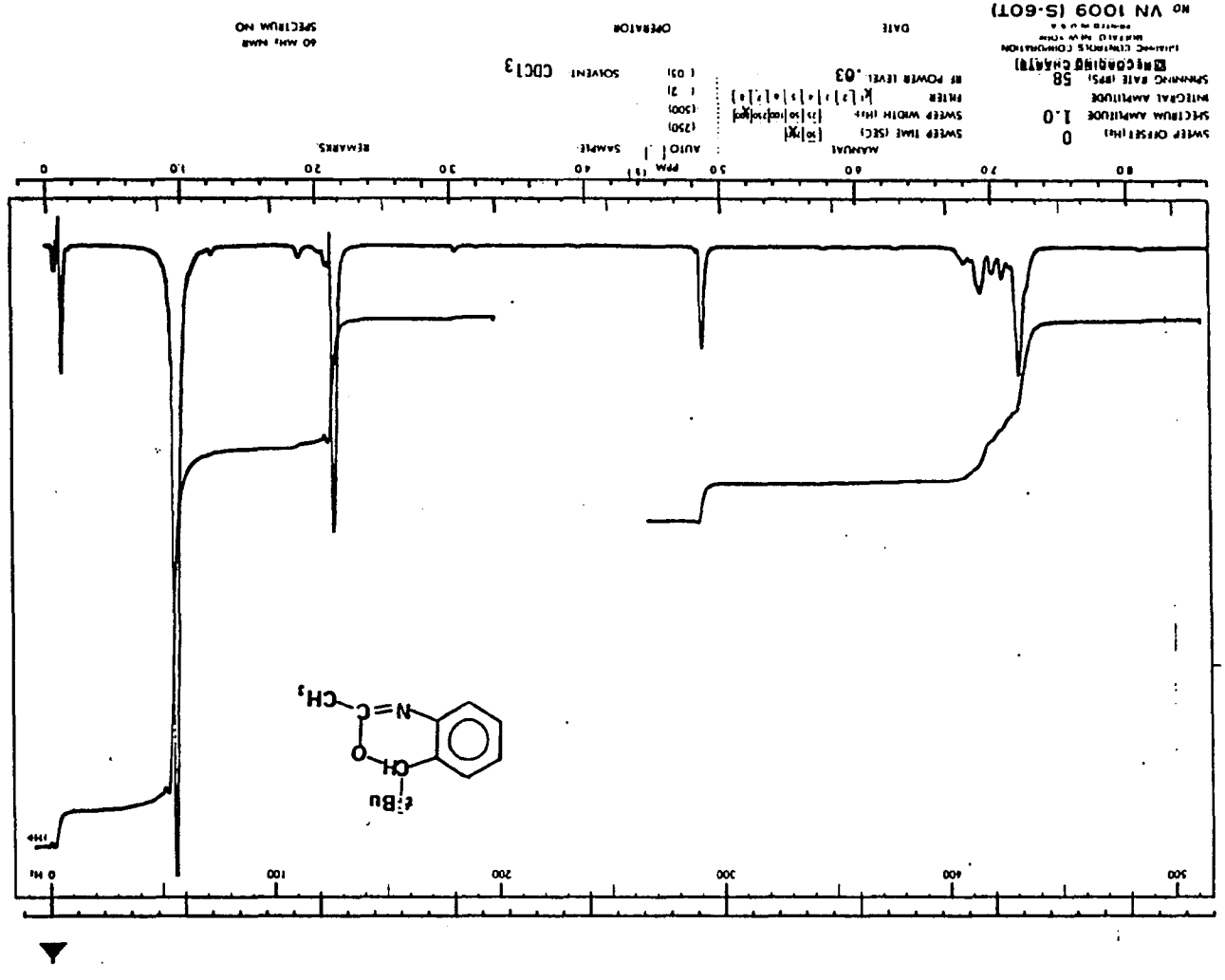
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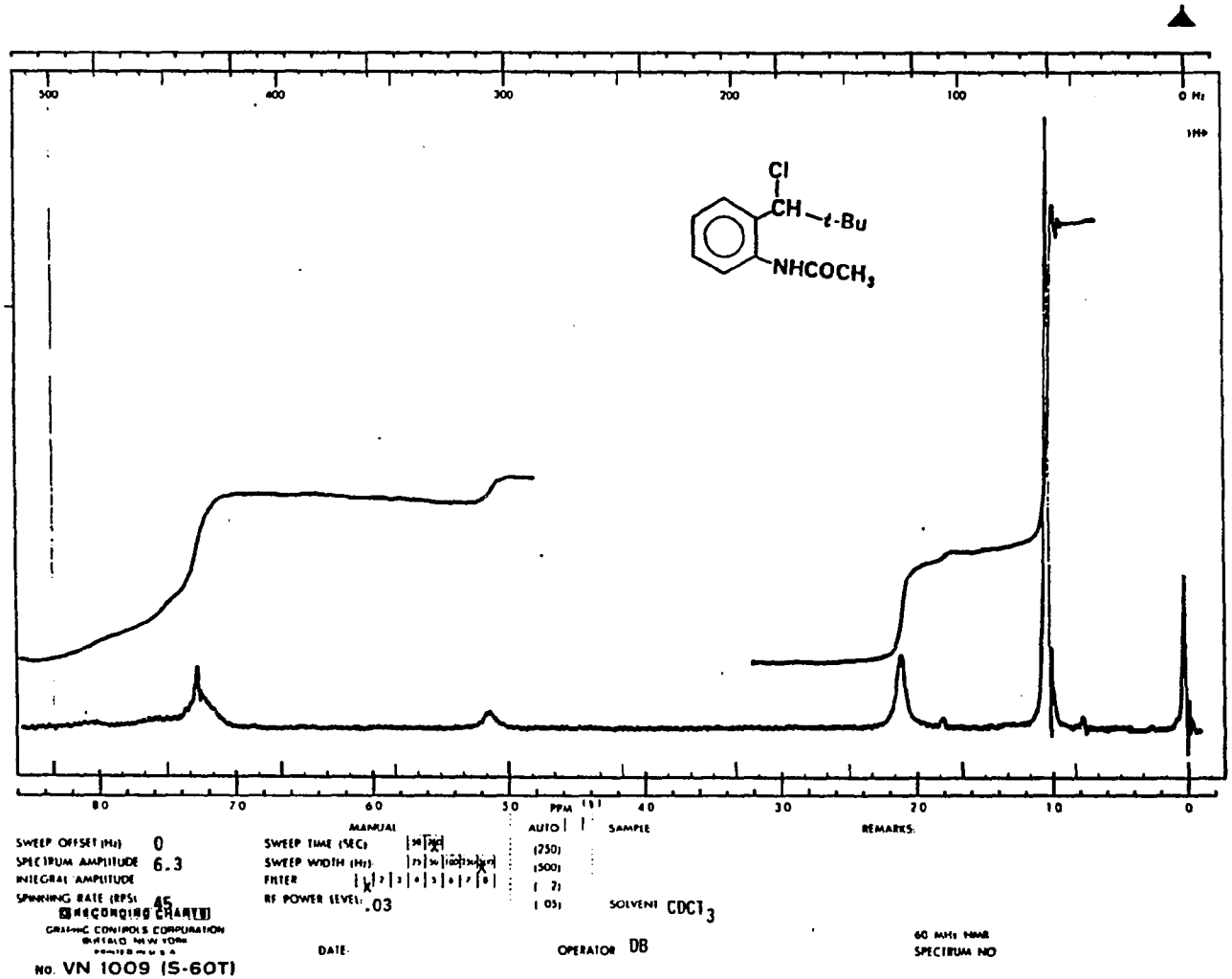

