HETEROAROTINOIDS AND POTENTIAL OXIDATIVE DERIVATIVES

By

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in partial fulfillment of the requirements
for the Degree of
DOCTOR OF PHILOSOPHY
May, 1987

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OXIDATIVE DERIVATIVES

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ACKNOWLEDGMENTS

I wish to express my sincere appreciation and special thanks to Dr. K. D. Berlin for his invaluable guidance, his continous interest, with enthusiasm and encouragement throughout this work. His faith, patience, and optimism are greatfully acknowledged. I express my special thanks to my colleagues in Dr. Berlin's research group for their suggestions and companionship.

I am also grateful to Dr. W. T. Ford, Dr. E. M. Holt, and Dr. E. C. Nelson for serving as my graduate advisory committee. Special gratitude is expressed to the Department of Chemistry at Oklahoma State University for a Teaching Assistantship and a Johnston Fellowship (for summer) and to Dow Chemical Company for summer fellowship.

I thank Mr. Stan Sigle for his help in obtaining the NMR data and Mr. Norman Perreira for his assistance in collecting mass spectral data.

Thanks are also extended to Dr. H. A. Mottola for granting permission to use the instrumental facilities in his laboratory and Miss Sudha Varma for her expertise in obtaining the UV spectral data.

I am particularly indebted to my wife, Seema, for her love and affection, and for her encouragement, faith, and understanding.

This thesis is dedicated to my parents, Mr. and Mrs. Narayan B. Rajadhyaksha whose inspirational encouragement, thorough understanding and love have made this goal possible.

Last but not least, I would like to thank Denise Smith for her friendship, and her hard work in typing this thesis.

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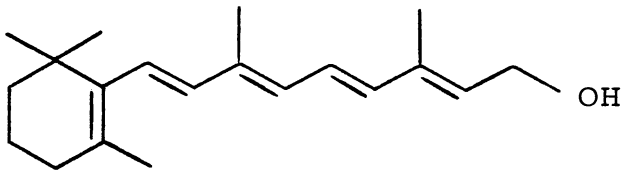
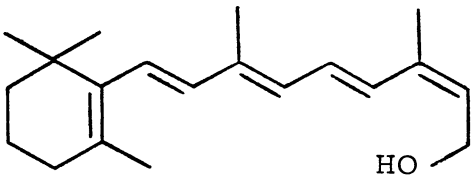
CHAPTER I

HISTORICAL

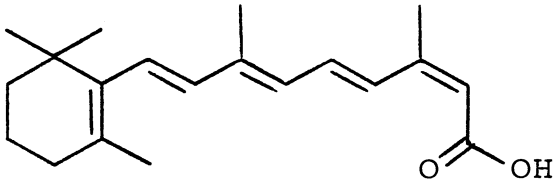
The name "retinoids" has come to symbolize both the natural forms of vitamin A (**1**) and derivatives **2-7** as well as modified synthetic analogues **8-26** regardless of biological activity or the lack of it. Actually, "vitamin A" is used as a generic term for related structures [except for carotenoids like β-carotene (**27**)] which exhibit, at least qualitatively, the biological activity of vitamin A or, more appropriately, retinol (**1**). Vitamin A (**1**) and closely related analogues, which have 20-carbon diterpene structures, were originally isolated from fish liver oils, visceral parts of fish, eggs, animal kidney, lungs, eyes, and intestinal mucosa.[29] These molecular systems bear a formal relationship to carotenes like **27**.[107] Discovered in 1913,[70] vitamin A (**1**) was initially labeled as "Fat-Soluble A" to distinguish it from essential water-soluble nutrients known as "Water-Soluble B".[40] A fat-soluble ingredient extracted from butter and egg yolk was able to maintain growth in rats and prevented xerophthalmia and night blindness.[40] Some controversy arose when Euler and co-workers found that carotene (**27**) from plants was totally different from vitamin A (**1**). Polyene **27** had different stability and chemical properties than vitamin A (**1**) the former was effective at a daily dose of about 5 μg in curing the symptoms of vitamin A deficiency.[22] Later, Capper[10] and Moore[75, 76] demonstrated the appearance of vitamin A (**1**) in the liver of vitamin A-deficient rats which had been given β-carotene (**27**). Karrer and co-workers established the structure of **27** in 1930.[55] Holmes and Corbet crystallized vitamin A (**1**) that had been isolated from fish liver.[48] Chemical synthesis was achieved by Isler and co-workers.[50] The first natural occurring cis isomer of the basic retinoid family identified was 13-*cis*-retinol (**2**) which was isolated by Robeson and Baxter in 1945.[98, 99]



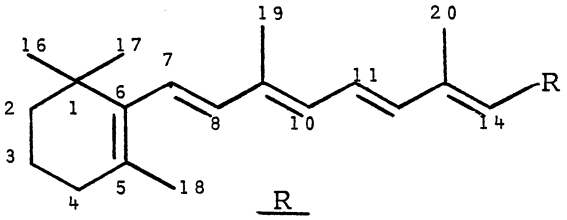
1 (Retinol-vitamin A)



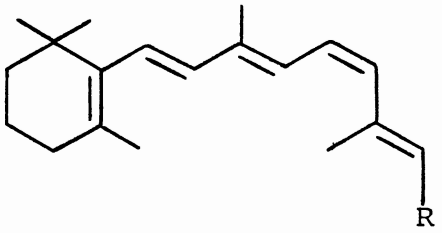
2 (13-cis-Retinol)



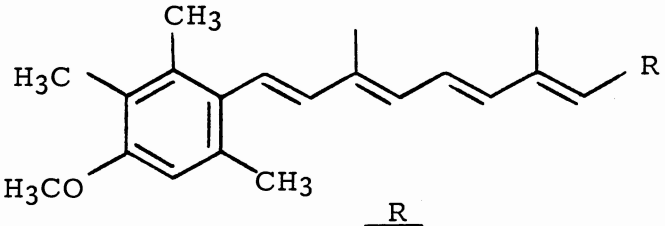
3 (13-cis-Retinoic Acid)



	R	
4	CHO	(Retinal)
5	CH_2OAc	(Retinyl Acetate)
6	CO_2H	(Retinoic Acid or "Tretinoin" or all(E)- Retinoic Acid)



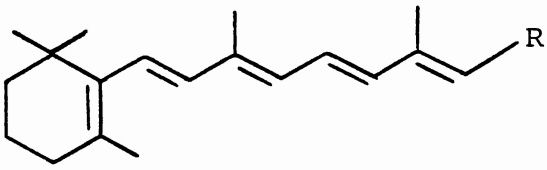
7 a. R = CO_2H (11-cis-Retinoic Acid)
b. R = CHO (11-cis-Retinal)



8 R = $CO_2C_2H_5$ (Etretinate)

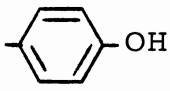
9 CO_2H

10 $C(O)NHC_2H_5$

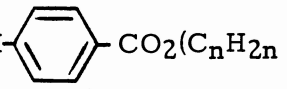


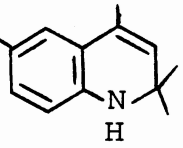
11 R = $CH_2NHCH_2CH_2OH$

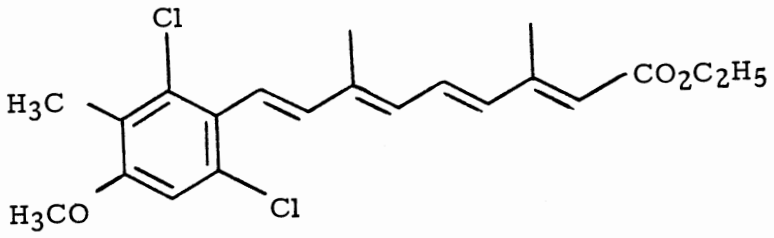
12 $C(O)NHC_2H_5$

13 

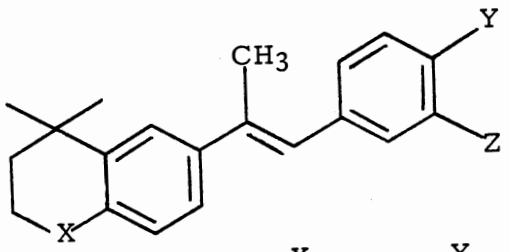
14 $CO_2C_2H_5$

15  [n = 1-18]

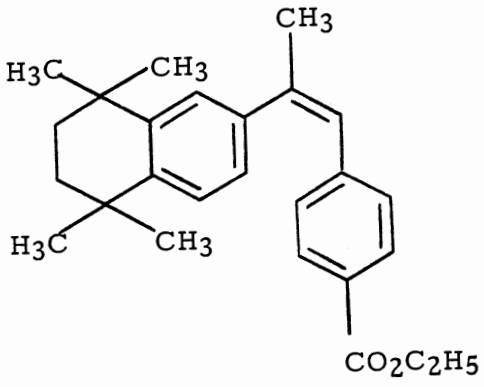
16 



17



	X	Y	Z
18	$C(CH_3)_2$	$CO_2C_2H_5$	H
19	$C(CH_3)_2$	CO_2H	H
20	$C(CH_3)_2$	H	CO_2H
21	O	CO_2H	H
22	S	CO_2H	H



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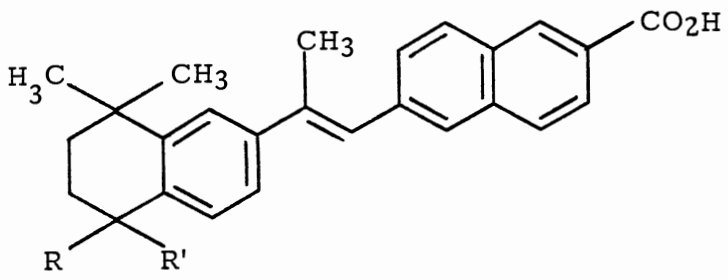
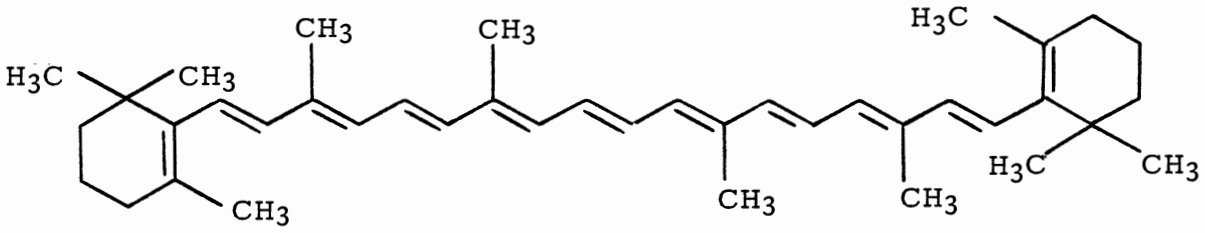
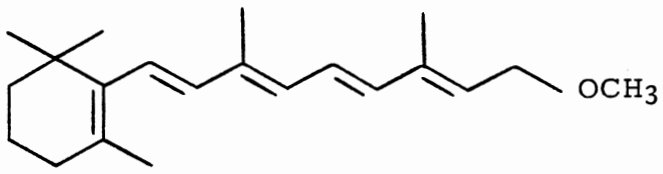


	R	R'
24	H	N_3
25	CH_3	N_3
26	CH_3	CH_3



27 (β-Carotene)



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Initially, it proved difficult to detect a difference in tumor production in rats with a normal diet and those fed a vitamin A-deficient diet.[32, 112] As reviewed by Frolik and Roller,[32] in 1926 Fujimaki,[38] recognized that a relationship existed between a vitamin A-deficient diet and greater susceptibility to the formation of carcinomas.[32] Research by Lasnitzki showed that the premalignant phenotype of mouse prostate glands, which had been treated with a chemical carcinogen, could be altered by addition of vitamin A (**1**).[59] More than 50% of the primary cancers found in humans occur in epithelial tissue which depends upon retinoids for cell differentiation and growth.[105] Epithelial tissue forms a coating or boundary on the internal and external surfaces of organs such as bronchii, blood vessels, skin, etc. Such tissues are mainly composed of closely packed columnar cells which have very little intracellular space.[78] Many of these tissues are cilliated and most secrete mucus. The dependency upon natural retinoids for cell differentiation and maintenance of the epithelia has been known for many years and was recently reviewed.[42, 125]

Aykroyd[1] mentioned that, Egyptian documents revealed the use of liver, which had a high content of vitamin A, as a treatment for night blindness.[77] In 1935, Wald reported the importance of vitamin A aldehyde or retinal (**4**) in vision. Moreover, he demonstrated that rhodopsin is composed of the protein opsin covalently bound to 11-*cis*-retinal (**7b**). The latter plays a very important role in the visual cycle.[122] Primary vitamin A deficiency in the liver results from inadequate dietary intake. Xerophthalmia results from insufficient retinol (**1**) to generate rhodopsin. Such a situation can occur at any age but appears to be more prevalent in young children, especially the form of the disease which can blind or be fatal.[119]

Another symptom of vitamin A deficiency is the abnormal keratinization of epithelia of the lungs, trachea, skin, gastrointestinal tract, and urinary tract.[3] For example, in rats a normal epithelium of the trachea consists of cells all of which have cilia pointing into the lumen. Within a few weeks, crowding and disarrangement of the epithelial cells occurs

because of vitamin A deficiency. In certain cases, cilia can be absent entirely.[78] After a few more weeks, squamous metaplasia can be observed in which flattened, stratified cells replace the original columnar arrangement of epithelial cells.[78] Use of an *in vitro* system demonstrated the ability of retinoids to reverse hyperplastic and anaplastic epithelial lesions commonly found after exposure of the tissue to chemical carcinogens.[33] Furthermore, others have shown that certain retinoids, rather than preventing carcinogenesis, can modify neoplastic states of cells during a latent period before the onset of an invasive malignancy.[105, 106]

Apart from the utility of natural retinoids as antineoplastic agents, suprisingly such retinoids may exhibit an acute systemic toxicity referred to as "Hypervitaminosis A".[104] Eskimos and arctic travelers who consumed polar bear meat or seal liver frequently experienced severe illness as a result of hypervitaminosis A.[101] In 1979, retinol poisoning was reported in fishermen who had ingested 20-300 g of fried halibut liver.[81] Symptoms such as dizziness, nausea, vomiting, etc. were observed, but recovery was common within a few weeks.[54, 81] Severe toxic effects from ingestion of large doses of retinoids over long periods include faulty formation of keratin in epithelial tissue, softening and fracture of the bones, hemorrhaging, and thickening of the skin.[53, 78, 79] As reviewed by Kamm and co-workers, most characteristic symptoms of chronic hypervitaminosis A in laboratory animals have been weight loss, anorexia, emaciation, anemia, cachexia, and finally death.[53] Macapinlac and Olson noted that young monkeys given single lethal doses of retinyl acetate (**5**) became progressively weak, had difficulty in breathing, lapsed into comas, and lost simple reflex action.[67]

Vitamin A (**1**) is mobilized from liver stores and carried to peripheral tissues by a highly regulated transport system. Evidence is available that suggests the system involves two plasma proteins, namely retinol-binding protein (RBP) and transthyretin.[41, 103] In plasma, vitamin A (**1**) normally circulates while bound specifically to RBP (Figure 1).[102] RBP in turn forms a protein-protein complex with transthyretin.[102] These proteins play an

important role in transporting vitamin A (**1**) from the liver to the tissues. Retinol deficiency specifically blocks the secretion of RBP so that the level of plasma RBP falls while the level of RBP in the liver rises. Studies in which retinol (**1**) was injected into vitamin A-deficient rats revealed a rapid secretion of RBP from the liver into plasma.[102] Cytotoxic symptoms appeared if the level of retinol (**1**) reached a concentration such that it could circulate in the plasma *unbound* to RBP. This cytotoxicity was also probably due, in part, to excessive levels of other retinoids which were also not bound to RBP in the plasma.[13, 102]

Recent treatises[86, 108] discuss retinoid involvement in the maintenance of normal epithelium in tissues such as skin, mammary glands, lungs, the colon, and the bladder. Some investigations into the effects of retinoids on human tumors have focused upon various skin abnormalities because of both the accessibility of the skin and the greater safety of topical treatment.[108] Several groups have reported that vitamin A (**1**) could be used in the treatment of Darier's disease (keratosis follicularis).[79, 90, 91] Retinal (**4**) has proven effective in treating actinic and non-actinic keratosis at concentrations between 0.05 and 1.00 weight percent in 95% ethanol or propylene glycol.[126] The overall effectiveness of this retinoid has been at least 50%.

Tretinoin (**6**) is probably the most effective topical agent in the treatment and prophylaxis of comedonal and inflammatory acne.[85] The agent reverses the primary event (abnormal follicular keratinization) in the pathogenesis of acne and prevents the formation of new comedones by increasing epithelial cell turnovers and reducing the cohesiveness of horny cells.[49] Lewis, in a recent review, reported that Etretinate (**8**) is extensively used in Europe and may become the agent of choice for severe cystic acne in topical treatment while isotretinoin [**3**,13-*cis*-retinoic acid] is used for oral treatment.[61, 62, 118] Marked therapeutic effects with prolonged remission of severe cystic acne were reported with oral isotretinoin (**3**) at 2 mg/kg/day (or less).[51, 62, 92] The mechanism of the drug action is not evident, but

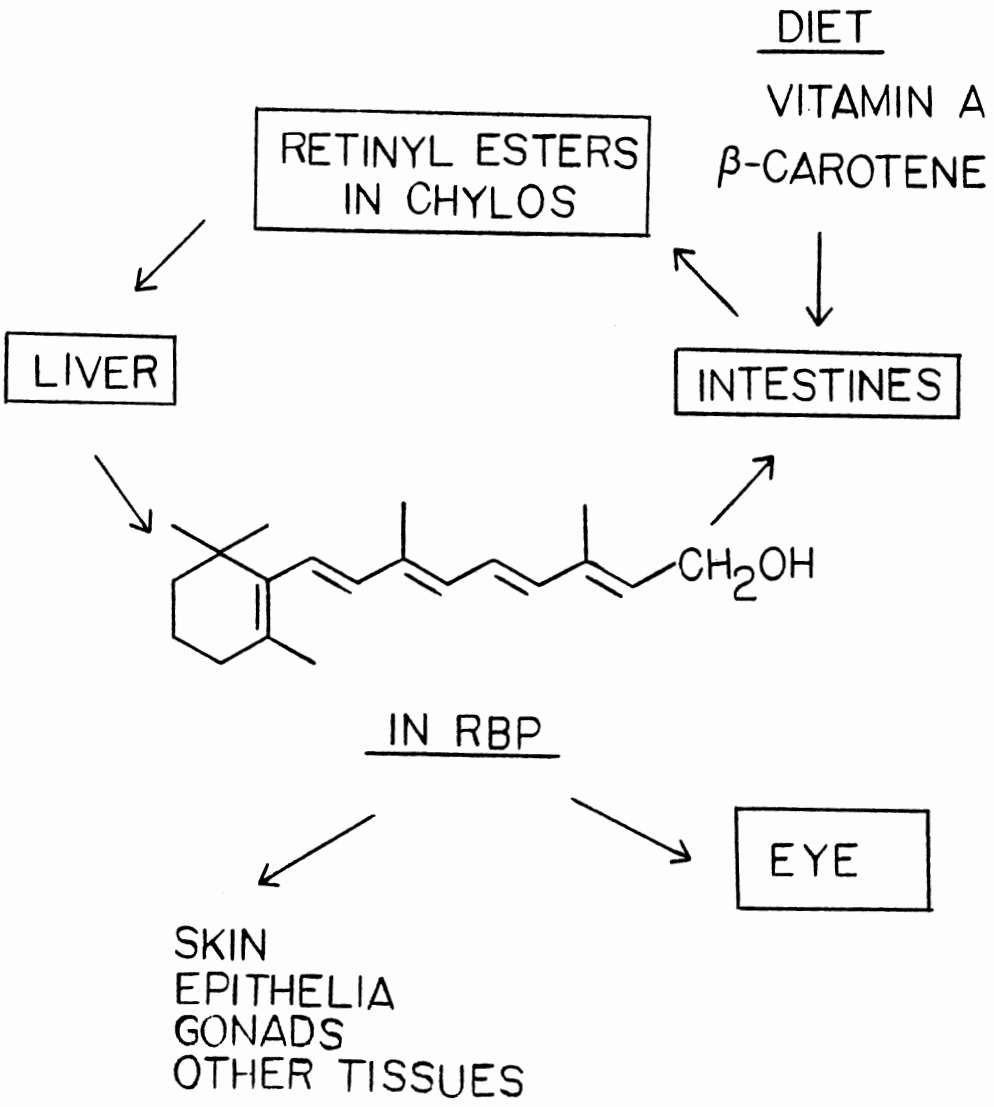


Figure 1. Processes Involved in Vitamin A Transport and Delivery

its therapeutic effect on severe cystic acne has been associated with a marked inhibition of sebum production.[110]

In laboratory animals, high doses of retinoids have led to embryotoxic and teratogenic effects (for recent review see [39]). Retinoic acid (**6**) influences various morphogenetic systems such as the central nervous system, facial and palatal development, and the axial skeleton.[57] The relationship between cancer and vitamin A-deficiency observed by Fujmaki,[32, 38] led various scientists to postulate an essential role of vitamin A (**1**) in pathogenesis and treatment of cutaneous disorders characterized by disturbances of keratinization such as ichthyosis.[95]

Natural versus Synthetic Retinoids

The toxicity of the natural retinoids must be overcome before they can be used as tumor preventing agents in humans. An additional problem also is that retinoid distribution *in vivo* is very modest. In contrast to dietary retinoic acid (**6**) natural retinoids such as retinol (**1**), retinal (**4**), and esters like **14** accumulate in the liver and do *not* promote a dose-dependent increase in vitamin A levels in the plasma.[34] Consequently, numerous chemically modified retinoids have been synthesized and screened for influence on cell growth, differentiation, and anticancer activity. Thus, the strategy for retinoid modification must consider the above action as well as an influence on the vision cycle and the general toxicity and specificity of action. A degree of separation of properties has been observed in that rats with a vitamin A-deficient diet supplemented with retinoic acid (**6**) grew normally but could *not* maintain a normal visual cycle.[20] Moreover, the separation of anticarcinogenic qualities from an influence on growth has been suggested by some experiments.[60]

There are several methods to examine the activity of modified retinoids. The ornithine decarboxylase (ODC) assay involves the following protocol.[121] Three sets of mice with two mice per set had their dorsal skin shaved 3-4 days before the experiment, and only

those mice which did *not* show regrowth of hair were used.[121] Selected test retinoids and 12-0-tetradecanoylphorbol-13-acetate (TPA) (Figure 2) were dissolved in acetone

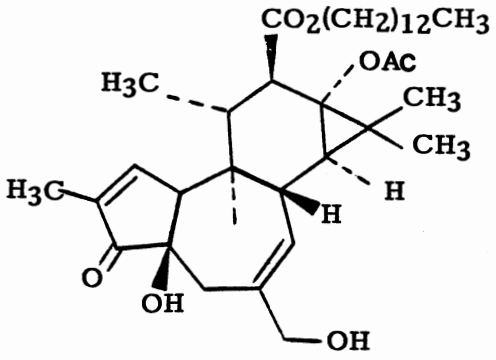


Figure 2. 12-0-Tetradecanoylphorbol-13-acetate (TPA)

(total volume ca 0.2 mL). These solutions were applied to the shaven backs of the mice. Control mice were treated with the same volume of acetone and TPA. After a specified amount of time, the mice are sacrificed, and the epidermis is separated by a brief heat treatment. The tissues are homogenized in 50 mM sodium phosphate buffer (pH = 7.2) containing 0.1 mM pyridoxal phosphate and 0.1 mM EDTA and then are centrifuged. Ornithine decarboxylase activity of the soluble epidermal extracts is determined by measuring the release of CO_2 from ^{14}C-labelled ornithine in nmole/30 min/mg of protein. From this value, the percent of inhibition can be calculated.[121]

In a second method, certain cultured cell lines, such as murine F-9 or HL-60 human leukemia cells, are induced to mature *in vitro* via treatment with one or more of a wide variety of agents such as dimethyl sulfoxide (DMSO).[111] The F-9 assay is based upon the ability of a retinoid to induce differentiation of tetracarcinoma stem cells to yield cells which

resemble parietal endoderm.[111] This assay measures the activity of a plasminogen activator which is used as a marker for differentiation. The HL-60 assay is based on the ability of retinoids to induce terminal differentiation of leukemic promyelocytes to cells having many of the morphological and functional characteristics of normal mature granulocytes.[111] In practice, the assay measures the ability of cells to reduce nitroblue tetrazolium (NBT see page 72) as a marker for differentiation.[111]

Until now, many analogues of vitamin A (**1**) have been synthesized but only a few of them have reached the stage of *in vitro* testing for ability to inhibit tumor promotion by carcinogens. These compounds include 13-*cis*-retinoic acid (**3**), the aromatic series of retinoids **9, 10**, amine **11**, amides **12** and **13**, and the ether analogue **28** of retinol (**1**). The synthetic analogue most extensively investigated is the 13-*cis*-acid **3**. Although this acid has lower toxicity than all *trans*-retinoic acid (**6**) in both mice and rats, it has not provided additional protection against 3-methylcholanthrene-induced lung cancer.[34, 46, 47, 82]

As described previously, several other analogues of retinoic acid (**6**) have been used to prevent cancer such as *N*-(4-hydroxyphenyl)-all-*trans* retinamide (**13**) which is an effective agent for the inhibition of breast cancer in rats.[74] Although this amide was less active than retinyl acetate (**5**) in test systems, its lower toxicity makes it a potentially superior chemopreventing agent.[35, 74]

Another group (**8-10, 18-26**) of synthetic retinoids investigated might be classified as arotinoids and contain aromatic systems.[64] The aromatic ester analogue **8** is more active and slightly less toxic than all-*trans*-retinoic acid (**6**) in retarding the growth of papillomas and reducing the incidence of the skin carcinoma induced in mice by 7-12-dimethylbenz[*a*]anthracene and croton oil.[4] The aromatic acid **9**, of ester **8**, and the amide **10** inhibited tumor growth and, at sufficiently high concentrations, caused regression of established tumors.[117] 13-*cis*-Retinoic acid (**3**) is also effective in this chondrosarcoma system.[117]

There are three regions in the vitamin A (**1**) molecule which might be modified (Figure 3). Retinoids have been reported with polar end modifications, ring modifications, and side chain alterations (Tables I-IV).[83] Several assays have been used to determine activity of such modified retinoids. The effective dose at which 50% reversal of keratinization occurs in the hamster tracheal organ culture (TOC) assay is 5 x 10^{-10} M for ethyl retinoate (**14**) (Table II) and 2 x 10^{-9} M for amide **12**[83] (see Table III). Retinoid **16** was 100% active in the tracheal organ culture assay at 10^{-9} M while *trans*-retinoic acid (**6**) was less active (88.4%) at the same concentration.[124] Thus the nature of the terminal polar group is important for activity at least in this assay.

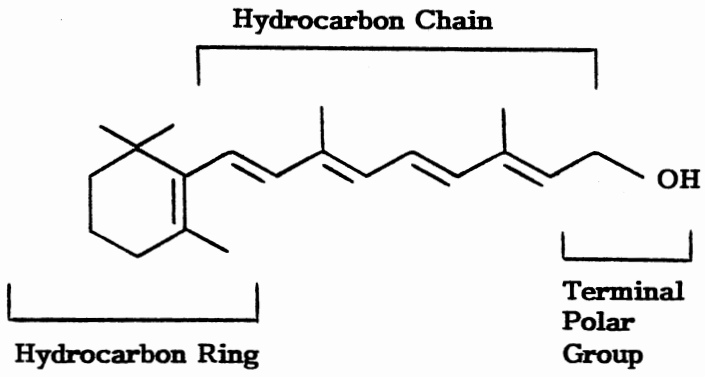


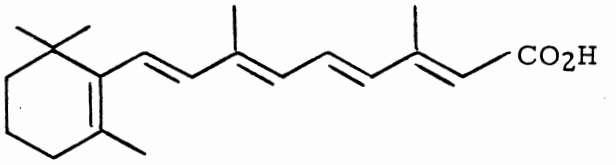
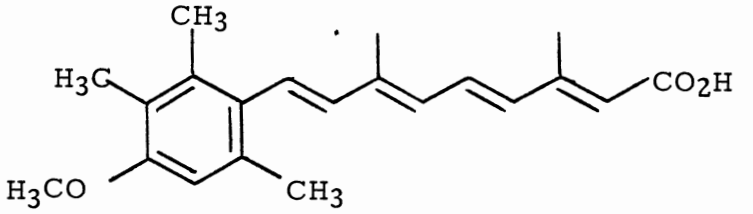
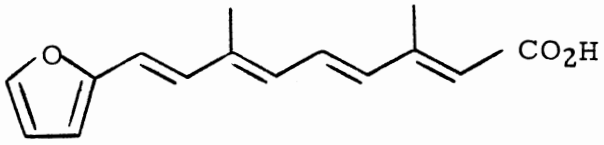
Figure 3. Regions of Vitamin A (**1**)

There are a few known examples in which the hydrocarbon chain of retinol (**1**) or retinoic acid (**6**) has been modified. For example, retinoic acid (**6**) has an ED_{50} of 3 x 10^{-11} M as compared to the ether analogue **28** which has an ED_{50} of 3 x 10^{-9} M. Biological activity of other modified retinoids are found in Tables I-IV.

The arotinoids (like **8-10, 17-26**) belong to a new class of retinoids whose chemical structure contains one or more aromatic rings and which appear to be somewhat peripherally related to vitamin A (**1**). However, ester **17** is active in animal models at dosages 500 times lower than those of Etretinate (**8**) but possesses an identical therapeutic

TABLE I

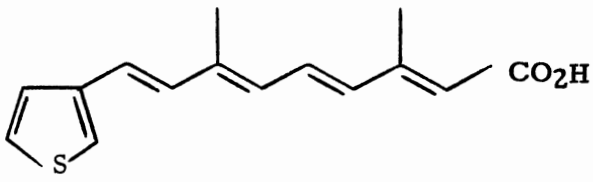
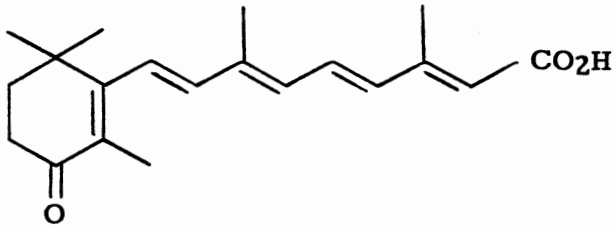
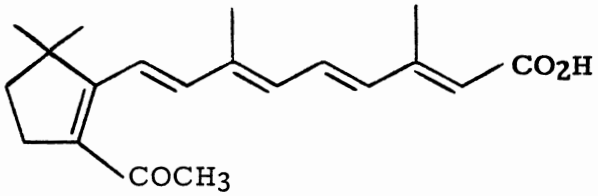
BIOLOGICAL ACTIVITY OF NATURAL RETINOIDS AND RING MODIFIED RETINOIDS[83]

Retinoid	ED_{50}, M*
 **6**+	3×10^{-11}
 **8** (Motretinid)	5×10^{-9}
 **29**	1×10^{-6}

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

+Standard used.

TABLE I (Continued)

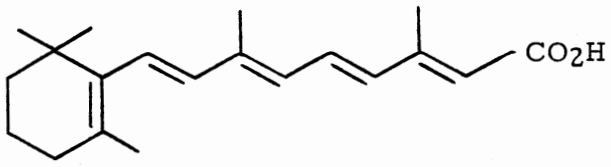
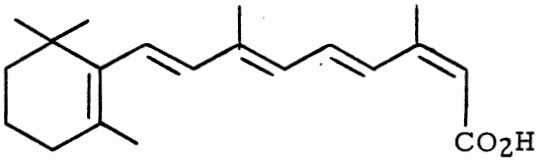
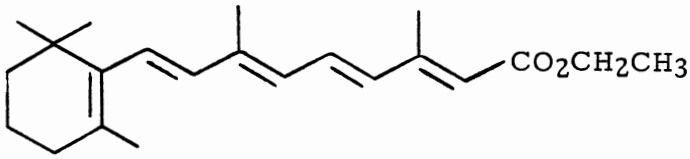
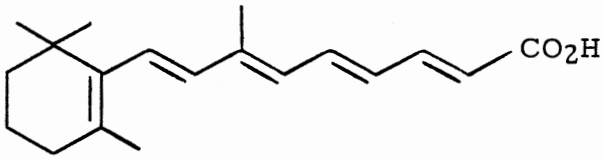
Retinoid	ED_{50}, M*
 **30**	$> 1 \times 10^{-8}$
 **31**	7×10^{-10}
 **32**	5×10^{-10}

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

+Standard used.

TABLE II

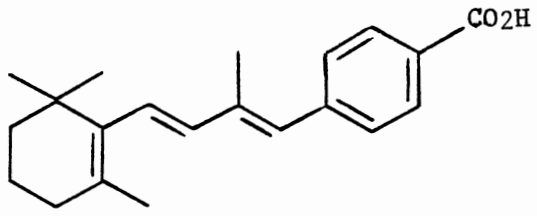
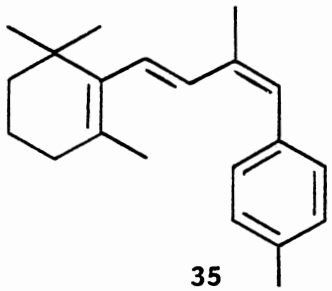
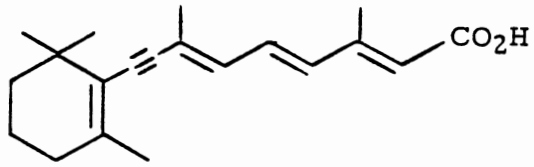
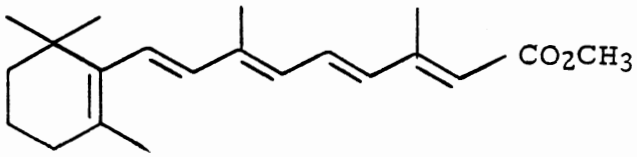
BIOLOGICAL ACTIVITY OF NATURAL RETINOIDS AND SIDE-CHAIN MODIFIED RETINOIDS[83]

Retinoid	ED_{50}, M*
 **6**+	3×10^{-11}
 **3**	3×10^{-11}
 **14**	5×10^{-10}
 **33**	1×10^{-9}

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

+Standard used.

TABLE II (Continued)

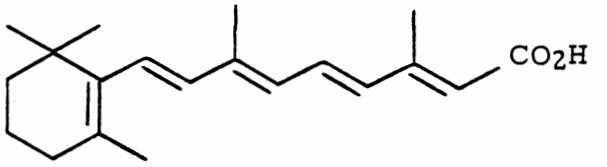
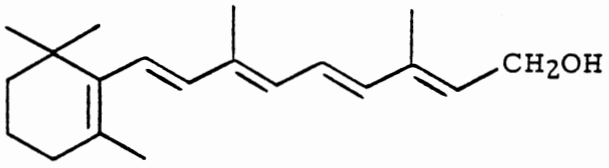
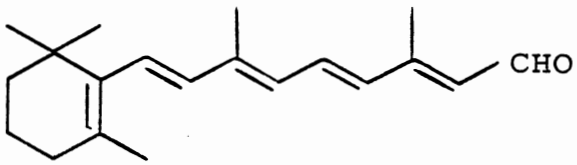
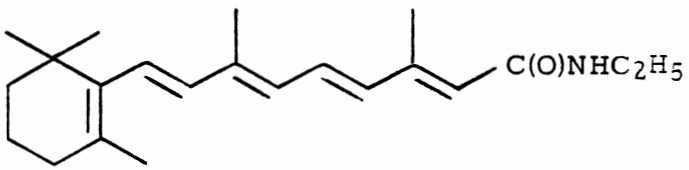
Retinoid	ED_{50}, M*
 **34**	2×10^{-11}
 **35**	$> 1 \times 10^{-9}$
 **36**	5×10^{-10}
 37	3×10^{-10}

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

+Standard used.

TABLE III

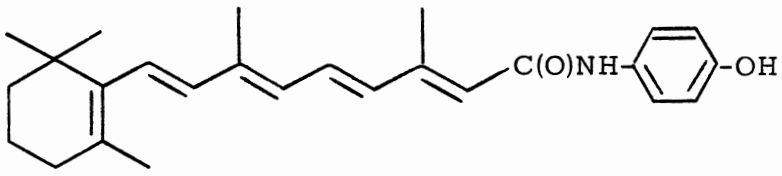
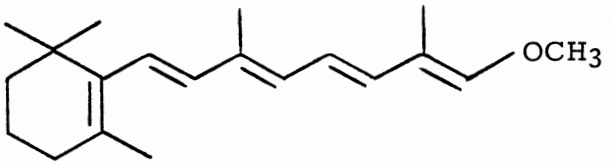
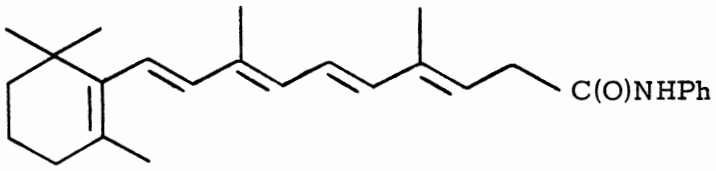
BIOLOGICAL ACTIVITY OF NATURAL RETINOIDS AND TERMINAL GROUP MODIFIED RETINOIDS[83]

Retinoid	ED_{50}, M*
 **6**+	3×10^{-11}
 **1**	7×10^{-10}
 **4**	3×10^{-10}
 **12**	1×10^{-9}

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

+Standard used.

TABLE III (Continued)

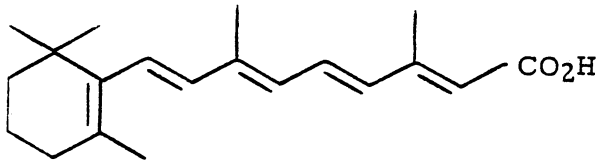
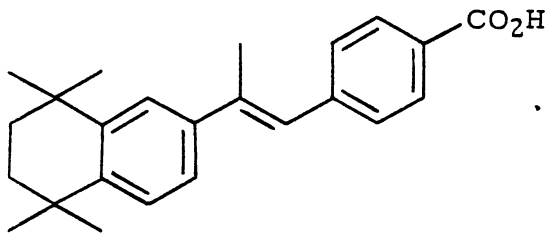
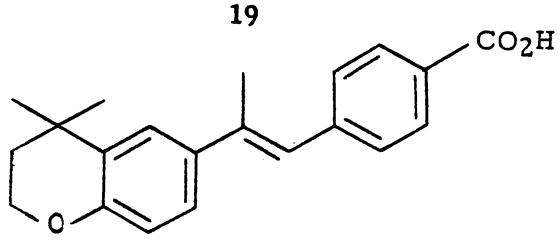
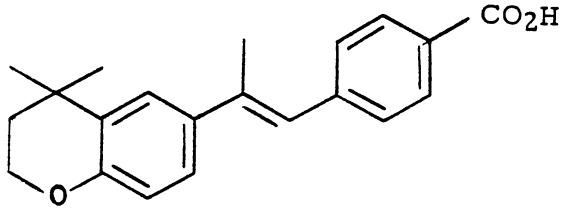
Retinoid	ED_{50}, M*
 **13**	3×10^{-10}
 **38**	3×10^{-9}
 **39**	1×10^{-9}

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

+Standard used.

TABLE IV

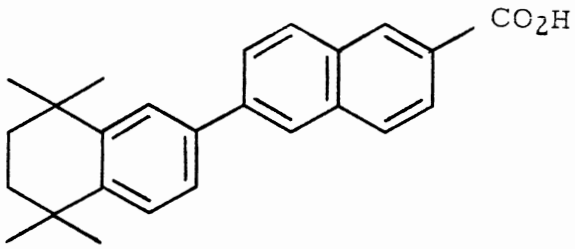
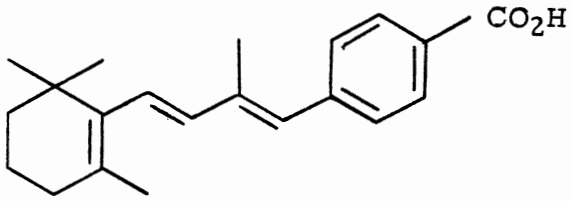
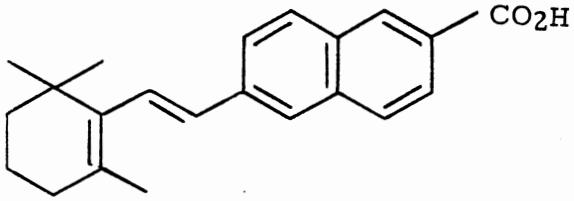
BIOLOGICAL ACTIVITY OF NATURAL RETINOIDS AND AROMATIC RETINOIDS-AROTINOIDS[18]

Retinoid	ED_{50}, M*
 6+	1×10^{-11}
 19	1×10^{-12}
 21	2×10^{-10}
 22	5×10^{-11}

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

+Standard used.

TABLE IV (Continued)

Retinoid	ED_{50}, M*
 **26**	3×10^{-12}
 **34**	3×10^{-10}
 40	1×10^{-10}

*ED_{50} is the molarity of retinoid required to effect reversal of keratinization in 50% of the culture.

index ($ED_{50} = 2 \times 10^{-8}$).[5, 6, 7, 104] Results obtained by Ott and co-workers in seventeen patients with severe psoriasis receiving a dose of only 1 μg/kg/day of ester **18** showed a slightly better therapeutic usefulness of **18** compared to **8**.[7, 87]

It was also discovered that the spatial arrangement of groups can dramatically increase or decrease the biological activity of a test retinoid.[17] For example, ester **18**, which has the (*E*)-configuration at the double bond, is the most active retinoid while the corresponding (*Z*)-isomer **23** is devoid of any biological activity in the papilloma system.[64] In acid **19** with a carboxyl function at the para position, the $ED_{50} = 3 \times 10^{-7}$, but if this function is changed to the meta position (as in **20**), the ability to induce differentiation in the HL-60 system drops dramatically ($ED_{50} > 1.0 \times 10^{-6}$).[111]

Recent work from our laboratory[123] as well as from Dawson and co-workers[18] reported the synthesis and biological activity of the chroman **21** and the thiochroman **22**, heterocylic analogues of acid **19** in which the geminal dimethyl-substituted benzylic group at the 1-position of tetrahydronaphthalene ring has been replaced by oxygen and sulfur, respectively. The 11,12,13,14-diene portion of the system was retained in a cisoid conformation by the incorporation of a phenyl ring in both **21** and **22** at the appropriate positions. Heterocyclic acids **21** and **22** were only slightly less active than acids **6** and **19** in both the TOC and the ODC assays.[18] The thiochroman acid **22** was far more active than the more polar chroman acid **21** in the TOC assay.[18] Retinoid **19** was reported to be a most toxic retinoid.[18] Interestingly, the heterocyclic analogues **21** and **22** were less toxic than retinoic acid (**6**) and acid **26** in the tracheal organ culture assay.

More recently two C(5)-azido substituted aromatic retinoids **24** and **25** were evaluated as photoaffinity probes for studying the mechanism of retinoid action.[68] Both azide systems, upon photolysis, became covalently bound to cellular retinoic acid-binding protein (CRABP).[68] However, the secondary azide **24** was twice as efficient as **25**, presumably because of less steric hindrance at $C\text{-}N_3$. Both azides had the same activity in

stimulating F-9 cell differentiation as compared to the C(5)-geminal-dimethyl analogue **26**.[68]

A comparison of a few active retinoids has been made in terms of effectiveness in reversing keratinization in organ cultures as correlated with ability to compete for cellular retinoic acid binding protein sites.[73] However, results indicated that a correlation between retinoid binding activity and biological activity was not entirely as expected. Acid **26** was an active retinoid and competed more effectively for the binding protein than sulfur analogue **22**.[73] Consequently, the presence of the naphthalene ring versus the phenyl ring near the chain terminus has an influence on activity.

Metabolites of Retinol (**1**), Retinal (**4**), Retinoic Acid (**6**),

There have been numerous reports concerning the metabolism of synthetic retinoids and natural retinoids.[20, 24, 121, 127] Many studies have concentrated on determining the structure of the final physiologically active form derived from retinol (**1**) which is involved in performing functions such as in vision, reproduction, and cell differentiation. However, it is still not clear what derivative is responsible for other biological functions. A possible scheme which relates retinol and its metabolites with activity is shown in Figure 4.[89] It has been shown by many investigators that retinoic acid (**6**) acts within cells to support growth, but it is unable to fulfill the function of retinol (**1**) in maintaining reproduction and the visual cycle.[20, 114, 115] Conversion of retinol (**1**) to retinal (**4**) and retinoic acid (**5**) is still a topic of intensive investigation.[24]

In the retina of the eye, retinol (**1**) is oxidized to retinal (**4**) by the enzyme retinol dehydrogenase,[122] and retinal (**4**) then performs a specific function in the vision process.[122] In other tissues, however, the complete metabolic fate of retinol (**1**) is unknown. As reviewed by Aszalos, several scientist have found that retinoic acid (**6**) is a documented metabolite of retinol (**1**) or of the ester **5** in several tissues of rats.[30] When a large intraportal dose of 6,7-^{14}C-retinol was administered to rats, a polar billary metabolite

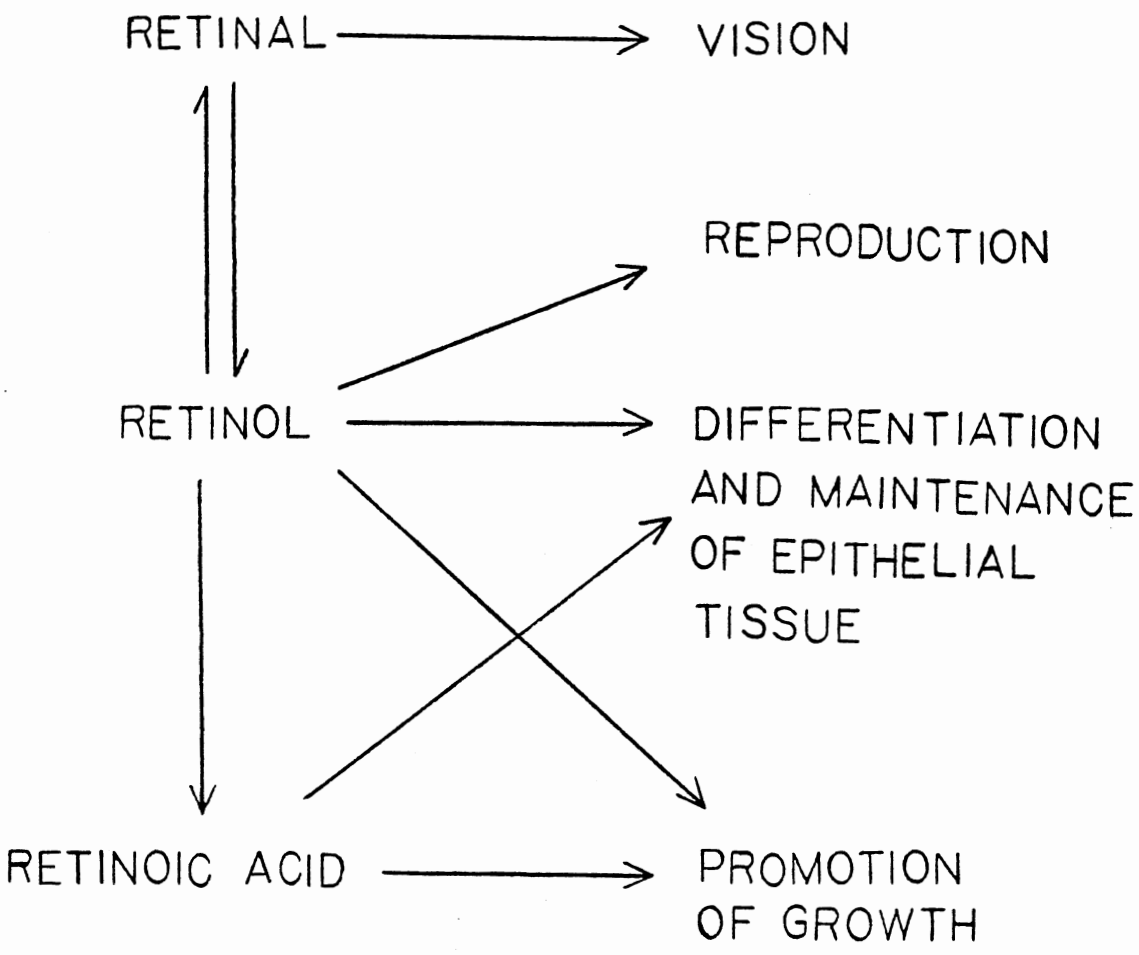
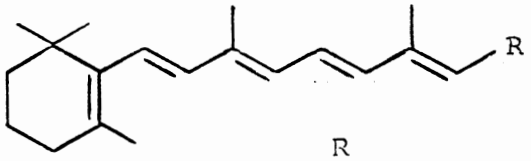


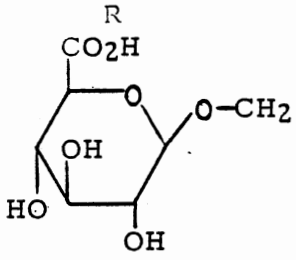
Figure 4. Interconversion and Biological Importance of Natural Retinoids

appeared and was characterized as retinyl glucuronic acid (**41a**).[63] The proposed metabolic pathways for retinol (**1**), retinal (**4**), and β-carotene (**27**) are shown in Figure 5.

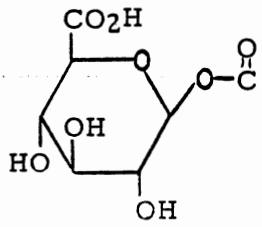
One other function of retinol (**1**), or its metabolite, is apparently to participate in a glycosyl transfer reaction.[69] Retinyl phosphate (**42**) was found in rat liver and may act as a carrier in the transfer of sugar moieties from nucleotide sugars to the growing oligosaccharide chains of glycoproteins.[2]



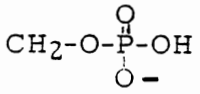
41a



41b



42



Extensive studies were reported in recent years for metabolites of retinoic acid (**6**) which would be more active than the parent compound.[31] Several investigations established certain metabolic profiles by using radioactively labeled substrates.[45, 71, 96] These results suggest that retinoic acid (**6**) is rapidly cleared from the body and, in some cases, decarboxylation occurs.[45, 96] Recently, the structures of several urinary metabolites were determined which included the four metabolites **43-46** from rats and humans.[96] In addition, urinary metabolites **47-49** were isolated from rats given an intraportal injection of retinoic aicd (**6**).[45] Earlier studies led to the identification of three fecal metabolites **45**, **50**

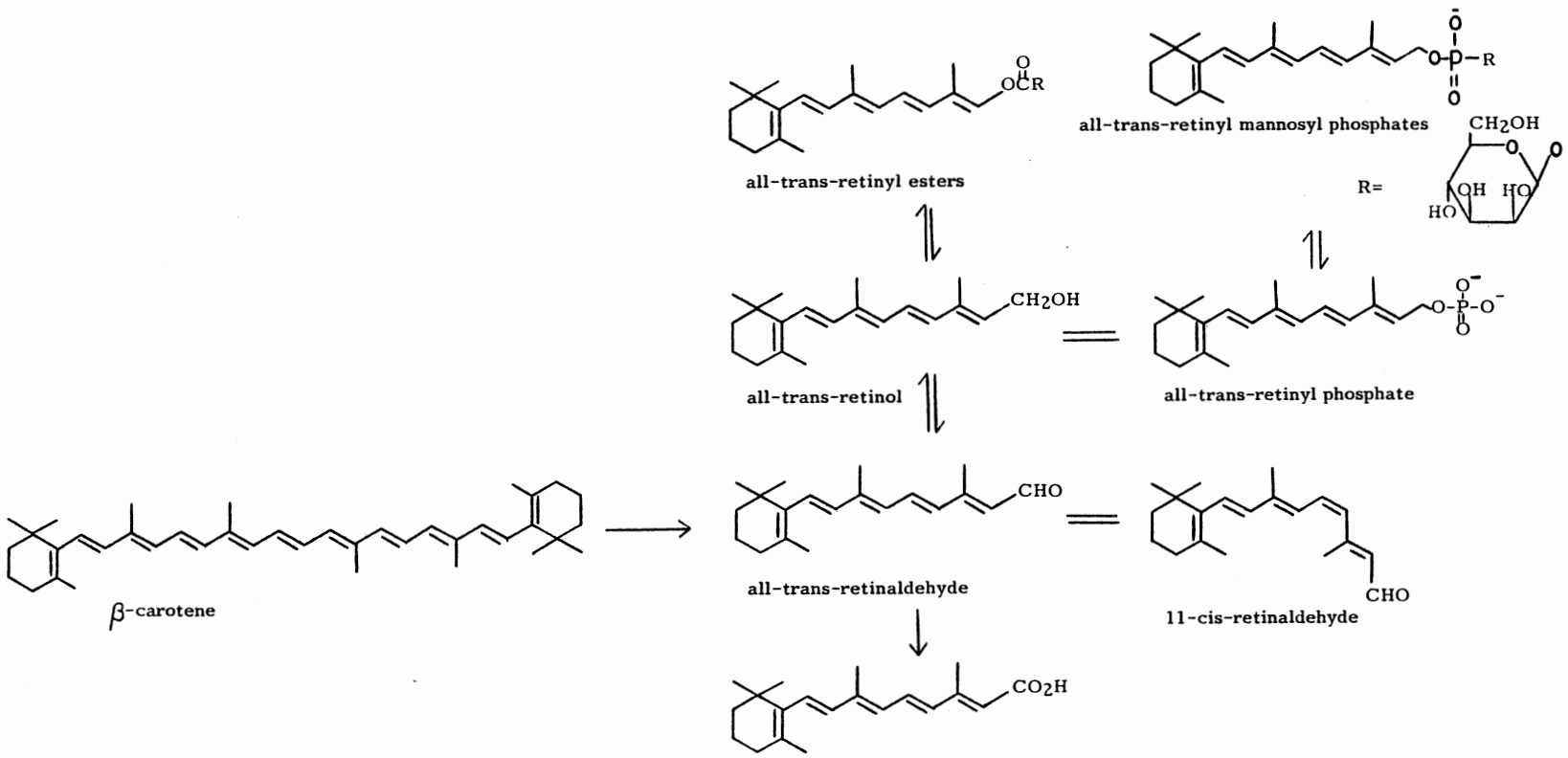
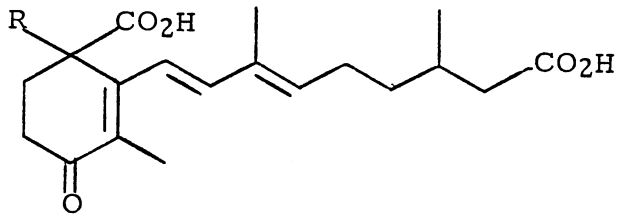
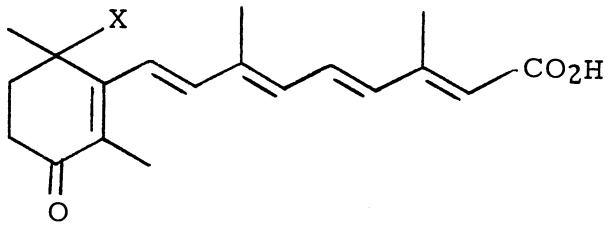


Figure 5. Metabolic Pathway for Retinol (**1**), Retinaldehyde (**4**), and β-Carotene (**27**)



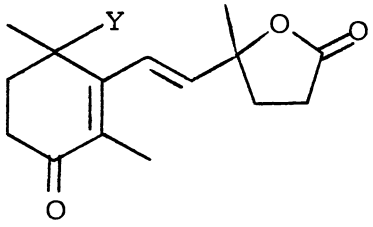
43 R=H

44 $R=CH_3$



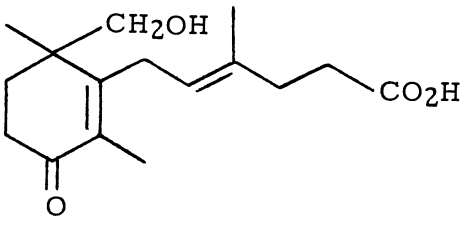
45 $X=CH_3$

46 $X=CH_2OH$

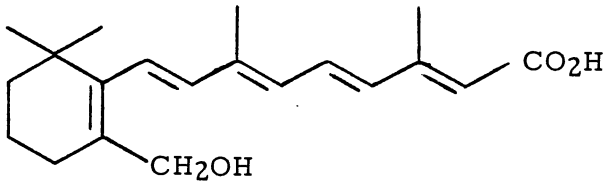


47 $Y=CH_3$

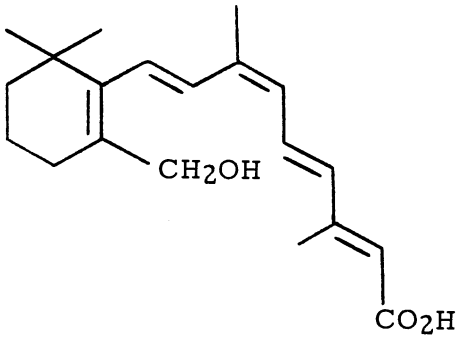
48 $Y=CH_2OH$



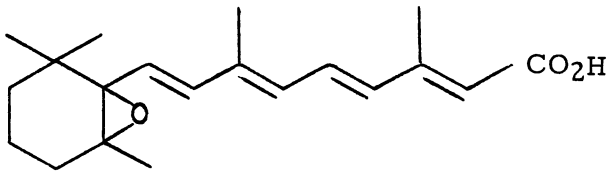
49



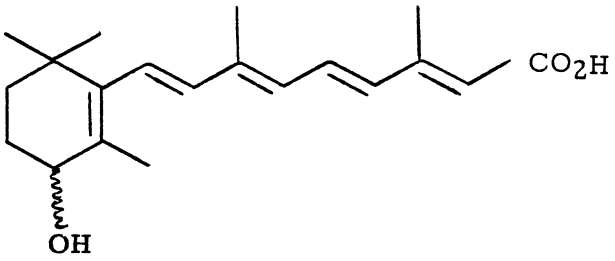
50



51



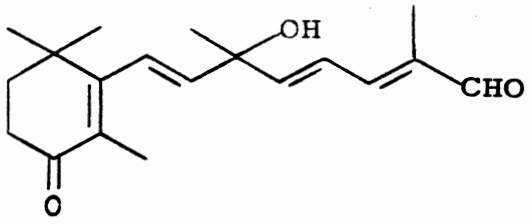
52



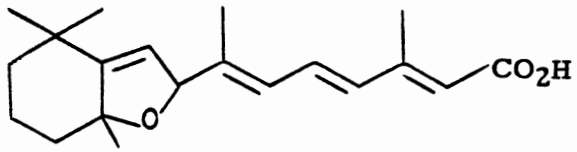
53

and **51** in addition to unchanged retinoic acid (**6**).[44] Administration of retinoic acid (**6**) to vitamin A-deficient rats permitted the isolation of 5,6-epoxyretinoic acid (**52**) from intestinal mucosa of these animals.[71] Earlier investigators had reported the isolation of a significant amount of 13-*cis*-retinoic acid (**3**) from the liver of rats fed with large doses of the all-*trans*-isomer (**6**).[128] Among the biliary metabolites was retinoyl β-glucuronic acid (**41b**) which could be identified after intraportal injection of retinoic acid (**6**).[21]

In vitro metabolism of retinoic acid (**6**) has been studied using either a hamster tracheal organ culture or a hamster liver cell-free system. From these systems, two metabolites of retinoic acid (**6**) were isolated, namely 4-oxo and 4-hydroxy analogues (**45** and **53**). These acids were found to be less active than all-*trans*-retinoic acid (**6**) in the TOC assay.[28] Apparently, metabolism at C(4) in acid **6** may be the initial step in one of the elimination pathways for retinoic acid (**6**) in the human body.[72, 100] Epoxidation of retinoic acid (**6**) at the 5,6-position has occurred to form 5,6-epoxy-5,6 dihydroretinoic acid (**52**). Epoxide **52** has been isolated from the intestinal mucosa of vitamin A-deficient rats which were subsequently given retinoic acid (**6**).[71] It was suggested that epoxide **52** had greater biological activity than the parent acid **6**.[37] Because chain metabolites with a shortened side chain have been isolated, it has been suggested that retinoic acid (**6**) might undergo decarboxylation as had been shown to occur in a system treated with horseradish peroxidase and from which was isolated a 4-oxo-C_{19} aldehyde **54**.[100] The origin of **54** is not intuitively obvious, however.



54



55

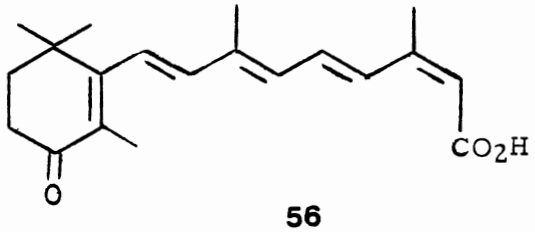
Several metabolites of retinoic acid (**6**) were discovered from target tissues such as the intestine.[80] Some metabolites possess biological activity similar to that of acid **6** in tracheal epithelial organ culture.[80] Isolation and characterization of a metabolite from intestinal tissue showed it to be 5,8-oxyretinoic acid (**55**).[19] However, during the isolation, an acid-base procedure was used for purification which may allow 5,8-oxyretinoic acid (**55**) to be formed from the known rat metabolite[19] 5,6-epoxyretinoic acid (**47**). The isolation procedure likely produces 5,8-oxyretinoic acid (**55**), as an artifact,[80] but this is a tentative assumption. The biological activity of 5,6-epoxyretinoic acid (**52**) is not well understood in humans. Some studies have involved oral administration of acid **52** which is converted to 5,8-oxyretinoic acid (**55**) after exposure of **52** to acid of the stomach. Converted acid **55** is less active than retinoic acid (**6**) in variety of tests[106] with rat fibroblast cells and murine melanoma cells.

