SELECTED BENZOTHIOPYRAN DERIVATIVES AS POTENTIAL CARCINOSTATS FOR THE TREATMENT OF BREAST CANCER

By

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To my Lord and Savior, Jesus Christ, I dedicate this work. It was his love and faithfulness that kept me going and allowed me to overcome the many mountains along the way.

I am especially thankful to my family and friends, whose prayers and encouragement gave me the strength to keep trying. I am also, grateful to Dr. K. D. Berlin for his guidance and to Dr. R. Bunce for his procedure for the preparation of ethyl 2-phenylacrylate. I want to thank Stan Sigle for the many NMR spectra he ran and Norm Perreira for the mass spectral data. I appreciate the help in typing this manuscript by my uncle, Al Hamilton, and my roommate, Rhonda Holman. I gratefully acknowledge the financial support provided by Phillips Petroleum Company in the form of a Summer Fellowship.

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CHAPTER I

HISTORICAL

Cancer is defined by medical science as a disorder of cellular growth and is considered to be not just one disease with one cause, but rather many distinct diseases with different origins.[26] Breast cancer is the single largest cause of cancer death among women in the United States. The disease strikes one out of every thirteen women sometime in their lifetime.[28]

In exploring the causes of breast cancer, several factors have been found associated with the disease.[25] One factor which has been suggested is the diet.[25,39] Many inhibitors of carcinogenesis have been found in the food consumed. There are also large quantities of anutrient foreign compounds found in vegetables, fruits, grains, nuts and other plant materials. These compounds are commonly excreted from the body. Moreover, the body has a built-in defense system used in the detoxification of the foreign compounds, that is via metabolism of the substance, with the aid of enzymes, to a metabolite that can be excreted. This detoxification system is able to protect the body against other toxic materials (natural occuring and synthetic compounds) including many drugs and poisons. This system may also play a role in protecting the body against chemical carcinogens. The detoxi-

fication system is labile but appears to respond to environmental influences such as the diet. It also appears that humans consuming larger amounts of fruits and vegetables have a stronger defense against carcinogenic compounds.

Recent studies have indicated that there may be a genetic link to many types of cancer, including breast cancer.[25,29] There is a two- to threefold higher risk for a person with a family history of breast cancer in first-degree relatives.[25] Oncogenes have been found in many human cancers and appear to promote its development.[29] An oncogene is a fragment of DNA which has been mutated. With the aid of genetic engineering techniques, scientists have found that a single gene from DNA which differs from its normal gene counterpart by only one nucleotide (out of approximately 5,000 nucleotides) could change normal cells into cancerous ones. It appears though that one mutation is not enough to cause a tumor and that several oncogenes must work together. Compounds that would control the actions of these oncogenes could possibly be used to treat certain types of cancers. Other factors which may increase the risk of breast cancer include: radiation, the use of non-contraceptive estrogens at the time of menopause, a history of benign breast disease, early menarche, late menopause, nulliparity, and giving birth to the first child after the age of 30.[25]

Hormone dependency of many breast cancers has been indicated by the observation that regression occurs after ovariectomy.[12] It is believed that estrogen may be directly involved in regulating tumor growth in mammary carcinoma.[8,12,21] Mammary tumors have been found to contain estrogen receptors (ER) which are thought to be involved in the

process by which estrogen causes these tumors to grow.[21] Several estrogens such as **1-3** are illustrated in Figure 1.

One main function of steriod hormones, such as **1-3**, is the regulation of protein synthesis in the target tissue.[8] Estradiol, estrone and estriol are the three main natural estrogenic harmones.[8,21] Estradiol is the most abundant and most potent estrogen and is released from the ovary. Estrogen enters the target cell by diffusion and is bound to the ER. This binding causes the complex to change to an "activated form" which is then translocated into the cell nucleus. In the nucleus, the complex reacts with the chromatin and there is a nuclear retention of the hormones. Then, by a process that is not fully understood, an increase in the RNA synthesis followed by an increase in protein synthesis is seen in the target cell (Figure 2).

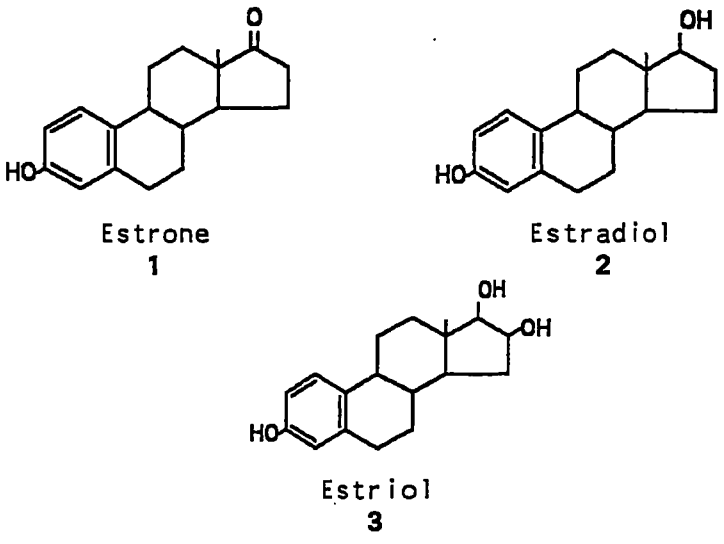


Figure 1. Structural Formulas of the Three Main Natural Estrogenic Hormones

Since the causes and nature of breast cancer are not fully understood, treatment for the disease has caused much controversy. Surgery is still the main form of treatment in most cases.[25] The most common types of surgery are: a) ultraradical mastectomy - removal of the breast, the muscles of the chest wall and the lymph nodes in the armpit; b) radical mastectomy - removal of the breast and axilliary lymph nodes and underlying chest muscle; c) total mastectomy with axilliary dissection - removal of the breast and axilliary lymph nodes; d) lumpectomy - removal of the cancerous lump.

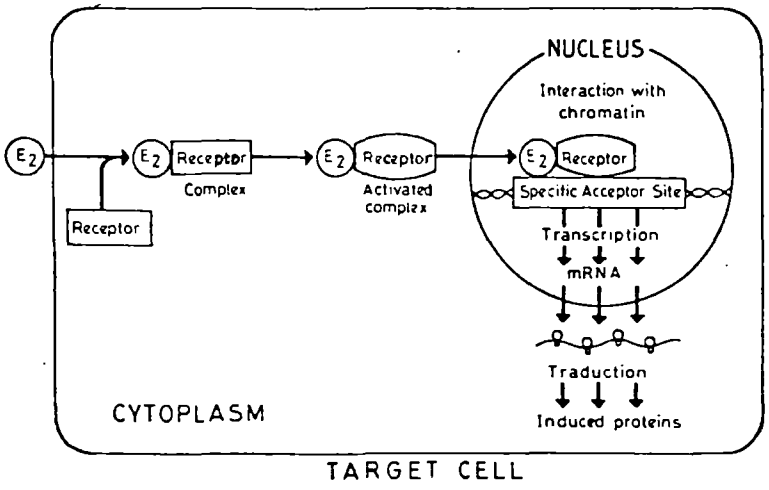


Figure 2. Schematic Representation of the Mode of Action of Estrogen Receptors in the Target Cells

Another form of treatment used for breast cancer is radiotherapy.[26] Radiation is sometimes used in conjunction with surgery, for

example after a lumpectomy. Although radiation therapy does not appear to prolong the life of patients with advanced breast cancer, it has been used to relieve some of the pain in those patients whose disease has spread to the bone.

Chemotherapy has been used after surgery in some patients who showed signs of recurring cancer.[26] Anticancer drugs are potentially dangerous and many side effects have been associated with the use of chemotherapy including: nausea, hair loss, bone marrow suppression, organ damage, and even second cancers caused by the carcinogenic nature of the drugs themselves.

Endocrine therapy is another form of treatment and, like radiotherapy, has been used mainly as a post surgical technique.[26] This method involves the surgical removal of any or all of the endocrine glands (ovaries, adrenal, or pituitary) or the use of hormone drugs to alter their function. Those tumors which were found to be estrogen receptor positive gave a greater response to this type of treatment.

Several compounds, including **4-7** shown in Figure 3 which are similar in structure to estradiol, have been found to have weak estrogenic and strong antiestrogenic activities.[21] Although the mode of action of these antiestrogens (sometimes referred to as estrogen antagonists) are not clearly understood, the two main modes of action are thought to be: 1) antiestrogens cause the target cell to be less sensitive to estrogen stimulation by decreasing the concentration of ER in the cytoplasm; or 2) the complex formed when antiestrogens bind to the ER is not able to initiate the events that lead to cell growth.

Cases have been reported showing that these antiestrogenic compounds can bind to the cytoplasmic ER and can also be translocated to the nucleus.[11,17,21] With many of the compounds there was a prolonged retention of the receptors in the nucleus causing a depletion of the ER in the cytoplasm. This then caused the cell to be insensitive to estradiol (Figure 4).

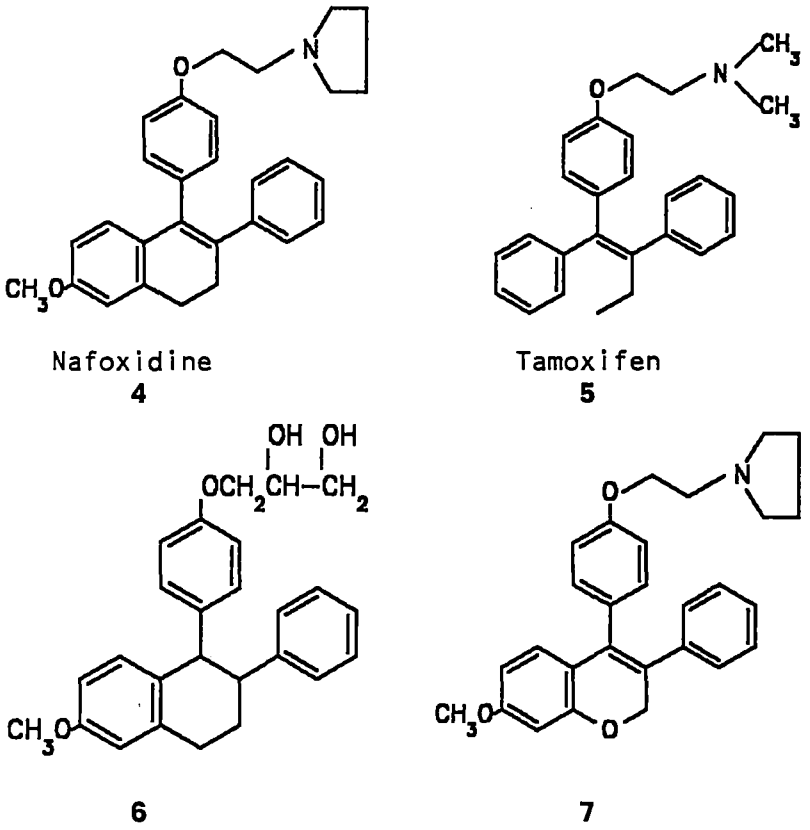


Figure 3. Structural Formula of Compounds Classified as Antiestrogens

Of those compounds shown in Figure 3, those which have been tested more frequently are Nafoxidine (**4**) and Tamoxifen (**5**). These compounds, in studies done on rat mammary tumors[16,20,27,36] as well as on human

mammary tumors,[1,4,6,15,32,38] have shown promising results as therapeutic agents for breast cancer treatment. In testing rat mammary carcinoma, tumors are induced with 7,12-dimethylbens(a)anthracene (DMBA) given orally or by injection of the compound suspended in an oil (peanut or sesame) to virgin female Sprague-Dawley rats which are 50 days old. After the tumors have reached a certain size, the animals are given injections of the antiestrogens suspended in an oil over a specified time period, and the results are compared to a control group which receive the oil by injection over the same period of time. At the end of the experiment, the animals were sacrificed and the tumors were removed and examined. The results of these tests showed that both Nafoxidine and Tamoxifen strongly inhibited the growth of certain tumors.[16,20,27,36] Nafoxidine was also found to prevent tumor formation to a very high degree.[16] Compounds **6** and **7** have also been found to have antiestrogenic activity in rat mammary tumors.[34,37]

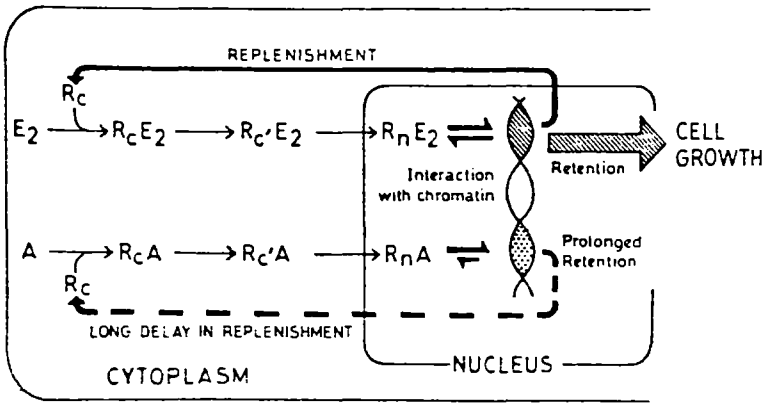


Figure 4. Comparative Representation of the Mode of Action of Estrogen and Antiestrogens in the Target Cells

In humans, oral dosages of the antiestrogen **4** or **5**, (as the amine salt), were given to patients with advanced, recurring, or metastatic breast carcinoma.[1,4,5,14,31,37] The most favorable response was seen in those cases where the tumors were found to be estrogen receptor positive.

The synthesis of compounds **4**[23], **5**[18], **6**[22] and **7**[30] have been described previously. The compounds were initially synthesized as antifertility agents and found to have antiestrogenic activity. The synthesis of Nafoxidine is shown in Figure 5.

As many as fifteen metabolites of estradiol have been found from *in vivo* and *in vitro* experiments involving studies of various mammals (Figure 6). It is assumed that any or all of these metabolites may be formed in any given species. Three metabolites of Tamoxifen have been found to form *in vivo* (Figure 7) The major metabolite appears to be 4-Hydroxytamoxifen (**8**). It has also been found that this metabolite binds to the estrogen receptor with a greater affinity than Tamoxifen. Studies show that 4-Hydroxytamoxifen inhibits the growth of hormone-dependent mouse mammary tumors more than Tamoxifen.[35] It is clear that oxidized metabolites show greater promise for antitumor activity.

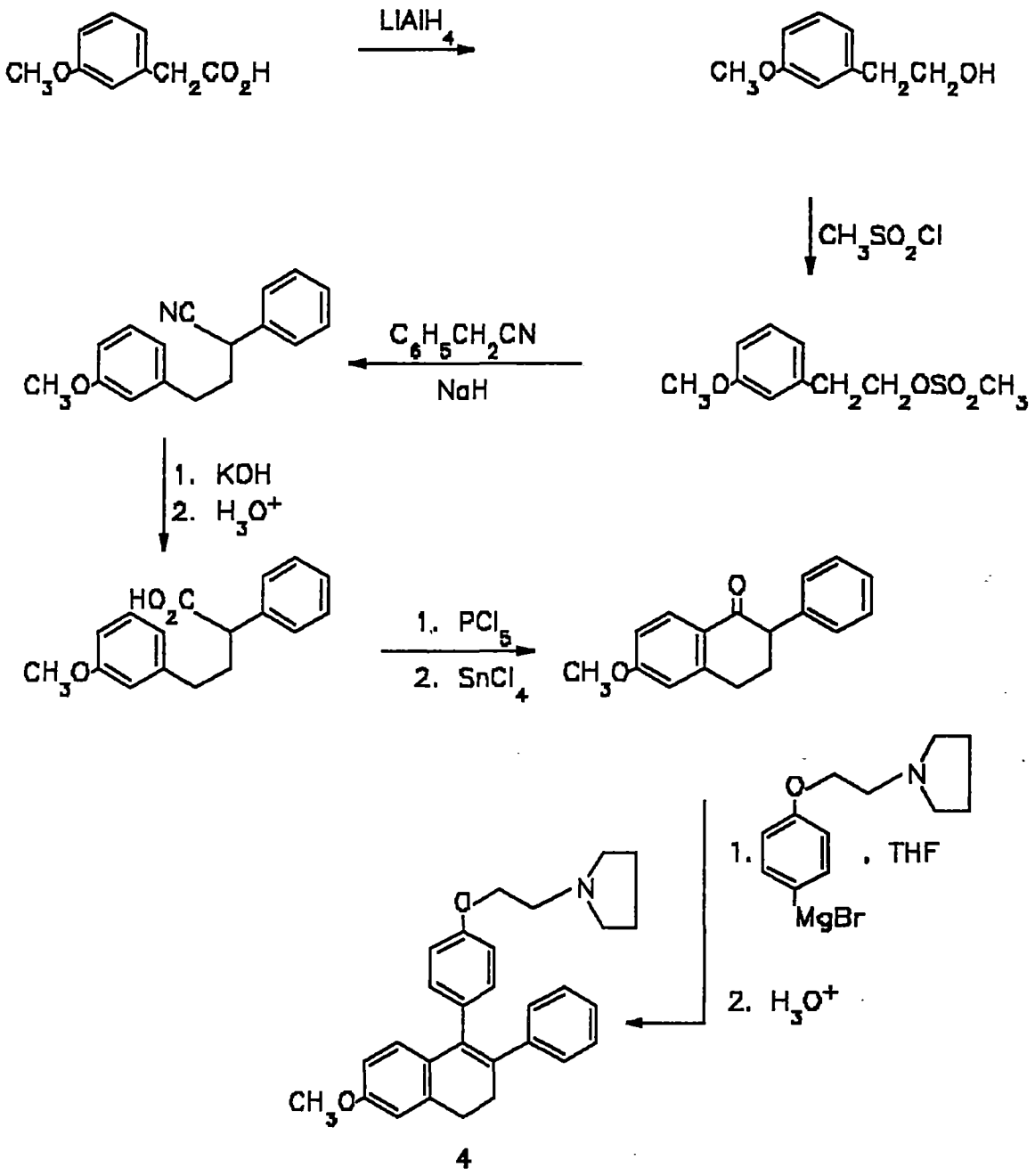


Figure 5. Synthesis of Nafoxidine (4)