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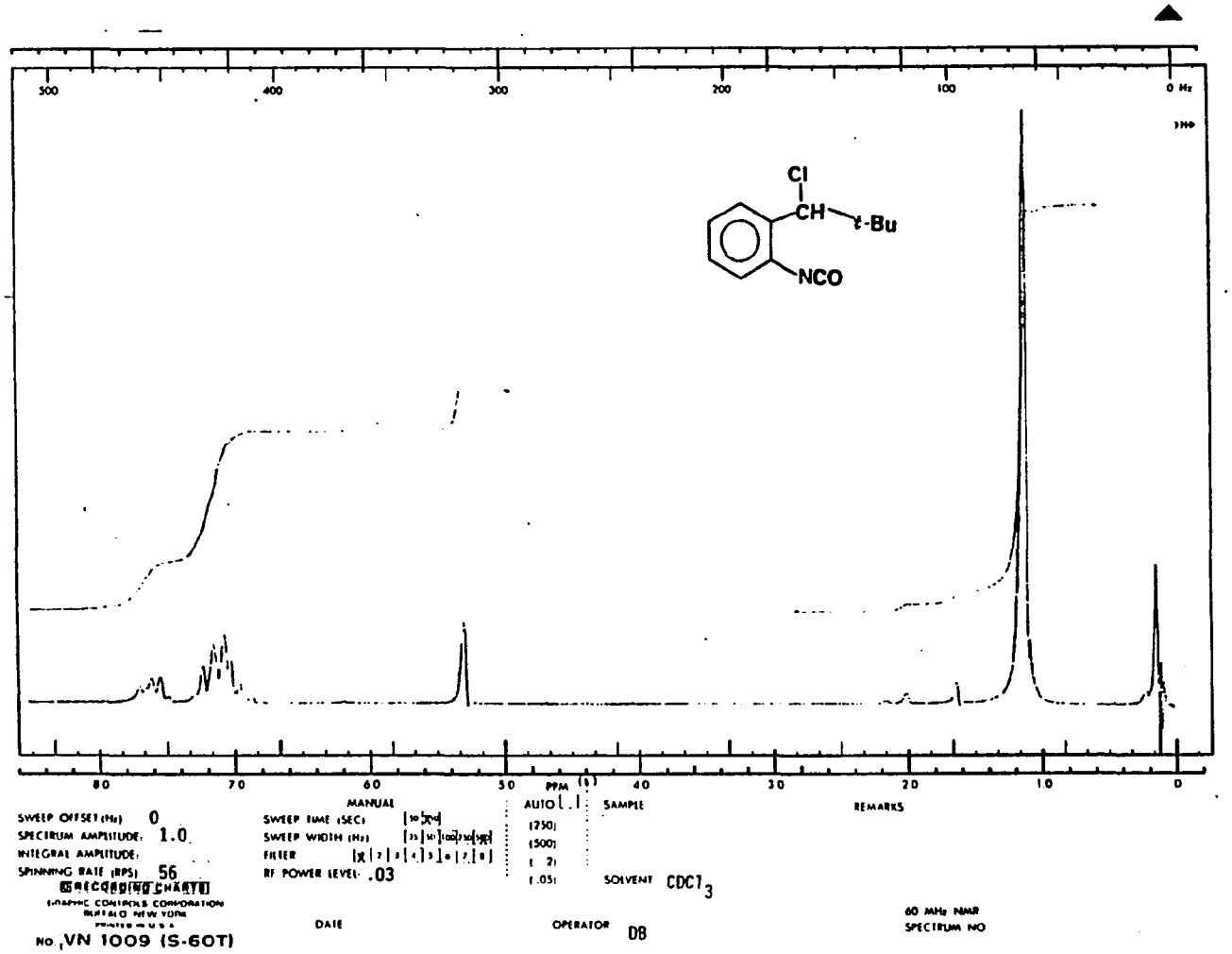
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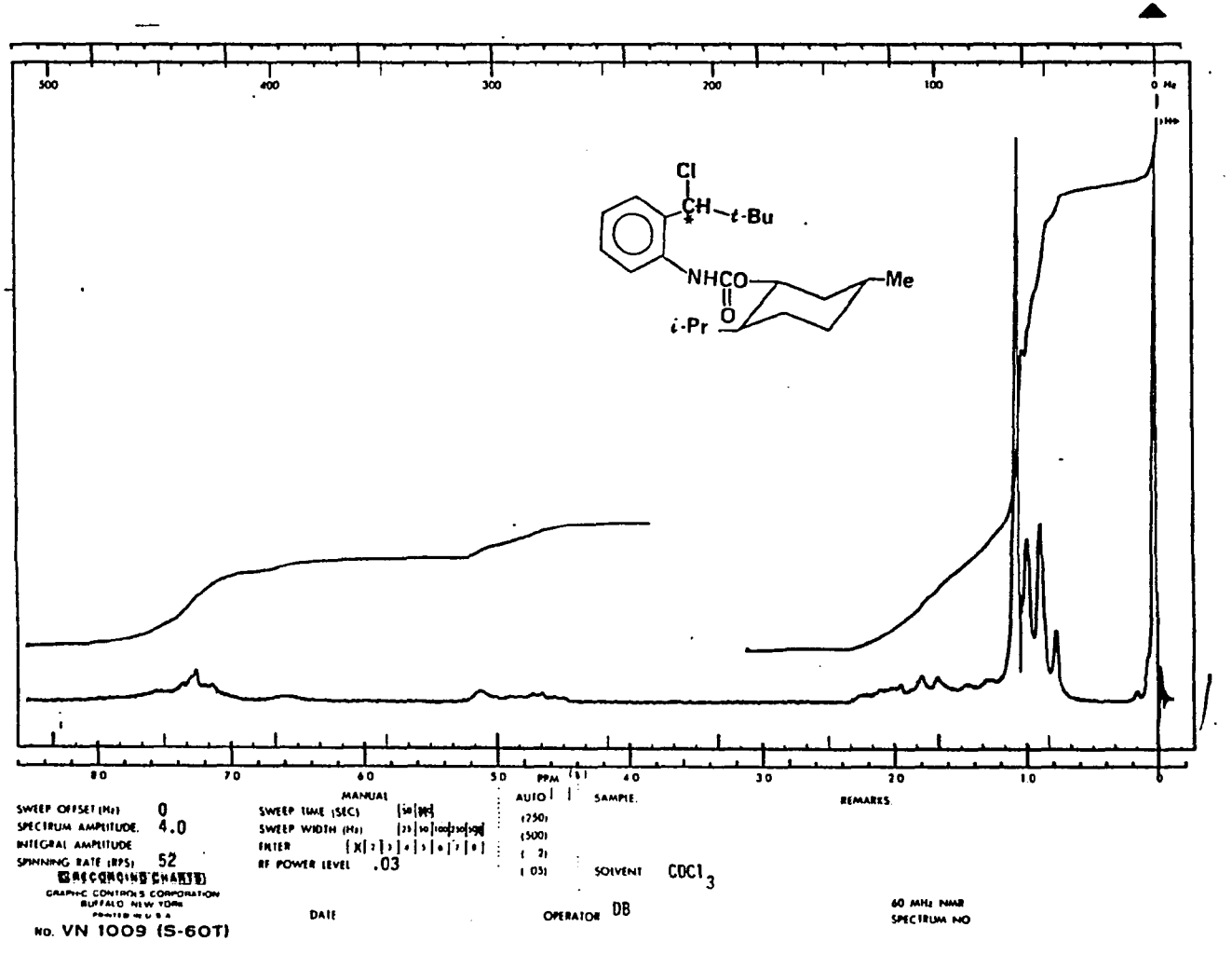
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BUFFALO NEW YORK
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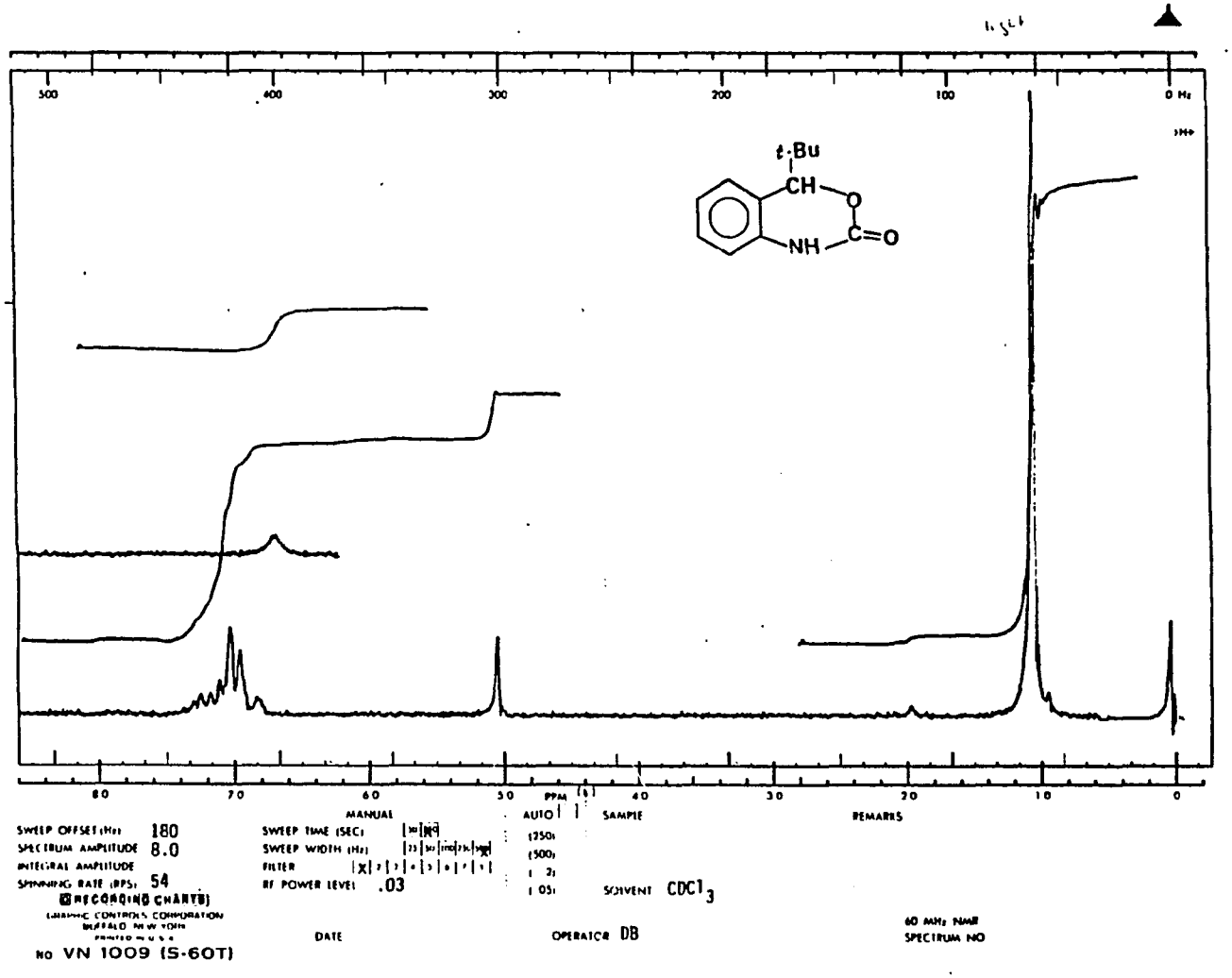
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SOLVENT $CDCl_3$
DATE
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BUFFALO, NEW YORK
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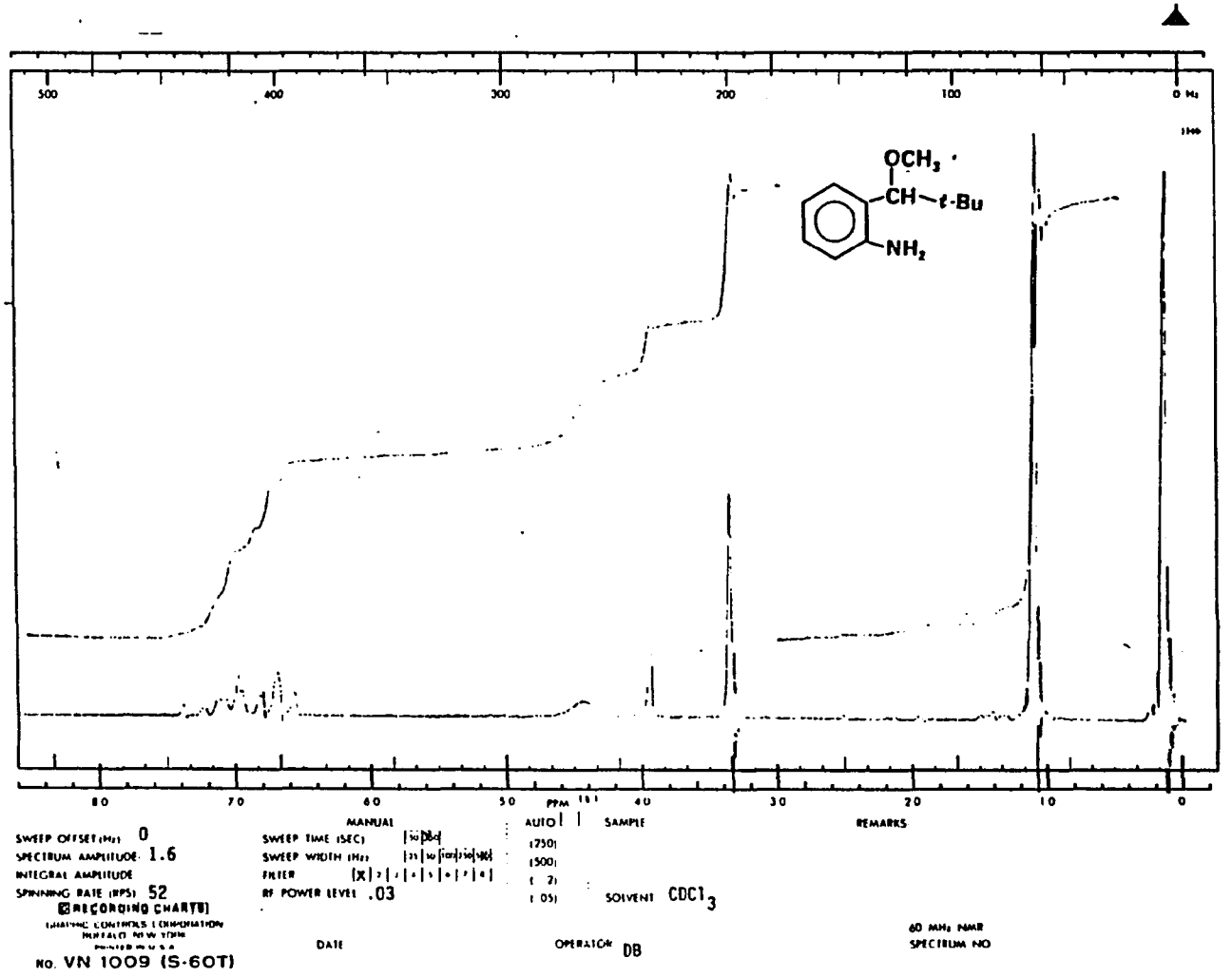