Apart from the metabolic studies of natural retinoids, several synthetic retinoids have been examined but the results lack an in depth analysis.[10, 52] Examples of investigations include the hydrolysis of retinoic acid anhydride to retinoic acid (**6**) in rats,[94] the metabolism of retinaldehyde hydrazone and *N*-acetylretinylamine to form retinol (**1**)[97] and many others.[52, 116]

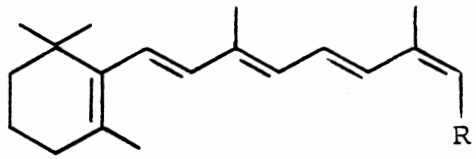
The most extensively studied synthetic retinoids for their metabolic activity are 13-*cis*-retinoic acid (**3**), amide **13**, and ester **8**.[25] The metabolism of 13-*cis*-retinoic acid (**3**) was examined in the hamster, the rat, and in humans. In the hamster, 13-*cis*-4-oxoretinoic acid (**56**) was detected in the plasma 2 hours after an intravenous dose (5.3 μg) of ^{3}H-labeled 13-*cis*-retinoic acid (**3**).[36] In rats, intravenous administration of acid **3** showed 69% of the dose in the bile after 24 hours while 9% was in urine.[25] This suggested that acid **3** and its

metabolites were rapidly eliminated from the body and that the major route of excretion was via the bile.[25] One of the metabolites analyzed showed the presence of the *cis*-ether **57** (an analogue of **41a**). In humans, the metabolism of 13-*cis*-retinoic acid (**3**) revealed 13-*cis*-4-oxo acid **56** as the major metabolite in blood.[120]

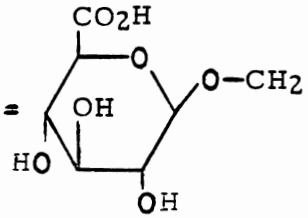
A second synthetic retinoid which has been studied extensively is Etretinate (**8**). Most of the metabolites (**58a-58g**) isolated from human urine after administration of (**8**) contain shortened tetraene side chains.[26] The metabolic cleavage of Etretinate (**8**) to the free acid



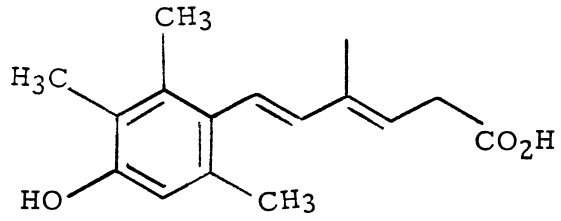
56



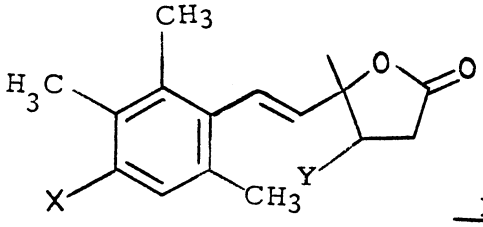
57 R =



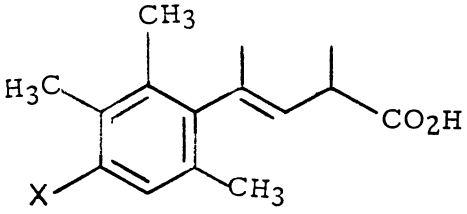
One other synthetic retinoid which has been investigated to some extent is amide **13**.[113] When a single intravenous dose (5 mg/kg) of ^{3}H-labeled amide **13** was given to rats, 64% of the label appeared in feces after 5 days and 13% in urine.[113] Less than 2% of these excreted compounds appeared as the unchanged retinoid **13**. Only one metabolite **59b** was identified in the bile of rats, other than few other minor polar metabolites.[113] After 24 hours of intravenous dosages of amide **13**, two tissue metabolites were isolated and identified. One was long-chain *N*-(4-hydroxyphenyl)retinamide fatty acid ester **59a** and the other was amide **59c**.[113]



58a

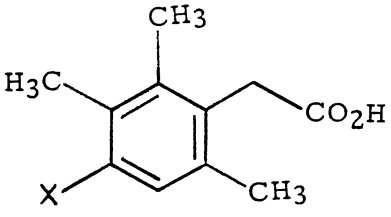


	X	Y
58b	OH	H
58c	OH	OH



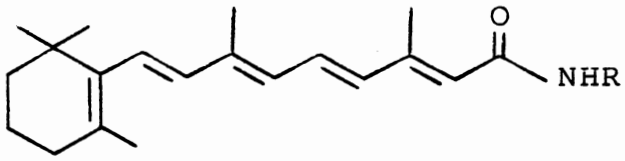
58d X=OH

58e X=OCH_3



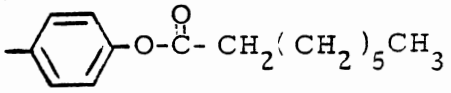
58f X=OH

58g X=OCH_3

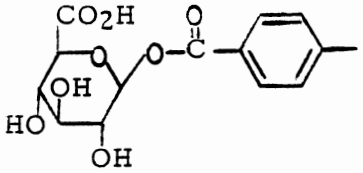


R

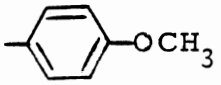
59a



59b



59c



From various biological studies, as well as from limited human trials, it is clear that future research might well focus upon synthetic retinoids as potentially more useful than natural retinoids. One goal of our research was to find an effective but less toxic synthetic retinoid that might display a high degree of tissue specificity for protection against cancer. However, actual toxicity studies would have to come at a later date in cooperation with a testing firm.

CHAPTER II

RESULTS AND DISCUSSION

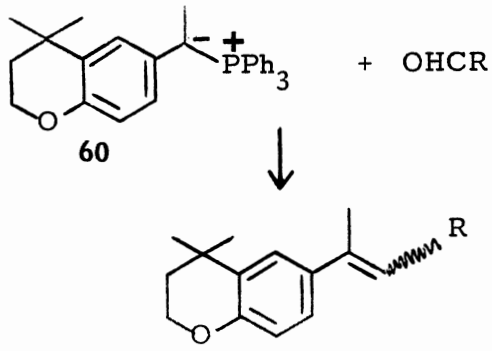
In recent years, several synthetic retinoids have been made, some of which do not support growth in experimental animals but which nevertheless have activity in preventing cancer and/or have the ability to control cell differentiation.[13] The toxicity of retinoids, however, is the main limitation to their practical use. Ideally a modified retinoid suitable for clinical use should be at least as active but less toxic than *trans*-retinoic acid (**6**). In order for these modified retinoids to be useful clinically, structural modifications must be made to increase hydrophilic properties of the molecule which will enhance transportation in the plasma thereby improving drug efficacy in terms of reaching tumor sites. This should allow smaller dosages of the retinoid since a higher percentage of the drug could be made available to the malignant tissue. Successful attempts in synthesizing the first heteroarotinoids came from both our lab as well as from Dawson and co-workers.[18, 123] It was our conception to incorporate a heteroatom such as oxygen into the cyclohexyl ring and to include in the side chain an aryl group with a polar, *para*-substituent such as a CH_2OH, CHO, or a CO_2R group. Such modifications should increase the polarity of the molecule and greatly increase its ability to hydrogen bond to polar substances. It was observed that some of the active metabolites obtained from the metabolism of the retinoic acid (**6**) contained polar groups.[66, 80]

We have successfully obtained a variety of heteroarotinoids which display activity comparable to that of all-*trans*-retinoic acid (**6**) in the hamster trachael organ culture assay.[103] Reported herein are the synthesis of a series of heteroarotinoids **21** and **60a-60l**

along with pharmacological activity of selected heteroarotinoids as **60a, 60b, 60c,** and **60d.** In these heteroarotinoids, oxygen has been incorporated into the fused ring moiety.

Synthesis of Heteroarotinoids

Various synthesis involve **21, 60a-60l** and **61-68** which are shown in Tables V and VI and Figures 6-10. Required intermediates are **61-68.** The final step used to form the C(11)-C(13) double bond in the heteroarotinoids **60a, 60b** and **60g** took advantage of a Wittig reaction by using the ylide **60** from **67** and the appropriate aldehyde such as **68-70.** The method parallels to some degree that reported previously from our lab.[123]

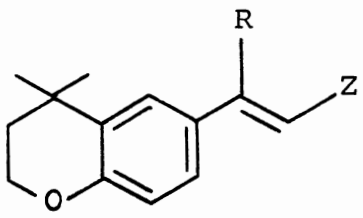


Reduction of ester **60a** with $LiAlH_4$ gave the primary alcohol **60d** in a modest yield of 25%. Apparently there is a steric factor since the yield could not be improved even after 48 h at reflux and in the presence of excess $LiAlH_4$. Saponification of ester **60a** gave acid **21** (86.1%).

Using *p*-formylbenzonitrile (**69**) in a Wittig reaction (ylide **60**) produced nitrile **60b** again in modest yield (26%) as a pure (*E*)-isomer. Reduction of nitrile **60b** with excess DIBAL-H in hexane gave aldehyde **60c** (26% as a single (*E*)-isomer). Primary amine **60e** (21%) was obtained from nitrile **60b** when the latter was reduced with $LiAlH_4$/THF. An unidentified by-product was noted in the TLC analysis. Addition of excess freshly prepared methylmagnesium iodide to nitrile **60b** gave, after the normal workup, ketone **60f** (22%). The unusual aldehyde **70** and the anion of salt **67** gave ester **60g** (19%) after a difficult purification. Very few related retinoids are known.

TABLE V

SYNTHETIC HETEROAROTINOIDS



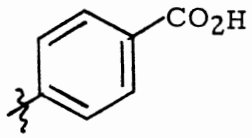
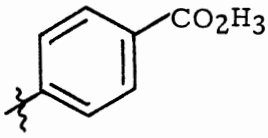
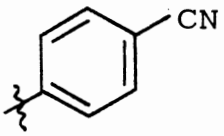
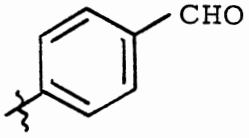
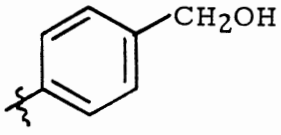
	Z	R
21		CH_3
60a		CH_3
60b		CH_3
60c		CH_3
60d		CH_3

TABLE V (Continued)

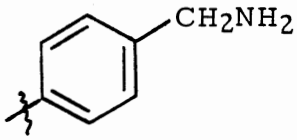
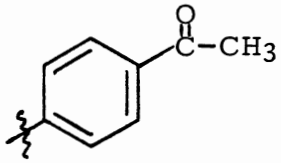
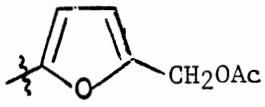
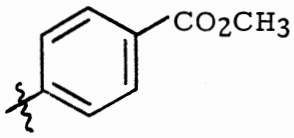
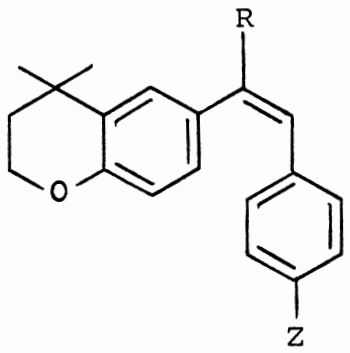
60e		CH_3
60f		CH_3
60g		CH_3
60h		CH_2OH

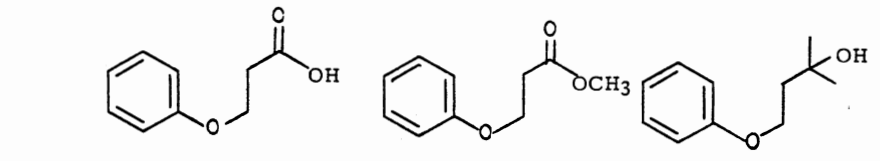
TABLE V (Continued)



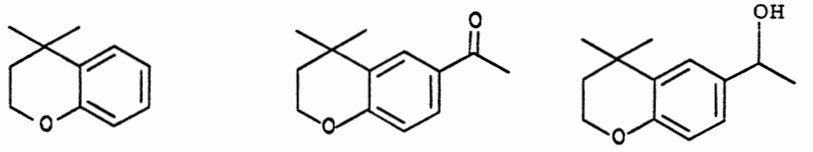
	Z	R
60i	CO_2CH_3	CH_3
60j	CN	CH_3
60k	CO_2CH_3	CH_2OH
60l	CO_2H	CH_2OH

TABLE VI

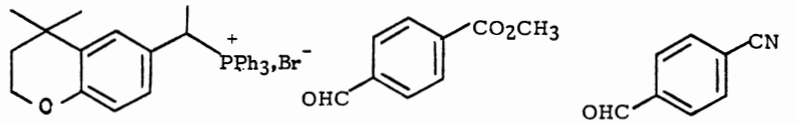
INTERMEDIATES FOR AROTINOID SYNTHESIS



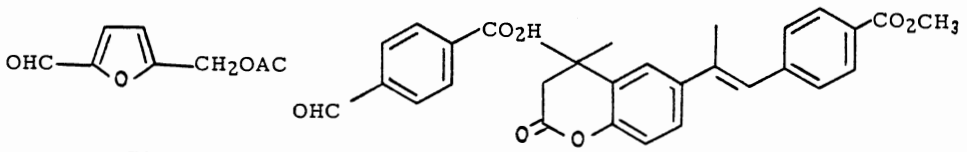
61 62 63



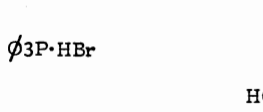
64 65 66



67 68 69



70 71 72



73 74

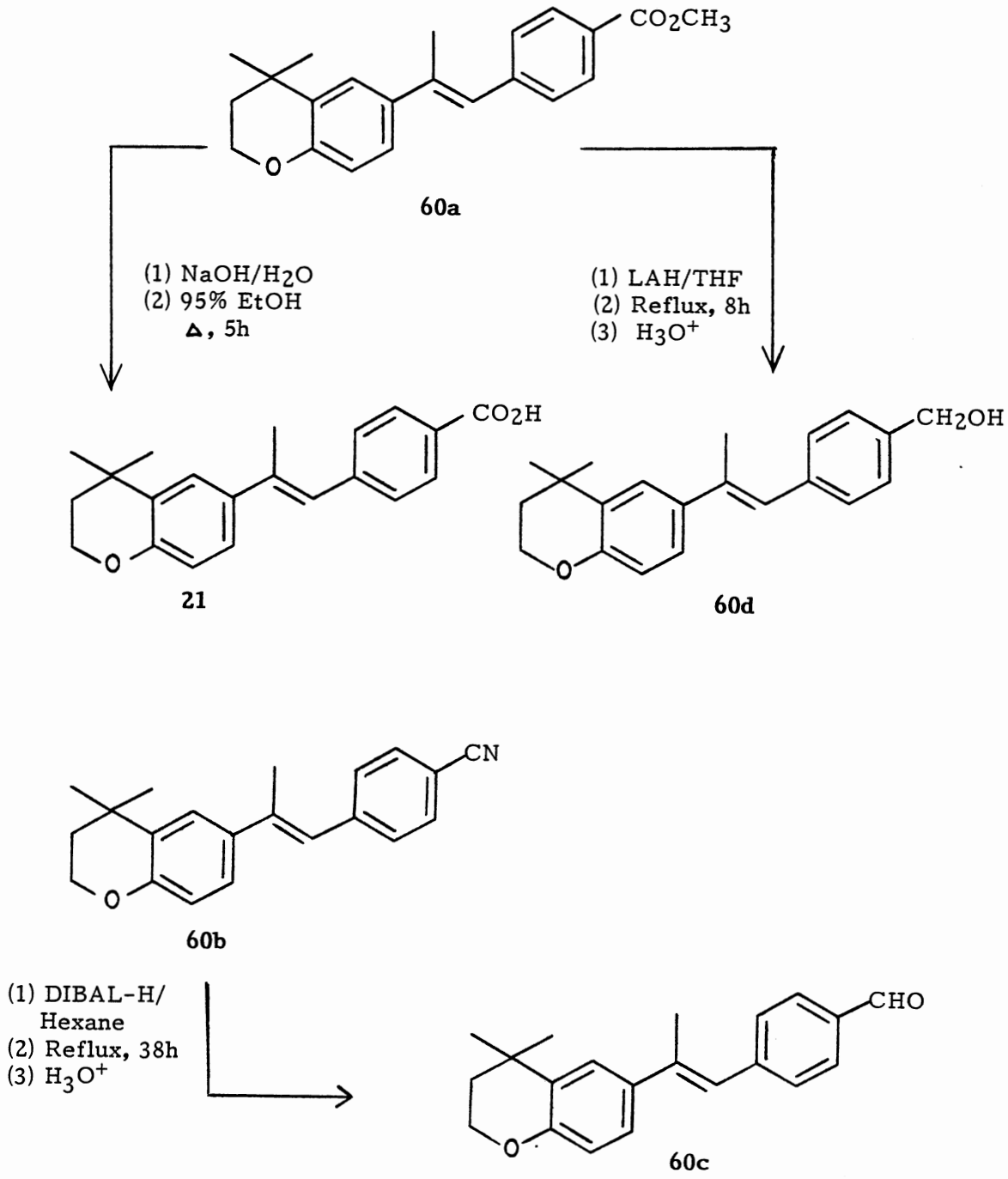


Figure 6. Conversions of **60a** and **60b** to **60c**, **60d**, and **21**.

Since metabolites of these arotinoids may be oxidized derivatives, attention was focused upon the synthesis of such derivatives. Initial attempts to oxidize the methylene carbon [C(2)] in ester **60a** with $RuO_2 \cdot x\ H_2O$ in CC14 in the presence of $NaIO_4$ at room temperature gave, after 48 h, unreacted ester **60a** (~ 20%) and 4-acetoxybenzoic acid (71, 15%) rather than the target lactone **72**. A few cyclic ethers have been reported to be converted to a corresponding lactone by this technique.[102] Thus, bond cleavage resulted in **60a** to some degree at C(11)-C(13). Another effort to obtain lactone **72** involved the use of the Sharpless method.[11] In $CC1_4$:H_2O:CH_3CN (the solvent system and ratios used is critical here) with RuO_4 prepared *in situ* (from $RuO_2 \cdot x\ H_2O$ and NaIO4) both ester **60a** (~ 15%) was recovered along with aldehyde-ester **68** (~ 12%). Again, cleavage of the double bond at C(11)-C(13) occurred. Preparing RuO_4 *in situ* from $RuO_2 \cdot x\ H_2O$ and K–metaperiodate and K_2CO_3 (same solvent system as above) did not produce lactone **72** from ester **60a** but did yield ketone **65** and aldehyde-ester **68** in high yields. This interesting cleavage appears to be nearly quantitative via TLC analysis of the reaction mixture. The same results were observed with $ZnCr_2O_7 \cdot 3H_2O$[23] or pyridinium chlorochromate.[8]

It was discovered, however, that the methyl carbon [C(12)] in ester **60a** could be oxidized by SeO_2 in 95% ethanol to give, surprisingly, (*E*)-alcohol **60k** (15%) along with the expected *Z*-isomer **60h** (2%). There is a peripherally related analogy in the literature where (*E*)-3-methyl-2 pentane was oxidized with SeO_2 to give isomeric mixture of the products.[109] Purification required tedious and careful handling to obtain pure alcohol **60k**. Oxidation of allylic carbons to produce allylic alcohols are known.[16] However, the isomerization of the double bond in the reaction **60a**-**60k** is difficult to explain. Additional experimental work is needed to determine a possible mechanism for this isomerization. The stereochemical designation for **60k** rests upon UV, and ^1H, and ^{13}C NMR analysis.

Saponification of **60k** gave the acid-alcohol **60l** (56%). To the best of our knowledge, these are the only examples of heteroarotinoid systems with an oxidized group on the side chain.

Several methods for the synthesis of the chroman ring system are available.[9, 14, 123] Phosphonium salt **67** was prepared by using a modified method from our laboratory.[123] All yields have been optimized and are in excess of those reported for **62-67**. 3-Phenoxy propionic acid (**61**) was esterified using a Soxhlet-extractor, 3 A type molecular sieve and methanol at reflux for 46 h. The yield of ester **62** from this reaction was excellent (94%). Addition of ester **62** in ether to freshly prepared solution of methylmagnesium iodide in ether afforded alcohol **63** (82.6%). Ring closure of the alcohol **63** to ether **64** was carried out with $AlCl_3$ (anhydrous) in freshly distilled nitromethane. A normal workup, consisting of acidification, neutralization, and extraction, gave the final pure ether **64** (95.6% after distillation).

4,4-Dimethylchroman **64** was acetylated by treatment with distilled acetyl chloride and anhydrous aluminium chloride in nitromethane. This reaction was stirred at room temperature for 6 h and after quenching in acid and extraction into ether, gave ketone **65** (89.0% after distillation).

Addition of the ketone **65** in dry ether to a suspension of $LiAlH_4$ in dry ether under nitrogen gave, after quenching in acid and extraction into ether, alcohol **66** as a yellow solid. After repeated decolorization with charcoal, a snow white, solid alcohol **66** (82.9%) was obtained. The triphenylphosphine hydrobromide (**73**) was prepared by using a known method [84] whereby HBr gas was passed through a solution of triphenylphosphine in ethyl acetate. Recrystallization of the final product from CH_2Cl_2/ethyl acetate gave a white crystalline solid **73** (80%). The phosphonium salt **67** was prepared by treatment of methanolic solution of alcohol **66** with triphenylphosphine hydrobromide (**73**) at room temperature for 24 h. Concentration of the resulting solution repeated trituration with ether resulted in, the targeted phosphonium salt **67** in an excellent yield of 96.9%.

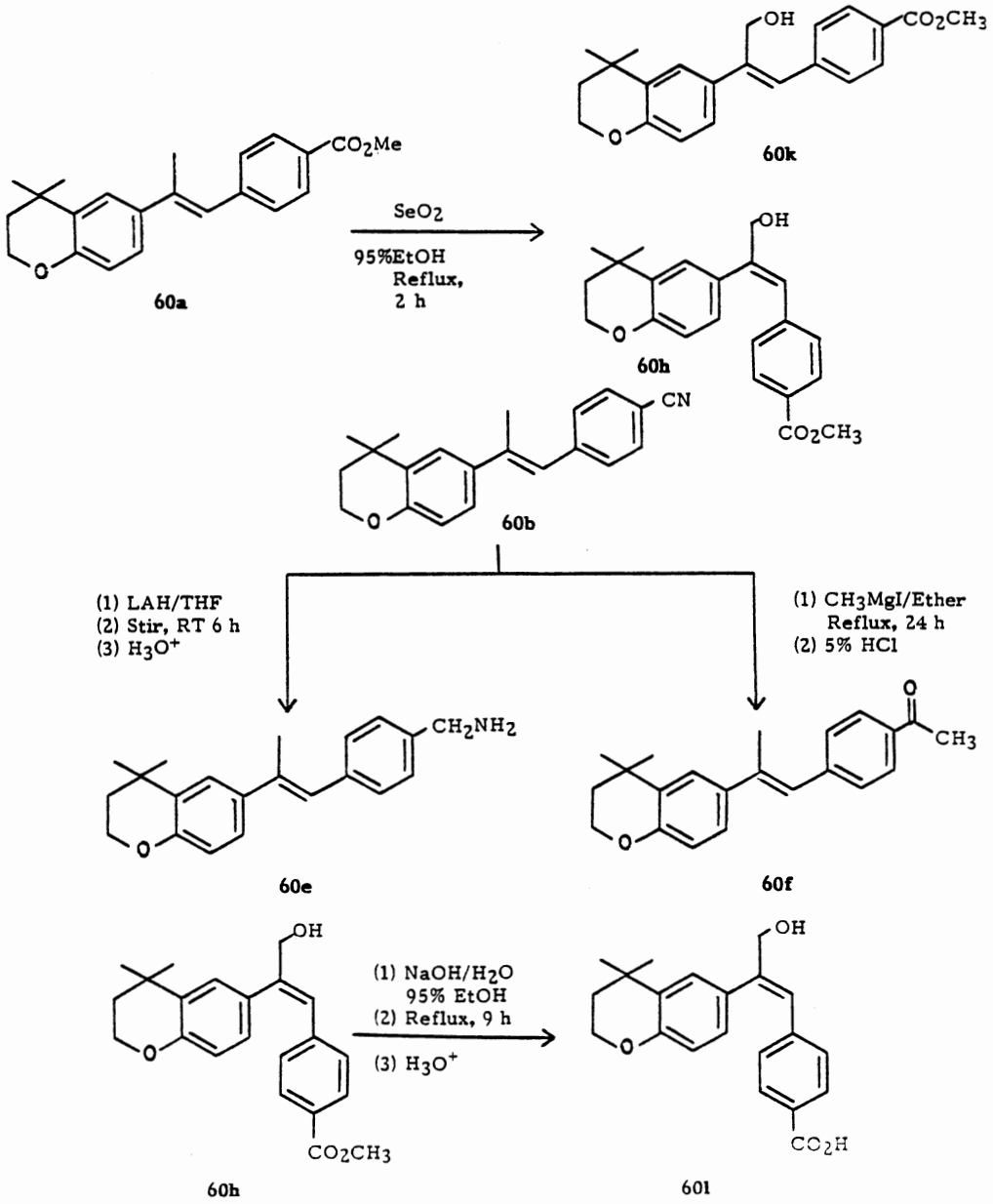


Figure 7. Conversion of **60a**, **60b**, and **60h**, to Yield **60k**, **60h**, **60f**, **60l**, Respectively

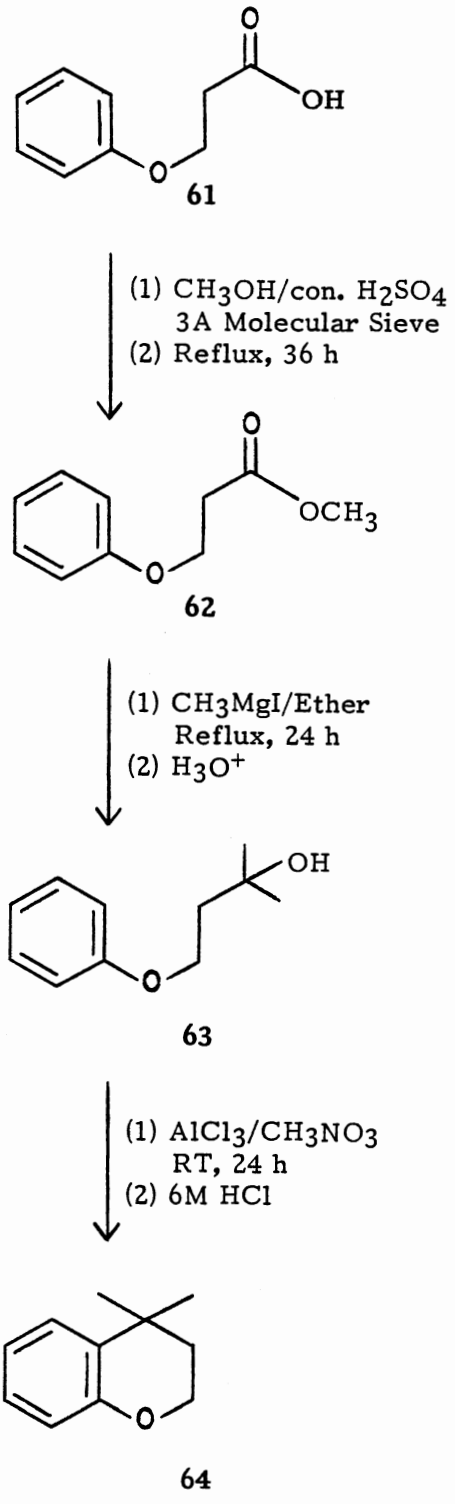


Figure 8. Synthesis of Ether **64**.

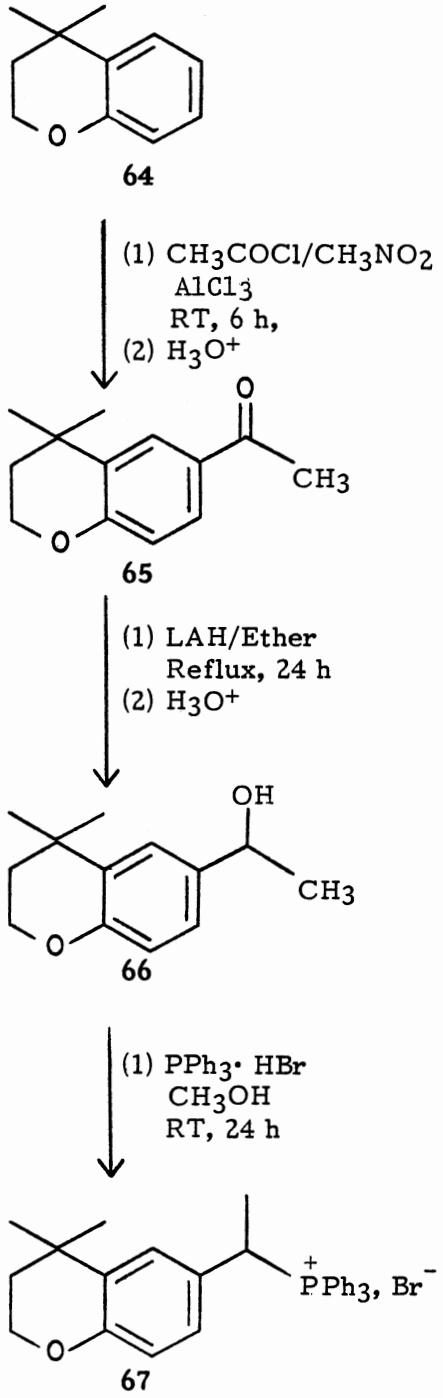


Figure 9. Synthesis of Phosphonium Salt **67**

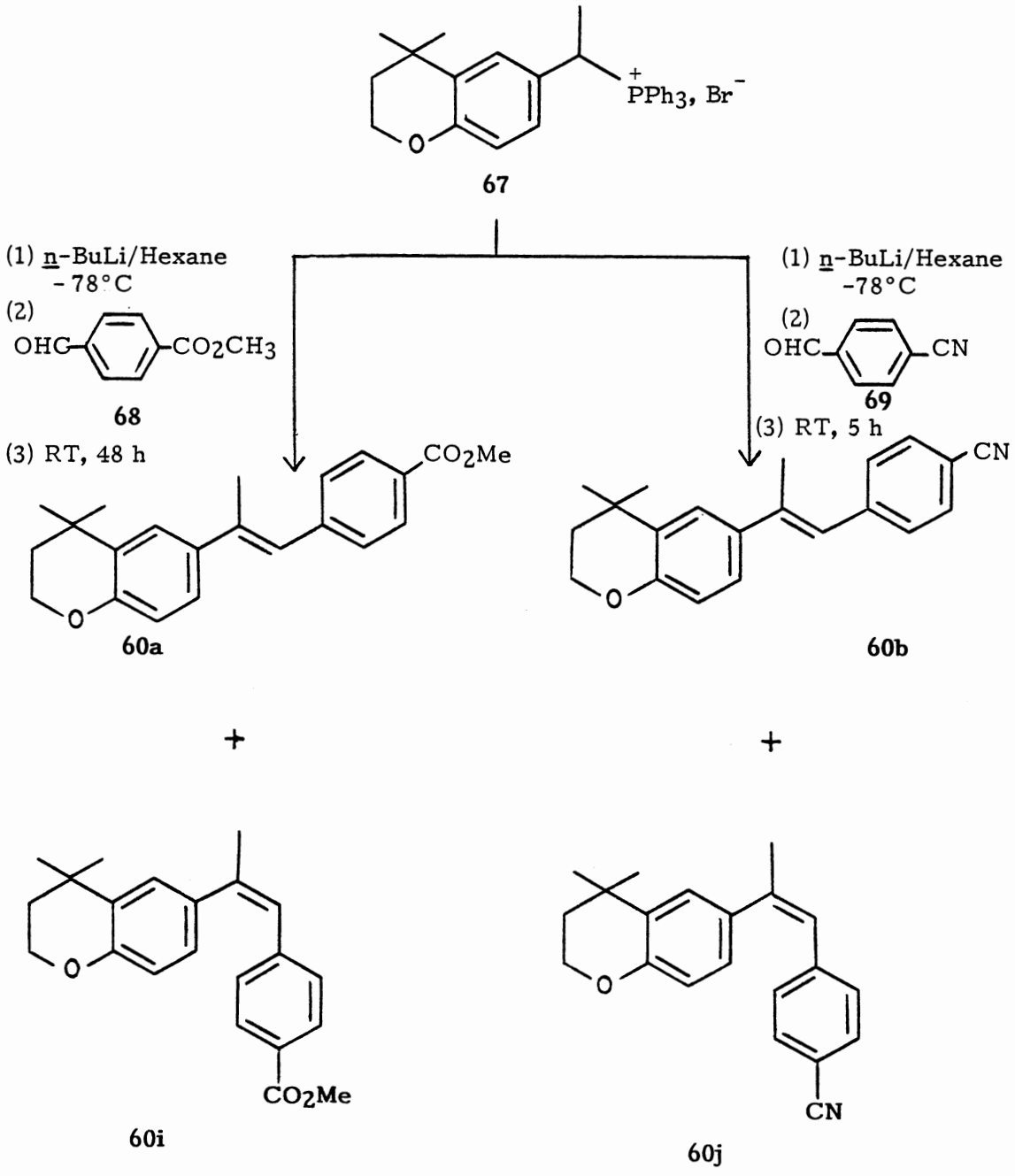


Figure 10. Synthesis of Heteroarotinoids **60a, 60i, 60b, 60j,** and **60g**

A Wittig reaction involving the anion from phosphonium salt **67** was attempted with methyl 4-formylbenzoate (**68**) under a variety of different conditions (Table VII). The anion of the phosphonium salt **67** was prepared in ether (dry) at the room temperature by using 1.5 equivalents of *n*-BuLi. The resulting solution was cooled to -78°C, and the resulting anion was treated with a solution of aldehyde **68** in ether. Workup produced a yellow oil which was most easily purified by using a silica gel column with 80% hexane:ethyl acetate as the elution system. ^{1}H NMR spectral analysis of the resulting solid indicated the presence of the desired heteroarotinoid **60a** and small amount of the corresponding isomer **60i** in a ratio of 10:1. The (*E*)-isomer **60a** was obtained in pure form (41%; mp 90-90.5°C) by recrystallization from 95% C_2H_5OH. The mother liquor contained predominantly the pure (Z)-isomer **60i** as white needles, mp 80-80.5°C.

Methyl 4-formyl benzoate (**68**) used in the Wittig reaction was prepared by treating 4-formyl benzoic acid (**74**-Aldrich) with methanol and a catalytic amount of sulfuric acid. Boiling the solution over 3 A molecular sieve for 48 h and gave, after a workup consisting of acidification to destroy any acetal of **68** formed during the reaction, neutralization and extraction, the final methyl 4-formylbenzoate (**68**), in a yield of 58% after recrystallization.

Reaction of ester **60a** with a suspension of $LiAlH_4$ in dry THF under nitrogen during 8 h at reflux gave, after quenching in acid an extraction into ether a thick yellow oil. Pure alcohol **60d** was obtained after separating the yellow oil on chromatotron by using a 4 mm silica gel plate with 80% hexane:ethylacetate as an eluent. The solid obtained was recrystallized to give **60d** (25%) with a mp 79-80°C.

The synthesis of a heteroarotinoid **60b** paralleled that for formation of ester **60a**. A Wittig reaction was applied involving the union of phosphonium salt **67** with 4–cyanobenzaldehyde (**69**) with two different solvents and with three different ratios of *n*–BuLi to (**67**). The results are summarized in Table VIII.

(*E*)-isomers **60b** predominated in ether when a 1.5 ratio of *n*-BuLi to **67** was utilized. The final yield of the heteroarotinoid (*E*)-isomer **60b** was, after recrystallization from 95%

TABLE VII

EFFECT OF SOLVENTS AND BASE ON WITTIG REACTION OF **67** → **60** → **68** → **60a** and **60i**

Solvent		*n*-BuLi	Yield (%) Of **60a** and **60i**	
Anion Preparation	Addition of Ester	Number of Equivalents	E	Z
Ether (dry)	Ether (dry)	1.0	35	1
Ether (dry)	Ether (dry)	1.5	41	2
Ether (dry)	THF (dry)	1.5	39	-
Ether (dry)	DMSO (dry)	1.5	4	-
THF (dry)	THF (dry)	1.2	28	-

TABLE VIII

EFFECT OF SOLVENTS AND BASE ON WITTIG REACTION OF **67** → **60** → $\xrightarrow{69}$ **60b and 60j**

Solvent		*n*-BuLi	Yield (%) Of **60b** and **60j**	
Anion Preparation	Addition of Ester	Number of Equivalents	E-Isomer	Z-Isomer
Ether (dry)	Ether (dry)	1.0	36	-
Ether (dry)	Ether (dry)	1.5	48	0.5
Ether (dry)	THF (dry)	1.2	10	-

ethanol, 48.6%. The mother liquor contained predominantly the (*Z*)-isomer **60j** in a very low yield (0.51%).

Reduction of the nitrile **60b** was achieved in dry THF with the aid of $LiAlH_4$ to give a yellow oil. Chromatography of the oil on a silica gel column using ethyl acetate:ethanol (1:1) as an eluting solvent gave a new oil. The final amine **60e** was obtained, after several days of refrigeration, as a solid which upon crystallization, melted at 103-105°C. No (*Z*)-isomer was observed in the crude mixture.

Addition of nitrile **60b** in ether to a solution of freshly prepared methylmagnesium iodide afforded, after workup, a yellow oil. The yellow oil was chromatographed using a silica gel column. Elution was effected with benzene. The final ketone **60f** was obtained, after recrystallization, as a solid and melted at 88-89°C.

Aldehyde **60c** was prepared by treating a solution of nitrile **60b** in ether with DIBAL–H in hexane. After workup, a viscous yellow oil was obtained which was chromatographed using a silica gel column with 80% hexane:ethyl acetate as a solvent system. After recrystallization (hot hexane), solid aldehyde **60c** (26%) melted at 85-86°C.

Heteroarotinoid **60g** was formed from reaction of the Wittig reagent from **67** (in ether using n-butyllithium in hexane) at room temperature. The resulting anion was treated with a solution of 5-acetoxymethyl-2-furaldehyde (**70**) in dry THF. A yellow oil formed and was chromatographed on a silica gel column using 80% hexane:ethyl acetate. The heteroarotinoid ester **60g** (19%) was obtained as a white crystalline solid (mp 80-81°C) after recrystallization (hexane). No (*Z*)-isomer was detected in the mixture.

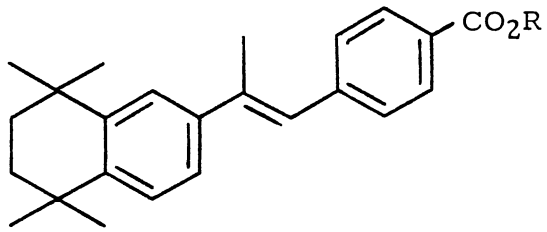
The allylic oxidation of ester **60a** to alcohol-ester **60k** was carried out with ester **60a** in 95% ethanol and SeO_2. The reaction mixture was heated at reflux for 24 h during which time elemental selenium formed as a black suspension. After workup, a yellow oil was obtained and was chromatographed using a silica gel column with 80% hexane:ethyl acetate. The ^1H NMR spectral data of the resulting oil indicated predominantly the presence of (*E*)-isomer **60k**. A small amount (≈ 5%) of the corresponding (*Z*)-isomer **60h**

was obtained as an oil and was estimated to have a purity of 86%. The (*E*)-isomer **60k** was obtained in pure form by recrystallization (absolute ethanol) with cooling in refrigerator for several days and scratching to induce crystallization, mp 85-86°C. Saponification of ester **60h** produced acid-alcohol **60l** (56%) mp 198-199°C (absolute ethanol/pentane).

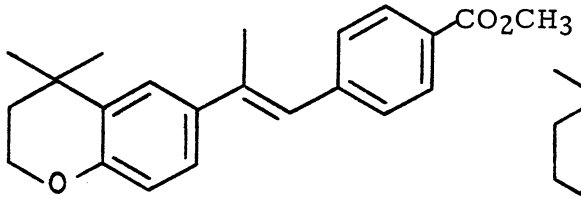
Spectral Analysis of the Heteroarotinoids

The ^{1}H NMR spectral analyses for the heteroarotinoids **21**, and **60a-60l** are given in the Experimental Section. The assignments for the ^{13}C resonances shown in Tables IX-XV were aided by observed splitting patterns from off-resonance spectra and from the comparison with the spectra of known heteroarotinoids such as **18**, **19**, and **75a-75d**.[18, 64, 123] In the compounds **21**, and **60a-60f**, the assignments for the aromatic protons H(5), H(7), and H(8) of the chroman ring were made from analysis of the actual splitting pattern in the spectra. In heteroarotinoids **21**, **60a-60f**, H(5) was expected to give a doublet with J = 2-3 Hz and the actual value observed was J = 3 Hz. Likewise, H(7) gave the expected ortho and meta couplings and a doublet of doublets pattern with J = 3 Hz for the meta-coupled proton [H(5)] and J = 9 Hz for ortho-coupled proton [H(8)]. Moreover, H(8) was expected to give a doublet for $^{3}J_{7,8}$ in the range of J = 7-10 Hz which was actually seen in **21**, and **60a-60f** with a value of 9 Hz.

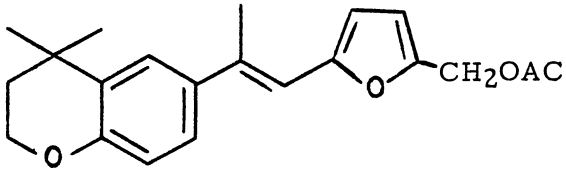
In **21**, and **60a-60f**, the vinylic proton [H(13)] gave a singlet in the region of δ 6.33-6.80. In known (*E*)-arotinoids **18**, **19**, **21**, and **75a-75d**[64, 123], the vinylic proton [H(13)] was a singlet at 6.82, 6.77, 6.77, 6.80, 6.82, 6.80 and 6.86, respectively. In the heteroarotinoids **21**, and **60a-60f**, the *vinylic methyl* group [H(12)] gave a singlet in the region of δ 2.2-2.3. In the known (*E*)-arotinoids **18**, **19**, **21**, and **75a-75d**, the corresponding signals at δ 2.30, 2.37, 2.30, 2.27, 2.28, 2.27, and 2.28, respectively. A comparison of these data with that for **21**, and **60a-60f** indicated the latter should have the (*E*)-configuration. In the heteroarotinoid **60g**, H(15), H(16) was expected to give a



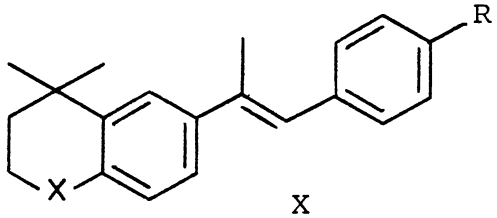
	R
18	C_2H_5
19	H



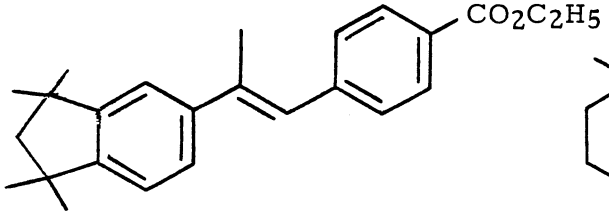
60a



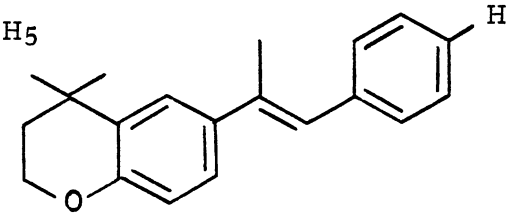
60g



	X	R
75a	O	CO_2Et
75b	S	CO_2Et



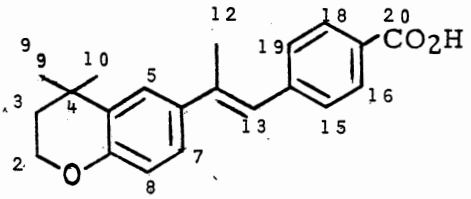
75c



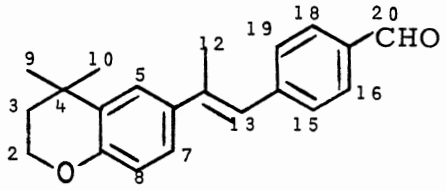
75d

TABLE IX

^{13}C NMR DATA FOR THE HETEROAROTINOIDS **21** and **60c**



21



60c

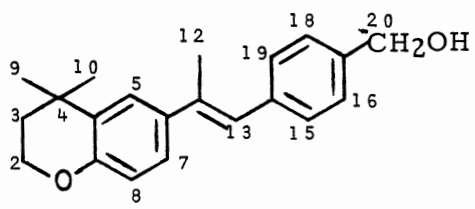
Carbon Number	Chemical Shifts*	
	21	**60c**
2	63.1	63.1
3	37.6	37.6
4	30.7	30.7
9	31.1	31.7
10	31.1	31.7
12	17.8	17.9
5	124.6	124.6
7	124.9	124.9
8	116.6	116.8
13	125.0	129.6
15(19)[a]	129.1	129.0
16(18)[a]	130.1	129.5
8a	153.5	153.4
20	172.0	191.8
Nonprotonated Aromatic and Vinylic Carbons	126.8	129.7
	131.4	131.4
	135.6	135.5
	139.9	140.4
	144.3	145.1

*Chemical Shifts in ppm.

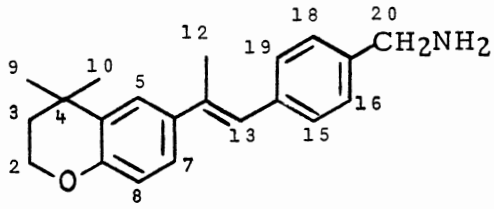
[a]May be interchanged.

TABLE X

^{13}C NMR DATA FOR THE HETEROAROTINOIDS **60d** and **60e**



60d



60e

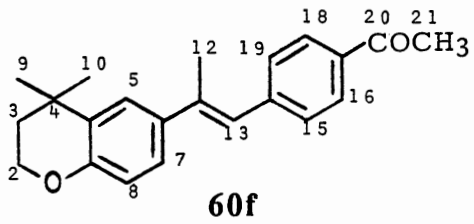
Carbon Number	Chemical Shifts*	
	60d	**60e**
2	63.1	61.1
3	37.7	37.7
4	30.7	30.7
9	31.3	31.1
10	31.1	31.1
12	17.6	17.6
5	124.4	124.4
7	124.8	124.8
8	116.7	116.8
13	125.4	125.4
15(19)[a]	129.6	127.7
16(18)[a]	130.1	129.5
8a	154.0	153.1
20	65.2	43.2
Nonprotonated Aromatic and Vinylic Carbons	131.2 136.0 137.4 138.7	127.9 131.1 136.0 137.6 138.0

*Chemical Shifts in ppm.

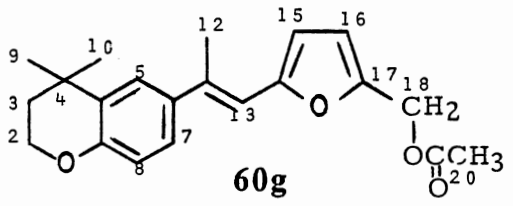
[a]May be interchanged.

TABLE XI

^{13}C NMR DATA FOR THE HETEROAROTINOIDS **60f** and **60g**



60f



60g

Carbon Number	Chemical Shifts*	
	60f	**60g**
2	63.1	63.1
3	37.6	37.6
4	30.7	30.7
9	31.0	31.1
10	31.0	31.1
12	17.8	18.2
21	26.6	
5	124.5	124.4
7	124.9	124.8
8	116.8	116.8
13	125.0	131.3
15(19)[a]	128.3	114.2[b]
16(18)[a]	129.2	109.5[c]
8a	153.4	-
18		58.3
20	197.7	20.9
19		170.7
Nonprotonated Aromatic and Vinylic Carbons	131.3	135.6
	134.7	136.9
	135.6	147.7
	139.7	153.3
	144.6	154.6

*Chemical Shifts in ppm.

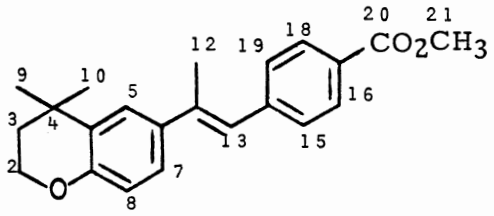
[a]May be interchanged.

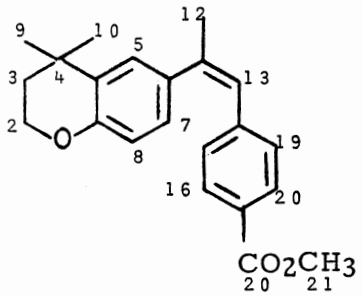
[b]Only for C(15).

[c]Only for C(16).

TABLE XII

^{1}H AND ^{13}C NMR DATA FOR THE HETEROAROTINOIDS **60a** and **60i**





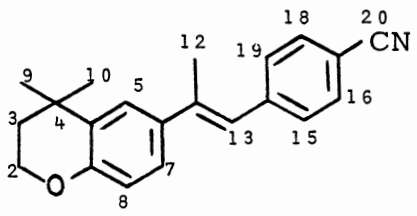
	60a		**60i**	
	E-Isomer		*Z*-Isomer	
Carbon Number	^{1}H NMR*	^{13}C NMR*	^{1}H NMR*	^{13}C NMR*
2	4.20	63.1	4.17	63.1
3	1.90	37.6	1.78	37.5
4	-	30.7	-	30.4
9	1.40	31.1	1.12	30.8
10	1.40	31.1	1.12	30.8
5	7.40	124.5	6.99	127.5
7	7.30	124.9	6.93	126.5
8	6.84	116.8	6.73	117.0
12	2.30	17.8	2.21	26.8
13	6.80	125.9	6.43	125.1
15(19)[a]	7.50	129.0	7.03	128.8
16(18)[a]	8.60	129.5	7.77	129.1
20	-	167.0	-	167.0
21	3.90	52.1	3.86	51.9
8a	-	154.4	-	153.0
Nonprotonated Aromatic and Vinylic Carbons		127.6 131.3 135.7 139.5 143.4		129.5 131.4 132.9 141.4 143.1

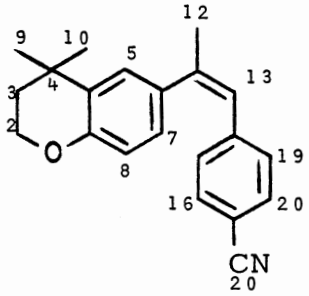
*Chemical Shifts are in ppm.

[a]May be interchanged.

TABLE XIII

^1H AND ^{13}C NMR DATA FOR THE HETEROAROTINOIDS **60b** and **60j**





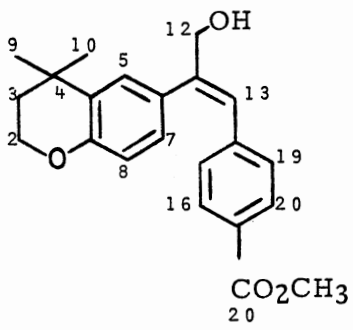
	60b		**60j**	
	E-Isomer		*Z*-Isomer	
Carbon Number	^1H NMR*	^{13}C NMR*	^1H NMR*	^{13}C NMR*
2	4.20	63.2	4.20	63.1
3	2.30	35.6	1.80	37.4
4	-	30.7	-	30.4
9	1.80	31.6	1.14	30.8
10	1.80	31.6	1.14	30.8
5	7.44	124.6	6.97	126.4
7	7.21	124.3	6.96	124.3
8	6.80	124.9	6.78	127.6
12	2.21	17.8	2.22	26.7
13	6.74	116.9	6.42	117.1
15(19)[a]	7.50	131.9	7.08	131.6
16(18)[a]	7.90	129.7	7.20	129.45
20	-	119.2	-	119.3
8a	-	153.6	-	153.2
Nonprotonated Aromatic and Vinylic Carbons		109.4 131.6 135.3 140.6		108.9 132.4 142.8 143.1

*Chemical Shifts are in ppm.

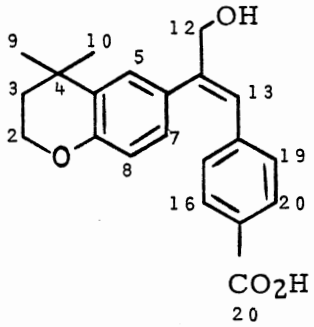
[a]May be interchanged.

TABLE XIV

^{13}C NMR DATA FOR THE HETEROAROTINOIDS **60k** and **60l**



60k



60l

Carbon Number	Chemical Shifts*	
	60k	**60l**
2	66.8	62.4
3	36.3	36.7
4	29.3	29.9
9	29.7	30.3
10	29.7	30.3
5	123.5	122.3
7	125.7	126.4
8	116.2	116.7
12	62.0	65.4
13	126.7	128.0
15(19)[a]	127.9	128.6
16(18)[a]	128.1	128.9
20	165.8	167.0
21	50.8	-
8a	152.3	152.6
Nonprotonated Aromatic and Vinylic Carbons	126.9	127.5
	128.0	129.7
	131.0	131.5
	140.8	141.9

*Chemical Shifts in ppm.

[a]May be interchanged.

doublet for each proton with J = 3.2-3.8 for the ortho-couplings[88] while the actual observed value was J = 3 Hz.

A HETCOR 2-D NMR experiment can be used to correlate the ^{1}H NMR chemical shift of a particular set of protons with ^{13}C NMR chemical shift of the corresponding carbon.[43] In order to utilize the information contained in a 2-D or contour plot, either the ^{1}H or ^{13}C NMR assignments must be known unequivocally. A comparison of the contour plot from the HETCOR 2-D NMR experiment, the ^{13}C NMR spectrum in the region between 25 and 65 ppm, and ^{1}H NMR spectrum between approximately δ 1.0 and 4.5 allowed confirmation of assignments for H(2) and H(3) in **60i** and **60j**. More detail concerning the use of HETCOR 2-D NMR experiment is available in Chapter II. The ^{13}C NMR assignments for the protonated aromatic and olefinic carbons of **60i** and **60j** (Table XII and XIII) were made by using HETCOR 2-D NMR experiments over the aromatic region. The results of these experiments are shown in spectra as Figures 11-16.

A comparison of an (*E*)-isomer with a (*Z*)-isomer of a modified retinoid with respect to the corresponding ^{1}H NMR and ^{13}C NMR chemical shifts could not be found in the literature. It is clear from data in Tables XII and XIII that in spectra of the (*E*)-isomers nearly all of the ^{1}H NMR shifts are downfield as compared to those of the (*Z*)-isomers. The ^{13}C NMR chemical shifts are comparable in both of the (*E*) and (*Z*)-isomers **60a** and **60b** except the chemical shift for C(12) which is upfield (17.8 ppm) in the (*E*)-isomer from that in the (*Z*)-isomer (26.8 ppm).

The (*E*)-geometry at the double bonds in **21**, and **60a-60h** was supported by making a comparison of the ^{1}H NMR spectra with that of the known (*E*)-isomers **18**, **19**, and **75a-75d**. In (*Z*)-isomers, **60i** and **60j**, vinylic protons H(13) signals were shifted upfield by approximately 0.33 ppm from that of the corresponding (*E*)-isomers **60a** and **60b**. Similar shifts have been reported for the vinylic protons of *cis*-stilbene (**76**) compared to those of *trans*-stilbene (**76**) [δ 6.67 versus δ 7.1].[12, 56]

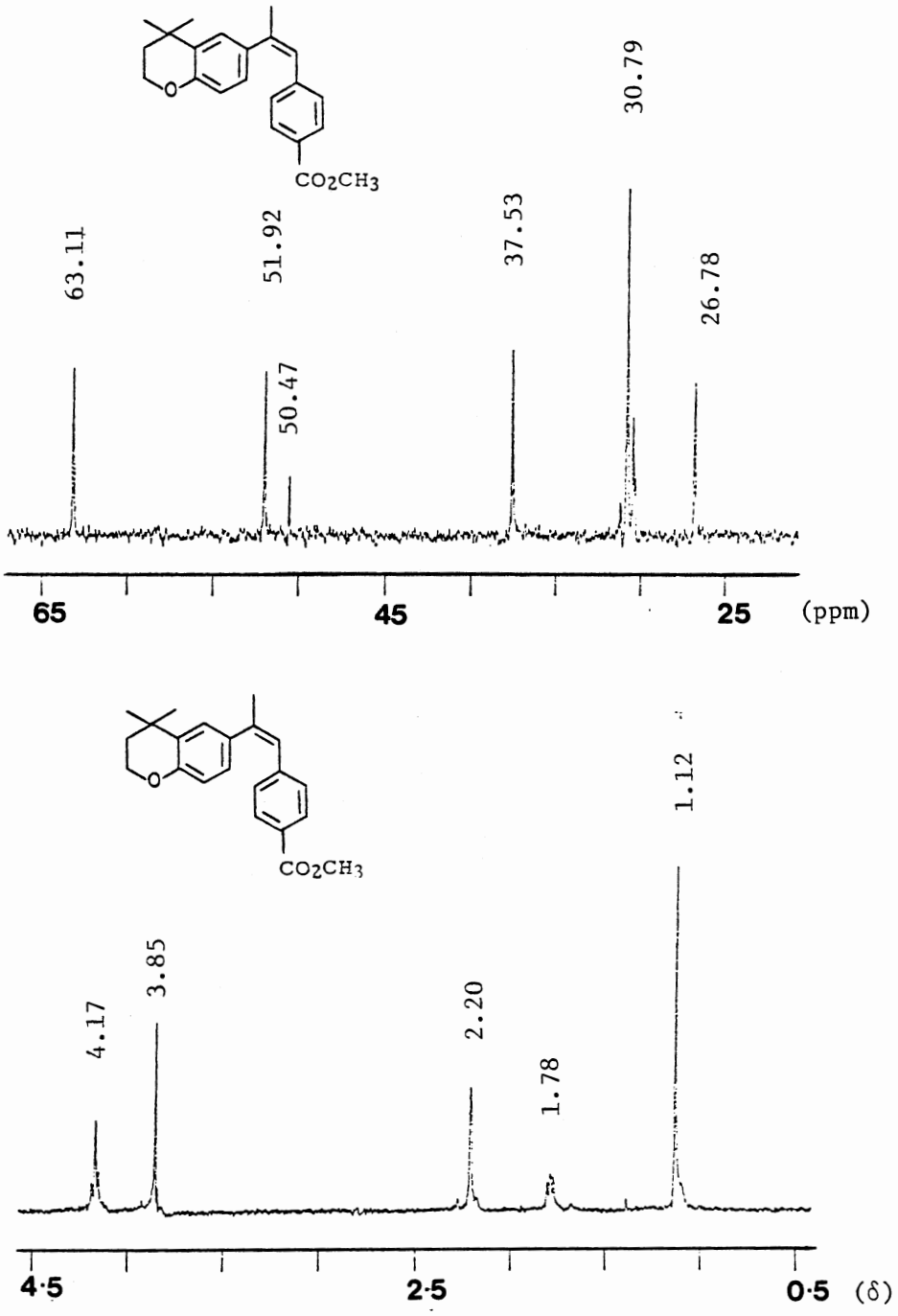


Figure 11. ^{13}C NMR and ^{1}H NMR Spectra of **60i** in the Aliphatic Region.

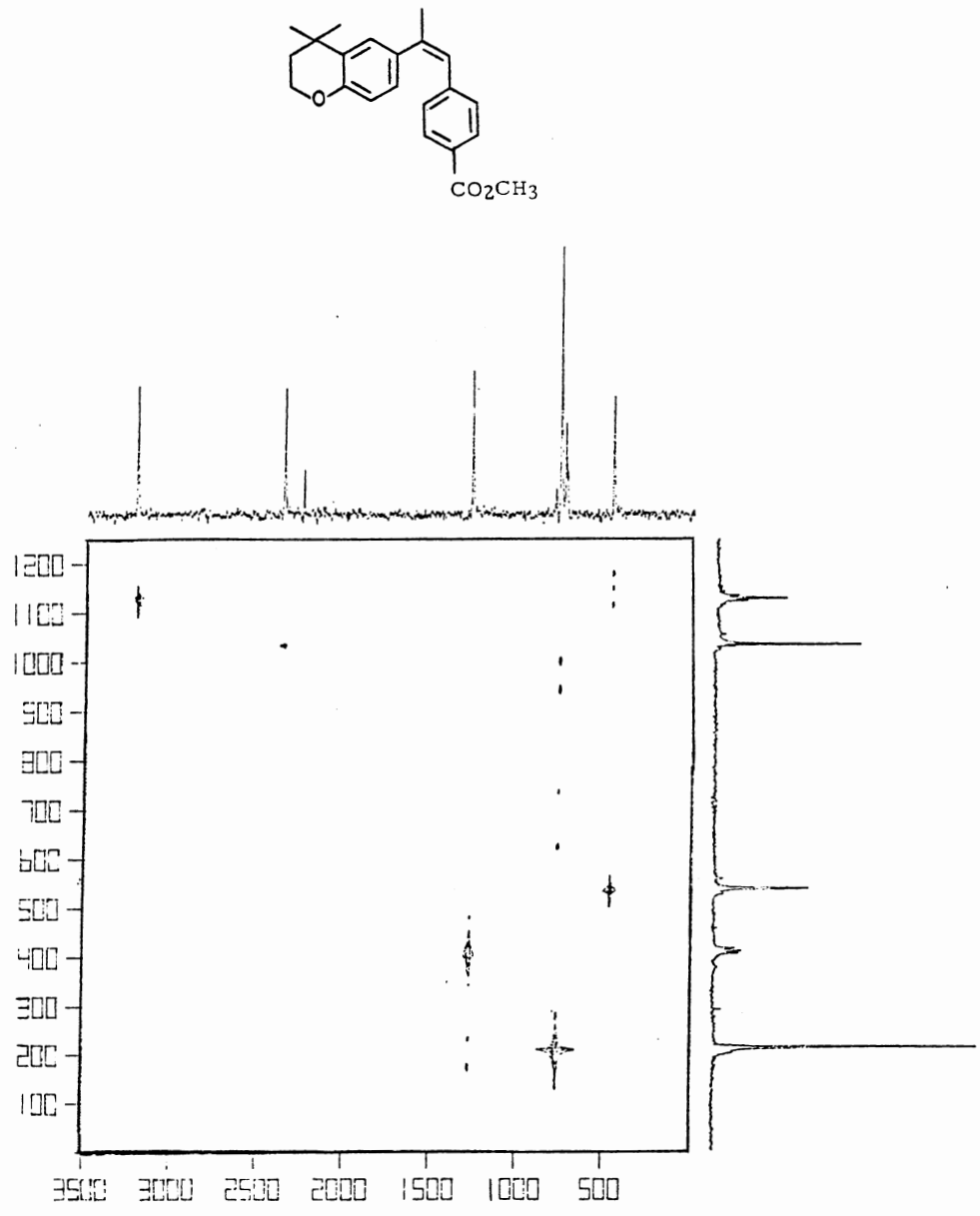


Figure 12. Contour Plot of HETCOR 2-D Spectrum of **60i** in the Aliphatic Region

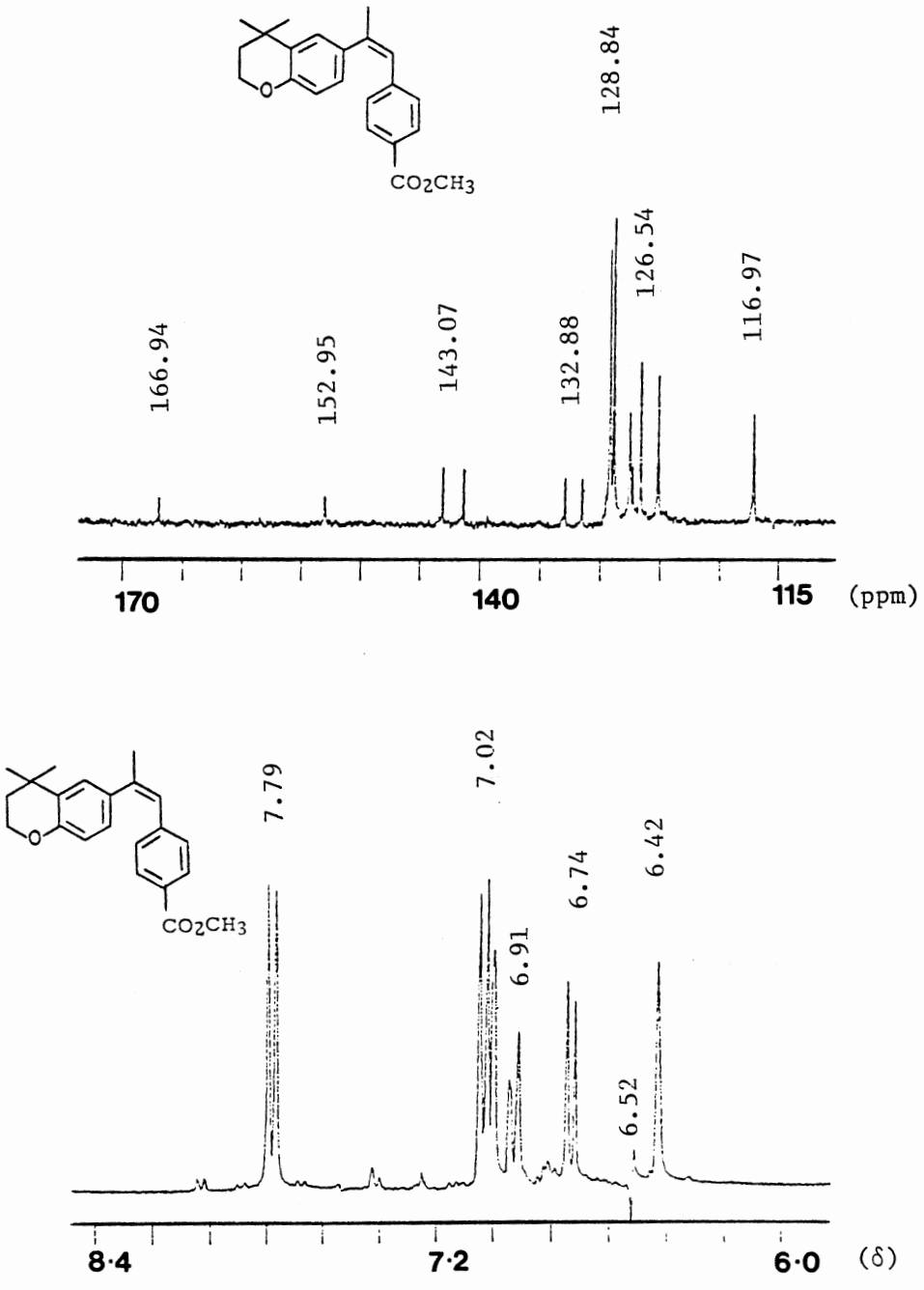


Figure 13. ^{13}C NMR and ^{1}H NMR Spectra of **60i** in the Aromatic Region.