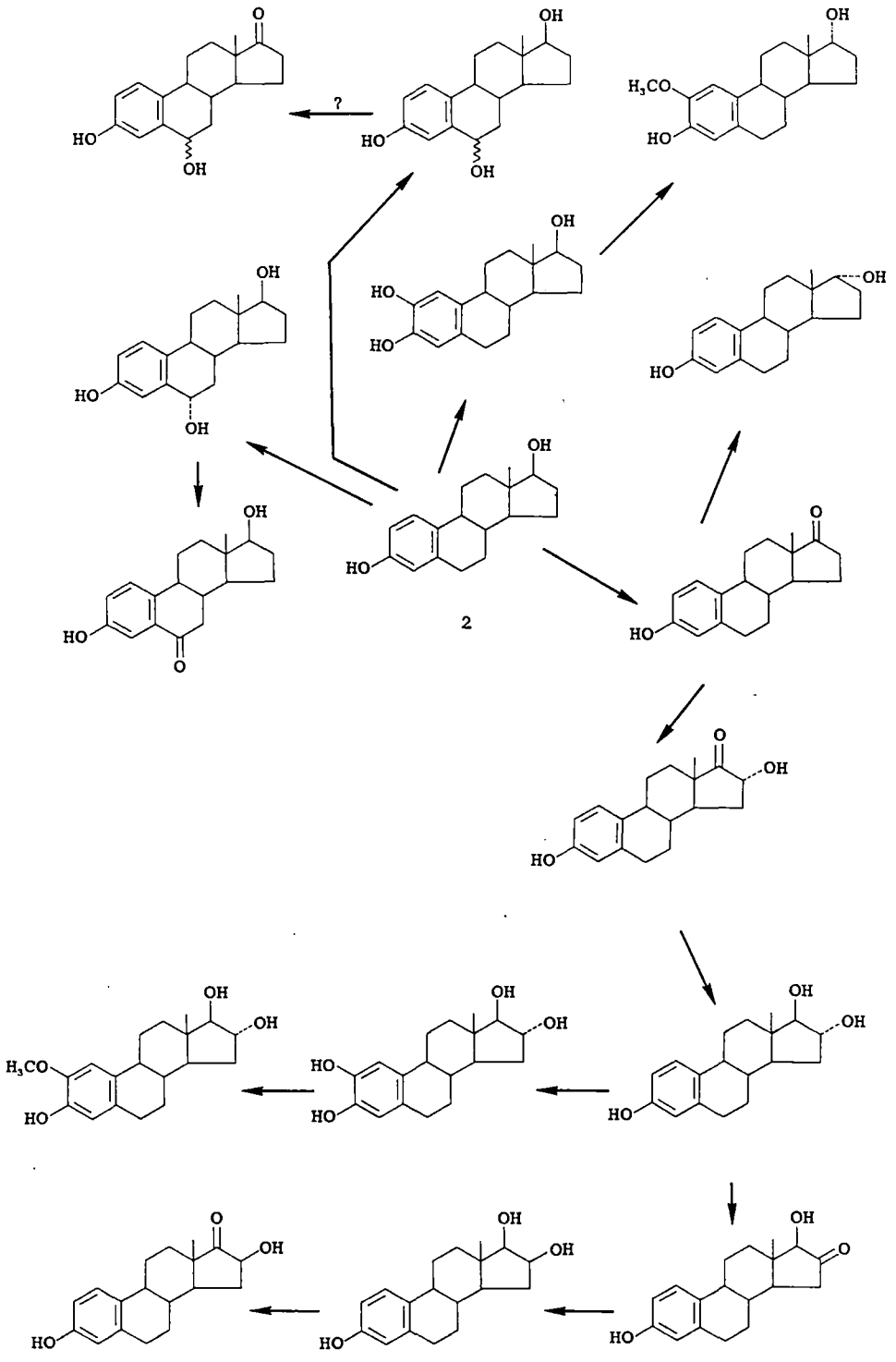


Figure 6. The Structural Formulas of Estradiol (**2**) and its Metabolites

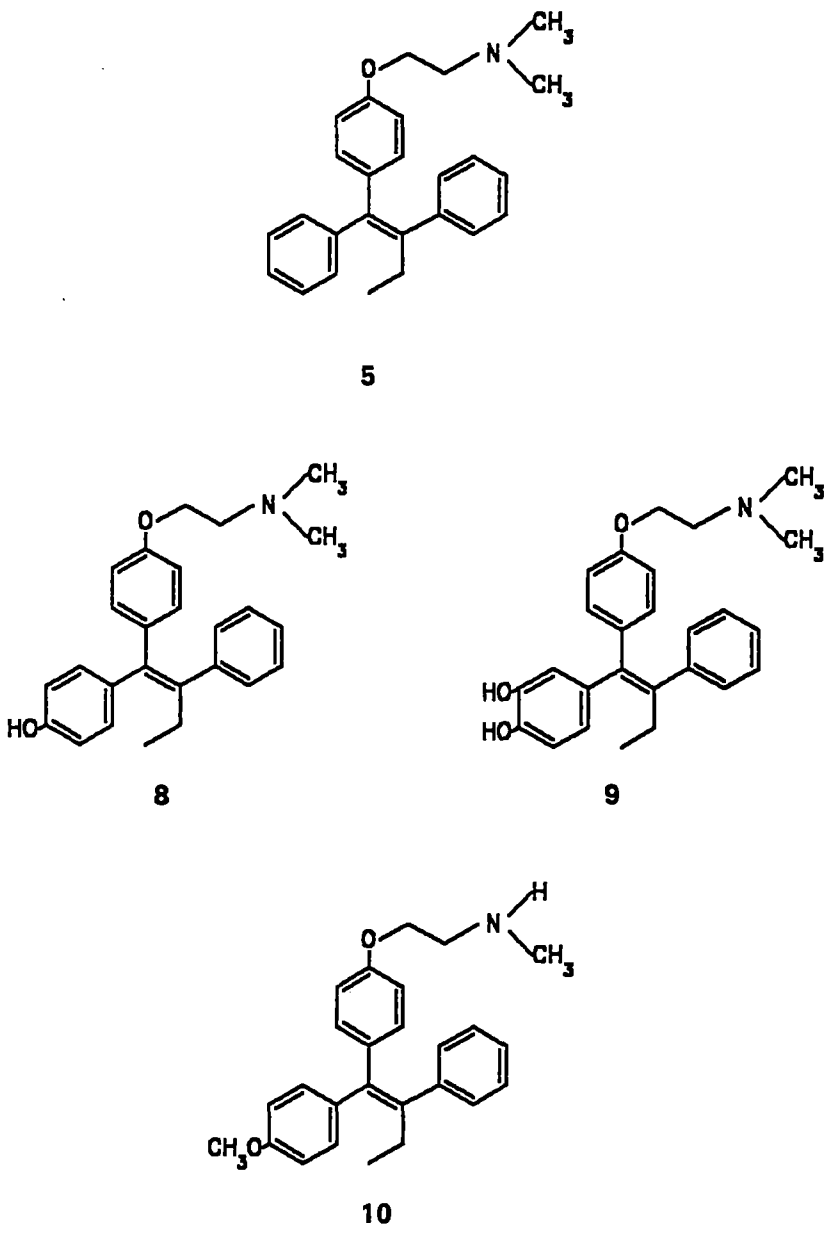


Figure 7. Structural Formulas of Tamoxifen (5) and Three of Its Metabolites

CHAPTER II

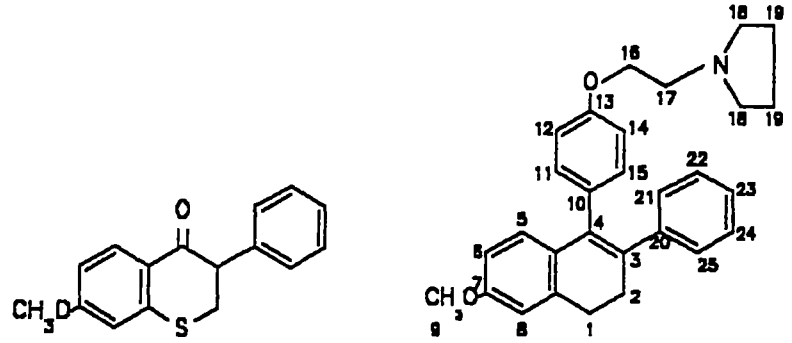
RESULTS AND DISCUSSION

The objective of this research was to synthesize several derivatives of 7-methoxy-3-phenyl-4-thiochromanone (**11**) as potential carcinostats for the treatment of breast cancer. The working hypothesis was that since the amino ether **12** was a clinically employed agent[6,15,32] for the treatment of breast cancer, such model systems like **13-14** (Figure 8) would have the advantage of possessing a heteroatom at the 1-position for improved hydrophilicity, as would the presence of the hydroxy group, and therefore for possible improved drug distribution *in vivo*. Moreover, the metabolic degradation pathway *in vivo* might be altered since the S atom replaced a benzylic methylene group, which has been a common vulnerable site for metabolism to occur.[13] The presence of the methoxy group in the 7-position has also been found to increase the antiestrogenic activity in the carbon derivative.[24] Of course, if activity is dependent upon the presence of the double bound at C(3)-C(4) as in **12**, any activity in **13** or **14** would require dehydration *in vivo*. This remains to be tested.

The synthesis of the ketone **11** has been reported previously,[10,11] but the yields were low and the intermediate acid was not characterized. We have modified the procedure and improved the overall yield to

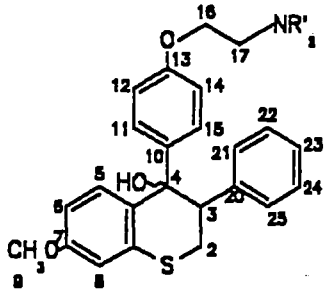
33%. Moreover, all intermediates were characterized by IR, ^{1}H, NMR, ^{13}C NMR, and elemental analyses.

Treatment of ketone **11** (Figure 9) with the Grignard reagents as shown produced the amino ethers **13**a and **13**b in yields of 25% and 15%, respectively. Both IR and NMR spectral data support the structures, as do the elemental analyses, and indicate the hydroxy group remains intact in all cases. In a similar fashion the amino ether **14** (Figure 10) without the methoxy group or the phenyl ring was prepared by the treatment of ketone **15** (commercially available) with the Grignard reagent shown to give the desired product in a low yield of 5%.

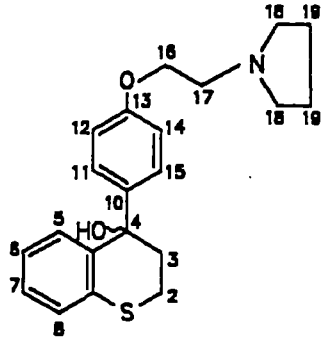


11

12



13 a. R'=CH_3
b. R'=C_2H_5



14

Figure 8. Structural Formulas of 7-Methoxy-3-phenyl-4-thiochromanone (**11**), Nafoxidine (**12**) and Heterocyclic Derivatives (**13-14**)

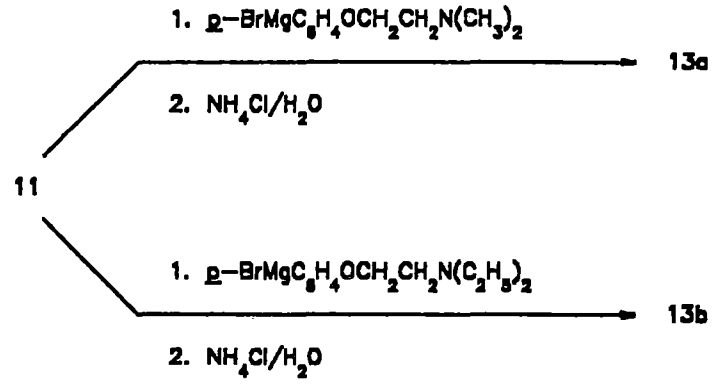


Figure 9. Treatment of Ketone **11** with the Grignard Reagents

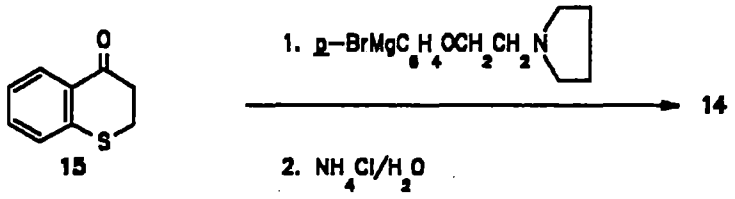


Figure 10. Treatment of Ketone **15** with the Grignard Reagent

Synthetic Techniques

The ketone **11** was previously prepared[10,11] by combining 3-methoxybenzenethiol[17] with atropic acid (**17**) and heating the mixture at high temperatures for several hours. The acid **18** was obtained as an oil and, without further purification, was cyclized by heating with polyphosphoric acid to ketone **11** in an overall yield of approximately 23% (see Figure 11).

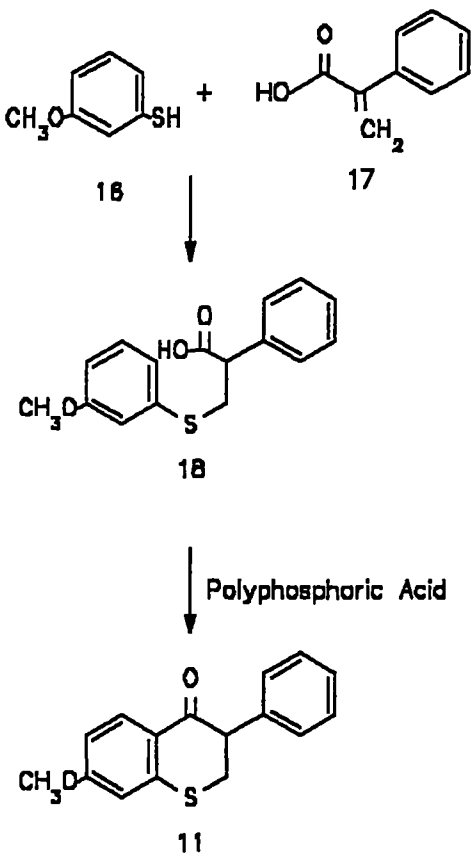


Figure 11. Previously Described Synthesis of Ketone **11**

In this work methyl 2-phenylacrylate, (the methyl ester of atropic acid) was prepared via a modified procedure previously described[2] to obtain the corresponding ethyl ester (Figure 12). Methyl phenylacetate and dimethyl oxalate were allowed to stand in the presence of sodium methoxide in thiophene-free benzene. The sodium salt obtained was acidified and then combined with formaldehyde and treated with an aqueous solution of potassium carbonate. After workup, an oil was obtained which was distilled to give the desired α-methylene-substituted ester contaminated with methyl phenylacetate. The mixture was not easily separable, but, since the contaminate did not appear to be a potential problem in the next step of the synthesis (namely a Michael addition reaction) and could be removed by distillation of the product, the mixture was used in crude form. However, it was found advantageous to use the mixture as soon as possible. Any unused material was kept in the freezer since methyl 2-phenylacrylate is known to polymerize on standing.[3]

The mechanism of formation of **20** from the formaldehyde condensation product is not straightforward. A proposed scheme for this reaction is shown in Figure 12. It is possible and it seems reasonable that during the reaction, the cyclic structure **19** could be formed and then decomposed during the distillation to give the desired product **20** along with carbon dioxide and carbon monoxide. No mechanistic studies have been done on this reaction and the conclusions are speculative.

