SYNTHETIC APPROACHES TO INTERMEDIATES REQUIRED FOR SELECTED NITROGEN-SUBSTITUTED AROTINOIDS

By

MARK DANIEL THOMPSON

Bachelor of Science

East Texas Baptist College

Marshall, Texas

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SYNTHETIC APPROACHES TO INTERMEDIATES REQUIRED FOR SELECTED NITROGEN-SUBSTITUTED AROTINOIDS

Thesis Approved:

K D Berlin
Thesis Adviser

Eldon C. Nelson

Elizabeth M. Holt

Norman N. Durham
Dean of the Graduate College

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My deepest thanks go to my wife, Lisa, for typing this thesis, for her constant love and encouragement, and also for her tolerance of me during it all.

I would like to dedicate this work to my yet unborn child.

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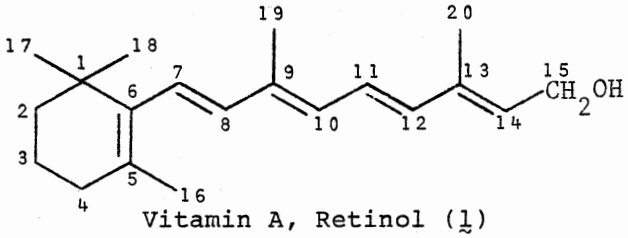
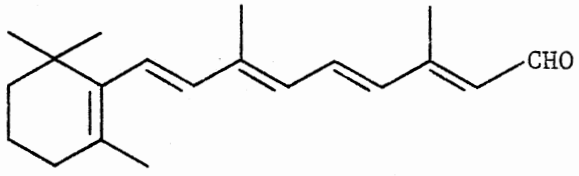
CHAPTER I

HISTORICAL

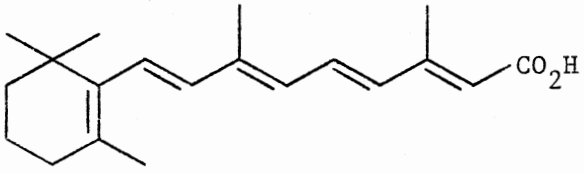
Vitamin A, or retinol, was discovered in 1913 by McCollum and Davis.[26] It was originally called "fat soluble A". This compound was found to be capable of maintaining growth, stimulating reproduction, participating in the visual cycle and also maintaining epithelial cell differentiation.[12,19,29,57] Retinol, along with its natural analogs (Figure 1), shares in this variety of biological activities (Figure 2).



Vitamin A, Retinol (1)



Retinal (2)



Retinoid Acid (3)

Figure 1. Natural Retinoids of Greatest Abundance

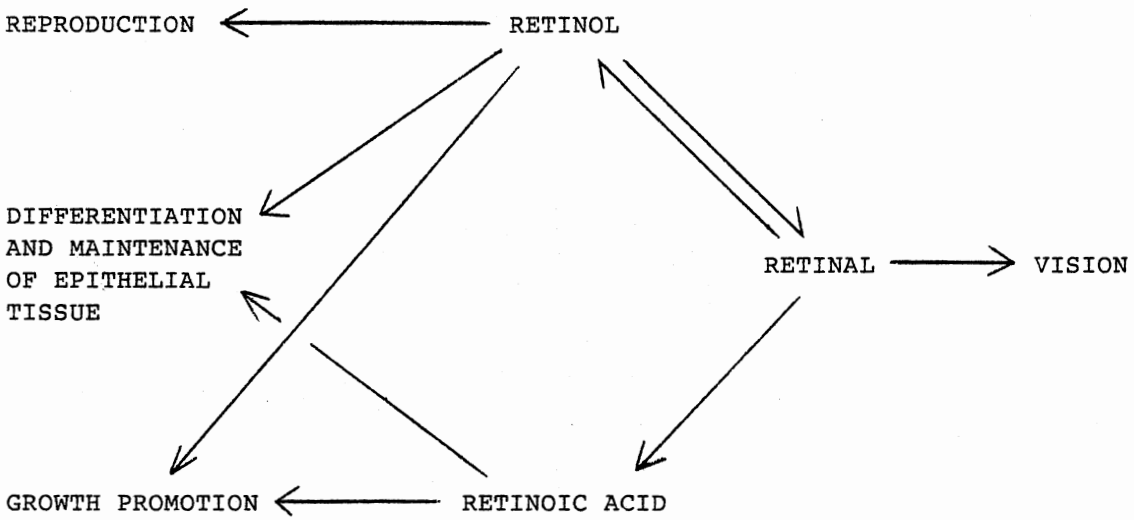


Figure 2. Biological Functions of Vitamin A[34]

Over half of the total primary cancer found in both men and women occur in epithelial tissue which depend upon retinoids for cell differentiation and growth.[43] Epithelia refers to tissues which form coatings or boundaries on internal and external surfaces of the body such as skin, blood vessels, organ coverings, bronchii, etc. These tissues are mainly made up of closely packed columnar cells which have very little intercellular space.[29,57] Many of these tissues are cilliated and most secrete mucus.

In the development of therapeutic substances to combat cancer as well as other maladies, it is necessary to consider four main criteria: biological activity, possible systemic toxicity and side effects, pathways of drug metabolism, and tissue distribution. For over fifty years it has been know that vitamin A (retinol) and other retinoids are necessary for proper cell growth and differentiation of epithelial tissues. Wolbach and Howe[57] discovered that a dietary deficiency of retinoids, in addition to causing xerophthalmia and night blindness, resulted in

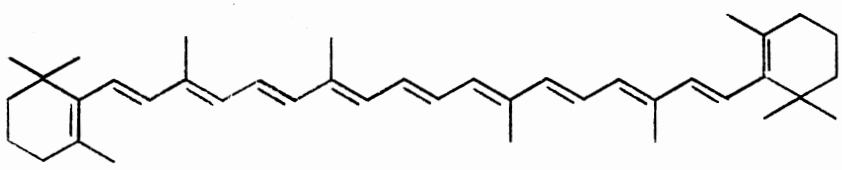
the atrophy of many glands and in the formation of lesions in epithelial tissues referred to as squamous metaplasia. These lesions have since been found to be similar to those caused by chemical carcinogens.[12] As the vitamin A deficiency, or avitaminosis, progresses, the normally columnar cells of the epithelium begin to stratify and lose their mucus-secreting ability. Keratinization takes place leaving the upper layers of cells dry and crusty. During this time, the basal cells proliferate rapidly causing the upper keratinized layer to peel and flake and thus leave the underlying tissue open to possible infection.[29] Because of these and other ill effects, if left unchecked, avitaminosis A would eventually lead to death. However, studies have shown that administration of a variety of retinoids, natural and synthetic, to the lesion can reinduce differentiation to the cells of the tissue thereby regenerating healthy tissue capable of assuming its normal function.[7,41,42,44,58] This reversal caused by application of retinoids can also be seen in hyperplastic and anaplastic epithelial lesions which have been caused by chemical carcinogens.[4,21,28,32,38,47-52] Studies by Sporn and co-workers[42,43,45] have indicated that retinoids, instead of preventing carcinogenesis, actually modify neoplastic states during a latent period before onset of invasive malignancy.

Along with this favorable antitumor activity, natural retinoids exhibit an acute systemic toxicity referred to as hypervitaminosis A. These two biological activities seem to parallel each other. For example, retinoic acid is one of the most active retinoids as an antitumor agent and one of the most toxic.[42]

At normal physiological concentration, retinol, the most abundant of the retinoids which occur in nature, is transported in the blood

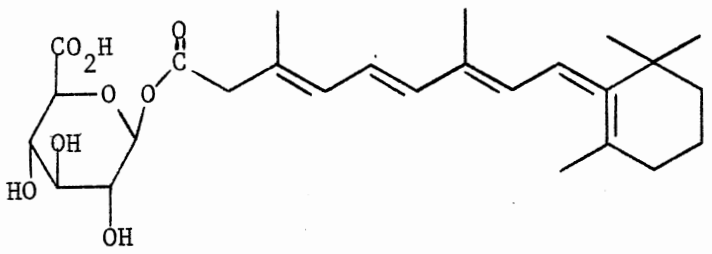
plasma bound to a retinol binding protein (RBP). This complex appears to be non-toxic. However, if the level of retinol reaches a point such that it is able to circulate unbound to RBP, then cytotoxic symptoms appear. This also occurs in the presence of excessive levels of other retinoids, most of which cannot be bound to RBP.[6,22,40] Among the most devastating of the cytotoxic reactions is the induction of increased synthesis and release of lysosomal enzymes giving the retinoid indirect "membranolytic" properties. This has also been shown to be involved in the breakdown of cartilage and bone tissue.[32] Some of the maladies initiated by high levels of retinoids in laboratory animals are severe hemorrhaging, paralysis of the hind legs, and progressive emaciation. Also reported was the fact that bones of young mice were made so fragile that even in restricted activity in the confines of the cage, the large leg bones were fractured.[29] This hypervitaminosis A also puts a severe restriction on the therapeutic usefulness of natural retinoids as antitumor agents.

Other potential problems associated with the utility of therapeutic substances is their tissue distribution and metabolic pathways. The description of retinol as "fat soluble A" by McCollum and Davis[26] gives indication of its lipophilic/hydrophobic character and a reason why many retinoids are stored in the liver and other fatty tissues. Retinol is acquired from the diet while oxidative cleavage of β-carotene (4) (also



β-Carotene (4)

acquired from the diet) produces retinal which is reduced to retinol. Since retinol exhibits a variety of biological activities, much work has been done attempting to elucidate its degradative pathways because of the possibility that it is broken down into active metabolites.[11] As shown by Figure 2, retinol, retinal, and retinoic acid promote growth and differentiation. However, retinoic acid is unable to participate in reproduction or the visual cycle, indicating that retinoic acid cannot be reduced to retinal or retinol in vivo. In view of these findings, it has been postulated that retinol, retinal, and retinoic acid are all broken down to the same active metabolite which is responsible for epithelial differentiation and growth.[11,13] Several workers have corraborated the fact that retinol is converted in vivo via retinal to retinoic acid[2,53,54] as the major metabolite.[23] One metabolite, discovered by Olson and coworkers,[15,16,24] was found to be retinoyl-β-glucuronide (5). Whether



5

this acid is further metabolized or whether it is actually in equilibrium with retinoic acid itself is not known at present. Oxidation products of retinoic acid metabolism have also been isolated. One of these pathways begins with oxidation of the allylic 4-position to the alcohol (6) and

then to the ketone (see Figure 3).[11,36,37] Ketone 7 appears to be the principle metabolite of retinoic acid. These metabolites represent intermediates in the detoxification and elimination pathways.[18,20,36] 4-Ketoretinoic acid (7) exhibits a reduction in biological activity as compared to that of trans-retinoic acid. Another of the metabolites of retinoic acid which has been isolated and identified is 5,6-epoxyretinoic acid (8).[27] It appears that epoxide 8 is comparable to trans-retinoic acid in some biological activity.[11,52]

Since many natural retinoids are too toxic to be therapeutically useful, many workers have studied the structure-activity relationships of a large variety of synthetic retinoids in order to aid in the design of therapeutic substances which are less toxic and at least as biologically active as natural retinoids.[30,31,34,42,50] In order to assess the degree of activity of these synthetic retinoids, several in vitro biological assays have been devised.[44,49,51] The most widely used method is the hamster tracheal organ culture devised by Sporn and co-workers[7,30] which has the ability to assay retinoid activity in the range of 10^{-9} to 10^{-14} M.[30] In this method, hamsters are raised on a vitamin A deficient diet from birth to about 30 days after which time they are killed and the tracheas are removed under sterile conditions. The tracheas are cultured at 37°C in a serum free medium[33] to which the following are added: crystalline bovine insulin, hydrocortisone hemisuccinate, glutamine, penicillin, and streptomycin. This medium contains insulin as the only protein. The cultures are gassed with 50% oxygen, 45% nitrogen, and 5% carbon dioxide. After four days, a retinoid is administered to some of the cultures and the rest are left as controls. Retinoid treatment is continued for six consecutive days and all the tracheas are harvested,

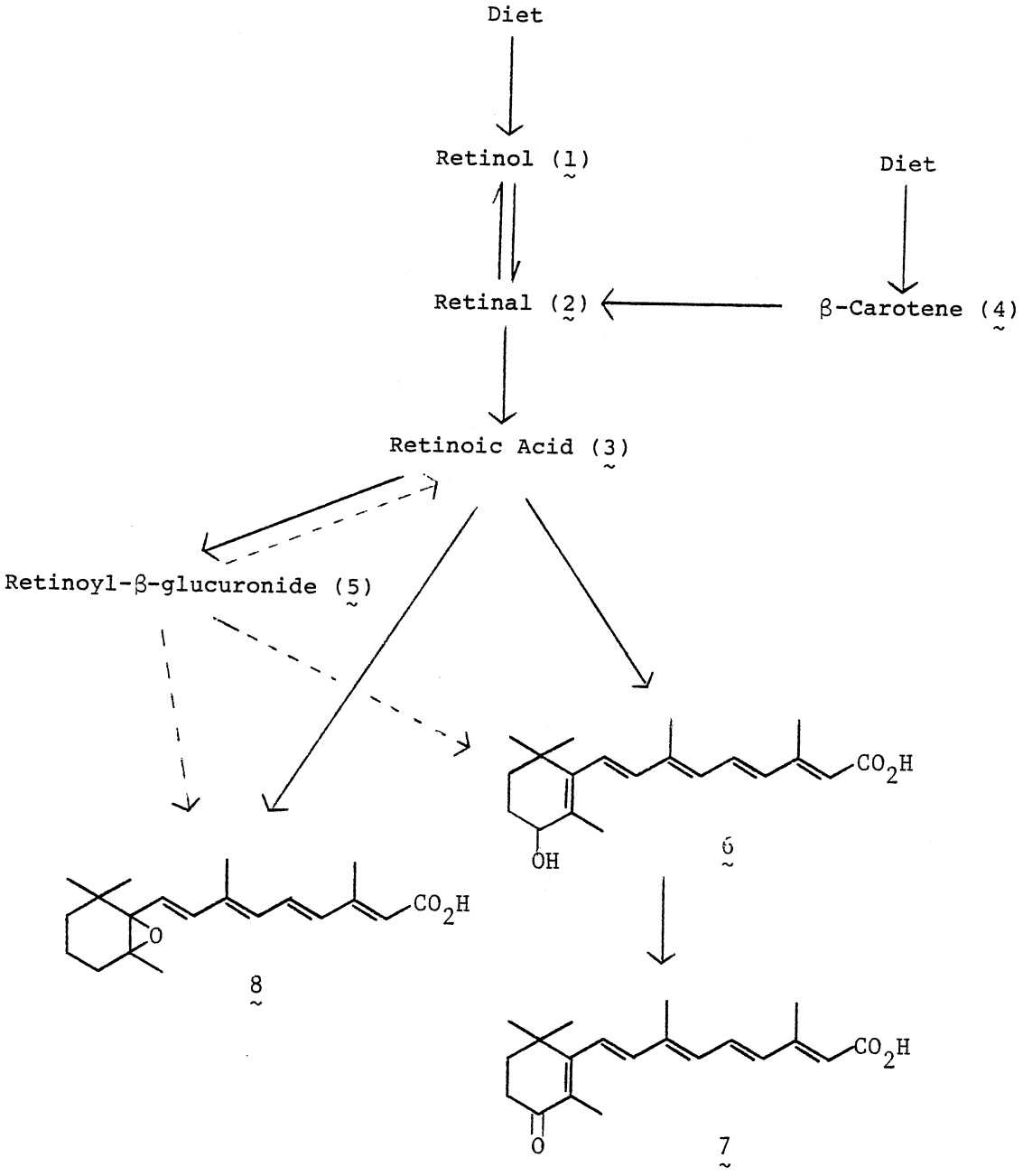
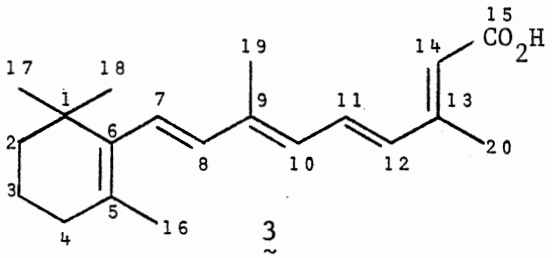


Figure 3. Retinoid Metabolism

fixed in 10% buffered formalin, and embedded in paraffin. The tracheas are then evaluated on the extent of squamous metaplasia found and also on the presence or absence of keratin as compared to the controls.