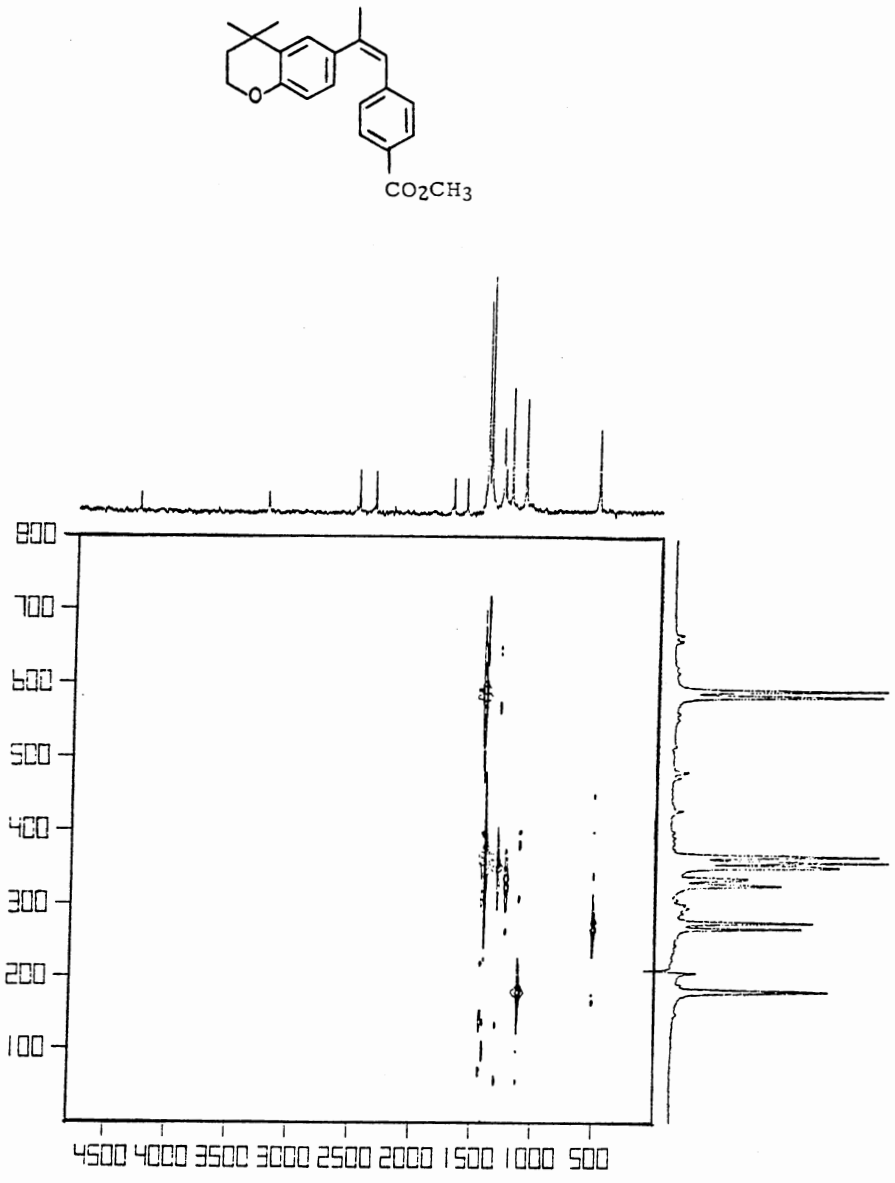


Figure 14. Contour Plot of HETCOR 2-D Spectrum of **60i** the Aromatic Region

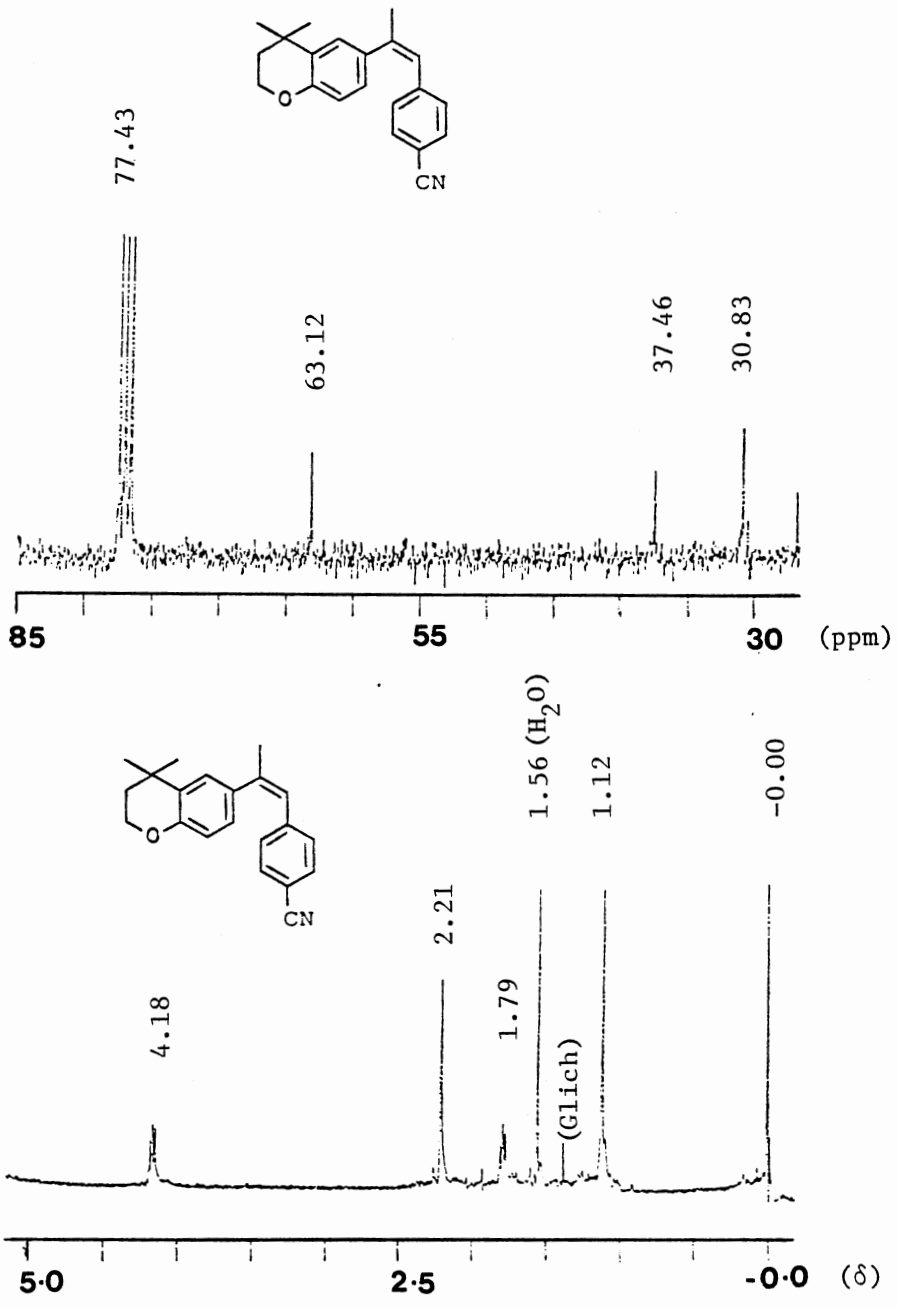


Figure 15. ^{13}C NMR and ^{1}H NMR Spectra of **60j** in the Aliphatic Region

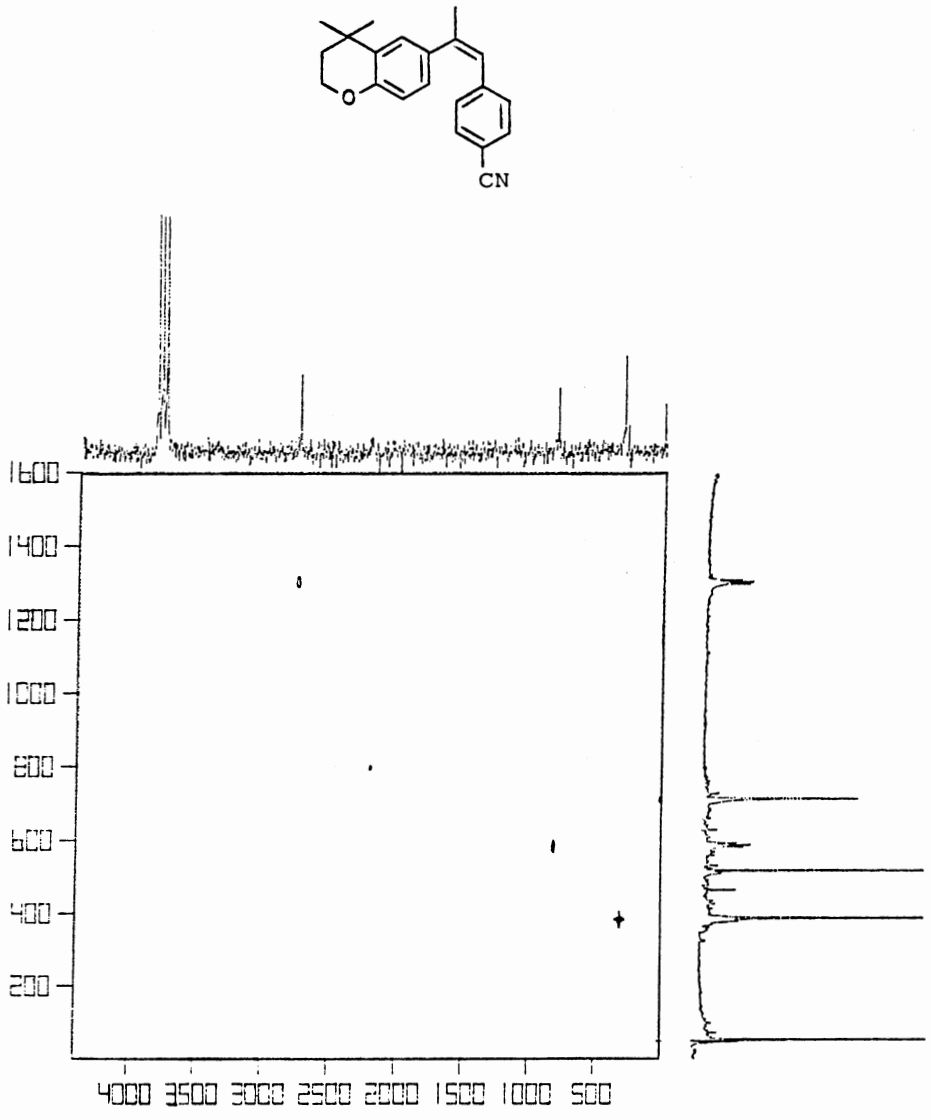
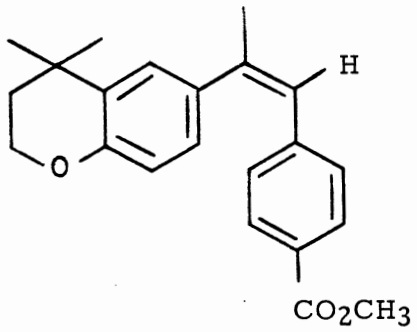
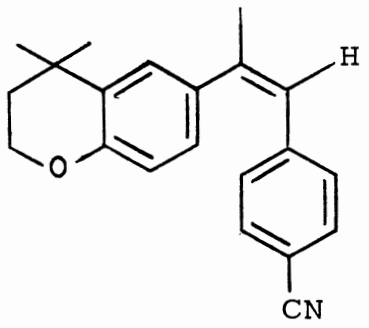


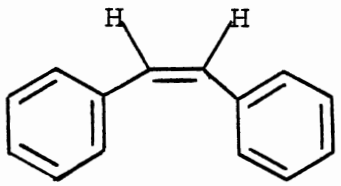
Figure 16. Contour Plot of HETCOR 2-D Spectrum of **60j** in the Aliphatic Region.



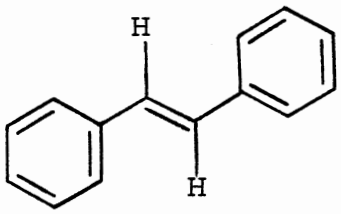
60i



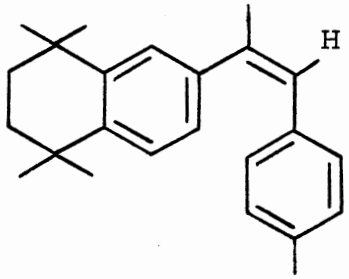
60j



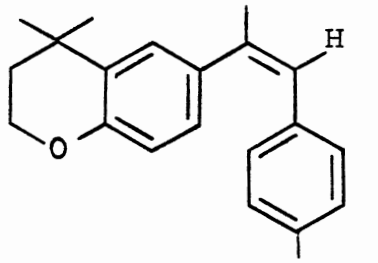
76a



76b



77a



77b

In related (Z)-arotinoids **77a** and **77b** the vinylic protons (CH = C-CH_3) gave singlets at δ 6.46, and 6.45, respectively, while (Z)-heteroarotinoids **60i** and **60j** gave singlets at δ 6.43 and 6.42, respectively. In the (Z)-arotinoids **77a** and **77b**, the vinylic methyl groups [CH = CH-C$\underline{H}_3$] gave singlet, at δ 2.23 and 2.20, respectively, while in (Z)-heteroarotinoids **60i** and **60j**, the singlets occurred at δ 2.21 and 2.22, respectively. Although none of the structures have been subjected to x-ray analysis, a comparison of these NMR data strongly suggests that heteroarotinoids **60i** and **60j** have the Z-configuration. Space filling models (Courtauld) imply that H(12) and H(13) in the (Z)-

isomers may be positioned to a small degree within the shielding cones of the respective aryl rings.

A study was made of the ultraviolet (UV) spectra of members of **60**. The extinction coefficients (ε) and the UV absorption maxima (λ_{max}) were greater in the (*E*)-isomer than in the (*Z*)-isomer (Table XV), which supported the stereochemical assignments for **60a**, **60h**, **60i**, and **60k**. As expected the *cis*-isomers **60i** and **60k** had smaller λ max values since misalignment of p-orbitals in the conjugated alkene system is suspected due to molecular crowding which results in disrupted conjugation. The oxidation product (alcohol-ester **60k**) obtained from the SeO_2 oxidation of **60a** surprisingly showed the presence of (*E*)-isomer **60k** with the aryl groups *syn* to each other. This syn arrangement for the aryl groups in **60k** was assigned after comparison of the ^1H NMR chemical shifts and of the UV maxima with those of model compounds **77a** [64] and **77b** (reported as a crude oil)[18]. For example, the UV spectrum of **60k** was comparable with that for *cis*-stilbene (**76b**) as well as with the arotinoids **77a** and **77b** (Table XV). In **77a**, the λ max was 297 nm with $\varepsilon = 1.4 \times 10^4$, while in heteroarotinoid **77b** the values were 306 nm and 1.2×10^4. Heteroarotinoid **60i**, had λ max at 310 nm with $\varepsilon = 1.61 \times 10^4$ while (*E*) isomer **60k** had values of λ max 302 nm and $\varepsilon = 1.5 \times 10^4$. In contrast, in isomers **60a**, **60h**, and **75a** larger λ max values and larger ε values were observed suggesting better conjugation as expected with the larger aryl rings in an anti arrangement around the double bond.

Pharmacological Activity of the Heteroarotinoids

Inhibition of ODC Induction. The pharmacological activity of heteroarotinoids **60a**, **60b**, **60c**, and **60d** was evaluated at the University of Wisconsin by Dr. A. K. Verma using ornithine decarboxylase (ODC) assay developed by Boutwell and Verma[121] as discussed in Chapter I. When mouse skin is treated with 12-O-tetradecanoylphorbal-13-acetate (TPA), (Figure 2) there is a marked induction of the synthesis of biosynthetic enzyme ODC which

TABLE XV

UV DATA FOR THE AROTINOIDS

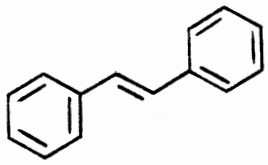
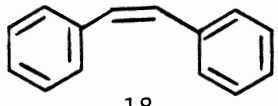
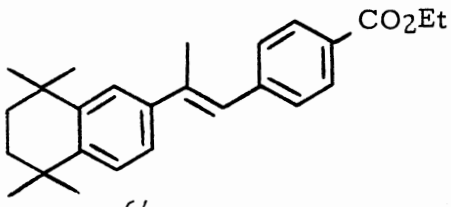
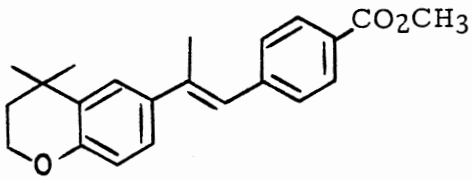
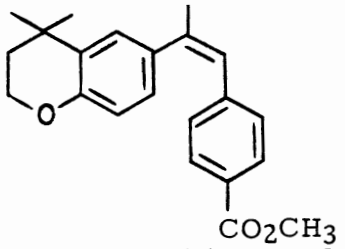
Compound	λmax in mn	ε (x 10^4)	Concentration in EtOH
 **76a**[18] [(E)-isomer]	321 236	1.79 1.1	
 **76b**[18] [(Z)-isomer]	280 224	1.0 2.4	
 **18**[64] [(E)-isomer]	306	2.6	
 **60a** [(E)-isomer]	318 237	2.5 1.5	4.8 x 10^{-5}M
 **60i** [(Z)-isomer]	310 245	1.6 2.2	9.5 x 10^{-5}M

TABLE XV (continued)

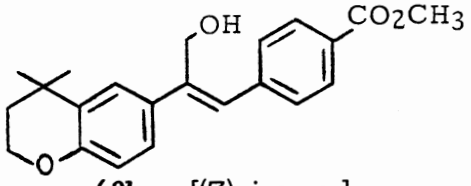
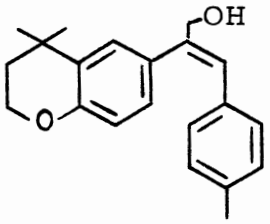
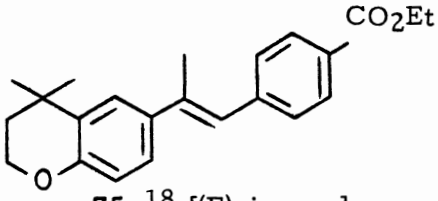
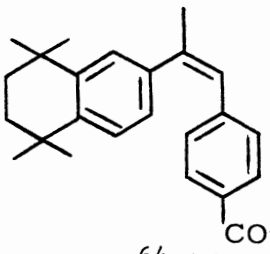
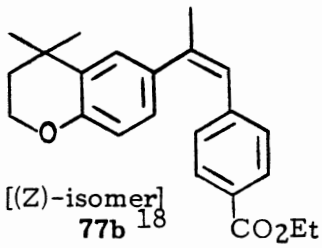
Compound	λmax in mn	ε (x 10^4)	Concentration in EtOH
 **60h** [(Z)-isomer]	314 241	2.4 1.7	9.1 x 10^{-5}M
 **60k** [(E)-isomer]	302 285	1.5 1.7	9.1 x 10^{-5}M
 **75a**[18] [(E)-isomer]	316 236	2.4 1.4	
 **77a**[64] [(Z)-isomer]	297	1.4	
 [(Z)-isomer] **77b**[18]	306 244	1.2 1.7	

TABLE XVI

DATA FROM THE ODC ASSAY WITH THE HETEROAROTINOIDS

Heteroarotinoid	Test System	Retinoid Dose, n mol	ODC Activity*	Percent of Inhibition as Compared to Control+
	Acetone	0.0	0.0 ± 0.0	-
	Acetone + TPA**	0.0	1.67 ± 0.14	Control
	3 + TPA**	17	0.14 ± 0.04	92
60a	**60a** + TPA**	34	0.95 ± 0.06	43
60b	**60b** + TPA**	34	1.77 ± 0.32	
	Acetone	0.0	0.0 ± 0.0	-
	Acetone + TPA**	0.0	5.3 ± 0.7	Control
	6 + TPA**	34	1.0 ± 0.1	81
60c	**60c** + TPA**	34	3.5 ± 0.2	34
60d	**60d** + TPA**	34	1.7 ± 0.1	68

*n mol CO_2/ 60 min/mg protein.

**Refer Figure 2 in the Chapter I.

+The percentage of Inhibition as compared to control was calculated as shown:

$$\frac{\text{(ODC with Acetone + TPA) - (ODC with retinoid)}}{\text{(ODC with Acetone + TPA)}} \times 100$$

is associated with an increase in the proliferative activity of the tissue. Retinoids prevent this induction, and the relative effectiveness of a retinoid to inhibit the TPA-induced production of ODC can be used as a basis for measuring biological activity of the test compound.

The preliminary assays of **60a**, **60b**, **60c**, and **60d** have been completed and summarized in Table (XVI). A comparison of the % inhibition of the formation of tumor, by **60a**, **60b**, **60c**, and **60d** (along with the % inhibition of the formation of tumors in systems with the standards 13-*cis*-retinoic acid (**3**) or *trans*-retinoic acid (**6**), indicate that heteroarotinoid **60d** inhibited tumor formation by 68% at the 34-nmol dose and had the strongest activity of any heterocycle tested. The heteroarotinoid **60a** prevented tumor formation by 43% at 34-nmol dose and heteroarotinoid **60c** showed 34% inhibition of cancerous cell growth. Both **60a** and **60c** exhibited much smaller activity than alcohol **60d**. The heteroarotinoid **60b** was essentially inactive at the 34 nmol dose and induced greater ODC activity than the control.

Recently, it was shown by Breitman and co-workers that retinoids, including arotinoids, can induce terminal differentiation of several types of neoplastic cells and that the measurement of such a response can be used for rapid and quantitative assays of activity.[111] The HL-60 cell line was used for this purpose and cell differentiation was induced by arotinoid such as heteroarotinoid **60a**. These mature cells, unlike the uninduced HL-60 cells, produced superoxide anion when stimulated with an appropriate agent such as TPA.[111] The ability of individual cells to produce superoxide was measured by incubating cells with water soluble yellow dye, nitroblue tetrazolium chloride (NBT) Figure 17. NBT was reduced to a water-insoluble, blue-black formazan by superoxide. The formazan precipitate was associated with those cells that produced superoxide. Thus, the percentage of cells in a population that produces superoxide (NBT-positive cells) was enumerated under a light microscope. The concentration of retinoid effective in achieving half-maximal response (ED_{50}) for heteroarotinoid **60a** was greater than 3 μM, the highest

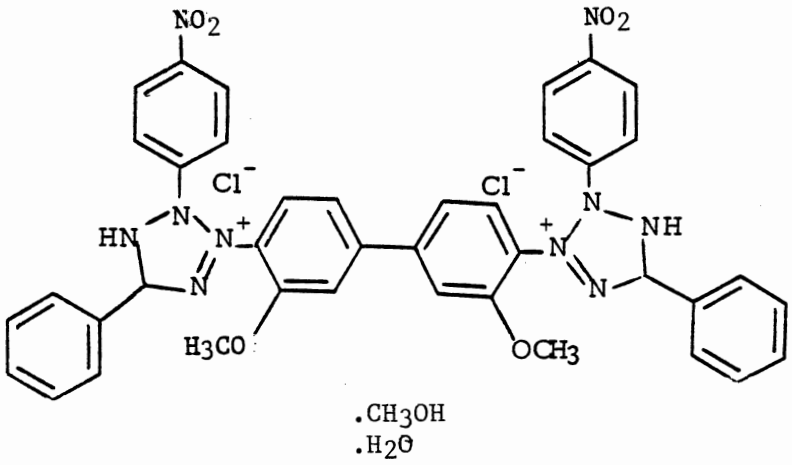


Figure 17. Nitro Blue Tetrazolium Chloride (NBT)

concentration tested, as compared to the ED_{50} of 41 nm for *trans*-retinoic acid (standard). At a concentration of 3 μM, heteroarotinoid **60a** induced approximately 15% of the cells, as compared to the control.

These screening results are still preliminary. To get ED_{50} values, these assays should be run at a variety of concentrations of the heteroarotinoids. Previous results with only a few related systems obtained from our laboratory are promising.[123] One objective of our work was to obtain heteroarotinoids which had increased hydrophilicity and lower lipophilicity with, hopefully, concomitant lower toxicity. The incorporation of the heteroatom, such as oxygen, into the basic arotinoid structure and with a *para* substituent on the aryl group resulted in good activity in terms of the ornithine decarboxylase assay for **60d**.[121] This appears to meet the first objective. Toxicity studies which are in progress will determine the overall effectiveness of heteroarotinoids **60a, 60d, 60c,** and **60d.** It also appears that the presence of the rigid *syn* arrangement of carbons at the 4-, 15(19)-, 16(18)- and 17-positions in the aryl ring do not alter significantly the activity normally

associated with long polyene chain, for example, as in 13-*cis*-retinoic acid (**3**). Biological activity studies of the heteroarotinoids **60g, 60e, 60f, 60i, 60k**, and **60l** are in progress.

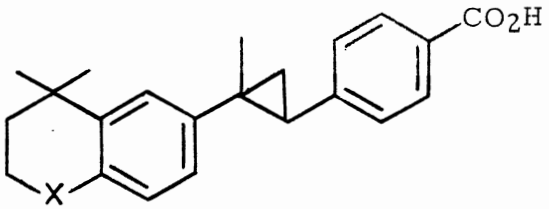
Suggestions for Future Work

Toxicity studies done by Dawson and co-workers with Femal Swiss mice suggested that acid **19** and acid **21** are *less* toxic than *trans*-retinoic acid (**6**) and therefore have potential value in the treatment of proliferative skin diseases.[18] Toxicity studies of the heteroarotinoids **21**, and **60a-60l** must be performed to determine what effect, if any, the para-substituent on phenyl ring has on activity along with the incorporation of oxygen heteroatom in the ring. Compare relative biological activity of 2 isomers such as the (*E*)–isomer and (*Z*)-isomer for the heteroarotinoids **60a, 60i, 60b, 60j, 60h**, and **60k**, respectively. At this point the reason is not evident why the E-configuration in the heteroarotinoid **60a** is not preserved to give the (*Z*)-isomer **60h** rather than the isolated (*E*)-isomer **60k** in the SeO_2 oxidation reaction. Additional heteroarotinoids should be examined under the same reaction conditions to confirm that syn arrangement of the phenyl rings results as a general rule. X-Ray diffraction analysis of the heteroarotinoid **60i** or **60j** should be useful to determine space orientation of groups in these supposedly strained systems.

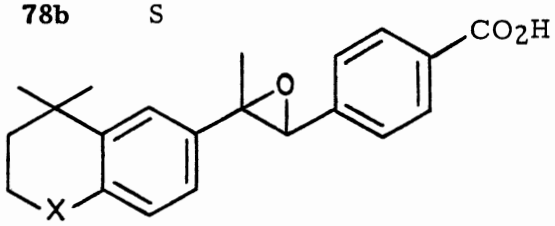
Other modifications which could prove useful include: (1) cyclopropination and epoxidation of the vinylic double bond to afford acids **78a** and **78b**; (2) oxidation of one methyl group of the gem-dimethyl function since such a system has been reported as a metabolite from the retinoic acid to give heteroarotinoids **79a** and **79b**; (3) oxidation of all methyl groups to yield heteroarotinoids **79c** and **79d**; (4) lactone formation by oxidizing C(2) to give **72**, for example.

Since attempts to make the lactone **72** from ester **60a** in one single step were unsuccessful to date an alternative route to the lactone **72** is postulated below. Phenol and 3-methylcrotonyl chloride are the suggested starting materials which can be obtained from

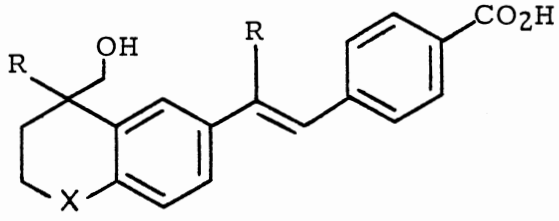
Aldrich Chemical Company, USA. Conversion of phenol (**80a**) to lactone **80c** is reported in the literature.[15] Lactone **80c**[18] can be protected by a specific reagent such as bis (dimethylaluminium) 1,2-ethanedithiolate[15] to give ketone **80e**.



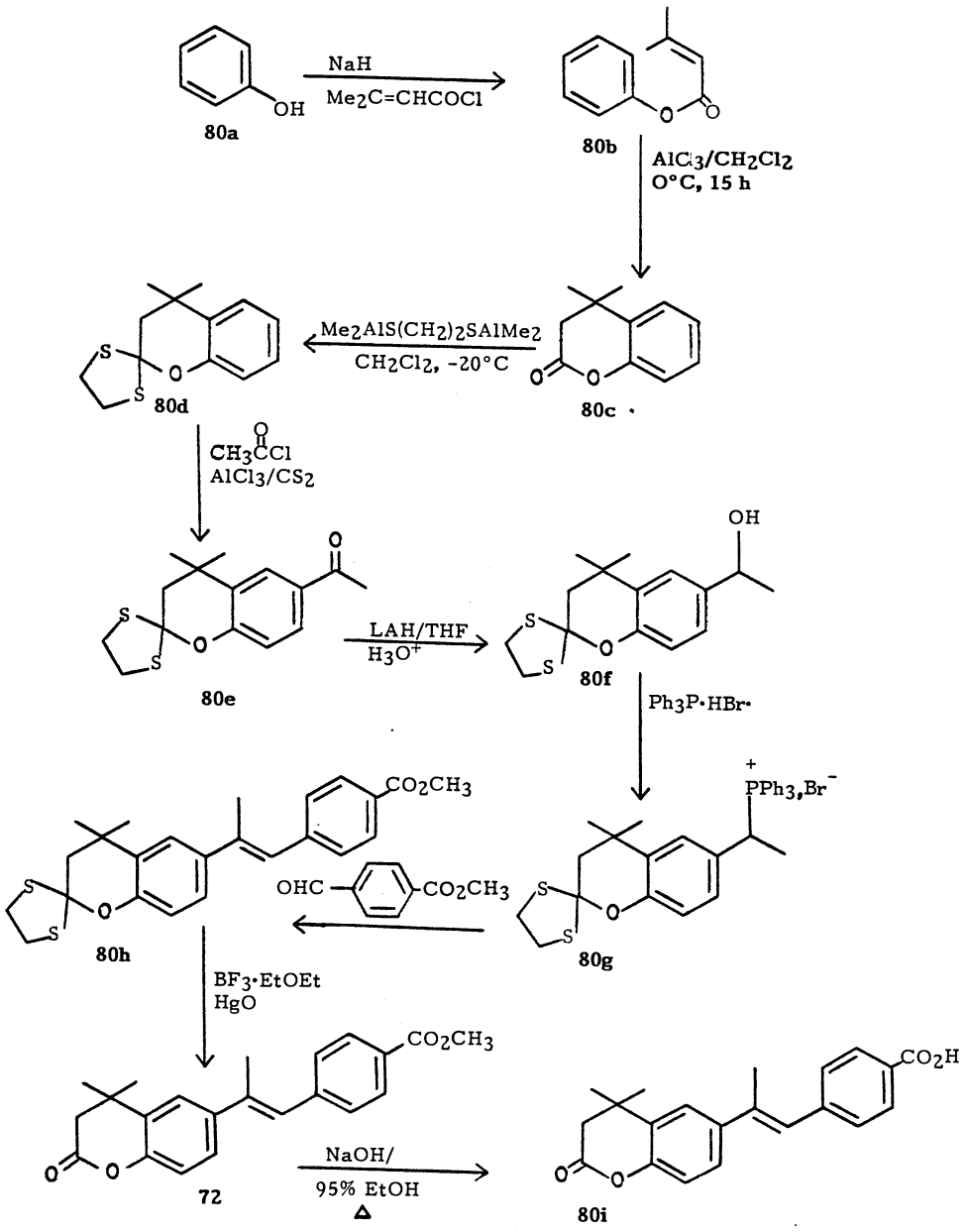
	X
78a	O
78b	S



X
O
S



	X	R
79a	O	H
79b	S	H
79c	O	OH
79d	S	OH


NaH
Me2C=CHCOCl
80a
80b
AlCl3/CH2Cl2
0°C, 15 h
Me2AlS(CH2)2SAlMe2
CH2Cl2, -20°C
80c
80d
CH3COCl
AlCl3/CS2
80e
LAH/THF
H3O+
80f
Ph3P·HBr·
PPh3,Br
CO2CH3
OHC
CO2CH3
80g
80h
BF3·EtOEt
HgO
72
NaOH/
95% EtOH
Δ
80i
CO2H

CHAPTER III

EXPERIMENTAL SECTION

General Information

Reactions were carried out under a nitrogen atmosphere when necessary. All reactions were stirred using a magnetic stirrer unless otherwise specified. During work-up, solvents were removed using a rotary evaporator unless otherwise stated. NMR spectral data were obtained using either a Varian XL-100 NMR spectrometer equipped with a Nicolet TT-100 PFT accessory or a Varian XL-300 NMR spectrometer. The ^{1}H spectra were recorded at 300 MHz while ^{13}C spectra were recorded at 25.14 or 75.42 MHz. All NMR data were reported in ppm or δ values downfield from TMS using either TMS, $CDCl_3$ or DMSO-d_6 as an internal reference. IR spectral data were obtained using a Perkin-Elmer 681 IR spectrophotometer. UV spectra were taken on the Perkin-Elmer Lamda Array 3840 UV-VIS Spectrophotometer with 7300 Professional Computer PR 210 Printer. Melting points were determined using a Thomas Hoover melting point apparatus and were uncorrected. All solvents were distilled prior to use except for reagent grade, anhydrous ether which was dried over sodium. Starting compounds **21**,[123] **62-67**,[123] and **68** [58] were prepared by modifications of reported procedures.

Methyl 3-Phenoxypropionate (**62**)

A solution of 3-phenoxypropionic acid (**61**, 48 g, 289.07 mmol) and concentrated H_2SO_4 (0.90 mL) in methanol (700 mL) was heated at reflux through 3 A molecular sieve for 46 h in a 1 L flask equipped with a Soxhlet extractor and a condenser. The solution was allowed to cool to room temperature and then was concentrated to a volume of 150 mL,

diluted with water (150 mL) and extracted with ether (4 x 50 mL). The combined organic layers were washed with 100 mL of 5% $NaHCO_3$ solution, 100 mL of water and 100 mL of saturated NaCl solution. After the solution was dried over $MgSO_4$ (30 min.), the solvent was removed (vacuum). Vacuum distillation gave 48.39 g (94%) of **62** as a colorless liquid: bp 69-72°C/0.03 mm (lit[123] 85-87°C/0.1 mm); IR (neat) 1740-1750 cm^{-1} (C=0); ^1H NMR ($DCCl_3$) δ 2.80 (t, 2 H, $C\underline{H}_2CO_2CH_3$), 3.66 (s, 3 H, $OC\underline{H}_3$), 4.23 (m, 2 H, $OC\underline{H}_2$), 6.98-7.16 (m, 5 H, Ar-H); ^{13}C NMR ($DCCl_3$) ppm 34.4 ($H_2\underline{C}CO_2$), 51.7 ($O\underline{C}H_3$), 63.3 ($O\underline{C}H_2$), Ar-$\underline{C}$ (114.5, 120.9, 129.3, 158.3), 171.1 (C=O); mass spectral data for $C_{10}H_{12}O_3$: m/e (M^+) 180.07864; found 180.0789.

2-Methyl-4-phenoxy-2-butanol (**63**)

To a freshly prepared solution [15.51 g (665.04 g at) of magnesium, 41.6 mL (665.0 mmol) of methyl iodide] of methylmagnesium iodide in dry ether (132 mL) was added a solution of methyl 3-phenoxypropionate (**62**, 44.6 g, 214.5 mmol) in dry ether (145 mL) in a 1-L, three-necked, round-bottom flask equipped with dry ice condenser, addition funnel and mechanical stirrer under N_2. The mixture was heated at reflux for 24 h with power stirring, allowed to cool to room temperature, and quenched with ice and saturated aqueous NH_4Cl. The two layers were separated and the aqueous layer was extracted (ether, 4 x 120 mL). The combined organic solution was washed with H_2O (2 x 100 mL) and saturated NaCl solution (100 mL). After the solution was dried ($MgSO_4$, 8 h), the solvent was removed (vacuum). Vacuum distillation gave 36.8 g (82.6%) of **63** as a colorless liquid: bp 84-85°C 0.05 mm (lit[123] 81-84°C/0.07 mm); IR (neat) 3140-3620 cm^{-1} (OH); ^1H NMR ($DCCl_3$) δ 1.27 [s, 6 H, $(C\underline{H}_3)_2$], 1.98 [t, 2 H, $C\underline{H}_2$], 2.9 [s, 1 H, O$\underline{H}$], 4.14 [t, 2 H, $OC\underline{H}_2$], 6.82-6.96 [m, 3 H, Ar-H], 7.16-7.34 [m, 2H, Ar-H]; ^{13}C NMR ($DCCl_3$) ppm 29.5 [$\underline{C}H_3$], 41.6 [$\underline{C}H_2$-C], 64.8 [$O\underline{C}H_2$], 70.4 [$(CH_3)_2\underline{C}$], Ar-$\underline{C}$ [114.3, 120.8, 129.4, 158.9]; mass spectral data for $C_{11}H_{16}O_2$: m/e (M^+) 180.11502; found 180.1153.

4,4-Dimethylchroman or 3,4-Dihydro-4,4-dimethyl-2H-1-benzopyran (**64**)

A solution of 2-methyl-4-phenoxy 2-butanol (**63**, 41.10 g, 228.33 mmol) in freshly distilled nitromethane (270 mL) was added dropwise under N_2 to a stirred suspension of anhydrous $AlCl_3$ (41.43 g, 308.1 mmol) in freshly distilled nitromethane (165 mL) in a 1-L three-necked, round-bottom flask, equipped with a condenser. After stirring at room temperature for an additional 24 h, a solution of 6 M HCl (425 mL) was added *slowly*. The resulting mixture was stirred for 10 min and diluted with ether (200 mL). The layers were separated, and the organic layer was washed with H_2O (200 mL), saturated $NaHCO_3$ (4 x 150 mL), H_2O (150 mL), and saturated solution of NaCl (150 mL). After the solution was dried ($MgSO_4$, 30 min), the solvent was removed (vacuum). Vacuum distillation of resulting dark brown oil gave 27.96 g (75.6%) of **64** as a colorless liquid: bp 43-44°C/0.2 mm (lit[123] 74-80°C/0.7 mm); ^{1}H NMR ($DCCl_3$) δ 1.27 [s, 6 H, (CH_3)C], 1.83 [m, 2 H, CH_2], 4.09 [m, 2 H, OCH_2], 6.88-7.24 [m, 4 H, Ar-H]; ^{13}C NMR ($DCCl_3$) ppm 30.5 [$C(CH_3)_2$], 31.1 [($CH_3)_2C$], 37.7 [CH_2], 63.0 [OCH_2], Ar-C [116.9, 120.4, 126.9, 127.0, 131.6, 153.6].

4,4-Dimethyl-6-chromanyl Methyl Ketone or 1-(3,4-Dihydro-4,4-dimethyl-2H-1-benzopyran-6-yl)ethanone (**65**)

Anhydrous $AlCl_3$ (2.99 g, 22.51 mmol) was added in small portions to 4,4-dimethyl-chroman (**64**, 3.45 g, 21.30 mmol) and acetyl chloride (1.51 mL, 21.30 mmol) in CH_3NO_2 (30 mL) under N_2 in a 100-mL, three-necked, round-bottom flask equipped with condenser. After stirring at room temperature for 6 h, 6 M HCl (30 mL) was added slowly, and the resulting mixture was stirred for 10 min. The mixture was diluted with ether (70 mL) and layers were separated. The organic layer was washed with H_2O (50 mL), saturated aqueous $NaHCO_3$ (4 x 40 mL), H_2O (50 mL), and a saturated solution of NaCl (50 mL). After the solution was dried ($MgSO_4$, 30 min), the solvent was removed to

leave a dark, reddish brown oil. Vacuum distillation gave 3.09 g (89.03%) of **65** as a pale yellow liquid: bp 94-95°C/0.1 mm [lit[123] 108-112°C/0.01 mm]; IR (neat) 1675-1685 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) δ 1.38 [s, 6 H, $(C\underline{H}_3)_2C$], 1.84 [m, 2 H, $C\underline{H}_2$], 2.52 [s, 3 H, $C\underline{H}_3C$], 4.26 [m, 2 H, $C\underline{H}_2O$], 6.82 [d, 1 H, H(8)], 7.71 [dd, 1 H, H(7)], 7.99 [d, 1 H, H(5)]; ^{13}C NMR ($DCCl_3$) ppm 26.1 [$\underline{C}H_3$], 30.5 [$\underline{C}(CH_3)_2$], 30.6 [$(\underline{C}H_3)_2C$], 37.0 [$\underline{C}H_2$], 63.3 [$\underline{C}H_2O$], 116.7 [C(8)], 127.5 [C(5)], 127.9 [C(7)], 130.0, 131.6 [C(4a), C(6)], 157.8 [C(8a)], 196.4 [C=O]; mass spectral data for $C_{13}H_{18}O_2$: m/e (M^+) 204.11500; found 204.1155.

α, 4,4-Trimethylchroman-6-methanol or 3,4-Dihydro-4,4-trimethyl-2H-1-benzopyran-6-methanol (**66**)

A solution of the previous ketone (**65**, 180 g, 88.1 mmol) in anhydrous ether (80 mL) was added dropwise under N_2 to a stirred suspension of $LiAlH_4$ (5.01 g, 132.27 mmol) in dry ether (315 mL) in a 500-mL, three-necked flask equipped with condenser. The mixture was heated at reflux for 24 h. After cooling to room temperature, ethyl acetate (85 mL) was added dropwise to destroy the excess of $LiAlH_4$. A solution of 5% HCl (255 mL) was then added, and the resulting mixture was stirred for 5 min. The layers were separated, and aqueous layer was washed with ether (3 x 150 mL). The combined organic layers were washed with 5% aqueous Na_2CO_3 (2 x 100 mL), water (150 mL), and saturated NaCl solution (150 mL). After the solution was dried ($MgSO_4$, 30 min), the solvent was removed leaving a yellow oil which solidifed after scratching. The yellow solid was dissolved in a minimum amount of hot hexane to which was added decolorizing carbon NORITE (0.4 g). This solution was boiled for 2 min. and filtered through celite. The solvent was removed on rotary evaporator which left behind a colorless oil. After overnight refrigeration, a white solid was obtained. Recrystallization (hexane) gave 15.25 g (82.9%) of **66** as a white solid: mp 71-72°C (lit[123] 70-71°C); IR (KBr) 3140-3640 cm^{-1} (OH); 1H NMR ($DCCl_3$) δ 1.32 [s, 6 H, $(C\underline{H}_3)_2C$], 1.50 [d, 3 H, $C\underline{H}_3$], 1.31 [s, 1 H,

OH], 4.20 [m, 2 H, H(2)], 4.84 [q, 1 H, CHOH], 6.76 [d, 1 H, H(8)], 7.07 [dd, 1 H, H(7)], 7.28 [d, 1 H, H(5)], ^{13}C NMR ($DCCl_3$) ppm 24.9 [CH_3], 30.6 [C(4)], 31.0 [$(CH_3)_2C$], 37.6 [C(3)], 62.9 [C(2)], 70.2 [C(9)], 116.8 [C(8)], 123.9, 124.2 [C(5), C(7)], 131.1, 137.6 [C(4a), C(6)]. 152.9 [C(8a)].

[1-(4,4-Dimethyl-6-chromanyl)ethyl]triphenylphosphonium Bromide or [1-(3,4-Dihydro-4,4-dimethyl-2H-1-benzo-pyran-6-yl)ethyl]triphenylphosphonium Bromide (**67**)

A solution of the alcohol **66** (0.70 g, 0.34 mmol) and triphenylphosphonium hydrobromide[84] (1.2 g, 3.5 mmol) in methanol (30 mL) was stirred under N_2 at room temperature for 24 h in a 50-mL, round-bottom flask. The solvent was removed (vacuum), and the resulting oil was triturated repeatedly with dry ether until it solidified. The resulting white solid was suspended and stirred in dry ether (30 mL) at room temperature under N_2 for 4 h, filtered, and dried (110°C/~ 2 mm) to give 1.75 g (96.9%) of **67** as a white powder: mp 152-156°C (dec) [lit[123] 149-155°C]; ^1H NMR ($DCCl_3$) δ 1.08 [s, 3 H, CH_3], 1.14 [s, 3 H, CH_3], 1.76 [m, 2 H, H(3)], 1.83 [d, 3 H, $CHCH_3$], 4.16 [m, 2 H, H(2)], 6.3 [m, 1 H, CHP^+Ph_3, Br^-], 6.57 [d, 1 H, H(8)], 6.67 [d, 1 H, H(7)], 7.74 [brs, 1 H, H(5)], 7.63-7.84 [m, 15 H, $P^+(C_6H_5)_3$]. The salt was used without further purification.

Methyl 4-Formylbenzoate (**68**)

A 500-mL, three-necked, round-bottom flask was equipped with a teflon-coated stirring bar, Soxhlet extractor and condensor with a drying tube at the top. The flask was charged with 10.0 g (66.6 mmol) of 4-formyl benzoic acid (**71**), about 320 mL of absolute CH_3OH, and 0.1 ml of concentrated H_2SO_4. The Soxhlet extractor was filled with 3 A molecular sieve. After the solution was boiled for 48 h, it was allowed to cool to room temperature and then was concentrated to a volume of about 50 mL; dilution with an equal amount of water followed and the new solution was extracted (ether 4 x 70 mL). The

combined organic layers were washed with saturated $NaHCO_3$ solution (5 x 50 mL), 0.1 N HCl (10 x 40 mL), H_2O (2 x 50 mL), and saturated NaCl solution (2 x 50 mL). The resulting organic solution was dried ($MgSO_4$, 2 h) and filtered and concentrated *in vacuo*. The white solid obtained was recrystallized (hexane) to give 6.3 g (58%) of ester **68**: mp 59.5-60°C (lit[58] 59-60°C); IR (KBr) 1680-1740 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) δ 4.00 (s, 3 H, OCH_3), 7.80-8.32 (m, 4 H, Ar-H), 10.10 (s 1 H, CHO); ^{13}C NMR ($DCCl_3$) ppm 52.6 [OCH_3], Ar-C [129.6, 130.4, 135.2, 139.2], 166.0 [CO_2CH_3], 191.7 [CHO]; mass spectral data for $C_9H_8O_3$: m/e (M^+): 164.0473. Found: 164.0473.

(*E*)-4-[2-(3,4-Dihydro-4,4-dimethyl-2H-1-benzopyran-6-yl)-1-propenyl]benzoic Acid (**21**)

The ester **60a** (1.20 g, 3.58 mmol) was heated at reflux under N_2 for 5 h in a solution of NaOH (0.625 g, 15.69 mmol) in 95% ethanol (14 mL) and H_2O (38 mL) in a 50-mL, three-necked, round-bottom flask equipped with a condenser. After cooling slowly to RT, the solution was acidified (litmus) with conc. HCl (pH ≈ 2.0). The resulting white solid was filtered, washed with water, and air dried. Recrystallization (95% ethanol) gave 1.02 g (86.14%) of acid **21** as a white crystalline solid: mp 180-180.5°C (lit[123] 183-183.5°C) IR (KBr) 2390-3320 (OH, CH), 1670-1695 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) δ 1.40 [s, 6 H, H(9), H(10)], 1.88 [m, 2 H, H(3)], 2.3 [s, 3 H, H(12)], 4.25 [m, 2 H, H(2)], 6.80 [s, 1 H, H(13)], 6.84 [d, J = 9 Hz, 1 H, H(8)], 7.3 [dd, J = 9 Hz, J = 3 Hz, 1 H, H(7)], 7.46 [d, J = 3 Hz, 1 H, H(5)], 7.5 [d, J = 9 Hz, 2 H, H(15), H(19)], 8.14 [d, J = 9 Hz, 2 H, H(16), H(18)]; ^{13}C NMR ($DCCl_3$) ppm 17.81 [C(12)], 30.72 [C(4)], 31.08 [C(9), C(10)], 37.63 [C(3)], 63.14 [C(2)], 116.85 [C(8)], 124.56 [C(5)], 124.93 [C(7)], 125.04 [C(13)], 129.12 [C(15, C(19)], 130.12 [C(16), C(18)], 153.46 [C(8a)], 172.03 [C(20)], nonprotonated and vinylic carbons [126.79, 131.36, 135.63, 139.91, 144.33]; mass spectral data for $C_{21}H_{22}O_3$: m/e (M^+) 322.1569; found 322.1559.

Methyl (*E*)-4-[2-(3,4-Dihydro-4,4-dimethyl-2-H-1-benzo-pyran-6-yl)-1-propenyl]benzoate (**60a**)

A solution of *n*-butyllithium in hexane (1.39 M, 9.98 mL, 13.80 mmol) was added dropwise under N_2 to a stirred suspension of phosphonium salt **67** (4.89 g, 9.20 mmol) in dry ether (90 mL) in a 250-mL, round-bottom flask. The resulting dark reddish brown mixture was cooled to -78°C, and a solution of methyl 4-formylbenzoate (**68**, 1.51 g, 9.2 mmol) was added over a period of 3 min. The solution was stirred for a few min at -78°C and then at room temperature for 48 h. The mixture changed from reddish-brown to an off white color. After 48 h, the reaction mixture was filtered. The resulting solid was washed with 250 mL of ether (anhydrous); the filtrate was concentrated to a yellow oil. This yellow oil was refrigerated for 8 h and became a yellow solid. This yellow solid was passed through 30 g of silica gel [column, (8 x 200 mm)]. The product was eluted with 300 mL of hexane:ethyl acetate (4:1). Concentration of the eluent gave a viscous oil from which a solid was obtained at room temperature. The white solid was dissolved in a minimum amount of boiling 95% ethanol and filtered hot. After the filtrate was concentrated, cooling this solution to room temperature gave 1.29 g of white crystals of **60a** [(*E*)-isomer)] (40.3%): mp 90-90.5°C; IR (KBr) 1710-1725 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) δ 1.4 [s, 6 H, H(9), H(10)], 1.9 [m, 2 H, H(3)], 2.3 [s, 3 H, H(12)], 3.9 [s, 3 H, H(21)], 4.2 [m, 2 H, H(2)], 6.80 [s, 1 H, H(13)], 6.84 [d, J = 9 Hz, 1 H, H(8)], 7.3 [dd, J = 9 Hz, J = 3 Hz, 1 H, H(7)], 7.4 [d, J = 3 Hz, 1 H, H(5)], 7.5 [d, J = 9 Hz, 2 H, H(15), H(19)], 8.6 [d, J = 9 Hz, 2 H, H(16), H(18)]; ^{13}C NMR ($DCCl_3$) ppm 17.8 [C(12)], 30.7 [C(4)], 31.1 [C(9), C(10)], 37.6 [C(3)], 52.1 [C(21)], 63.1 [C(2)], 116.8 [C(8)], 124.5 [C(5)], 124.9 [C(7)], 125.9 [C(13)], 129.0 [C(15), C(19)], 129.5 [C(16), C(18)], 153.4 [C(8a)], 167.0 [C(20], non-protonated and vinylic carbons (127.6, 131.3, 135.7, 139.5, 143.4); UV (EtOH) λ_{max} 237 nm (ε 1.5 x 10^4), 318 (2.5 x 10^4); mass spectral data for $C_{22}H_{24}O_3$: m/e (M^+) 336.1725; found 336.1728. Anal for $C_{22}H_{24}O_3$: C, 78.59; H, 7.18. Found C, 78.39; H, 7.10. The mother liquor from the crystallization

of the (*E*)-isomer **60a** contained predominantly the (Z)-isomer **60i** (50 mg, 1.6%) as a white needles: mp 80-80.5°C; ^{1}H NMR ($DCCl_3$) δ 1.12 [s, 6 H, H(9), H(10)], 1.78 [m, 2 H, H(3)], 2.20 [s, 3 H, H(12)], 3.86 [s, 3 H, H(21)], 4.17 [m, 2 H, H(2)], 6.43 [s, 1 H, H(13)], 6.73 [d, J = 9 Hz, H(8)], 6.95 [dd, J = 9 Hz, J = 3 Hz, 1 H, H(7)], 7.03 [d, J = 3 Hz, 1 H, H(5)], 7.51 [d, J = 9 Hz, 2 H, H(15), H(19)], 7.78 [d, J = 9 Hz, 2 H, H(16), H(18)]; ^{13}C NMR ($DCCl_3$) ppm 26.79 [C(12)], 30.42 [C(4)], 30.78 [C(9), C(10)], 37.48 [C(3)], 51.91 [C(21)], 63.08 [C(2)], 116.9 [C(8)], 125.0 [C(13)], 126.5 [C(7)], 126.5 [C(5)], 128.8 [C(15), C(19)], 129.1 [C(16), C(18)], 143.1 [C(8a)], 167.0 [C(20)], nonprotonated and vinylic carbons (127.5, 128.8, 128.97, 132.9, 141.4); UV (EtOH) λ_{max} 245 nm (ε 2.2 x 10^4), 310 (1.6 x 10^4); mass spectral data for $C_{22}H_{24}O_3$: m/e (M^+) 336.17254; found 336.1729. Anal for $C_{22}H_{24}O_3$: C, 78.59; H, 7.18. Found C, 78.24; H, 7.38.

(*E*)-4-[2-Methyl-2-(4,4-dimethyl-6-chromanyl)-1-propenyl]-benzonitrile (**60b**)

A solution of *n*-butyllithium in hexane (1.39 M, 14.1 mmol, 10.15 mL) was added dropwise under N_2 to a stirred suspension of phosphonium salt **67**. (5.00 g, 9.40 mmol) in dry ether (100 mL) in a 250-mL, three-necked flask. The resulting dark, reddish-brown mixture was cooled to -78°C and to this was added a solution of 1.56 g (9.4 mmol) 4-cyanobenzaldehyde (**69**) in 50 mL of anhydrous ether over a period of 1 min. The solution was stirred for 5 min at -78°C and then at room temperature for 5 h. A new reaction mixture was filtered and the solid material was washed with anhydrous ether (30 mL). The ethereal filtrate was evaporated to give a yellow oil which was refrigerated overnight to yield a yellow solid. The yellow solid was dissolved in a minimum amount of boiling 95% ethanol from which fine pale yellow crystals of nitrile **60b** were deposited [1.43 g, 48.6%]: mp 134-134.5°C; IR (KBr) 2220-2240 cm^{-1} (C≡N); ^{1}H NMR ($DCCl_3$) δ 1.80 [s, 6 H, H(9), H(10)], 2.21 [s, 3 H, H(12)], 2.30 [m, 2 H, H(3)], 4.22 [m, 2 H, H(2)], 6.33

[s, 1 H, H(13)], 6.80 [d, J = 9 Hz, 1 H, H(8)], 7.21 [dd, J = 9 Hz, J = 3 Hz, 1 H, H(7)], 7.44 [d, J = 3 Hz, 1 H, H(5)], 7.50 [d, J = 9 Hz, 2 H, H(15), H(19)], 7.90 [d, J = 9 Hz, 2 H, H(16), H(18)]; ^{13}C NMR ($DCCl_3$) ppm 17.8 [C(12)], 30.7 [C(4)], 31.6 [C(9), C(10)], 35.6 [C(3)], 63.2 [C(2)], 116.9 [C(13)], 119.2 [C(20)], 124.3 [C(7)], 124.6 [C(5)], 124.9 [C(8)], 129.7 [C(16), C(18)], 131.9 [C(15), C(19)], 153.6 [C(8a)], Non-protonated and vinylic carbons [109.4, 131.6, 135.3, 140.6]; mass spectral data for $C_{21}H_{21}NO$: m/e (M^+) 303.1623; Found 303.1627. Anal for $C_{21}H_{21}NO$: C, 83.13; H, 6.97; N, 4.17. Found: C, 83.31 H, 6.72; N, 4.23. The mother liquor from the crystallization of the (*E*)-isomer **72** contained predominantly the (*Z*)-isomer **60j** (15 mg, 0.51%) as a white solid: mp 89-90°C; ^1H NMR ($DCCl_3$) δ 1.14 [s, 6 H, H(9), H(10)], 1.80 [m, 2 H, H(3)], 2.22 [s, 3 H, H(12)], 4.20 [m, 2 H, H(2)], 6.74 [s, 1 H, H(13)], 6.78 [d, J = 9 Hz, 1 H, H(8)], 6.96 [dd, 1 H, H(7)], 6.97 [d, 1 H, H(5)], 7.08 [d, J = 9 Hz, 2 H, H(15), H(19)], 7.20 [d, J = 9 Hz, 2 H, H(16), H(18)]; ^{13}C NMR ($DCCl_3$) ppm 26.74 [C(12)], 30.41 [C(4)], 30.75 [C(9), C(10)], 37.40 [C(3)], 63.10 [C(2)], 117.11 [C(13)], 119.25 [C(20)], 124.27 [C(7)], 126.43 [C(5)], 127.63 [C(8)], 129.45 [C(16), C(18)], 131.58 [C(15), C(19)], 153.15 [C(8a)], non-protonated and vinylic carbons [108.86, 132.41, 142.77, 143.13]. Anal for $C_{21}H_{21}NO$: C, 83.16; H, 6.97; N, 4.17. Found: C, 83.24 H, 7.16; N, 4.48.

(*E*)-4-[2-Methyl-2-(4,4-dimethyl-6-chromanyl)-1-propenyl]-benzaldehyde (**60c**)

A solution of the nitrile **60b** (0.20 g, 0.66 mmol) in 25 mL of dry ether under N_2 was stirred at room temperature in a 50-mL, three-necked, round-bottom flask equipped with a condenser, and a solution of diisobutylaluminium hydride (DIBAL-H) in hexane (1.0 M, 1.34 mL, 1.34 mmol) was added dropwise. When the addition was complete (2 min), the mixture was allowed to boil with stirring for 38 h and was then allowed to cool to room temperature. The resulting solution was diluted with CH_3OH (10 mL). Dilute H_2SO_4

(5%, 25 mL) was added cautiously until the aqueous phase was acidic. This aqueous layer was washed with ether (2 x 25 mL). The combined organic phase and extracts were washed with 5% $NaHCO_3$ (2 x 50 mL), water (50 mL), and finally with brine (25 mL). After drying ($MgSO_4$, 30 min), the solution was evaporated to a viscous yellow oil. Chromatography of the oil was performed using silica gel (≈ 12 grams) through a vertical column (8 x 200 mm). Elution was effected with hexane:ethyl acetate (4:1, 200 mL). Concentration of the eluent gave a viscous oil which solidified upon standing in an ice bath for 2 h. Solution of the solid in minimum amount of hot hexane gave, upon cooling, 51 mg (26%) of aldehyde **60c** as a white crystalline material: mp 85-86°C (lit[65] 102-104°). IR (KBr) 2750 (CH=O), 1700 (C=O) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.39 [s, 6 H, H(9), H(10)], 1.86 [m, 2 H, H(3)], 2.29 [s, 3 H, H(12)], 4.22 [m, 2 H, H(2)], 6.77 [s, 1 H, C(13)], 6.88 [d, J = 9 Hz, 1 H, H(8)], 7.26 [dd, J = 9 Hz, J = 3 Hz, 1 H, H(5)], 7.51 [d, J = 9 Hz, 2 H, H(15), H(17)], 7.87 [d, J = 9 Hz, 2 H, H(16), H(18)], 10.0 [s, 1 H, CHO]. ^{13}C NMR ($DCCl_3$) ppm 17.88 [C(12)], 30.7 [C(4)], 31.65 [C(9) C(10)], 37.60 [C(3)], 63.14 [C(2)], 116.8 [C(8)], 124.56 [C(5)], 124.93 [C(7)], 129.0 [C(15), C(19)] 129.5 [C(16), C(18)], 129.61 [C(13)], 153.39 [C(8a)], 191.79 [CHO], non-protonated and vinyl carbons: 129.67, 131.39, 134.14, 135.50, 140.39, 145.08. Mass spectral data for $C_{21}H_{22}O_2$ m/e (M^+): 306.1619. Found: 306.1617. Anal. for $C_{21}H_{22}O_2$: C, 82.38; H, 7.24. Found: C, 82.17; H, 7.60.

(*E*)-4-[2-Methyl-2-(4,4-dimethyl-6-chromanyl)-1-propenyl]-benzyl Alcohol (**60d**)

A solution of methyl (E)-4-[2-(3,4-dihydro-4,4-dimethyl-2H-benzopyran-6-yl)-1-propenyl] benzoate (**60a** 0.29 g, 0.86 mmol) in anhydrous tetrahydrofuran (2 mL) was added dropwise under N_2 to a stirred suspension of $LiAlH_4$ (0.04 g, 1.10 mmol) in dry THF in a 25-mL, three-necked, round-bottom flask equipped with a condenser. The mixture was heated at reflux for 8 h and, after cooling to room temperature, ethyl acetate (8

mL) was added to destroy residual $LiAlH_4$. The resulting mixture was stirred for 5 min. The two layers were separated, and the aqueous layer was washed (ether, 2 x 25 mL). The combined organic layers were washed with 5% Na_2CO_3 (50 mL), H_2O (25 mL), and brine (25 mL). After drying ($MgSO_4$, 2 h), the organic solution was evaporated leaving a thick yellow oil. Chromatography of the oil using a Chromatotron with a silica gel plate (4 mm) and eluting with 80% hexane:ethyl acetate (200 mL total) gave, after concentration, a viscous oil which solidified upon refrigeration overnight. Dissolving this solid in a minimum amount of boiling hexane produced, after cooling, 65 mg (25%) of alcohol **60d** as a white amorphous powder mp 79-80°C (lit[65] 80-81°). IR (KBr) 3060-3510 (O-H) cm^{-1}. ^1H NMR ($DCCl_3$) δ 1.18 [s, 6 H, H(9), H(10)], 1.86 [m, 2 H, H(3)], 1.90 [s, 1 H, OH], 2.26 [s, 3 H, H(12)], 4.22 [m, 2 H, H(2)], 4.70 [s, 2 H, H(20)], 6.76 [s, 1 H, H(13)], 6.82 [d, J = 9 Hz, 1 H, H(8)], 7.28 [dd, J = 9 Hz, 1 H, H(7)], 7.38 [s, 4 H, H(15), H(16), H(18), H(19)], 7.44 [d, J = 3 Hz, 1 H, H(5)]. ^{13}C NMR ($DCCl_3$) ppm 17.56 [C(12)], 30.70 [C(4)], 31.31 [C(9), C(10)], 37.66 [C(3)], 63.10 [C(2)], 65.18 [C(20)], 116.70 [C(8)], 124.40 [C(5)], 124.8 [C(7)], 125.37 [C(13)], 129.6 [C(15), C(19)], 134.4 [C(16), C(18), 154.0 [8a]. There are other non-protonated and vinyl carbons which could not be distinguished. 131.22, 136.02, 137.42, 138.70, 153.04. Mass spectral data for $C_{21}H_{24}O_2$: m/e (M^+) 308.1776. Found: 308.1765. Anal. for $C_{21}H_{24}O_2$: C, 81.76; H, 7.78. Found: C, 82.05; H, 7.41.

(*E*)-4-[2-(3,4-Dihydro-4,4-dimethyl-2H-1-benzopyran-6-yl)-1-propenyl]benzylamine (**60e**)

A 50-mL, flame dried, three-necked, round-bottom flask was equipped with a teflon-coated stirring bar, an addition funnel, a condenser fitted with a bubbler for a nitrogen outlet, and a rubber septum connected to a nitrogen inlet. The flask was charged with $LiAlH_4$ (73 mg, 1.80 mmol) and 9.5 mL of dry THF. Dropwise addition of a solution of nitrile **60b** (0.315 g, 1.04 mmol) in 6 mL of dry THF was effected with constant stirring.