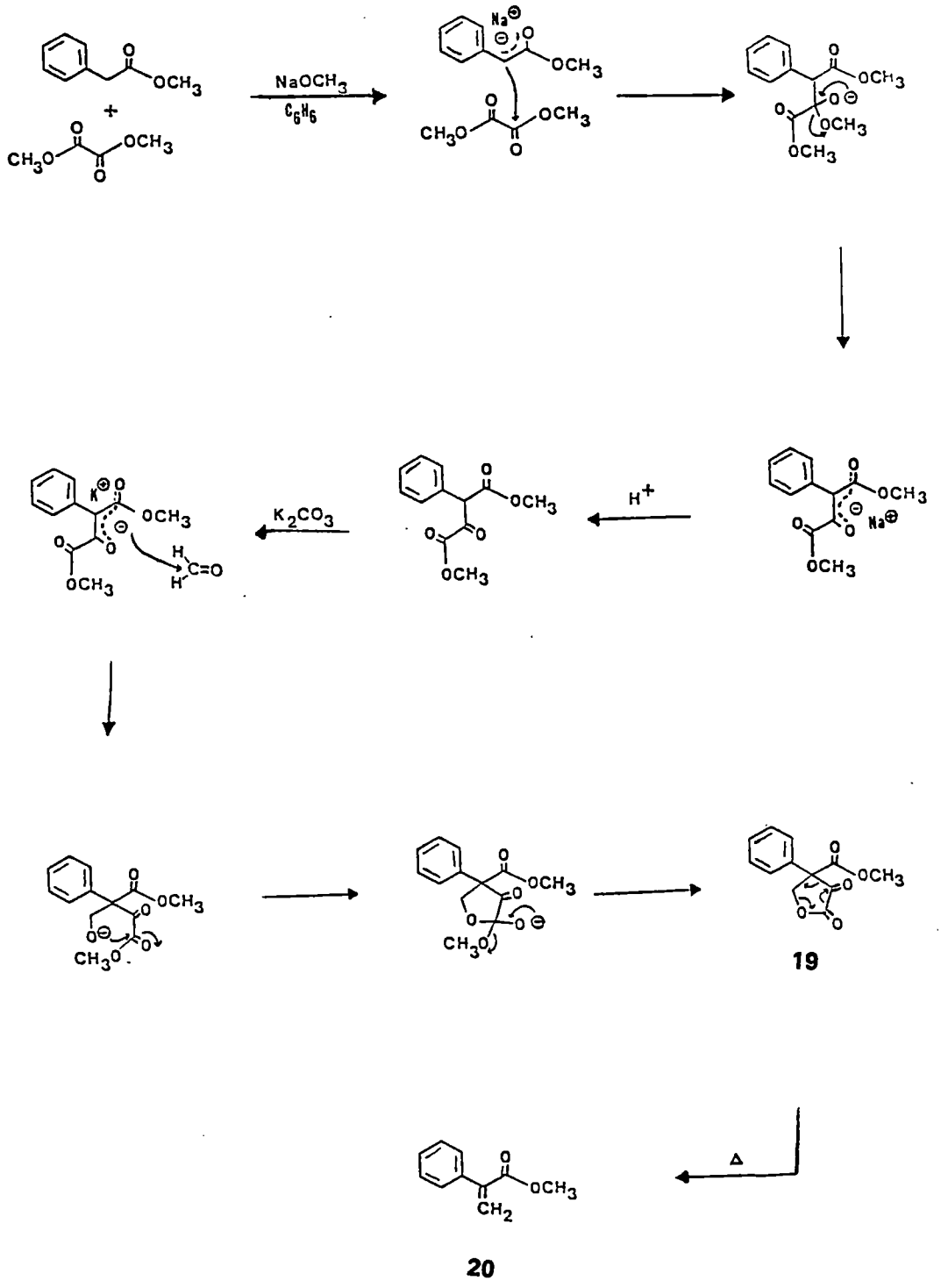


Figure 12. Proposed Mechanism for the Preparation of Ester **20**

The Michael addition (Figure 13) was carried out by the treatment of 3-methoxybenzenethiol with methyl 2-phenylacrylate using a catalytic amount of triethylamine and dry chloroform as a solvent. After the mixture was stirred at room temperature for several hours followed by the normal workup and distillation, ester **21** was obtained. Cleavage of ester **21** was effected under mild conditions with iodotrimethylsilane to give acid **22**. Cyclization of **22** was accomplished by initial conversion to the acid chloride using phosphorus pentachloride. The acid chloride was not isolated but was treated directly with tin(IV) chloride at room temperature in methylene chloride and gave ketone **11** via an intramolecular Friedel-Crafts acylation in an overall yield of 33%.

Initially the synthesis was tried using the ethyl ester **23**. Ethyl 2-phenylacrylate **23** was prepared under the same conditions employed to prepare the corresponding methyl ester **20**. The product obtained was a mixture of the desired α-methylene substituted ester contaminated with ethyl phenylacetate. The crude ester **23** was then combined (Figure 14) with 3-methoxybenzenethiol in chloroform, and a catalytic amount of triethylamine was added to the mixture. The solution was stirred at room temperature for several hours. After workup, the oil obtained was distilled to give the addition ester **24**. Cleavage of the ester was attempted by boiling in sodium hydroxide solution (10% and 15%), but the acid **23** could not be obtained from the mixture. Using excess iodotrimethylsilane under the same conditions as described for methyl ester **21**, the acid **22** was obtained but in a yield of only 27%. Thus, as the literature[33] suggests, since methyl esters are cleaved easier than the ethyl esters with iodotrimethylsilane, the reaction scheme was modified to incorporate the methyl ester.

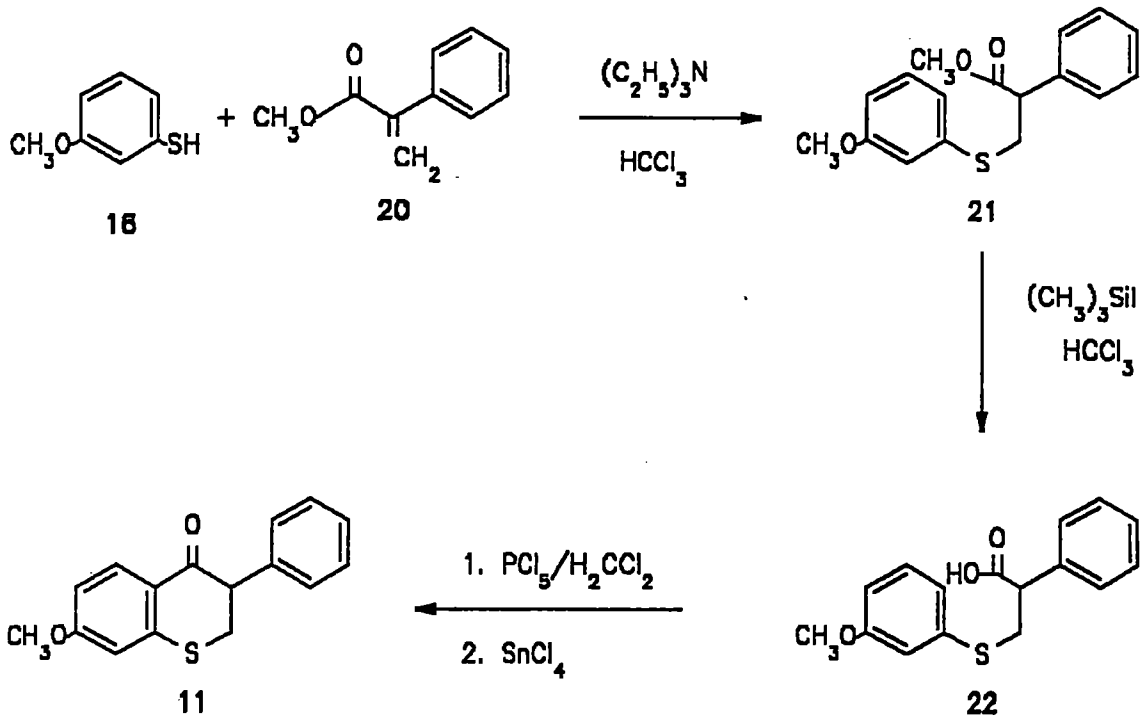


Figure 13. Synthesis of Ketone **11**

Cyclization of acid **22** was tried using 115% polyphosphoric acid. The acid was heated at the boiling point of xylene with 115% of polyphosphoric acid for 2.5 hours. After workup, the ketone was obtained but in a low yield of 11%.

The required aromatic bromoethers, **25** and **26**, were prepared by O-alkylation of p-bromophenol with the alkyl chloride necessary to give the desired amino derivative (Figure 15). p-Bromophenol, potassium carbonate and dimethylformamide (DMF) were combined and boiled 30-45 min. After the mixture was cooled slightly, the amine hydrochloride

was added all at once. The mixture was boiled for several hours and after workup and distillation the desired products were obtained in modest yields of 41% and 11%, respectively.

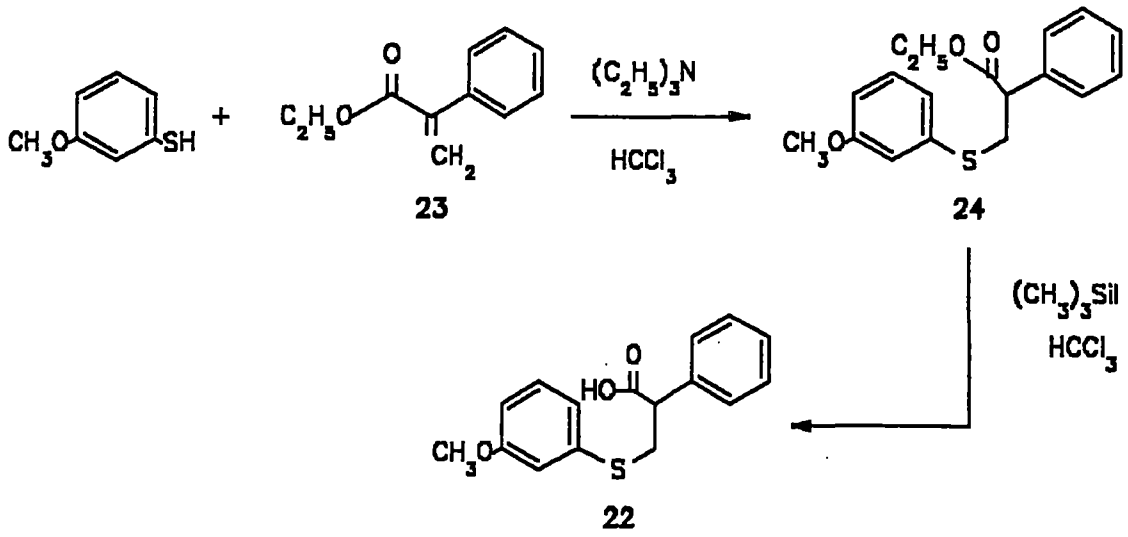


Figure 14. Synthesis of the Acid **22** from the Ethyl Ester **23**

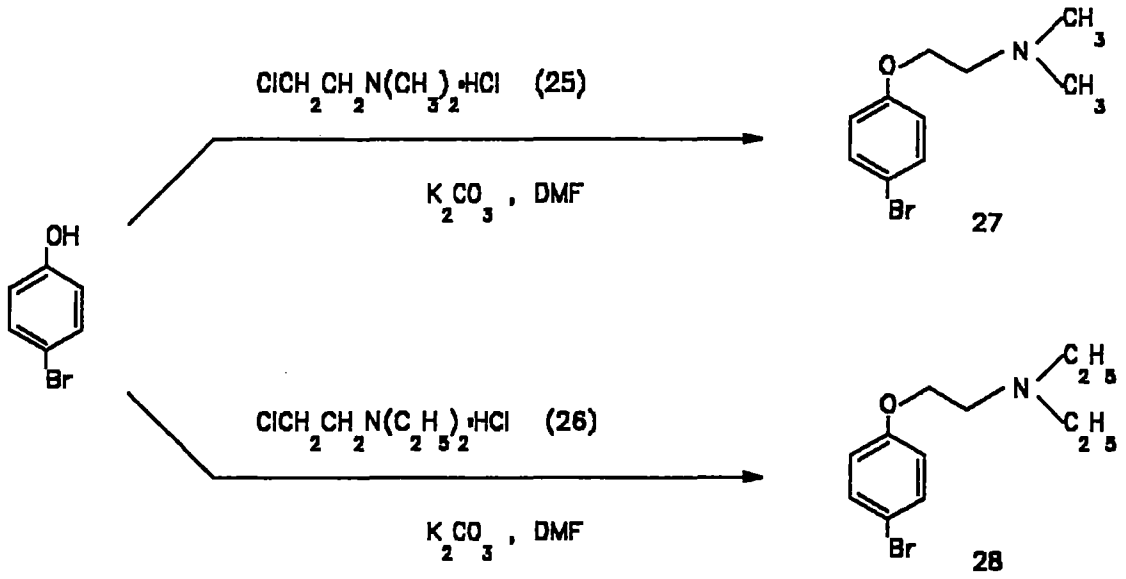
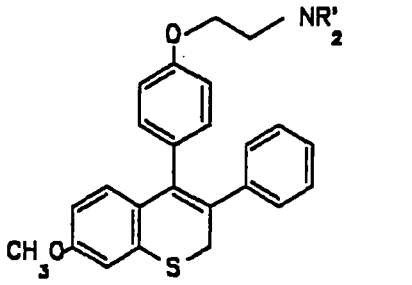


Figure 15. Preparation of the Amino Ethers **27** and **28**

The Grignard reactions were carried out by first preparing the Grignard reagents of the aromatic halides **25** and **26** as follows. One drop of the halide was added to a flask containing magnesium metal and a small amount of dry tetrahydrofuran. After initiation of the reaction, the remaining halide, diluted with tetrahydrofuran, was added dropwise over 30 min. The mixture was heated over a period of time and then cooled in an ice bath. Ketone **11** in tetrahydrofuran was added dropwise over 30 min and the reaction mixture was warmed to room temperature and stirred for several hours. During workup, the magnesium salts were precipitated by adding water dropwise until no more precipitate was deposited from the solution. The precipitate was

then filtered off and washed several times with ether. The combined organic layers were washed with water and 15% ammonium chloride solution. Under these conditions, the tertiary alcohols **13** and **14** have been obtained.

To date, the dehydrated products **29a** and **29b** (Figure 16) have not been isolated from the reaction mixture. It is conceivable that the formation of the cation **31** (Figure 17), via the sequence illustrated from **13**, may not be facile under mild conditions. It is doubtful that all three of the aryl groups can be planar simultaneously to stabilize the cation **31** formed from loss of water. Quite possibly treatment of **13** or **14** with p-toluenesulfonic acid in a boiling hydrocarbon solvent (benzene or toluene) might effect the dehydration to **29**.[24]



29 a. R' = CH_3
b. R' = C_2H_5

Figure 16. Structural Formulas for the Alkenes **29a** and **29b**

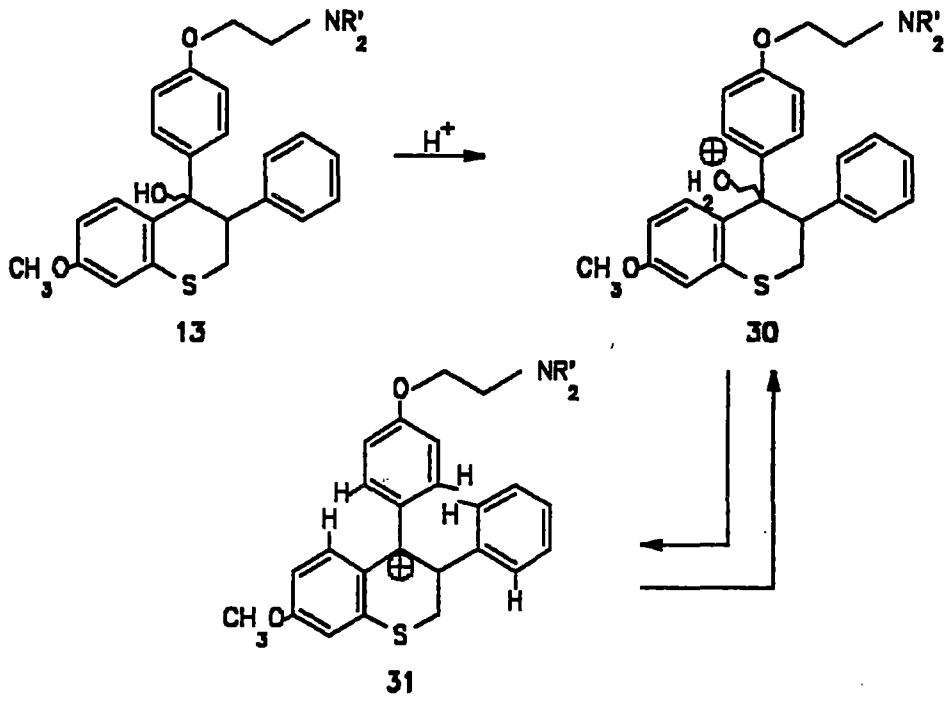


Figure 17. Possible Sequence for the Formation of Cation **31**

Spectral Analysis

The assignments for ^{1}H and ^{13}C NMR signals were made by comparing spectral data of the products and starting materials and by use of heteronuclear correlated 2-dimensional (HETCOR 2-D) NMR experiments. Due to the chirality of the carbon attached to the phenyl ring (C-3) in ketone **11** (and its precursors **21** and **22**), the protons on the carbon alpha to S (C-2) are not equivalent. Thus each proton (two on C-2 and one on C-3) appeared as a doublet of doublets in the ^{1}H NMR spectra. In order to determine which protons were attached to which carbon, a HETCOR 2-D NMR

experiment[13] was done on the methyl ester **21** (see Figure 18) and on the ketone **11** (see Figure 19). The J values were determined and are compared on Table I. From the data obtained, the doublet of doublets at lowest field were assigned to H-3 and the other two signals were assigned to the protons H-2. The other assignments were fairly straightforward and are listed in Table II.