The retinoid molecule consists of three main portions: the hydrocarbon ring, the hydrocarbon side chain, and the polar terminal group. Retinoic acid analogs with alterations in each area have been designed, synthesized, and assayed for activity.[34] Data of a selected few of these which have shown good biological activity are collected in Tables I-III.[8,10,14,30,31,46,50,52,55,56]

Along with the types of structural variations shown, a variety of compounds have been synthesized in which certain portions of the hydrocarbon chain are rigidly held in a set conformation by the incorporation of aromatic rings.[9,25] For example, one of the compounds, 9, synthesized



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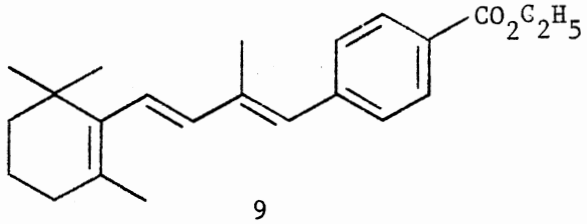

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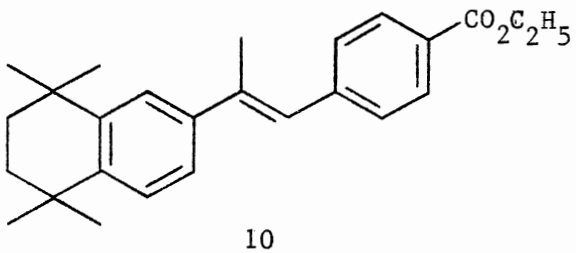
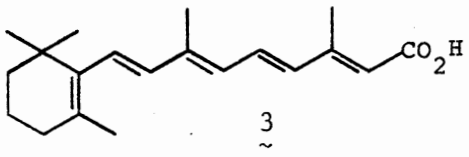
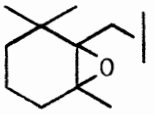
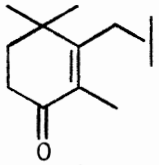
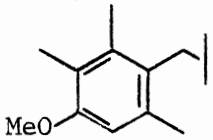
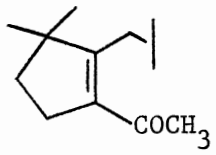
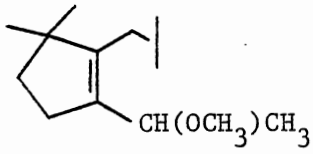
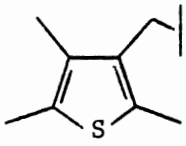


10

by Dawson and co-workers[9] holds the 11,12,13,14-diene system in a cisoid conformation by incorporation of a phenyl ring. This compound has been shown to have very good biological activity as measured by the ornithine decarboxylase inhibition assay.[49] It is interesting to note that this compound is missing the C(20) methyl. When this methyl is included, the activity drops to zero. Loeliger[25] coined the name "arotinoids" for the aromatic retinoids which he and his co-workers synthesized. A selection of some of their compounds along with their assayed activities is found in Table IV. One expecially active arotinoid is 10. This particular ester was found to be one of the most active ever synthesized. It is 8000 times more active than trans-retinoic acid itself and even though it is 800 times more toxic, it exhibits a therapeutic ratio ten times better than retinoic acid. This activity could be due in part to the fact that metabolic degradation via allylic oxidation has been blocked by the gem-dimethyls at that site. The possibility of epoxidation of the 5,6-double bond has also been drastically reduced due to its incorporation in an aromatic ring.

TABLE I

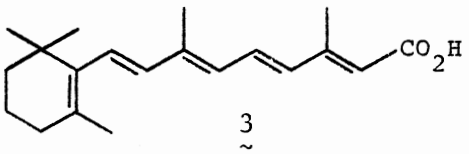
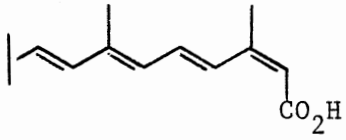
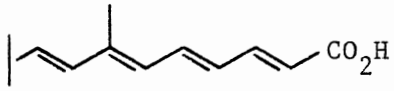
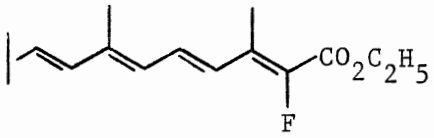
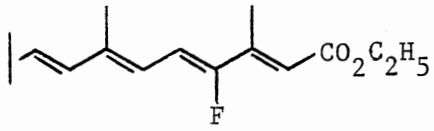
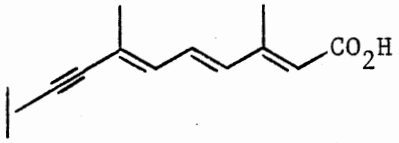
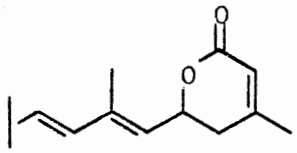
RETINOIDS WITH RING MODIFICATIONS[8,10,30,31,50,52]

Retinoid	ED_{50} (M)*
 3	3×10^{-11}
 8	10^{-8}
 7	7×10^{-10}
	5×10^{-9}
	5×10^{-10}
	2×10^{-10}
	10^{-8}

*ED_{50} is the minimum effective dose required to reverse keratinization in half of the test group.

TABLE II

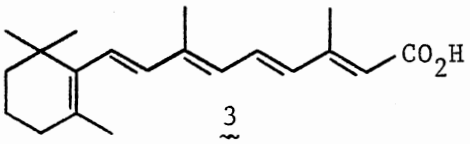
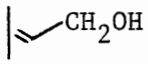
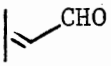
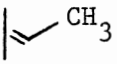
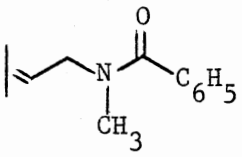
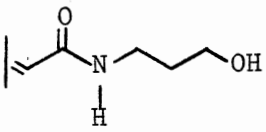
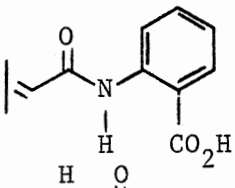
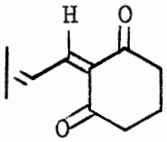
RETINOIDS WITH SIDE CHAIN MODIFICATIONS[14,40,31,46,50,56]

Retinoid	ED_{50} (M)*
	3×10^{-11}
	3×10^{-11}
	10^{-9}
	$< 10^{-9}$
	$< 10^{-9}$
	5×10^{-10}
	5×10^{-9}

*ED_{50} is the minimum effective dose required to reverse keratinization in half of the test group.

TABLE III

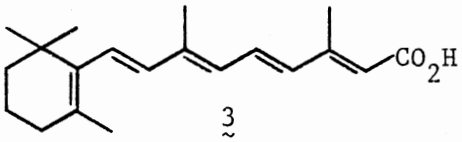
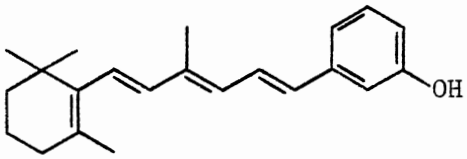
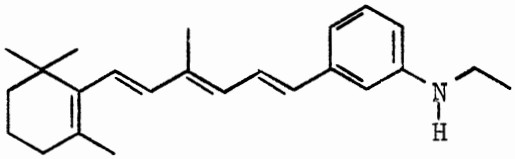
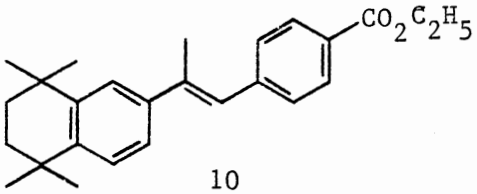
RETINOIDS WITH TERMINAL GROUP MODIFICATIONS[30,31,55]

Retinoid	ED_{50} (M)*
 3	3×10^{-11}
1 	7×10^{-10}
2 	3×10^{-10}
	2×10^{-9}
	1×10^{-9}
	1×10^{-10}
	$< 1 \times 10^{-10}$
	1×10^{-10}

*ED_{50} is the minimum effective dose required to reverse keratinization in half of the test group.

TABLE IV

AROMATIC RETINOIDS - AROTINOIDS[9,25,30,31]

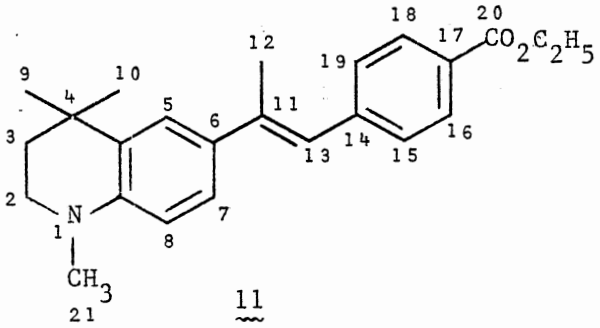
Retinoid	ED_{50} (M)*
 3	3×10^{-11}
	1×10^{-9}
	1×10^{-8}
 10	1×10^{-11}

*ED_{50} is the minimum effective dose required to reverse keratinization in half of the test group.

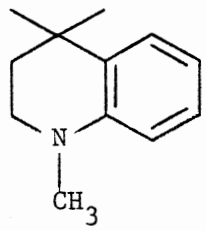
CHAPTER II

RESULTS AND DISCUSSION

One of the problems associated with the therapeutic administration of retinoids is the unfavorable tissue distribution due to the lipophilic character of the molecules.[34] A synthetic retinoid with increased hydrophilic properties could possibly exhibit enhanced transport in the plasma and thereby show improved efficacy in reaching tumor sites. This in turn would permit the use of smaller dosages since a higher percentage of the dose would be available to the malignant tissue. Consequently, one objective of the present work was to incorporate a nitrogen atom into the retinoid ring system. The presence of such an atom should increase the polarity of the molecule and greatly increase its ability to hydrogen bond to polar substances. Loeliger's success[25] with the arotinoid 10 suggested to us that the preparation of the heterocyclic arotinoid 11 would be a good candidate to have improved hydrophilicity and



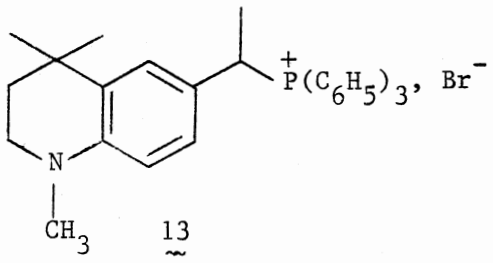
11



12

possibly enhanced antitumor activity. Thus, an initial target compound

to serve as an intermediate for 11 was 1,4,4-trimethyl-1,2,3,4-tetrahydroquinoline (12). Theoretically, the exocyclic double bond at C(11)-C(13) could possibly be formed via a condensation of the Wittig reagent made from 13 and the aldehyde 14. Figure 4 contains the outline of the



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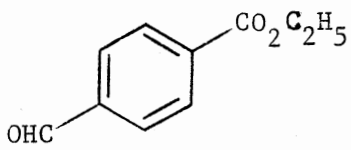


14

successful procedure (15→16→12) which has produced 1,4,4-trimethyl-1,2,3,4-tetrahydroquinoline (12) and aldehyde 14 (17→18→19→14) (see Figure 5).

Ethyl acrylate condensed with N-methylaniline in a Michael reaction (Figure 4) in the presence of acetic acid as a catalyst.[1] The overall yield of 15 was 78.2%. Spectral data for 15 are given in Plates IX-XII and will be discussed later. Addition of methylmagnesium chloride to the ester 15 in THF afforded the tertiary alcohol 16 in good yield (80.1%).

Ring closure of the alcohol 16 to amine 12 proved more difficult than anticipated. The successful approach involved treatment of a benzene solution of the alcohol 16 containing a few mL of 85% H_3PO_4 with P_2O_5 in small quantities over a period of several hours of reflux. A normal workup consisting of hydrolysis, neutralization, and extraction