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SOLVENT $CDCl_3$

REMARKS

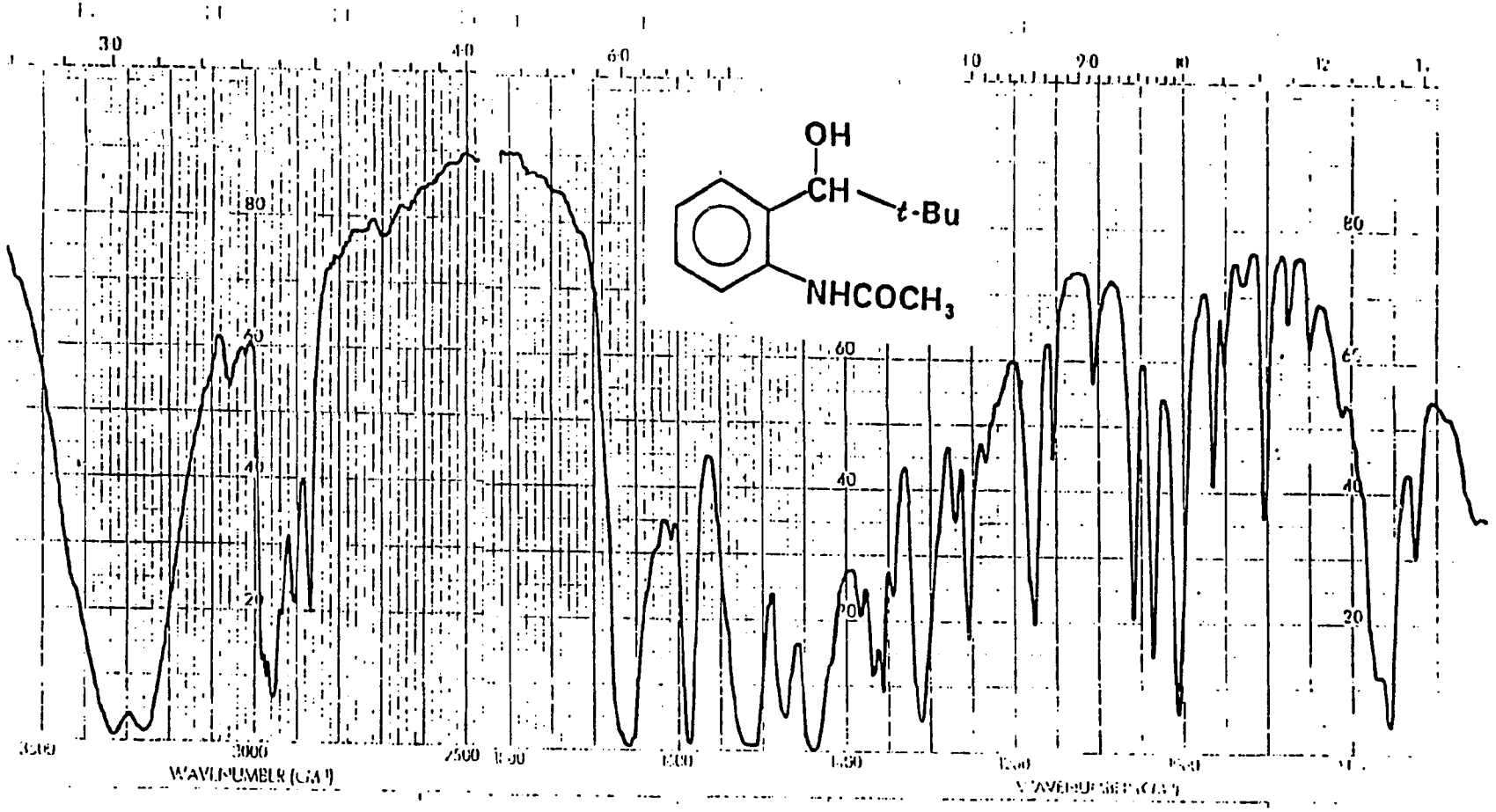
DATE

OPERATOR DB

60 MHz NMR
SPECTRUM NO

APPENDIX B