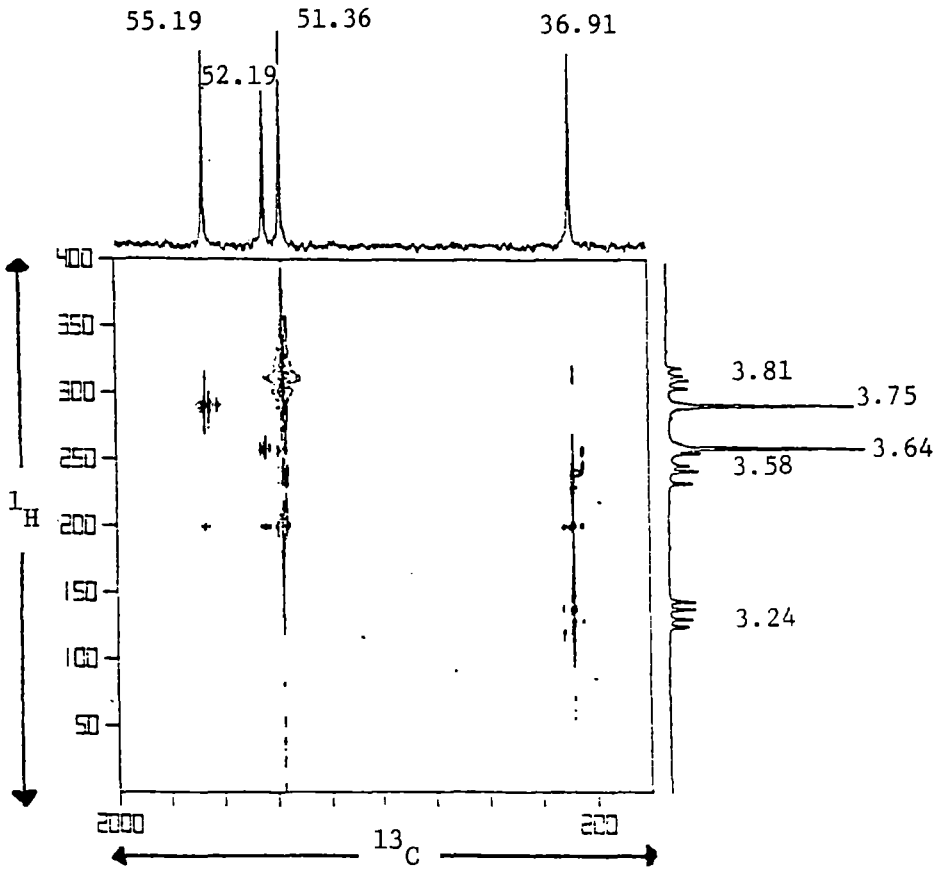


Figure 18. HETCOR 2-D NMR Spectrum of **21**

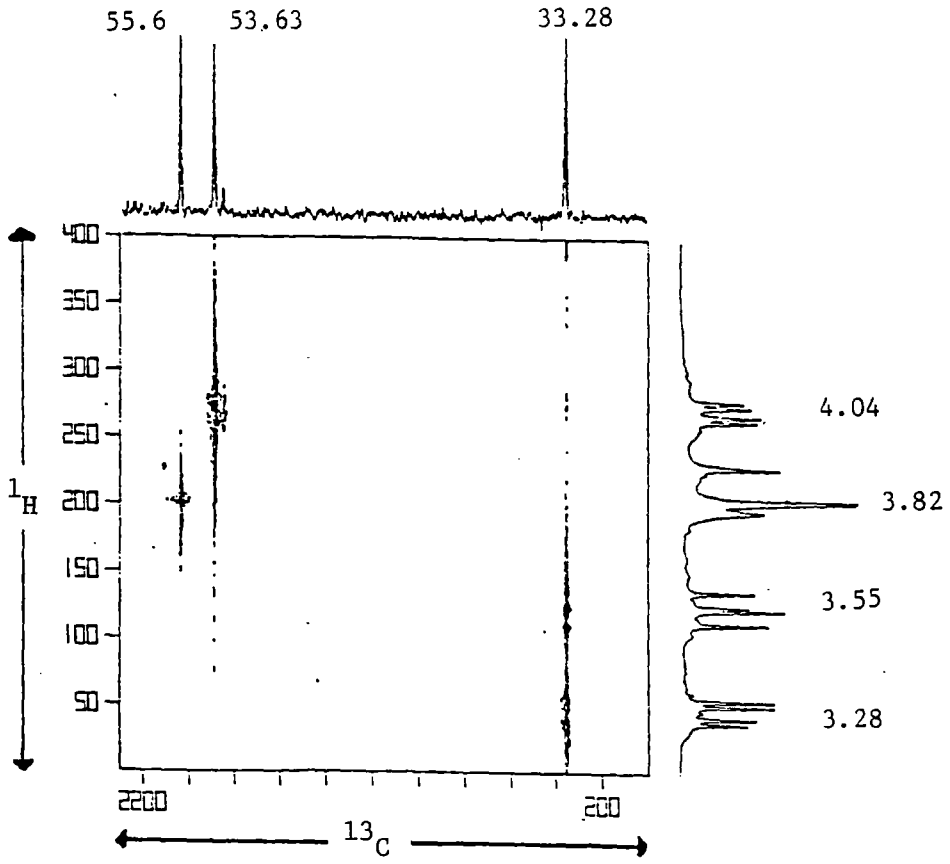


Figure 19. HETCOR 2-D NMR Spectrum of **11**

TABLE I

COMPARISON OF THE J VALUES (HZ) FOR THE PROTONS ON H-2 AND H-3 IN KETONE **11** AND ITS PRECURSORS

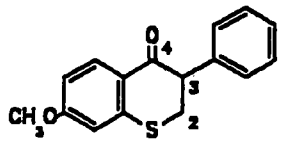
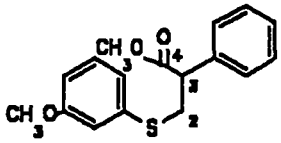
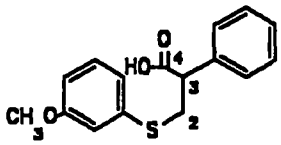
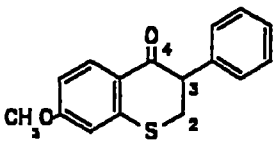
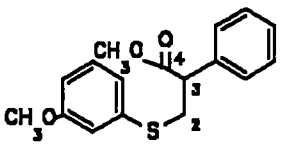
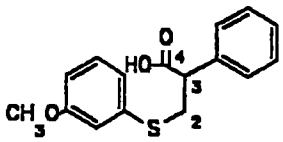
	J Values		
	$^{2}J_{gem}$	$^{3}J_{vic}$	
 **11**	14	12	6
 **21**	14	10	6
 **22**	14	10	6

TABLE II

COMPARISON OF THE ^{1}H AND ^{13}C NMR SPECTRAL DATA FOR KETONE **11** AND ITS PRECURSORS

Atom Number	Chemical Shift[a] (splitting pattern[b])		
	 **11**	 **21**	 **22**
^{1}H			
H-2	3.30 (dd)	3.24 (dd)	3.24 (dd)
H-2	3.55 (dd)	3.58 (dd)	3.58 (dd)
H-3	4.05 (s)	3.84 (dd)	3.84 (dd)
$ArO\underline{C}H_3$	3.83 (s)	3.74 (s)	3.80 (s)
^{13}C			
C-2	33.33	36.19	36.70
C-3	53.64	51.36	51.46
C-4	193.22	172.84	177.99
$ArO\underline{C}H_3$	55.57	55.19	55.29

[a]Measured downfield (δ values for ^{1}H and ppm for ^{13}C) from TMS.

[b]s=singlet, dd=doublet of doublets.

The IR data was also useful. The C=O stretching frequency appeared at 1745 cm^{-1}, 1720 cm^{-1}, and 1665 cm^{-1} for the methyl ester **21**, the acid **22**, and the ketone **11**, respectively. The acid **22** showed a broad stretching band for O-H at 3010 cm^{-1}.

The ^{1}H and ^{13}C NMR signal assignments for the alkyl protons and carbons in the aromatic bromides **25** and **26** were relatively simple. Splitting patterns and the extreme chemical shift induced by the heteroatoms made identification easy. The NMR data for the dimethylamino aromatic bromide **25** and the diethylamino aromatic bromide **26** are listed in Table III.

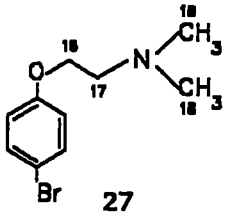
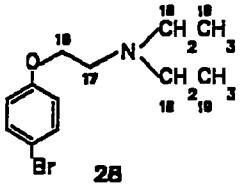
The spectral data for the final alcohols **13a** and **13b** were compared to the starting ketone **11** and the respective aryl bromide used to prepare the compound. The tertiary alcohols were found to have ^{1}H and ^{13}C NMR peaks that correlated very well with both starting materials (Table IV). The aromatic methoxy group appeared as a large singlet in the ^{1}H NMR spectra at δ 3.83, 3.80 and 3.80 for the ketone **11** and alcohols **13a** and **13b**, respectively. In the ^{13}C NMR spectrum, these peaks appeared at 55.57, 55.27 and 55.27 ppm for **11**, **13a**, and **13b**, respectively. The ^{1}H signals for the two protons H-2 of the alcohols appeared as two doublet of doublets for ketone **11**. The proton H-3 appeared as a broad doublet. Also, the two triplets for aliphatic protons H-16 and H-17 corresponded well with those for the aryl bromides **25** and **26**.

Evidence that the -OH group remained intact was seen by the presence of a broad O-H stretching band at 3200 cm^{-1} in the IR spectra of both alcohols **13a** and **13b**. The disappearance of the C=O stretching

band in ketone **11** at 1665 cm^{-1} was noted. A broad singlet at δ 2.03 in the ^1H NMR spectrum for **13b** was determined to be the hydrogen attached to the oxygen by the disappearance of the peak via D_2O exchange. The carbon attached to the hydroxy group (C-4) appeared at 75.75 and 75.76 ppm for **13a** and **13b**, respectively. These data were compared to those from a model system, benzhydrol (Figure 20), wherein the carbon attached to the hydroxy group has been reported at 75.8 ppm.[18]

TABLE III

COMPARISON OF THE ^{1}H AND ^{13}C NMR SPECTRAL DATA FOR THE AROMATIC BROMIDES **27** AND **28**

Atom Number	Chemical shift[a] (Splitting pattern[b])	
	 **27**	 **28**
^{1}H		
H-16	4.05 (t)	4.04 (t)
H-17	2.72 (t)	2.90 (t)
H-18	2.35 (s)	2.67 (q)
H-19		1.08 (t)
^{13}C		
C-16	66.13	66.45
C-17	58.05	51.46
C-18	45.78	47.57
C-19		11.47

[a]Measured downfield (δ values for ^{1}H and ppm for ^{13}C) from TMS.

[b]s=singlet, dd=doublet of doublets.

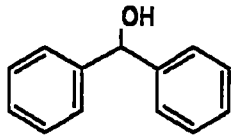


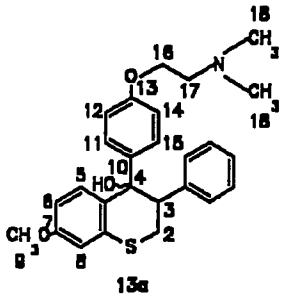
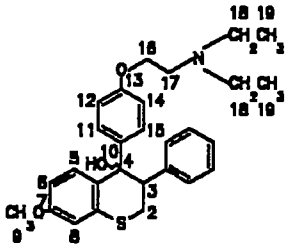
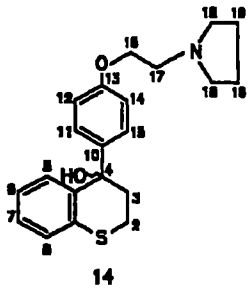
Figure 20. Benzhydrol

The alcohol **14** had NMR signals similar to those seen in the spectra for **13a** and **13b**. The splitting patterns for the protons H-2 and H-3 were different due to the loss of chirality of C-3. The NMR data for **13a**, **13b** and **14** are compared in Tables IV and V.

In the formation of **13a** and **13b**, the possibility exists for cis-trans-isomers to form. The sharpness of the melting points, the observation of only one spot on a TLC plate, and the NMR spectral data support only one isomer for **13a** and **13b**. In the ^{13}C NMR spectra, we note that the carbon signals for C-2 and C-3 have very similar chemical shifts and therefore it is reasonable that the stereochemistry at the chiral center (C-4) is the same in both compounds. Models (Courtauld, space filling models) imply that the two aryl groups are probably in an anti arrangement with respect to each other.

TABLE IV

COMPARISON OF THE ^{1}H NMR SPECTRAL DATA FOR ALCOHOLS **13A, 13B** AND **14**

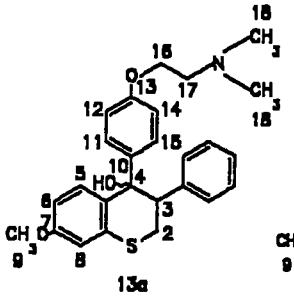
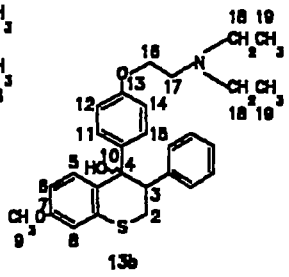
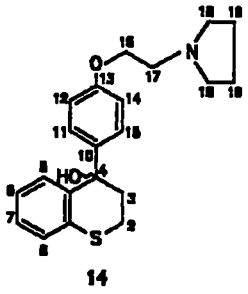
Atom Number	Chemical Shift[a] (Splitting Pattern)[b]		
	 13a	 13b	 14
H-2	2.90(dd)	2.92(dd)	2.40(m)
	3.55(dd)	3.56(dd)	
H-3	3.76(bd)	3.74(bd)	2.75(m)
			3.20(m)
H-9	3.80(s)	3.80(s)	
H-16	4.02(t)	4.02(t)	4.10(t)
H-17	2.70(t)	2.86(t)	2.94(t)
H-18	2.32(s)	2.72(q)	2.62(bs)
H-19		1.05(t)	1.80(m)

[a]Measured downfield (δ values) from TMS.

[b]s=singlet, t=triplet, q=quartet,. dd=doublet of doublets, bs=broad singlet, bd=broad doublet, m=multiplet.

TABLE V

COMPARISON OF THE ^{13}C NMR SPECTRAL DATA FOR THE ALCOHOLS **13A, 13B** AND **14**

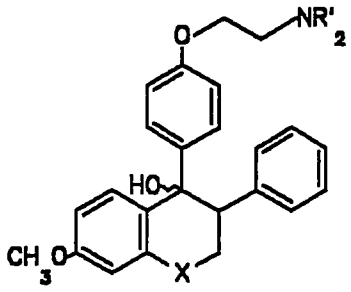
Atom Number	Chemical Shift[a]		
	 13a	 13b	 14
C-2	28.30	28.29	23.20
C-3	53.22	53.20	39.54
C-4	75.75	75.76	73.56
C-9	55.27	55.27	
C-16	65.80	66.42	66.95
C-17	58.27	51.67	55.04
C-18	45.88	47.86	54.67
C-19		11.83	23.46

[a]Measured downfield (ppm) from TMS.

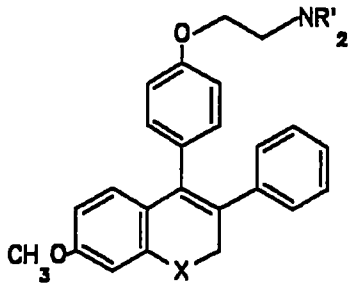
SUGGESTIONS FOR FUTURE WORK

Biological testing of the alcohols **13-14** must be performed to determine their activity and possible usefulness in the treatment of breast cancer. If the biological studies are promising, toxicity studies would also have to be performed for the compounds. The alcohols should be dehydrated to the corresponding alkenes. The biological activity of the alkenes should also be determined and their activities compared to the alcohols.

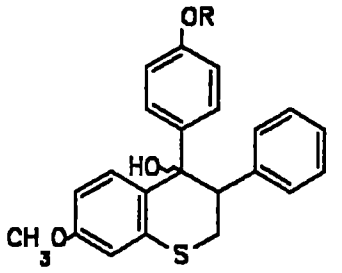
Modifications in the basic structure which could be made, include: (1) the incorporation of other heteroatoms such as N or P (**30-31**), (2) changes in the side chain by replacing the amino group (**32, 33**) (Figure 21).