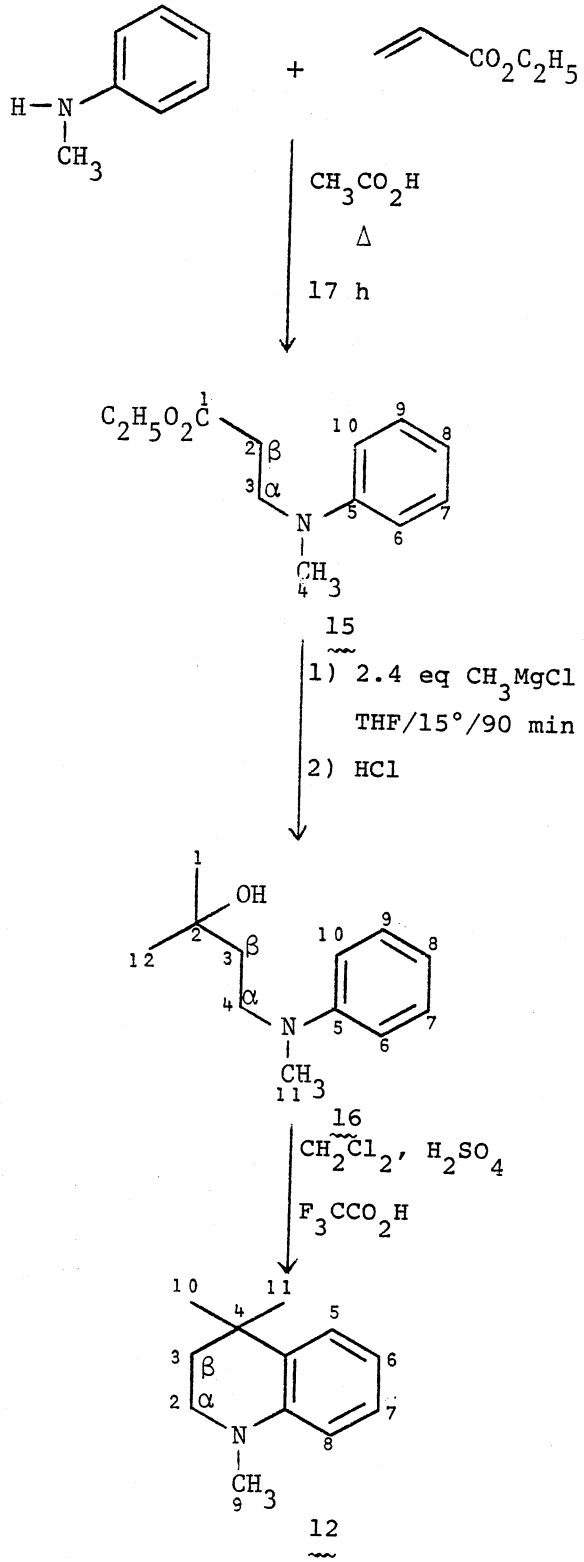


Figure 4. Synthetic Scheme for 12

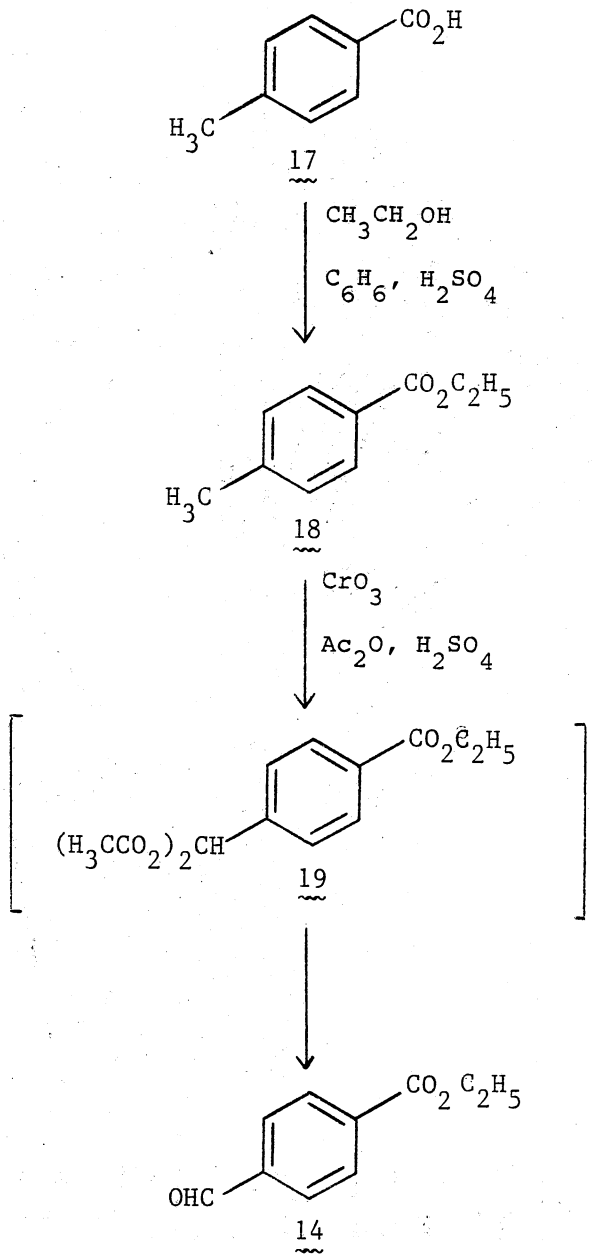
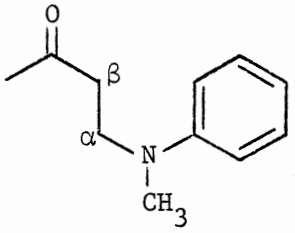


Figure 5. Synthetic Scheme for 14

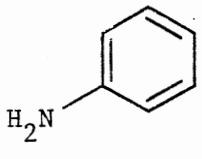
gave the final amine 12, after distillation, in a yield of 77%.

A more easily accomplished method was later found. A solution of alcohol 16 in H_2CCl_2 was treated with a 1:10 solution (by volume) of F_3CCO_2H/H_2SO_4, and the resulting solution was heated at reflux for three hours. Decomposition of the reaction mixture with water followed by distillation of the product gave 12 as an oil (77%). Although the yields were comparable from both sequences, the latter methodology proved easier to accomplish, especially in the work-up.

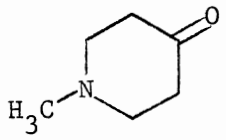
NMR analysis was performed using both ^1H and ^{13}C spectral data. Ester 15 showed the expected triplet for the CH_2 alpha to the nitrogen at δ 3.59 and another triplet for the CH_2 beta to the nitrogen at δ 2.46. As a model system, compound 20[3] proved of some value since it had an ^1H spectrum with H(α) and H(β) [on corresponding methylenes] at δ 3.66 and 2.70, respectively. Alcohol 16 showed signals for the same methylene protons on the specified carbons at δ 3.81 and 2.06, respectively. The protons from the methyl group attached to nitrogen showed peaks at δ 2.94 (20), 2.80 (15), and 3.24 (16). Other signals can be found in the Experimental Section (complete spectra shown in Plates I-XVI).



20



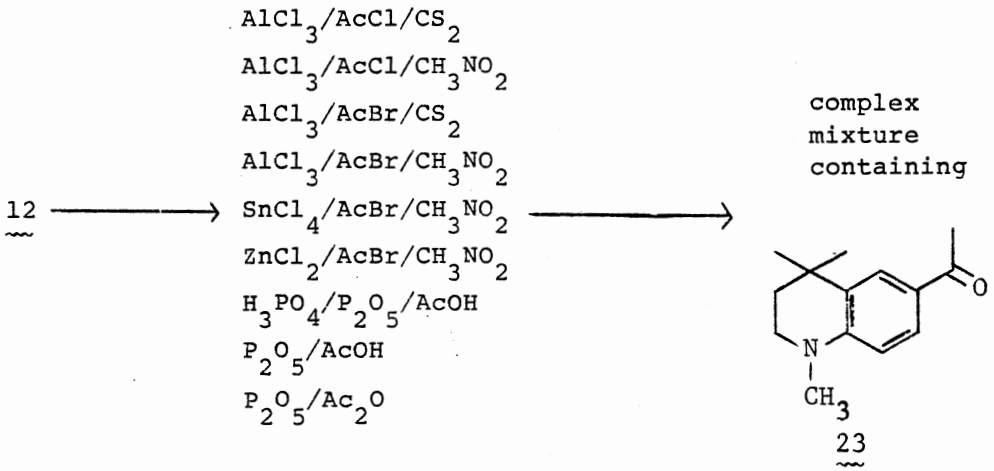
21



22

Assignments for the ^{13}C resonances were aided by observed splitting patterns from off-resonance spectra and from comparison with the spectra of model compounds 21 and 22. Ester 15 showed a signal for C(3) [alpha to the nitrogen atom] at 48.4 ppm and a signal at 31.6 ppm for C(2). The carbonyl carbon had a signal at 171.7 ppm and the methyl attached to the nitrogen appeared at 37.9 ppm. The signals for C(4), C(3), and the methyl carbon bonded to nitrogen in alcohol 16 were visible at 48.5, 38.5, and 38.1 ppm, respectively. These same carbons produced resonances in the final amine 12 at 47.6, 37.3, and 39.2 ppm, respectively. Other signals for the remaining carbons were detected in all three compounds in the expected positions and are summarized in the Experimental Section.

A number of approaches to the preparation of ketone 23 have not been fruitful to date. Spectral data from crude reaction mixtures produced from the attempted condensations shown below have indicated that ketone 23 is likely formed but in low yield and as part of a complex mixture. The final synthesis of 23 awaits completion.



Concurrent with our effort to obtain ketone 23, we have been able to obtain the aldehyde 14 shown in Figure 5. Based on previous experience in our laboratory, it was reasoned that hydrolysis of the diacetate 19 to the corresponding aldehyde should be facile. The projected use of the aldehyde in a condensation with the Wittig reagent from the phosphonium salt 13 is shown in Figure 6.

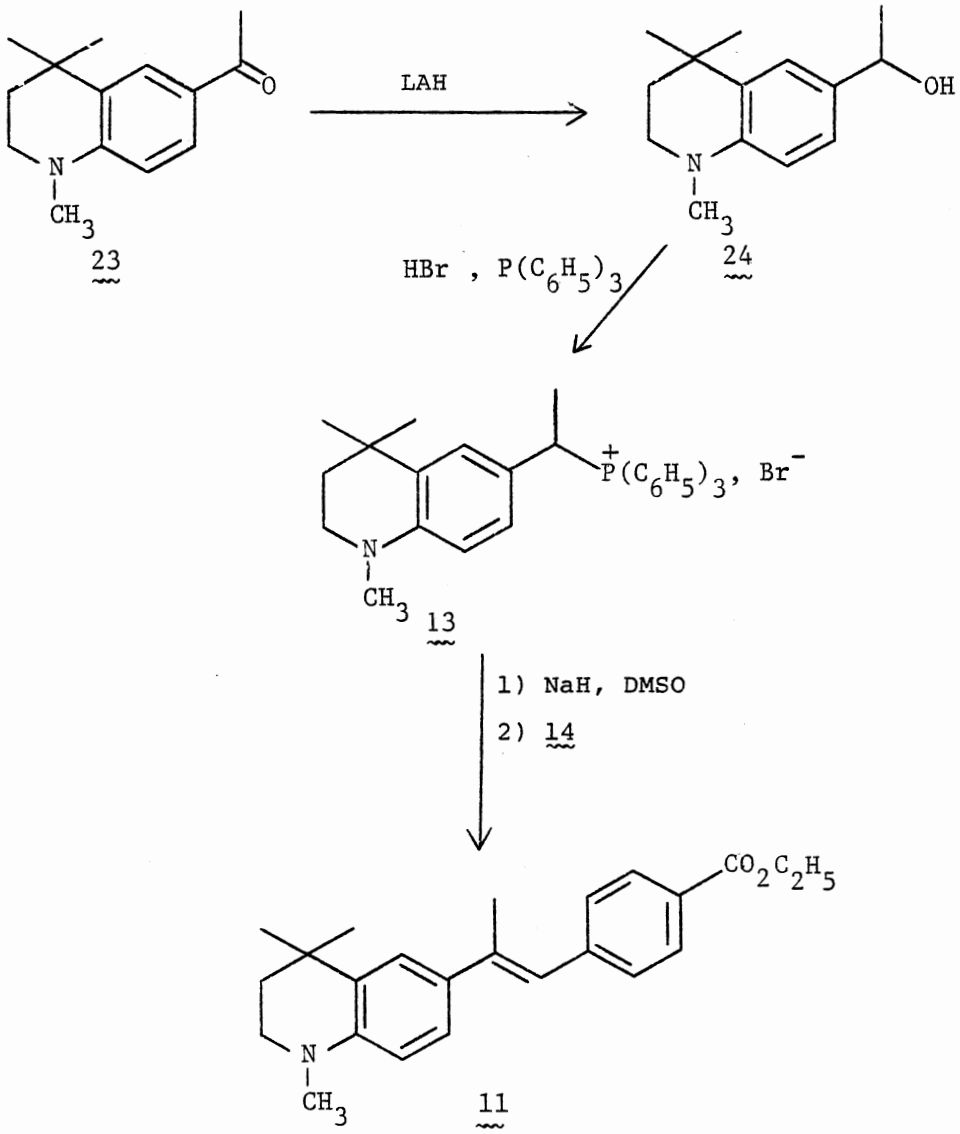


Figure 6. Proposed Synthetic Scheme for 11

Suggestions for Future Work

Since attempts to make the ketone 23 from the tetrahydroquinoline 16 were frustrated because of complex mixtures formed, an alternative route to the intermediate alcohol 24 is postulated below. 4-Chloroaniline, which is available from Aldrich, is the suggested starting material.

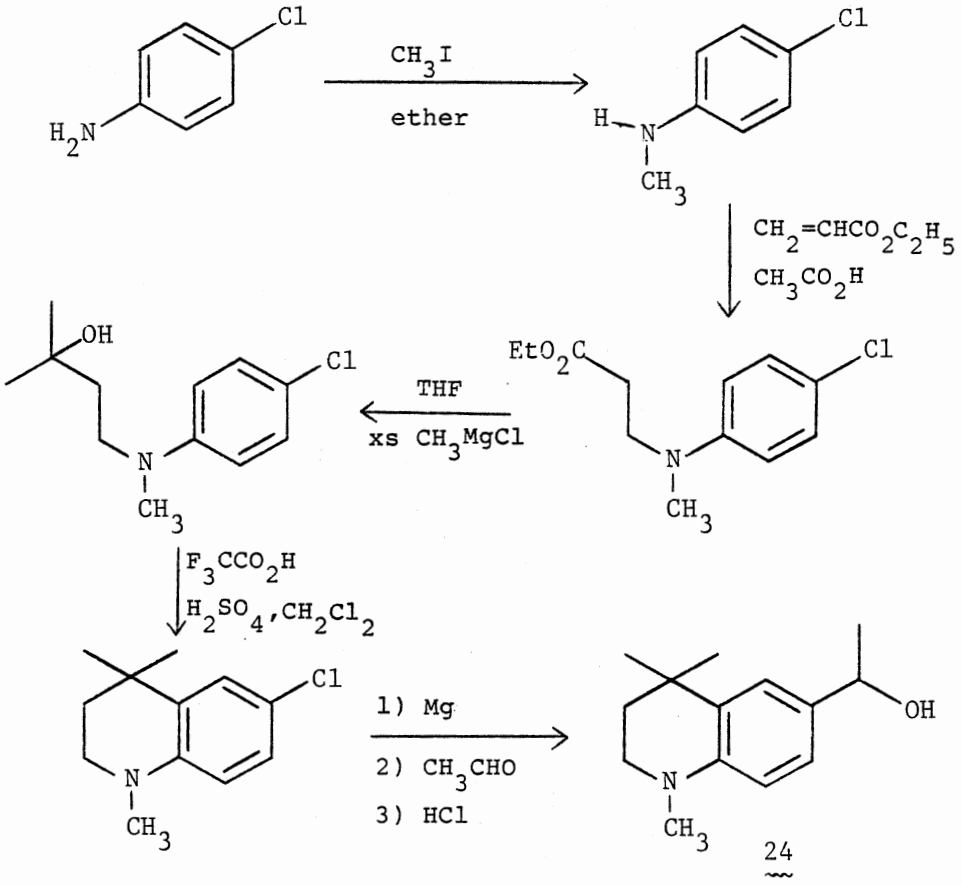


Figure 7. Proposed Synthetic Scheme for 24

CHAPTER III

EXPERIMENTAL SECTION

General Information

^{1}H NMR spectral data were obtained using a Varian XL-300 spectrometer. ^{13}C NMR spectral data were obtained using a Varian XL-100(15) NMR spectrometer equipped with a Nicolet TT-100 PFT accessory. All NMR data are reported in δ or ppm values downfield from TMS used as the internal reference. Solvent for all NMR spectra was $DCCl_3$. IR spectral data were obtained using a Perkin-Elmer 681 IR spetrophotometer. Mass spectral data were obtained on a CEC Model 21-110B HR mass spectrometer.

Starting Materials

The following materials and special reagents were purchased from the source listed and were used without purification unless otherwise specified: N-methylaniline (Aldrich, freshly distilled from zinc dust, bp 194-195°C), ethyl acrylate (Aldrich, bp 99°C), methylmagnesium chloride (Aldrich, 2.9 M in THF), trifluoroacetic acid (Eastman, bp 72°C), p-toluic acid (Aldrich, mp 180-182°C), and chromic oxide (Mallinckrodt).