The mixture was stirred at room temperature for 8 h. To this was added about 14 mL of ethyl acetate to destroy the excess $LiAlH_4$. A solution of 5% HCl (5 mL) was then added, and resulting mixture was stirred for 5 min. The layers were separated, and the aqueous layer was washed with ether (2 x 30 mL). The combined organic layers were washed with 5% aqueous $NaHCO_3$ (2 x 30 mL), H_2O (30 mL), and saturated NaCl solution (50 mL). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated *in vacuo* to give yellow oil, which was passed through 15 g of silica gel [column, 8 x 200 mm]. The product was eluted with 250 mL of ethyl acetate:ethanol (1:1). Concentration of the eluent gave a viscous oil from which a yellow solid was obtained after refrigeration for 4 days. Recrystallization (hexane) gave 68 mg (21%) of **60e** as a pale yellow solid: mp 103-105°C; IR (KBr) 3300-3500 cm^{-1} (primary NH_2); ^1H NMR ($DCCl_3$) δ 1.36 [s, 6 H, H(9), H(10)], 1.85 [m, 2 H, H(3)], 2.20 [s, 3 H, H(12)], 3.95 [s, 2 H, C(20)], 4.20 [m, 2 H, H(2)], 4.42 [brs, 2 H, NH_2], 6.66 [s, 1 H, H(13)], 6.75 [d, J = 9 Hz, 1 H, H(8)], 7.17 [dd, J = 9 Hz, J = 3 Hz, 1 H, H(7)], 7.26 [d, 1 H, H(5)], 7.31-7.38 [m, 4 H, Ar-H]; ^{13}C NMR ($DCCl_3$) ppm 17.57 [C(12)], 30.72 [C(4)], 31.12 [C(9), C(10)], 37.72 [C(3)], 43.60 [C(20)], 63.13 [C(2)], 116.75 [C(8)], 124.42 [C(5)], 124.82 [C(7)], 125.40 [C(13)], 127.69 [C(15), C(19)], 129.47 [C(16), C(18)], 153.14 [C(8a)], nonprotonated and vinylic carbons [127.94, 131.26, 136.01, 137.58, 138.04]; mass spectral data for $C_{21}H_{25}NO$: m/e (M^+) 307.1936; found 307.1948.

(*E*)-4-[2-(3,4-Dihydro-4,4-dimethyl-2H-1-benzopyran-6-yl)-1-propenyl]acetophenone (**60f**)

To a 100-mL, flame-dried, three-necked, round-bottom flask equipped with a mechanical stirrer, an addition funnel with rubber septum connected to nitrogen inlet, and a dry-ice condenser was added 0.06 g (2.65 g at) of magnesium turnings and 0.5 mL of dry ether. Dropwise addition of a solution of 0.15 mL (2.40 mmol) of methyl iodide in about 1 mL of dry ether was effected with constant stirring. After complete addition of the methyl

iodide solution, the reaction mixture was stirred for 25 min at room temperature. The reaction mixture was then cooled to 0°C by using an ice bath, and a solution of nitrile **60b** (0.44 g, 1.45 mmol) in 35 mL of dry ether was added over a period of 2 min. When the addition was complete, the reaction mixture was boiled for 24 h. After cooling to room temperature, the mixture was poured into a 250 mL beaker containing ice and produced a turbid solution. To this solution was added about 10 mL of 5% HCl solution and the new mixture was boiled overnight to give two separate layers. The organic layer was separated and the water layer was washed with ether (2 x 50 mL). The combined organic layers were washed with dil. $NaHCO_3$ (2 x 50 mL), 50 mL of H_2O, and 50 mL of saturated NaCl solution. The combined ethereal layers were dried over anhydrous magnesium sulfate (2 h), filtered and concentrated *in vacuo* to give thick yellow oil. Chromatography of oil was performed using silica gel (15 g) through vertical column (8 x 200 mm). Elution was effected with benzene (150 mL). Concentration of the eluent gave a viscous oil which solidified upon refrigeration overnight. The crude solid was recrystallized (95% ethanol) to afford 0.102 g (22%) of **60f** as a pale yellowish white crystalline solid: mp 88-89°C (lit[65] 109-110°C). IR (KBr) 1690 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) δ 1.39 [s, 6 H, H(9), H(10)], 1.87 [m, 2 H, H(3)], 2.28 [s, 3 H, H(12)], 2.62 [s, 3 H, H(21)], 4.22 [m, 2 H, H(2)], 6.75 [s, 1 H, H(13)], 6.80 [d, J = 9 Hz, 1 H, H(8)], 7.26 [dd, 1 H, H(7)], 7.28 [d, J = 3 Hz, 1 H, H(5)], 7.28 [d, J = 3 Hz, 1 H, H(5)], 7.44 [d, J = 9 Hz, 2 H, H(15), H(19)], 7.96 [d, J = 9 Hz, 2 H, H(16), H(18)]; ^{13}C NMR ($DCCl_3$) ppm 17.79 [C(12)], 26.57 [C(21)], 30.70 [C(4)], 31.06 [C(9), C(10)], 37.61 [C(3)], 63.12 [C(2)], 116.82 [C(8)], 124.52 [C(5)], 124.89 [C(7)], 124.99 [C(13)], 128.28 [C(15), C(19)], 129.18 [C(16), C(18)], 153.43 [C(8a)], 197.68 [C(20)], nonprotonated and vinylic carbons [131.33, 134.73, 135.61, 139.73, 143.63]; Mass spectral data for $C_{22}H_{24}O_2$: m/e (M^+) 320.17762; found 320.1777. Anal for $C_{22}H_{24}O_2$: C, 82.53; H, 7.56. Found: C, 82.60; H, 7.64.

(*E*)-1-(5-Acetoxymethyl-2-furanyl)-2-(3,4-dihydro-4,4-dimethyl-2H-1-benzopyran-6-yl)propane (**60g**)

A solution of *n*-butyllithium in hexane (1.55 M, 1.23 mL, 1.88 mmol) was added dropwise under N_2 to a stirred suspension of phosphonium salt **67** (1 g, 1.88 mmol) in dry ether (20 mL) in a 50-mL, three-necked, round-bottom flask. The resulting solution was cooled to -78°C, and a solution of 5-acetoxymethyl-2-furaldehyde (**70**, 0.316 g, 1.88 mmol) was added over a period of 1 min. The solution was stirred for a few min at -78°C and then at room temperature for 24 h. The mixture changed from reddish-brown to a pale brown color. After 24 h, the reaction mixture was filtered. The resulting solid was washed with 45 mL of ether (anhydrous), and the filtrate was concentrated to give a yellow oil. This yellow oil was refrigerated for 24 h and became a dark yellow solid. This solid was passed through 20 g of silica gel [column, (8 x 200 mm)]. The product was eluted with 300 mL of hexane:ethyl acetate (4:1). Concentration of the eluent gave a viscous oil from which a yellow solid was obtained after keeping the oil in an ice bath at 0°C for 5 h. Recrystallization (hexane) gave 0.12 g (19%) of **60g** as a white crystalline solid: mp 80-81°C. ^{1}H NMR ($DCCl_3$) δ 1.37 [s, 6 H, H(9), H(10)], 1.85 [m, 2 H, H(3)], 2.1 [s, 3 H, H(20)], 2.36 [s, 3 H, H(12)], 4.20 [m, 2 H, H(2)], 5.08 [s, 2 H, H(18)], 6.31 [d, 1 H, J = 3 Hz, H(16)], 6.46 [d, 1 H, J = 3 Hz, H(5)], 6.53 [s, 1 H, H(13)], 6.77 [d, 1 H, J = 9 Hz, J = 3 Hz, H(8)], 7.21 [dd, 1 H, H(7)], 7.39 [d, 1 H, H(15)]; ^{13}C NMR ($DCCl_3$) ppm 18.24 [C(12)], 20.94 [C(20)], 30.69 [C(4)], 31.06 [C(9), C(10)], 37.63 [C(3)], 58.31 [C(18)], 63.11 [C(2)], 109.54 [C(16)], 114.15 [C(15)], 116.8 [C(8)], 124.36 [C(5)], 124.77 [C(7)], 170.69 [C(19)], nonprotonated and vinylic carbons [131.3, 135.6, 136.9, 147.7, 153.3, 154.64], mass spectral data for $C_{21}H_{24}O_4$: m/e (M^+) 340.16745; Found 340.1679. Anal. for $C_{21}H_{24}O_4$: C, 74.08; H, 7.06. Found C, 73.88; H, 7.09.

Methyl (*E*)-4-[2-(3,4-Dihydro-4,4-dimethyl-2-H-1-benzo-pyran-6-yl)-3-hydroxy-1-propenyl]benzoate (**60k**)

In a 200-mL, three-necked, round-bottom flask equipped with nitrogen inlet, reflux condenser, bubbler for nitrogen outlet, and magnetic stirrer were mixed ester **60a** (1.29 g, 3.84 mmol) and selenium dioxide (1.28 g, 11.52 mmol) in 75 mL of 95% ethanol. The reaction mixture was stirred at reflux for 24 h, and then the solution was allowed to cool to room temperature. The solution was filtered through cotton plug to remove elemental selenium which was formed during the course of the reaction. The solution was concentrated under reduced pressure to a volume of 15 mL and this solution was diluted with 75 mL of ether. The new solution was washed with saturated $NaHCO_3$ solution (2 x 50 mL), H_2O (50 mL), and saturated NaCl solution (50 mL). After drying ($MgSO_4$, 2 h), the organic solution was evaporated leaving a yellow oil. Chromatography of the oil was performed using silica gel (≈ 15 grams) through a vertical column (8 x 200 mm). Elution was effected with hexane:ethyl acetate (4:1, 200 mL). Concentration of the eluent gave a viscous oil which solidified upon refrigeration for 5 days. The off white solid obtained was recrystallized (absolute ethanol) to give 0.202 g (15%) of **60k** as a pale yellow crystals: mp 85-86°C. IR (KBr) 3150-3600 (O-H) cm^{-1}, 1740 (C=O) cm^{-1} , ^1H NMR ($DCCl_3$) δ 1.18 [s, 6 H, H(9), H(10)], 1.62 [t, 1 H, OH], 1.81 [m, 2 H, H(3)], 3.9 [s, 1 H, H(21)], 4.2 [m, 2 H, H(2)], 4.5 [d, 2 H, H(12)], 6.7 [s, 1 H, H(13)], 6.79 [d, J = 9 Hz, 1 H, H(8)], 6.96 [dd, J = 9 Hz, J = 3 Hz, 1 H, H(7)], 7.06 [d, J = 3 Hz, 1 H, H(5)], 7.1 [d, J = 9 Hz, 2 H, H(15), H(19)], 7.79 [d, J = 9 Hz, 2 H, H(16), H(18)]. ^{13}C NMR ($DCCl_3$) 29.33 [C(4)], 29.68 [C(9), C(10)], 36.27 [C(3)], 50.83 [C(21)], 61.98 [C(12)], 66.77 [C(2)], 116.24 [C(8)], 123.46 [C(5)], 125.69 [C(7)], 126.73 [C(13)], 127.91 [C(15), C(19)], 128.08 [C(16), C(18)], 152.32 [C(8a)], 165.81 [C(20)], nonprotonated and vinylic carbons [126.91, 127.99, 130.95, 140.77, 142.86]; UV (EtOH) λ_{max} 285 nm (ε 1.7 x 10^4), 302 (1.5 x 10^4); mass spectral data for $C_{22}H_{24}O_4$: m/e (M^+) 352.16745; found 352.1673. Anal for $C_{22}H_{24}O_4$: C, 75.03; H, 6.87. Found C, 74.84; H, 7.00.

The presence of the (*Z*)-isomer **60h** as a slightly impure oil from chromatography was indicated by the following ^{1}H NMR signals: ($DCCl_3$) δ 1.38 [2, 6 H, H(9), H(10)], 1.62 [t, 1 H, OH], 1.86 [m, 2 H, H(3), 3.9 [s, 1 H, H(21)], 4.2 [m, 2 H, H(2)], 4.7 [d, 2 H, H(12)], 6.8 [s, 1 H, H(13)], 6.9 [d, J = 9 Hz, 1 H, H(8)], 7.3 [dd, J = 9 Hz, J = 3 Hz, 1 H, H(7)], 7.5 [d, j = 3 Hz, 1 H, H(5)], 7.5 [d, J = 9 Hz, 2 H, H(15), H(19)], 8.0 [d, J = 9 Hz, 1 H, H(16), H(18)]; UV (EtOH) λ_{max} 241 nm (ε 1.7 x 10^4), 314 (2.4 x 10^4)

(*E*)-4-[2-(3,4-Dihydro-4,4-dimethyl-2H-1-benzopyran-6-yl)-3-hydroxy-1-propenyl]benzoic Acid (**60l**)

A 15-mL, flame dried, two-necked, round-bottom flask was equipped with a teflon-coated stirring bar, a condenser, bubbler, and a rubber septum connected to a nitrogen inlet. The flask was charged with ester **60k** (60 mg, 0.171 mmol) and a solution of NaOH (0.06 g, 1.52 mmol) in 95% ethanol (2 mL) and H_2O (3 mL). The reaction mixture was heated at reflux for 9 h. After cooling slowly to RT (≈ 1 h), the solution was acidified (litmus) with conc. HCl (pH ≈ 2.0). The resulting off-white solid was filtered, washed with water, and air dried. Recrystallization (absolute C_2H_5OH) gave 32 mg (56%) of acid **60l** as an off-white solid: mp 198-199°C; IR (KBr) 2400-3500 (OH), 1680 cm^{-1} (C=O); ^{1}H NMR (DMSO d_6) δ 1.1 [s, 6 H, H(9), H(10)], 1.78 [m, 2 H, H(3)], 2.52 [s, 1 H, OH], 4.14 [m, 2 H, H(2)], 4.26 [brs, 2 H, H(12)], 6.68 [s, 1 H, H(13)], 6.72 [d, J = 9 Hz, 1 H, H(8)], 6.93 [dd, J = 9 Hz, J = 3 Hz, 1 H, H(7)], 7.02 [d, J = 3 Hz, 1 H, H(5)], 7.09 [d, J = 9 Hz, 2 H, H(15), H(19)], 7.71 [d, J = 9 Hz, 2 H, H(16), H(18)]; ^{13}NMR (DMSO d_6) 29.91 [C(4)], 30.33 [C(9), C(10)], 36.70 [C(3)], 62.40 [C(2)], 65.37 [C(12)], 116.7 [C(8)], 122.34 [C(5)], 126.38 [C(7)], 128.04 [C(13)], 128.60 [C(15), C(19)], 128.89 [C(16), C(18)], 152.64 [C(8a)], 167.0 [C(20)], nonprotonated and vinylic carbons (127.54, 129.73, 131.52, 141.89, 145.26); mass spectral data for $C_{21}H_{22}O_4$: m/e (M^+) 338.15180; found 338.1515. The elemental analysis indicated a slight impurity.

Attempted Preparation of Lactone **72**: Attempted Oxidation of C(2) in **60a** with RuO_4 in CCl_4/H_2O

To a solution containing $RuO_2 \cdot x\ H_2O$ (200 mg, 1.5 mmol, Alfa Products, Denvers, Massachusetts 01923) in 25 mL of CCl_4 cooled to -5 to -12°C (ice/Nacl) was added a solution of $NaIO_4$ (1.70 g, 7.98 mmol) in 25 mL of H_2O in a 100-mL, single-necked, round-bottom flask. Vigorous stirring of the two layers was continued for 1 h. The CCl_4 layer containing RuO_4 was separated, filtered through glass wool, and collected in a 50-mL, three-neck, round bottom flask. This yellow solution was cooled to -4°C and to this solution was slowly added a solution of ester **60a** (0.336 g, 1 mmol) in 2 mL of CCl_4 via a syringe over a period of 3 min. At the end of the addition, the reaction mixture changed color from a clear yellow to an off-yellow with a black suspension present. The reaction mixture was then allowed to warm slowly to room temperature and was stirred for 48 h. The precipitated RuO_2 was removed by filtration through celite, and the solvent was removed *in vacuo* to afford the yellow oil. This yellow oil was passed through silica gel [28 g, column was 8 x 200 mm]. The product was eluted with 150 mL of hexane:ethyl acetate (9:1) followed by ethyl acetate:ethanol (1:1). Fractions 1-8 contained ester **60a** and fractions 17-22 contained acid **71** in approximately equivalent amounts. Crude **60a** had the following data. ^{1}H NMR ($DCCl_3$) δ 1.38 [s, 6 H, H(9), H(10)], 1.9 [m, 2 H, H(3)], 2.3 [s, 3 H, H(12)], 3.89 [s, 3 H, H(21)], 4.21 [m, 2 H, H(2)], 6.78 [s, 1 H, H(13)], 6.84 [d, J = 9 Hz, 1 H, H(8)], 7.3 [dd, J = 9 Hz, J = 3 Hz, 1 H, H(7)], 7.4 [d, J = 3 Hz, 1 H, H(5)], 7.49 [d, J = 9 Hz, 2 H, H(15), H(19)], 8.6 [d, J = 9 Hz, 2 H, H(16)], H(18)]. The ^{1}H NMR spectrum was superimposable on that from a known sample. Data for **71** are mp 201-203°C (lit[93] 194-196°C). ^{1} NMR ($DCCl_3$) δ 4.0 [s, 3 H, OC$\underline{H_3}$], 7.3-8.4 [m, 4 H, Ar-H]. R_f values (TLC) were 0.56 for **60a** and 0.10 for **71** (the solvent system was 80% hexane:ethyl acetate).

Attempted Preparation of Lactone **72**: Attempted Oxidation of C(2) in **60a** with RuO_4 in $CH_3CN/H_2O/CCl_4$

A 25-mL, two-necked, round-bottom flask was equipped with a *power* stirrer and a glass stopper. The flask was charged with 2 mL of carbon tetrachloride, 2 mL of acetonitrile, 3 mL of H_2O, ester **60a** (0.336 g, 1.0 mmol), and $NaIO_4$ (0.641 g, 3 mmol). This mixture was stirred for 10 min. To the biphasic solution was added $RuO_2 \cdot x\ H_2O$ (3.3 mg, 2.2 mmol %). The entire mixture was stirred vigorously for 5 h at room temperature. Then 10 mL of CH_2Cl_2 was added, and the phases were separated. The upper aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$, 30 min), filtered, and concentrated *in vacuo*. The resulting residue was diluted with 20 mL of ether, filtered through a celite pad, and concentrated to give an off-white solid. Chromatography of this solid was performed using silica gel (18 g) through a vertical column (8 x 200 mm). Elution was effected with 80% hexane:ethyl acetate (150 mL). Concentration of the fractions 1-11 and 14-21 revealed the presence of ester **60a** and aldehyde **68**, respectively. Crude **60a** had the following data. ^1H NMR ($DCCl_3$) δ 1.4 [s, 6 H, H(9), H(10)], 1.9 [m, 2 H, H(3)], 2.3 [s, 3 H, H(12)], 3.90 [s, 3 H, H(21)], 4.21 [m, 2 H, H(2)], 6.78 [s, 1 H, H(13)], 6.84 [d, J = 9 Hz, 1 H, H(8)], 7.28 [dd, J = 9 Hz, J = 3 Hz, 1 H, H(7)], 7.4 [d, J = 3 Hz, 1 H, H(5)], 7.49 [d, J = 9 Hz, 2 H, H(15), H(19)], 8.6 [d, J = 9 Hz, 2 H, H(16), H(18)]. The ^1H NMR spectrum was superimposable on that from a known sample. Data for crude ester **68** was as follows. ^1H NMR ($DCCl_3$) δ 3.38 [s, 3 H, OCH_3], 7.80-8.40 [m, 4 H, Ar-H], 10.10 [s, 1 H, CHO]. The ^1H NMR spectrum was superimposable on that from a known sample.

Attempted Preparation of Lactone **72**: Attempted Oxidation of C(2) in **60a** with KIO_4 in $CCl_4/CH_3CN/H_2O$

A 200-mL, three-necked, round-bottom flask was equipped with a *mechanical* stirrer. The flask was charged with 30 mL of CCl_4, 30 mL of CH_3CN, 45 mL of H_2O, KIO_4 (1.0

g, 4.2 mmol) and K_2CO_3 (78 mg, 0.79 mmol). This reaction mixture was stirred for 5 min. To this biphasic solution was added ester **60a** (0.336 g, 1 mmol) and $RuO_2 \cdot x\ H_2O$ (4 mg, 2.6 mmol %), and the entire mixture was stirred vigorously for 6 h at RT. Then 15 mL of CH_2Cl_2 was added, and two phases were separated. The upper aqueous phase was extracted with CH_2Cl_2 (3 x 45 mL). The combined organic extracts were dried ($MgSO_4$), 30 min), filtered, and concentrated *in vacuo*. The resulting residue was diluted with 30 mL of ether, filtered through a celite pad, and concentrated to give oil. Chromatography of this solid was performed using silica gel (18 g) through vertical column (8 x 200 mm). Elution was effected with 80% hexane:ethyl acetate (100 mL). Concentration of the fractions 1-9 adn 12-18 showed the presence of liquid ketone **65** and aldehyde **68**. Crude **65** had the following data. ^{1}H NMR ($DCCl_3$) δ 1.38 [s, 6 H, $(C\underline{H}_3)_2C$], 4.28 [m, 2 H, $C\underline{H}_2O$], 6.82 [d, 1 H, H(8)], 7.71 [dd, 1 H, H(7)], 7.99 [d, 1 H, H(5)]. The ^{1}H NMR spectrum was superimposable on that from a known sample. Data for crude **68** was as follows; ^{1}H NMR ($DCCl_3$) δ 4.0 [s, 3 H, $OC\underline{H}_3$], 7.80-8.32 [m, 4 H, Ar-H], 10.10 [s, 1 H, $C\underline{H}O$]. the ^{1}H NMR spectrum was superimposable on that from a known sample.

Attempted Preparation of Lactone **72**: Attempted Oxidation of C(2) in **60a** with $ZnCr_2O_7 \cdot 3H_2O$ in CH_2Cl_2

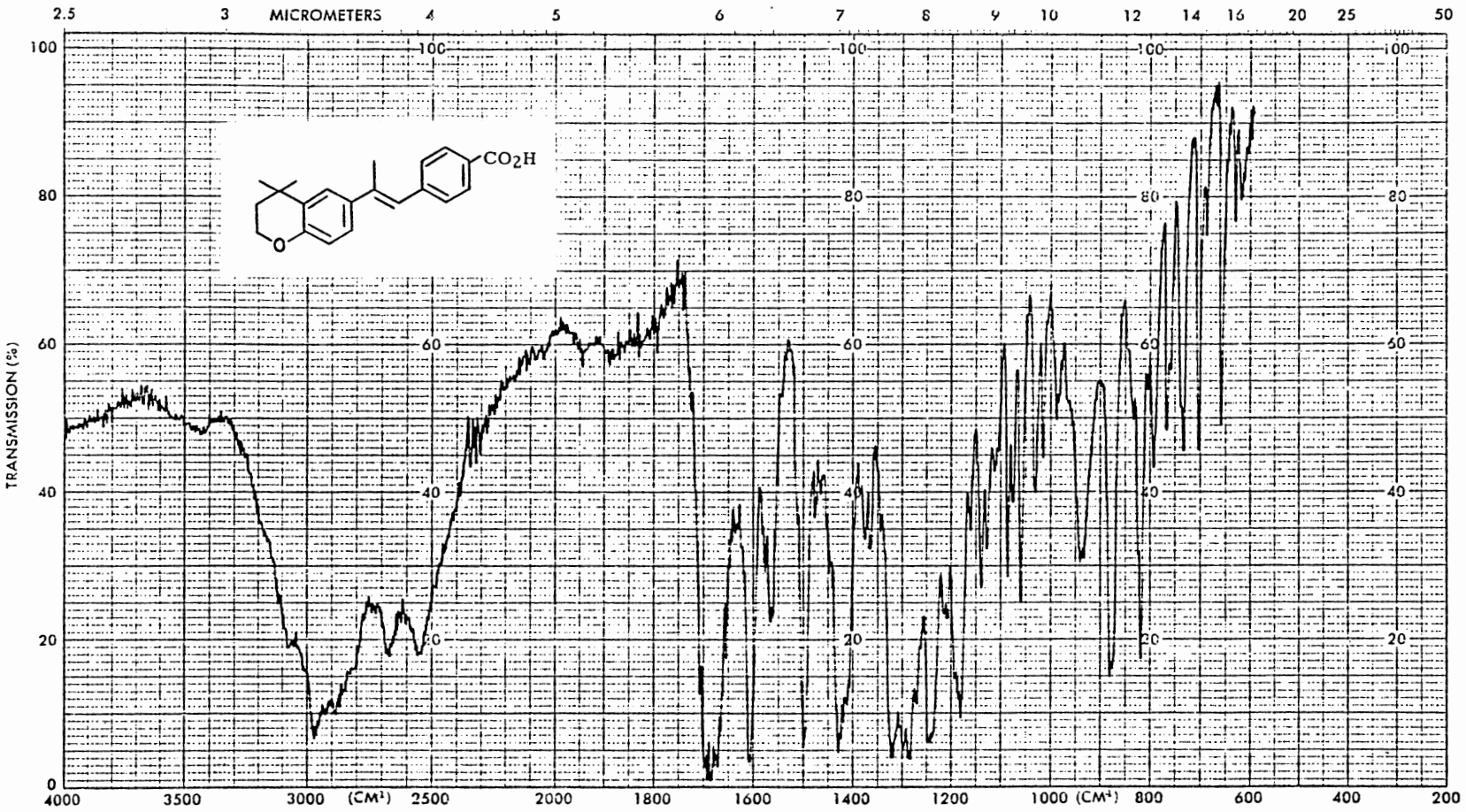
A 50-mL, three-necked, round-bottom flask was equipped with teflon-coated magnetic stirrer, and condenser. The flask was charged with ester **60a** (0.18 g, 0.52 mmol) and 10 ml of dry CH_2Cl_2. To this was added $ZnCr_2O_7 \cdot 3H_2O$ [23] (1.06 g, 3.12 mmol) and reaction mixture was stirred at RT for 48 h. The mixture was filtered and the filter cake was washed with CH_2Cl_2 (20 mL). The filtrates were combined, and evaporated to give pale yellow liquid. The resulting liquid was chromatographed on silica gel (18 g) [column was 8 x 200 mm] and elutions were carried out with 150 mL of 80% hexane:ethyl acetate. Fractions with the same R_f values were mixed together and, upon concentration, showed the presence of ketone **65** and aldehyde **68**. Crude **65** had the following data. ^{1}H NMR

($DCCl_3$) δ 1.38 [s, 6 H, $(CH_3)_2C$], 4.28 [m, 2 H, CH_2O], 6.82 [d, 1 H, H(8)], 7.71 [dd, 1 H, H(7)], 7.99 [d, 1 H, H(5)]. The ^1H NMR ($DCCl_3$) δ 4.00 [s, 3 H, OCH_3], 7.80-8.32 [m, 4 H, Ar-H], 10.10 [s, 1 H, CHO]. The ^1H NMR spectrum was superimposable on that from a known sample of **65**.

Attempted Preparation of Lactone **72**: Attempted Oxidation of C(2) in **60a** with Pyridinium Chlorochromate in CH_2Cl_2

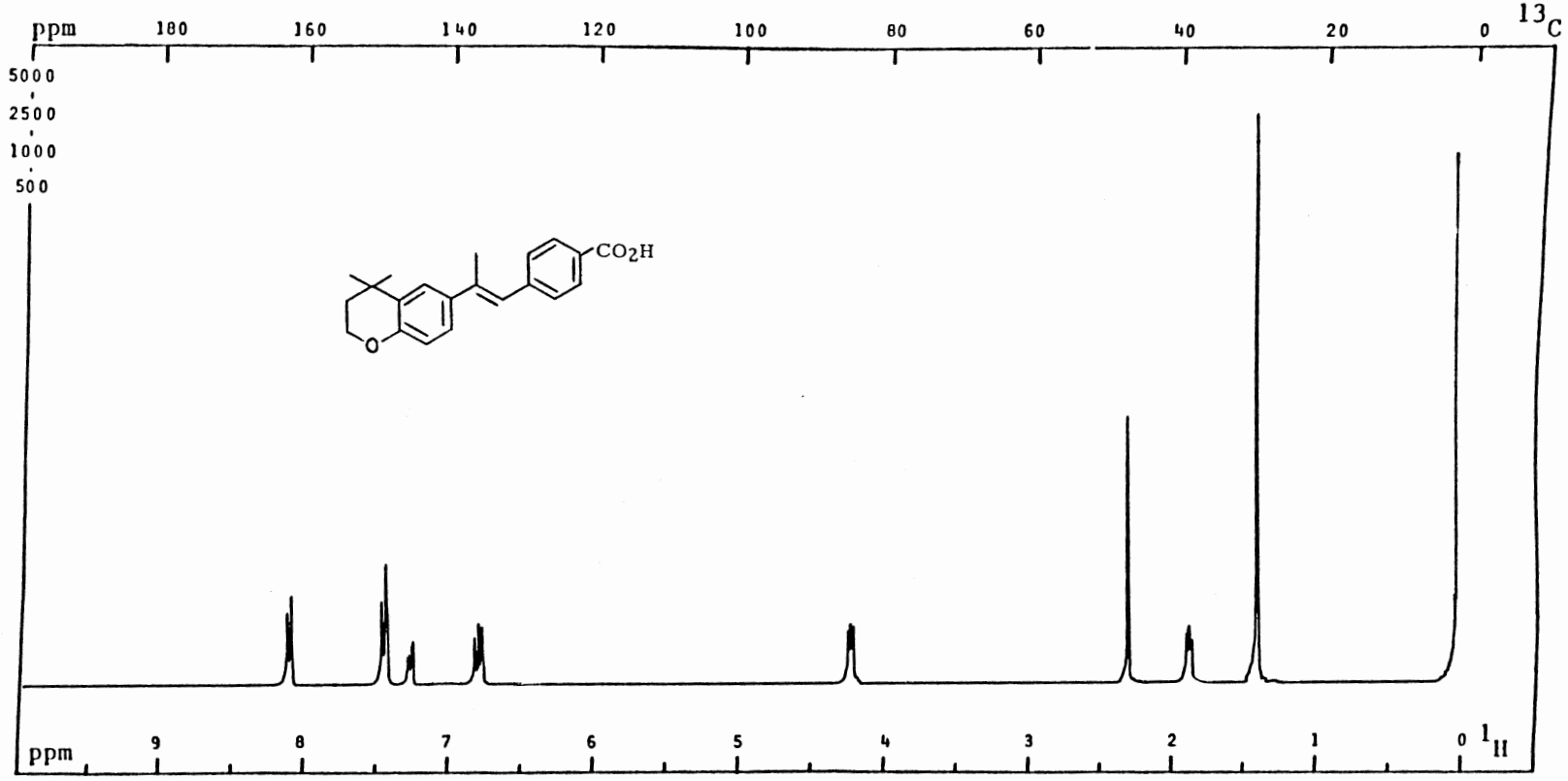
A solution of the ester **60a** (0.336 g, 1 mmol) in 5 mL of dry CH_2Cl_2 was placed under N_2 in a 50-mL, three-necked, round-bottom flask equipped with a magnetic stirrer and a condenser. To this was added pyridinium chlorochromate (PCC) (0.645 g, 3 mmol, Aldrich Chemical Co., Milwaukee, Wisconsin 53233). The reaction mixture was heated at reflux for 24 h. The cooled mixture was added through a silica gel (25 g) column [8 x 200 mm]. Elutions were carried out with 80% hexane:ethyl acetate (150 mL). Fractions with same R_f values were mixed together and, upon concentration, showed the presence of ketone **65** and aldehyde **68**. Crude **65** had the following data. ^1H NMR ($DCCl_3$) δ 1.38 [s, 6 H, $(CH_3)_2C$], 1.84 [m, 2 H, CH_2], 2.52 [s, 3 H, CH_3C], 4.28 [m, 2 H, CH_2O], 6.84 [d, 1 H, H(8)], 7.71 [dd, 1 H, H(7)], 7.99 [d, 1 H, H(5)]. The ^1H NMR spectrum was superimposable on that from a known sample. Data for crude **68** were as follows: ^1H NMR ($DCCl_3$) δ 4.00 [s, 3 H, OCH_3], 7.80-8.32 [m, 4 H, Ar-H], 10.10 [s, 1 H, CHO]. The ^1H NMR spectrum was superimposable on that from a known sample of **68**.

PLATE I



IR Spectrum of 21

PLATE II



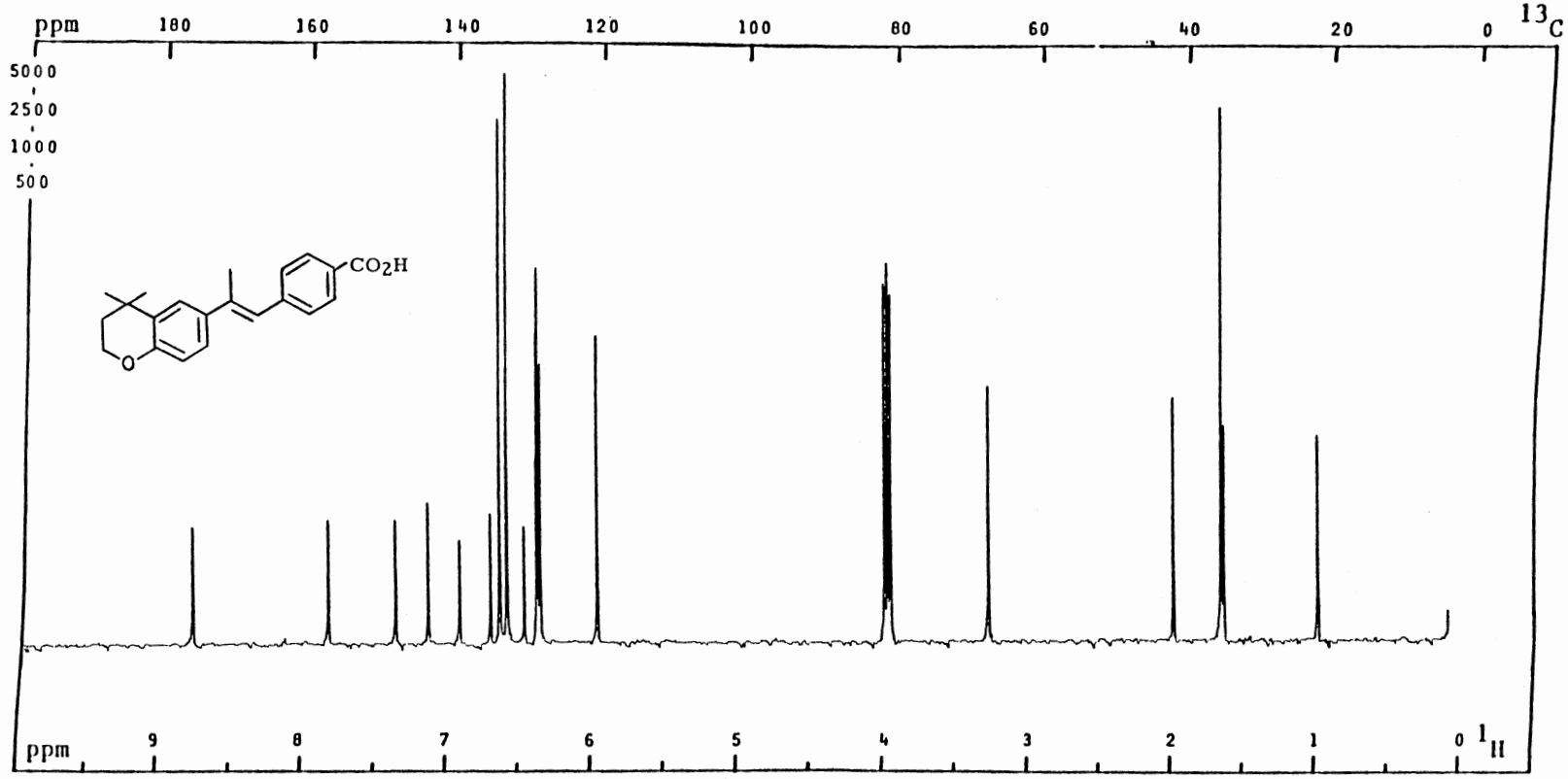
^{1}H NMR Spectrum of 21

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.94 MHz; WC: 2999.4 Hz; T: RT °C; NT: 100 .

Size: 8 K; PW/RF: 6. µs/dB; TO: 0 Hz; FB: Hz; Lock: ^{2}H ; D1,D5: 0 s.

DC: N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 15 W/dB; NBW: 200 Hz; LB: Hz.

PLATE III



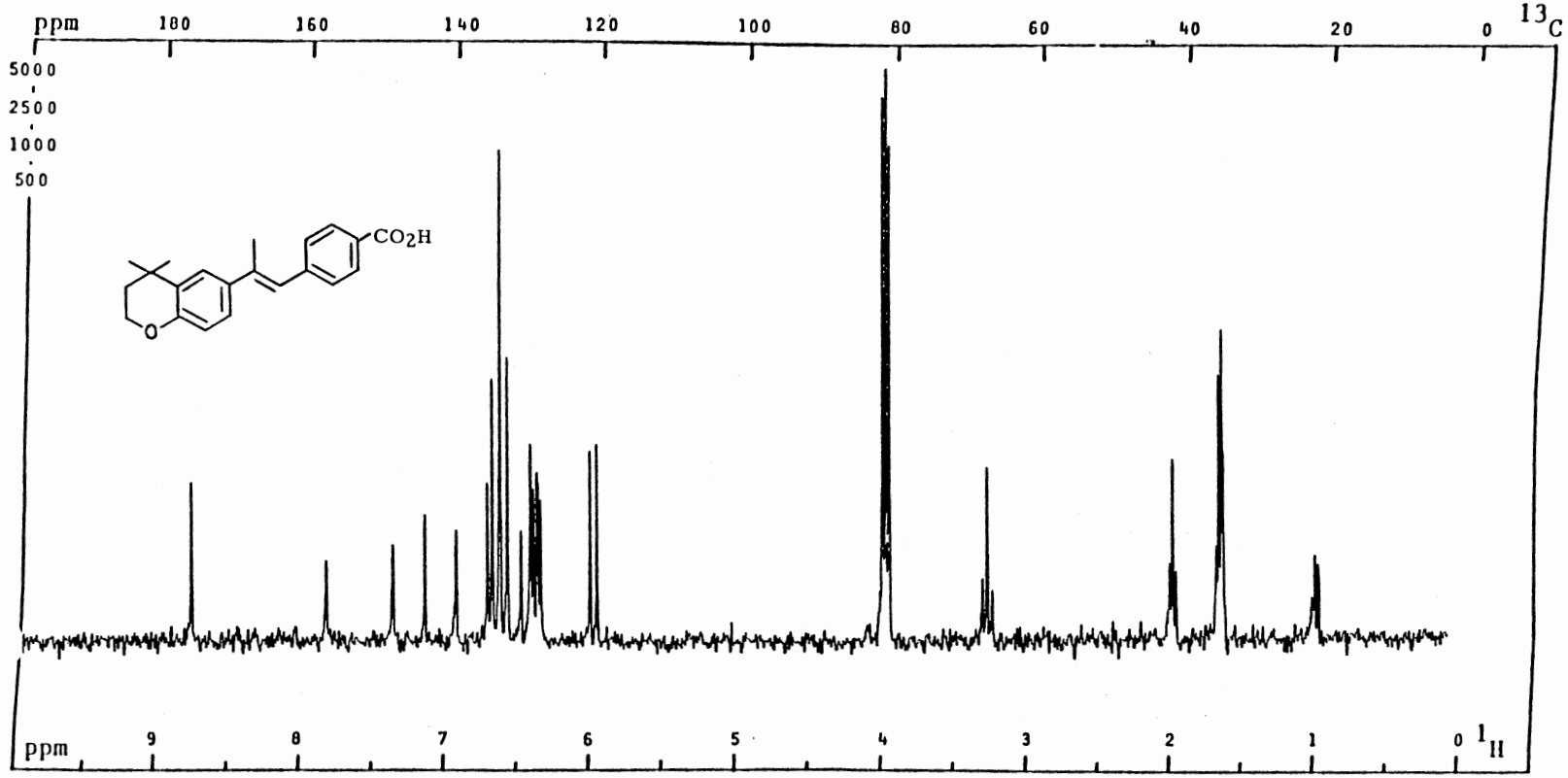
^{13}C NMR Spectrum of 21

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 264

Size: 16 K; PW/RF: 12.0 µs/dB; TO: 1000 Hz; FB: - Hz; Lock: ^2H ; D1,D5: 5.000 s.

DC: Y ; Gated Off: A or D ; DO: Hz; RF(Power): W/dB; NBW: Hz; LB: 2.000 Hz.

PLATE IV



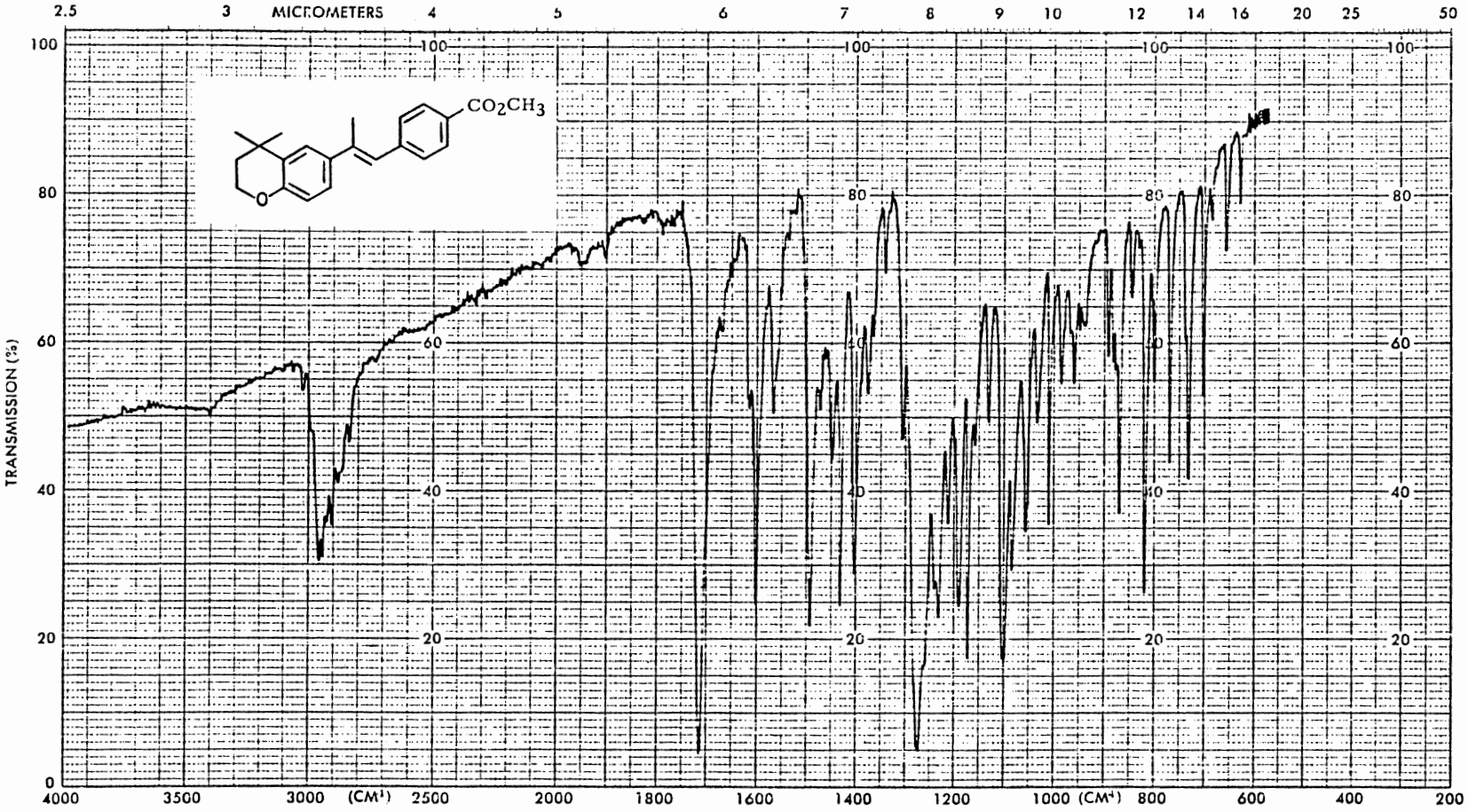
Off Resonance ^{13}C NMR Spectrum of 21

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 176 .

Size: 16 K; PW/RF: 12.0 µs/dB; TO: 1000 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 5.000 s.

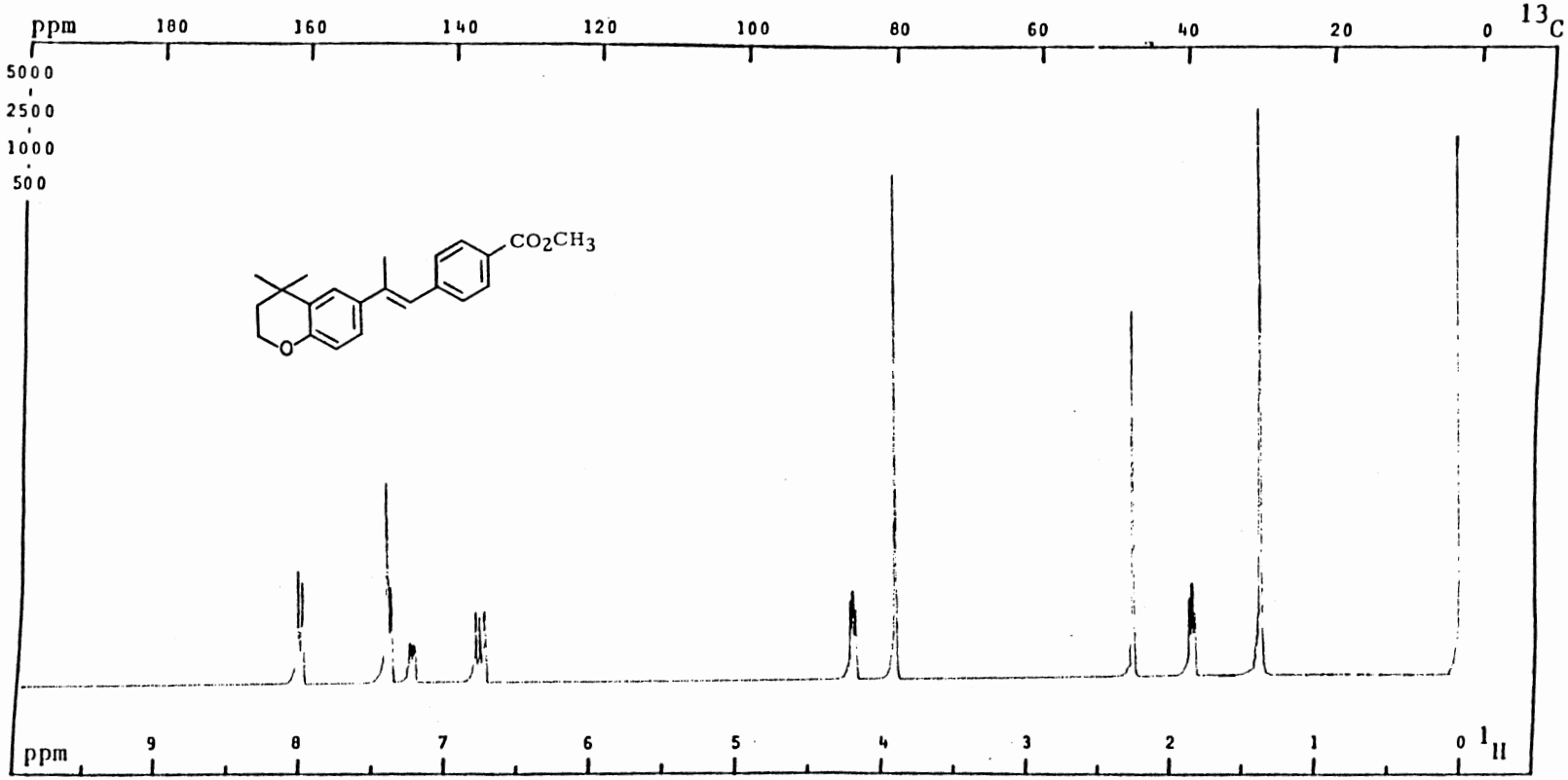
DC: Y ; Gated Off: A or D ; DO: Hz; RF(Power): W/dB; NBW: Hz; LB: 2.000 Hz.

PLATE V



IR Spectrum of 60a

PLATE VI



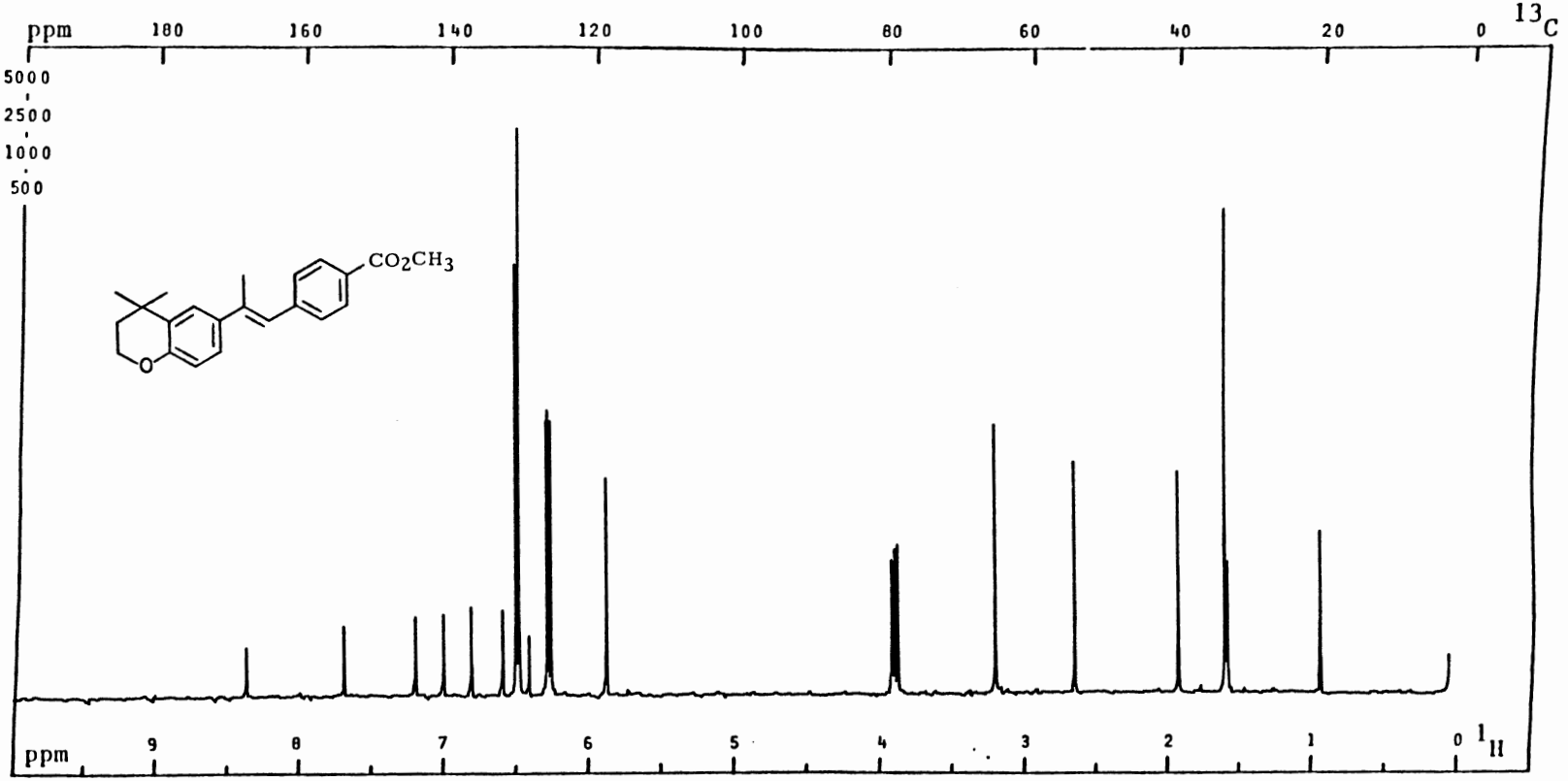
^{1}H NMR Spectrum of 60a

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 2999.4 Hz; T:RT °C; NT: 16

Size: 8 K; PW/RF: 5.0 µs/dB; TO: 0 Hz; FB:_ Hz; Lock: ^{2}H ;D1,D5: 0.500 s.

DC: N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 10 W/dB; NBW: 200 Hz; LB: 0 Hz.

PLATE VII



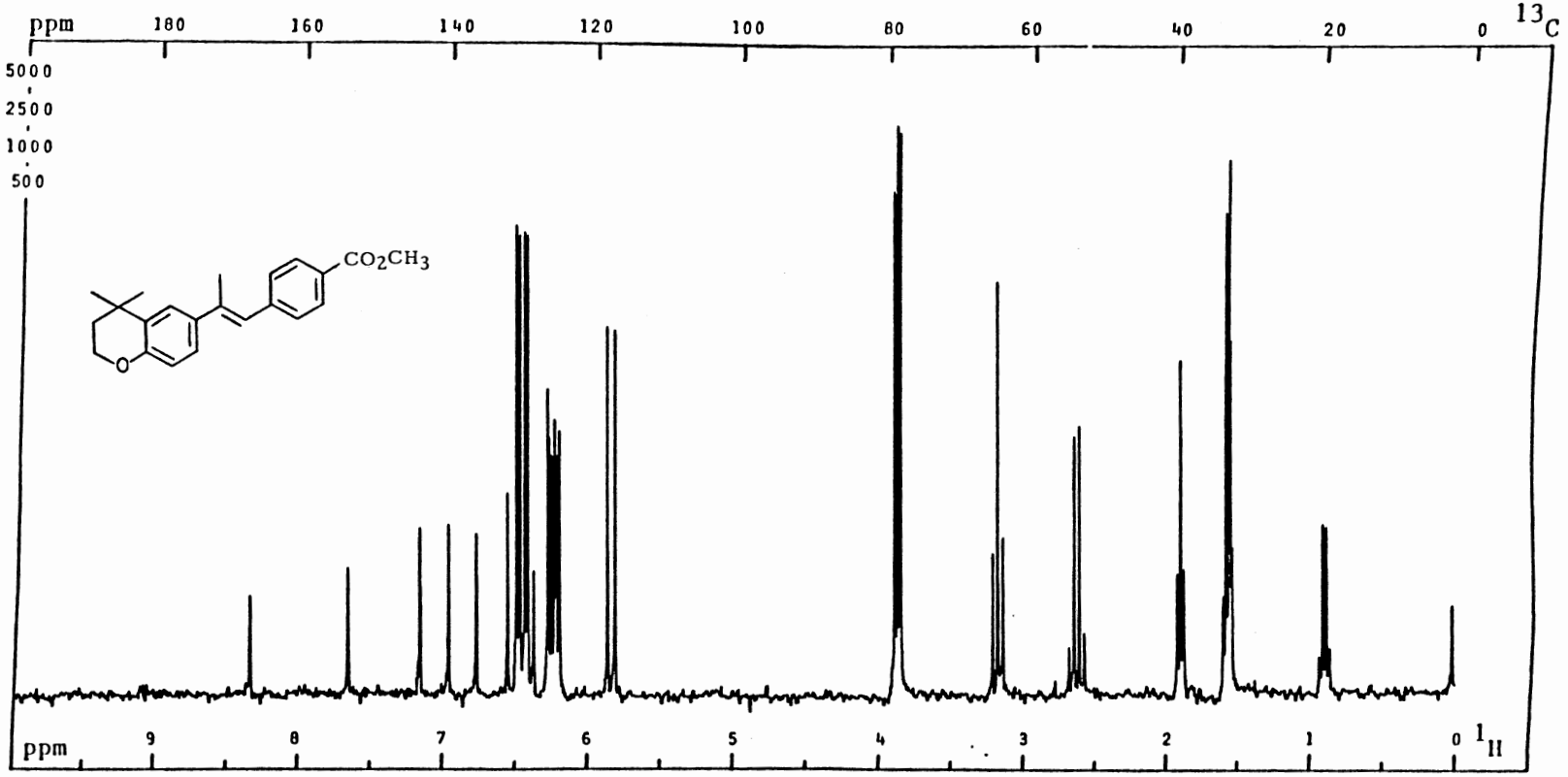
^{13}C NMR Spectrum of 60a

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 192

Size: 16 K; PW/RF: 12.0 µs/dB; TO: 1000 Hz; FB: _ Hz; Lock: ^{2}H ; D1,D5: 4.000 s.

DC: Y ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 2.000 Hz.

PLATE VIII



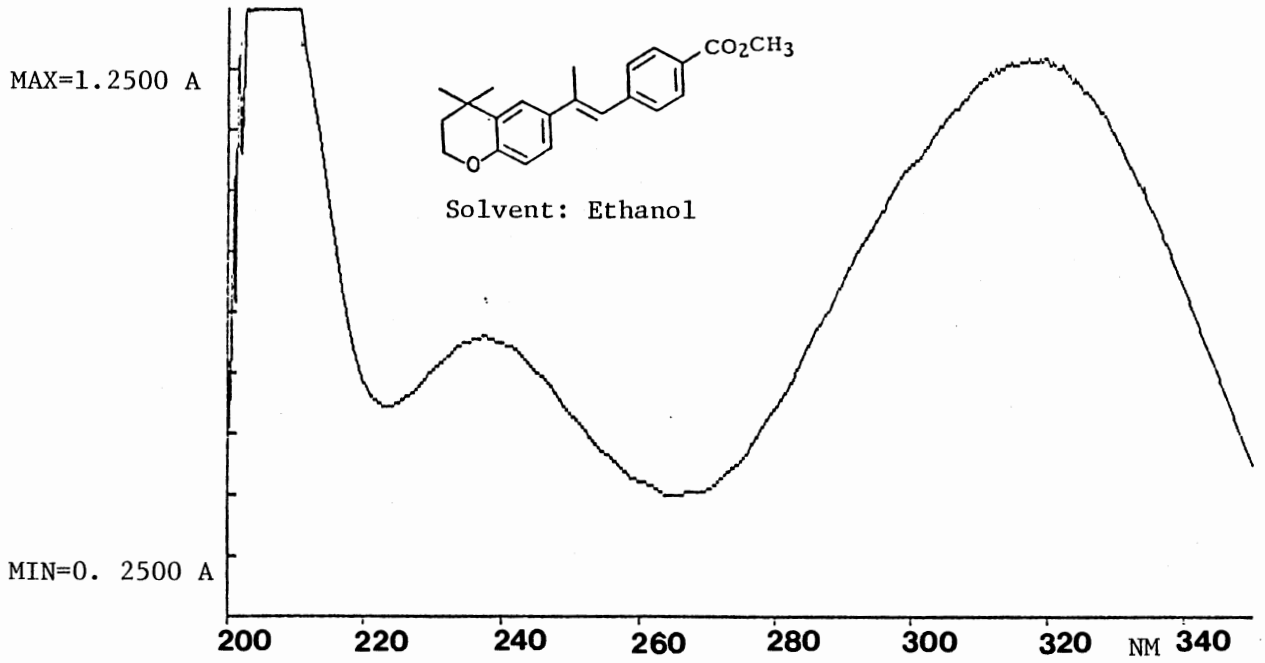
Off Resonance ^{13}C NMR Spectrum of 60a

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 1508.9 Hz; T: RT °C; NT: 416

Size: 16 K; PW/RF: 12.0 µs/dB; TO: 1000 Hz; FB: _ Hz; Lock: ^2H ; D1,D5: 4.000 s.

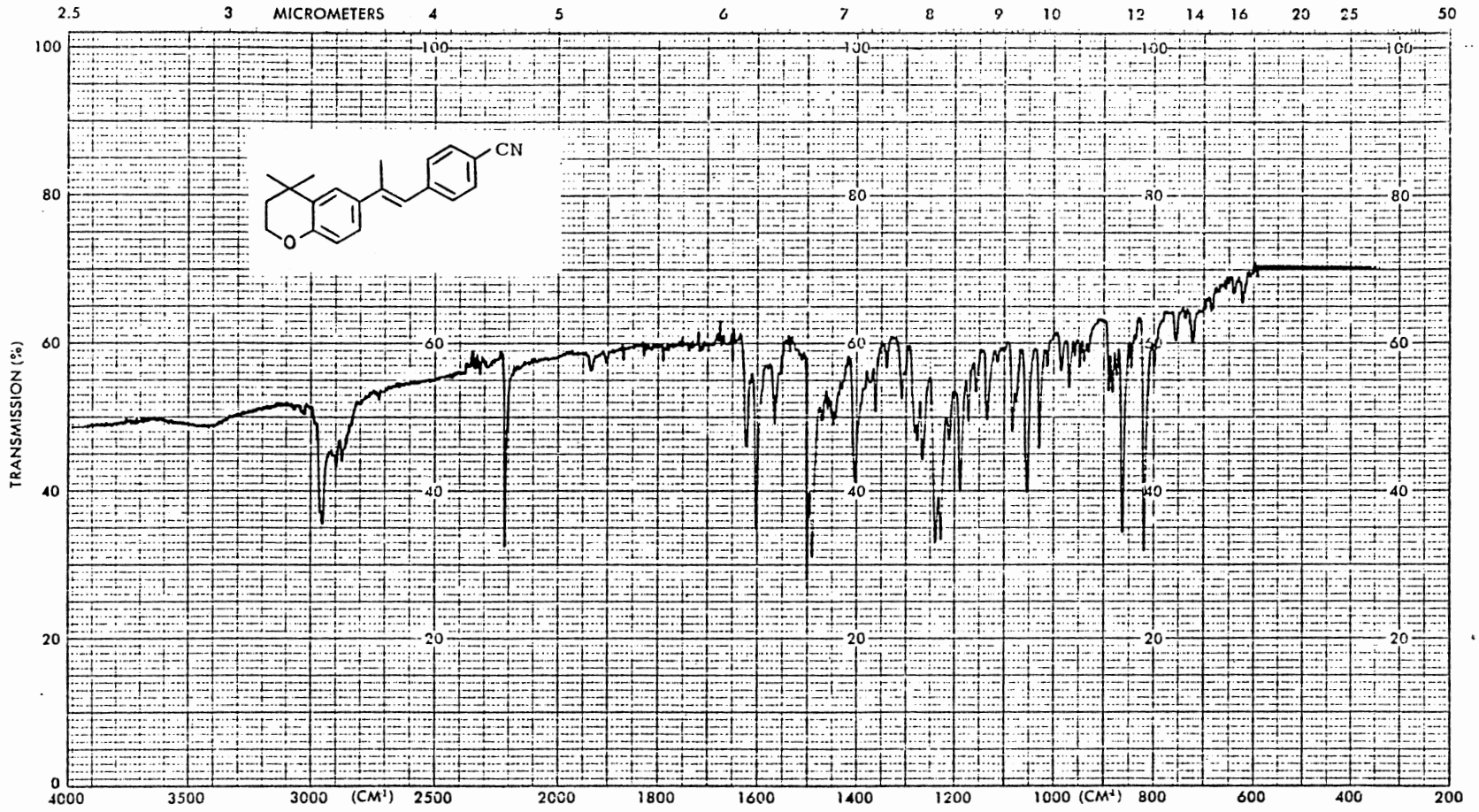
DC: Y ; Gated Off:A or D ; DO: -2500 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 2.000 Hz.