IR Spectra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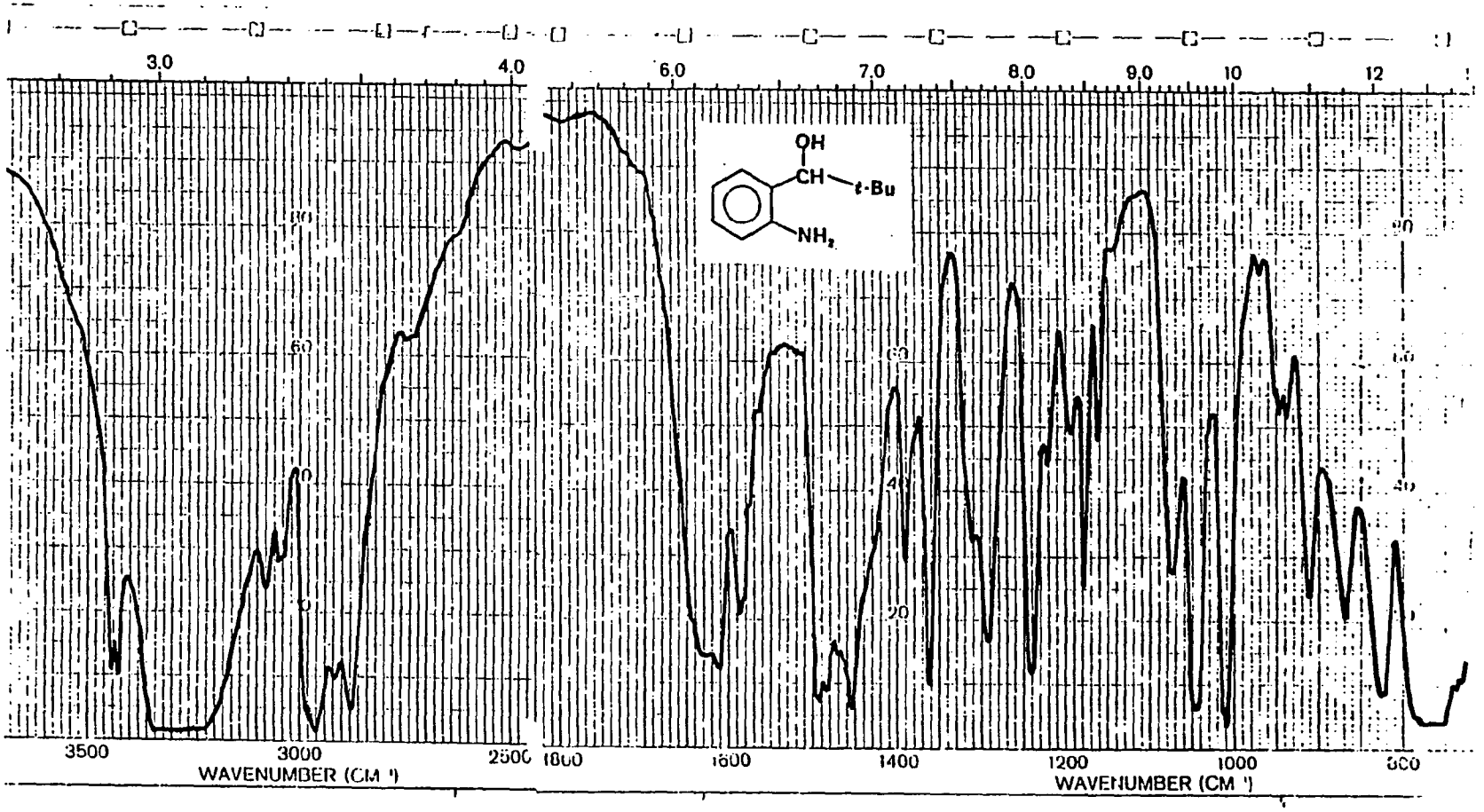
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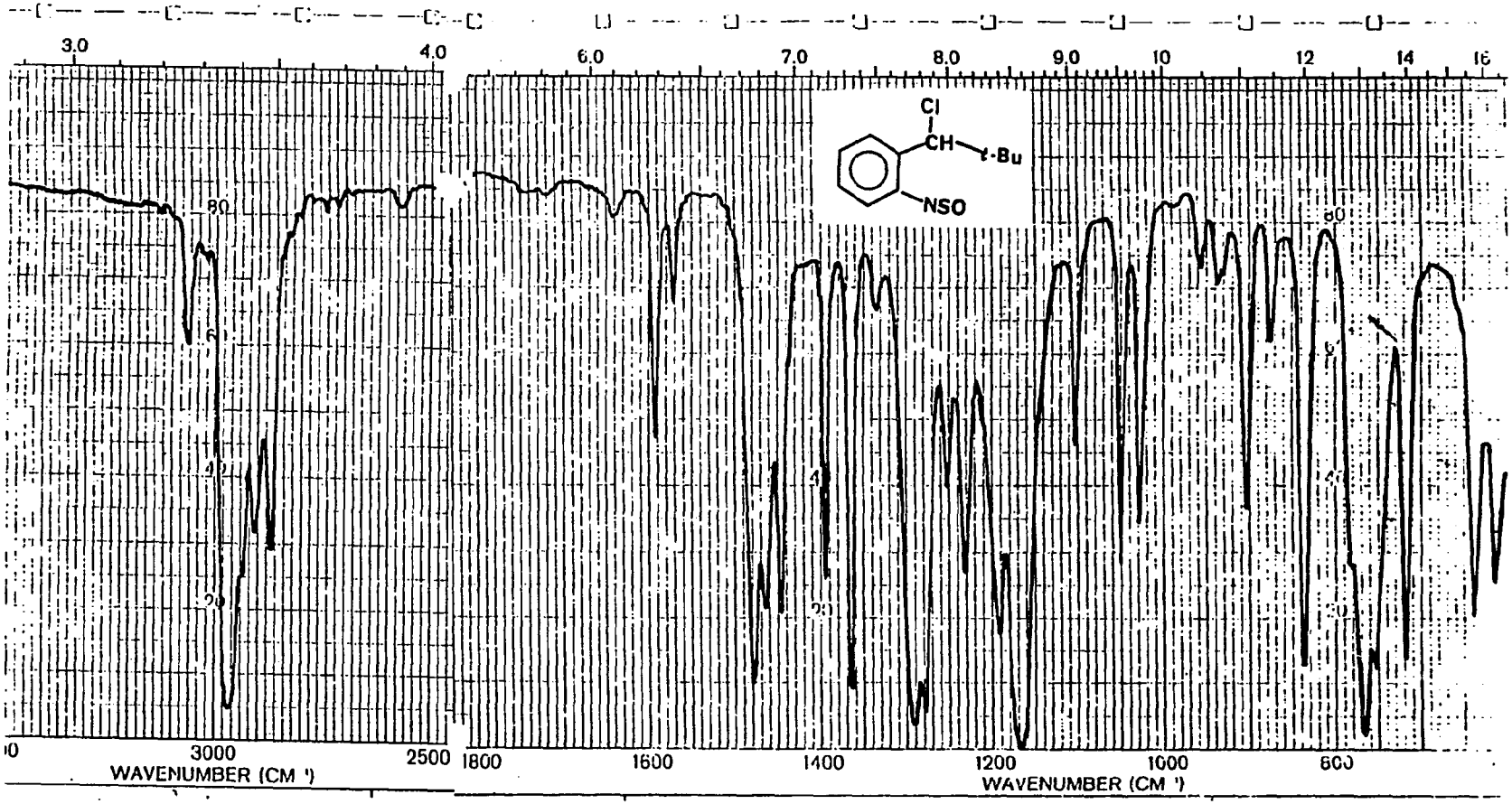
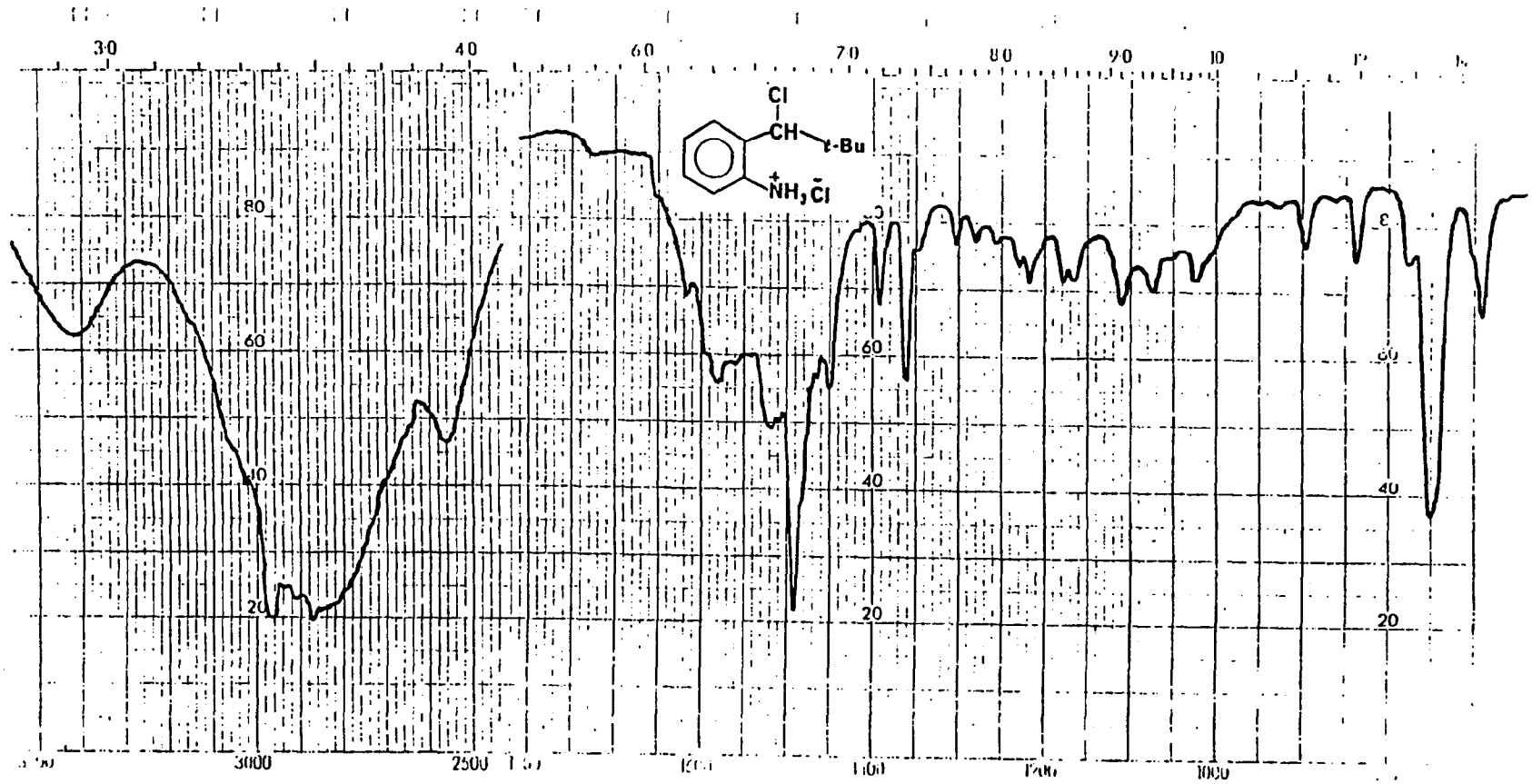