Ethyl 3-Phenylmethylaminopropionate (15)

A solution of freshly distilled N-methylaniline (267.5 g, 2.50 mol) and glacial acetic acid (50 mL) was placed in a 1 l, 3-necked flask equipped with a water cooled condenser (carrying a $CaCl_2$ drying tube)

and an addition funnel charged with ethyl acrylate (250 g, 2.50 mol). The flask was warmed on a steam bath and the ethyl acrylate was added dropwise over a 25 min period. The resulting yellow solution was heated with occasional swirling for 17 h during which time it turned deep red. This solution was washed with 5% $NaHCO_3$ (4 x 75 mL) and then with brine (3 x 75 mL). During the first wash, an emulsion formed, and 50 mL of diethyl ether was added to destroy it. After drying ($MgSO_4$) the solution, evaporation gave a red oil which was distilled to give 404.5 g of 15 (78.2%) as a yellow oil: bp 105-109°C/0.2 mm (lit[1] 98-100°C/0.05 mm); IR (neat) cm^{-1} 1740 (C=O); ^1H NMR ($DCCl_3$) δ 1.15 [t, 3 H, $OCH_2\underline{CH}_3$], 2.46 [t, 2 H, $\underline{CH}_2CO_2CH_2CH_3$, J = 7.08 Hz], 2.80 [s, 3 H, $NC\underline{H}_3$], 3.59 [t, 2 H, $NC\underline{H}_2$, J = 7.08 Hz], 4.04 [q, 2 H, $OC\underline{H}_2CH_3$], 6.67 [m, 3 H, o & p-Ar$\underline{H}$], 7.18 [m, 2 H, m-Ar$\underline{H}$]; ^{13}C NMR ($DCCl_3$) ppm 14.1 [$OCH_2\underline{CH}_3$], 31.6 [C(2)], 37.9 [C(4)], 48.4 [C(3)], 60.2 [$O\underline{CH}_2$], 112.3 [C(6,10)], 116.5 [C(8)], 129.0 [C(7,9)], 148.4 [C(5)], 171.7 [C(1)]; mass spec. calcd for $C_{12}H_{17}NO_2$: 207.1259; Found: 207.1261.

2-Methyl-4-(phenylmethylamino)-2-butanol (16)

A solution of methylmagnesium chloride (Aldrich, 2.9 M in THF, 414 mL, 1.20 mol) was placed in a 1 l, 3-necked, round-bottom flask along with a magnetic stirring bar. The flask was equipped with a thermometer, a dry ice condenser carrying a $CaCl_2$ drying tube, and an addition funnel charged with ethyl 3-phenylmethylaminopropionate (15, 100 g, 0.483 mol). The apparatus was flushed with nitrogen and the flask and contents were cooled to -5°C in an ice-salt bath. The ester 15 was then added dropwise at such a rate that the temperature stayed below 15°C (45 min). After warming slowly to RT, the solution was stirred for

an additional 90 min. The mixture was poured onto 400 g of crushed ice contained in a 2 l Erlenmeyer flask, and then 85 mL of conc HCl was slowly added with stirring. Stirring was continued for 1 h and then water was added to dissolve the precipitated salts which brought the total volume to 1400 mL. The solution was then neutralized by addition of solid K_2CO_3 (50 g). Two layers separated and the aqueous layer was extracted with $HCCl_3$ (3 x 100 mL). The combined organic portions were washed with brine (50 mL) and dried (K_2CO_3). Evaporation of the solvent gave an orange oil which was distilled under vacuum to give 74.7 g (80.1%) of 16 as a pale yellow liquid: bp 95-99°C/0.08 mm; IR (neat) cm^{-1} 3150-3650 (OH); ^1H NMR ($DCCl_3$) δ 1.62 [s, 6 H, $HOC(CH_3)_2$], 2.06 (t, 2 H, NCH_2CH_2, J = 7.82 Hz], 3.24 [s, 3 H, NCH_3], 3.34 [s, 1 H, OH], 3.81 [t, 2 H, NCH_2, J = 7.86 Hz], 7.15 [m, 3 H, o & p-ArH], 7.64 (t, 2 H, m-ArH]; ^{13}C NMR ($DCCl_3$) ppm 29.3 [C(1,12)], 38.1 [C(11)], 38.5 (C(3)], 48.5 [C(4)], 69.8 [C(2)], 112.8 [C(6,10)], 116.4 [C(8)], 128.9 [C(7,9)], 149.1 [C(5)]; mass spec. calcd for $C_{12}H_{19}NO$: 193.1467; Found: 193.1464.

1,4,4-Trimethyl-1,2,3,4-tetrahydroquinoline (12)

A solution of 16 (21.3 g, 0.110 mol) in CH_2Cl_2 (350 mL) was placed in a 500 mL, round-bottom flask equipped with a magnetic stirring bar. To this was added cautiously a solution of F_3CCO_2H (5 mL) in conc H_2SO_4 (50 mL). The mixture was boiled for 3 h after which time the CH_2Cl_2 was evaporated. The residue was neutralized by the addition of a saturated aqueous solution of K_2CO_3. The resulting slurry was extracted with $HCCl_3$ (3 x 75 mL), and the combined extracts were washed with 5% $NaHCO_3$ (3 x 50 mL) and then with brine (2 x 50 mL). After drying (K_2CO_3), the solution gave a red oil which was distilled under vacuum to yield 12 (14.8 g,

77.1%) as a colorless oil: bp 137-139°C/0.06 mm; ^{1}H NMR ($DCCl_3$) δ 1.24 [s, 6 H, $C(C\underline{H}_3)_2$], 1.69 [t, 2 H, $NCH_2C\underline{H}_2$, J = 5.96 Hz], 2.79 [s, 3 H, $HC\underline{H}_3$], 3.11 [t, 2 H, $NC\underline{H}_2$, J = 5.94 Hz], 6.51-7.14 [m, 4 H, Ar$\underline{H}$]; ^{13}C NMR ($DCCl_3$) ppm 31.0 [C(10,11)], 31.9 [C(4)], 37.3 [C(3)], 39.2 [C(9)], 47.6 [C(2)], 131.2 [C(4a)], 145.3 [C(8a)]; mass spec. calcd for $C_{12}H_{17}N$: 175.1361; Found: 175.1358.

Ethyl p-Toluate (18)

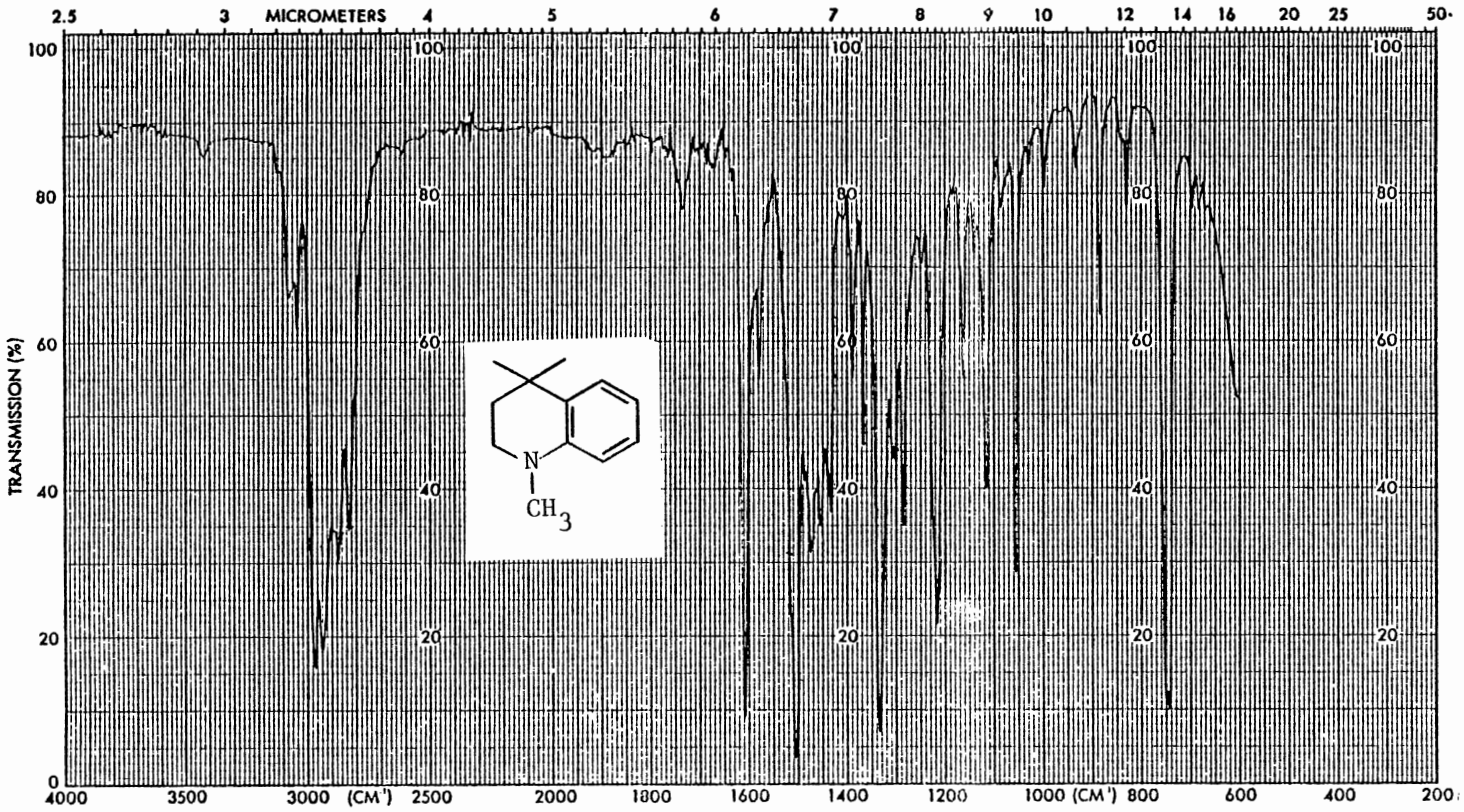
Absolute ethanol (75 mL) and p-toluic acid (10.0 g, 0.073 mol) were dissolved in dry benzene (55 mL) in a 250 mL, round-bottom flask. Concentrated sulfuric acid (10 mL) was added, and the flask was equipped with a Dean-Stark trap. The mixture was boiled for 4 h (a small amount of H_2O was removed) and then poured onto ice (100 g). Two layers separated, and the aqueous layer was extracted with ether (3 x 50 mL). The combined organic portions were washed with brine (2 x 25 mL), 5% $NaHCO_3$ (25 mL), and again with brine (25 mL). The bicarbonate wash was acidified with conc HCl, and unreacted p-toluic acid was collected on a Buchner funnel (0.57 g). The organic portion was dried ($MgSO_4$) and then evaporated to a colorless liquid which was distilled to give 10.32 g (90.8%) of 18; bp 233-234°C (lit[5] 235°C/760 mm); IR (neat) cm^{-1} 1730 (C=O).

Ethyl-4-Formylbenzoate (14)

A solution of ethyl p-toluate (18, 10.0 g, 0.61 mol) in acetic anhydride (60 mL) was placed in a 500 mL, 3-necked flask equipped with a mechanical stirrer, a thermometer, and an addition funnel charged with a solution of CrO_3 (17.0 g, 0.327 mol) in acetic anhydride (85 mL). The

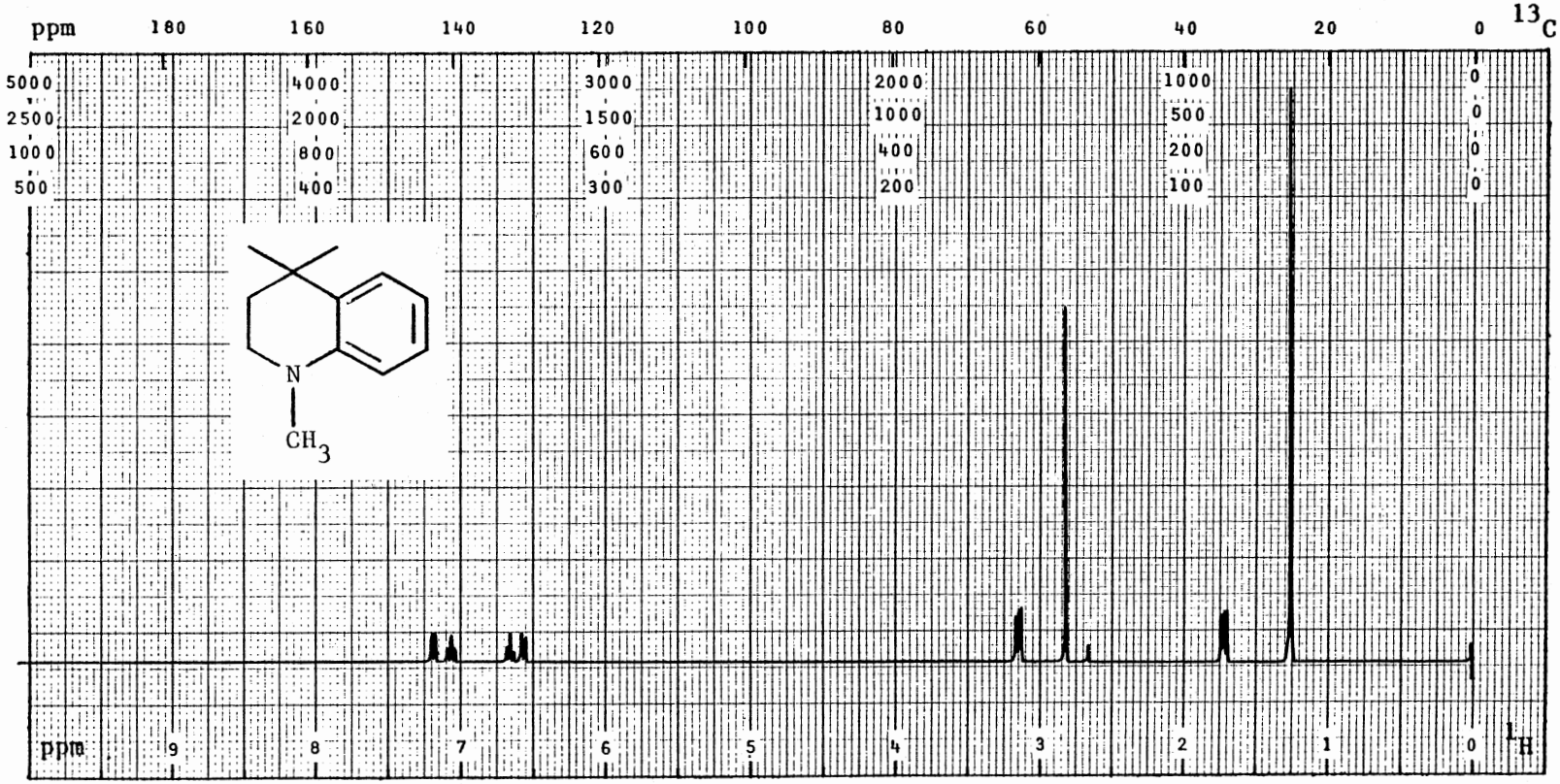
flask was immersed in an ice-salt bath and allowed to cool to 0°C after which time conc H_2SO_4 (15 mL) was cautiously added. Once the temperature returned to 0°C, the CrO_3 solution was added dropwise at such a rate as to keep the temperature below 10°C (30 min). After the addition was completed, the light green reaction mixture was stirred for an additional 2.5 h in the ice-salt bath. During this time, the color deepened to a very dark green. The contents of the flask were cautiously poured onto crushed ice (300 g) and water was added to bring the total volume to 600 mL. The resulting solution was extracted with chloroform (3 x 75 mL). The combined extracts were washed with water (50 mL), 5% $NaHCO_3$ (3 x 100 mL), and also with brine (2 x 100 mL). The solution was then dried (Na_2SO_4). Evaporation of solvent gave a light yellow oil which darkened upon standing. This oil was left for several weeks before distillation under vacuum which gave a light purple oil (22 g). Mass spectral analysis did not reveal the expected diacetate, ethyl 4-formylbenzoate (14) was recovered (35%). Apparently, ester 19 underwent hydrolysis upon standing to give the aldehyde: bp 125-132°C/0.8 mm (lit[39] bp 142°C/13 mm); IR (neat) cm^{-1} 2750 [C(O)-H], 1730 [C(O)-OC_2H_5], 1720 [HC=O], 830 [Ar-H]; ^1H NMR ($DCCl_3$) δ 1.42 [t, 3 H, $OCH_2C\underline{H}_3$], 4.43 [q, 2 H, $OC\underline{H}_2CH_3$], 7.94-8.21 [m, 4 H, Ar$\underline{H}$], 10.12 [s, 1 H, C$\underline{H}$O]; ^{13}C NMR ($DCCl_3$) ppm 14.2 [$\underline{C}H_3$], 61.4 [$O\underline{C}H_2$], 129.2 [C(2,6) or C(3,5)], 129.9 [C(2,5) or C(3,5)], 135.2 [C(1) or C(4)], 139.0 [C(1) or C(4)], 165.2 [$\underline{C}(O)OCH_2$], 191.2 [H$\underline{C}$=O]; mass spec. calcd for $C_{10}H_{10}O_3$: 178.0629; Found: 178.0627.