PLATE IX



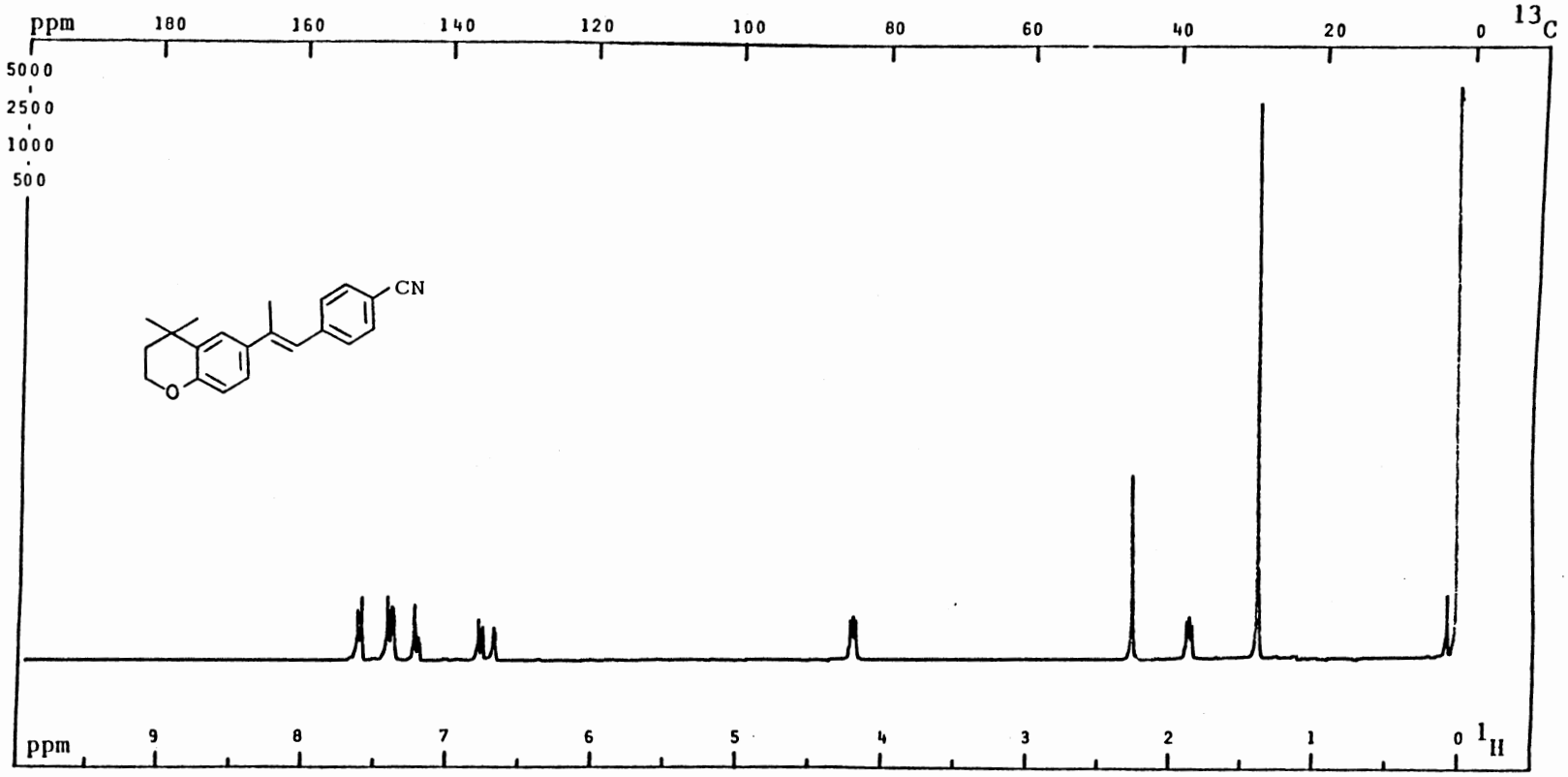
UV Spectrum of 60a

PLATE X



IR Spectrum of 60b

PLATE XI



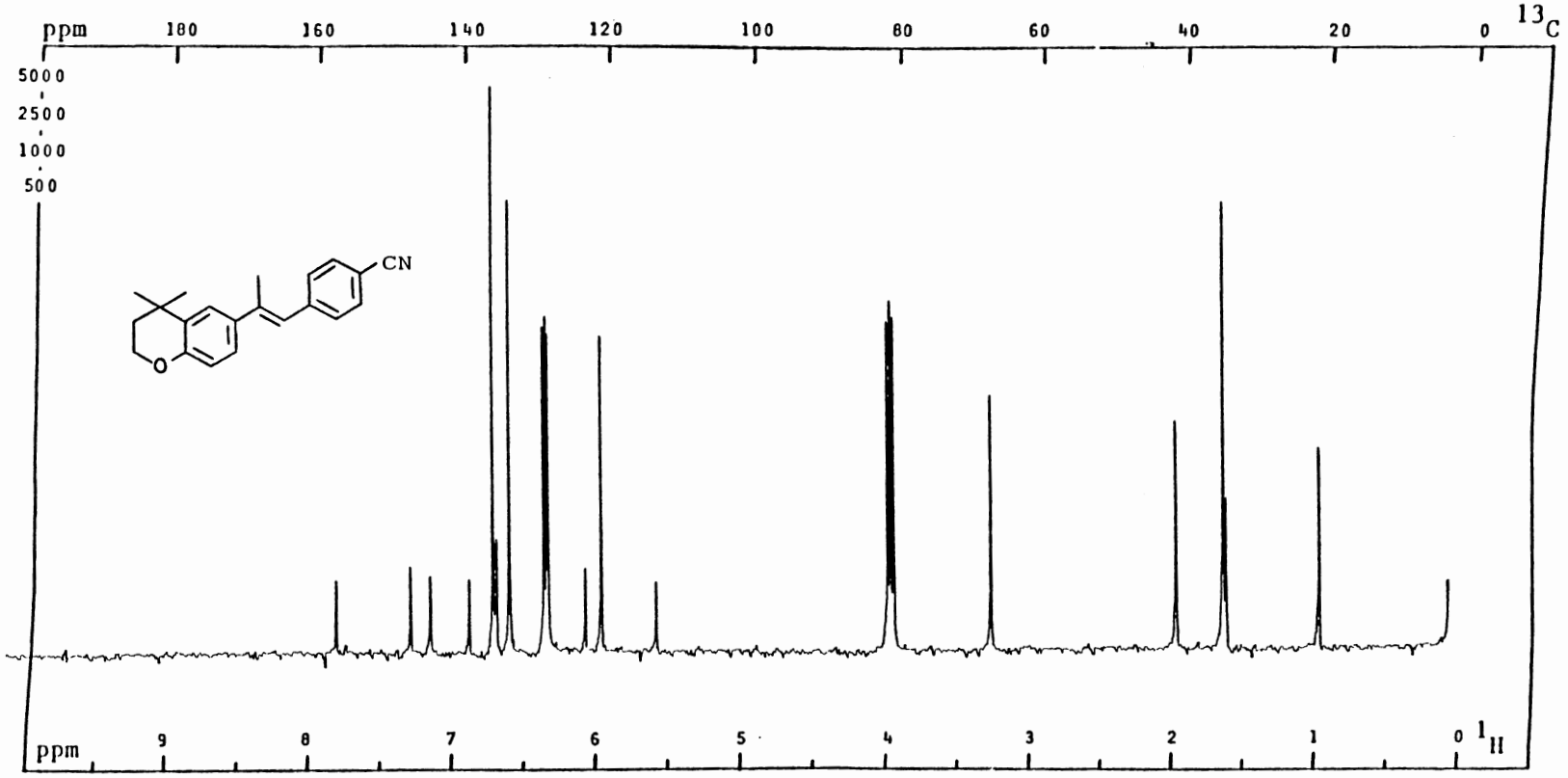
^{1}H NMR Spectrum of 60b

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 2999.4 Hz; T: RT °C; NT: 8 .

Size: 8 K; PW/RF: 5.0 µs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 0 s.

DC: N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 15 W/dB; NBW: 200 Hz; LB: Hz.

PLATE XII



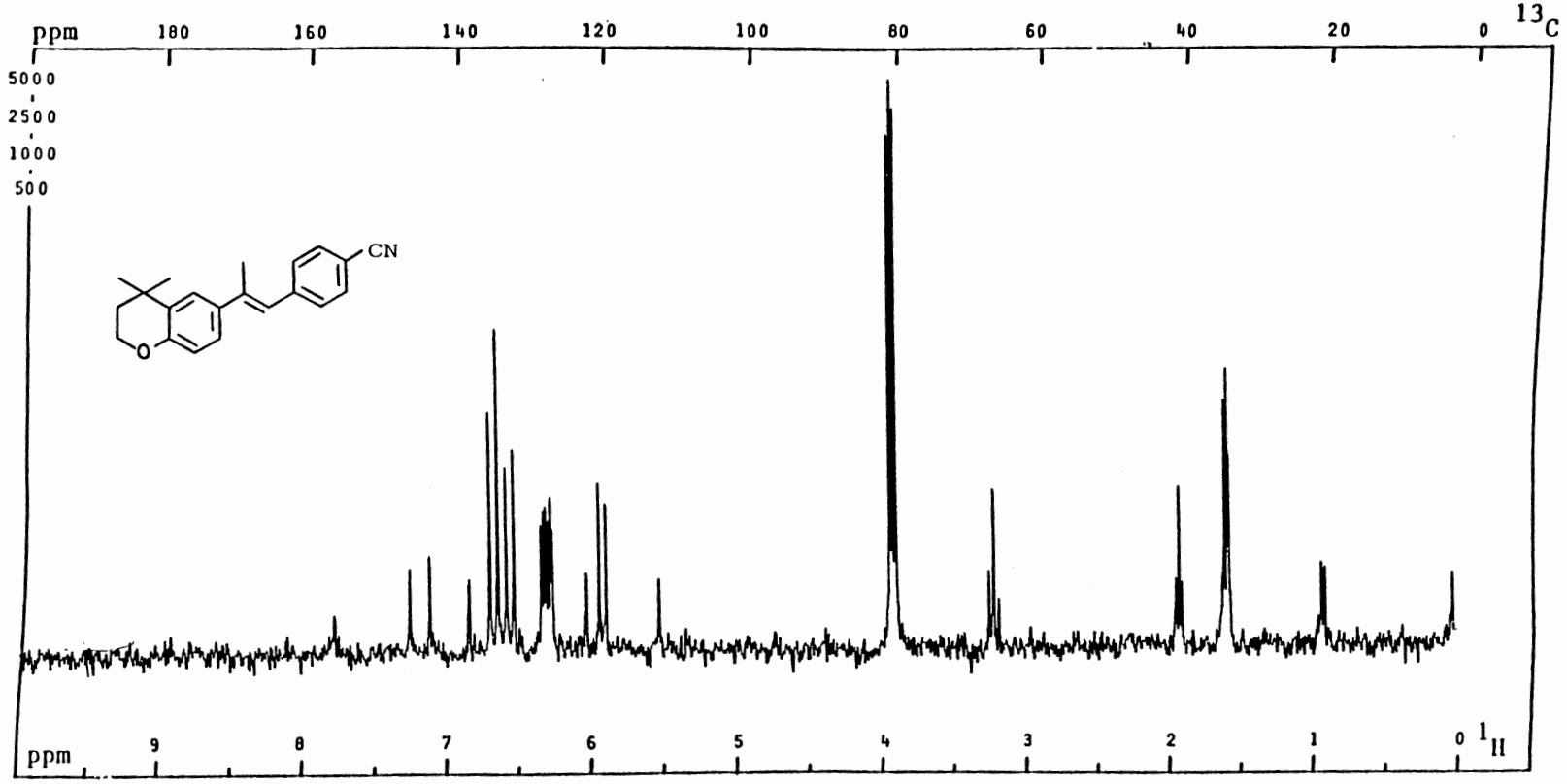
^{13}C NMR Spectrum of 60b

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9Hz; T: RT °C; NT: 308

Size: 16K; PW/RF: 12.0 µs/dB; TO: 1000 Hz; FB: - Hz; Lock: ^2H ; D1,D5: 5.000 s.

DC: Y ; Gated Off:A or D ; DO: Hz; RF(Power): W/dB; NBW: Hz; LB: Hz.

PLATE XIII



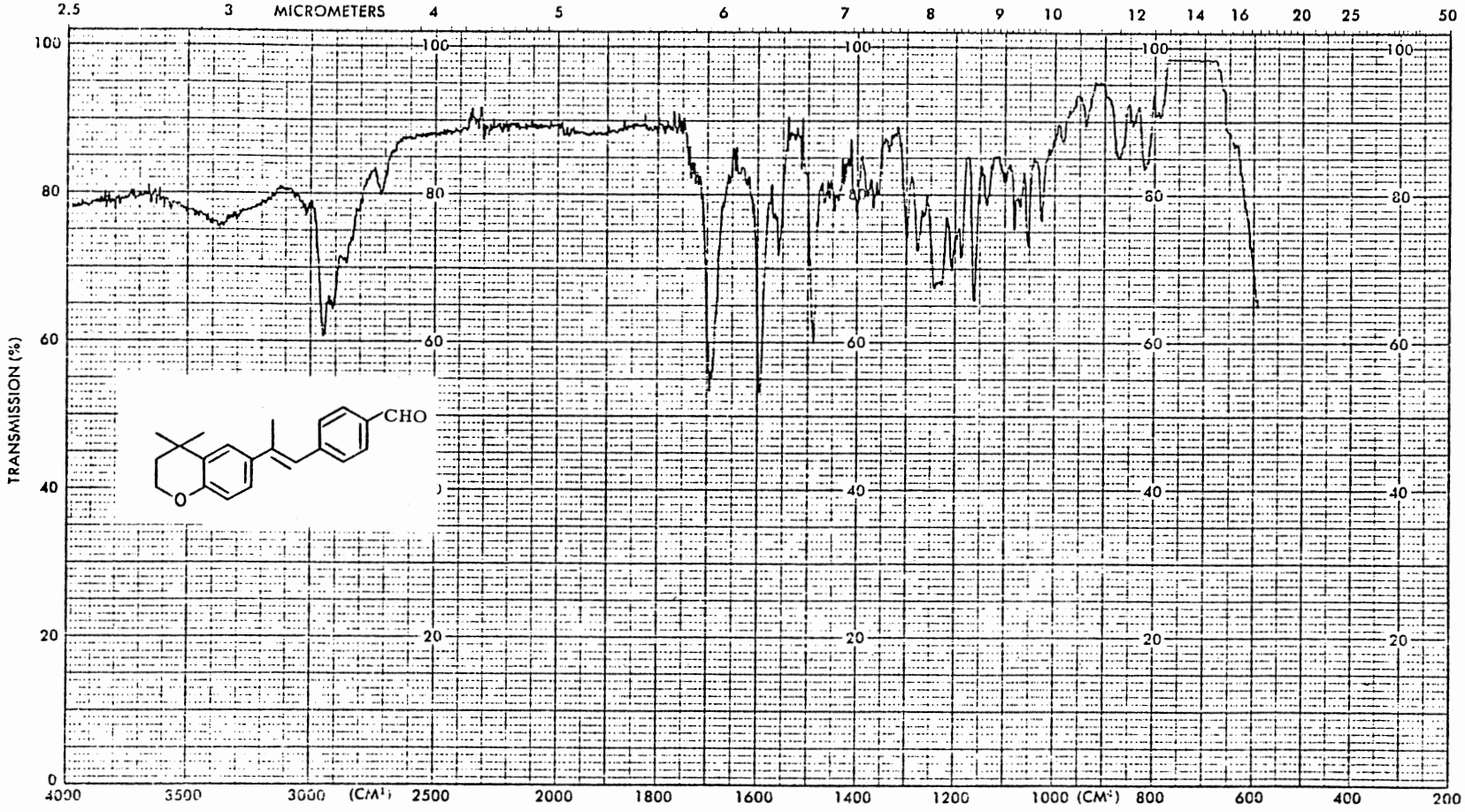
Off Resonance ^{13}C NMR Spectrum of 60b

PFT X CW __ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 132

Size: 16 K; PW/RF: 12.0 µs/dB; TO: 1000 Hz; FB: Hz; Lock: ^{2}H ; D1,D5: 5.000 s.

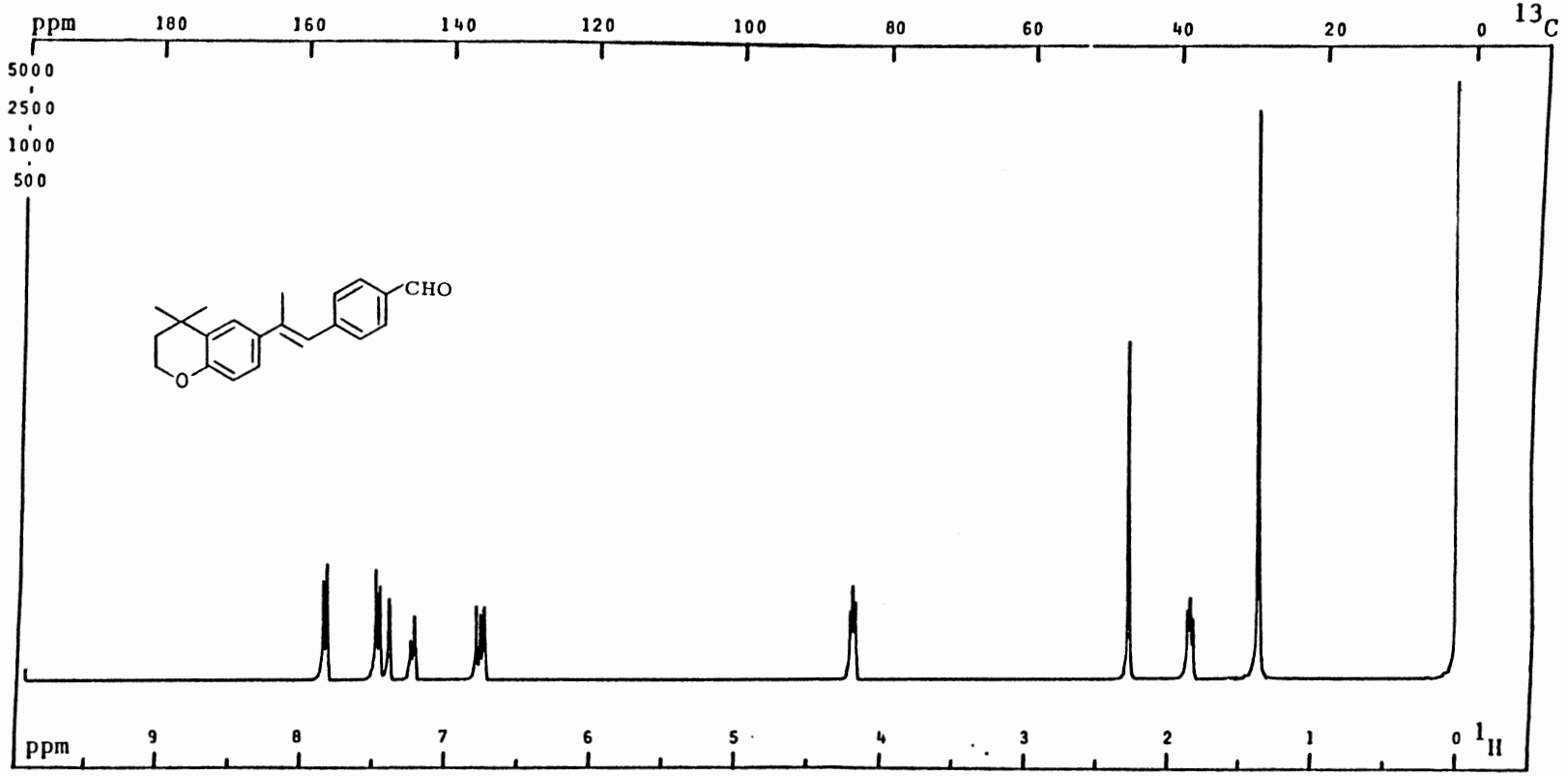
DC: Y ; Gated Off:A or D ; DO: Hz; RF(Power): W/dB; NBW: Hz; LB: 2.000 Hz.

PLATE XIV



IR Spectrum of 60c

PLATE XV



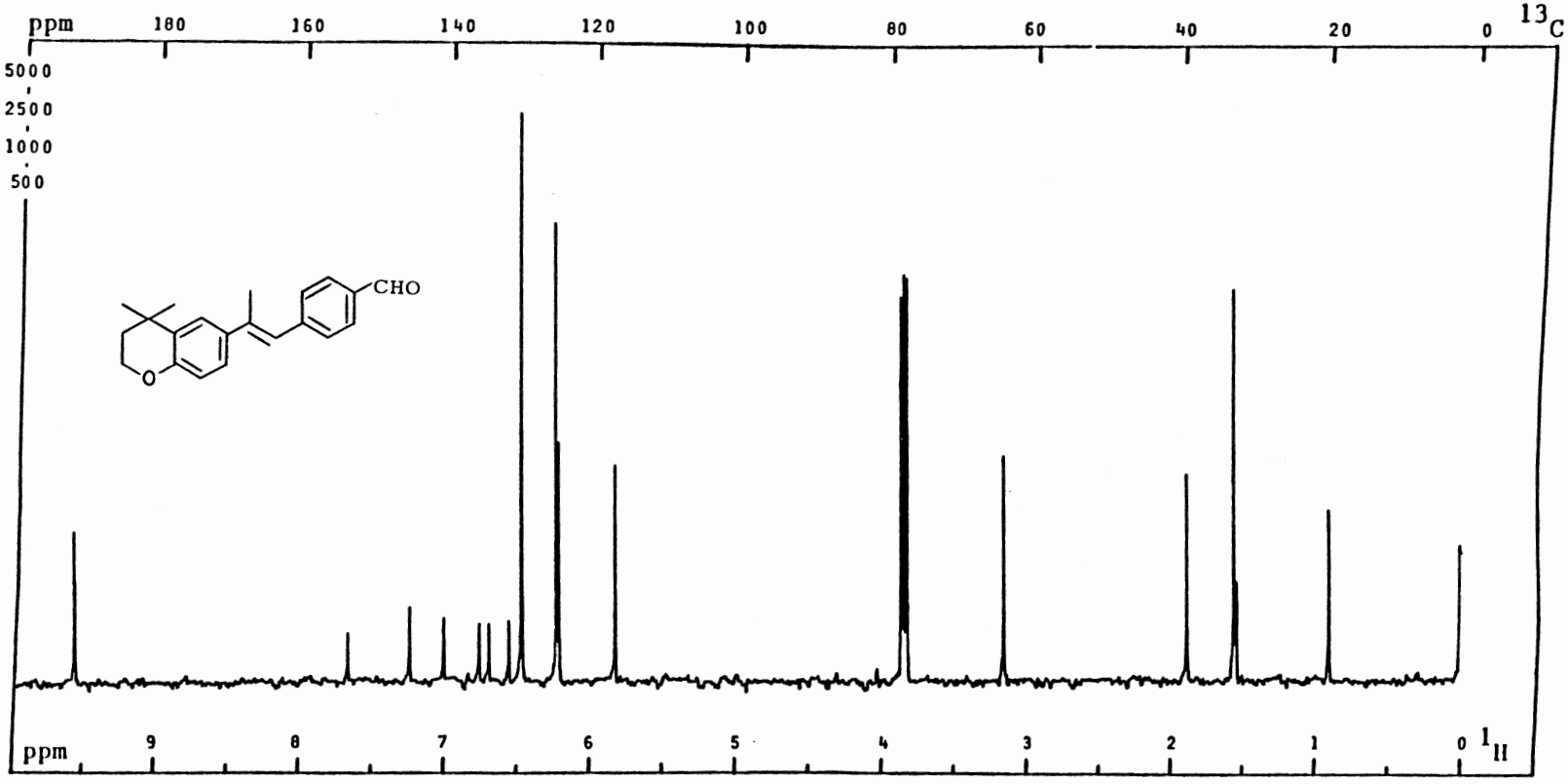
^{1}H NMR Spectrum of 60c

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 2999.4 Hz; T: RT °C; NT: 16

Size: 12 K; PW/RF: 5.0 µs/dB; TO: 0 Hz; FB: _ Hz; Lock: ^{2}H ; D1,D5: 0 s.

DC: N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 15 W/dB; NBW: 200 Hz; LB: 0 Hz.

PLATE XVI



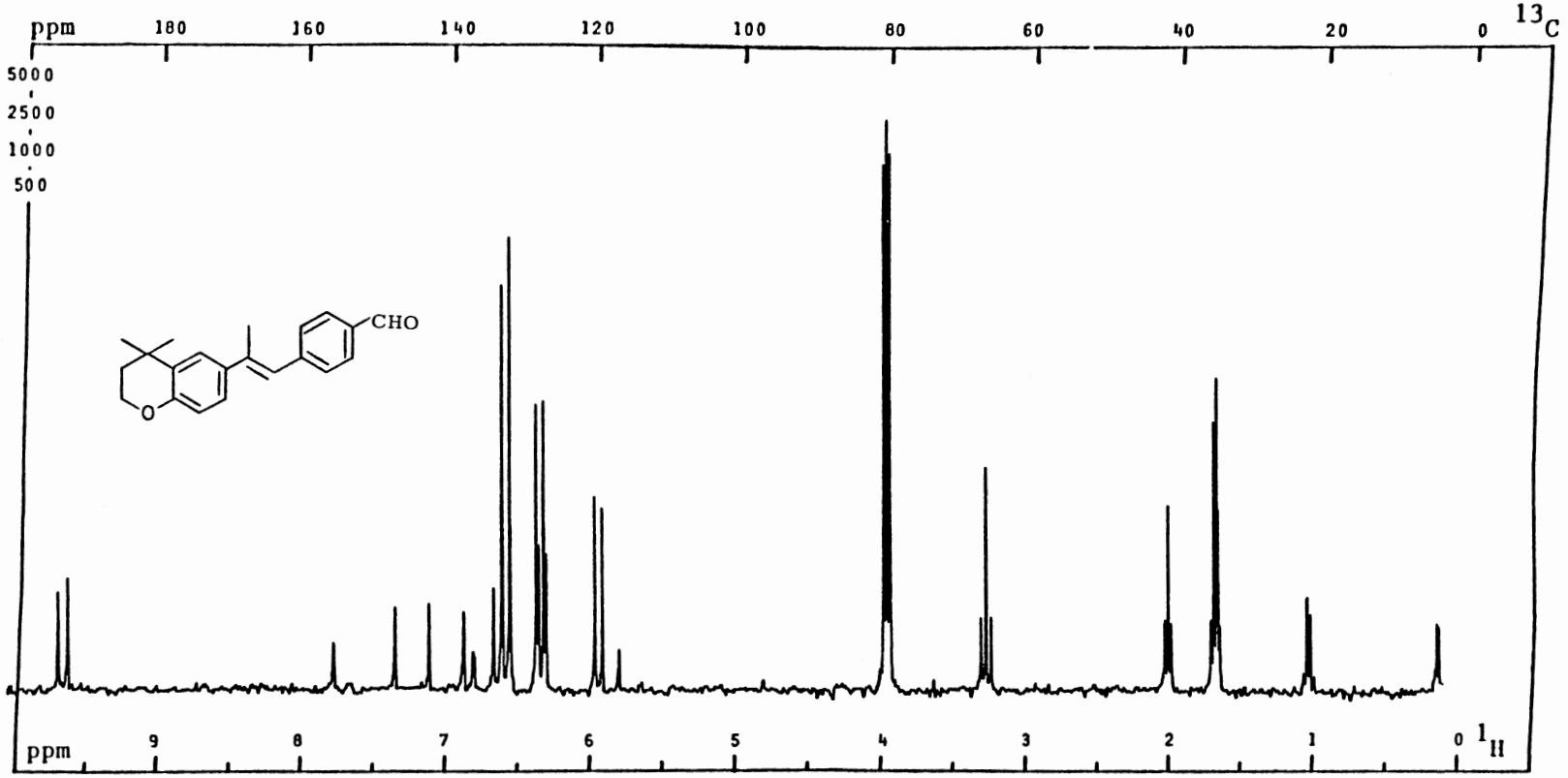
^{13}C NMR Spectrum of 60c

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 176 .

Size: 20 K; PW/RF: 12.0 µs/dB; TO: 1000 Hz; FB: _ Hz; Lock: ^2H ; D1,D5: 4.000 s.

DC: Y ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 4.000 Hz.

PLATE XVII



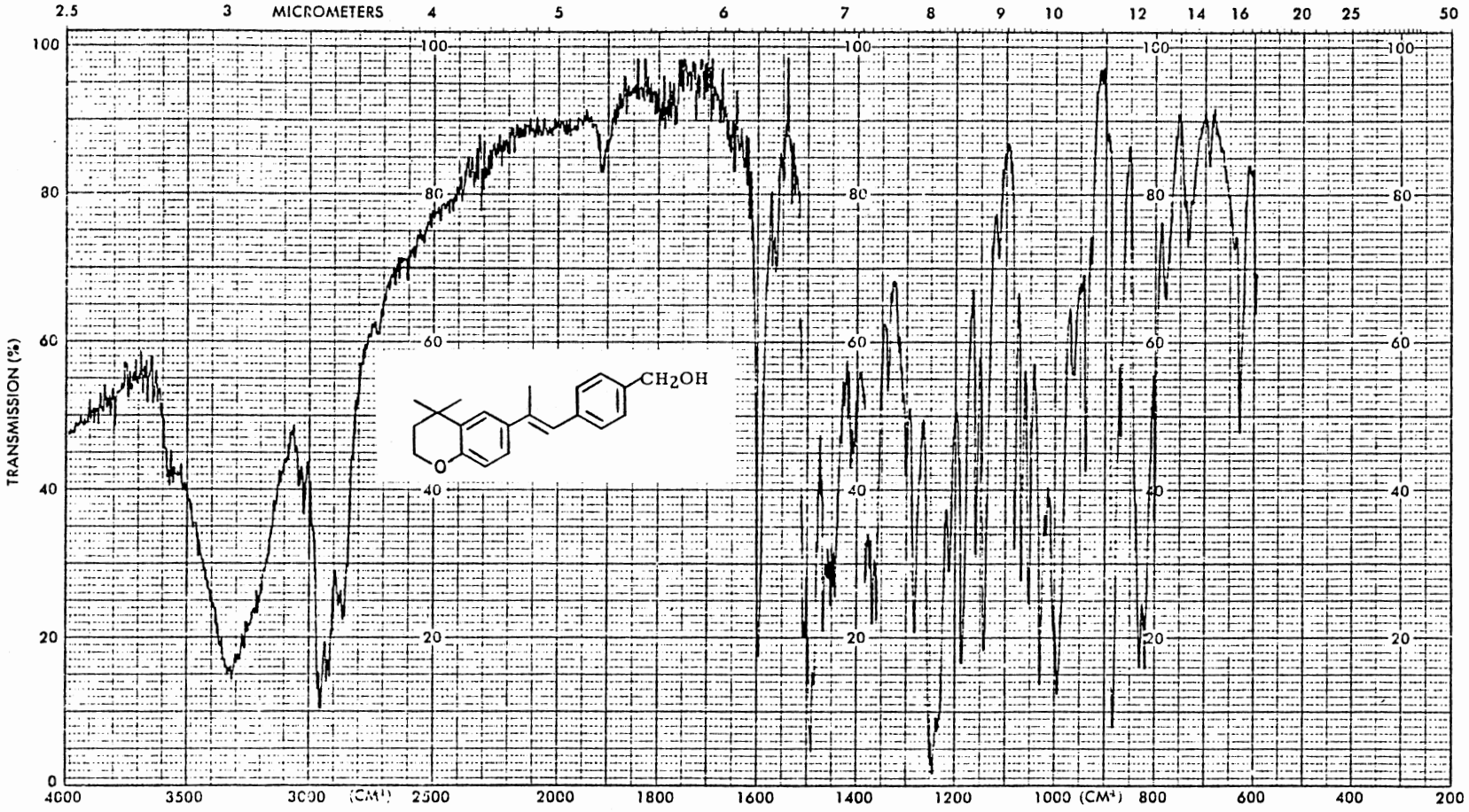
Off Resonance ^{13}C NMR Spectrum of 60c

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 176 .

Size: 20 K; PW/RF: 12.0 µs/dB; TO: 1000 Hz; FB: _ Hz; Lock: ^2H ; D1,D5: 4.000 s.

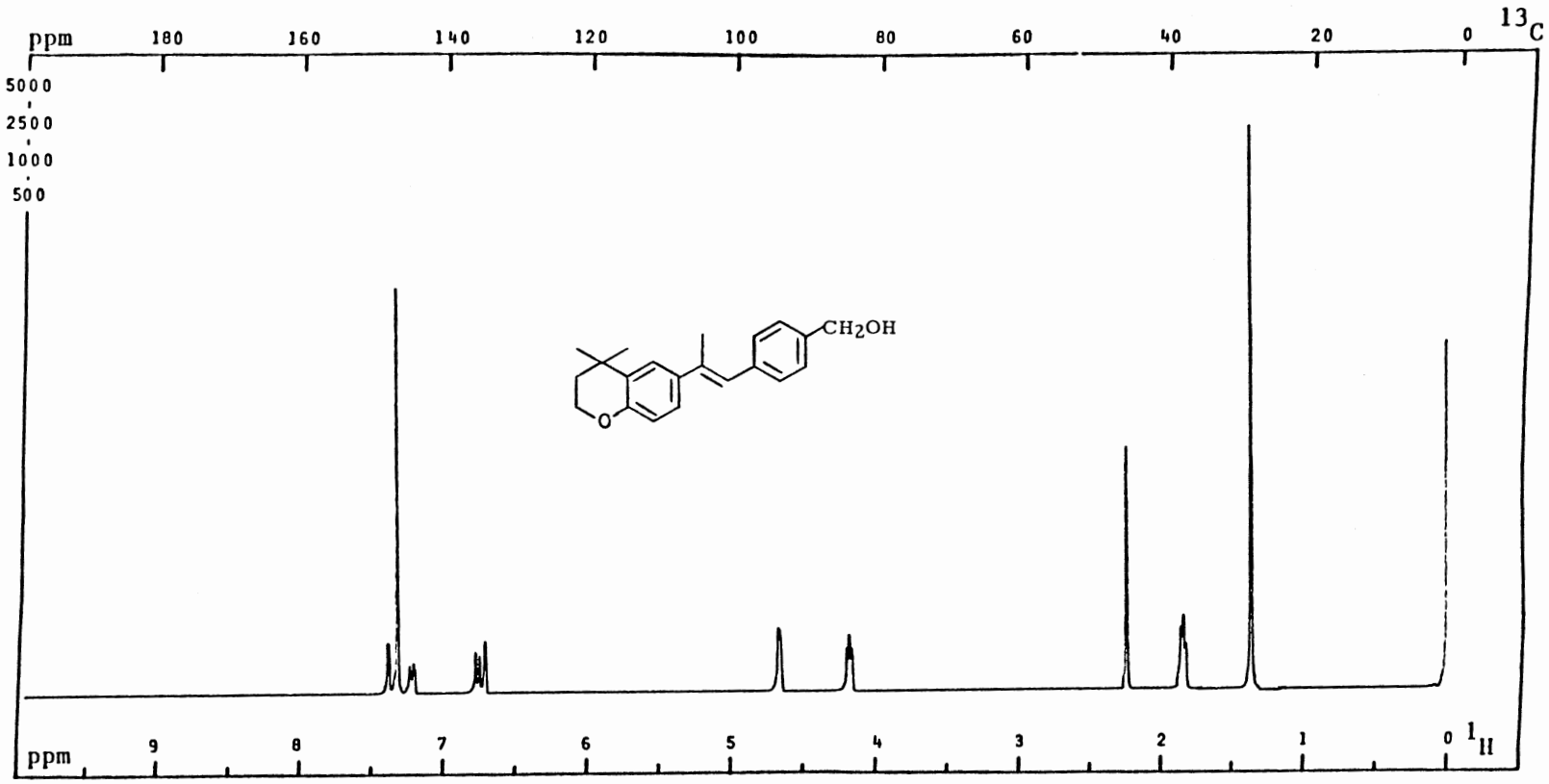
DC: Y ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 4.000 Hz.

PLATE XVIII



IRSpectrum of 60d

PLATE XIX



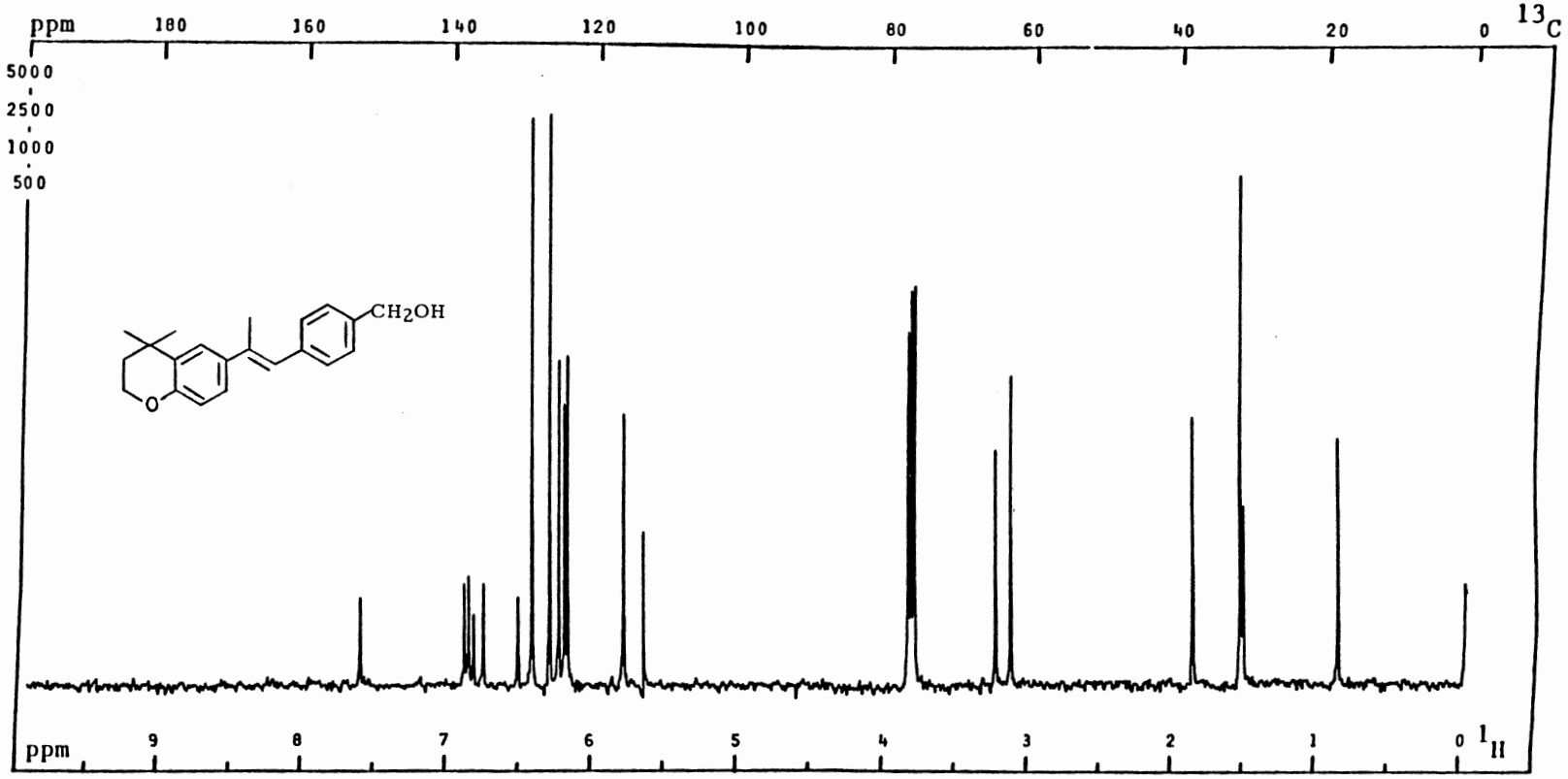
^{1}H NMR Spectrum of 60d

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 2999.4 Hz; T: RT °C; NT: 12 .

Size: 12 K; PW/RF: 5.0 µs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 0 s.

DC: N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 15 W/dB; NBW: 200 Hz; LB: 0.500 Hz.

PLATE XX



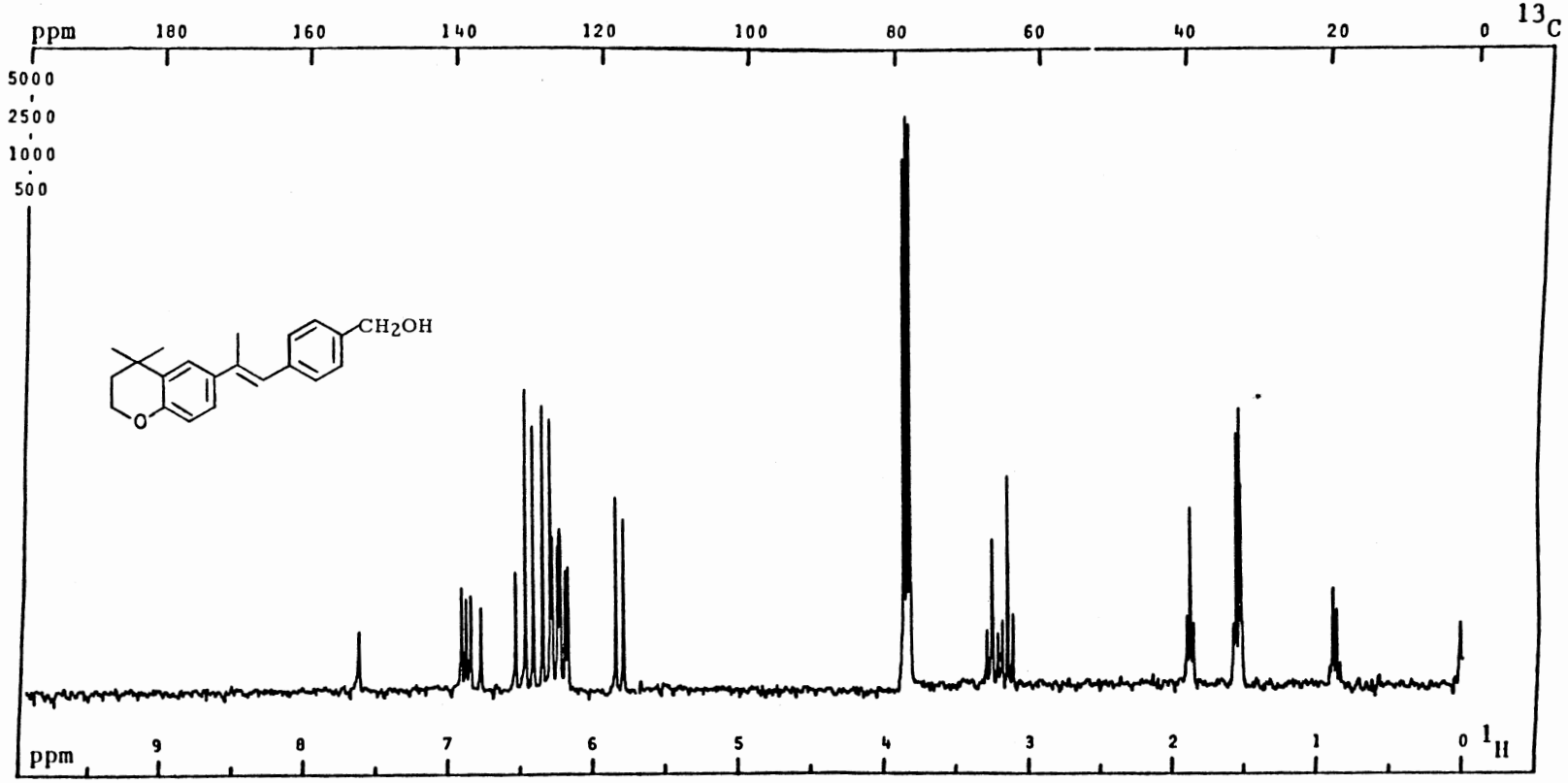
^{13}C NMR Spectrum of 60d

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 220 .

Size: 16 K; PW/RF: 12.0 µs/dB; TO: 1000 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 4.000 s.

DC: Y ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 2.500 Hz.

PLATE XXI



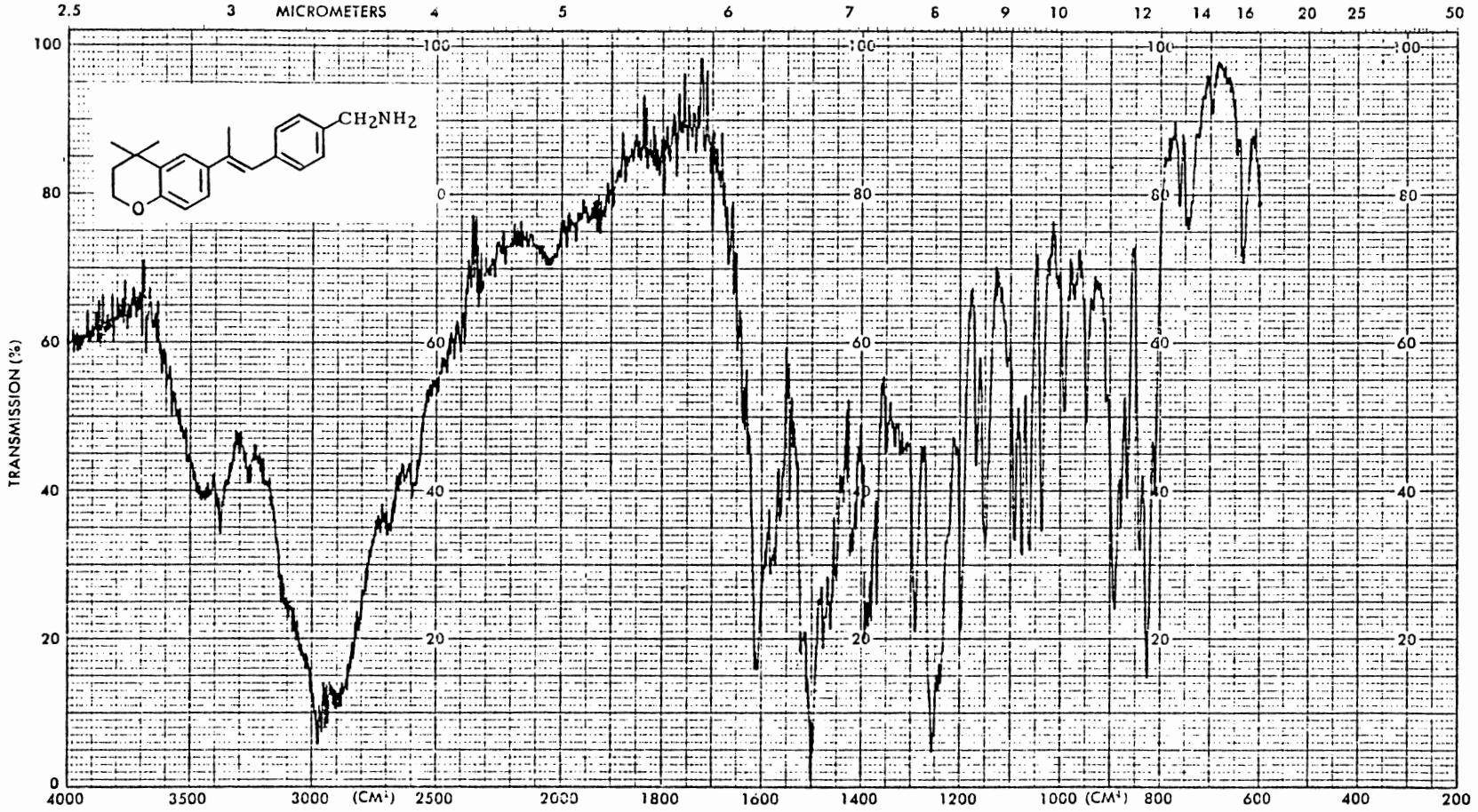
Off Resonance ^{13}C NMR Spectrum of 60d

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 528

Size: 16 K; PW/RF: 12.0 µs/dB; TO: 1000 Hz; FB: _ Hz; Lock: ^{2}H ; D1,D5: 4.000 s.

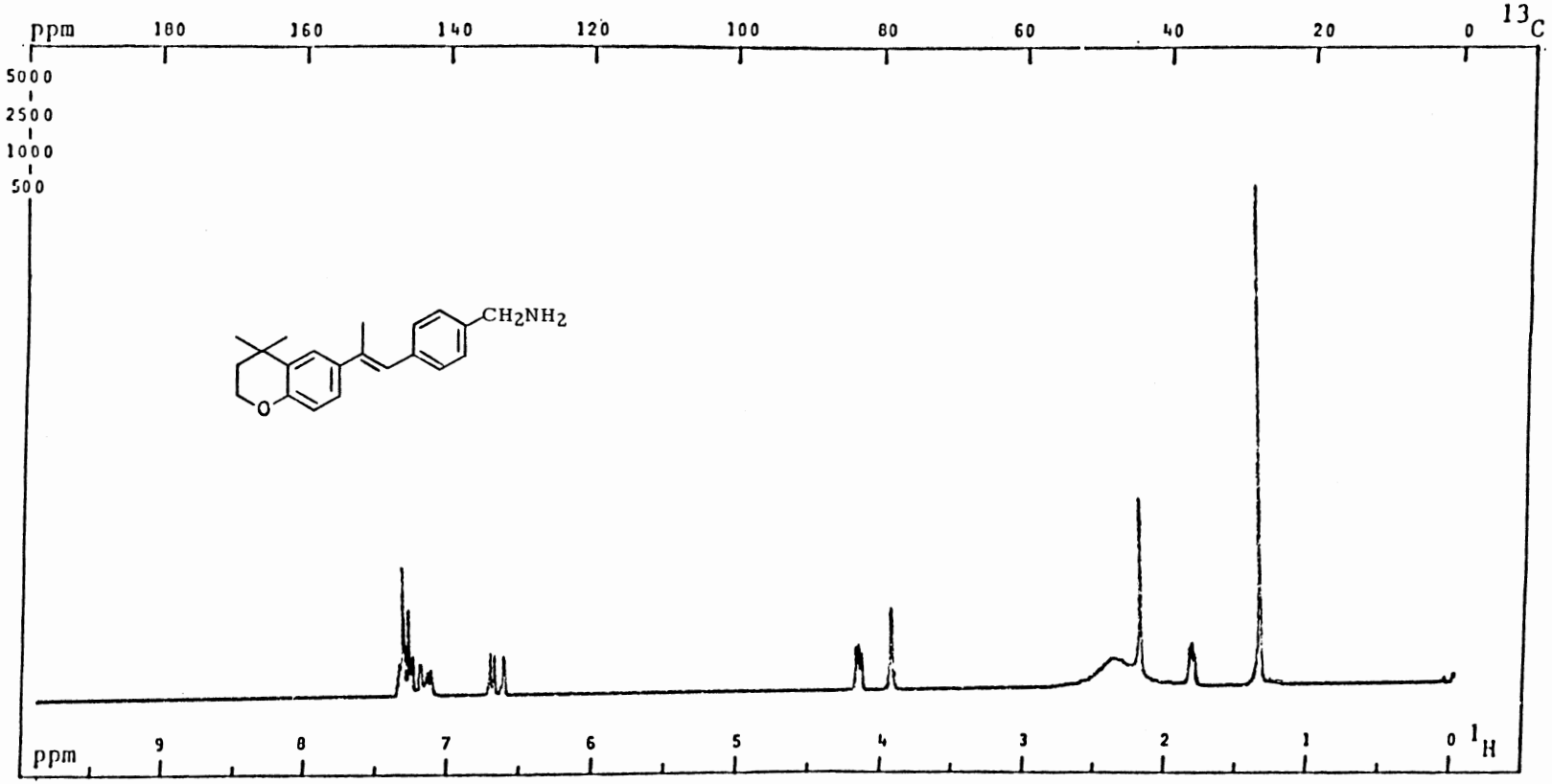
DC: Y ; Gated Off: A or D ; DO: -2500.0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 2.500 Hz.

PLATE XXII



IR Spectrum of 60e

PLATE XXIII



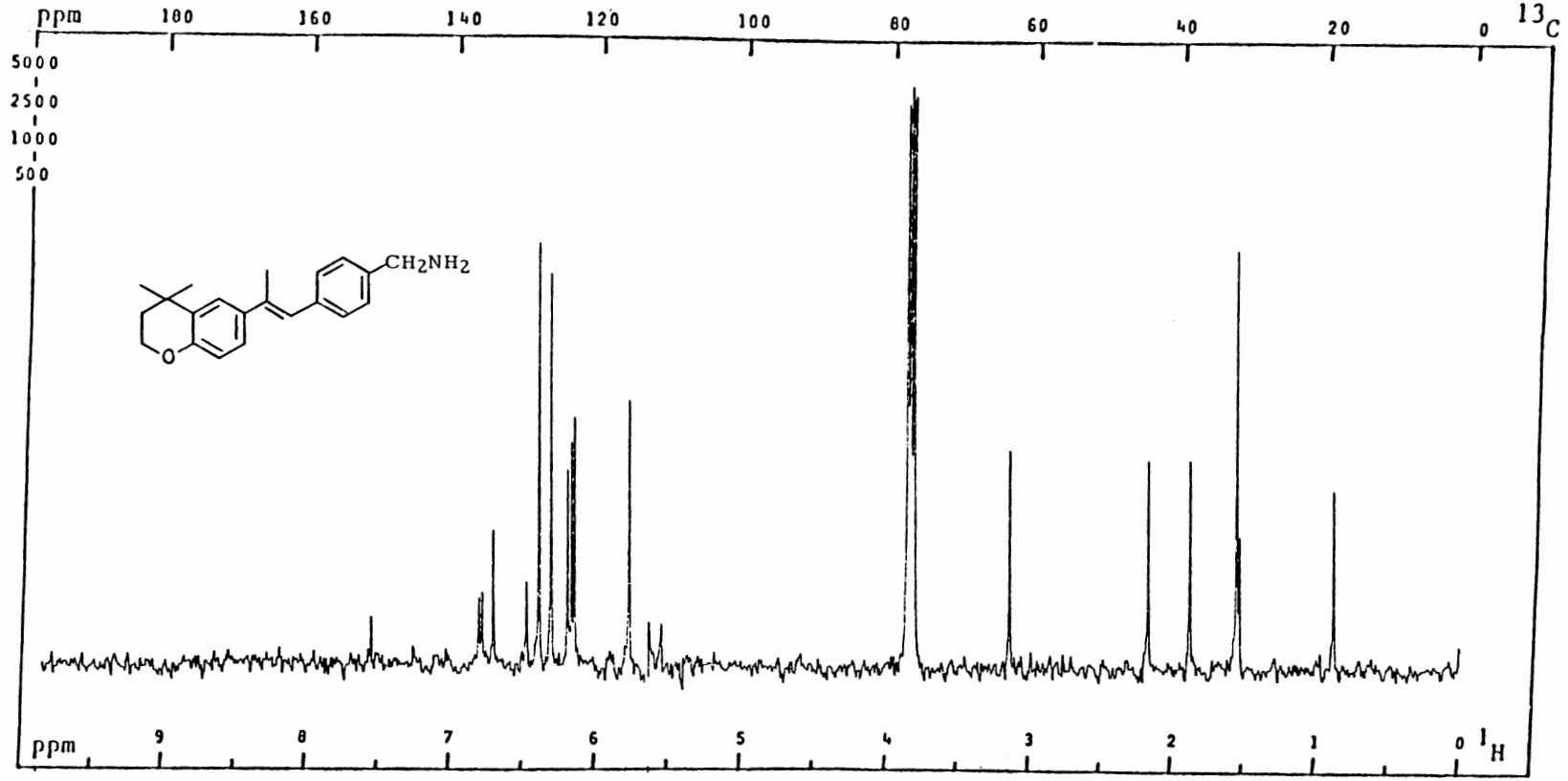
^{1}H NMR Spectrum of 60e

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 2999.4 Hz; T: RT °C; NT: 80 .

Size: 16 K; PW/RF: 5.0 µs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 0 s.

DC: N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: Hz; LB: 0 Hz.

PLATE XXIV



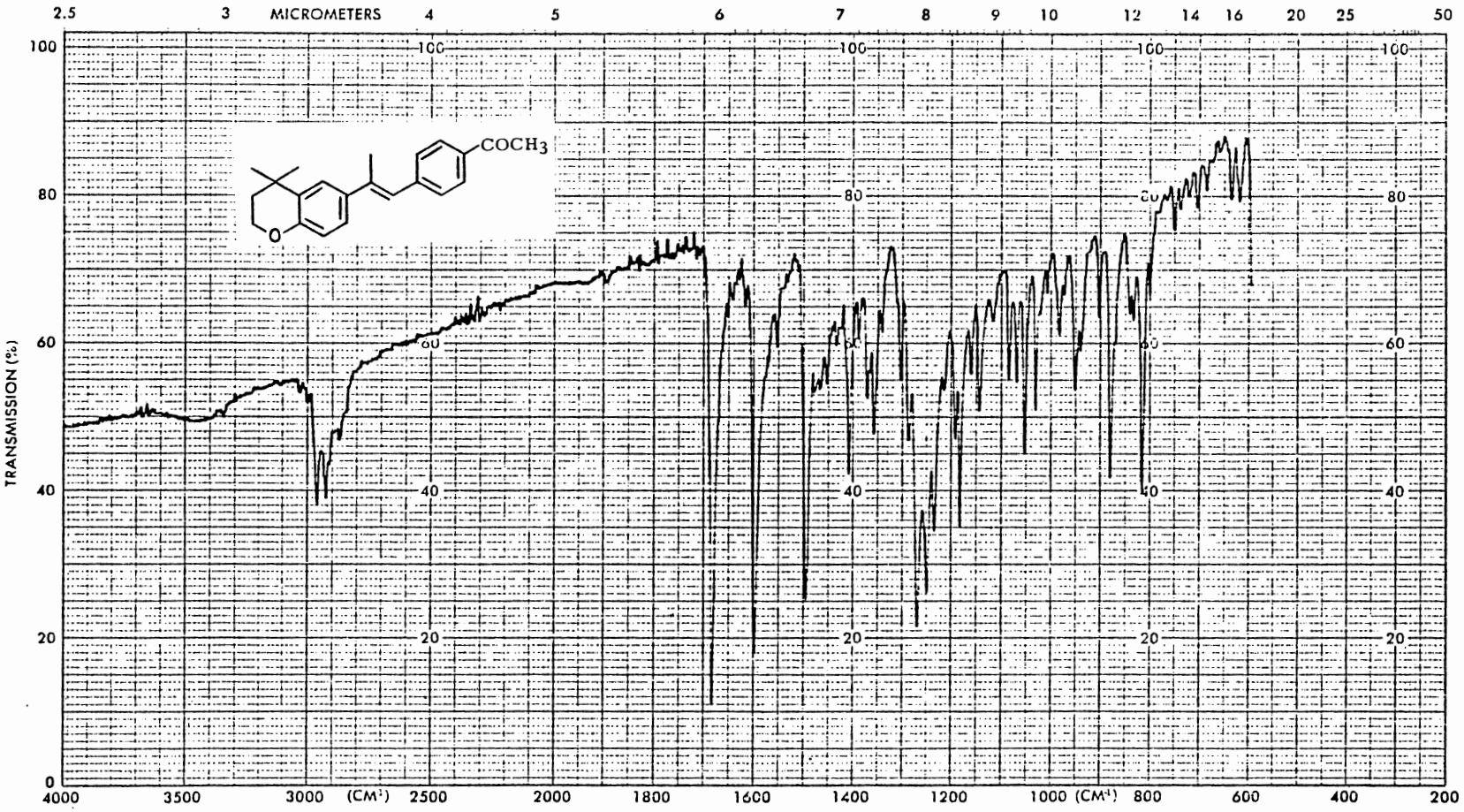
^{13}C NMR Spectrum of 60e

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 760 .

Size: 16 K; PW/RF: 12.0 μs/dB; TO: 1000 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 4.000 s.

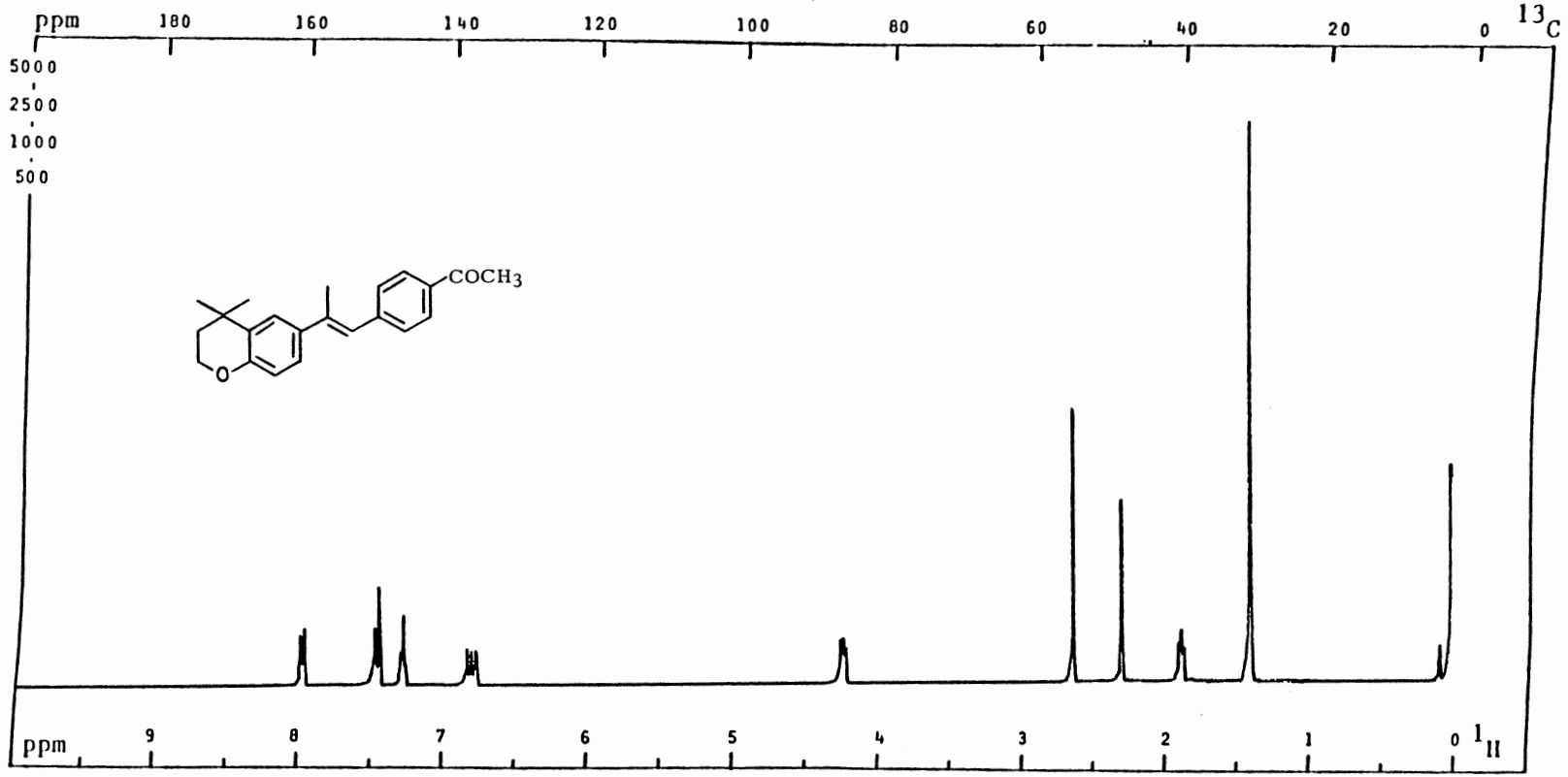
DC: Y ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 5.000 Hz.

PLATE XXV



IR Spectrum of 60f

PLATE XXVI



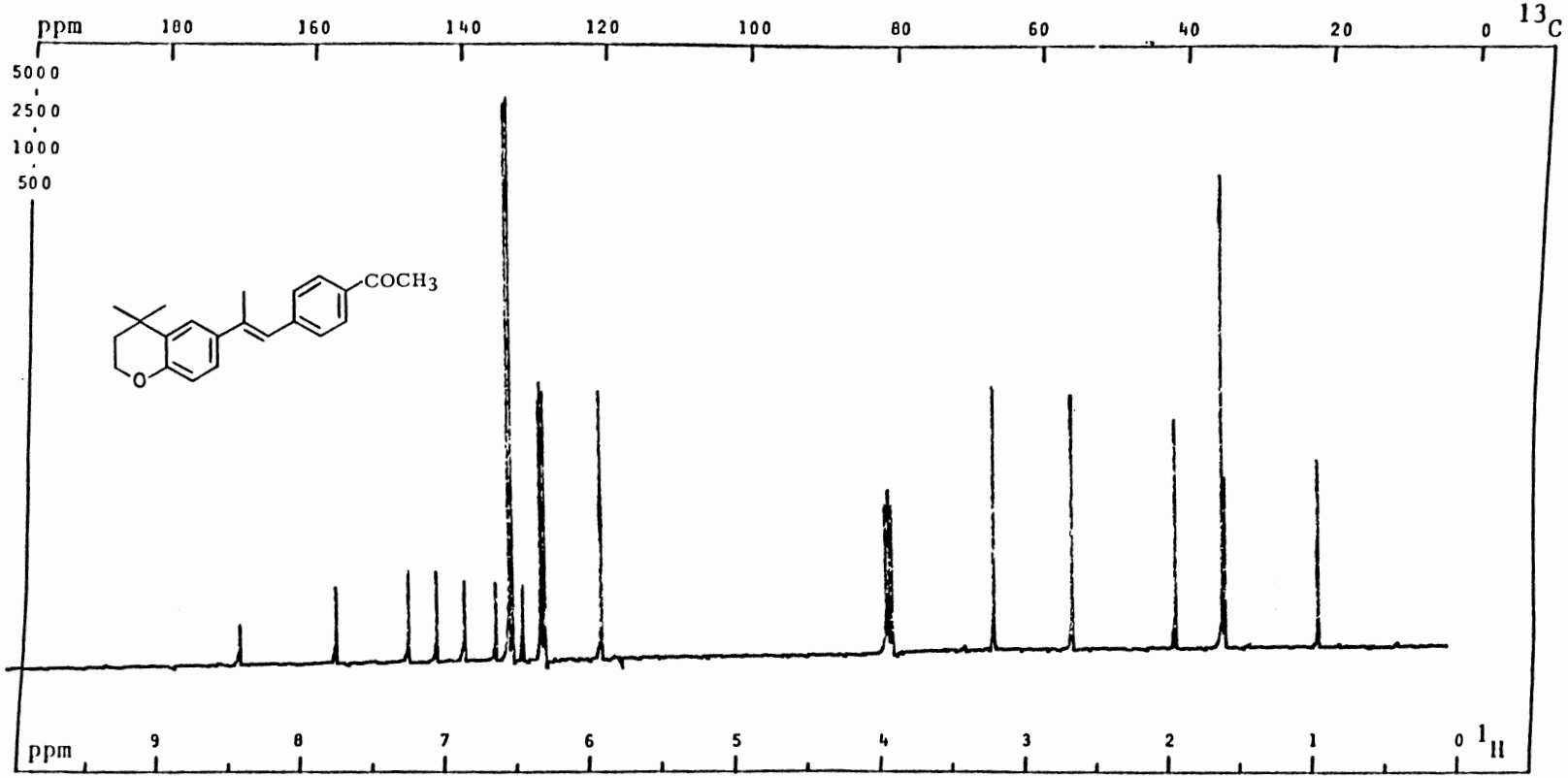
^{1}H NMR Spectrum of 60f

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 2999.4 Hz; T: RT °C; NT: 16 .