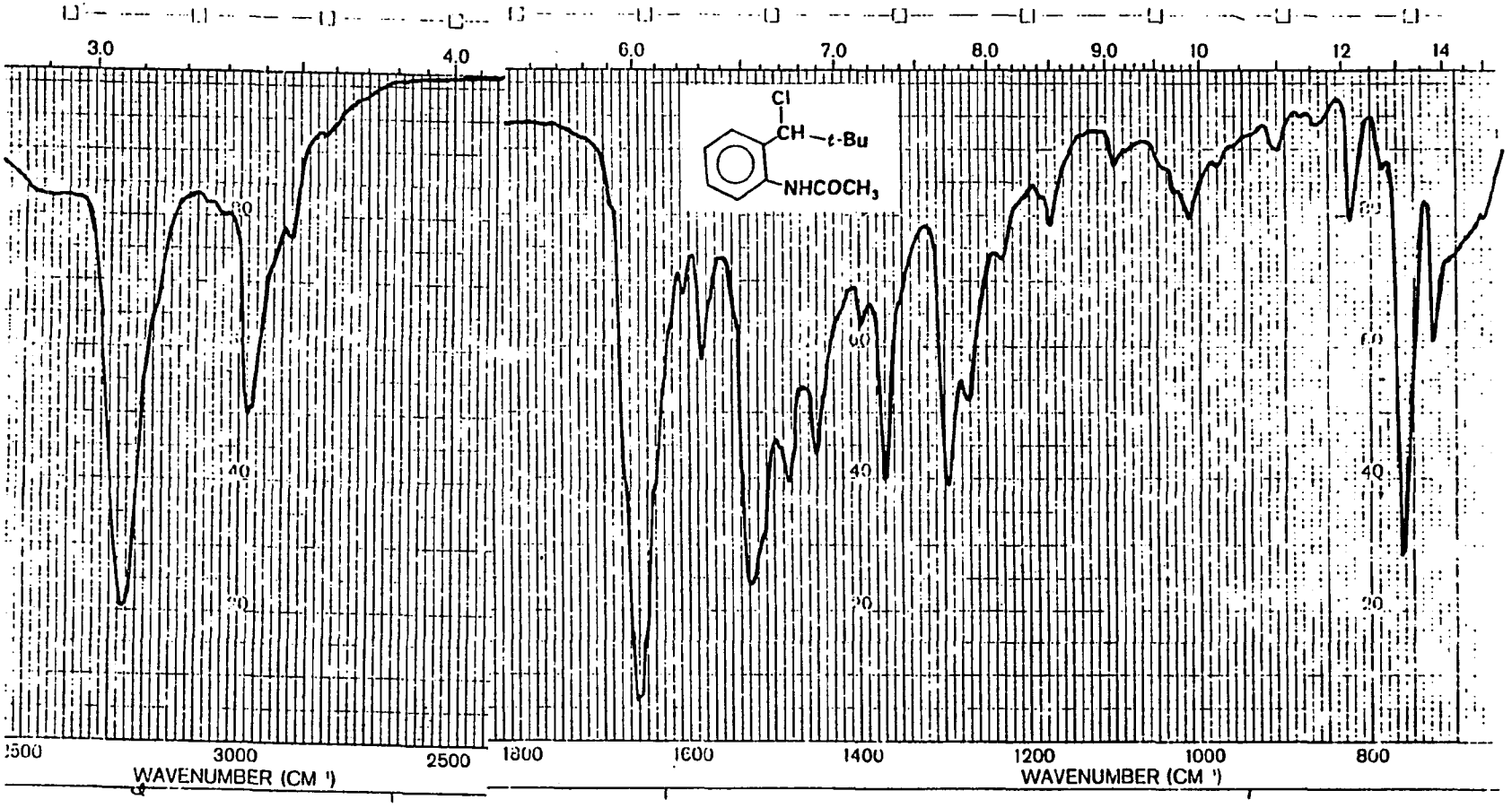
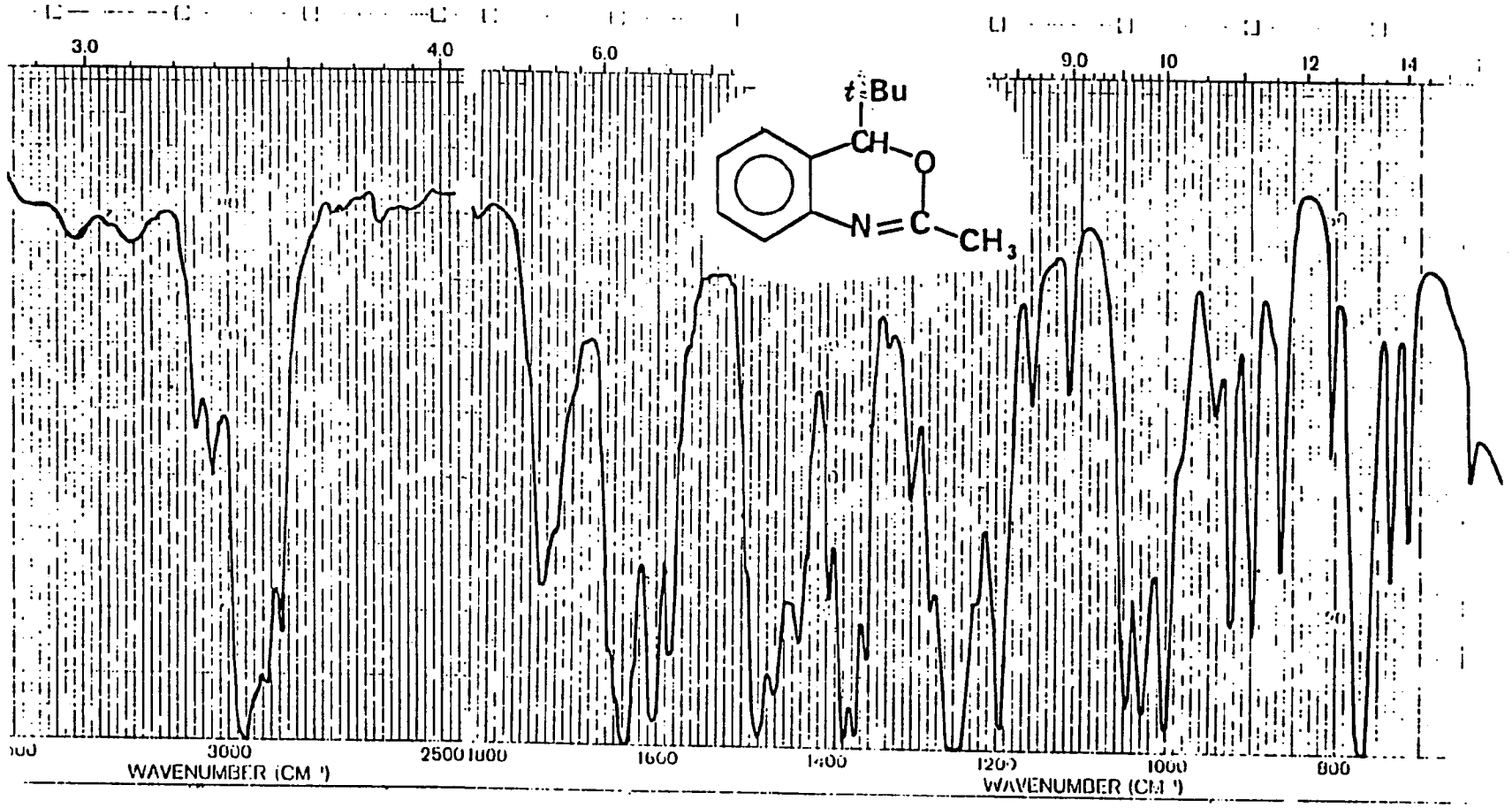
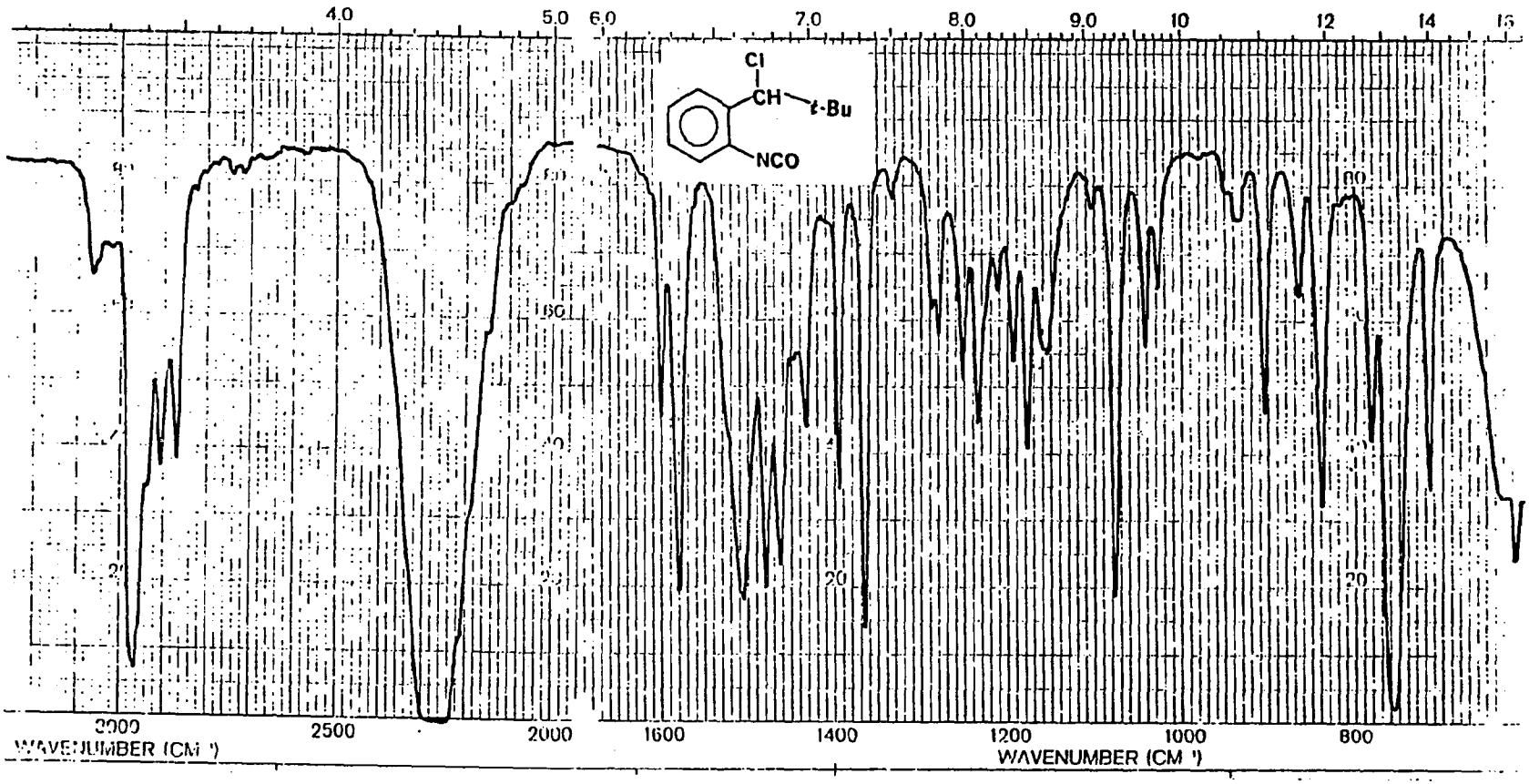
1400
1200
1000
800
WAVENUMBER (CM ⁻¹)
WAVENUMBER (CM ⁻¹)