32 a. X = NR', NR'R"
b. X = PR, PR'R"
P(O)R, P(S)R



33 a. X = NR', NR'R"
b. X = PR, PR'R"
P(O)R, P(S)R

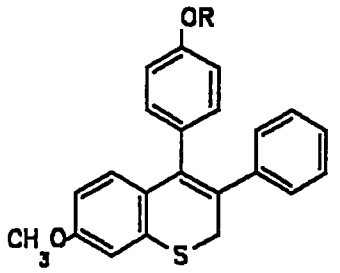


34 a. R = $CH_2CH(OH)CH(OH)CH_2$

b. R = $CH_2CH(O)CH_2$

c. R = H

d. R =



35 a. R = $CH_2CH(OH)CH(OH)CH_2$

b. R = $CH_2CH(O)CH_2$

c. R = H

d. R =

Figure 21. Structural Formulas of Compounds Suggested for Future Work

CHAPTER III

EXPERIMENTAL

General Information

All reactions were carried out in an inert nitrogen atmosphere using magnetic stirring unless otherwise stated. The NMR spectra were taken on a Varian XL-300 NMR spectrometer operating at 299.99 MHz and 75. MHz for the detection of ^{1}H and ^{13}C, respectively, or on a Varian XL-100 NMR spectrometer operating at 25. MHz for the detection of ^{13}C. All ^{13}C NMR signals are reported in ppm downfield from tetramethylsilane with $DCCl_3$ as the solvent. IR data was collected on a Perkin-Elmer 681 IR spectrophotometer. Melting points were obtained using a Thomas-Hoover melting point apparatus or a Fisher-John's melting point apparatus and are uncorrected. Chromatography was accomplished using a Chromatotron Model 7924 (Harrison Research, 840 Moena Court, Palo Alto, Ca 94306) with silica gel. Elemental analyses were performed by Galbraith Laboratories of Knoxville, TN.

Starting Materials

The following starting materials were purchased from Aldrich and were used without further purification: methyl phenylacetate, ethyl

phenylacetate, dimethyl oxalate, diethyl oxalate, iodotrimethylsilane, p-bromophenol, 2-dimethylaminoethyl chloride hydrochloride, thiochroman-4-one (**15**), 1-[2-(p-bromophenoxy)ethyl]pyrrolidine and 3-methoxybenzenthiol (**16**). Thiophene-free benzene was purified by washing with concentrated H_2SO_4 (until yellow coloration was slight), H_2O, $KMnO_4$ in 10% H_2SO_4 and 10% NaOH. The benzene was then dried ($MgSO_4$) overnight, filtered and distilled from CaH. Dry tetrahydrofuran was obtained by distillation from sodium. Chloroform was dried over alumina. All other solvents were used without purification.

Preparation of Methyl 2-Phenylacrylate (**20**)

Sodium methoxide was prepared by reacting clean, shiny sodium metal (5.8 g, 0.25 g-at) with absolute methanol (100 mL) in a 500 mL, round-bottom flask with separable top having three necks (Kontes, K-612000 and K-613000) and a nitrogen inlet. The flask was fitted with a condenser and two ground glass stoppers. After the reaction of the sodium was complete (30 min), the condenser was replaced with a distillation apparatus. The excess methanol was distilled from the sodium methoxide with a nitrogen stream flowing over the mixture to leave a dry, white solid. The solid was allowed to cool to room temperature (15 min), and the distillation apparatus was replaced with a condenser. Purified thiophene-free benzene (100 mL) was added to the flask, and a glass stirring rod was used to break up the solid. The solid was suspended in the benzene with the aid of magnetic stirring. Dimethyl oxa-

late (29.8 g, 0,25 mol) and methyl phenylacetate (49.6 g, 0.33 mol) were added successively all at once to the sodium methoxide slurry. The mixture was stirred under nitrogen for 30 min; part of the sodium methoxide dissolved during this time and a pale yellow solution resulted. The mixture was then allowed to stand overnight (18 h) and a white solid was precipitated. The solid was collected on a Buchner funnel and washed with benzene (100 mL) and anhydrous ether (3 × 100 mL). The solid was then transferred to a 1000 mL beaker and acidified with 2 N sulfuric acid (100 mL). The resulting mixture was stirred until all the solid dissolved (30 min). Two layers resulted and were separated in a separatory funnel. The bottom layer (water layer) was extracted with ether (3 × 100 mL) and the ether layers were combined with the top layer (organic layer) and dried ($MgSO_4$) overnight. The solution was filtered and concentrated (rotovap) in a 250 mL, round-bottom flask to give a light yellow oil. Without further purification, the oil was mixed with 37% aqueous formaldehyde (31 mL) and H_2O (100 mL). The temperature of the mixture was lowered to 15°C with an ice water bath. To this solution was added dropwise a solution of K_2CO_3 (27 g, 0.20 mol) in H_2O (50 mL) from an addition funnel over 30 min. The mixture was then allowed to warm to room temperature and stirred for 2 h. The mixture was extracted with ether (3 × 50 mL) and the combined ether layers were dried ($MgSO_4$) overnight. The solution was filtered, concentrated (rotovap) and distilled to give 30.8 g of a clear, colorless liquid; bp 62-66°C/0.65 mm Hg (lit bp[3] 95-98°C/6 mm). From ^1H NMR analysis, the product was determined to be a mixture of starting material and the desired ester **20**. IR (film) cm^{-1}: 1731

(C=O); ^{1}H NMR ($DCCl_3$) δ 3.84 (s, 3 H, $OC\underline{H}_3$), 5.91 (s, 1 H, $=C\underline{H}_2$) and 6.38 (s, 1 H, $=C\underline{H}_2$), 7.3-7.45 (m, 5 H, Ar$\underline{H}$)

Preparation of Ethyl 2-Phenylacrylate (**23**)

The reactions were carried out under the same conditions as with the methyl derivative **20** with the following changes: absolute ethanol (100 mL) was used in place of absolute methanol. Dimethyl oxalate and methyl 2-phenylacetate were replaced with diethyl oxalate (36.5 g, 0.25 mol) and ethyl phenylacetate (54.3 g, 0.33 mol). Distillation of the product (bp 73°C/0.175 mm Hg; lit bp[2] 76-77°C/1.2 mm Hg) gave 26.5 g of the desired product **23** with approximately 1% of an impurity which was determined from NMR analysis to be starting material. IR (film) cm^{-1}: 1727 (C=O); ^{1}H NMR ($DCCl_3$) δ 1.36 (t, 3 H, $-OCH_2C\underline{H}_3$), 4.30 (q, 2 H, $OC\underline{H}_2CH_3$), 5.91 (s, 1 H, $=C\underline{H}_2$) and 6.37 (s, 1 H, $=C\underline{H}_2$), 7.24-7.48 (m, 5 H, Ar$\underline{H}$); ^{13}C NMR ($DCCl_3$) ppm 14.17 ($OCH_2\underline{C}H_3$), 60.95 ($-O\underline{C}H_2CH_3$), 166.49 ($\underline{C}$=O), Ar$\underline{C}$: 126.14, 127.86, 128.07, 136.59, 141.40.

Preparation of Methyl 3-(3-Methoxyphenyl-thio)-2-phenylpropanoate (**21**)

Methyl 2-phenylacrylate (**20**, 11.7g, 0.039 mol, crude) and 3-methoxybenzenethiol (**16**, 5.0 g, 0.034 mol) and 12 mL of $HCCl_3$ were combined in a 50 mL, 3 necked, round-bottom flask fitted with a condenser, addition funnel with a nitrogen inlet, and a glass stopper. The mixture was cooled to 0°C with a salt/ice/water bath.

Triethylamine (0.2 mL) was added to the mixture by syringe. The solution was allowed to warm to room temperature and the clear, colorless liquid was stirred for 20 h. The mixture was diluted with ether (20 mL), transferred to a 125 mL separatory funnel, and washed with 5% NaOH (2 × 15 mL), H_2O (3 × 15 mL), and sat NaCl (2 × 15 mL). The ether layer was dried (Na_2SO_4) overnight. The solution was filtered and the ether was removed (rotovap); the remaining liquid was vacuum distilled to give a clear, colorless liquid **21**: bp 143-160°C/ 0.04 mm Hg (8.96 g, 0.03 mol, 88%).

Anal. Calcd. for $C_{17}H_{18}O_3S$: C, 67.52; H, 6.00: S, 10.60.
Found: C, 67.74; H, 6.09: S, 10.55.

IR (film) cm^{-1}: 1745 (C=O); ^1H NMR ($DCCl_3$) δ 3.24 (dd, 1 H, -S-C$\underline{H}_2$-) and 3.58 (dd, 1 H, -S-C$\underline{H}_2$-), 3.64 (s, 3 H, [C=O]-OC$\underline{H}_3$), 3.75 (s, 3 H, -OC$\underline{H}_3$), 3.81 (dd, 1 H, C_6H_5- C$\underline{H}$-C=O), 6.7-7.3 (m, 9 H, Ar$\underline{H}$); ^{13}C NMR ($DCCl_3$) ppm 36.19 (t, -S-$\underline{C}H_2$), 51.36 (d, C_6H_5-$\underline{C}$H-C=O), 52.19 (q, [C=O]-O$\underline{C}H_3$), 55.19 (q, -O$\underline{C}H_3$), 172.84 (s, $\underline{C}$=O).

Preparation of Ethyl 3-(3-Methoxyphenyl-thio)-2-phenylpropanoate (**24**)

The ethyl ester **24** was prepared in the same manner as the methyl ester **21** with the following changes: methyl 2-phenylacrylate was replaced with ethyl 2-phenylacrylate (6.3 g, 0.035 mol, crude). The remaining oil was distilled to give 6.7 g (0.021 mol, 62%) of a clear, colorless oil **24**; bp 142-158°C/0.015 mm Hg. IR (film) cm^{-1}: 1740 (C=O); ^1H NMR ($DCCl_3$) δ 1.22 (t, 3 H, -OCH$_2$C$\underline{H}_3$), 3.25 (dd, 1 H,

S-C<u>H</u>$_2$-CH-) and 3.60 (dd, 1 H, S-C<u>H</u>$_2$-CH-), 3.78 (s, 3 H, -OC<u>H</u>$_3$), 3.80 (dd, 1 H, S-CH$_2$-C<u>H</u>-), 4.18 (q, 2 H, -OC<u>H</u>$_2$CH$_3$), 6.7-7.4 (m, 9 H, Ar<u>H</u>); ^{13}C NMR ($DCCl_3$) ppm 14.14 (q, -OCH$_2$<u>C</u>H$_3$), 37.07 (t, S-<u>C</u>H$_2$-CH-), 51.55 (d, -S-CH$_2$-<u>C</u>H-), 55.23 (q, -O<u>C</u>H$_3$), 61.09 (t, -O<u>C</u>H$_2$CH$_3$), 172.18 (s, <u>C</u>=O), Ar<u>C</u>: 112.21, 115.22, 121.96, 127.63, 128.65, 129.69, 136.61, 137.55, 159.69.

Preparation of 3-(3-Methoxyphenylthio)-2-phenylpropanoic Acid (**22**) from the Methyl Ester **21**

The methyl ester **21** (5.0 g, 0.0166 mol) and 30 mL of dried spect grade $HCCl_3$ were combined in a 50 mL, 3-necked round-bottom flask fitted with a condenser, an addition funnel with a nitrogen inlet, and a septum. The solution was stirred at room temperature for 10 min. Iodotrimethylsilane (8.0 mL, 11.25 g, 0.056 mol) was then added with the aid of a dry syringe. As the iodotrimethylsilane was added, the solution went from colorless to yellow to dark orange. The mixture was boiled for 21.5 h. The dark red solution was then cooled to room temperature (15 min) and diluted with 50 mL of ether. The solution was transferred to a separatory funnel and washed with 0.5 <u>N</u> NaOH (5 × 25 mL). At this point, the orange color disappeared and both layers were colorless. The water layers were combined and acidified with 10% HCl (added dropwise slowly while cooling in an ice bath) to a pH of approximately 1. At a pH of approximately 7, the solution became cloudy and at a pH of 1, a pale yellow oil could be seen at the bottom

of the flask. The solution was extracted with $HCCl_3$ (4 × 50 mL) and the combined $HCCl_3$ layers were dried (Na_2SO_4) overnight. The solution was filtered, concentrated on rotovap and then kept under high vacuum for 30 min. An oil **22** was obtained which crystallized after refrigeration for several h (4.45 g, 94%) mp 54-56°C.

Anal. Calcd. for $C_{16}H_{16}O_3S$: C, 66.67; H, 5.56; S, 11.11.
Found: C, 66.46; H, 5.65; S, 11.24.

IR (film) cm^{-1}: 1720 (b) (C=O); 3010 (vb) (O-H); ^1H NMR ($DCCl_3$) δ 3.24 (dd, 1 H, S-C<u>H</u>$_2$-) and 3.58 (dd, 1 H, -S-C<u>H</u>$_2$-), 3.80 (s, 3 H, -OC<u>H</u>$_3$), 3.84 (dd, 1 H, -S-CH$_2$-C<u>H</u>-), 6.7-7.4 (m, 9 H, Ar<u>H</u>), 8.6-8.9 (bs, 1 H, -O<u>H</u>); ^{13}C NMR ($DCCl_3$) ppm 36.70 (S-<u>C</u>H$_2$-), 51.46 (-S-CH$_2$-<u>C</u>H-), 55.29 (-O<u>C</u>H$_3$), 177.99 (-<u>C</u>=O), Ar<u>C</u>: 112.57, 115.54, 122.31, 127.83, 127.98, 128.79, 129.78, 135.8, 136.78, 159.72 (Ar<u>C</u> -OCH$_3$).

Preparation of 3-(3-Methoxyphenylthio)-2-phenylpropanoic Acid (**22**) from the Ethyl Ester **24**

To a 25 mL 3-necked, round-bottom flask, fitted with an addition funnel with a nitrogen inlet, 2 condensers and a septum, was added the ethyl ester **24** (1.0 g, 0.0032 mol) and $HCCl_3$ (5 mL). The mixture was stirred at room temperature (10 min). Iodotrimethylsilane (1.2 mL, 1.69 g, 0.0084 mol) was added to the solution with the aid of a dry syringe. The solution changed from a pale yellow to a deep red color as the iodotrimethylsilane was added. After the solution was heated

(45-50°C sand bath) for 14 h, it was cooled for 15 min and diluted with ether (10 mL). The ether solution was then extracted with 0.5 N NaOH (2 × 25 mL); at this time the red color disappeared and both layers became colorless. The aqueous layers were combined and acidified carefully with 15% HCl to a pH of 4.0 and then were extracted with $HCCl_3$ (2 × 25 mL). The combined $HCCl_3$ layers were dried (Na_2SO_4) overnight. After removal of the $HCCl_3$ (rotovap), a yellow gummy material was obtained (250 mg, 27%) which appeared to be the crude acid **22** from IR analysis. Purification of the acid was not attempted.

Attempted Preparation of 3-(3-Methoxyphenyl-thio)-2-phenylpropanoic Acid **22** from the Ethyl Ester **24**

To a 25 mL, 3-necked, round-bottom flask, fitted with an addition funnel with nitrogen inlet, a condenser and a glass stopper was added the ethyl ester **24** (1.0 g, 0.0032 mol) and 15% NaOH (15 mL). Two layers resulted and the mixture was boiled for 23 h. The mixture was then stirred at room temperature for 2 h. The pale yellow mixture was transferred to a 125 mL Erlenmeyer flask and acidified with 15% HCl to an approximate pH of 3.8. The solution was extracted with $HCCl_3$ (3 × 25 mL) and the $HCCl_3$ layers were combined and dried ($MgSO_4$) overnight. After removal of the $HCCl_3$, a yellow oil (1.3 g) was obtained which appeared to be crude starting material **24** from IR analysis. The reaction was also attempted using 10% NaOH and boiling for shorter times but none of the acid was obtained from the mixture under these conditions.

Preparation of 7-Methoxy-3-phenyl-4-thiochromanone (**11**)

To a 50 mL, 3-necked, round-bottom flask fitted with a condenser connected to nitrogen flow and two ground glass stoppers was added acid **22** (2,0 g, 6.94 mmol) and H_2CCl_2 (30 mL). The colorless solution was stirred in an ice/salt/water bath under nitrogen for 15 min. Solid PCl_5 (1.6 g, 7.68 mmol) was added all at once to the flask and the mixture was stirred at 0°C for 1 h. To the resulting light yellow solution was added $SnCl_4$ (240 µL, 0.534 g, 2.0 mmol) with an airtight syringe. The mixture turned a dark red color as the $SnCl_4$ was added. The mixture was stirred at 0°C for 30 min and then warmed to room temperature and stirred for 6 h. The dark red mixture was then poured into a 250 mL Erlenmeyer flask containing 100 mL of ice water and the resulting mixture was stirred vigorously for 15 min. A yellow emulsion formed and the entire mixture was poured into a 250 mL separatory funnel and mixed with H_2CCl_2 (20 mL) and 10% NaOH (25 mL). Two layers separated and the water layer was washed with H_2CCl_2 (3 × 100 mL). The combined H_2CCl_2 layers were dried (Na_2SO_4) overnight. The yellow solution was filtered and the H_2CCl_2 was removed (rotovap). An orange oil was obtained and 10 mL of absolute methanol was added; the resulting mixture was refrigerated overnight. An off-white solid (0.7557 g, 40%) was obtained after recrystallization (CH_3OH) mp 147-148°C (lit mp[34,35] 151-152.5°C). Mass spectral analysis gave the following data

M.S. Calcd. for $C_{16}H_{14}O_2S$: m/e 270.0714 (M^+)

Found: m/e 270.0726 (M^+)

IR (KBr) cm^{-1}: 1665 (C=O); ^1H NMR ($DCCl_3$) δ 3.30 (dd, 1 H, S-C<u>H</u>$_2$-CH-) and 3.55 (dd, 1 H, S-C<u>H</u>$_2$-CH-), 3.83 (s, 3 H, -OC<u>H</u>$_3$), 4.05 (dd, 1 H, S-CH$_2$-C<u>H</u>-), 6.7-8.2 (m, 8 H, Ar<u>H</u>); ^{13}C NMR ($DCCl_3$) ppm 33.33 (S-<u>C</u>H$_2$-CH-), 53.64 (S-CH$_2$-<u>C</u>H-), 55.57 (-O<u>C</u>H$_3$), 193.12 (<u>C</u>=O), Ar<u>C</u>: 110.63, 112.76, 124.95, 127.46, 128.43, 128.68, 132.15, 138.23, 144.12, 163.25 (Ar<u>C</u>-OCH$_3$).