PLATE I. IR OF 12



1,4,4-Trimethyl-1,2,3,4-tetrahydroquinoline (12, neat)

PLATE II. ^{1}H NMR OF 12

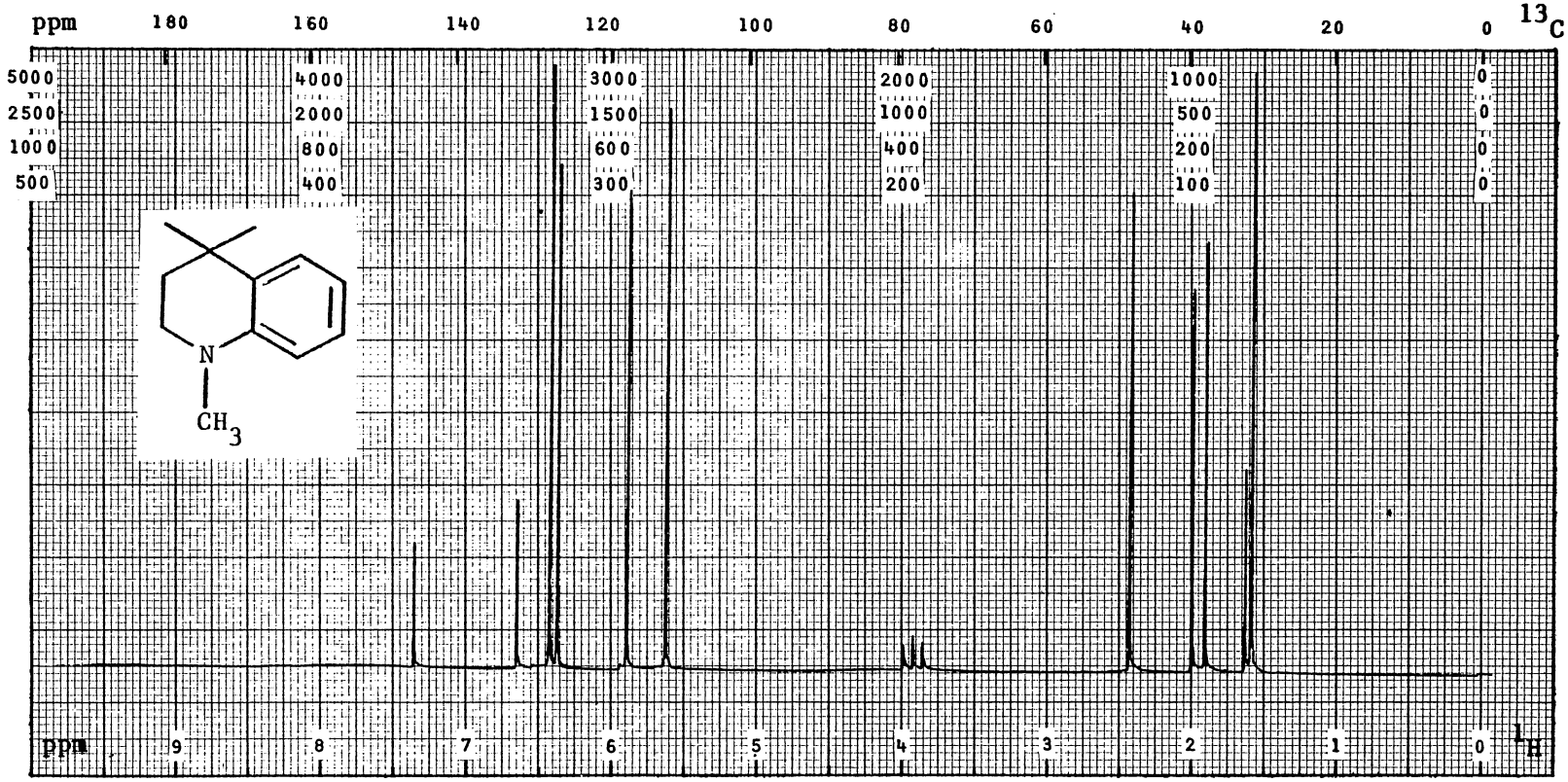


PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.94 MHz; WC: 3000 Hz; T: 25 °C; NT: 16

Size: 12 K; PW/RF: 3.0 µs/dB; SO: 0 Hz; FB: Hz; Lock: ^{2}D ; Delay: 0.500 s

DC: N ; Gated Off: ; Offset: Hz; RF: W/dB; NBW: Hz; LB:

PLATE III. ^{13}C NMR OF 12

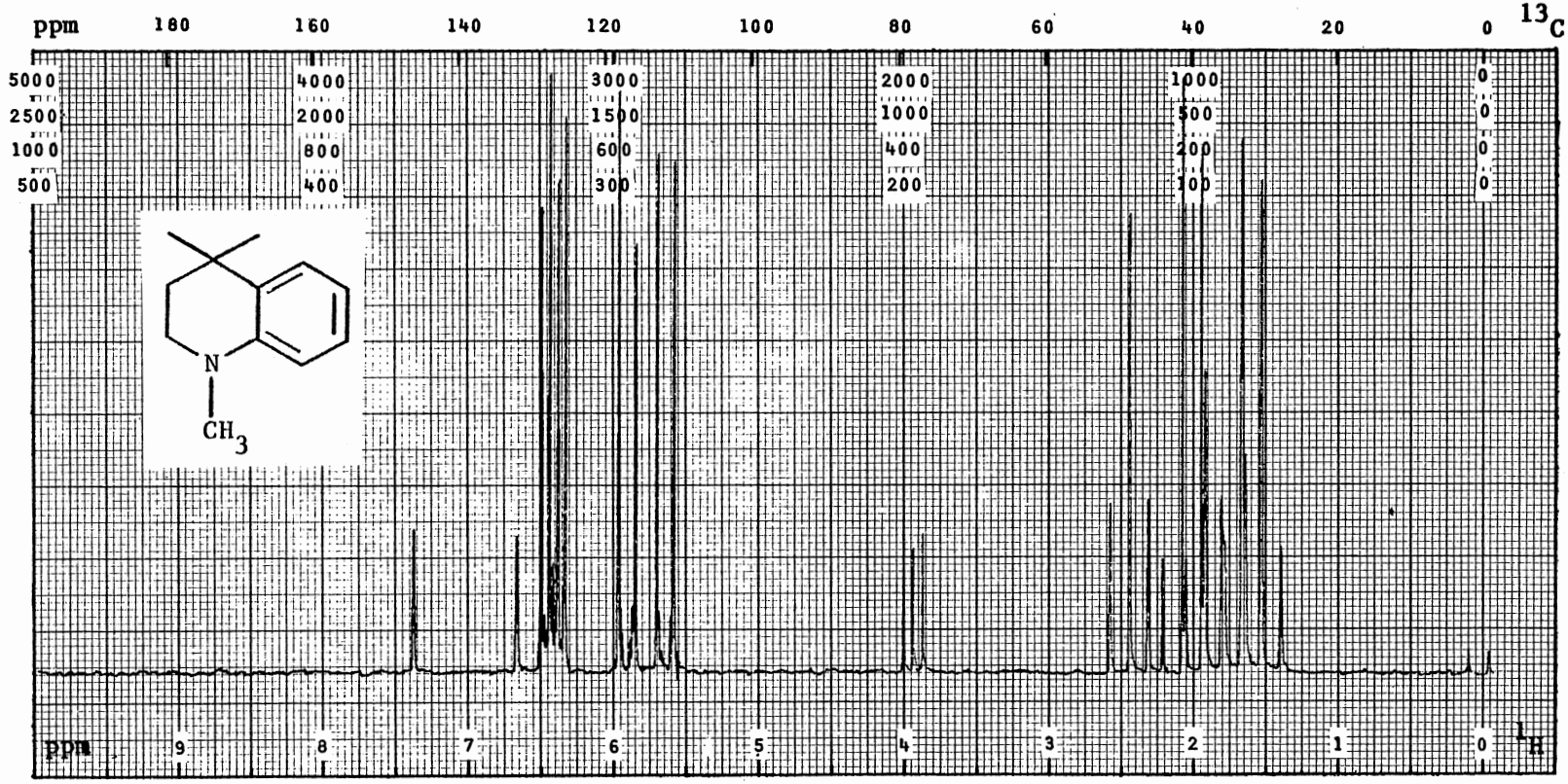


PFT X CW _ ; Solvent. $DCCl_3$; SO. 1500 Hz; PW. Hz; T. 24 °C; Acq/SA. 400

Size. 20 K; P2/RF. 14 μs/dB; SF. 75.4 M Hz; FB. ±10 K Hz; Lock. ^2D ; D5/ST. . 4 s