Size: 8 K; PW/RF: 5.0 µs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 0.500 s.

DC: N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 10 W/dB; NBW: 200 Hz; LB: 0.500 Hz.

PLATE XXVII



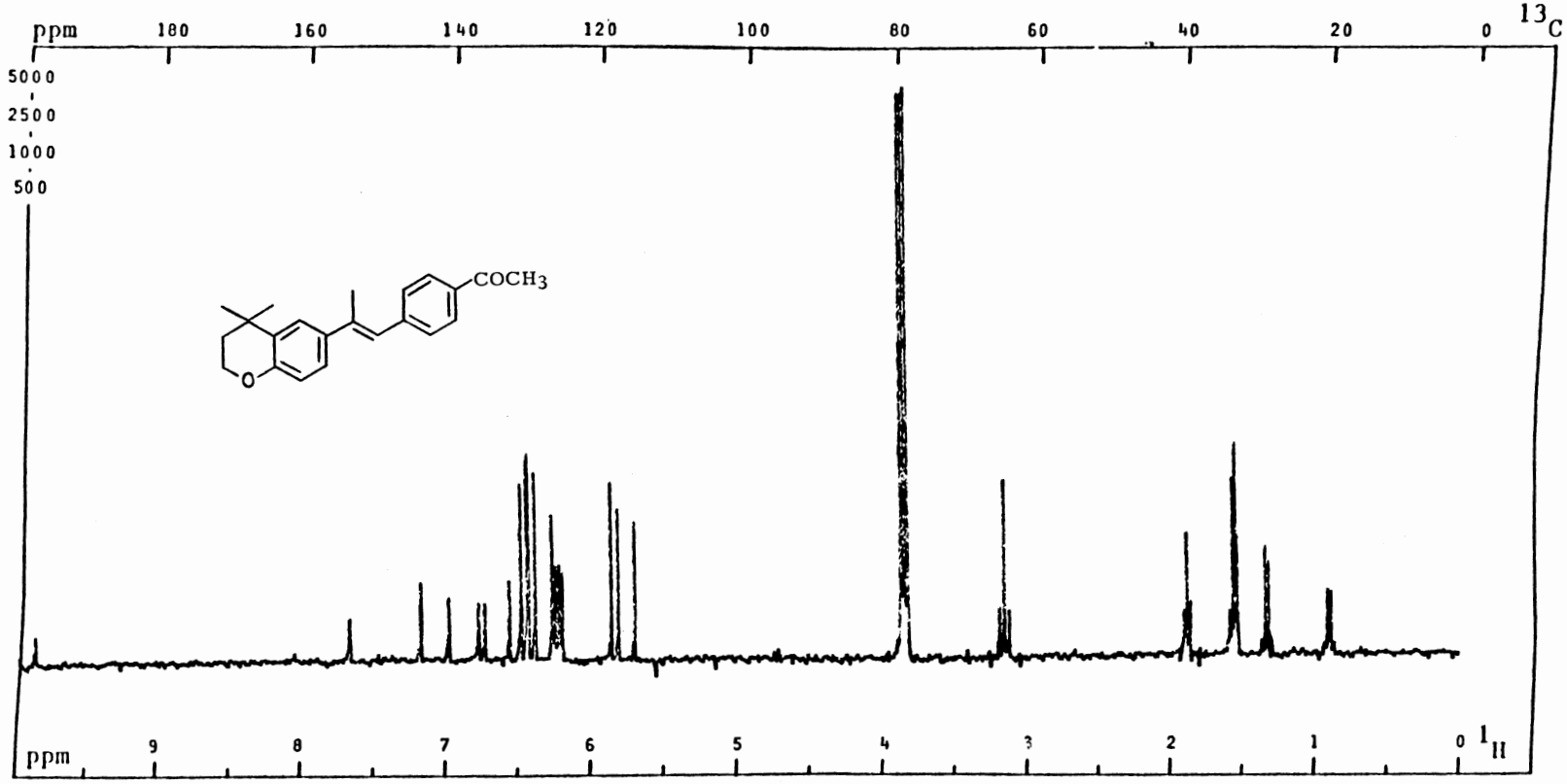
^{13}C NMR Spectrum of 60f

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9Hz; T: RT °C; NT: 1100 .

Size: 20 K; PW/RF: 12.0 µs/dB; TO: 1000 Hz; FB: - Hz; Lock: ^2H ; D1,D5: 4.000 s.

DC: Y ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 1.000 Hz.

PLATE XXVIII



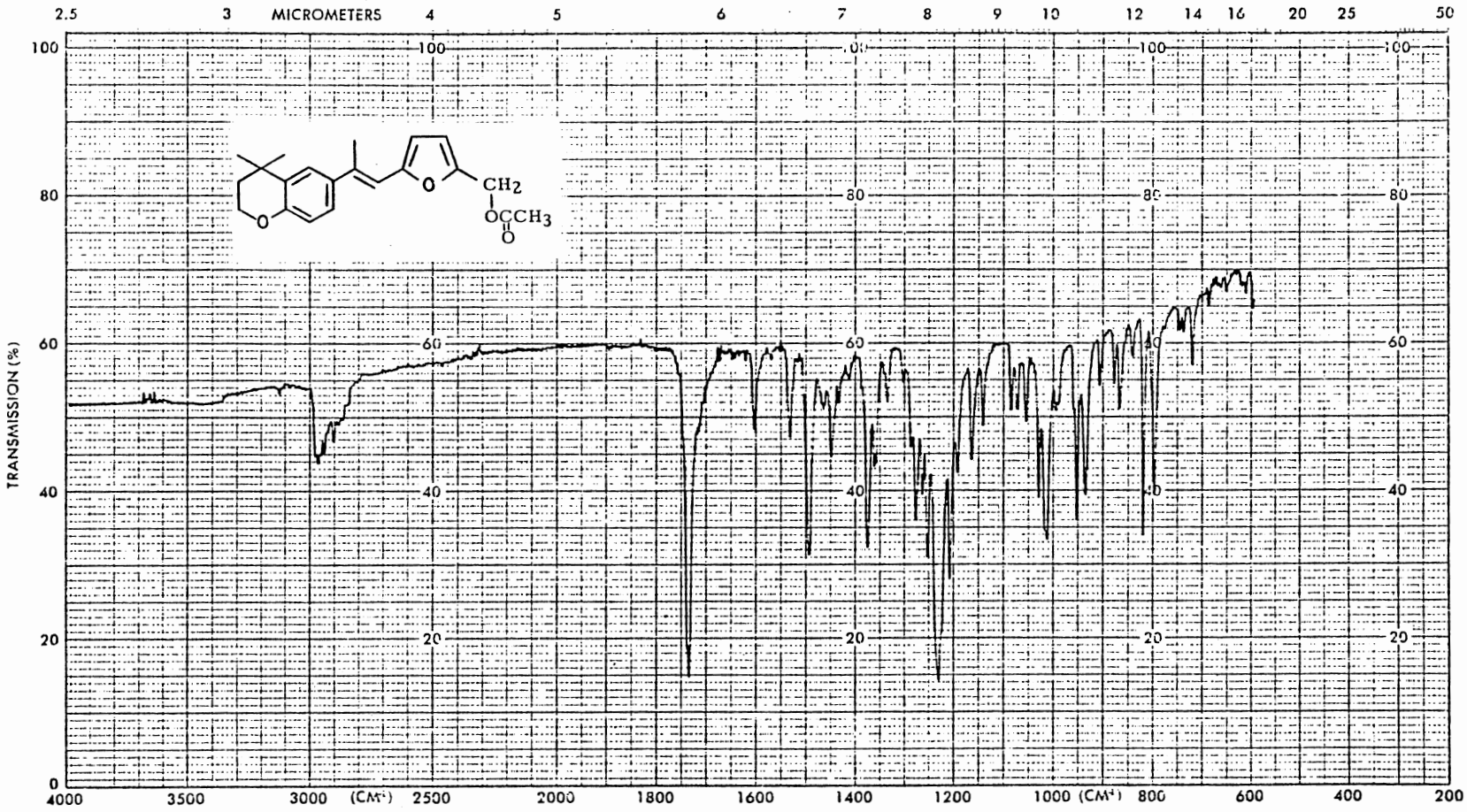
Off Resonance ^{13}C NMR Spectrum of 60f

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 1200 .

Size: 20 K; PW/RF: 12.0 µs/dB; TO: 1000 Hz; FB: Hz; Lock: ^2H ; D1,D5: 6.000 s.

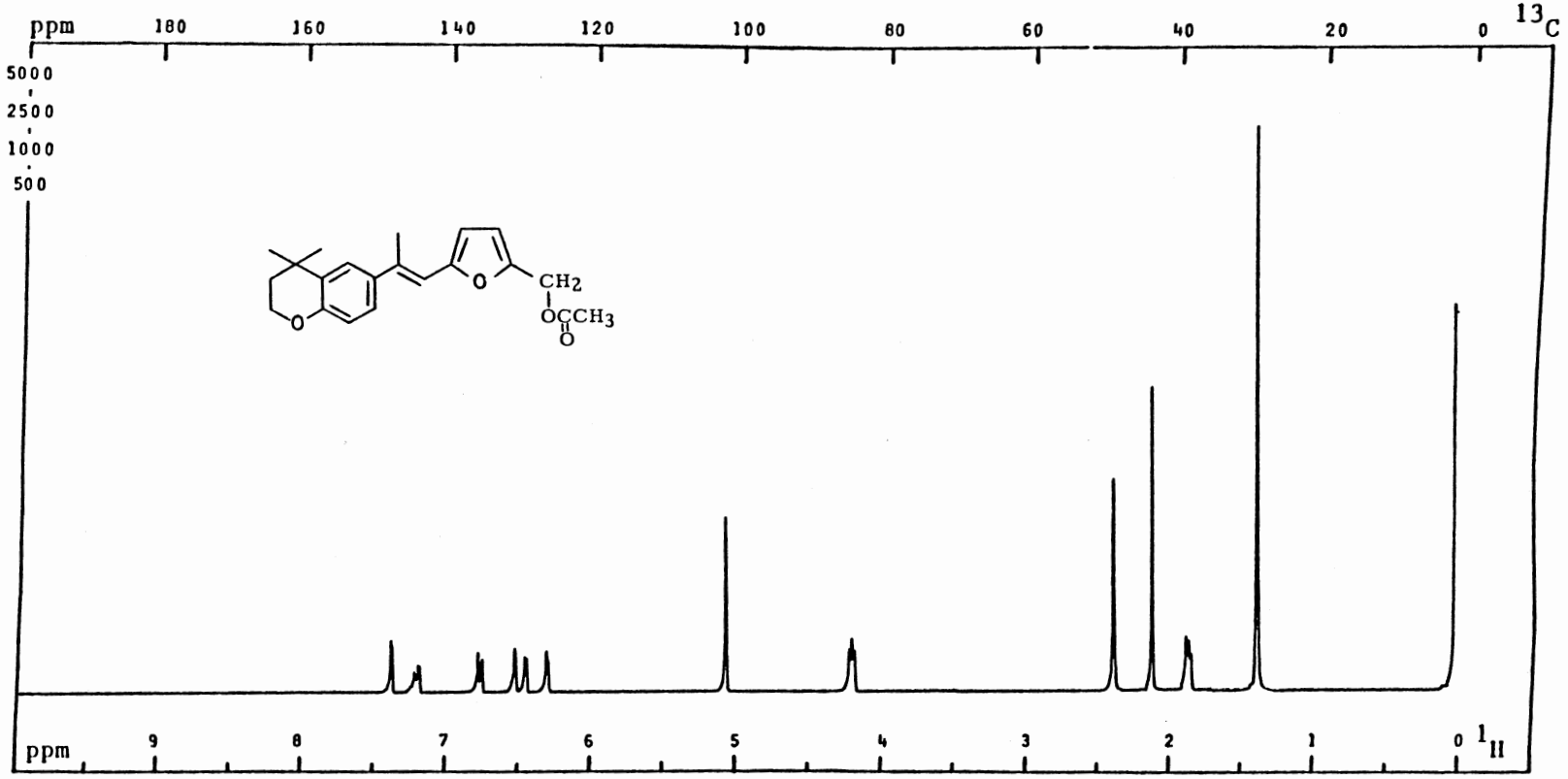
DC: Y ; Gated Off: A or D ; DO: -2500.0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 1.000 Hz.

PLATE XXIX



IR Spectrum of 60g

PLATE XXX



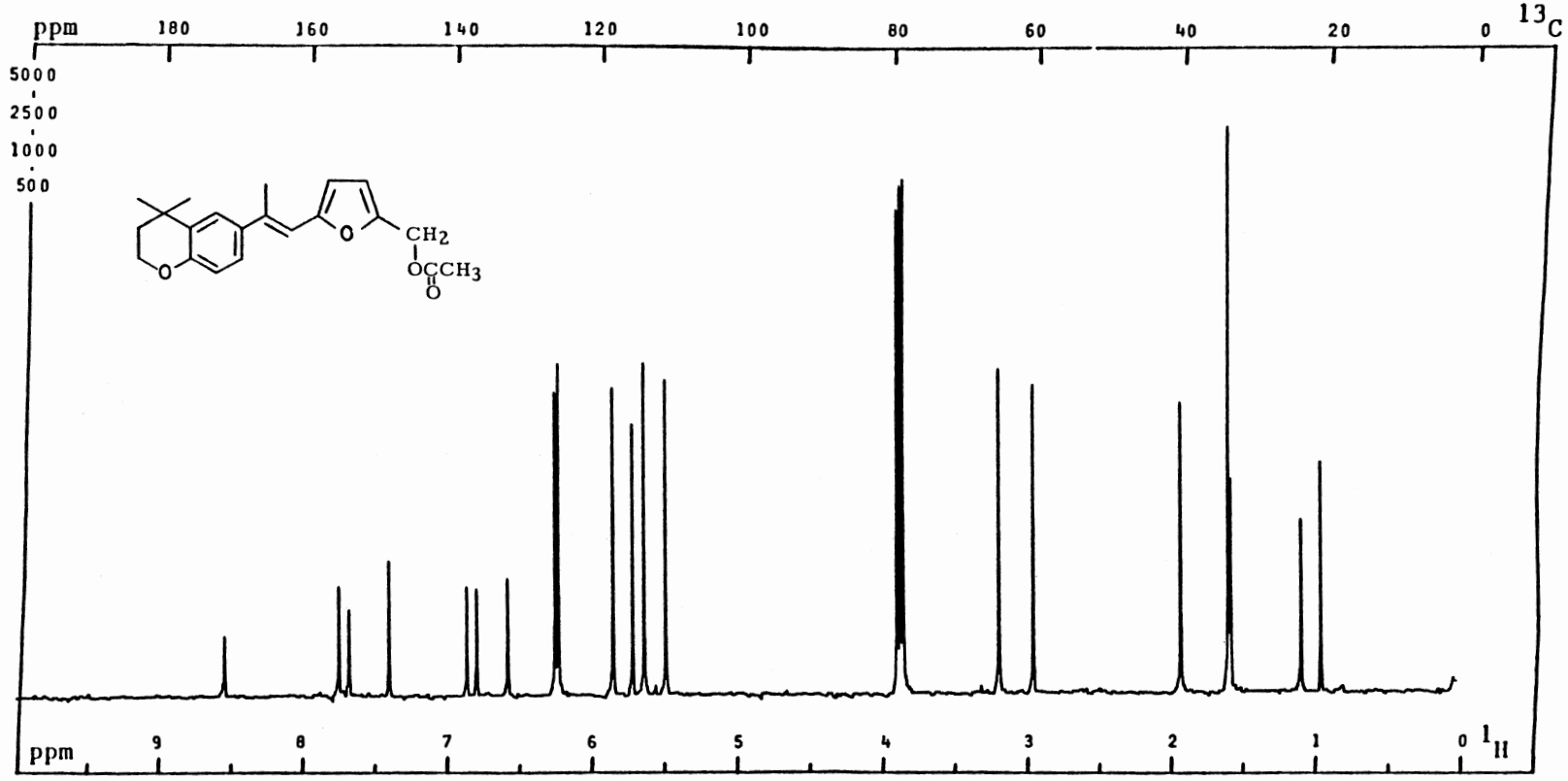
^{1}H NMR Spectrum of 60g

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 2999.4 Hz; T: RT °C; NT: 20 .

Size: 12 K; PW/RF: 5.0 µs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ;D1,D5: 0 s.

DC: N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 15 W/dB; NBW: 200 Hz; LB: 0.700 Hz.

PLATE XXXI



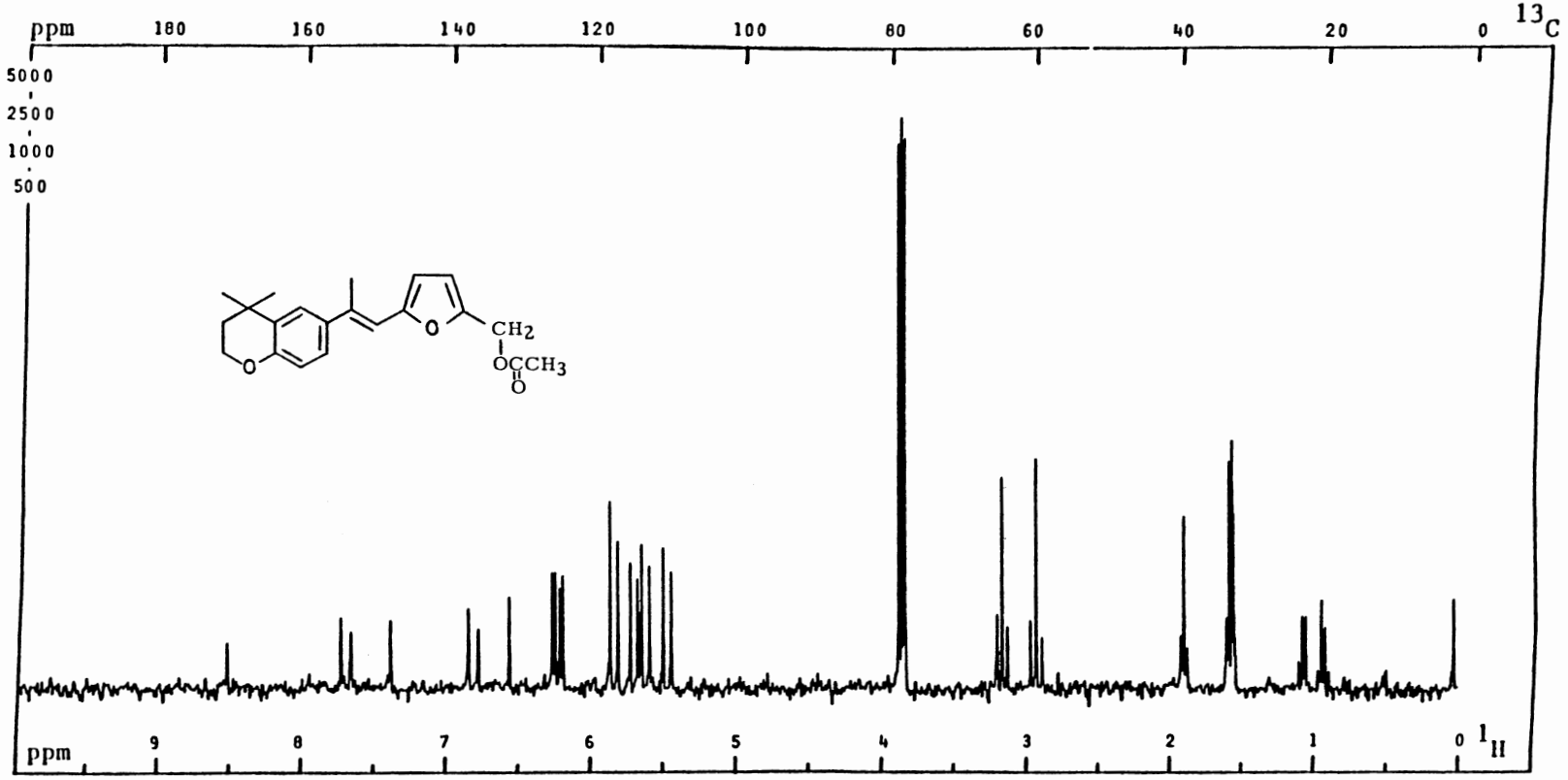
^{13}C NMR Spectrum of 60g

PFT _XCW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9Hz; T: RT °C; NT: 800 .

Size: 20 K; PW/RF: 12.0 µs/dB; TO: 1000 Hz; FB: - Hz; Lock: ^2H ; D1,D5: 4.000 s.

DC: Y ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 4.000 Hz.

PLATE XXXII



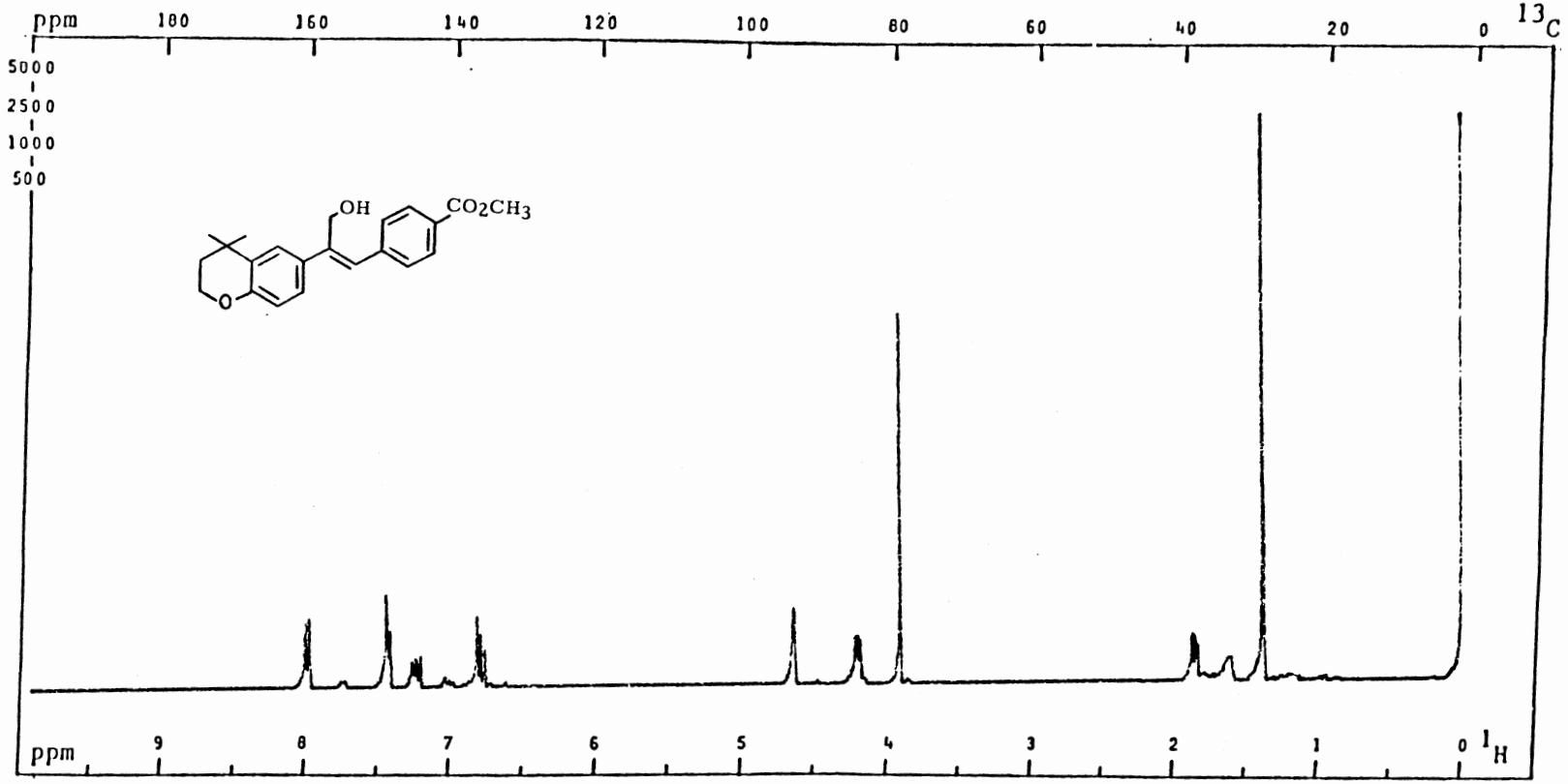
Off Resonance ^{13}C NMR Spectrum of 60g

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 176 .

Size: 20 K; PW/RF: 12.5 µs/dB; TO: 1000 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 4.000 s.

DC: Y ; Gated Off: A or D ; DO: -2500.0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 2.500 Hz.

PLATE XXXIII



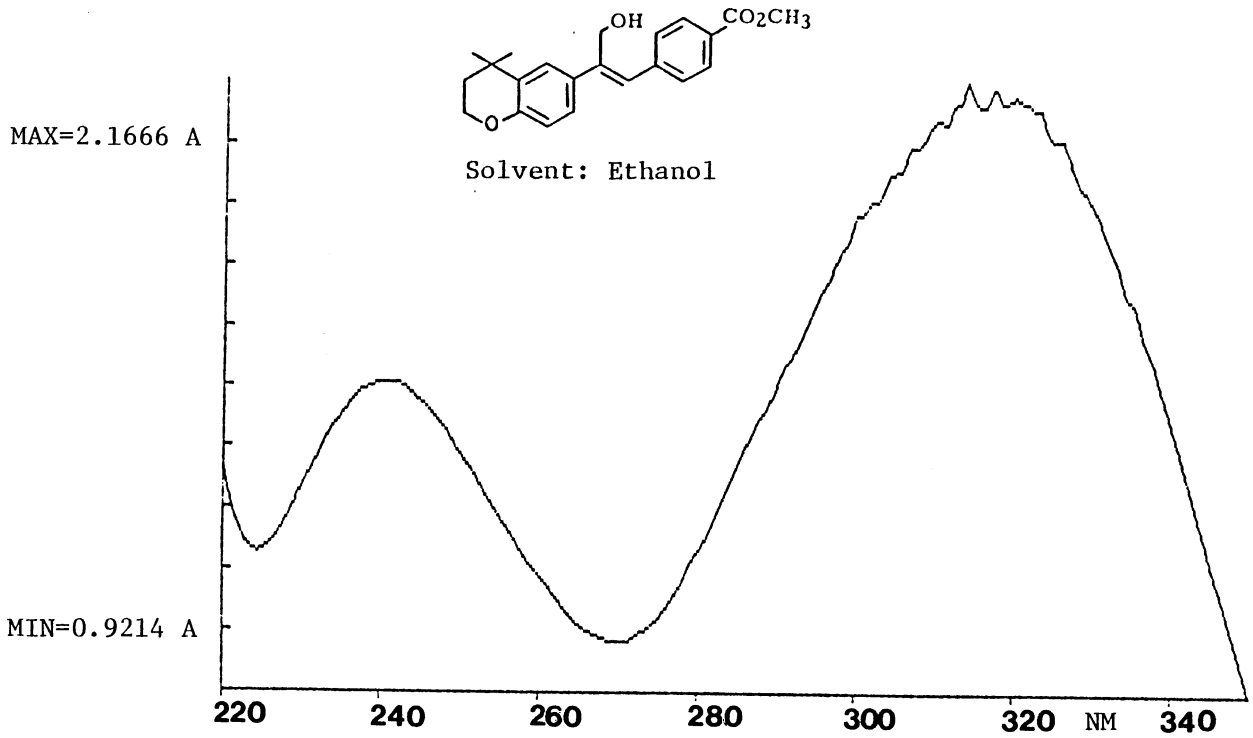
^{1}H NMR Spectrum of 60h

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 2999.4 Hz; T: RT °C; NT: 44 .

Size: 16 K; PW/RF: 5.0 μs/dB; TO: 0 Hz; FB: _ Hz; Lock: ^{2}H ; D1,D5: 0 s.

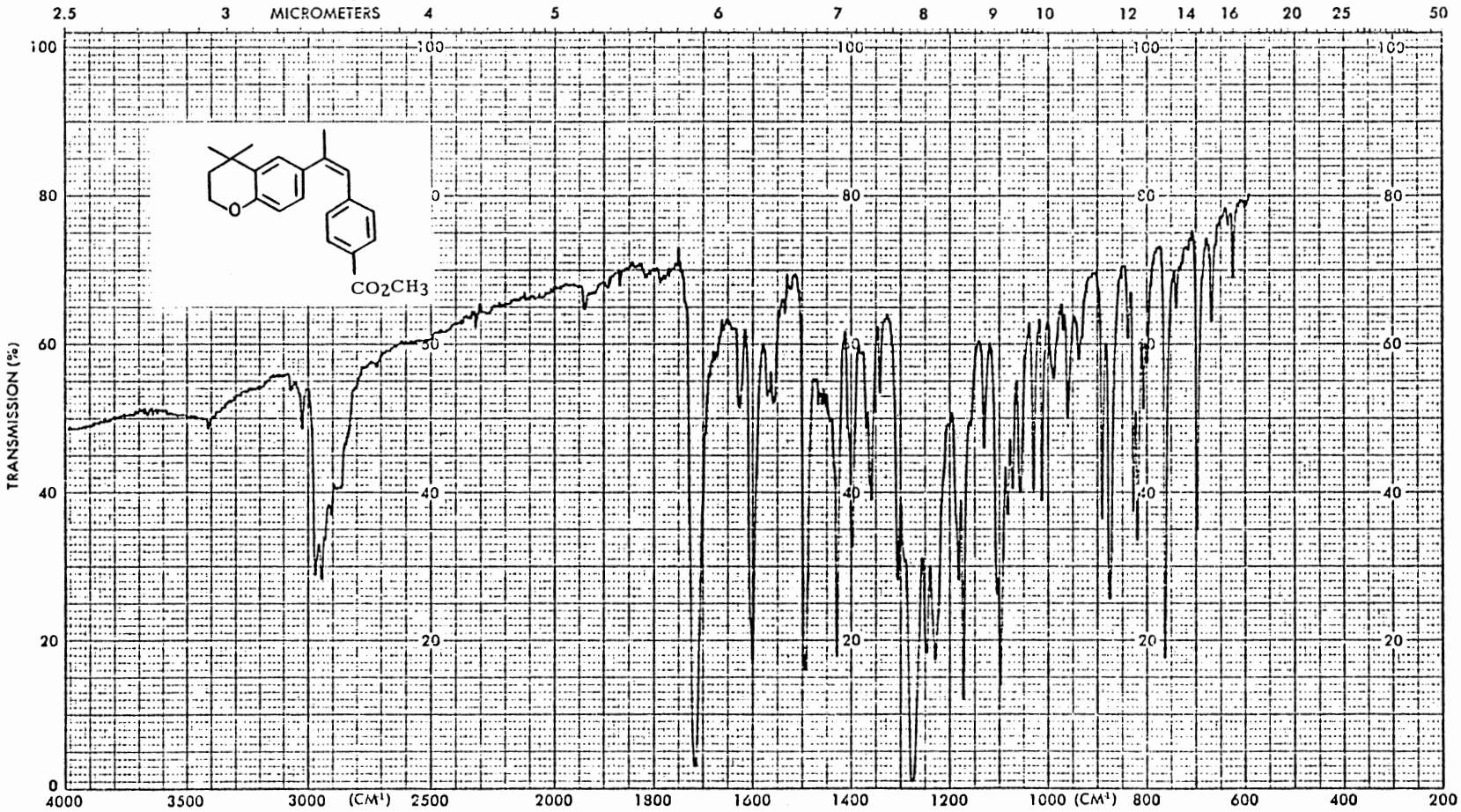
DC: N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: Hz; LB: 0 Hz.

PLATE XXIV



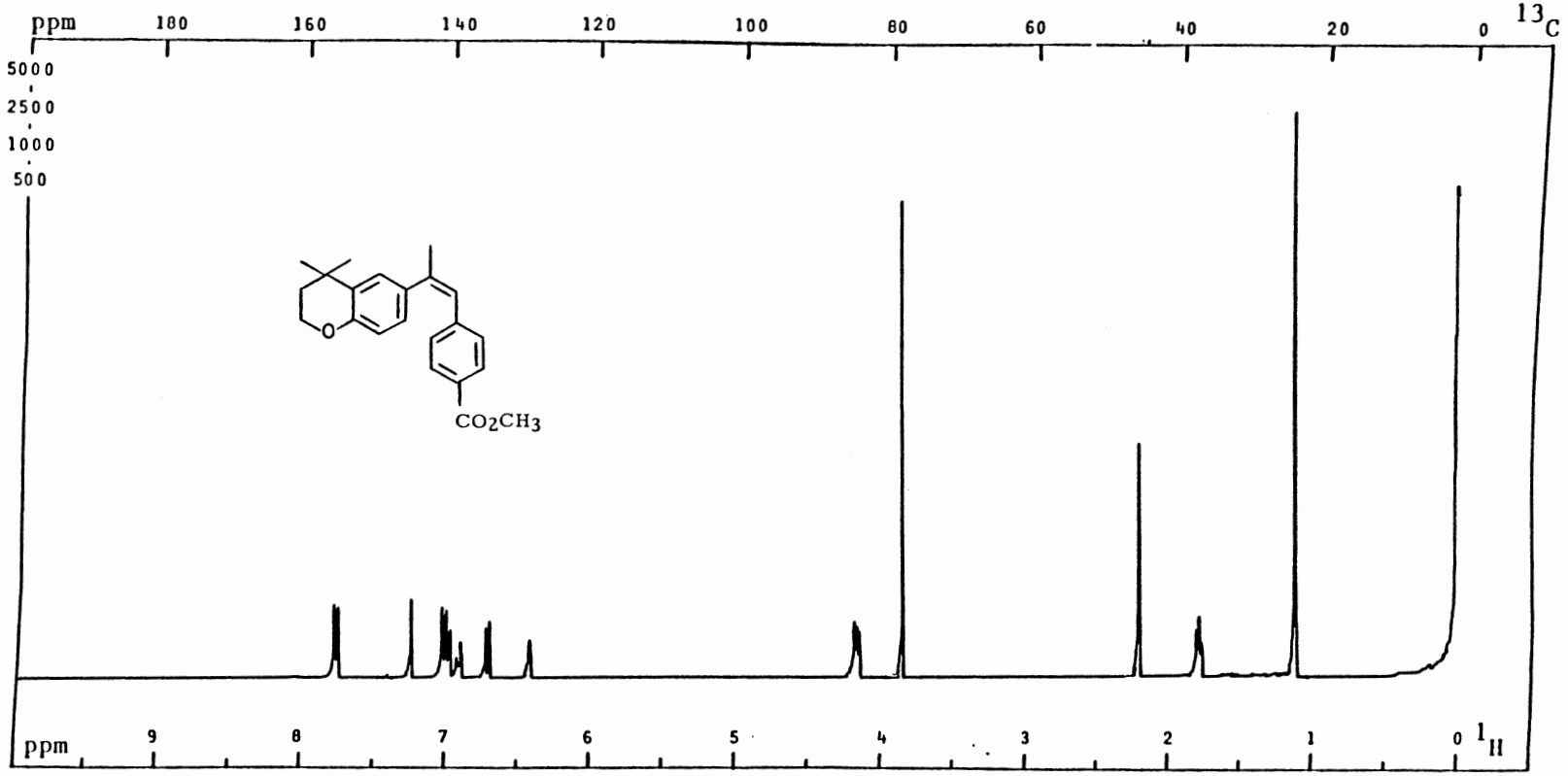
UV Spectrum of 60h

PLATE XXXV



IR Spectrum of 60i

PLATE XXXVI



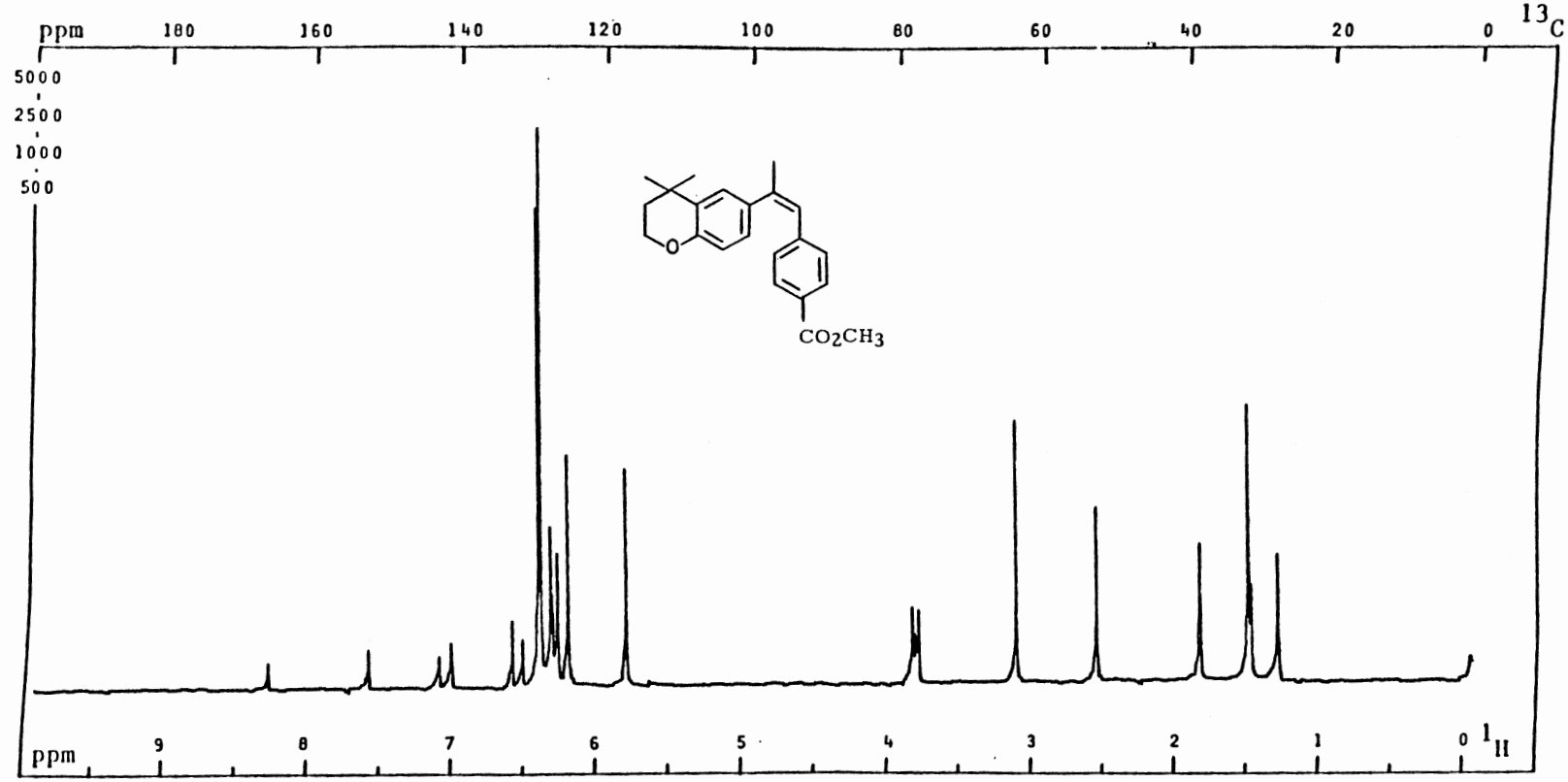
^{1}H NMR Spectrum of 60i

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 2999.4 Hz; T: RT °C; NT: 16 .

Size: 12 K; PW/RF: 5.0 µs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 0 s.

DC: N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 12 W/dB; NBW: 200 Hz; LB: 0 Hz.

PLATE XXXVII



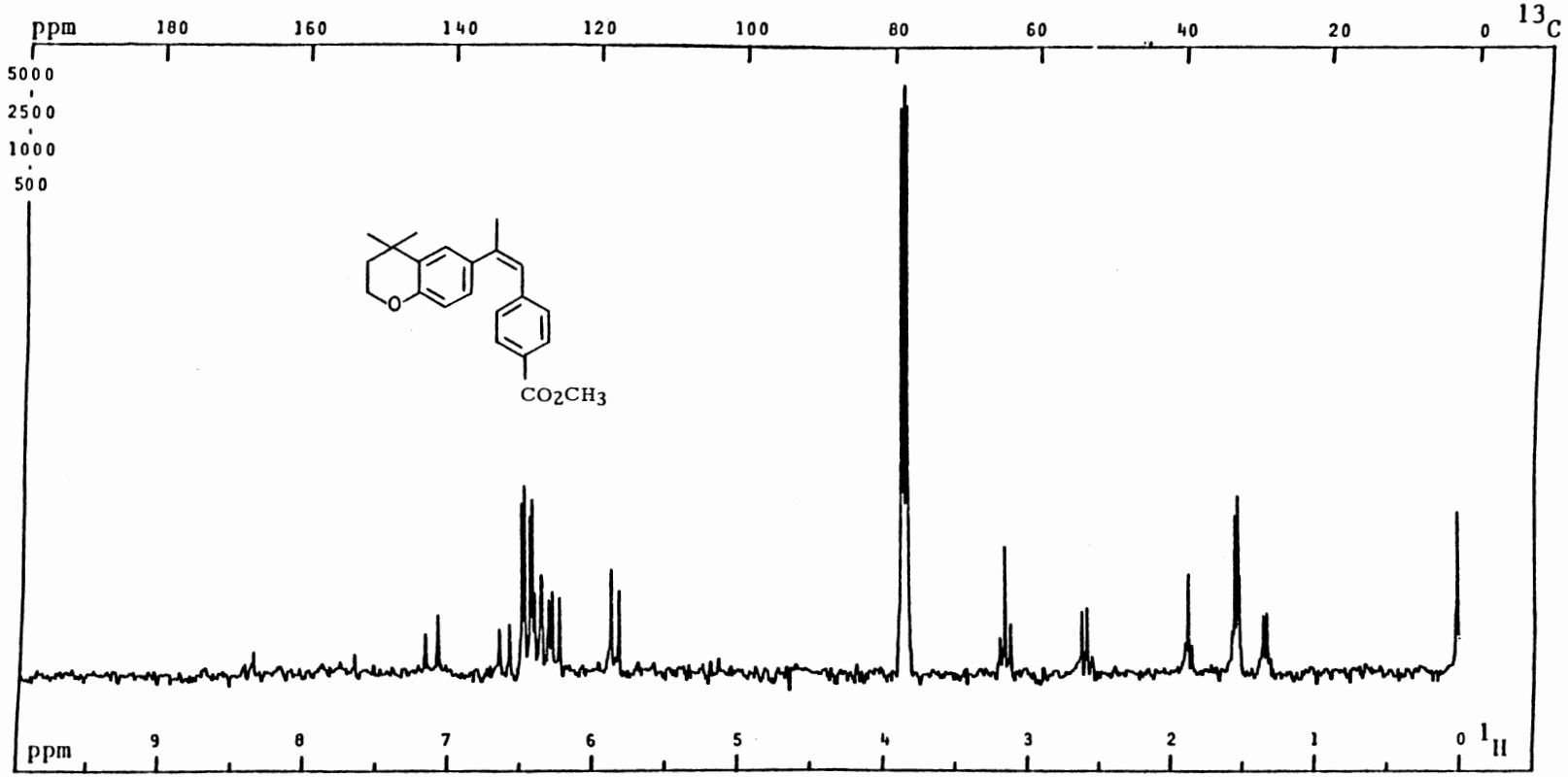
^{13}C NMR Spectrum of 60i

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 96

Size: 8 K; PW/RF: 14.0 μs/dB; TO: 1000 Hz; FB: - Hz; Lock: ^2H ; D1,D5: 4.000 s.

DC: Y ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 2.000 Hz.

PLATE XXXVIII



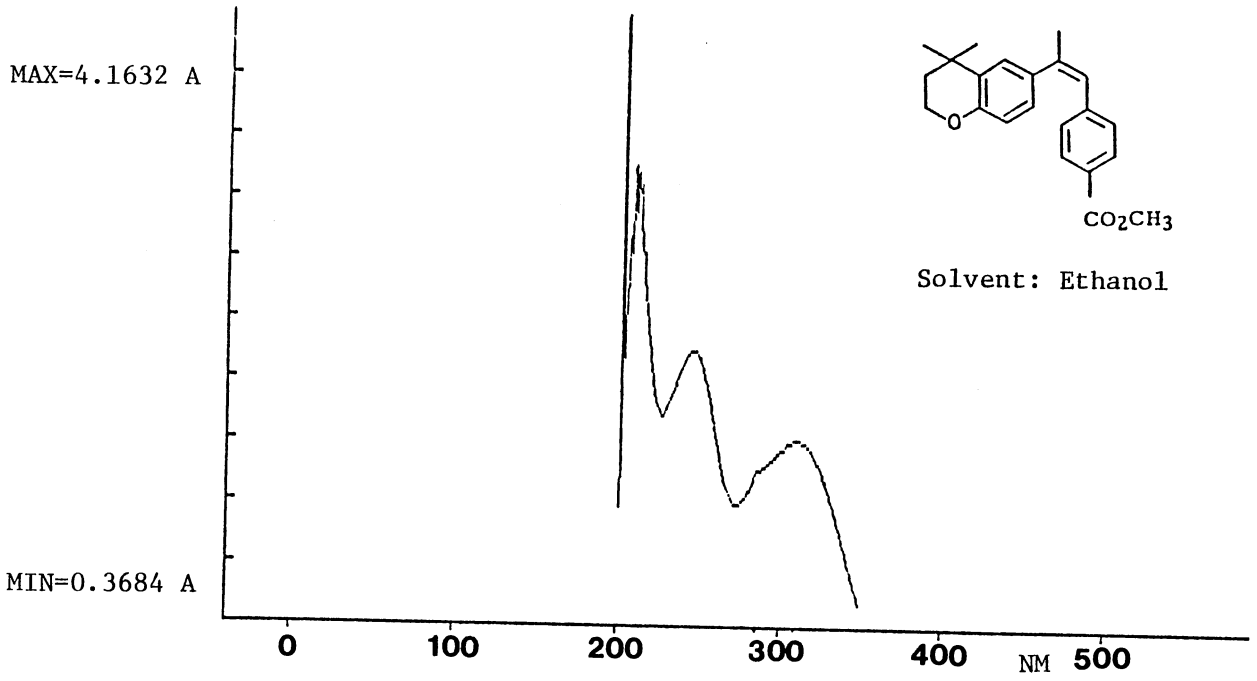
Off Resonance ^{13}C NMR Spectrum of 60i

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 820 .

Size: 16 K; PW/RF: 12.5 μs/dB; TO: 1000 Hz; FB: - Hz; Lock: ^2H ; D1,D5: 4.000 s.

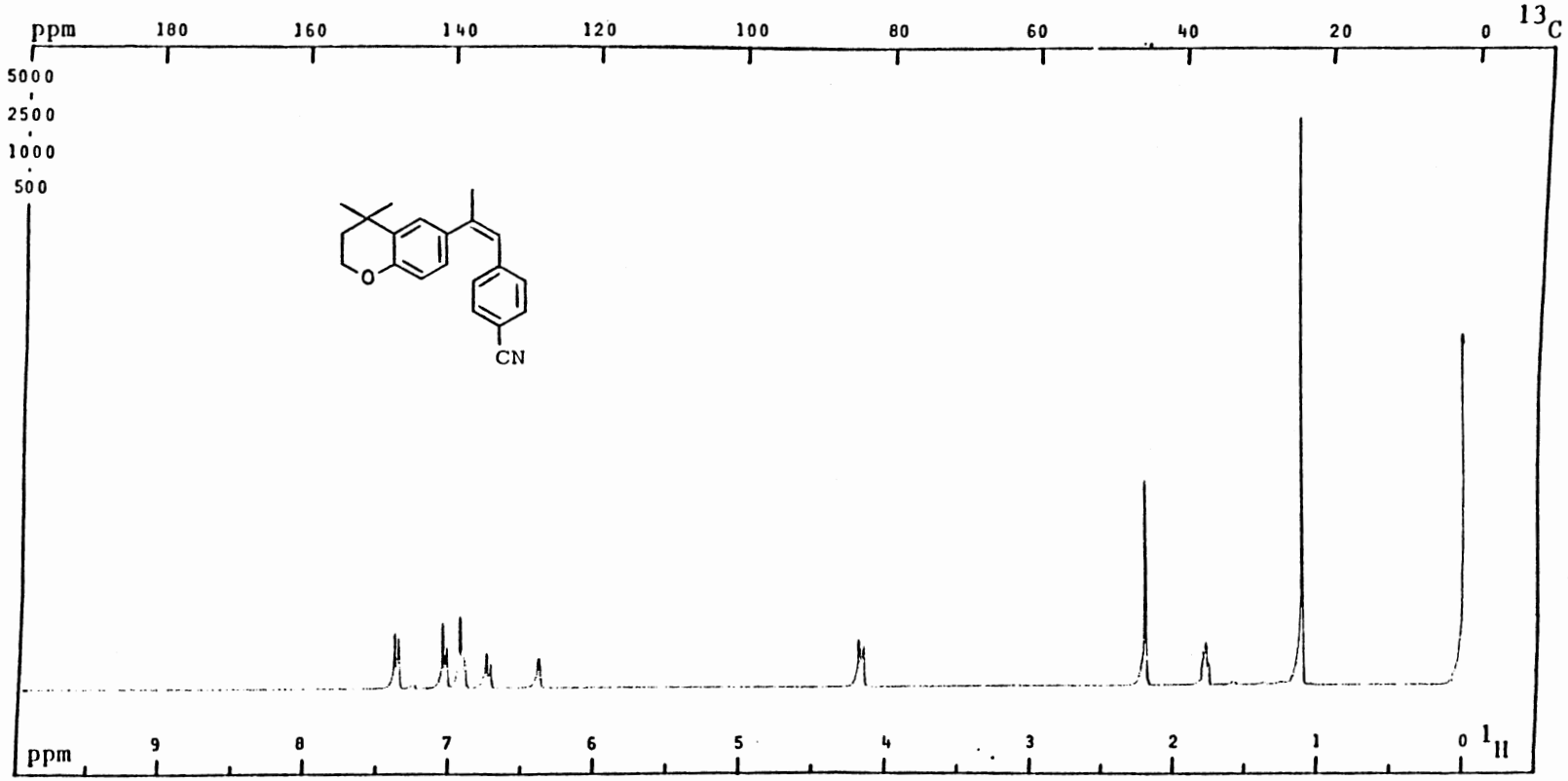
DC: Y ; Gated Off: A or D ; DO: -2500.0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 4.000 Hz.

PLATE XXXIX



UV Spectrum of 60i

PLATE XL



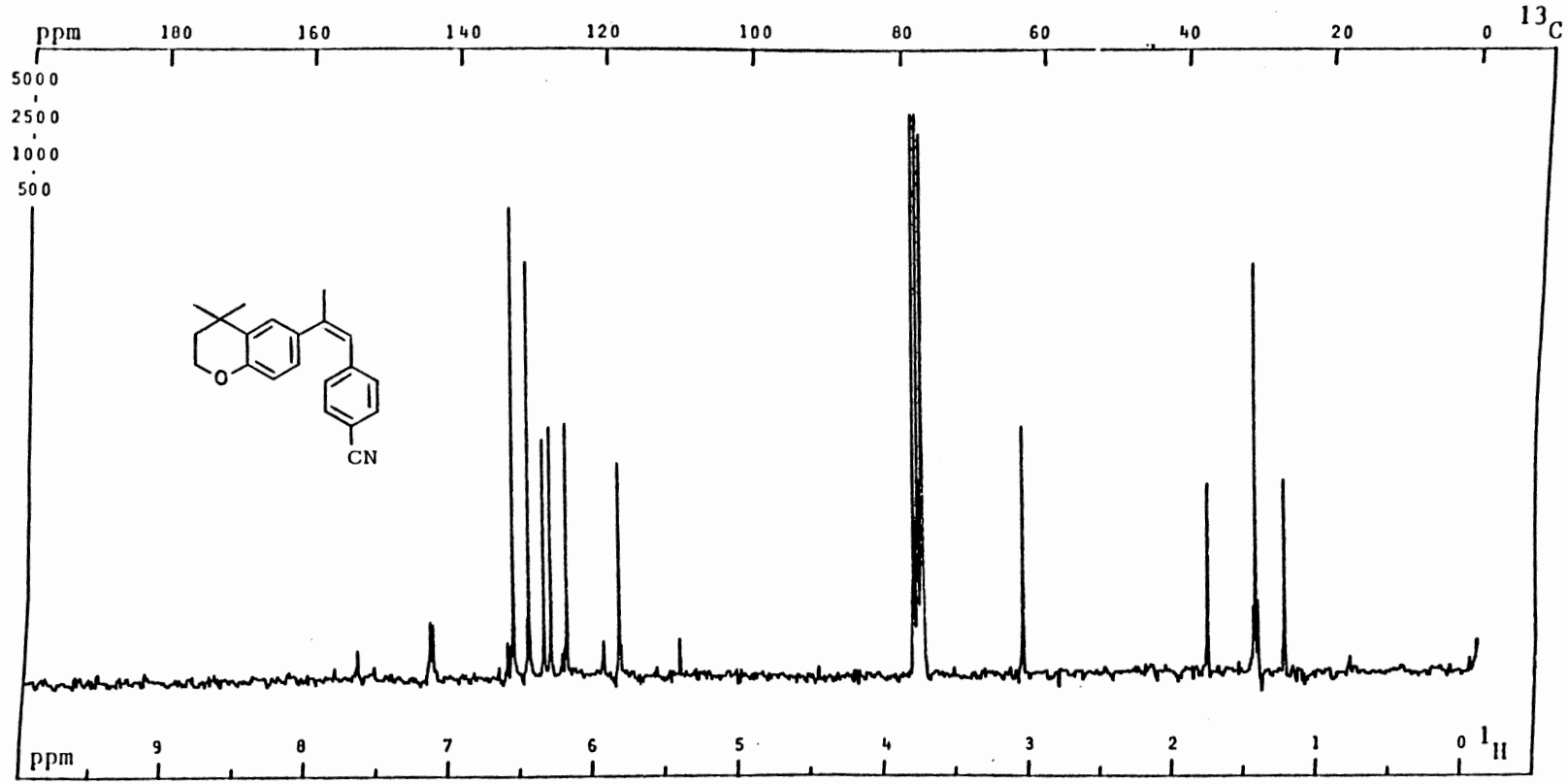
^{1}H NMR Spectrum of 60j

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 2999.4 Hz; T: RT °C; NT: 16

Size: 8 K; PW/RF: 5.0 µs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 0.500 s.

DC: N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 8 W/dB; NBW: 200 Hz; LB: 0 Hz.

PLATE XLI



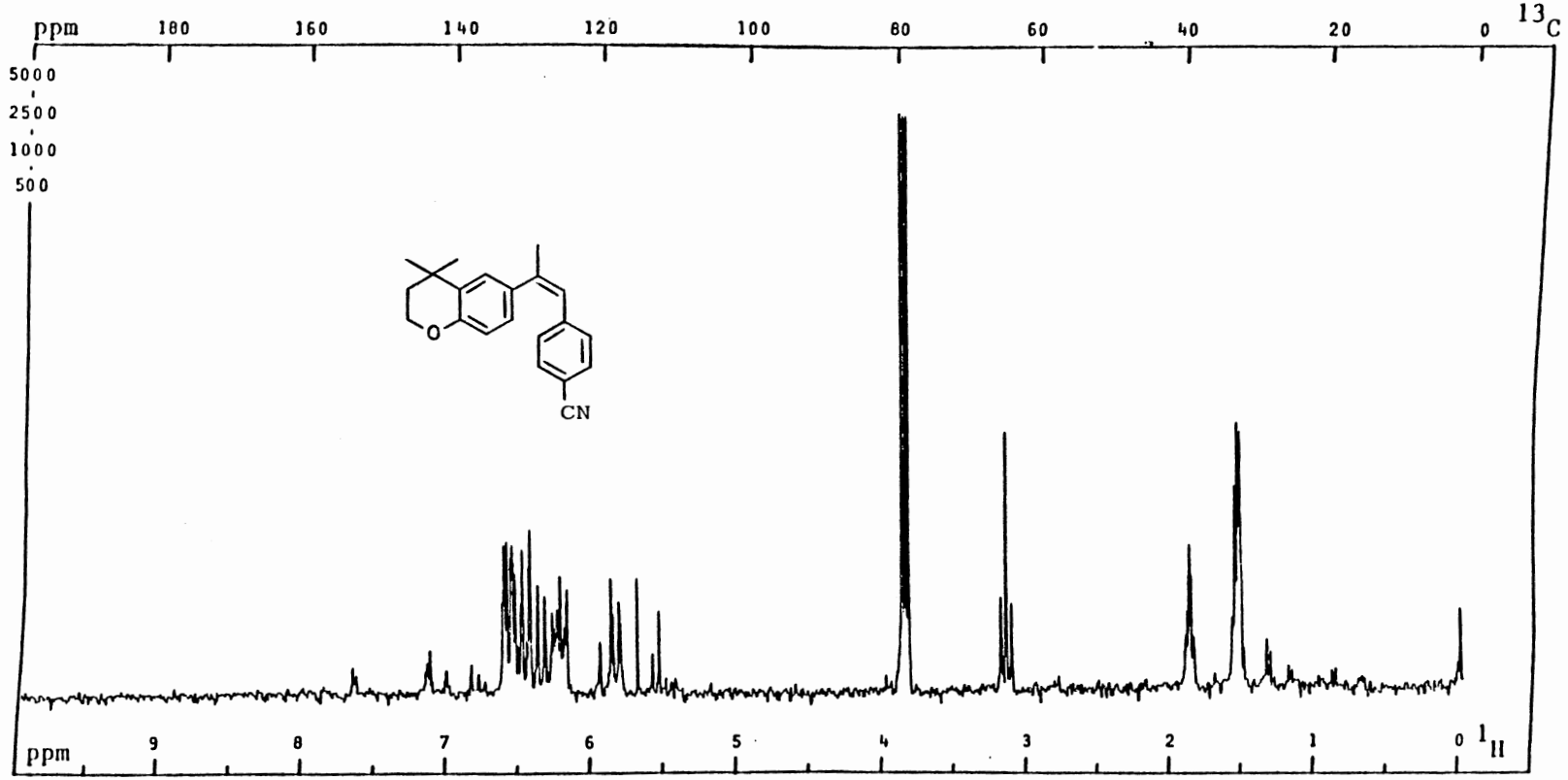
^{13}C NMR Spectrum of 60j

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 400

Size: 12 K; PW/RF: 14.0 µs/dB; TO: 1000 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 4.000 s.

DC: Y ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 2.000 Hz.

PLATE XLII



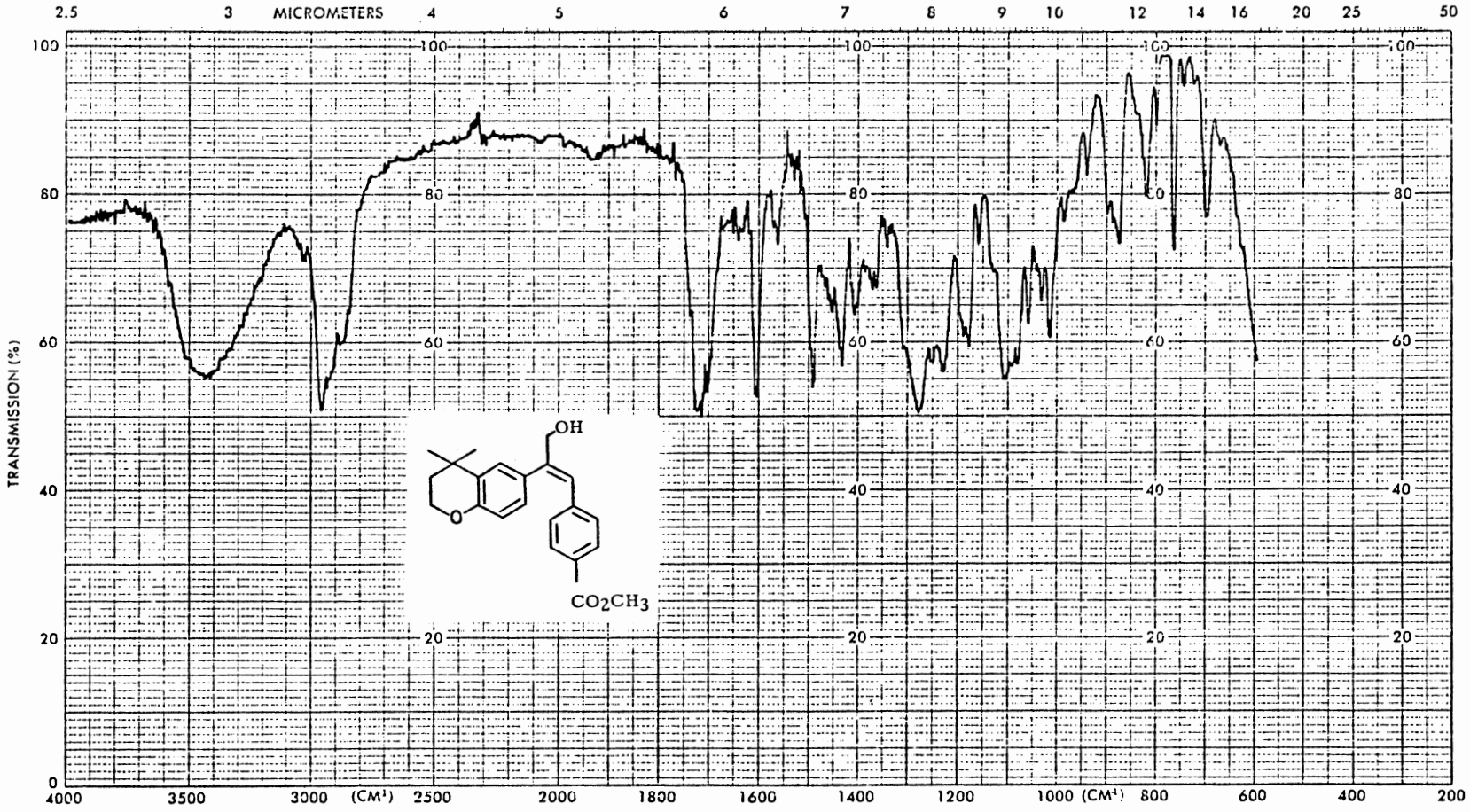
Off Resonance ^{13}C NMR Spectrum of 60j

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 720 .

Size: 16 K; PW/RF: 14.0 µs/dB; TO: 1000 Hz; FB: - Hz; Lock: ^2H ; D1,D5: 4.000 s.