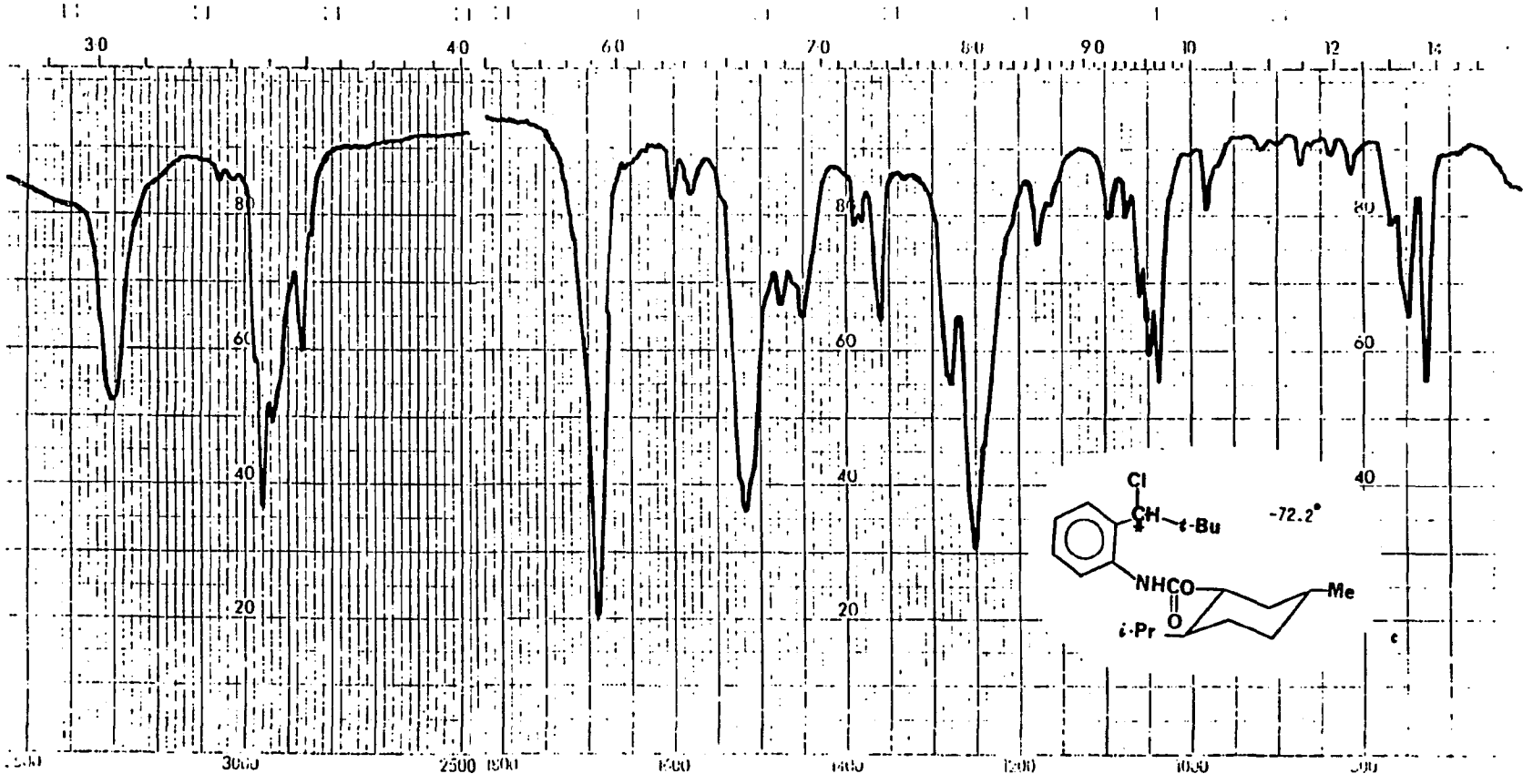

3.0
4.0
6.0
7.0
8.0
9.0
10
12
14
16
Cl
CH
t-Bu
NSO
80
60
40
20
3000
2500
1800
1600
1400
1200
1000
800
WAVENUMBER (CM ')
WAVENUMBER (CM ')