DC. Y ; Gated Off. ; Offset. 0 Hz; RF. 20 W/dB; NBW. 100 Hz

PLATE IV. OFF RESONANCE ^{13}C NMR OF 12

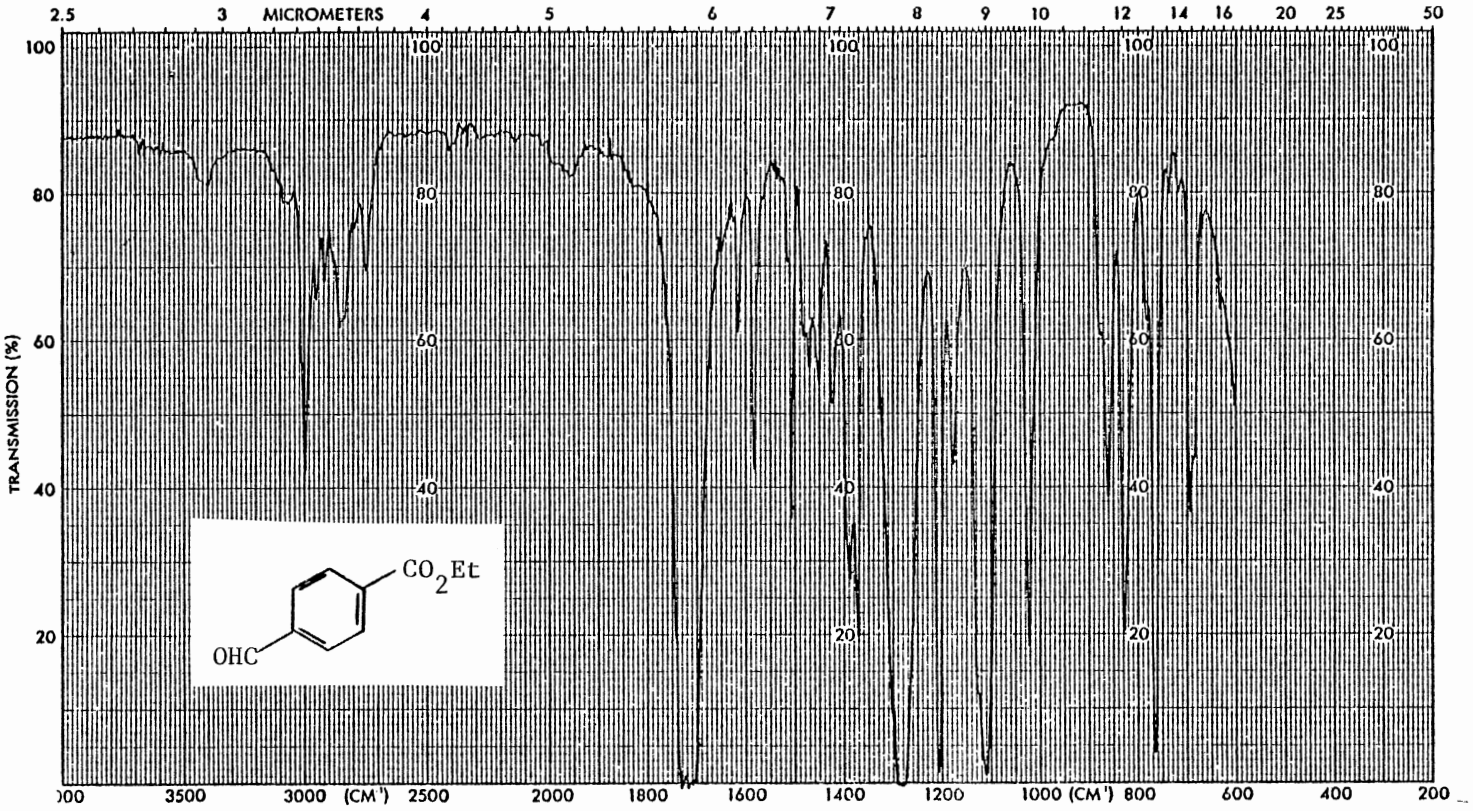


PFT X CW _ ; Solvent. $DCCl_3$; SO. 35101 Hz; PW. Hz; T. 28 °C; Acq/SA. 8000

Size. 8 K; P2/RF. 10 µs/dB; SF. 25.2 MHz; FB. ±3 KHz; Lock. ^2D ; D5/ST. 5 s

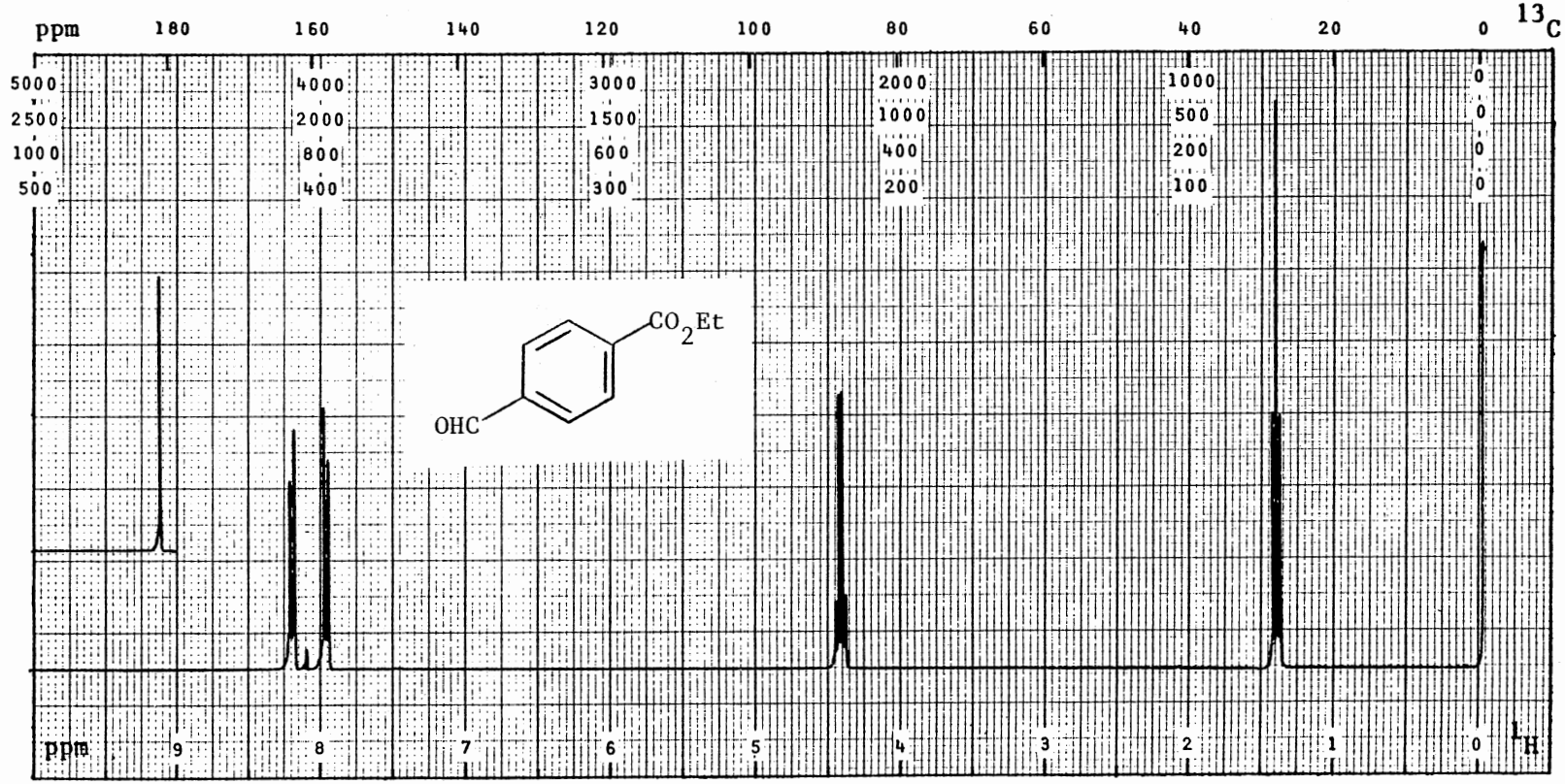
DC. Y ; Gated Off. ; Offset. 46316 Hz; RF. 7.5 W/dB; NBW. 200 Hz

PLATE V. IR OF 14



Ethyl 4-formylbenzoate (14, neat)

PLATE VI. ^{1}H NMR OF 14

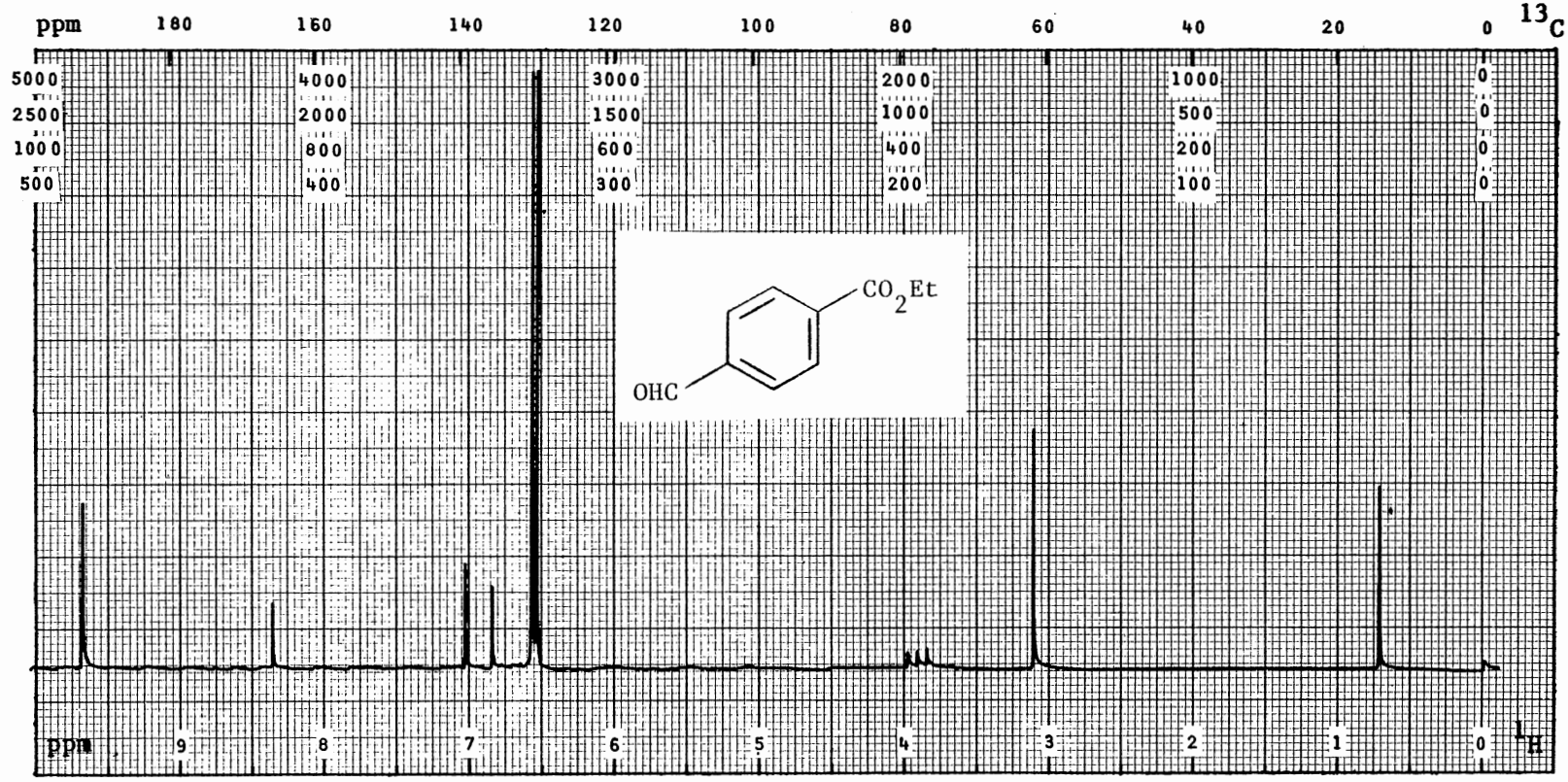


PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.94 MHz; WC: 3000 Hz; T: 25 °C; NT: 4

Size: 12 K; PW/RF: 3.0 μs/dB; SO: 0 Hz; FB: Hz; Lock: ^{2}D ; Delay: 0.500 s

DC: N ; Gated Off: ; Offset: Hz; RF: W/dB; NBW: Hz; LB:

PLATE VII. ^{13}C NMR OF 14

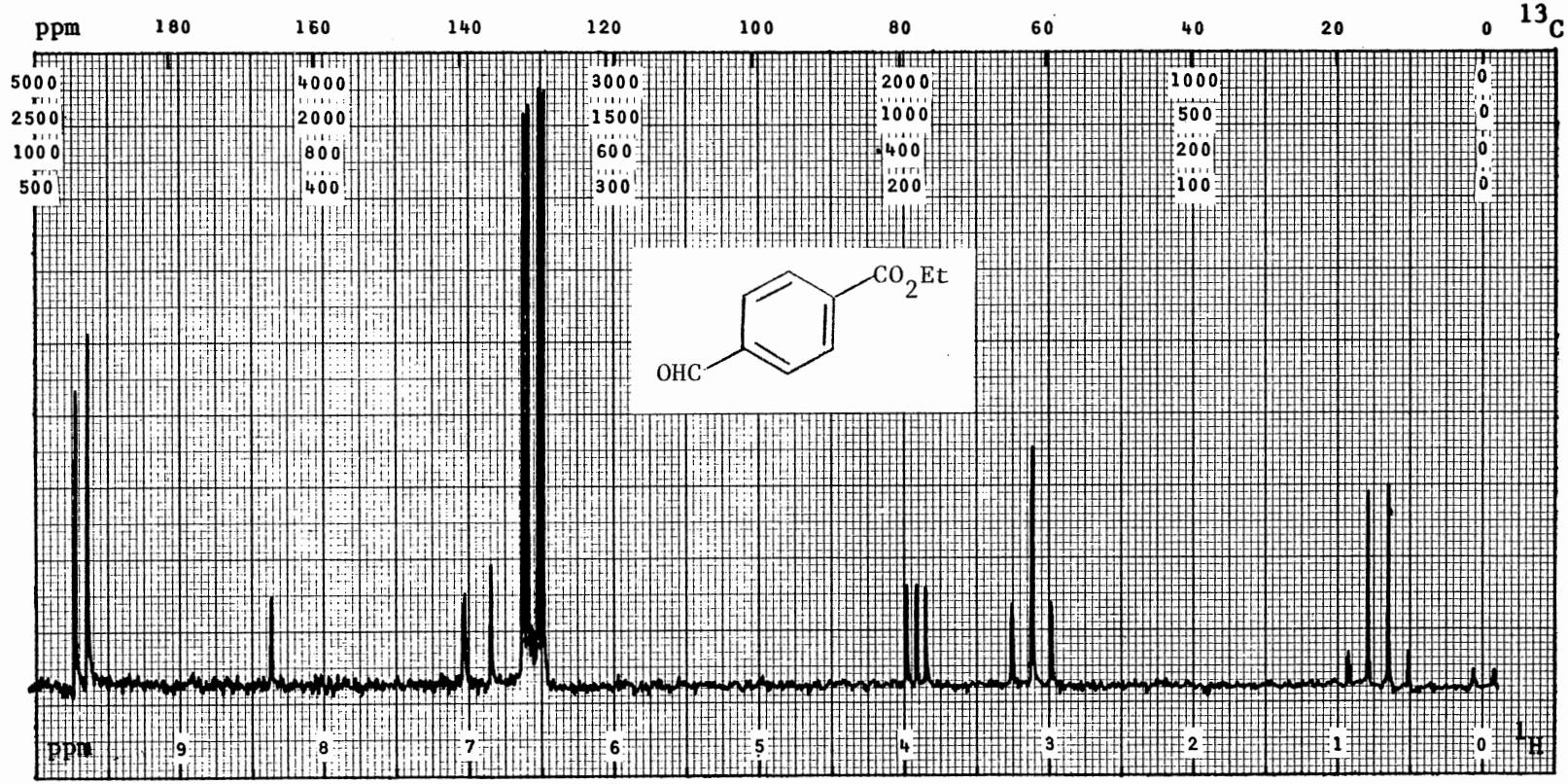


PFT X CW _ ; Solvent. $DCCl_3$; SO. 35101 Hz; PW. Hz; T. 28 °C; Acq/SA. 1000

Size. 8 K; P2/RF. 10 µs/dB; SF. 25.2 MHz; FB. ±3 KHz; Lock. ^2D ; D5/ST. 5 s

DC. Y ; Gated Off. ; Offset. 46316 Hz; RF. 7.5 W/dB; NBW. 200 Hz

PLATE VIII. OFF RESONANCE ^{13}C NMR OF 14

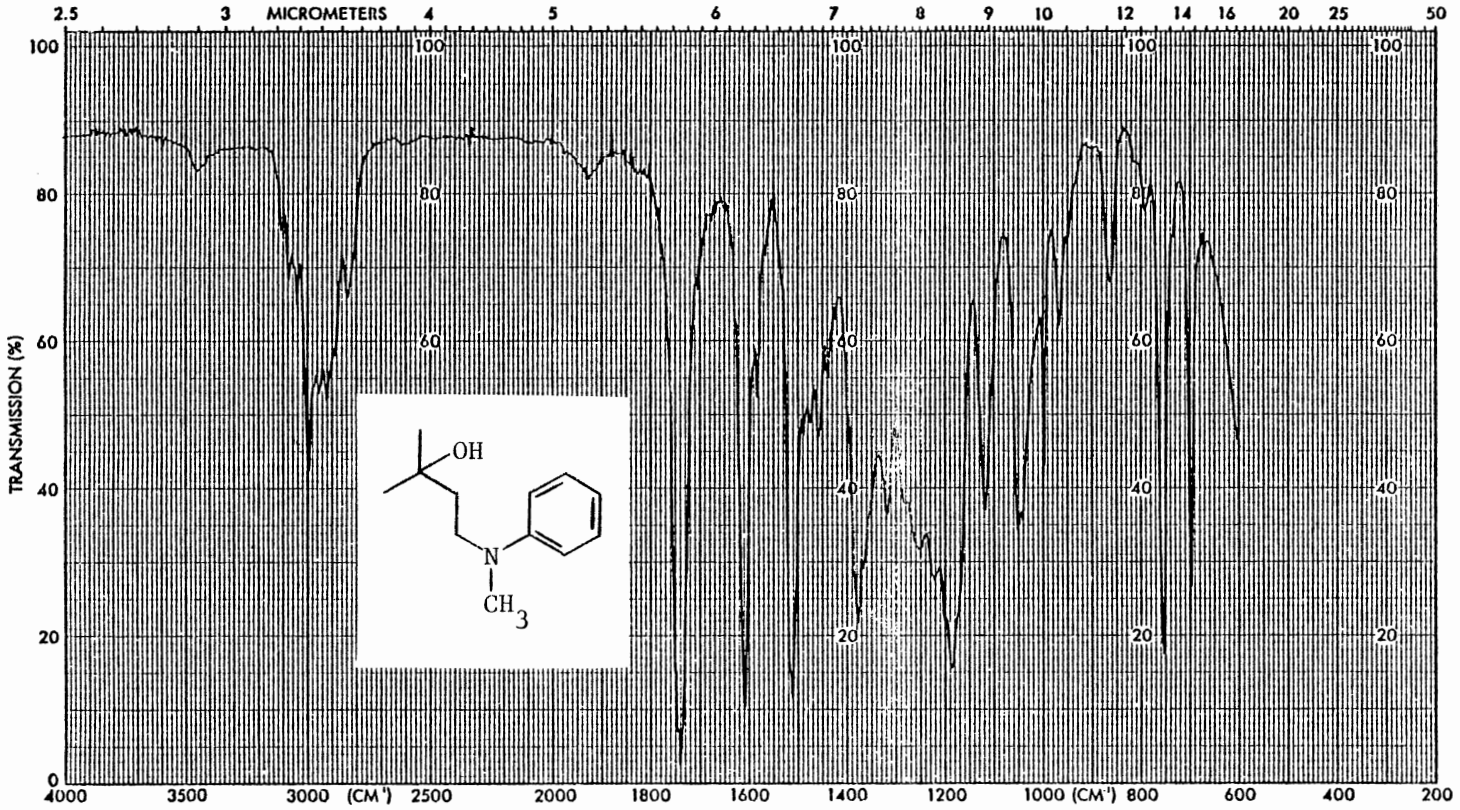


PFT X CW _ ; Solvent. $DCCl_3$; SO. 35101 Hz; PW. Hz; T. 28 °C; Acq/SA. 1446

Size. 8 K; P2/RF. 10 μs/dB; SF. 25.2 MHz; FB. ±3 KHz; Lock. ^2D ; D5/ST. 5 s

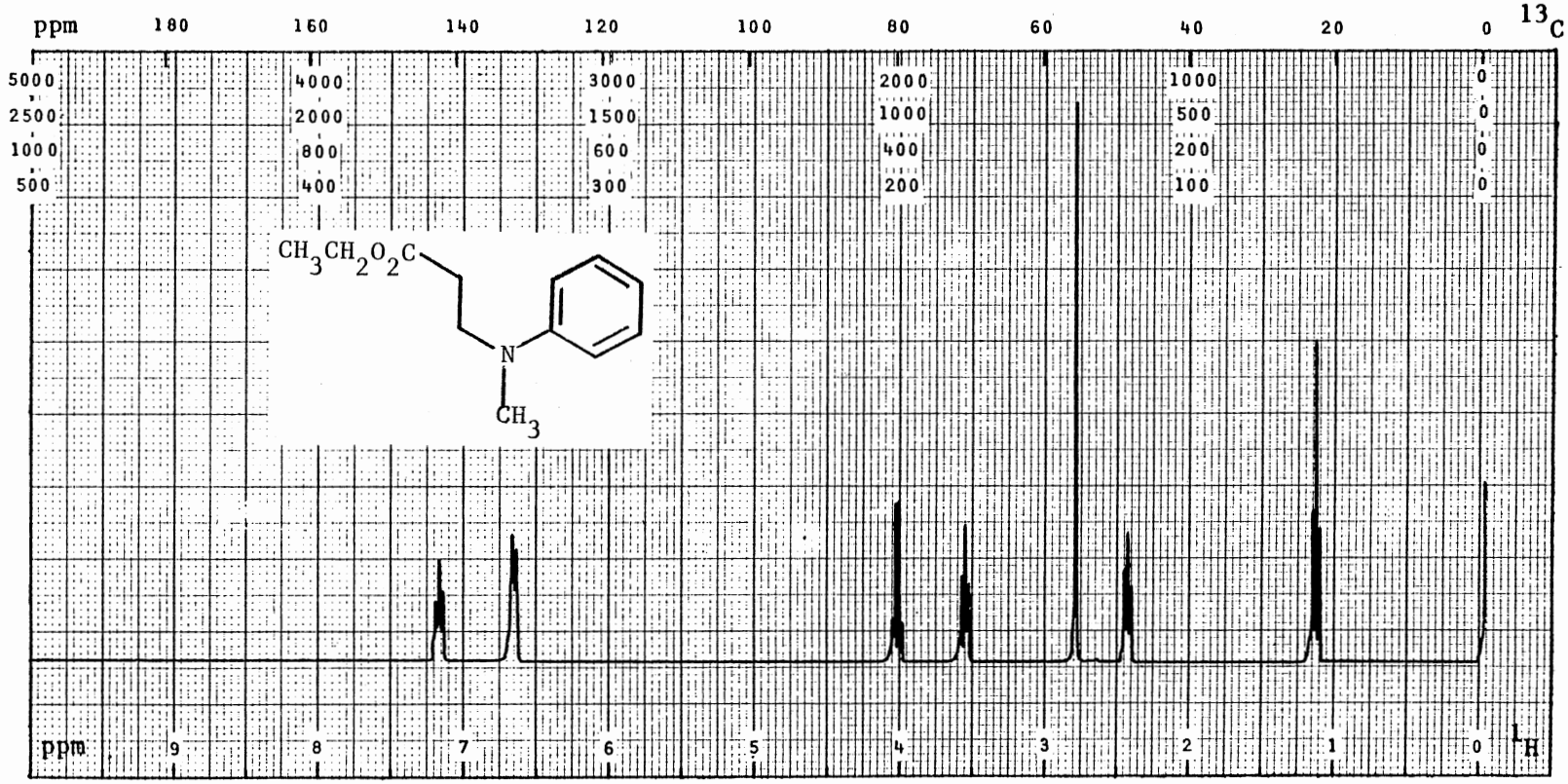
DC. Y ; Gated Off. ; Offset. 46316 Hz; RF. 7.5 W/dB; NBW. 200 Hz

PLATE IX. IR OF 15



2-Methyl-4-(phenylmethylamino)-2-butanol (15, neat)

PLATE X. ^{1}H NMR OF 15

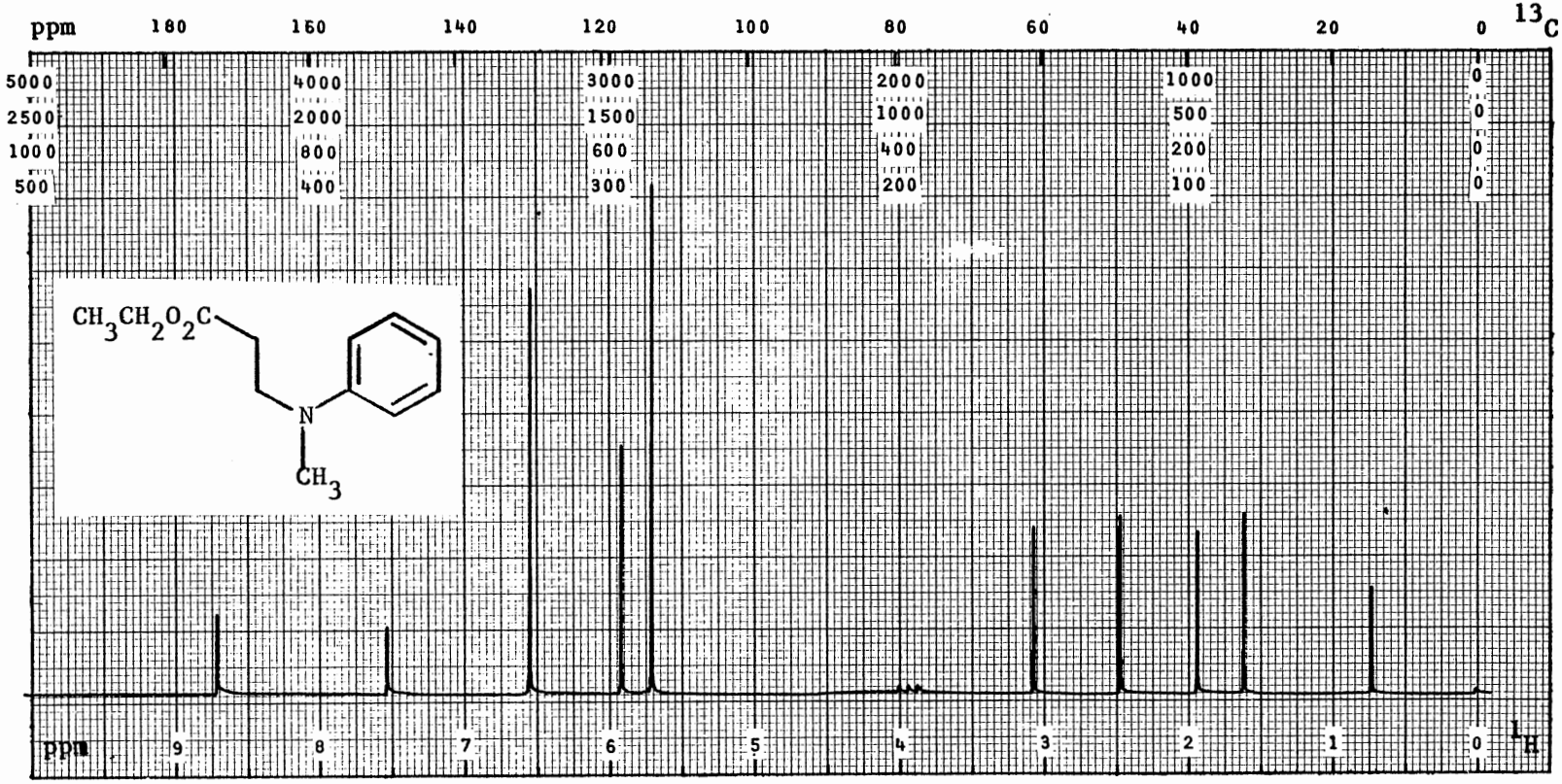


PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.94 MHz; WC: 3000 Hz; T: 25 °C; NT: 4

Size: 12 K; PW/RF: 3.0 µs/dB; SO: 100 Hz; FB: Hz; Lock: ^{2}D ; Delay: 0.500 s

DC: N ; Gated Off: ; Offset: Hz; RF: W/dB; NBW: Hz; LB:

PLATE XI. ^{13}C NMR OF 15

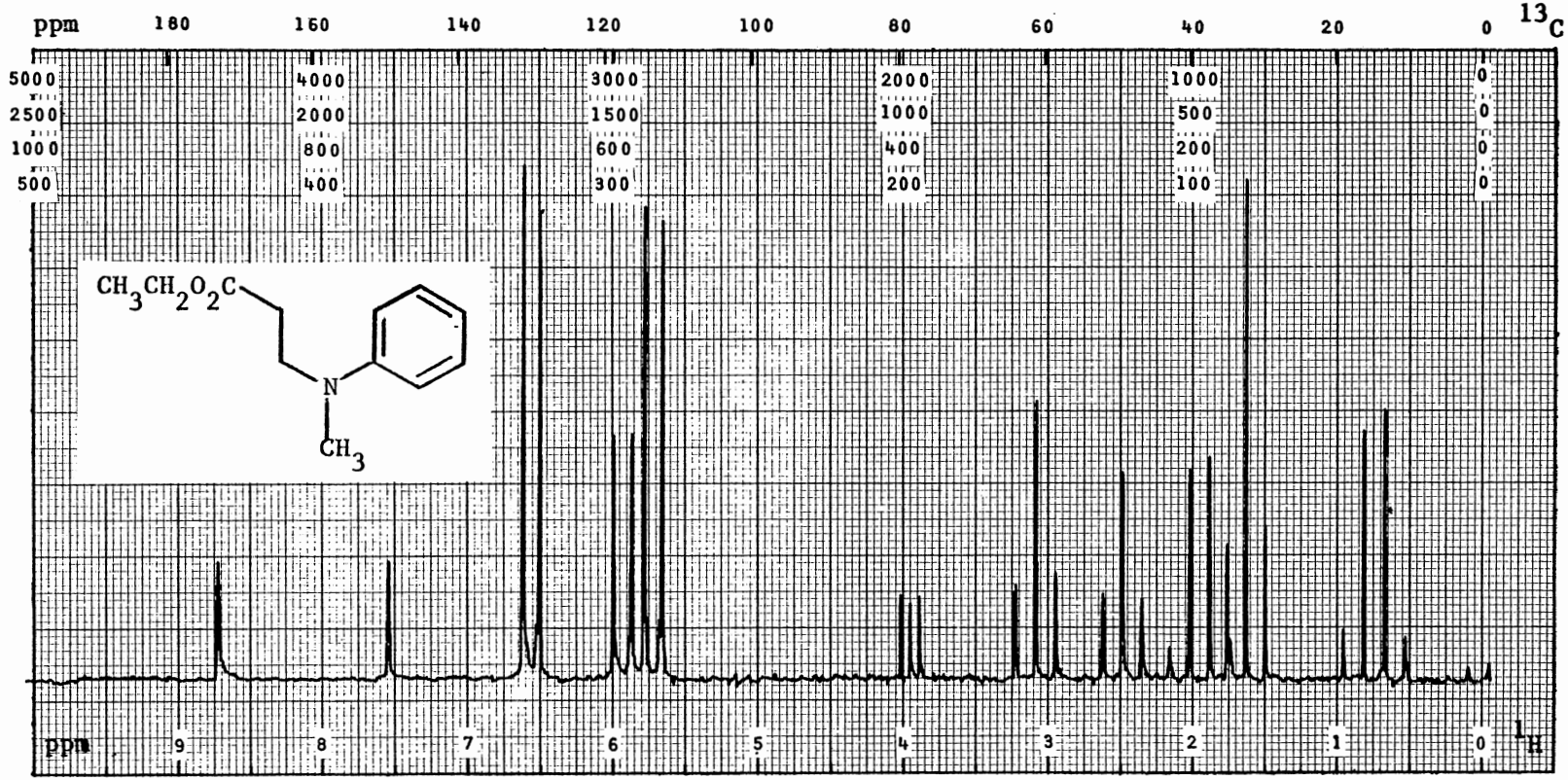


PFT X CW _ ; Solvent. $DCCl_3$; SO. 35101 Hz; PW. Hz; T. 28 °C; Acq/SA. 1025

Size. 8 K; P2/RF. 10 µs/dB; SF. 25.2 MHz; FB. ± 3 KHz; Lock. ^2D ; D5/ST. 5 s

DC. Y ; Gated Off. ; Offset. 45316 Hz; RF. 7.5 W/dB; NBW. 200 Hz

PLATE XII. OFF RESONANCE ^{13}C NMR OF 15

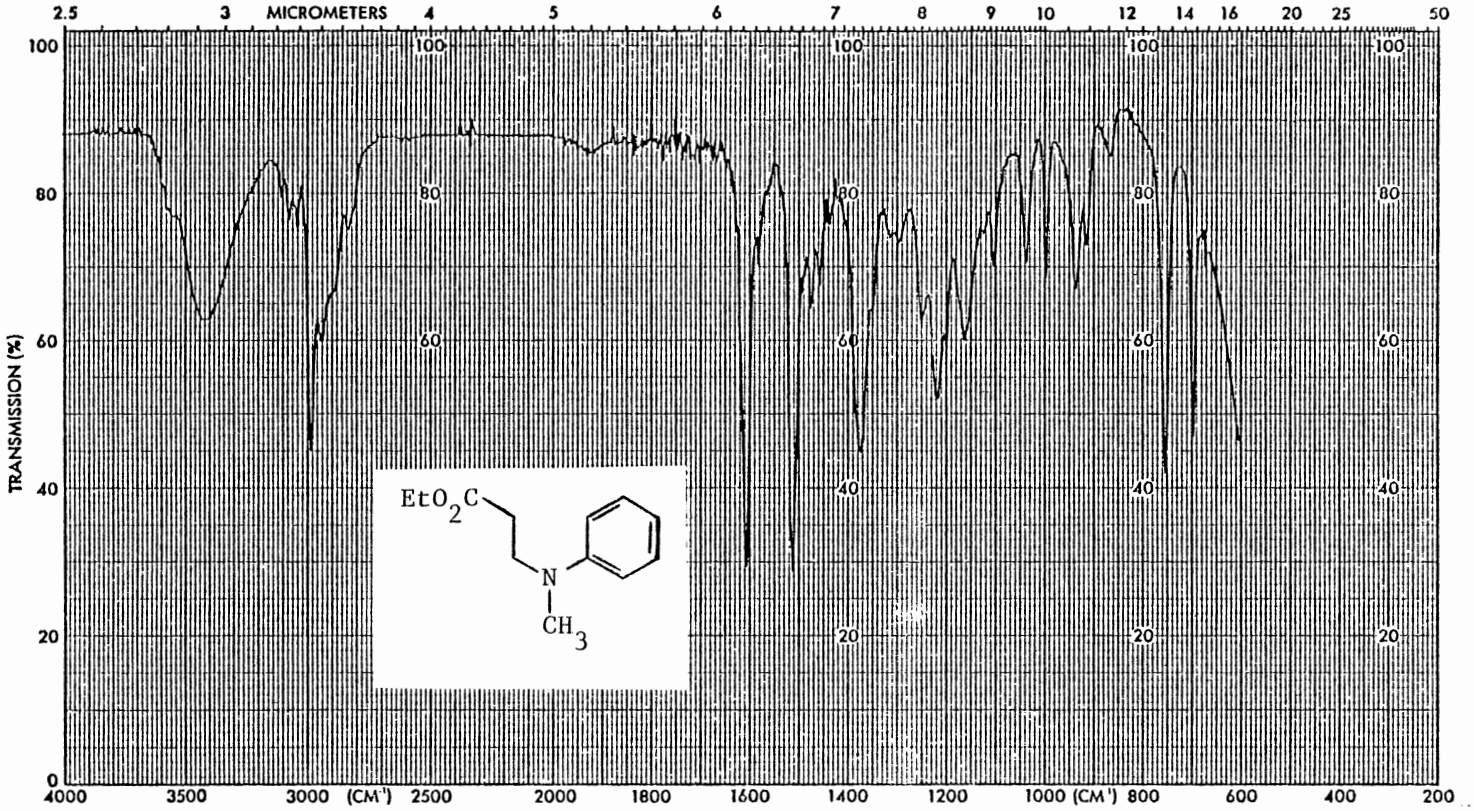


PFT X CW _ ; Solvent. $DCCl_3$; SO. 35101 Hz; PW. Hz; T. 28 °C; Acq/SA. 1500

Size. 8 K; P2/RF. 10 µs/dB; SF. 25.2 MHz; FB. ±3 KHz; Lock. ^2D ; D5/ST. 5 s

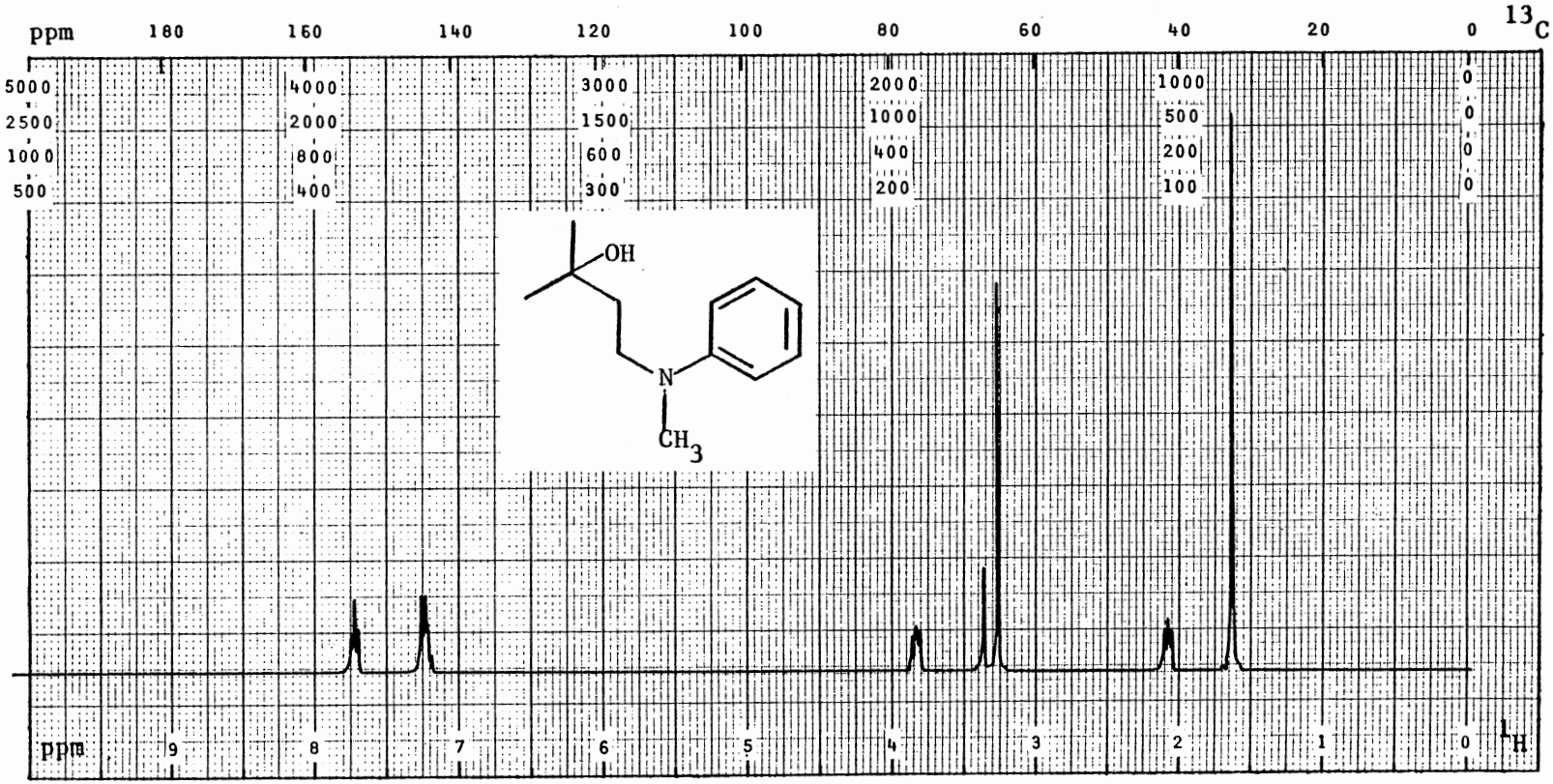
DC. Y ; Gated Off. ; Offset. 46316 Hz; RF. 7.5 W/dB; NBW. 200 Hz

PLATE XIII. IR OF 16



Ethyl 3-phenylmethylaminopropionate (16, neat)

PLATE XIV. ^{1}H NMR OF 16

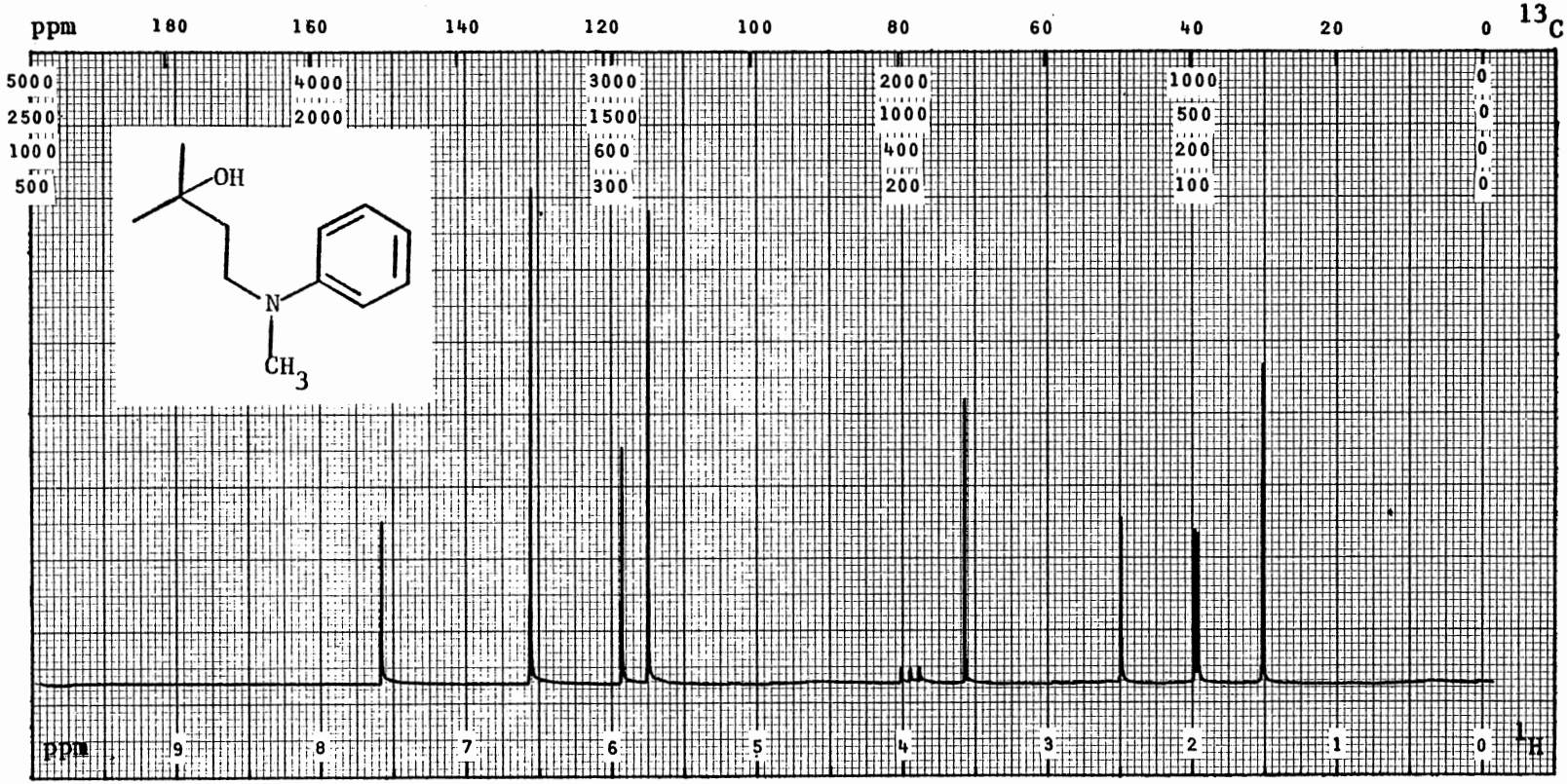


PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.94 MHz; WC: 3000 Hz; T: 25 °C; NT: 4

Size: 12 K; PW/RF: 3.0 μs/dB; SO: 100 Hz; FB: Hz; Lock: ^{2}D ; Delay: .500 s

DC: N ; Gated Off: ; Offset: Hz; RF: W/dB; NBW: Hz; LB:

PLATE XV. ^{13}C NMR OF 16

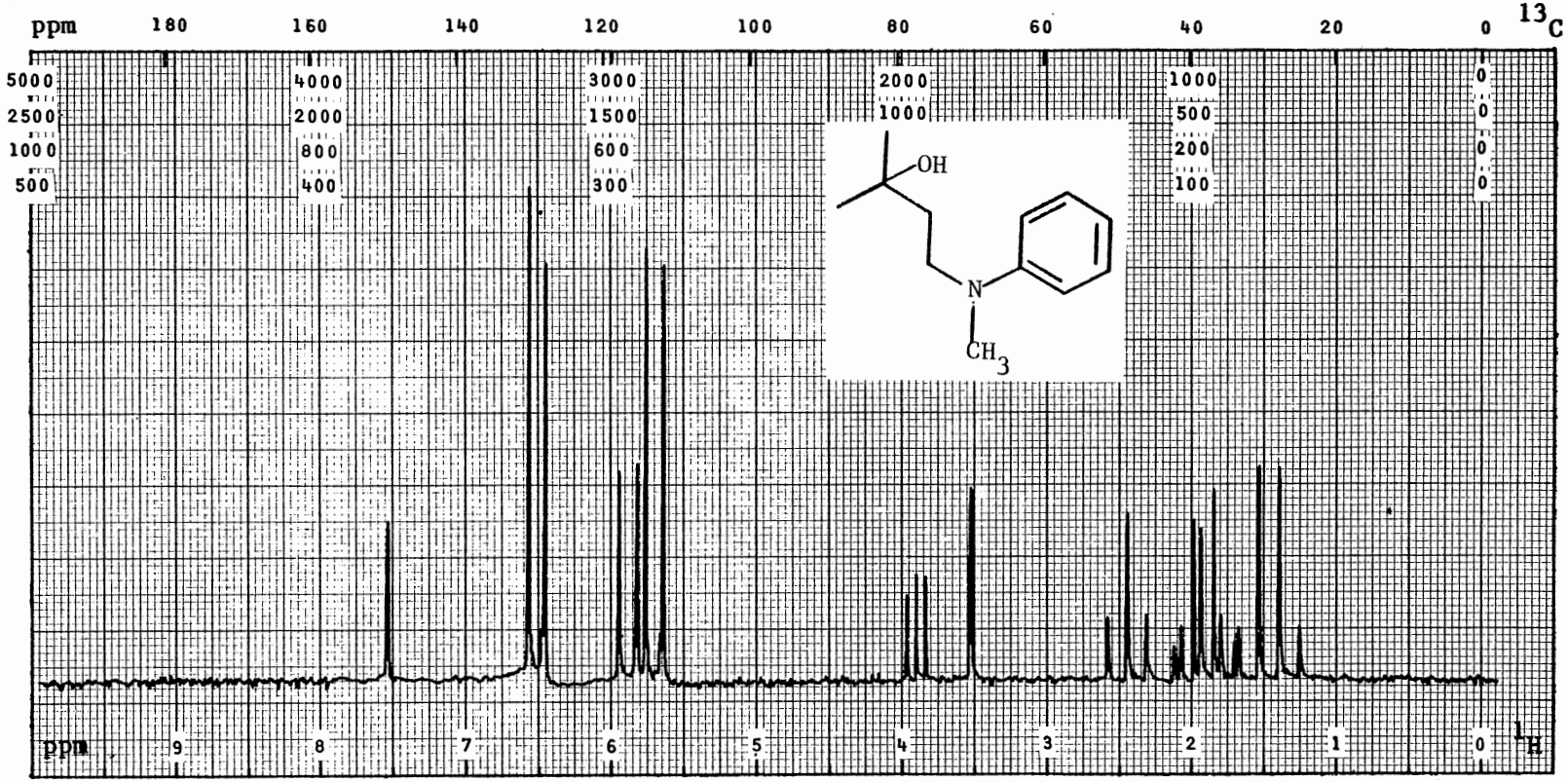


PFT X CW _ ; Solvent. $DCCl_3$; SO. 35101 Hz; PW. Hz; T. 28 °C; Acq/SA. 1115

Size. 8 K; P2/RF. 10 μs/dB; SF. 25.2 MHz; FB. ±3 KHz; Lock. ^2D ; D5/ST. 5 s

DC. Y ; Gated Off. ; Offset. 45316 Hz; RF. 7.5 W/dB; NBW. 200 Hz

PLATE XVI. OFF RESONANCE ^{13}C NMR OF 16



PFT X CW _ ; Solvent. $DCCl_3$; SO. 35101 Hz; PW. Hz; T. 28 °C; Acq/SA. 1215

Size. 8 K; P2/RF. 10 µs/dB; SF. 25.2 M Hz; FB. ±3 KHz; Lock. ^2D ; D5/ST. 5 s

DC. Y ; Gated Off. ; Offset. 46316 Hz; RF. 7.5 W/dB; NBW. 200 Hz

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VITA 2

Mark Daniel Thompson

Candidate for the Degree of

Master of Science

Thesis: SYNTHETIC APPROACHES TO INTERMEDIATES REQUIRED FOR SELECTED NITROGEN-SUBSTITUTED AROTINOIDS

Major Field: Chemistry

Biographical:

Personal Data: Born in Clayton, New Mexico, May 1, 1958, the son of Rev. and Mrs. Marvin R. Thompson.

Education: Graduated from Queen Elizabeth Composite High School, Edmonton, Alberta, Canada, in May, 1976; received Bachelor of Science degree in Chemistry and Mathematics from East Texas Baptist College, Marshall, Texas, in May, 1980; completed requirements for the Master of Science degree at Oklahoma State University, Stillwater, Oklahoma, in December, 1983.

Professional Experience: Undergraduate teaching assistant, East Texas Baptist College, 1977-1980; Graduate teaching assistant, Department of Chemistry, Oklahoma State University, 1980-82; Technician on Varian XL-100 NMR spectrometer, Spring, 1983; Member Phi Lambda Upsilon.