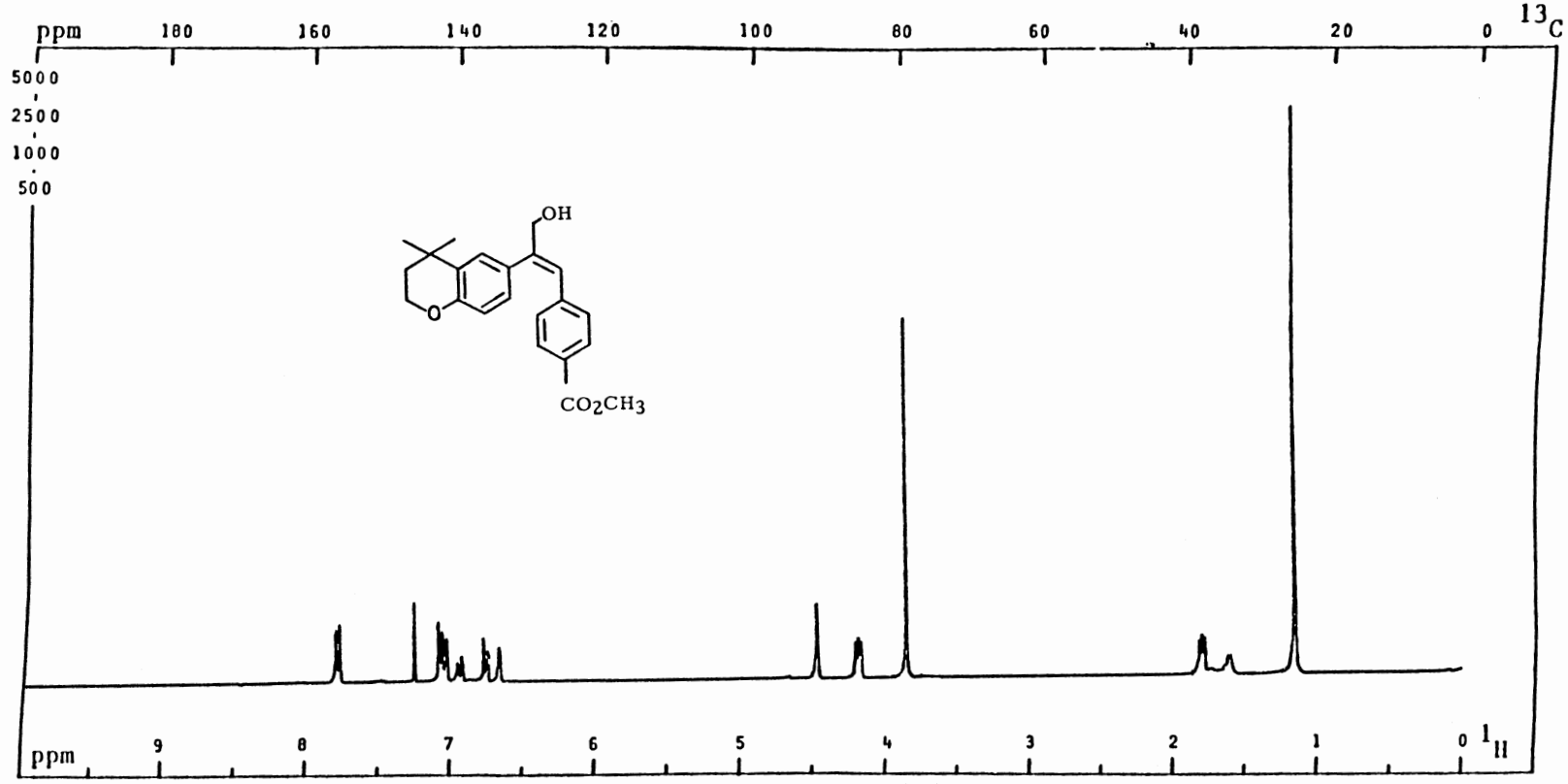
DC: Y ; Gated Off: A or D ; DO: -2500.0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 2.000 Hz.

PLATE XLIII



IR Spectrum of 60k

PLATE XLIV



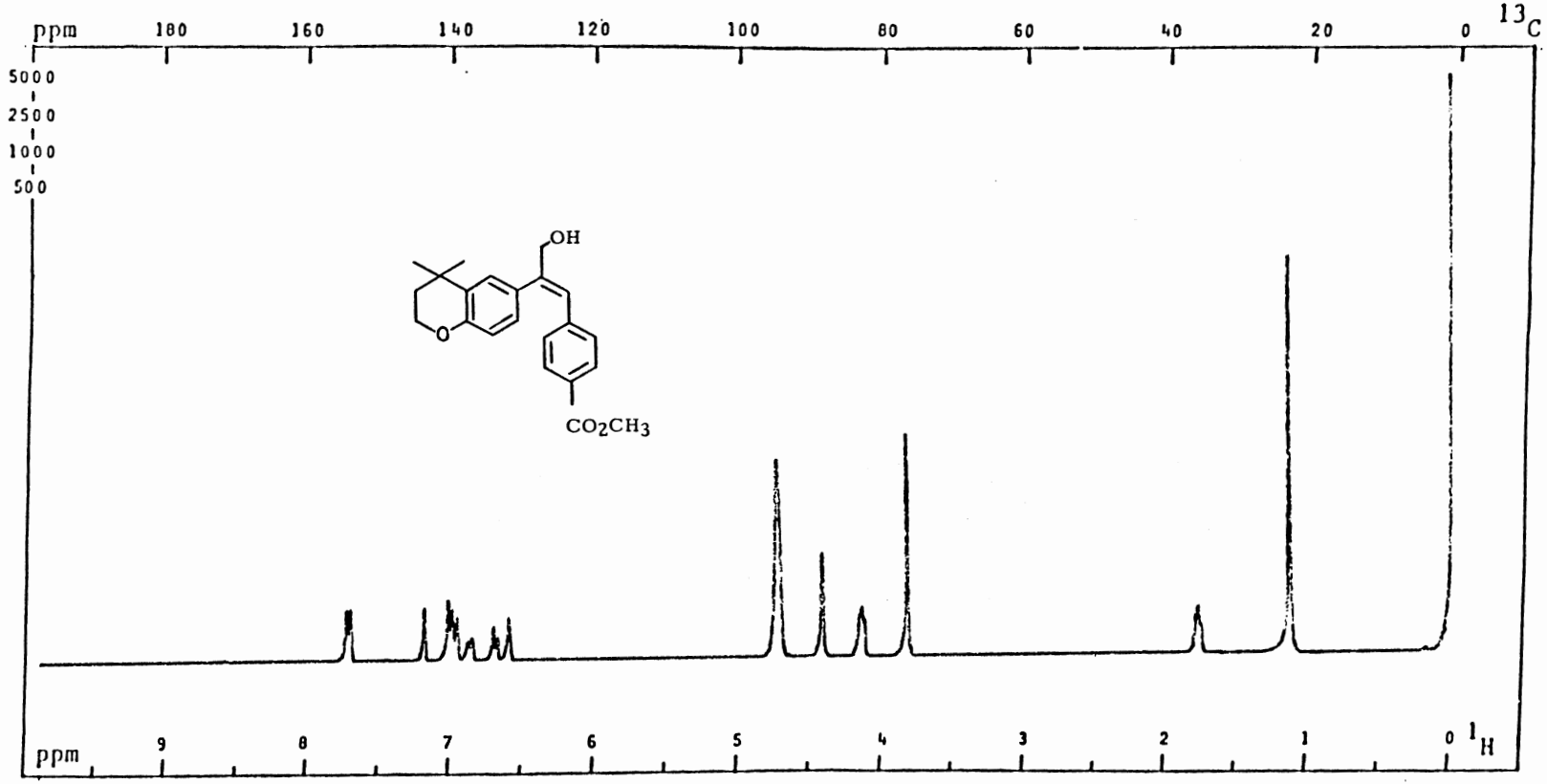
^{1}H NMR Spectrum of 60k

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 2999.4 Hz; T: RT °C; NT: 8 .

Size: 12 K; PW/RF: 5.0 μs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 0 s.

DC: N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: Hz; LB: 0 Hz.

PLATE XLV



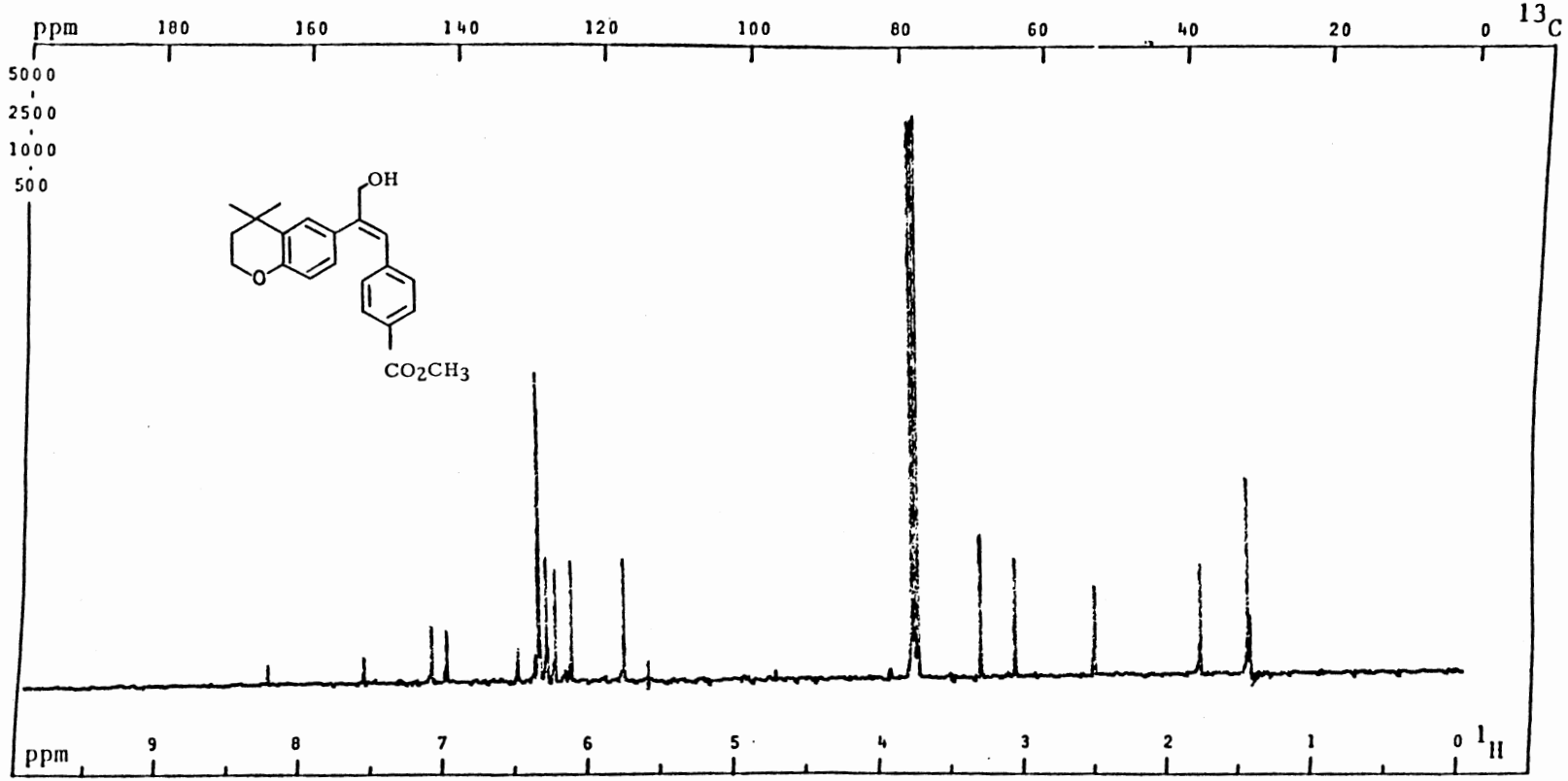
^{1}H NMR Spectrum (Deuterium Exchange) of 60k

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC:2999.4 Hz; T: RT °C; NT: 120 .

Size: 16 K; PW/RF: 5.0 µs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 0 s.

DC: N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: Hz; LB: Hz.

PLATE XLVI



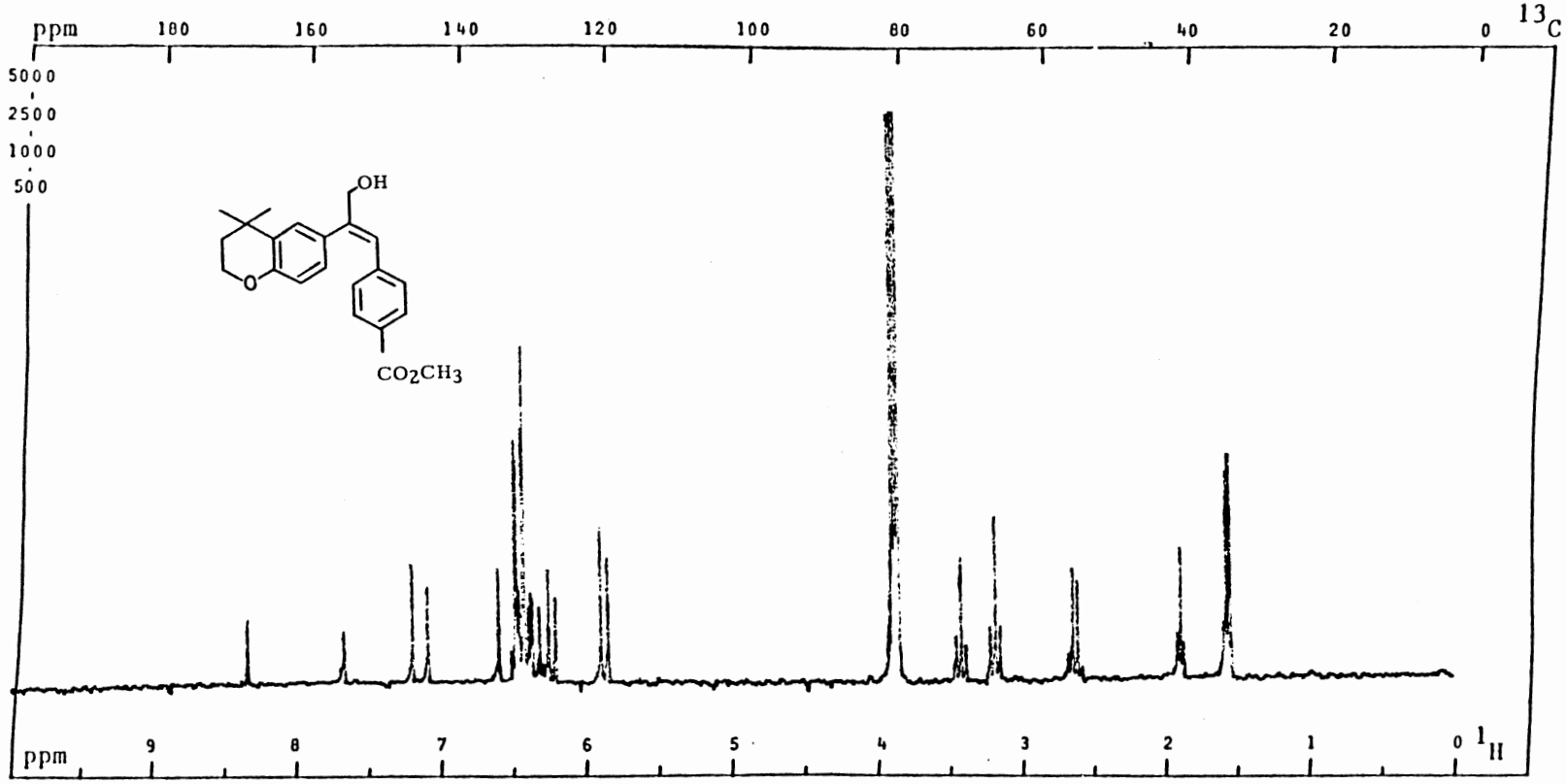
^{13}C NMR Spectrum of 60k

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 1496 .

Size: 20 K; PW/RF: 12.0 µs/dB; TO: 1000 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 4.000 s.

DC: Y ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 1.000 Hz.

PLATE XLVII



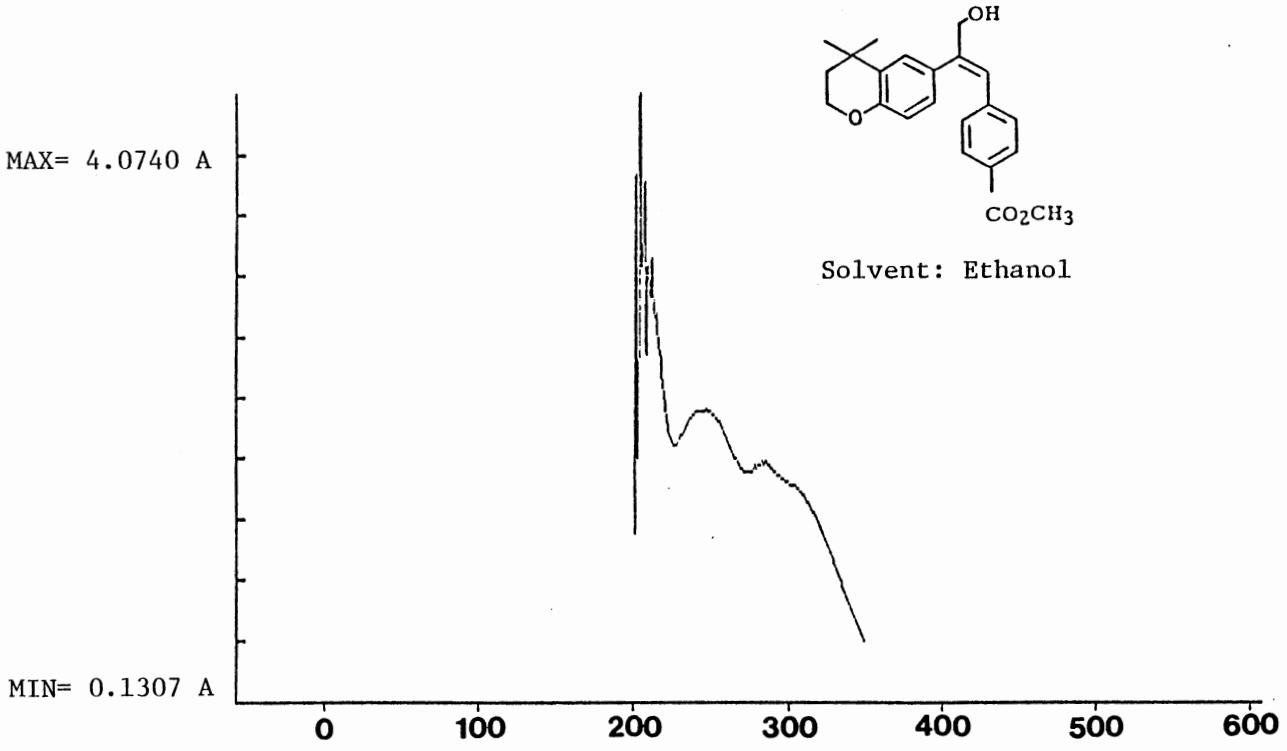
Off Resonance ^{13}C NMR Spectrum of 60k

PFT _X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC:15085.9 Hz; T: RT °C; NT: 9300

Size: 20 K; PW/RF: 12.0 μs/dB; TO: 1500 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 6.000 s.

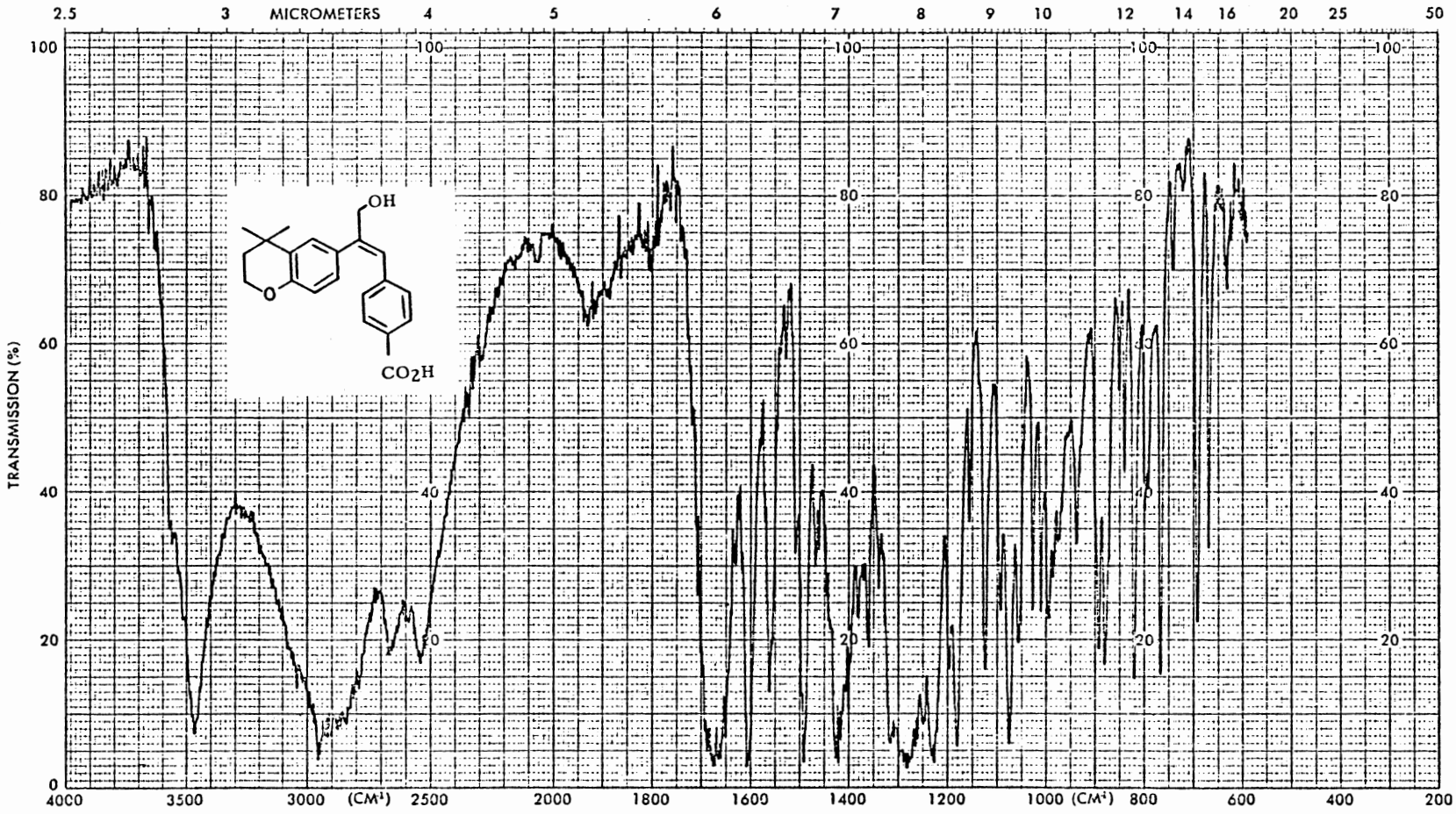
DC: Y ; Gated Off:A or D ; DO: -2500.0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 2.000 Hz.

PLATE XLVIII



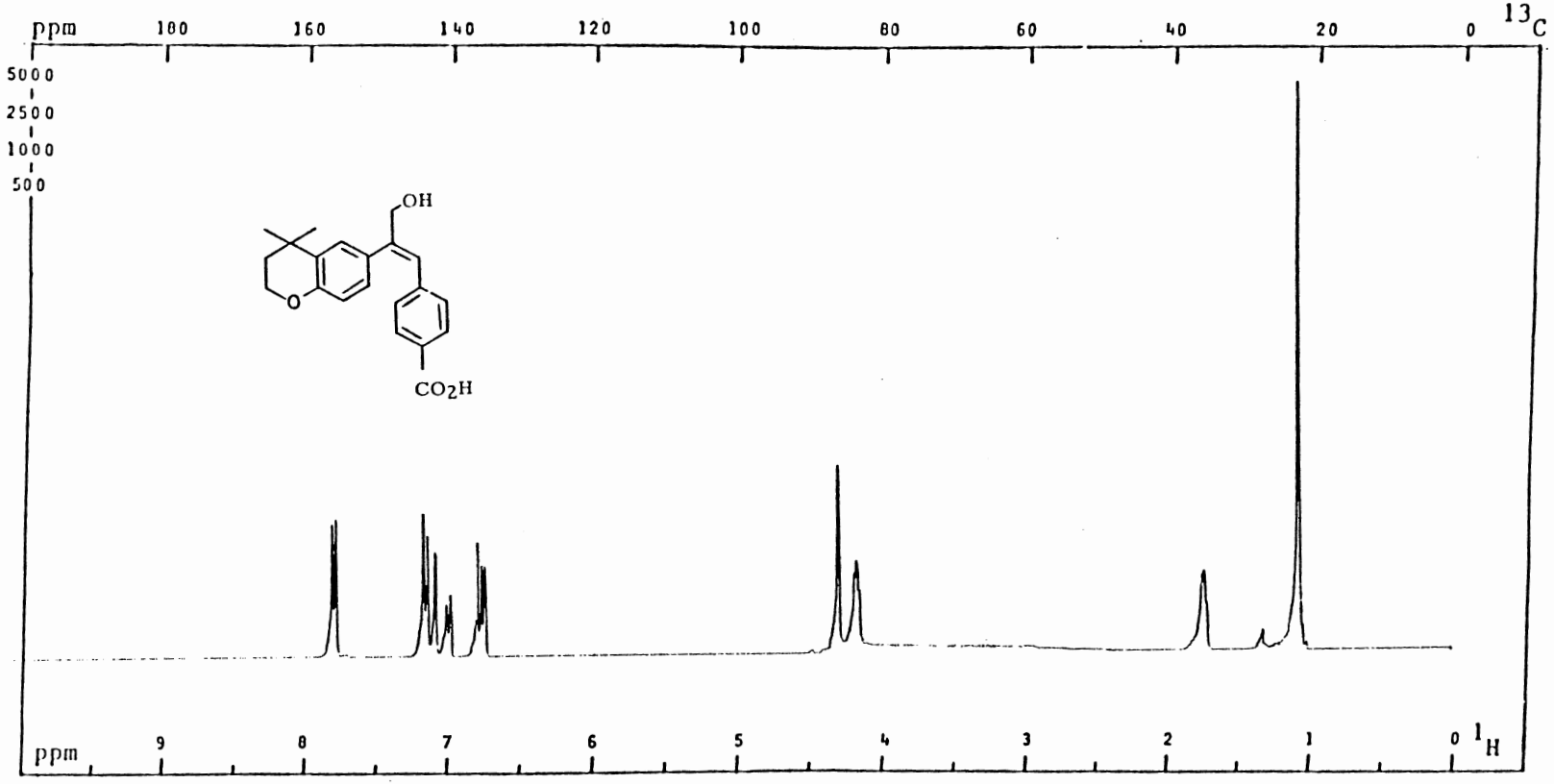
UV Spectrum of 60k

PLATE XLIX



IR Spectrum of 601

PLATE L



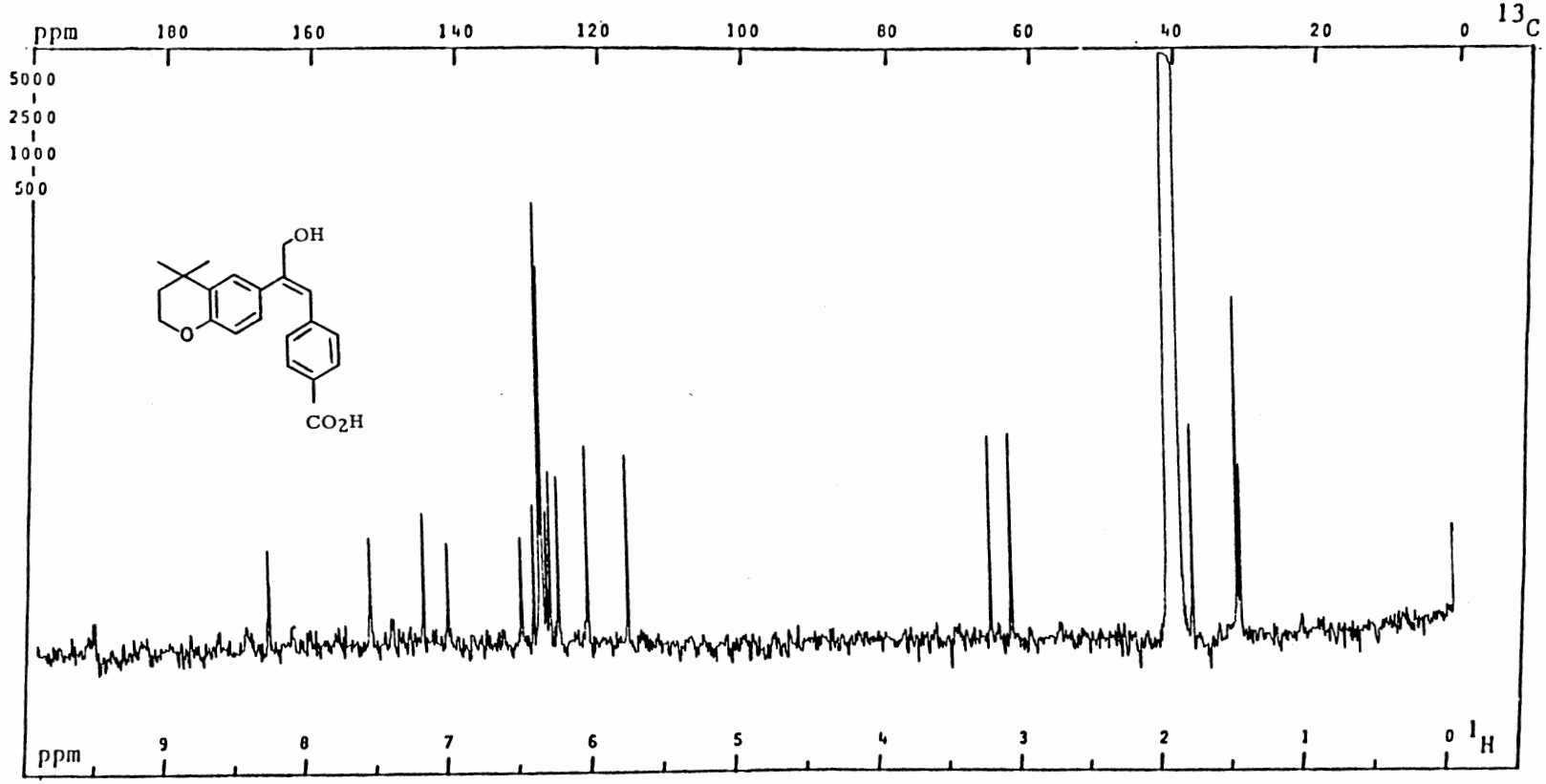
^{1}H NMR Spectrum of 601

PFT X CW _ ; Solvent: DMSO-d_6 ; SF: 299.944 MHz; WC: 2999.4 Hz; T: RT °C; NT: 12 .

Size: 12 K; PW/RF: 4.0μs/dB; TO: 1500 Hz; FB: _ Hz; Lock: ^{2}H ; D1,D5: 0 s.

DC: N ; Gated Off:A or D ; DO: Hz; RF(Power): W/dB; NBW: Hz; LB: Hz.

PLATE LI



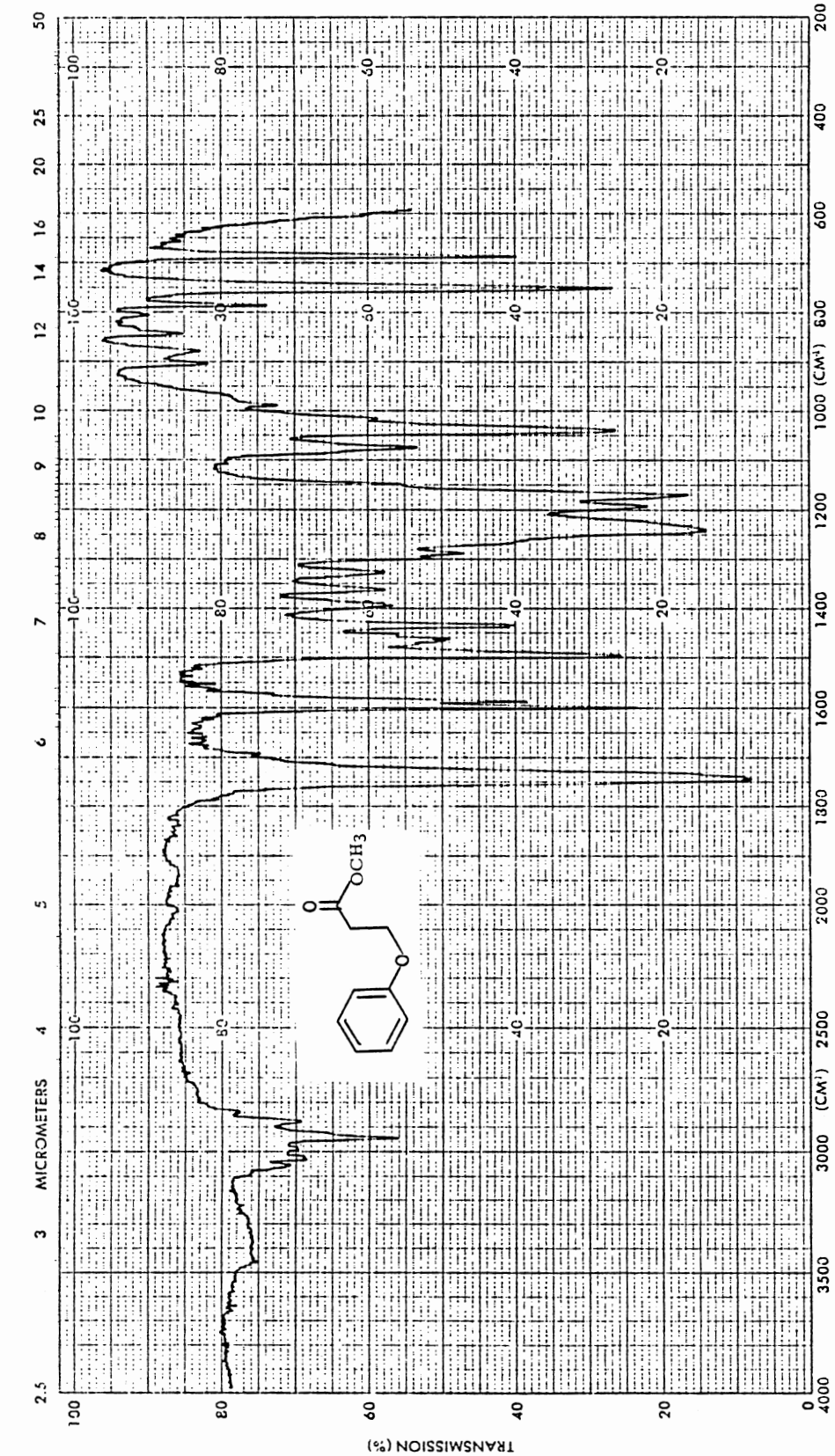
^{13}C NMR Spectrum of 601

PFT _X_CW _ ; Solvent: DMSO-d_6 ; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 4152 .

Size: 8K; PW/RF: 14.0 µs/dB; TO: 1500 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 5.000 s.

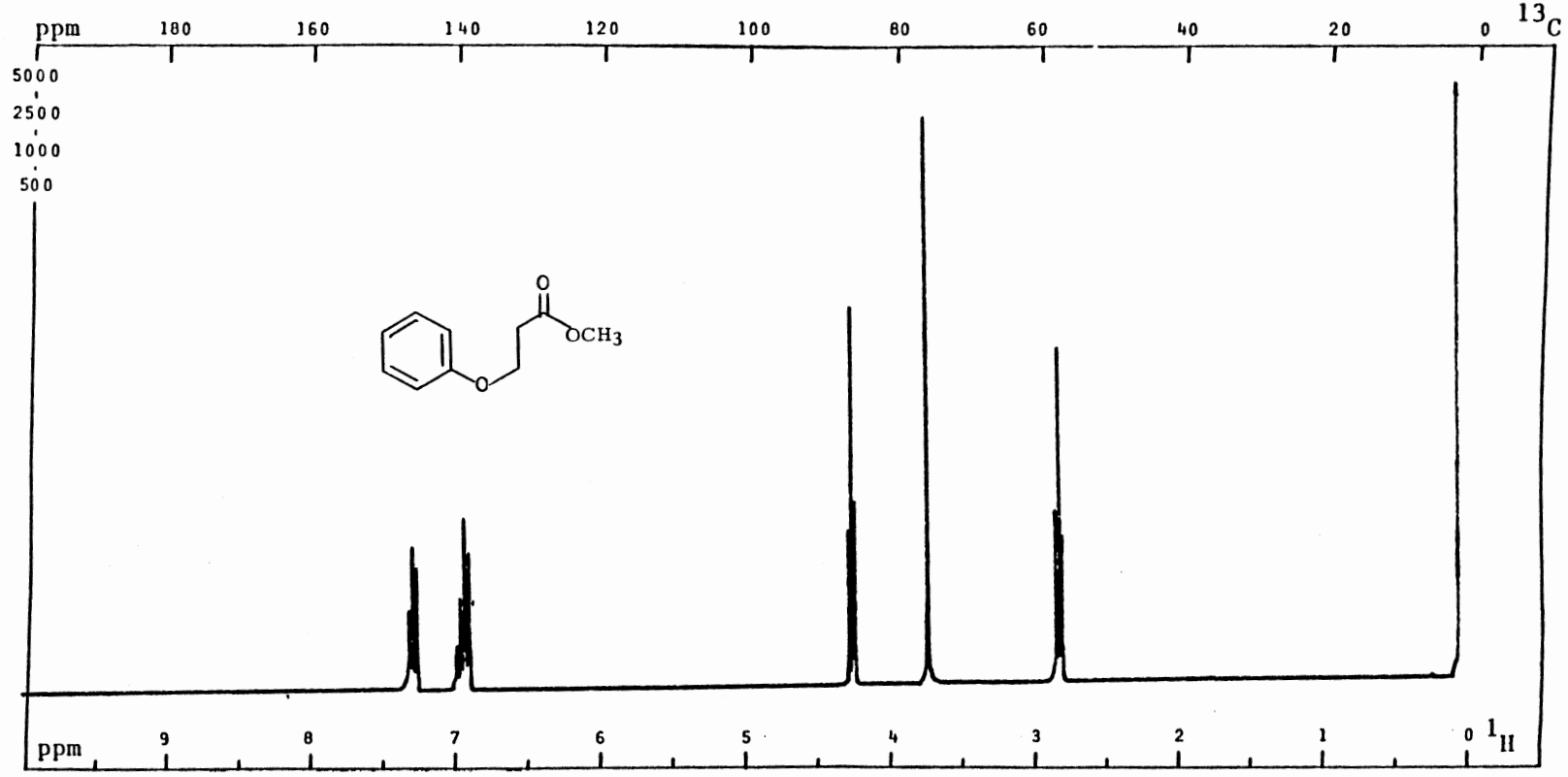
DC: N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 3.000 Hz.

PLATE LII



IR Spectrum of 62

PLATE LIII



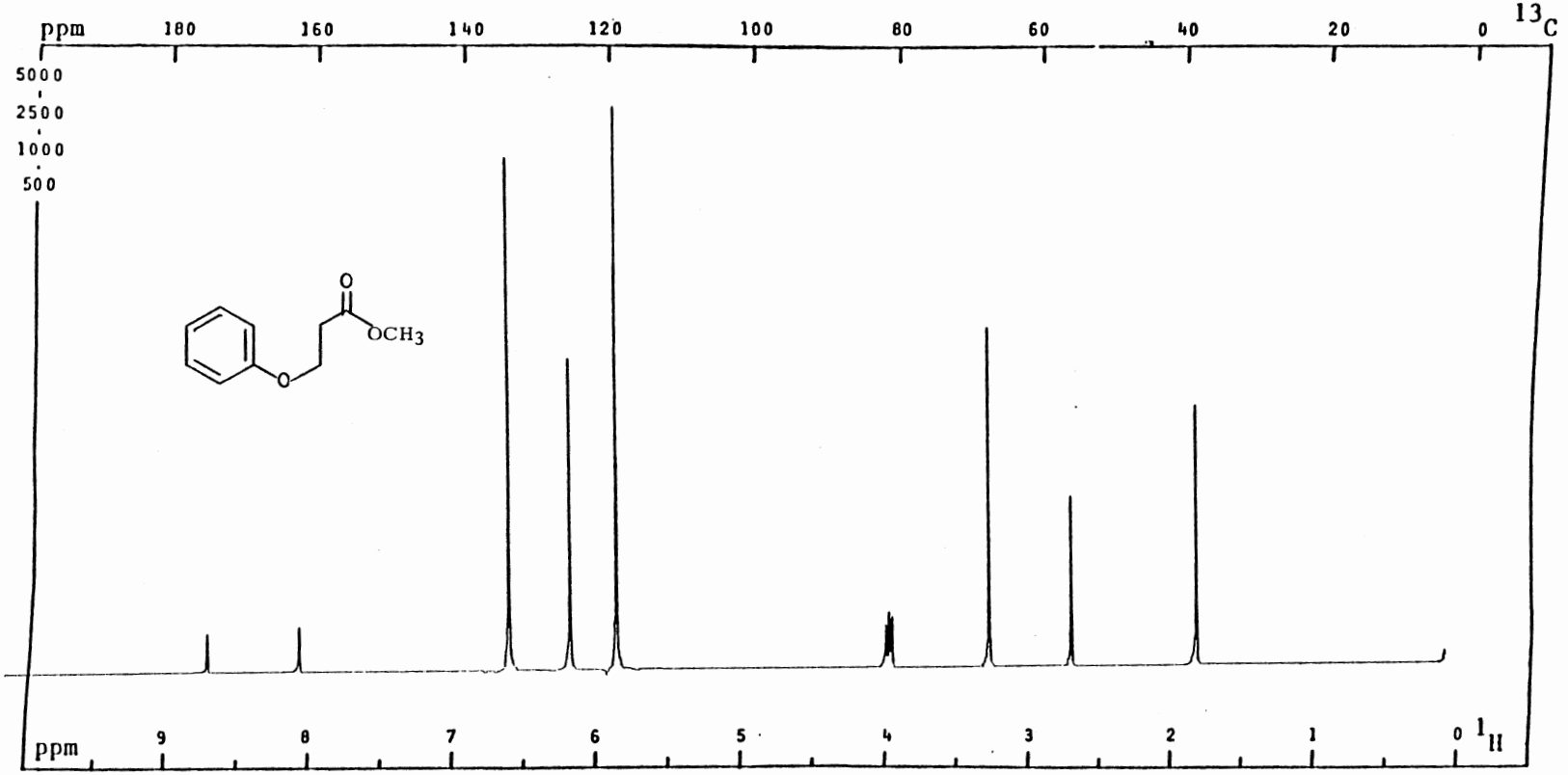
^{1}H NMR Spectrum of 62

PFTX_ CW _ : Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 2999.4 Hz; T: RT °C; NT: 8 .

Size: 8 K; PW/RF: 5.0 μs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 0 s.

DC: N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 20W/dB; NBW: Hz; LB: Hz.

PLATE LIV



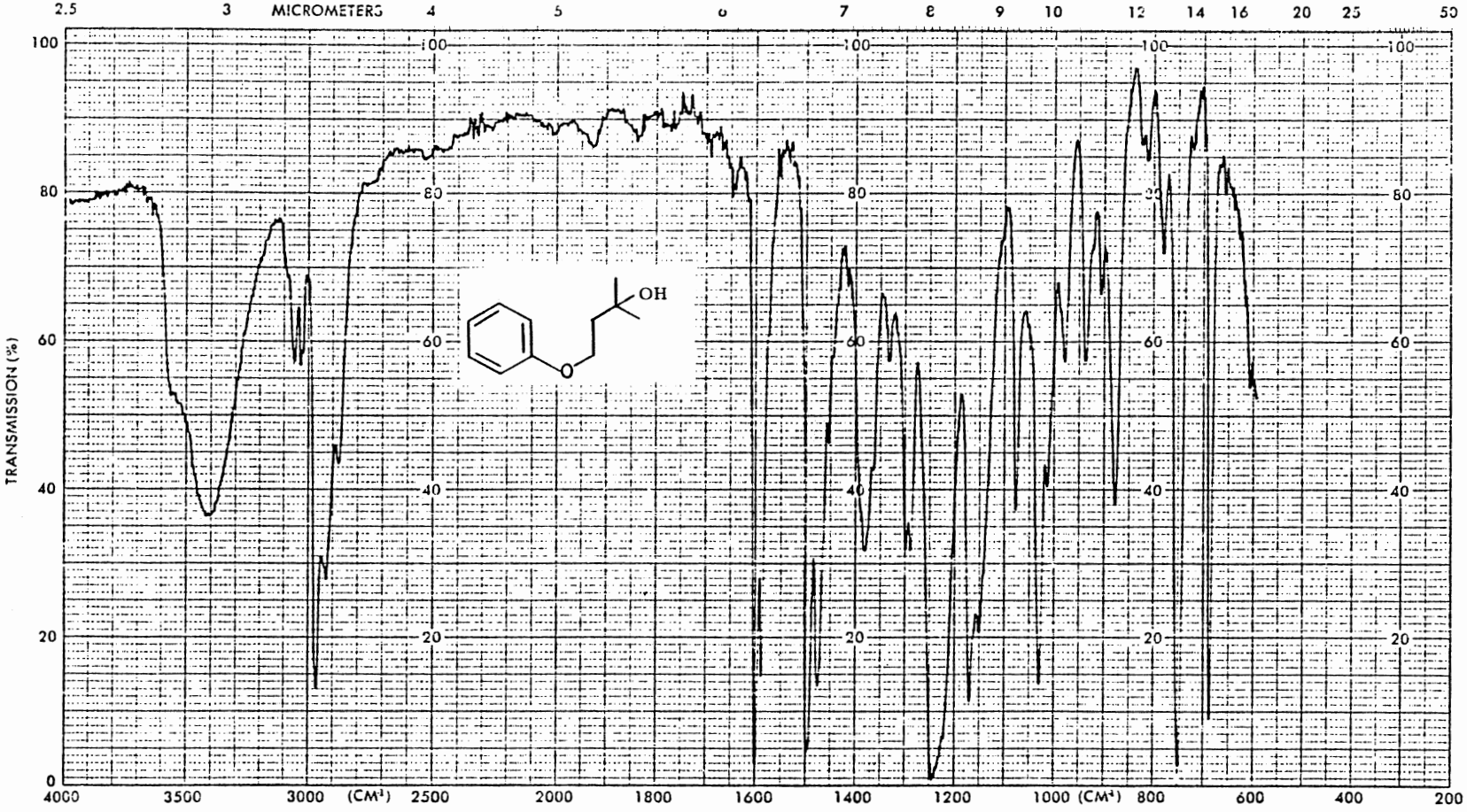
^{13}C NMR Spectrum of 62

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 132 .

Size: 16 K; PW/RF: 12.0 µs/dB; TO: 1000 Hz; FB: - Hz; Lock: ^2H ; D1,D5: 5.000 s.

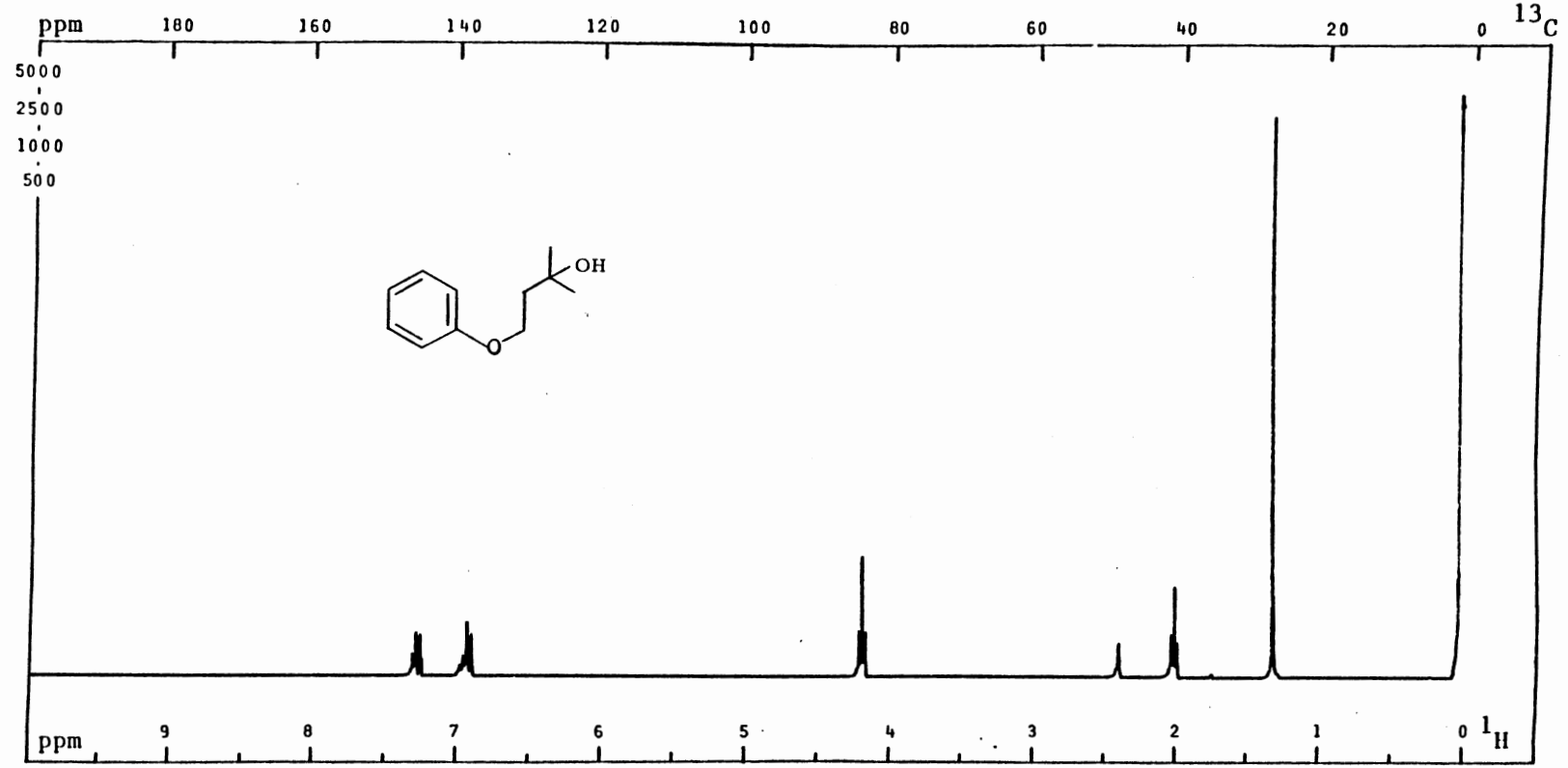
DC: Y ; Gated Off: A or D ; DO: Hz; RF(Power): W/dB; NBW: Hz; LB: 2.000 Hz.

PLATE LV



IR Spectrum of 63

PLATE LVI



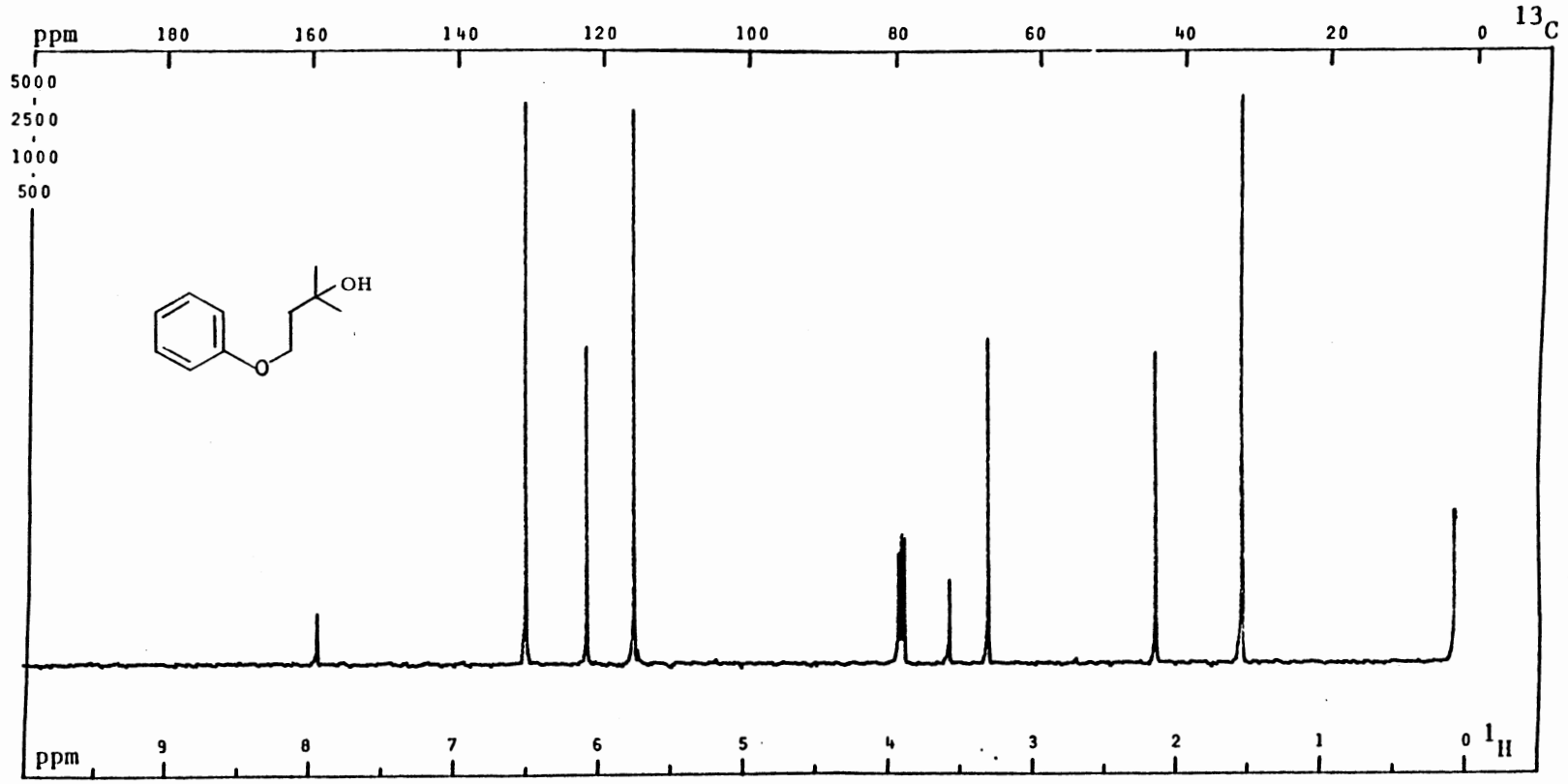
^{1}H NMR Spectrum of 63

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 2999.4 Hz; T: RT °C; NT: 8 .

Size: 8 K; PW/RF: 5.0 µs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 0 s.

DC: N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: Hz; LB: Hz.

PLATE LVII



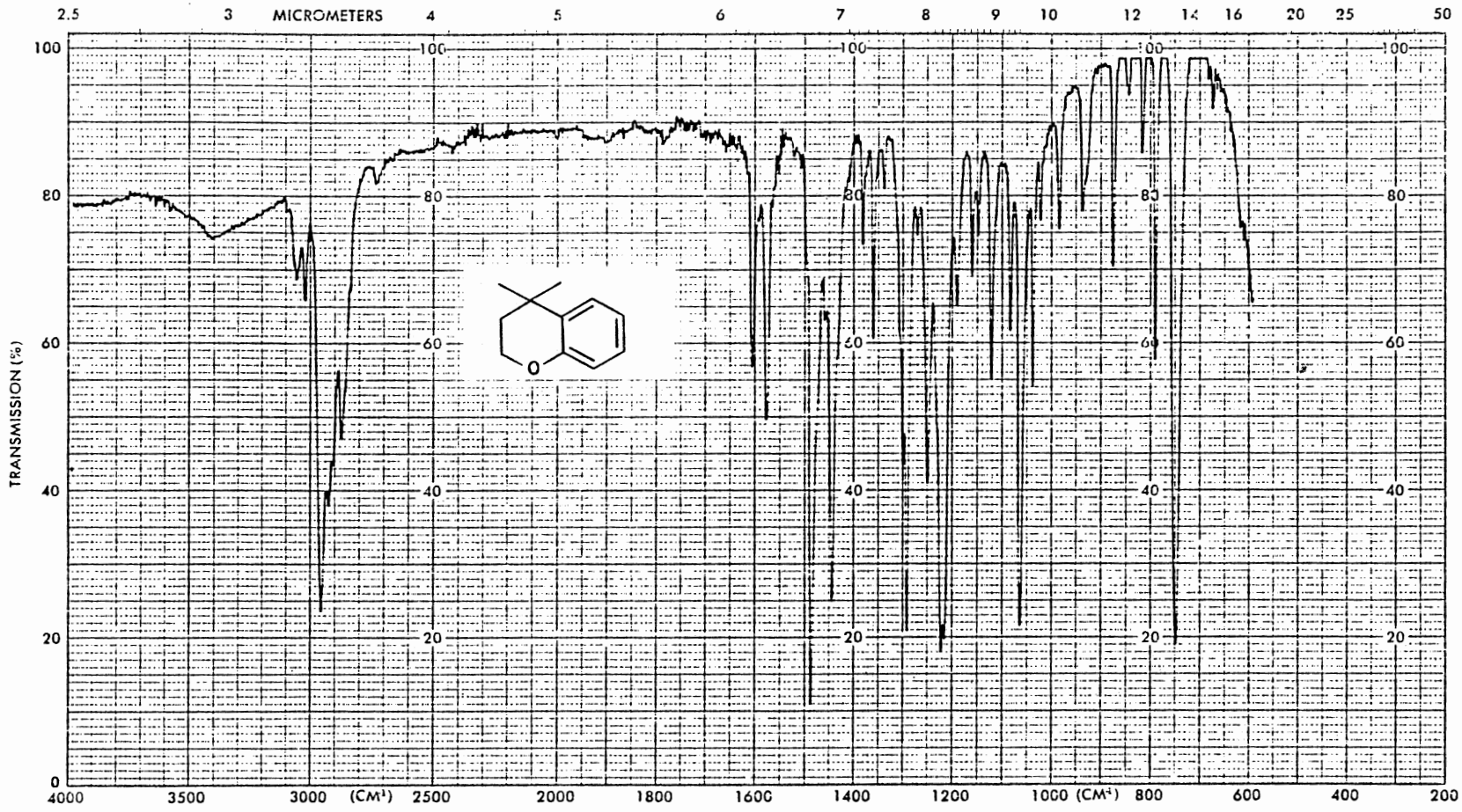
^{13}C NMR Spectrum of 63

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 264

Size: 16 K; PW/RF: 12.0 µs/dB; TO: 1000 Hz; FB: - Hz; Lock: ^2H ; D1,D5: 5.000 s.

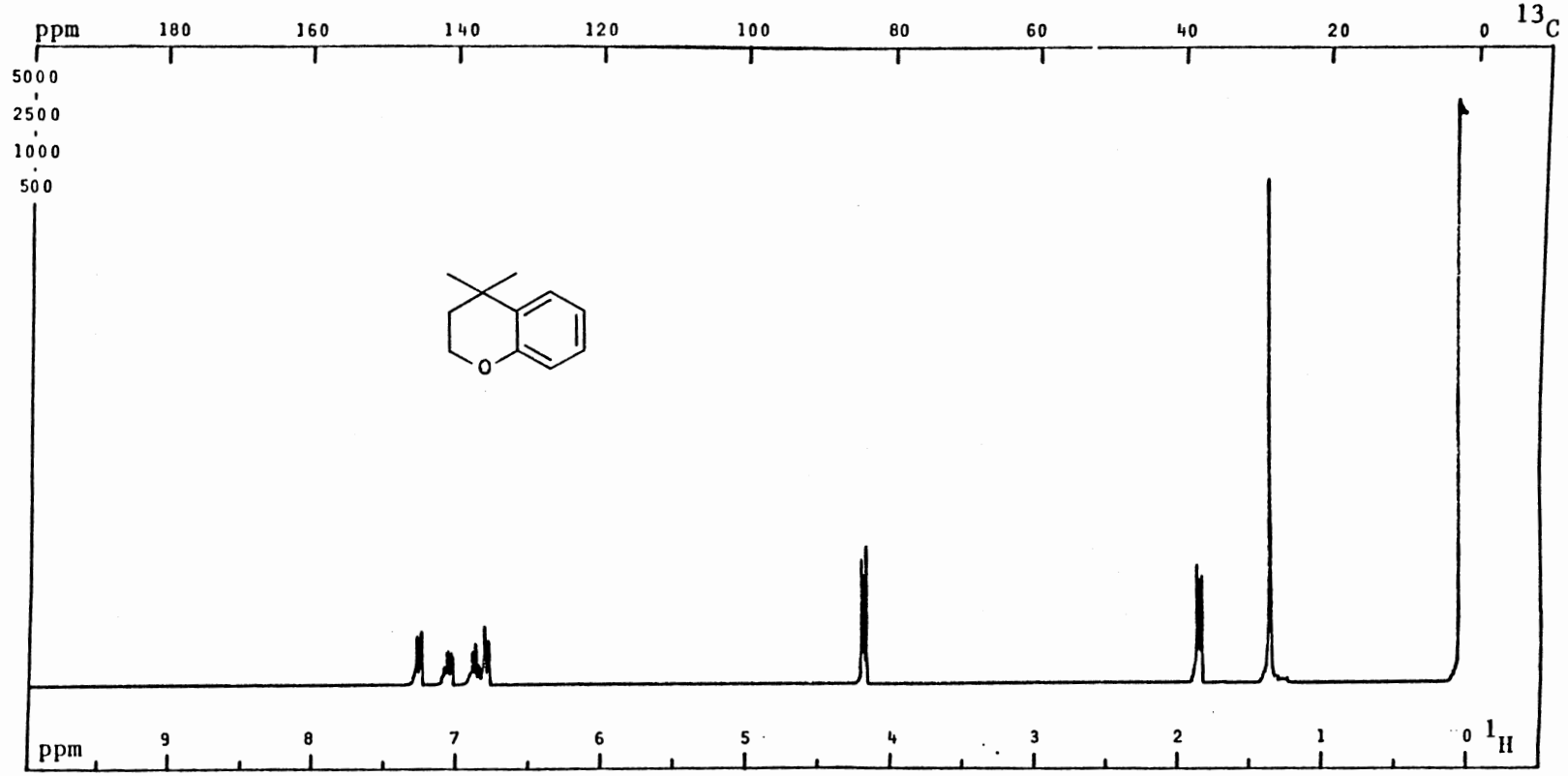
DC: Y ; Gated Off: A or D ; DO: Hz; RF(Power): W/dB; NBW: Hz; LB: 2.000 Hz.