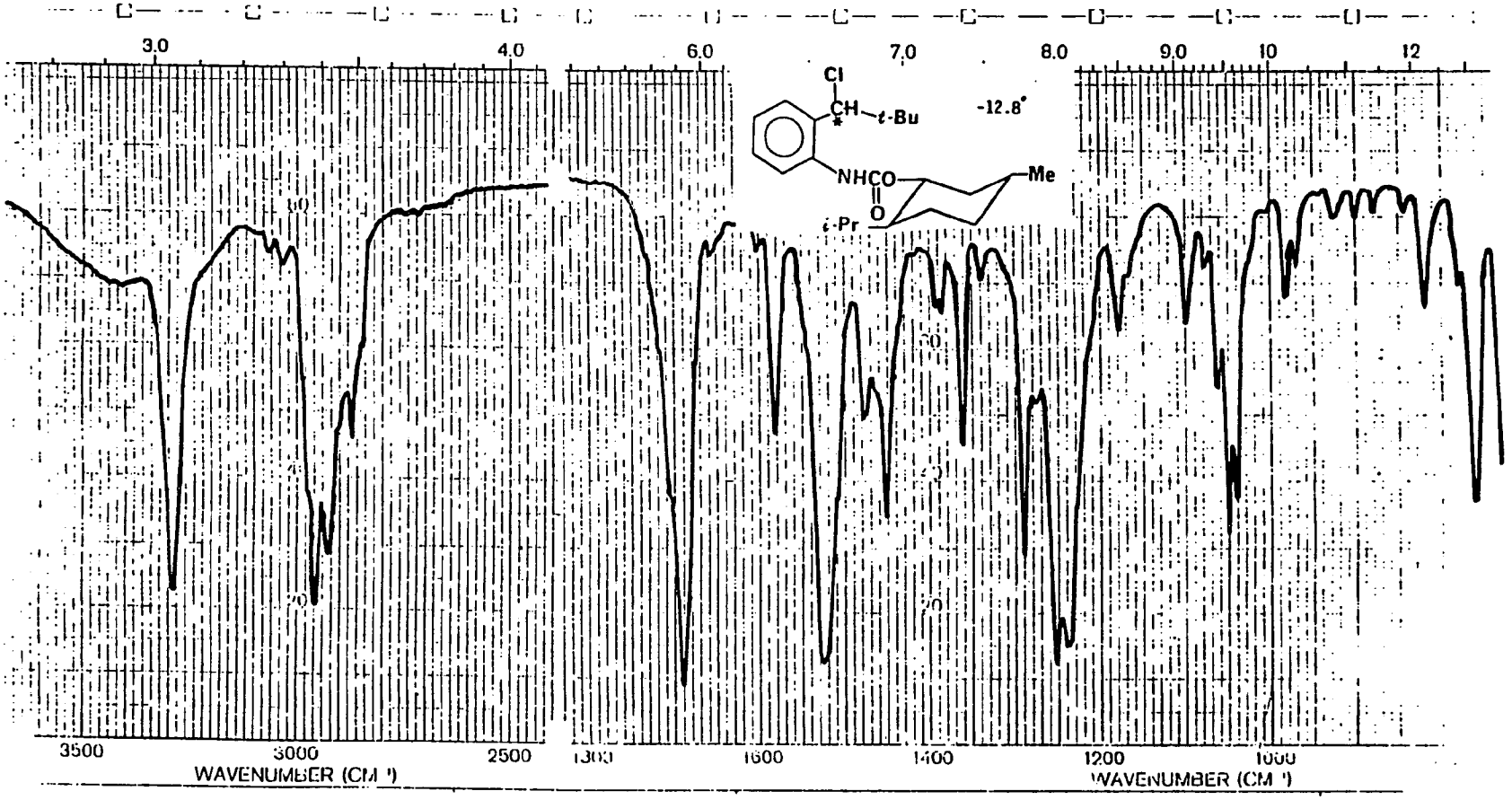

Cl
CH
t-Bu
+
NH, Cl⁻
3000
2500
1000

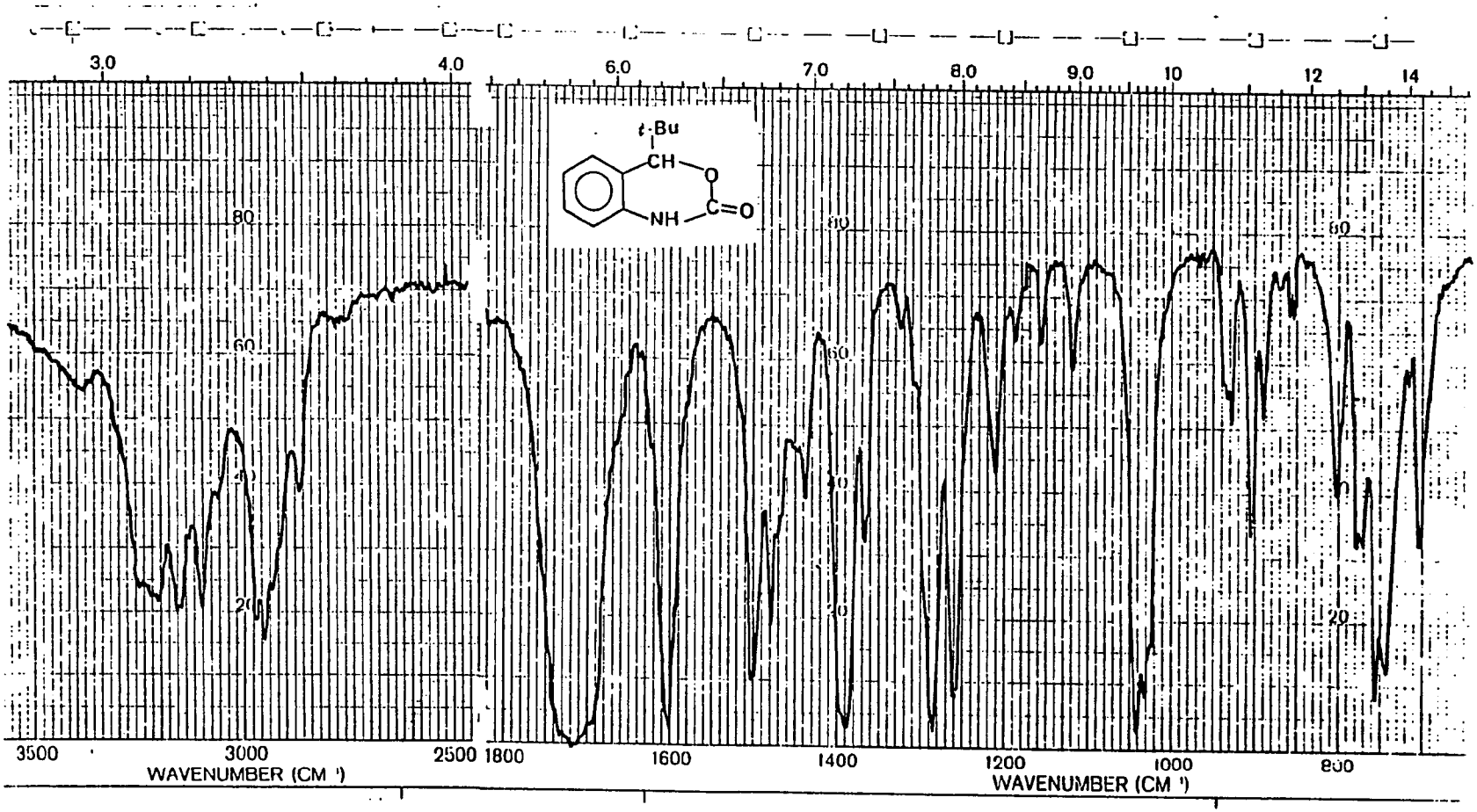

3.0
4.0
6.0
7.0
8.0
9.0
10
12
14
Cl
CH—t-Bu
NHCOCH3
60
40
20
3000
2500
1800
1600
1400
1200
1000
800
WAVENUMBER (CM ⁻¹)
WAVENUMBER (CM ⁻¹)