Preparation of 7-Methoxy-3-phenyl-4-thiochromanone (**11**) using 115% Polyphosphoric Acid

To a 50 mL, 3-necked, round-bottom flask fitted with a condenser, nitrogen inlet and a glass stopper and surrounded by an outer flask containing xylene was added acid **22** (2.0 g, 0.0069 mol) and 115% polyphosphoric acid (20 g). The mixture was heated at the boiling point of xylene for 2.5 h. The color changed from colorless to dark orange. Without cooling, the mixture was poured into a 50 mL beaker containing ice water (20 mL) and was stirred with a glass rod. A yellow gummy solid precipitated from solution. The mixture was extracted with ether (5 × 20 mL). The ether layers were combined and washed with a cold H_2O (50 mL), sat $NaHCO_3$ (25 mL), again with cold H_2O (50 mL) and dried (Na_2SO_4) overnight. Removal of ether (rotovap) gave an orange oil. The oil was dissolved in ethyl acetate and hexane was added until the solution became cloudy. The mixture was refrigerated overnight and ketone **11** was obtained as pale yellow crystals (0.200 g, 11%); mp 146-147°C. Spectral data corresponds to that obtained in the previous experiment.

Preparation of 4-(2-N,N-Dimethylaminoethoxy)-
bromobenzene (**25**)

p-Bromophenol (5.2 g, 0.03 mol), K_2CO_3 (10.4 g, 0.075 mol), and 150 mL of dimethylformamide were combined in a 250 mL, round-bottom flask fitted with a Claisen adapter, an addition funnel with a nitrogen inlet and a condenser. The mixture was boiled for 45 min. After the mixture was cooled for 30 min (not to room temperature), 2-(dimethylamino)ethyl chloride hydrochloride (**25**, 3.6 g, 0.025 mol) was added all at once. The resulting mixture was boiled for 2 h and then cooled to room temperature and stirred for 12 h. This mixture was brown colored but there was a white solid in the bottom of the flask. The solid was filtered from the solution and the filtrate was combined with H_2O (50 mL) and ether (50 mL); the final mixture was extracted with 10% HCl (30 mL). The orange, aqueous layer was basified with 10% NaOH to a pH of 12.5 and was then extracted with ether (5 × 50 mL) and the extracts were dried ($MgSO_4$) overnight. Evaporation of the ether gave a yellow oil which was distilled to give 3.0 g (41%) of the desired ether **27** as a light yellow oil; bp 80-84°C/0.075 mm Hg (lit bp[5] 152-153°C/4 mm Hg); ^{1}H NMR ($DCCl_3$) δ 2.35 [s, 6 H, $N(CH_3)_2$], 2.72 (t, 2 H, $O-CH_2-CH_2-N$), 4.05 (t, 2 H, $O-CH_2-CH_2-N$), 6.85 (d, 2 H, ArH, ortho to Br), 7.40 (d, 2 H, ArH, ortho to O), ^{13}C NMR ($DCCl_3$) ppm 45.78 [$N(CH_3)_2$], 58.05 ($O-CH_2-CH_2-N$), 66.13 ($O-CH_2-CH_2-N$), ArC: 112.65, 116.16, 131.94, 157.65.

Preparation of 4-(2-N,N-Diethylaminoethoxy)-bromobenzene (**28**)

p-Bromophenol (10.4 g, 0.06 mol), K_2CO_3 (20.8 g, 0.15 mol), and 200 mL of dimethylformamide were combined in a 500 mL, round-bottom flask fitted with a Claisen adapter, a condenser and a glass stopper. The mixture was boiled for 30 min and then allowed to cool for 15 min (not to room temperature). 2-(Diethylamino)ethyl chloride hydrochloride (**26**, 8.6 g, 0.05 mol) was added all at once to the flask and the mixture was boiled for 16 h. At this time, the mixture was a dark red color and had a solid in the bottom of the flask. The solid was filtered off and the filtrate was combined with ether (100 mL) and H_2O (100 mL) in a separatory funnel. The layers were separated, and the ether layer was washed with 10% HCl (3 × 100 mL). The yellow aqueous layers were combined and made basic with 10% NaOH to a pH of 12.0; the solution was extracted with ether (3 × 100 mL). The yellow ether layers were dried ($MgSO_4$) overnight. Removal of the ether and distillation of the remaining oil gave the desired aryl bromide **28** (1.5 g, 11%) bp 131-135°C/0.26 mm Hg (lit bp[5] 174-178°C/4 mm Hg); ^{1}H NMR ($DCCl_3$) δ 1.08 [t, 6 H, $N(CH_2-CH_3)_2$], 2.67 [q, 4 H, $N(CH_2-CH_3)_2$], 2.90 (t, 2 H, $O-CH_2-CH_2-N$), 4.04 (t, 2 H, $O-CH_2-CH_2-N$), 6.62-7.42 (m, 4 H, ArH); ^{13}C NMR ($DCCl_3$) ppm 11.47 [$N(CH_2-CH_3)_2$], 47.57 [$N(CH_2-CH_3)_2$], 51.46 ($O-CH_2-CH_2-N$), 66.45 ($O-CH_2-CH_2-N$).

Preparation of 3,4-Dihydro-7-methoxy-3-phenyl-4-[4-[2-(*N*,*N*-dimethyl)ethoxy]phenyl]-2*H*-1-benzothiopyran-4-ol (**13a**)

To a 3-necked, round-bottom flask fitted with two condensers, mechanical stirrer and an addition funnel was added Mg metal (0.45 g, 0.0185 g-at) that had been crushed with a mortar and pestle and approximately 0.5 mL of dry tetrahydrofuran (THF). To the addition funnel was added 4-(2-*N*,*N*-dimethylaminoethoxy)bromobenzene (**27**) (1.5 g, 0.006 mol). One drop of halide **27** was added to the flask and heating with a heat gun was used to initiate the reaction. The halide in the addition funnel was then diluted with 10 mL THF and the solution was added dropwise over 30 min. The mixture was boiled for 2 h and the color changed from yellow to green. The flask was allowed to cool to room temperature (15 min) and then cooled in an ice bath (15 min). Ketone **11** (1.0 g, 0.0037 mol) was added dropwise over 30 min while cooling in the ice bath. The dark red solution was then warmed to room temperature and stirred for 48 h; the color changed to yellow-green. The mixture was diluted with THF and filtered to remove the unreacted Mg metal. Water was added dropwise to the flask to precipitate the Mg salts. The solid was filtered from the solution and washed several times with ether. The filtrate was separated in a 125 mL separatory funnel. The ether layer was washed with H_2O (6 × 15 mL) and 15% NH_4Cl (3 × 15 mL), and the yellow solution was dried (Na_2SO_4) overnight. Evaporation of the ether (rotovap) gave a yellow oil which was chromatographed on a column (2 mm × 35 mm) using neutral alumina packed

in a slurry with hexanes and eluted with ethyl acetate:hexanes, (1:20) Alcohol **13a** was obtained as a white solid (0.40 g, 25%) mp 151-152.5°C.

Anal. Calcd. for $C_{26}H_{29}O_3NS$: C, 71.72; H, 6.67; N, 3.22; S, 7.36.
Found: C, 71.59; H, 6.72; N, 3.21; S, 7.35.

IR (KBr) cm^{-1}; 3200 (b) (O-H); ^1H NMR ($DCCl_3$) δ 2.32 [s, 6 H, $N(C\underline{H}_3)_2$], 2.70 (t, 2 H, $O-CH_2-C\underline{H}_2-N$), 2.90 (dd, 1 H, $S-C\underline{H}_2-CH-$) and 3.55 (dd, 1 H, $S-C\underline{H}_2-CH-$), 3.76 (bd, 1 H, $S-CH_2-C\underline{H}-$), 3.80 (s, 3 H, $-OC\underline{H}_3$), 4.02 (t, 2 H, $O-C\underline{H}_2-CH-N$), 6.5-7.3 (m, 12 H, $Ar\underline{H}$); ^{13}C NMR ($DCCl_3$) (ppm 28.30 (t, $S-\underline{C}H_2CH-$), 45.88 [q, $N(\underline{C}H_3)_2$], 53.22 (d, $S-CH_2\underline{C}H-$), 55.27 (q, $-O\underline{C}H_3$), 58.27 (t, $O-CH_2-\underline{C}H_2-N$), 65.84 (t, $O-\underline{C}H_2-CH_2-N$), 75.75 (s, $\underline{C}$-OH).

Preparation of 3,4-Dihydro-7-methoxy-3-phenyl-4-[4-[2-(N,N-diethyl)ethoxy]phenyl]-2H-1-benzothiopyran-4-ol (**13b**)

The reaction was performed under the same conditions as with the dimethyl derivative **13a** with the following changes: Mg metal (0.40 g, 0.016 g-at) and 4-(2-N,N-diethylaminoethoxy)bromobenzene (**26**, 2.0 g, 0.0074 mol) were used in place of the Mg and the halide **25**. After ketone **11** (1.0 g, 0.0037 mol) was added, the reaction was stirred at room temperature for 22.5 h and then boiled for 9.5 h. The workup was the same as described previously. The desired alcohol **13b** was obtained as a white solid (0.250 g, 15%); mp 102-104°C.

Anal. Calcd. for $C_{28}H_{33}O_3NS$: C, 72.57; H, 7.13; S, 6.91

Found: C, 72.58; H, 7.29; S, 6.84

IR (KBr) cm^{-1}: 3200 (b) (O-H); ^1H NMR ($DCCl_3$) δ 1.05 [t, 6 H, $N(CH_2\underline{CH_3})_2$], 2.13 (bs, 1 H, -O<u>H</u>), 2.72 [q, 4 H, $N(\underline{CH_2}CH_3)_2$], 2.86 (t, 2 H, $O-CH_2-\underline{CH_2}-N$), 2.92 (bd, 1 H, $S-\underline{CH_2}-CH-$) and 3.56 (bd, 1 H, $S-\underline{CH_2}-CH-$), 3.74 (d, 1 H, $S-CH_2-\underline{CH}-$), 3.80 (s, 3 H, $-OCH_3$), 4.02 (t, 2 H, $O-\underline{CH_2}-CH_2-N$), 6.46-7.4 (m, 12 H, Ar<u>H</u>); ^{13}C NMR ($DCCl_3$) ppm 11.83 [$N(CH_2-\underline{CH_3})_2$), 28.29 ($S-\underline{CH_2}-CH-$), 47.86 [$N(\underline{CH_2}-CH_3)_2$], 51.67 ($O-CH_2-\underline{CH_2}-N$), 53.20 ($S-CH_2-\underline{CH}-$), 55.27 ($-O\underline{CH_3}$), 66.42 ($O-\underline{CH_2}-CH_2-N$), 75.76 (<u>C</u>-OH).

Preparation of 3,4-Dihydro-4-[4-[2-(<u>N</u>-pyrrolidinyl)ethoxy]phenyl]-2<u>H</u>-1-benzothiopyran-4-ol (**14**)

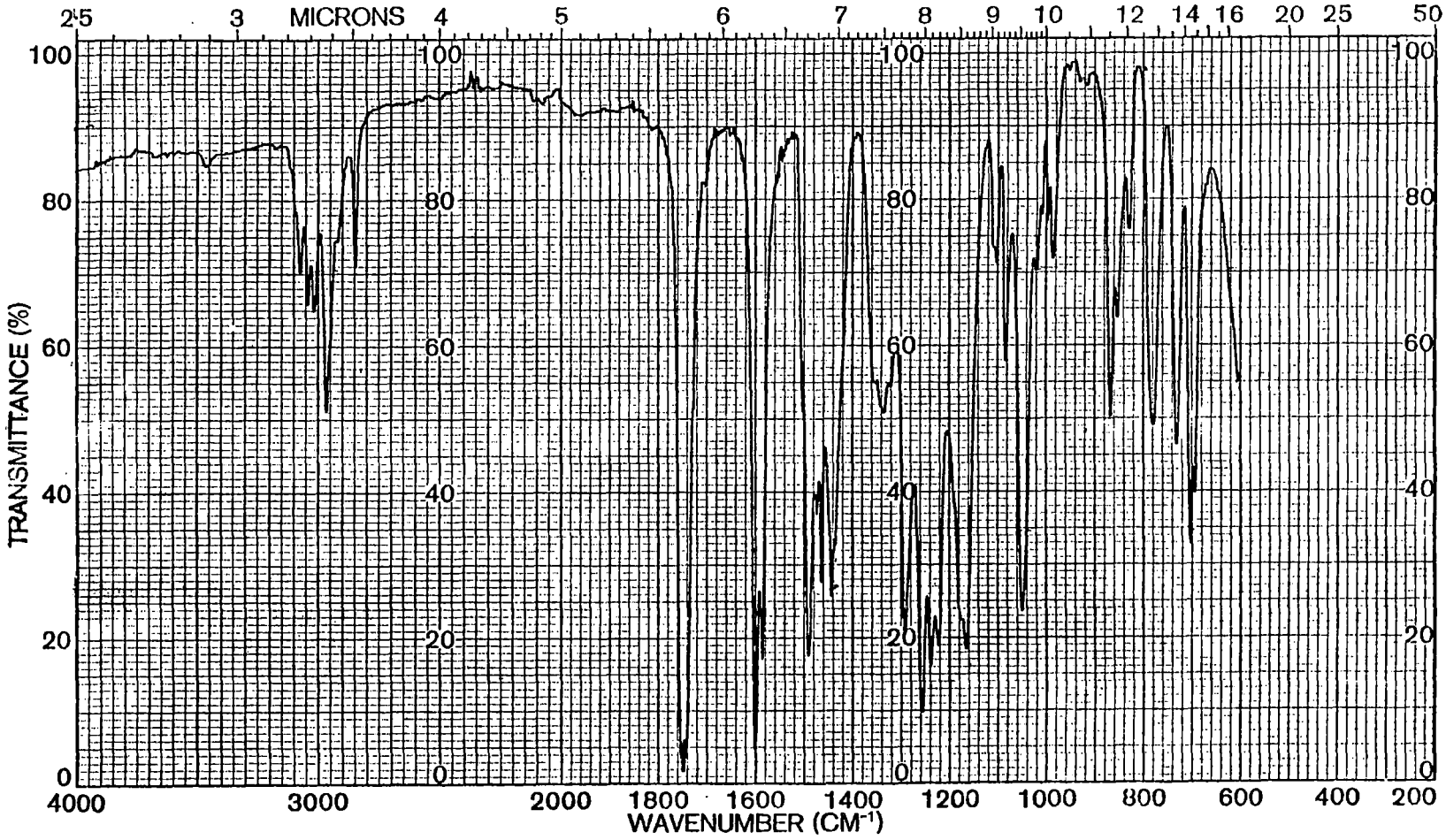
The reaction was performed under the same conditions as with the dimethyl derivative **13a** with the following changes: Mg metal (0.9 g, 0.037 g-at), 1-[2-(<u>p</u>-bromophenoxy)ethyl]pyrrolidine (5.0 g, 0.0185 mol) in 25 mL of dry THF, and thiochroman-4-one (**15**, 2.0 g, 0.012 mol) in 15 mL of dry THF were used in place of the Mg metal, the halide **27**, and the ketone **11**. 1-[2-<u>p</u>-Bromophenoxy)ethyl]pyrrolidine and thiochroman-4-one were commercially available (Aldrich) and were not synthesized. After the ketone **13** was added, the mixture was stirred at room temperature for 4 h and then boiled for 25 h. The workup was the same as described previously. The alcohol **14** was obtained as a white solid (0.200g, 5%); mp 129.5-131°C.

Anal. Calcd. for $C_{21}H_{25}O_2NS$: C, 70.99; H, 7.04; S, 9.01.

Found: C, 70.73; H, 7.01; S, 9.12.