PLATE LVIII



IR Spectrum of 64

PLATE LIX



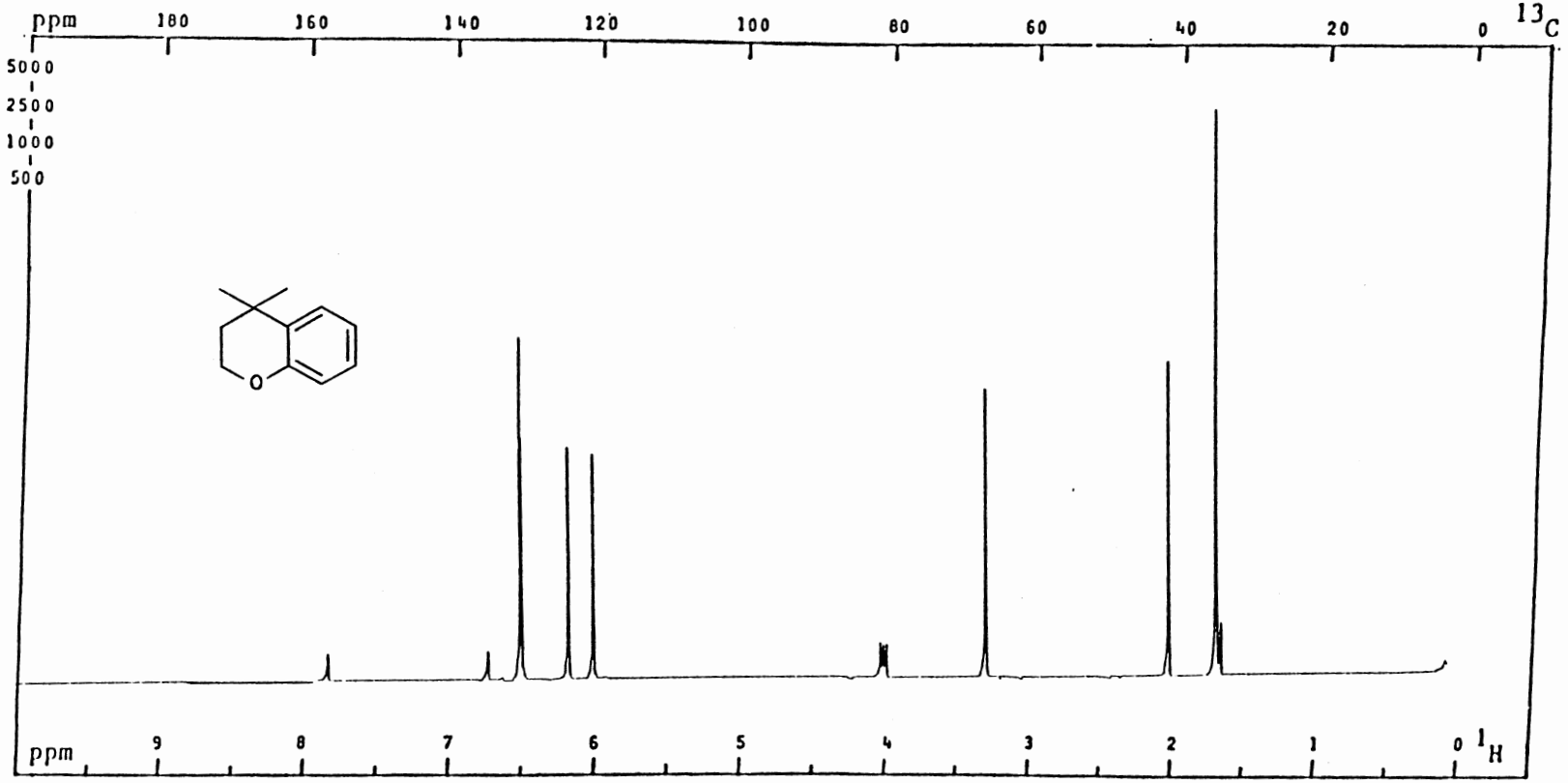
^{1}H NMR Spectrum of 64

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 2999.4 Hz; T: RT °C; NT: 16

Size: 12 K; PW/RF: 7.0 μs/dB; TO: 0 Hz; FB: _ Hz; Lock: ^{2}H ; D1,D5: 0 s.

DC: N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: Hz; LB: Hz.

PLATE LX



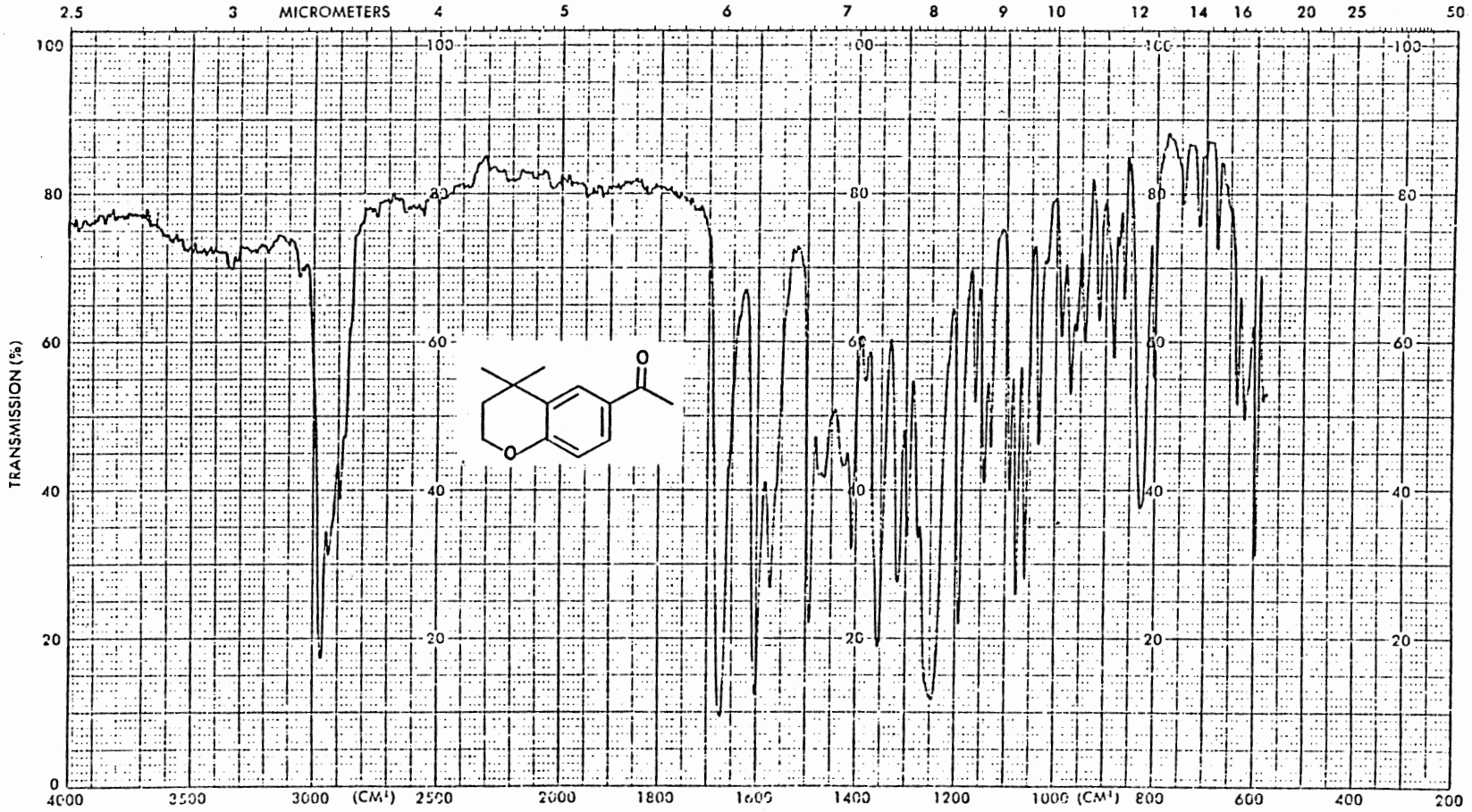
^{13}C NMR Spectrum of 64

PFT _XCW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 12272 .

Size: 16 K; PW/RF: 12.0 μs/dB; TO: 1000 Hz; FB: - Hz; Lock: ^2H ; D1,D5: 5.000 s.

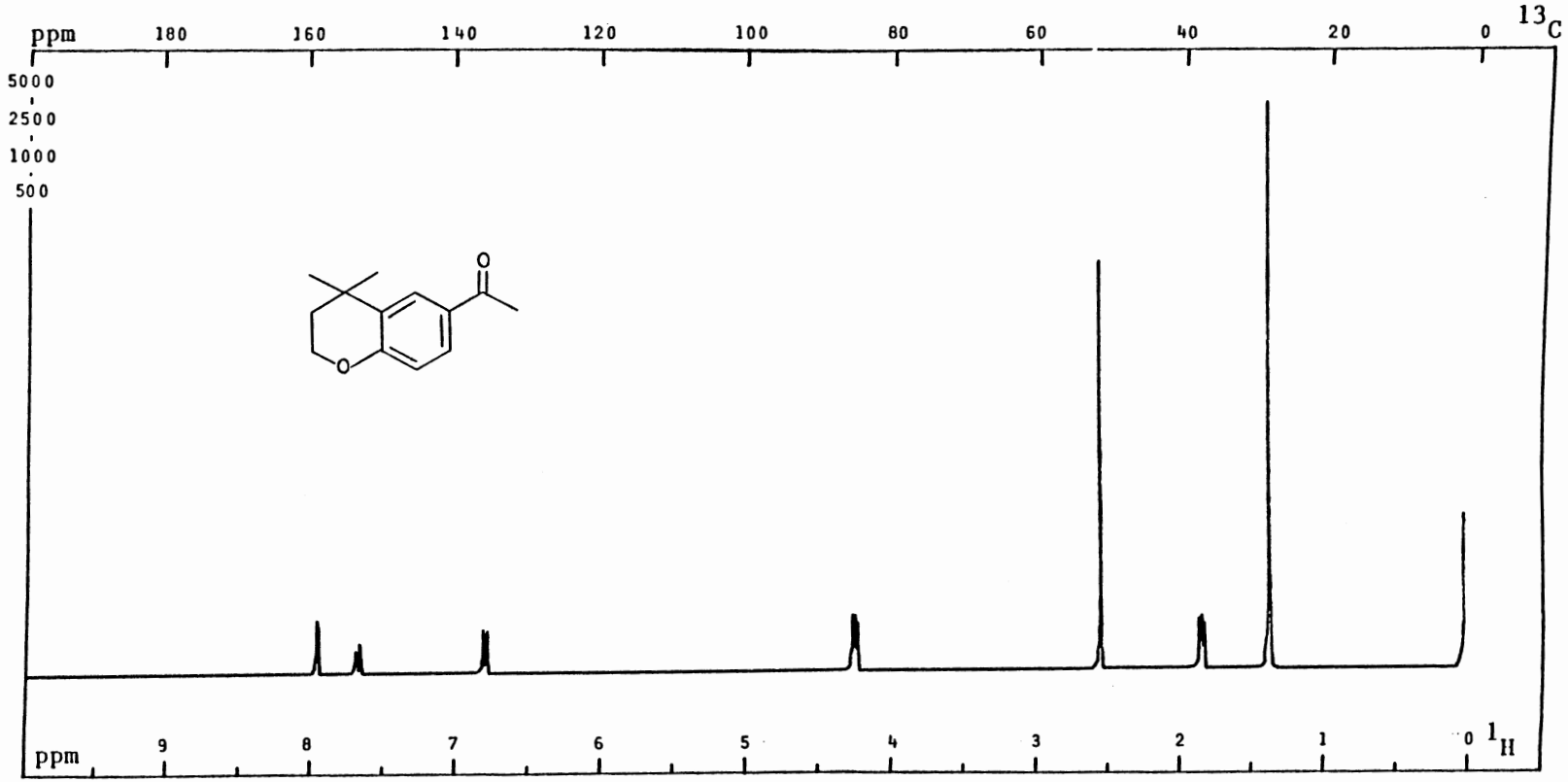
DC: Y ; Gated Off: A or D ; DO: Hz; RF(Power): W/dB; NBW: Hz; LB: 2.000 Hz.

PLATE LXI



IR Spetrum of 65

PLATE LXII



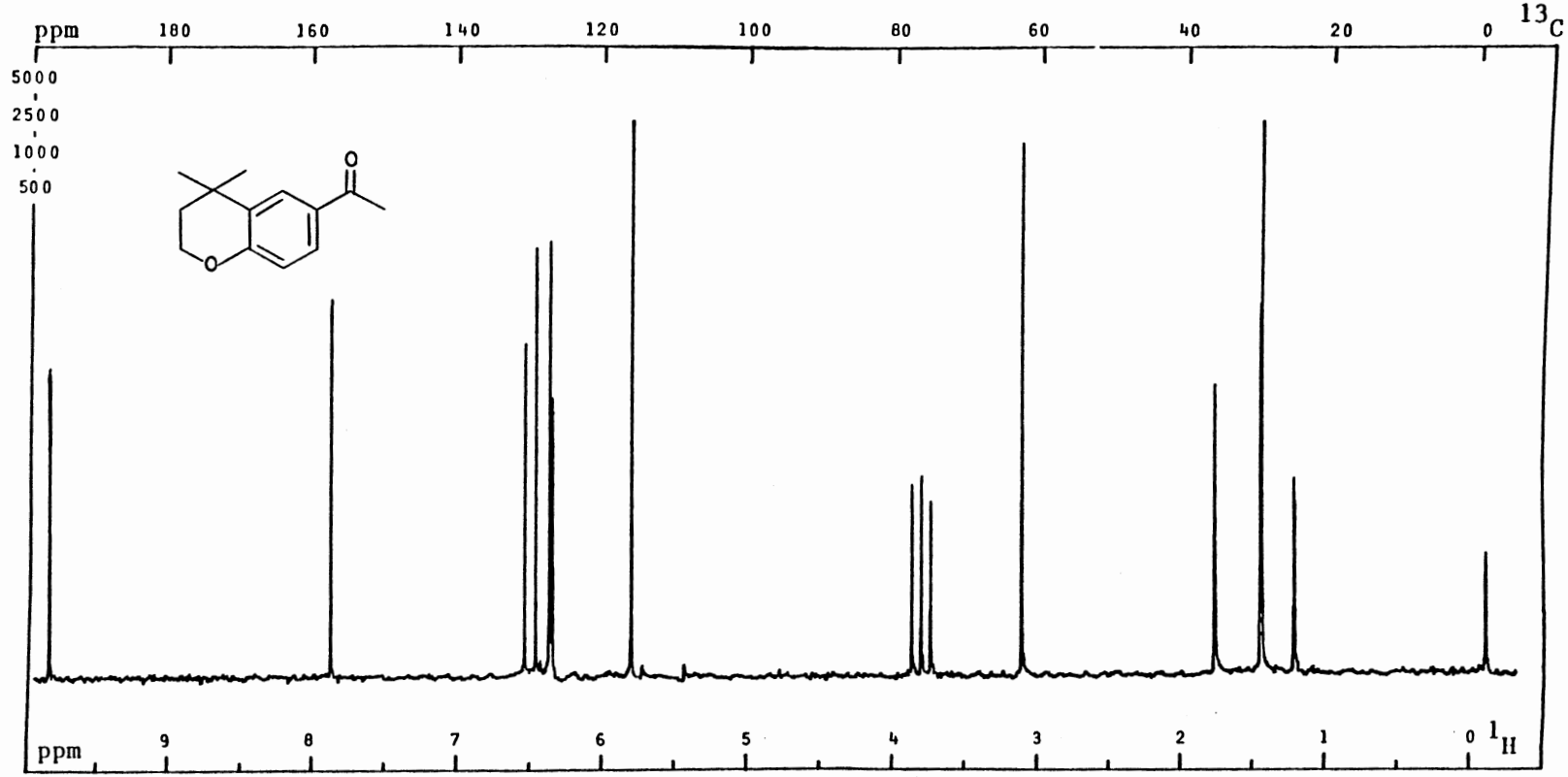
^{1}H NMR Spectrum of 65

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 2999.4 Hz; T: RT °C; NT: 16 .

Size: 12 K; PW/RF: 5.0 μs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 0 s.

DC: N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: Hz; LB: Hz.

PLATE LXIII



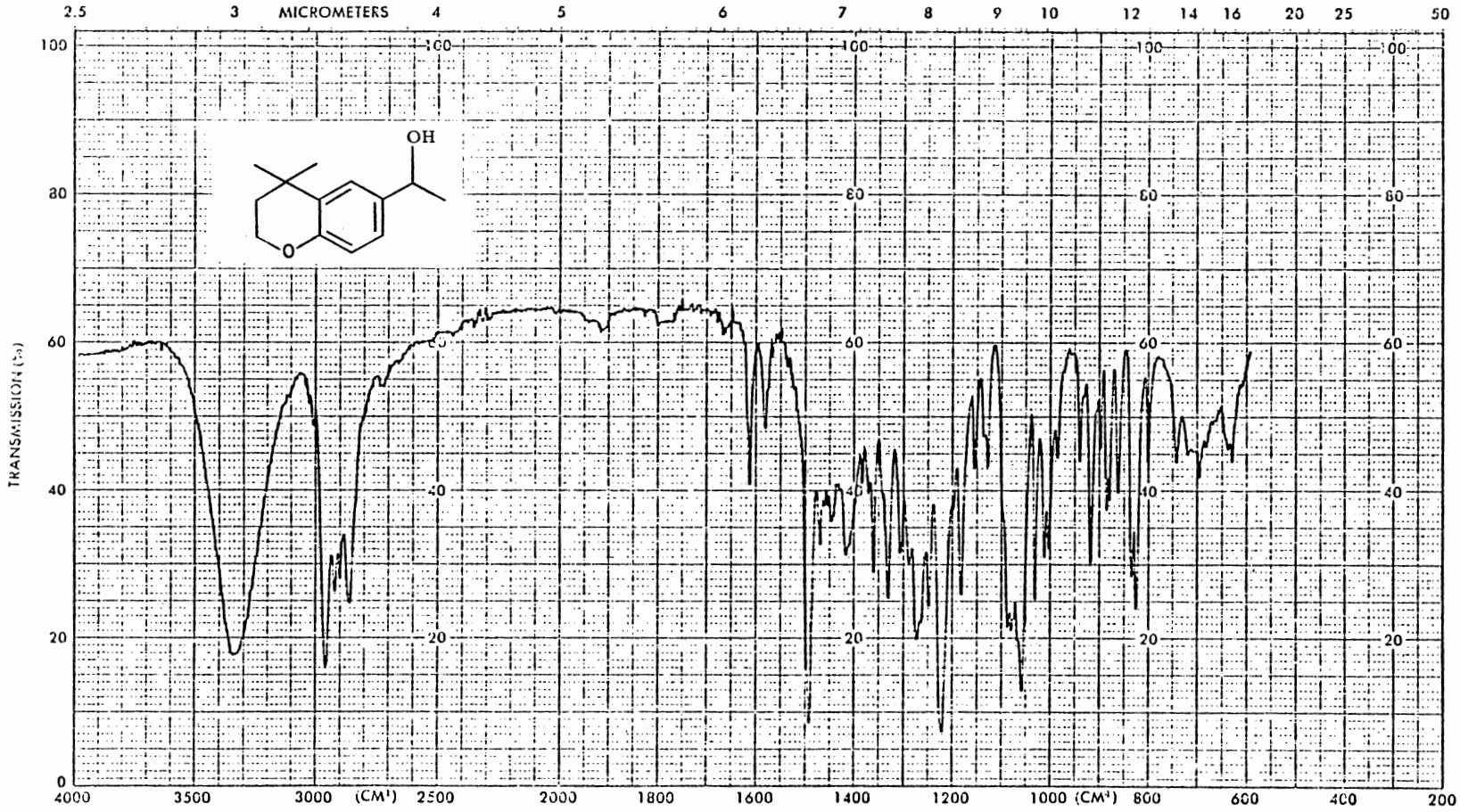
^{13}C NMR Spectrum of 65

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 64 .

Size: 16 K; PW/RF: 12.0 µs/dB; TO: 1000 Hz; FB: - Hz; Lock: ^2H ; D1,D5: 4/--- s.

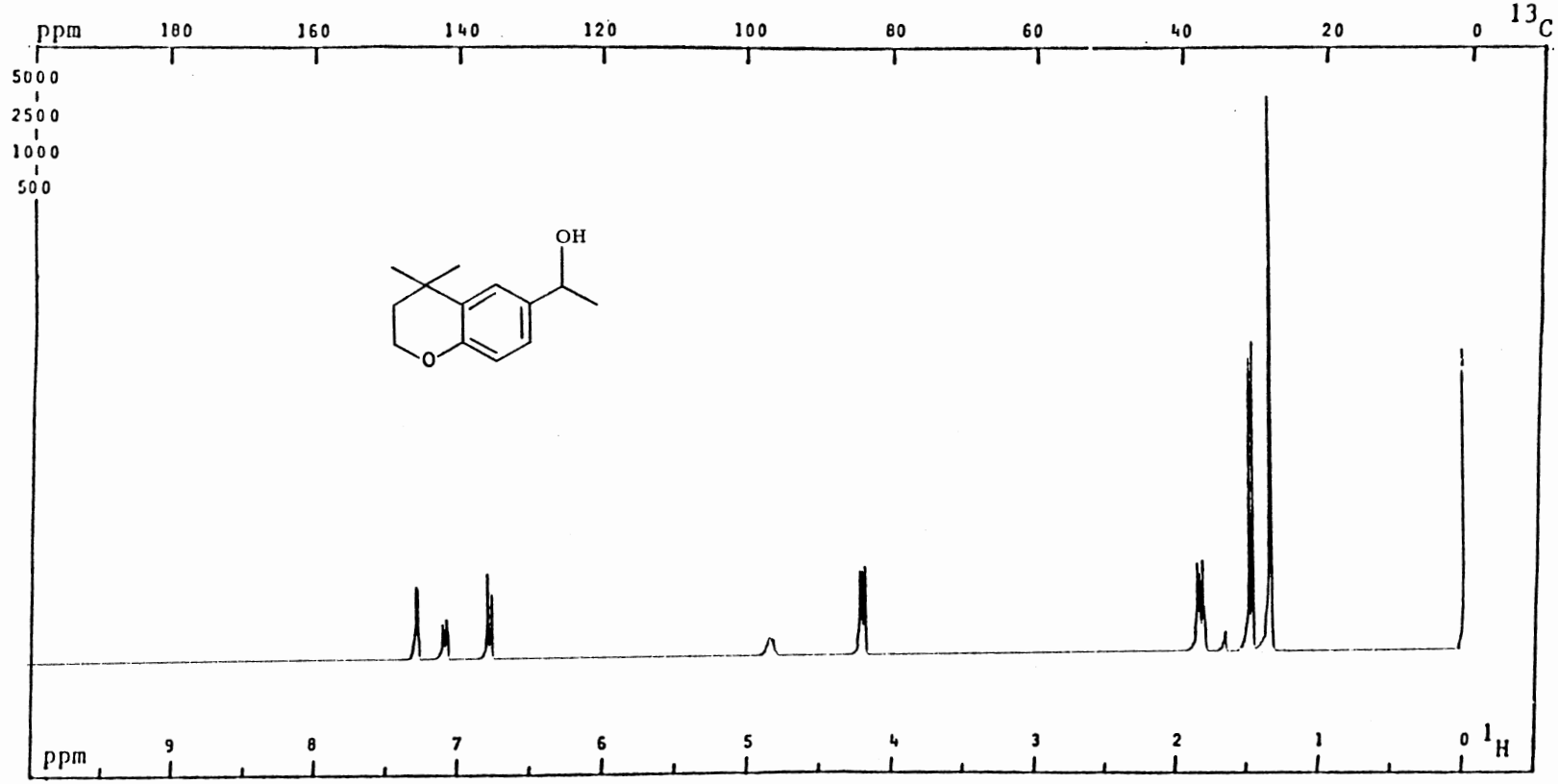
DC: Y ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 1.500 Hz.

PLATE LXIV



IR Spectrum of 66

PLATE LXV



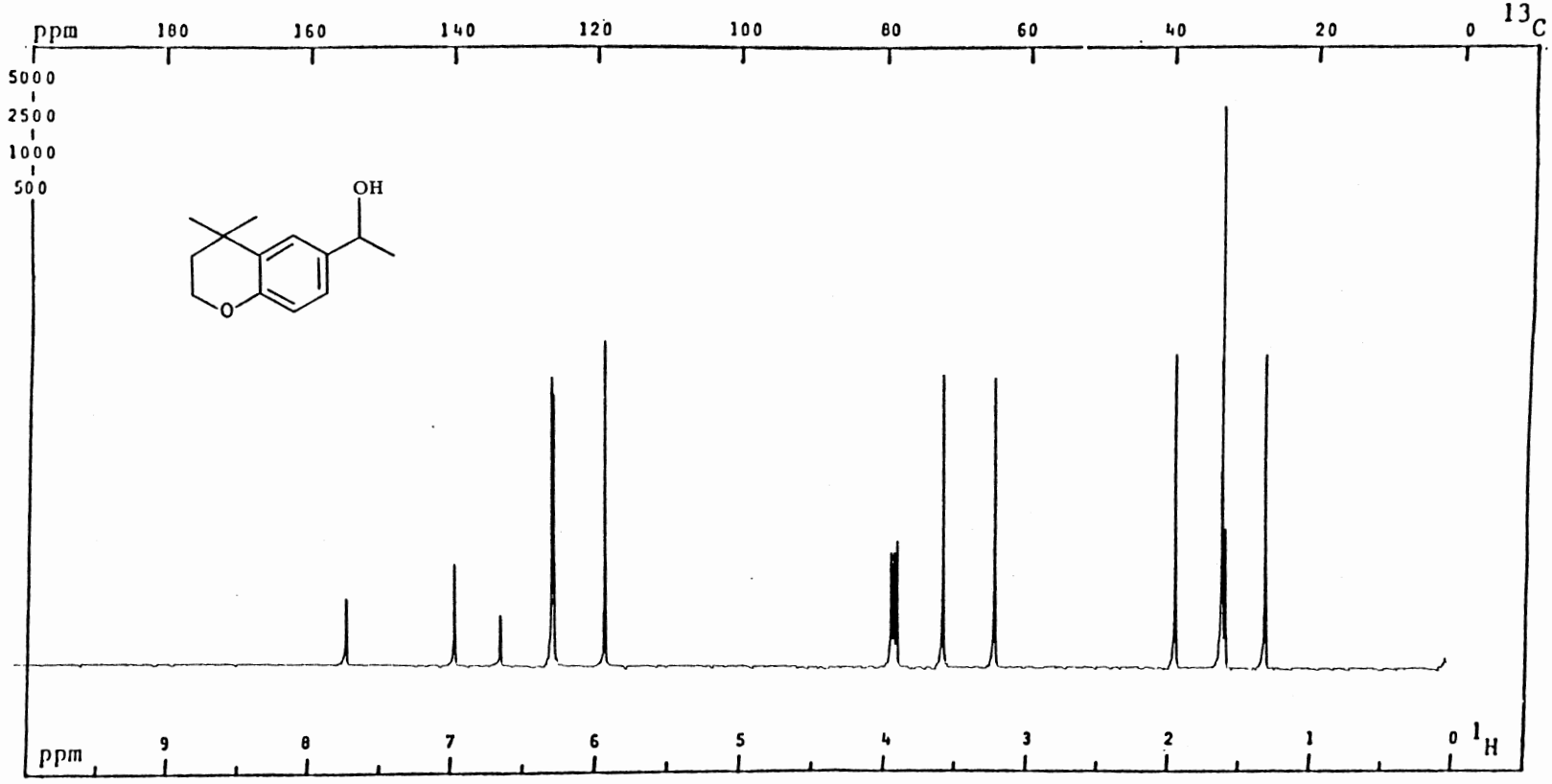
^{1}H NMR Spectrum of 66

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 2999.4 Hz; T: RT °C; NT: 8 .

Size: 12 K; PW/RF: 7.0 µs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 0 s.

DC: N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: Hz; LB: Hz.

PLATE LXVI



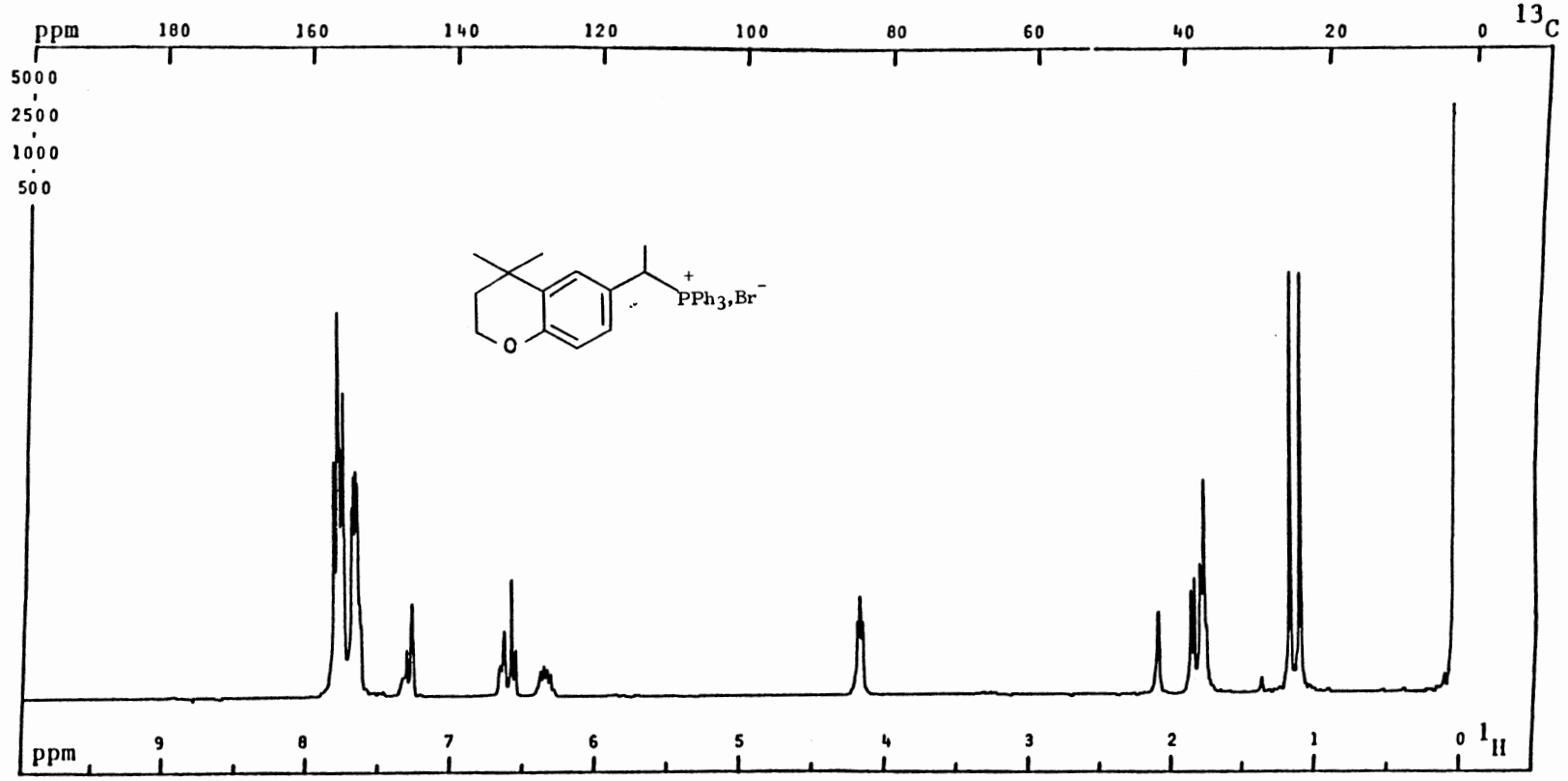
^{13}C NMR Spectrum of 66

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9Hz; T: RT °C; NT: 64

Size: 64 K; PW/RF: 12.0 µs/dB; TO: 1000 Hz; FB: - Hz; Lock: ^2H ; D1,D5: 4.000 s.

DC: Y ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 1.500 Hz.

PLATE LXVII



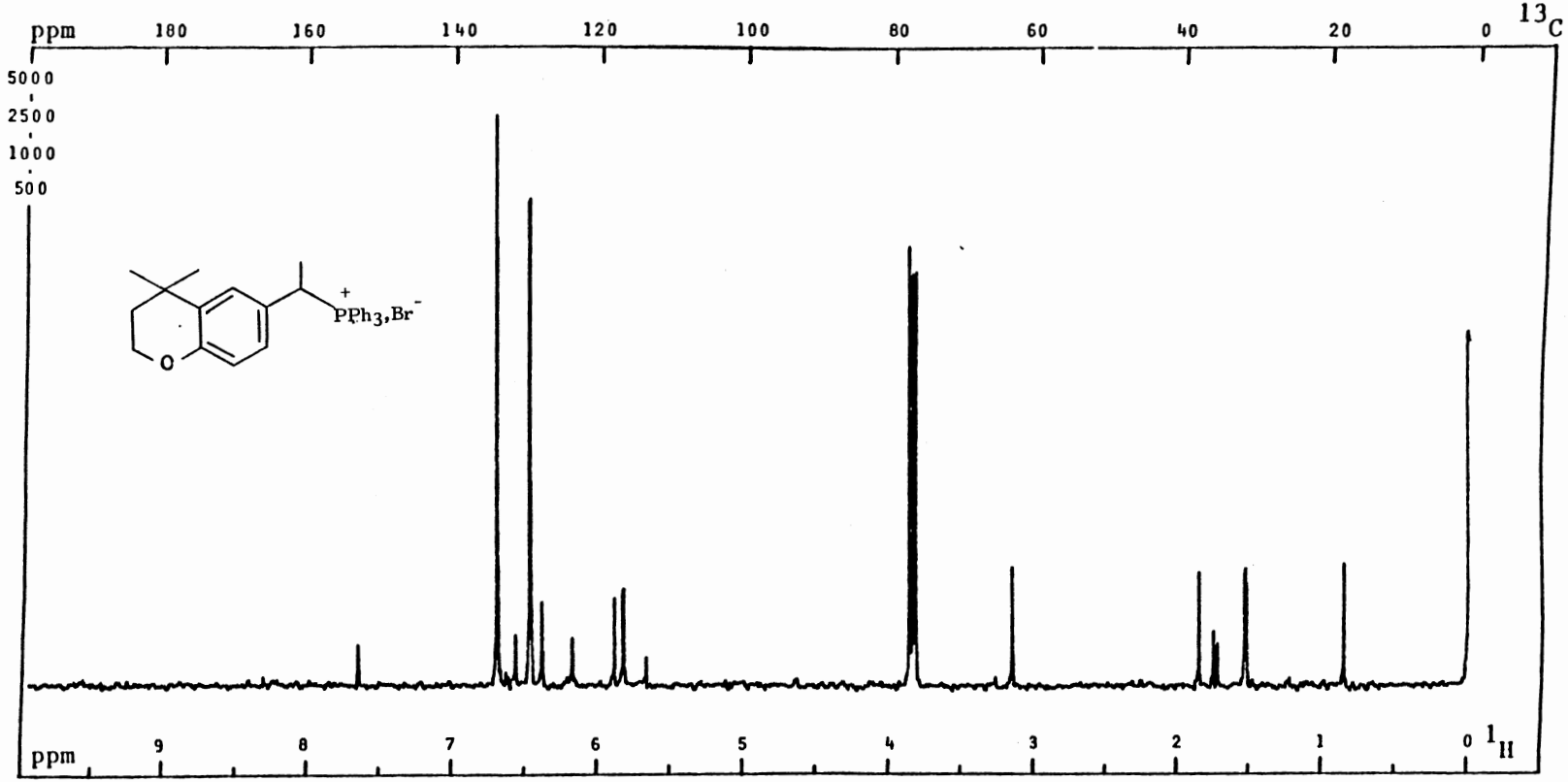
^{1}H NMR Spectrum of 67

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 2999.4 Hz; T: RT °C; NT: 4 .

Size: ^{12}K; PW/RF: 5.0 μs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 0 s.

DC: N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 15 W/dB; NBW: 200 Hz; LB: 0.500 Hz.

PLATE LXVIII



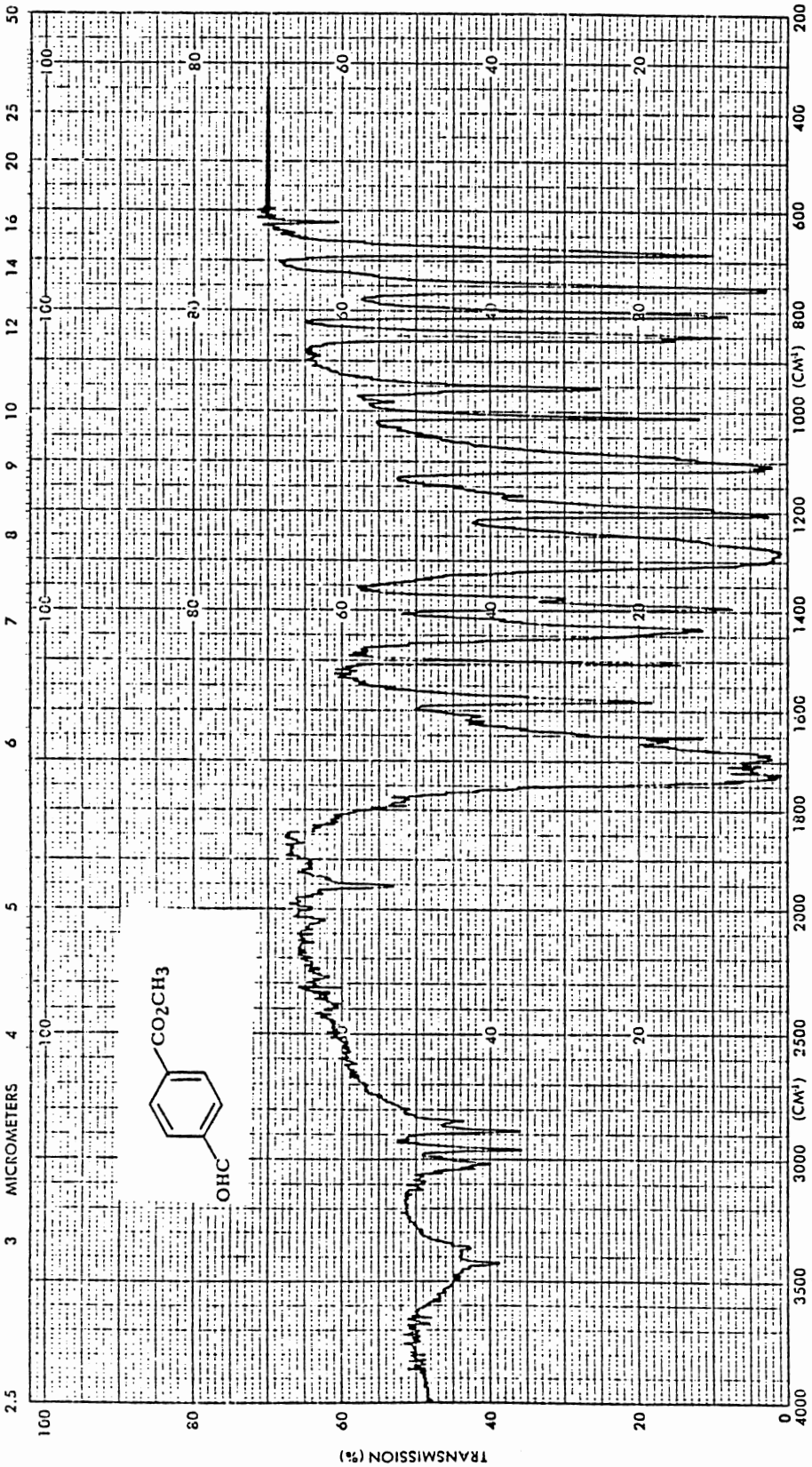
^{13}C NMR Spectrum of 67

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 720

Size: 16_K; PW/RF: 12.0 µs/dB; TO: 1000 Hz; FB: - Hz; Lock: ^2H ; D1,D5: 4.000 s.

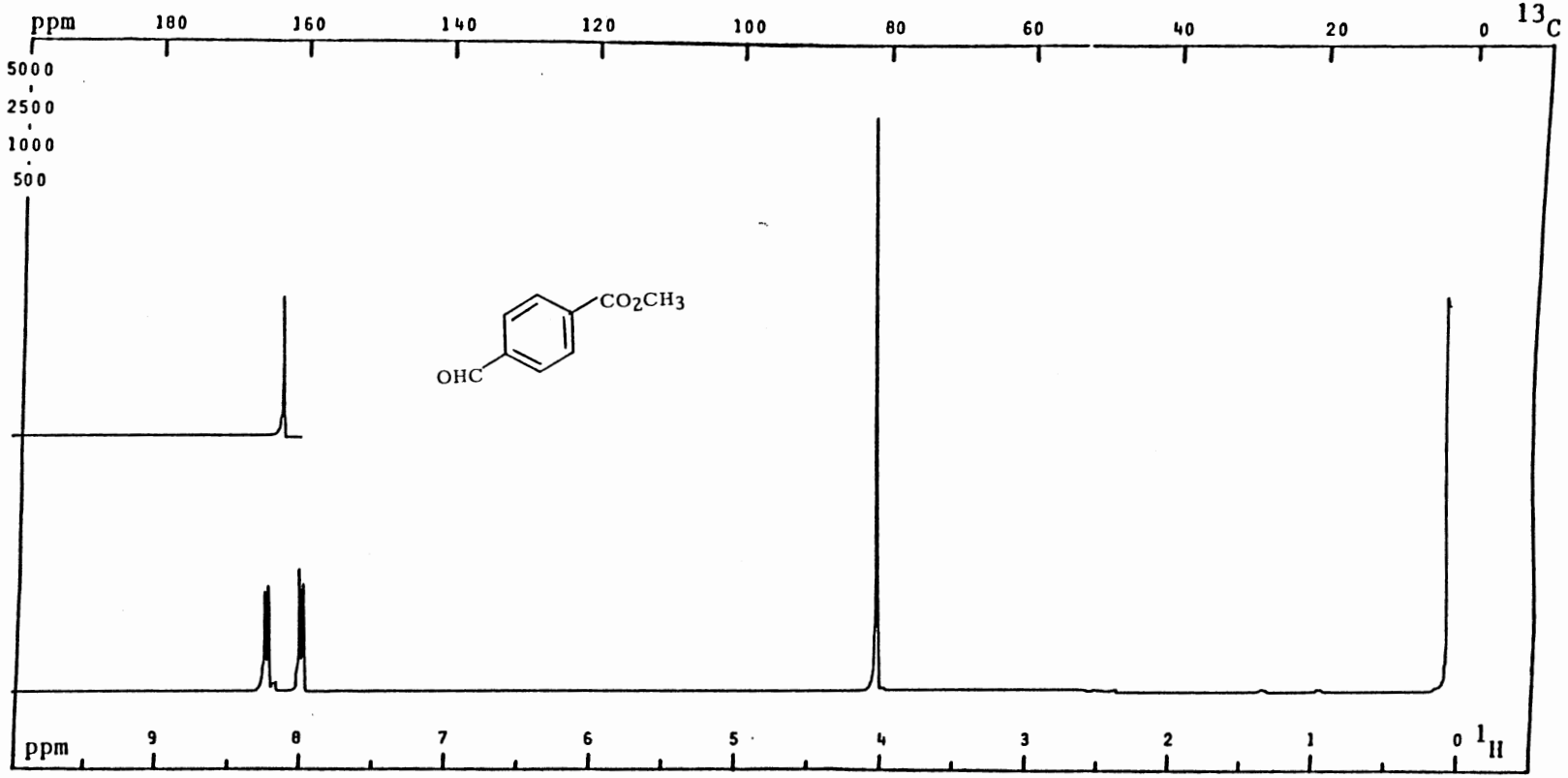
DC: Y ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 5.000 Hz.

PLATE LXIX



IR Spectrum of 68

PLATE LXX



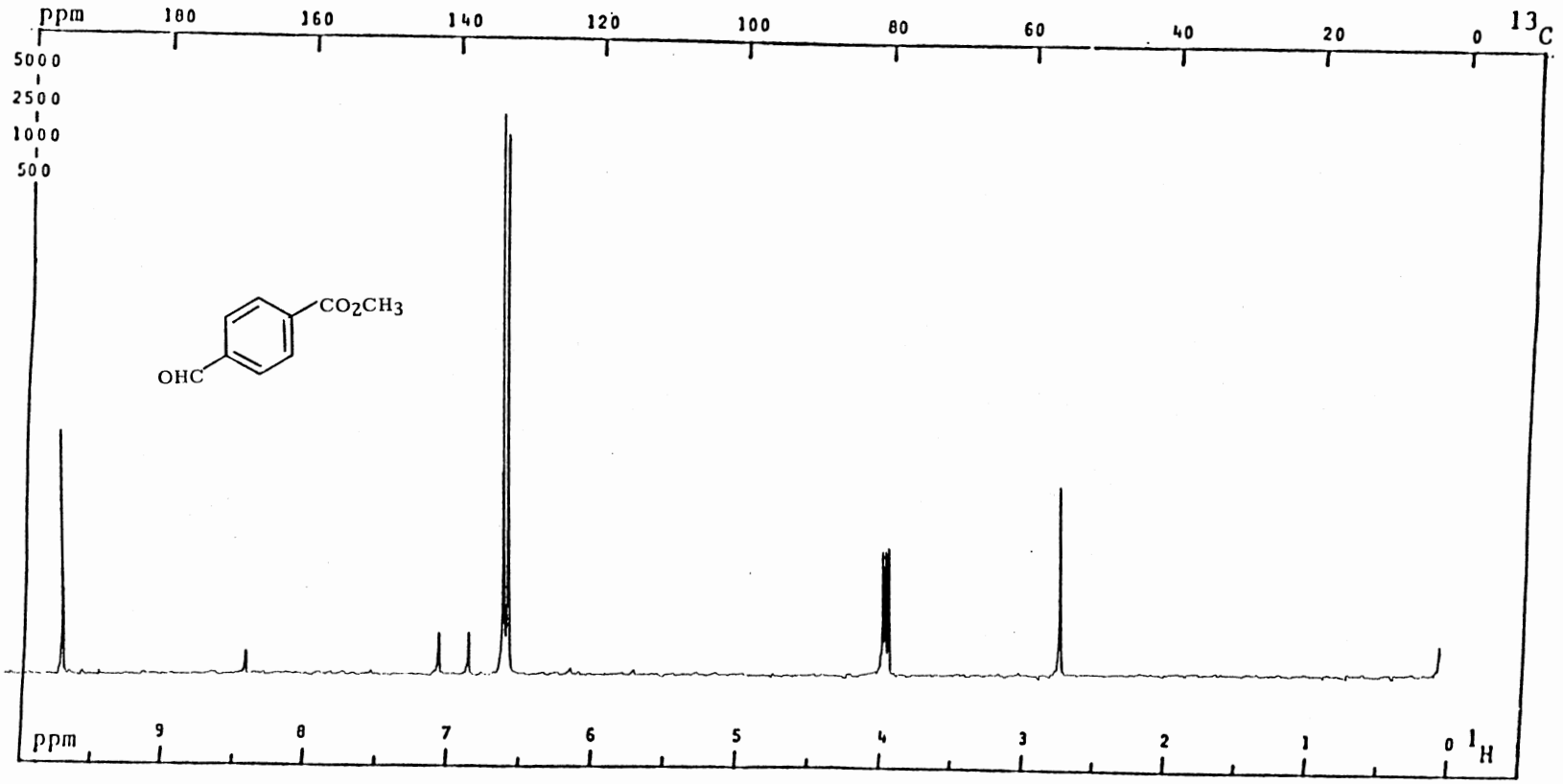
^{1}H NMR Spectrum of 68

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 2999.4 Hz; T: RT °C; NT: 4 .

Size: 8 K; PW/RF: 6.0 µs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 0.500 s.

DC: N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 13 W/dB; NBW: 200 Hz; LB: Hz.

PLATE LXXI



^{13}C NMR Spectrum of 68

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 176 .

Size: 20 K; PW/RF: 12.0 µs/dB; TO: 1000 Hz; FB: - Hz; Lock: ^2H ; D1,D5: 4.000 s.

DC: N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 4.000 Hz.

REFERENCES

1. Aykroyd, W. R. Curr. Sci. **1944**, 13, 149.

2. Barr, R. M.; De Luca, L. M. Biochem. Biophys. Res. Commun. **1974**, 60, 355.

3. Berkow, R., Ed.; The Merck Manual; 13th ed., Merck and Co.: Rahway, N.J., 1977; p. 1151.

4. Bollag, W. Eur. J. Cancer **1975**, 11, 721.

5. Bollag, W. Cancer Chemother. Pharmacol. **1979**, 3, 207.

6. Bollag, W. Cancer Chemother. Pharmacol. **1981**, 7, 27.

7. Bollag, W.; Geiger, J.-M. In Retinoid Therapy; Cunliffe, W. J.; Miller, A. J., Eds.; MTP Press Limited: Boston, 1984; Chapter 1.

8. Bonadies, F.; DiFabio, R. J. Org. Chem. **1984**, 49, 1647.

9. Butsugan, Y.; Tsukamoto, H.; Morito, N.; Bito, T. Chem. Lett. **1976**, 523.

10. Capper, N. S. Biochem. J. **1930**, 24, 980.

11. Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. J. Org. Chem. **1981**, 46, 3936.

12. Casey, A. F.; Parulkar, A. P.; Pocha, P. Tetrahedron **1968**, 24, 3031.

13. Chytil, F.; Ong, D. E. Federation Proc. **1979**, 38, 2510.

14. Colonge, J.; LeSech, E.; Marey, R. Bull Soc. Chim. France **1957**, 776.

15. Corey, E. J.; Beames, J. D. J. Amer. Chem. Soc. **1973**, 95, 2824.

16. Curley, R. W.; Ticoras, C. J. J. Org. Chem. **1986**, 51, 256.

17. Dawson, M. I.; Hobbs, P. D.; Chan, K.; Derdzinski, K.; Helmes, C. T.; Chao, W.; Meirhenry, E.; Schiff, L. J. In Retinoids, Differentiation and Diseases; Nugent, J.; Clark, S., Eds.; Ciba Foundation Symposium 113; Pitman: London, 1985; p. 6.

18. Dawson, M. I.; Hobbs, P. D.; Derdzinski, K.; Chan, Rebecca L.-S.; Gruber, J.; Chao, W.; Smith, S.; Thies, R. W.; Schiff, L. J. J. Med. Chem. **1984**, 27, 1516. For UV model systems, see Suzuki, H. Bull soc. Chem. Jpn. **1960**, 33, 379.

19. DeLuca, H. F. Federation Proc. **1979**, 38, 2519.

20. Dowling, J. E.; Wald, G. Proc. Natl. Acad. Sci. USA **1960**, 46, 587.

21. Dunagin, P. E.; Meadows, H. E.; Olson, J. A. Science **1965**, 148, 86.

22. Euler, B.; Euler, H.; Hellstrom, H. Biochem. Z. **1928**, 203, 370.

23. Firouzabadi, H.; Sardarian, A. R.; Moosavirpour, H.; Afshari, G. M. Synthesis **1986**, 4, 285.

24. Frolik, C. A. In The Retinoids; Sporn, M. B.; Roberts, A. B.; Goodman, D. S., Eds.; Academic Press Inc.: Orlando, 1984; Vol. 2, Chapter 11.

25. Frolik, C. A. In The Retinoids; Sporn, M. B.; Roberts, A. B.; Goodman, D. S., Eds.; Academic Press Inc.: Orlando, 1984; Vol. 2, 198-203.

26. Frolik, C. A. In The Retinoids; Sporn, M. B.; Roberts, A. B.; Goodman, D. S., Eds.; Academic Press Inc.: Orlando, 1984; Vol. 2, p. 200.

27. Frolik, C. A. In The Retinoids; Sporn, M. B.; Roberts, A. B.; Goodman, D. S., Eds.; Academic Press Inc.: Orlando, 1984; Vol. 2, p. 201.

28. Frolik, C. A.; Roberts, A. B.; Tavela, T. E.; Roller, P. P.; Newton, D. L.; Sporn, M. B. Biochem. **1979**, 18, 2092.

29. Frolik, C. A.; Roller, P. P. In Antitumor Compounds of Natural Origin: Chemistry and Biochemistry; Aszalos, A., Ed.; CRC: Boca Raton, FL, 1981; Vol. 2, p. 89.

30. Frolik, C. A.; Roller, P. P. In Antitumor Compounds of Natural Origin: Chemistry and Biochemistry; Aszalos, A., Ed.; CRC: Boca Raton, FL, 1981; Vol. 2, p. 98.

31. Frolik, C. A.; Roller, P. P. In Antitumor Compounds of Natural Origin: Chemistry and Biochemistry; Aszalos, A., Ed.; CRC: Boca Raton, FL, 1981; Vol. 2, p. 99.

32. Frolik, C. A.; Roller, P. P. In Antitumor Compounds of Natural Origin: Chemistry and Biochemistry; Aszalos, A., Ed.; CRC: Boca, Raton, FL, 1981; Vol. 2, p. 101.

33. Frolik, C. A.; Roller, P. P. In Antitumor Compounds of Natural Origin: Chemistry and Biochemistry, Aszalos, A., Ed., CRC: Boca, Raton, FL., 1981; Vol. 2, p. 105.

34. Frolik, C. A.; Roller, P. P. In Antitumor Compounds of Natural Origin: Chemistry and Biochemistry, Aszalos, A., Ed., CRC: Boca, Raton, FL., 1981; Vol. 2, p. 111.

35. Frolik, C. A.; Roller, P. P. In Antitumor Compounds of Natural Origin: Chemistry and Biochemistry, Aszalos, A., Ed., CRC: Boca, Raton, FL., 1981; Vol. 2, p. 112.

36. Frolik, C. A.; Roller, P. P.; Roberts, A. B.; Sporn, M. B. J. Biol. Chem. **1980**, 255, 8057.

37. Frolik, C. A.; Tavela, T. E.; Newton, D. L.; Sporn, M. B. J. Biol. Chem. **1978**, 253, 7319.

38. Fujimaki, Y. J. Cancer Res. **1926**, 10, 469.

39. Geelen, J. A. G. Crit. Rev. Toxicol **1979**, 6, 351.

40. Goodman, D. S. Federation Proc. **1979**, 38, 2501.

41. Goodman, D. S. In The Retinoids; Sporn, M. B.; Roberts, A. B.; Goodman, D. S., Eds.; Academic Press, Inc.: Orlando, 1984; Vol. 2, p. 47.

42. Goodman, D. S. The New Eng. J. Med. **1984**, 310, 1023.

43. Gray, G. A. Varian Instrument Application **1982**, 16, 11.

44. Hänni, R.; Bigler, F. Helv. Chim. Acta **1977**, 60, 881.

45. Hänni, R.; Bigler, F.; Meister, W.; Englert, G. Helv. Chim. Acta **1976**, 59, 2221.

46. Hixson, E. J.; Burdeshaw, J. A.; Denine, E. P.; Harrison, S. D. Toxicol. Appl. Pharm. **1979**, 47, 359.

47. Hixson, J.; Denine, E. P. Toxicol. Appl. Pharm. **1978**, 44, 29.

48. Holmes, H. N.; Corbet, R. E. J. Am. Chem. Soc. **1937**, 59, 2042.

49. Hurwitz, S. Am. J. Dis. Child. **1979**, 133, 536.

50. Isler, O.; Huber, W.; Ronco, A.; Kofler, M. Helv. Chim. Acta **1947**, 30, 1911.

51. Jones, H.; Blanc, D.; Cunliffe, W. J. Lancet **1980**, 1048.

52. Jungalwala, F. G.; Cama, H. R. Biochem. J. **1965**, 95, 17.

53. Kamm, J. J.; Ashenfelter, K. O.; Ehmann, C. W. In The Retinoids; Sporn, M. B.; Roberts, A. B.; Goodman, D. S., Eds.; Academic Press, Inc.: Orlando, 1984; Vol. 2, p. 290.

54. Kamm, J. J.; Ashenfelter, K. O.; Ehmann, C. W. In The Retinoids; Sporn, M. B.; Roberts, A. B.; Goodman, D. S., Eds.; Academic Press, Inc.: Orlando, 1984; Vol. 2, p. 311.

55. Karrer, P.; Helfenstein, A.; Wessttstein, A.; Wehril, H. Helv. Chim. Acta **1930**, 13, 1084.

56. Katayama, M.; Fujiwara, S.; Suzuki, H.; Nagai, Y.; Simamura, O. J. Mol. Spectrosc. **1960**, 5, 85.

57. Kochar, D. M. Teratology **1973**, 7, 289.

58. Landesberg, J. M.; Slam, M. A.; Mandel, M. J. Org. Chem. **1981**, 46, 5025.

59. Lansnitzki, I. Br. J. Cancer **1955**, 9, 434.

60. Lansnitzki, I. Br. J. Cancer **1976**, 34, 239.

61. Lassus, A. Br. J. Dermatol. **1980**, 102, 195.

62. Lewis, A. J.; Capetola, R. J.; Mezick, J. A. In Annual Reports in Medicinal Chemistry; Hess, Hans-Jürgen, Ed.; Academic Press: New York, 1983; Vol. 18, Chapter 19.

63. Lippel, K.; Olson, J. A. J. Lipid Res. **1968**, 9, 168.

64. Loeliger, P.; Bollag, W.; Mayer, H. Eur. J. Med. Chem. **1980**, 15, 9.

65. Loeliger, P.; Klaus, M. (Hoffman-LaRoche, F., and Co. A.-G.) Ger. Offen. DE 3, 316, 932 (Cl. CO7D311/58), Nov. 17, 1983, CH Appl. 82/2, 956, May 12, 1982; Chem. Abstr. **1984**, 100, 51468Z.

66. Lotan, R.; Giotta, E. N.; Nork, E.; Nicolson, G. L. J. Natl. Cancer Inst. **1978**, 60, 1035.

67. Macapinlac, M. P.; Olson, J. A. Int. J. Vitam. Nutr. Res. **1981**, 51, 331.

68. Martin, C. A.; Dawson, M. I.; McCormick, A. M.; Napoli, J. L. Biochem. and Biophys. Res. Comm. **1986**, 135, 124.

69. Masushige, S.; Rosso, G. C.; Wolf, G. World Rev. Nutr. Diet. **1978**, 31, 16.

70. McCollum, E. V.; Davis, M. J. Biol. Chem. **1913**, 15, 167.

71. McCormick, A. M.; Napoli, J. L.; Schnoes, H. K.; DeLuca, H. F. Biochem. **1978**, 17, 4085.

72. McKenzie, R. M.; Nelson, E. C. Biochem. Biophys. Acta **1979**, 574, 1.

73. Mehta, R. G.; Schiff, L. J.; Moore, S. J.; Buckly, A. M.; Dawson, M. I. In Vitro Cell. and Dev. Biol. **1986**, 22, 164.

74. Moon, R. C.; Thompson, H. J.; Becci, P. J.; Grubbs, C. J.; Gander, R. J.; Newton, D. L.; Smith, J. M.; Phillips, S. L.; Henderson, W. R.; Mullen, L. T.; Brown, C. C.; Sporn, M. B. Cancer Res. **1979**, 39, 1339.

75. Moore, T. Lancet **1929**, 217, 380.

76. Moore, T. Biochem. J. **1930**, 24, 696.

77. Moore, T. Vitamin A; Elsevier Publishing Co., New York, 1957; Chapter 1, p. 3.

78. Moore, T. Vitamin A; Elsevier Publishing Co., New York, 1957; Chapters 24-25, p. 301-306.

79. Moore, T. Vitamin A; Elsevier Publishing Co., New York, 1957; Chapters 26, 28; p. 409.

80. Napoli, J. L.; McCormick, A. M.; Schnoes, H. K.; DeLuca H. F. Proc. Natl. Acad. Sci. USA **1978**, 75, 2603.

81. Nater, J. P.; Doegtas, H. M. G. Acta Derm. Venerol. **1970**, 50, 109.

82. Nettesheim, P.; Williams, M. L. Int. J. Cancer **1976**, 17, 351.

83. Newton, D. L.; Henderson, W. R.; Sporn, M. B. Cancer Res. **1980**, 40, 3413.

84. Ofner, A.; Surmatis, J. D. J. Org. Chem. **1963**, 28, 2735.

85. Olsen, T. G. Med. Clin. N. Amer. **1982**, 66, 851.

86. Orfanos, C. E.; Braun-Falco, O.; Farber, E. M.; Grupper, Ch.; Polano, M. K.; Schuppi, R., Eds.; Retinoids: Advances in Basic Research and Therapy; Springer-Verlag: New York, 1981.

87. Ott, F.; Bollag, W. Schweiz. Med. Wochenschr **1975**, 105, 439.

88. Pavia, L. D.; Lampman, G. M; Kriz, S. G., Eds.; Introduction to Spectroscopy; Saunders Golden Sunburst Series: Pennsylvania, 1979; p. 353.

89. Pawson, B. A.; Ehmann, C. W.; Itri, L. M.; Sherman, M. I. J. Med. Chem. **1982**, 25, 1269.

90. Peck, G. L. In The Retinoids; Sporn, M. B.; Roberts, A. B.; Goodman, D. S., Eds.; Academic Press Inc.: Orlando, 1984; Vol. 2, p. 408.

91. Peck, S. M.; Chargin, L.; Sobotka, H. Arch Dermatol. Syphilol. **1941**, 43, 223.

92. Peck, G. L.; Olsen, T. G.; Butkus, D.; Pandya, M.; Arnaud-Battandier, J.; Gross, E. G.; Windhorst, D. B.; Cheripko, J. J. Am. Acad. Dermatol. **1982**, 6, 735.

93. Piutti, C. Bull Soc. Chim. Fr. **1919**, 27, 618.

94. Premachandra, B. R.; Cama, H. R. Ind. J. Vitam. Nut. Res. **1975**, 45, 305.

95. Rapaport, H. G.; Herman, H.; Lehman, E. J. Pediatr. **1942**, 21, 733.

96. Rietz, P.; Wiss, O.; Weber, F. In Vitamins and Hormones; Harris, R. S.; Munson, R. L.; Diczfalusy, G. J., Eds.; Academic Press: New York, 1974; Vol. 32, p. 237.

97. Roberts, A. B.; Nichols, M. D.; Frolik, C. A.; Newton, D. L.; Sporn, M. B. Cancer Res. **1978**, 38, 3327.

98. Robeson, C. D.; Baxter, J. G. Nature **1945**, 155, 300.

99. Robeson, C. D.; Baxter, J. G. J. Am. Chem. Soc. **1947**, 69, 136.

100. Rockley, N. L.; Halley, B. A.; Nelson, E. C. Biochem. Biophys. Acta **1980**, 627, 270.

101. Rodahl, K.; Moore, T. Biochem. J. **1943**, 37, 166.

102. Smith, A. B.; Scarborough, R. M. Synth. Commun. **1980**, 10, 205.

103. Smith, J. E.; Goodman, D. S. Federation Proc. **1979**, 38, 2504.

104. Sporn, M. B.; Dunlop, N. M.; Newton, D. L.; Henderson, W. R. Nature **1976**, 263, 110.

105. Sporn, M. B.; Dunlop, N. M.; Newton, D. L., Smith, J. M. Federation Proc. **1976**, 35, 1332.

106. Sporn, M. B.; Newton, D. L. Federation Proc. **1979**, 38, 2528.

107. Sporn, M. B.; Roberts, A. B.; Goodman, D. S. In The Retinoids; Sporn, M. B.; Roberts, A. B.; Goodman, D. S., Eds.; Academic Press, Inc.: Orlando, 1984; Vol. 1, p. 2.

108. Sporn, M. B.; Roberts, A. B.; Goodman, D. S., Eds.; The Retinoids; Academic Press Inc.: Orlando, 1984; Vol. 1, 2.

109. Stephenson, L. M.; Speth, D. R. J. Org. Chem. **1979**, 44, 4683.

110. Strauss, J. S.; Stranieri, A. M.; Farrell, L. N.; Downing, D. T. J. Invest. Dermatol. **1980**, 74, 66.

111. Strickland, S.; Breitman, T. R.; Frickle, F.; Nürrenbach, A.; Hädicke, E.; Sporn, M. B. Cancer Res. **1983**, 43, 5268.

112. Sugiura, K.; Benedict, S. R. J. Cancer Res. **1930**, 14, 306.

113. Swanson, B. N.; Newton, D. L.; Roller, P. P.; Sporn, M. B. J. Pharmacol. Exp. Ther. **1981**, 219, 632.

114. Thompson, J. N.; Howell, J. M.; Pitt, G. A. J. Biochem. J. **1961**, 80, 16 p.

115. Thompson, J. N.; Howell, J. M.; Pitt, G. A. J. Biochem. J. **1960**, 80, 25 p.

116. Tosukhowong, P.; Olson, J. A. Biochim. Biophys. Acta **1978**, 529, 438.

117. Trown, P. W.; Buck, M. J.; Hansen, R. Cancer Treat Rep. **1976**, 60, 1647.

118. Tsambaos, D.; Orfanos, C. A. Pharmac. Ther. **1981**, 14, 355.

119. Underwood, B. A. In The Retinoids; Sporn, M. B.; Roberts, A. B.; Goodman, D. S., Eds.; Academic Press, Inc.: Orlando, 1984; Vol. 1, p. 355.

120. Vane, F. M., Buggé, C. J. Drug Metab. Dispos. **1981**, 9, 515.

121. Verma, A. K.; Boutwell, R. K. Cancer Res. **1977**, 37, 2196.

122. Wald, G. Science **1968**, 162, 230.

123. Waugh, K. M.; Berlin, K. D.; Ford, W. T.; Holt, E. M.; Carrol, J. P.; Schomber, P. R.; Thompson, M. D.; Schiff, L. J. J. Med. Chem. **1985**, 28, 116.

124. Welch, S. C.; Gruber, J. M.; Rao, A. S. C. P. J. Med. Chem. **1982**, 25, 81.

125. Wolf, G. Physiolog. Rev. **1984**, 873.

126. Yu, R. J.; Van Scott, E. J. U.S. Patent 3, 932, 665; January 13, 1976; Chem. Abstr. **1976**, 84, 84451.

127. Zile, M.; DeLuca, H. F. J. Nutr. **1968**, 94, 302.

128. Zile, M. H.; Emerick, R. J.; DeLuca, H. F. Biochem. Biophys. Acta **1967**, 141, 639.

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