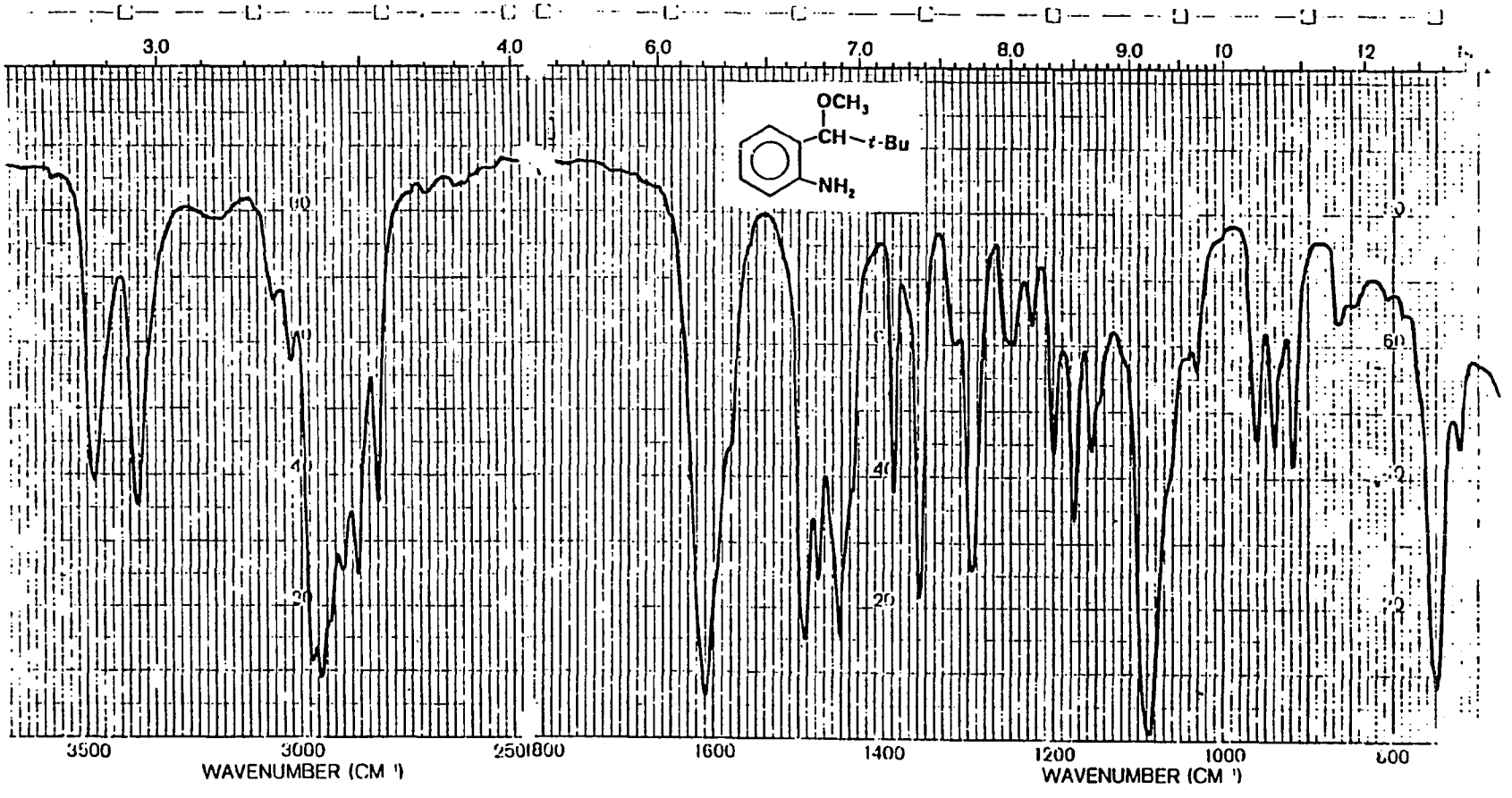

3.0
4.0
6.0
9.0
10
12
14
t-Bu
CH
O
N=C
CH3
3000
2500
1600
1400
1200
1000
800
WAVENUMBER (CM ')
WAVENUMBER (CM ')

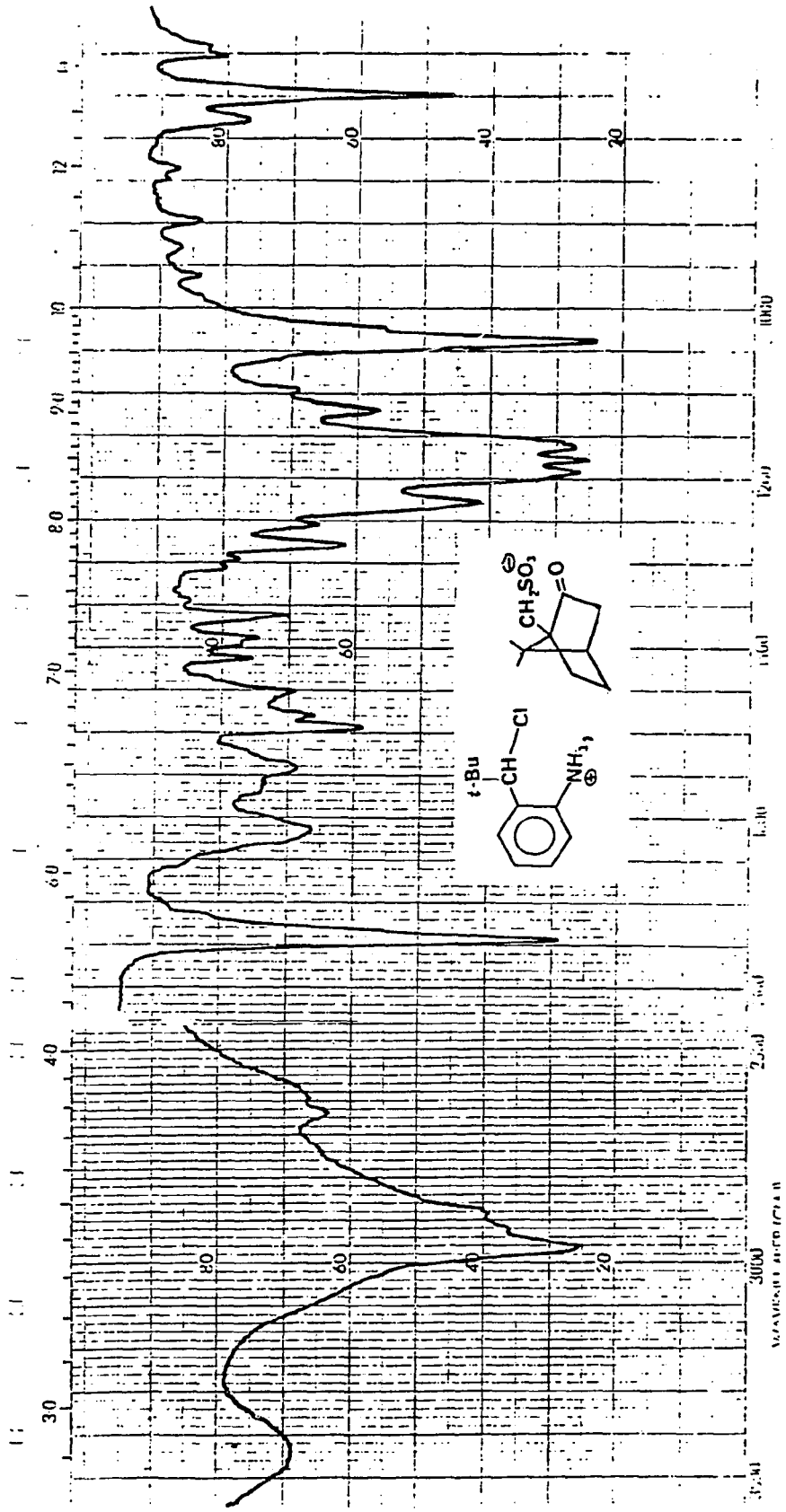

4.0
5.0
6.0
7.0
8.0
9.0
10
12
14
Cl
CH
t-Bu
NCO
80
20
3000
2500
2000
1600
1400
1200
1000
800
WAVENUMBER (CM ⁻¹)
WAVENUMBER (CM ⁻¹)


Cl
CH
t-Bu
-72.2°
NHCO
Me
O
i-Pr


3.0
4.0
6.0
7.0
8.0
9.0
10
12
Cl
CH
t-Bu
-12.8°
NHCO
Me
O
i-Pr
3500
3000
2500
WAVENUMBER (CM ⁻¹)
1800
1600
1400
1200
1000
WAVENUMBER (CM ⁻¹)


3.0
4.0
6.0
7.0
8.0
9.0
10
12
14
t-Bu
CH
O
NH
C=O
80
60
40
20
3500
3000
2500
WAVENUMBER (CM ⁻¹)
1800
1600
1400
1200
1000
800
WAVENUMBER (CM ⁻¹)


3.0
4.0
6.0
7.0
8.0
9.0
10
12
OCH3
CH—t-Bu
NH2
3500
3000
2501800
1600
1400
1200
1000
600
WAVENUMBER (CM ')
WAVENUMBER (CM ')


$\ominus$
CH_2SO_3
O
t-Bu
CH
Cl
NH_3
$\oplus$