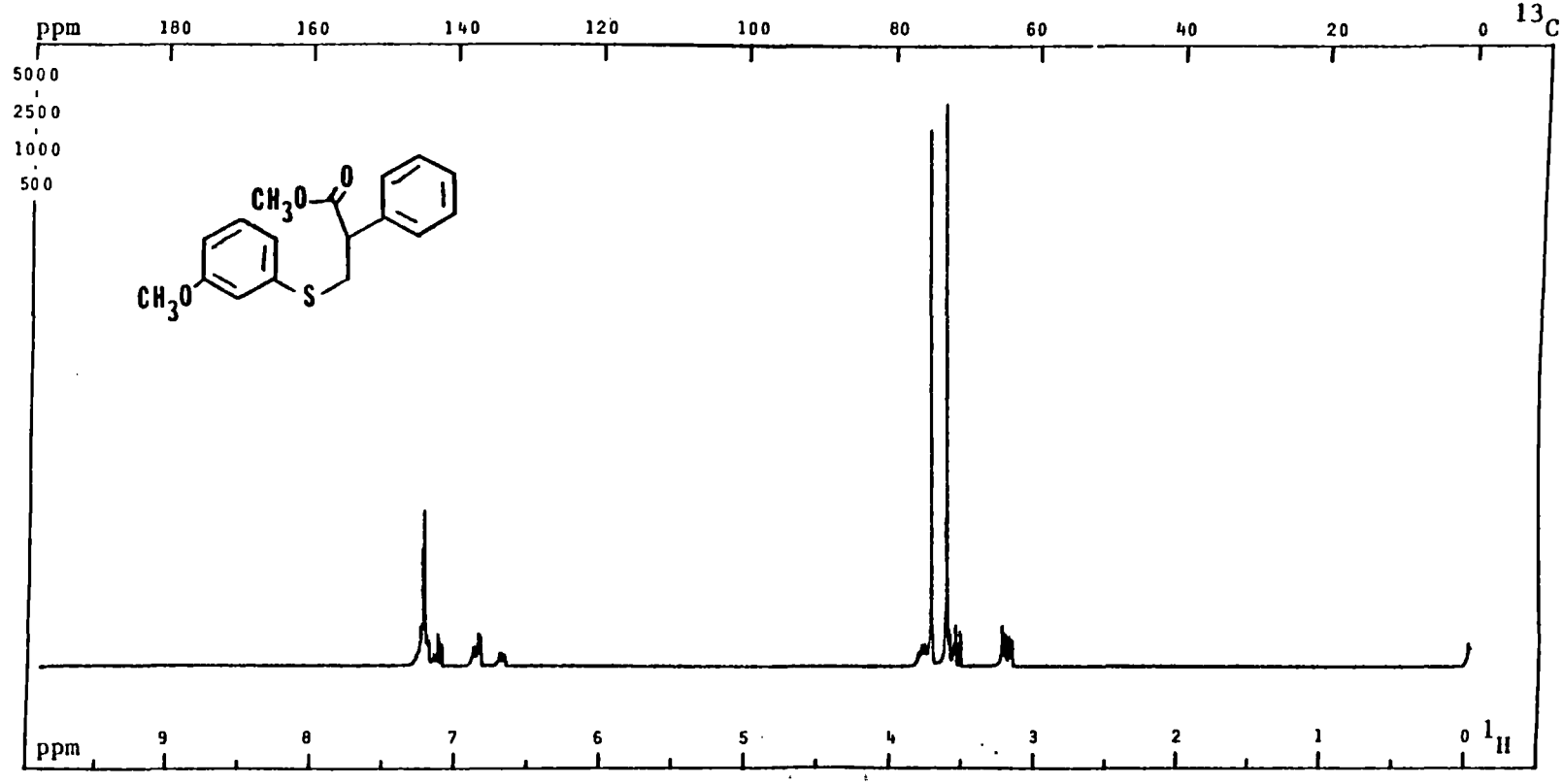
IR (KBr) cm^{-1}; 3350 (b) (O-H); ^1H NMR ($DCCl_3$) δ 1.80 [bs, 4 H, $N(-CH_2-\underline{C}H_2-)_2$], 2.40 (m, 2 H, $S-\underline{C}H_2-CH_2-$), 2.5 (bs, 1 H, $-O\underline{H}$), 2.62 [bs, 4 H, $N(-\underline{C}H_2-CH_2-)_2$], 2.75 (m, 1 H, $S-CH_2-\underline{C}H_2-$) and 3.2 (m, 1 H, $S-CH_2-\underline{C}H_2$), 2.94 (t, 2 H, $O-CH_2-\underline{C}H_2-N$), 4.10 (t, 2 H, $O-\underline{C}H_2-CH_2-N$), 6.7-7.4 (m, 8 H, $Ar\underline{H}$); ^{13}C NMR ($DCCl_3$) ppm 23.20 ($S-\underline{C}H_2-CH_2-$), 23.46 [$N(-CH_2-\underline{C}H_2-)_2$], 39.54 ($S-CH_2-\underline{C}H_2-$), 54.67 [$N(-\underline{C}H_2-CH_2-)_2$], 55.04 ($O-CH_2-\underline{C}H_2-N$), 66.95 ($O-\underline{C}H_2-CH_2-N$), 73.56 ($\underline{C}-OH$).

PLATE I



IR SPECTRUM OF **21**

PLATE II



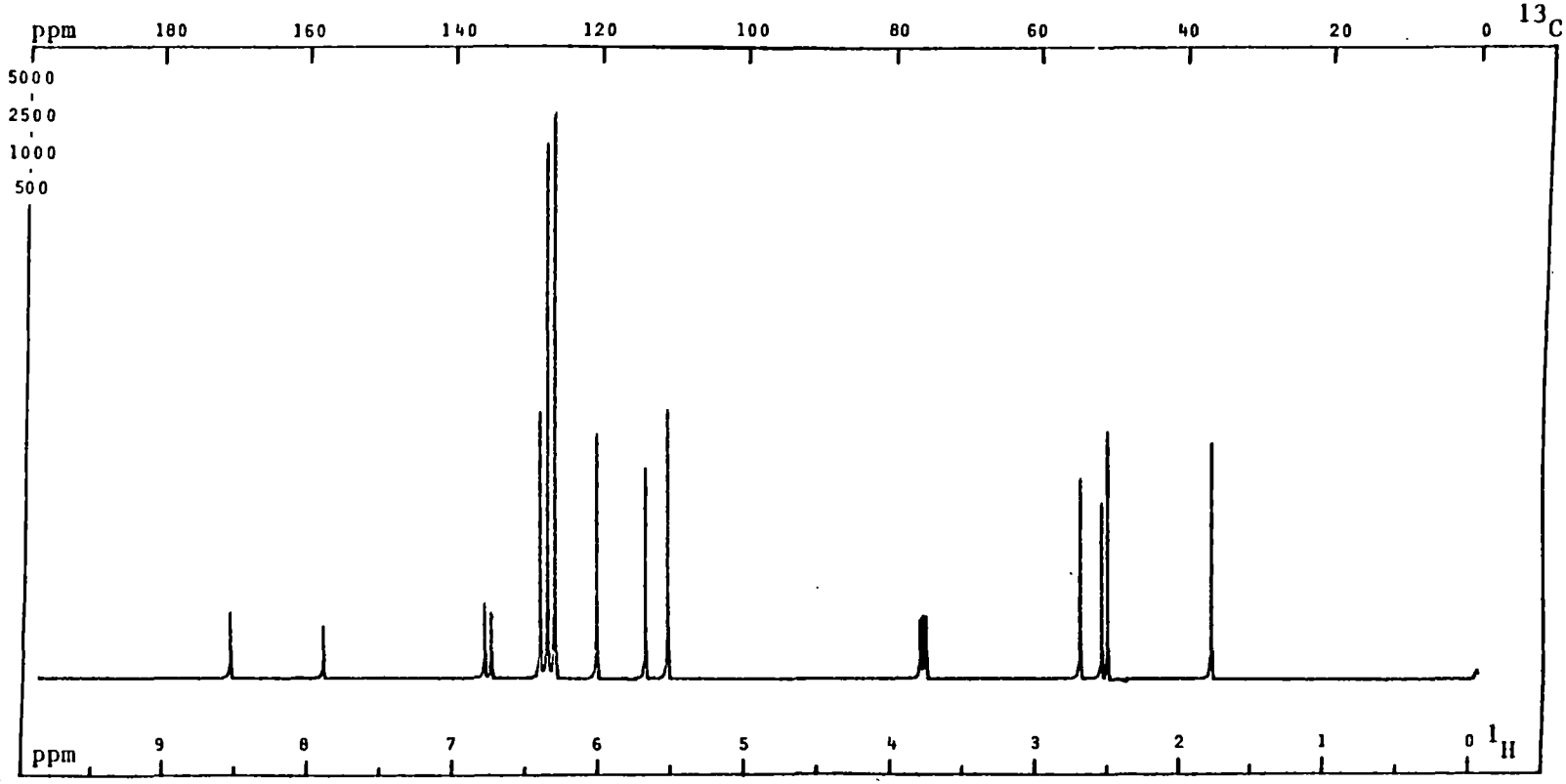
^{1}H NMR SPECTRUM OF **21**

PFT X CW _; Solvent: $CDCl_3$; SF: 299.9 MHz; WC: 500 Hz; T: ^{0}C; NT: 16 .

Size K; PW/RF 10 µs/dB ; TO: 0 Hz; FB: Hz; Lock: ^{2}H; D1,D5: 0 s.

DC: Y, N ; Gated off: A or D; Do: Hz; RF(Power); W/dB; NBW: Hz; LB: Hz.

PLATE III



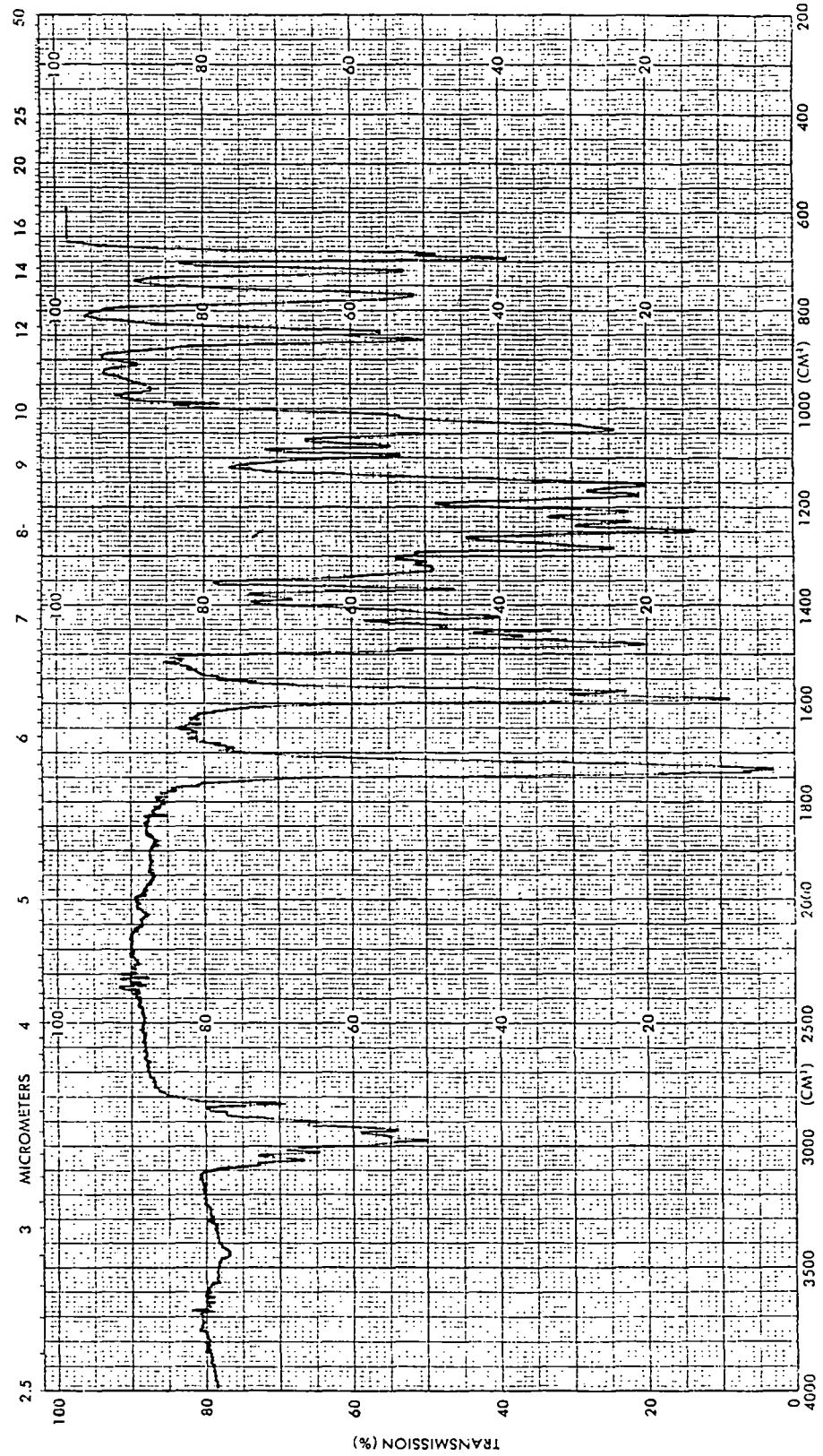
^{13}C NMR SPECTRUM OF **21**

PFT X CW _; Solvent: $CDCl_3$; SF: 75.4 MHz; WC: 500 Hz; T: ^{o}C; NT: 600 .

Size K; PW/RF 12 µs/dB ; TO: 1000 Hz; FB: Hz; Lock: ^{2}H; D1,D5: 4.0 s.

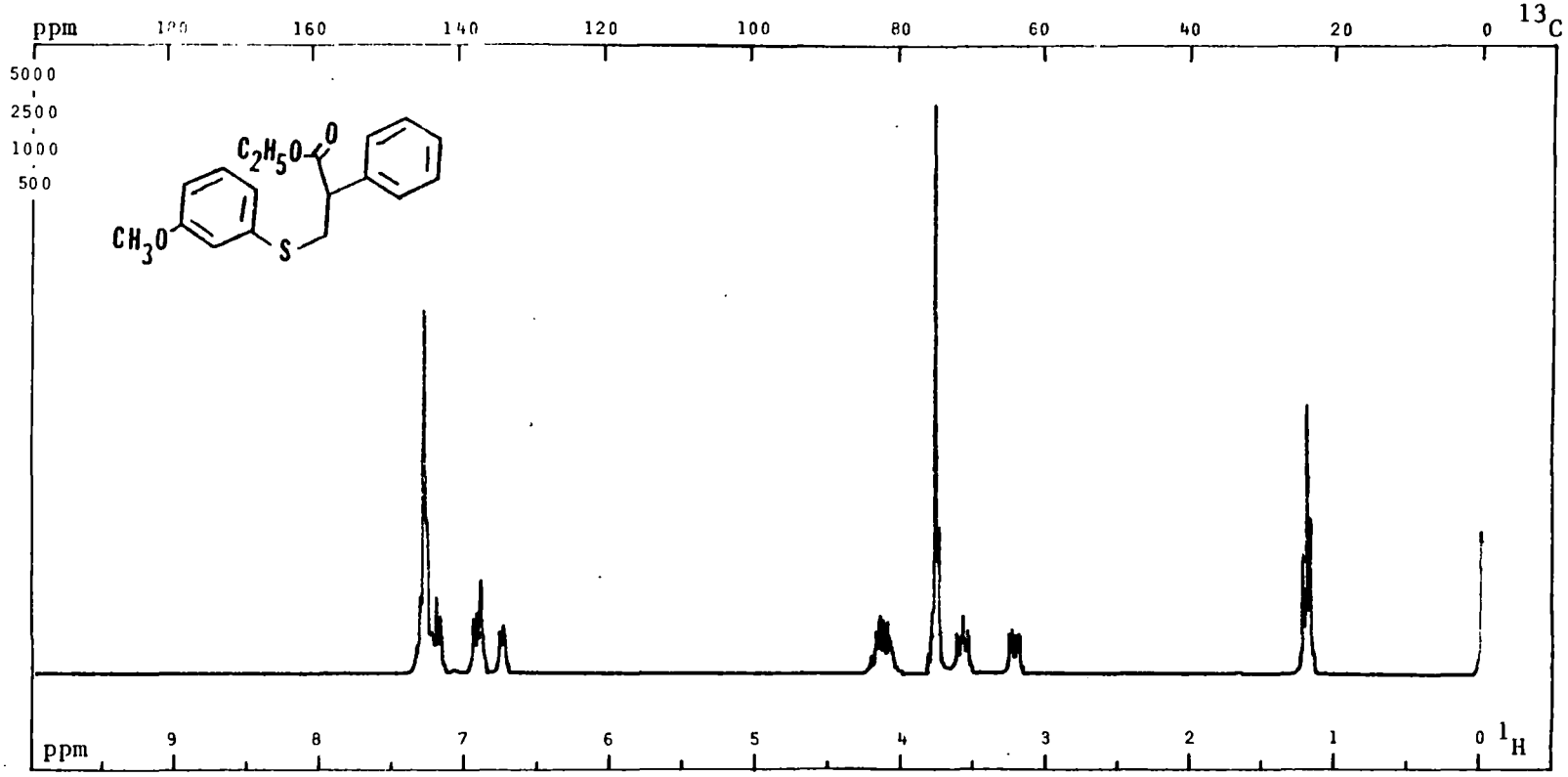
DC: (Y), N ; Gated off: A or D; Do: Hz; RF(Power); W/dB; NBW; Hz; LB; 2.0 Hz.

PLATE IV



IR SPECTRUM OF 24

PLATE V



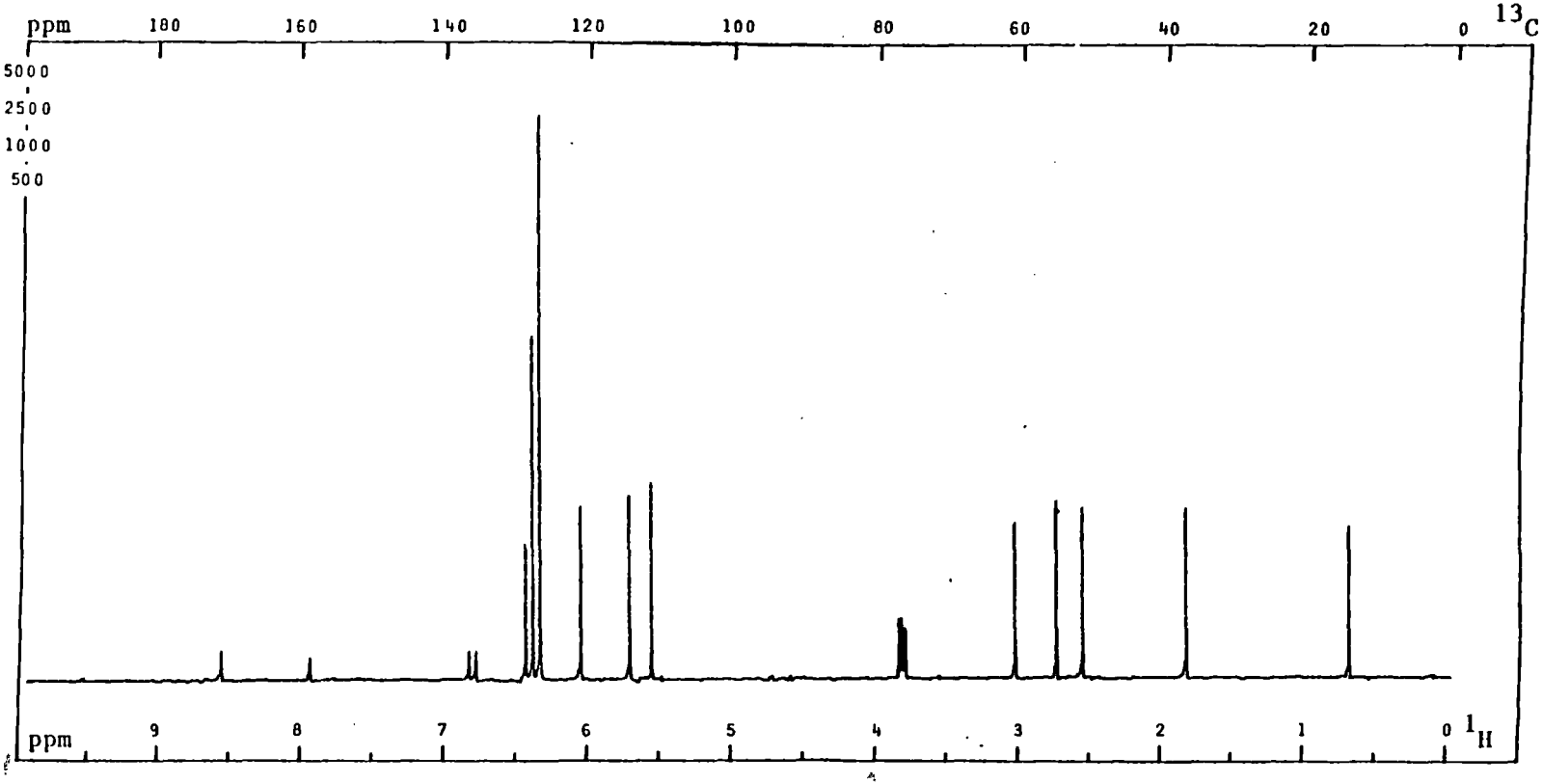
^{1}H NMR SPECTRUM OF **24**

PFT X CW _; Solvent: $CDCl_3$; SF: 299.9 MHz; WC: 500 Hz; T: ^{o}C; NT: 12 .

Size K; PW/RF 5 µs/dB ; TO: Hz; FB: Hz; Lock: ^{2}H; Delay: 0.50 s.

DC: ; Gated off: Offset Hz; RF: W/dB; NBW: Hz; LB: .

PLATE VI



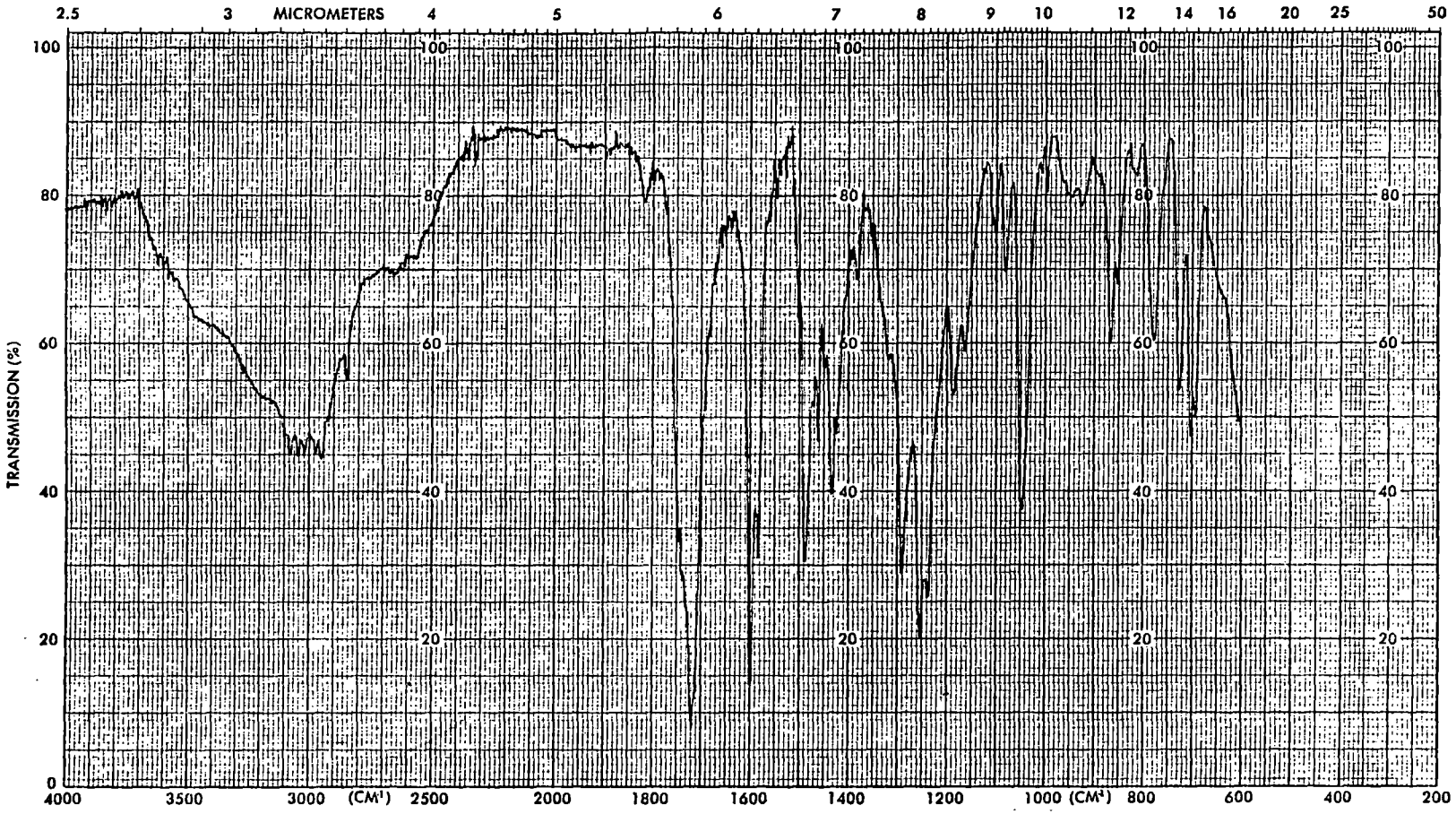
^{13}C NMR SPECTRUM OF **24**

PFT X CW _; Solvent: $CDCl_3$; SF: 75.4 MHz; WC: 500 Hz; T: ^{o}C; NT: 980 .

Size K; PW/RF 10 µs/dB ; TO: 1000 Hz; FB: Hz; Lock: ^{2}H; D1,D5: 4.0 s.

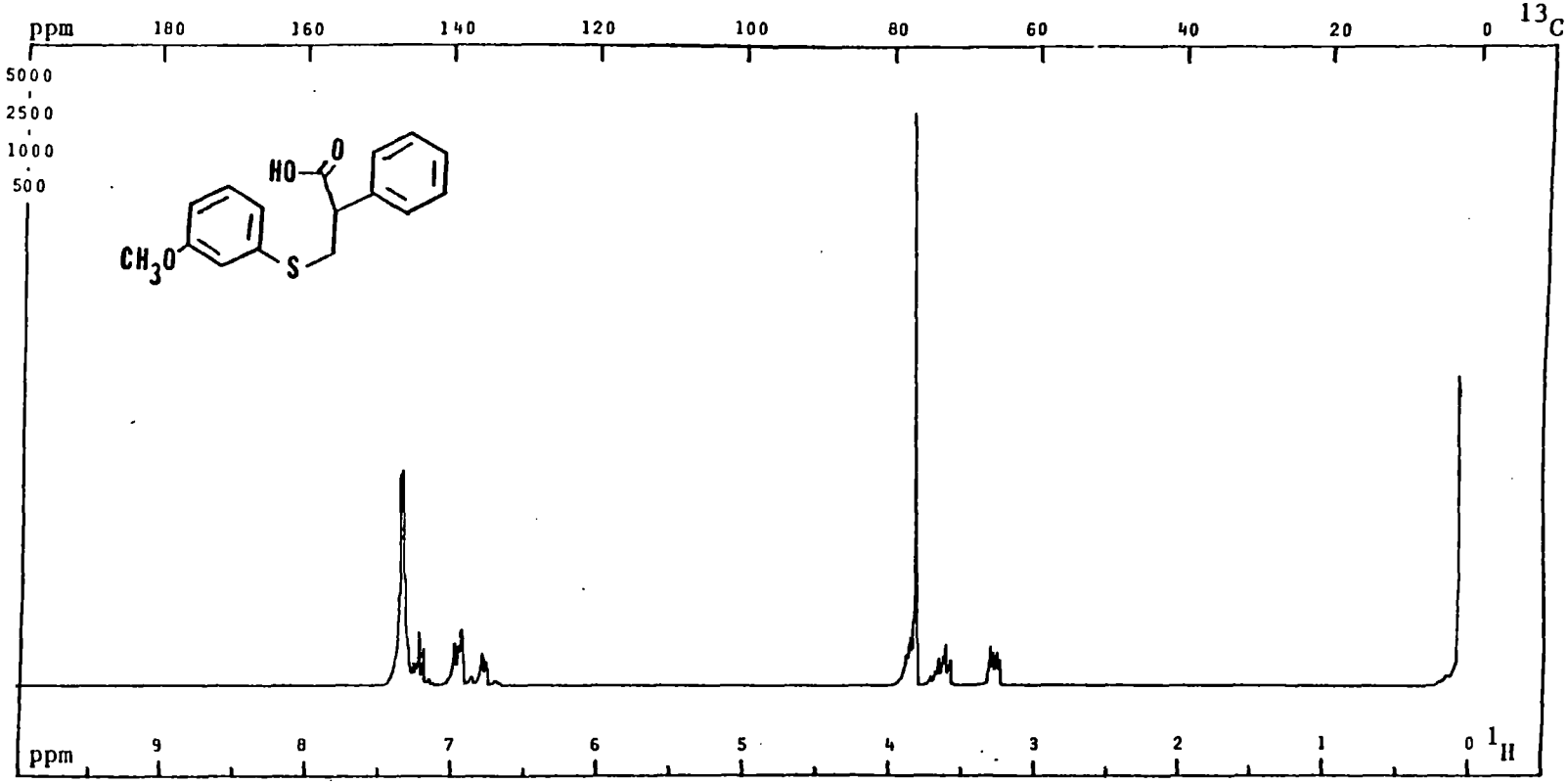
DC: (Y), N ; Gated off: A or D; Do: Hz; RF(Power); W/dB; NBW; Hz; LB; Hz.

PLATE VII



IR SPECTRUM OF **22**

PLATE VIII



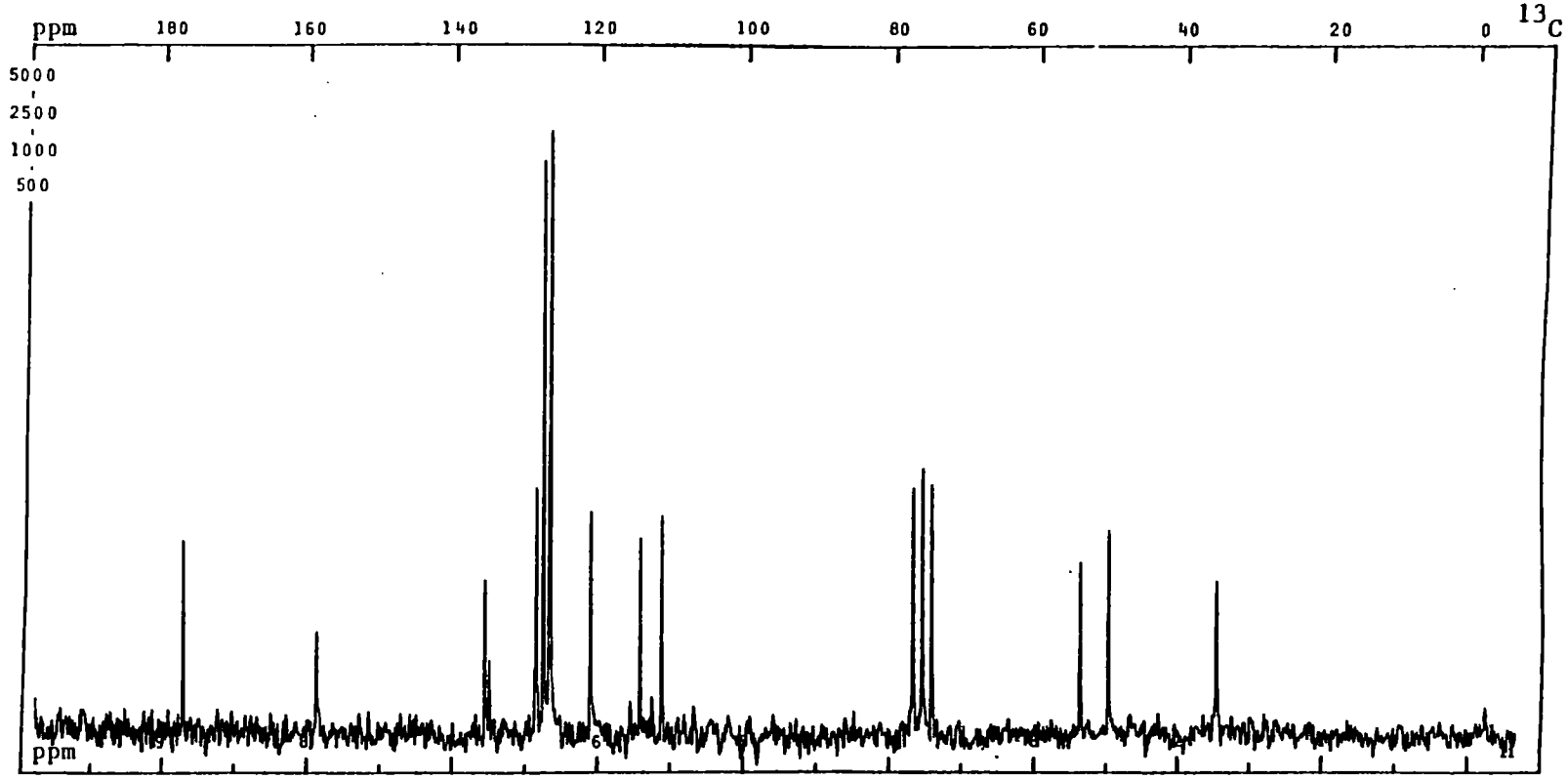
^{1}H NMR SPECTRUM OF **22**

PFT X CW _; Solvent: $CDCl_3$; SF: 299.9 MHz; WC: 500 Hz; T: ^{0}C; NT: 16 .

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

DC: Y, N ; Gated off: A or D; Do: Hz; RF(Power); W/dB; NBW: Hz; LB: Hz.

PLATE IX



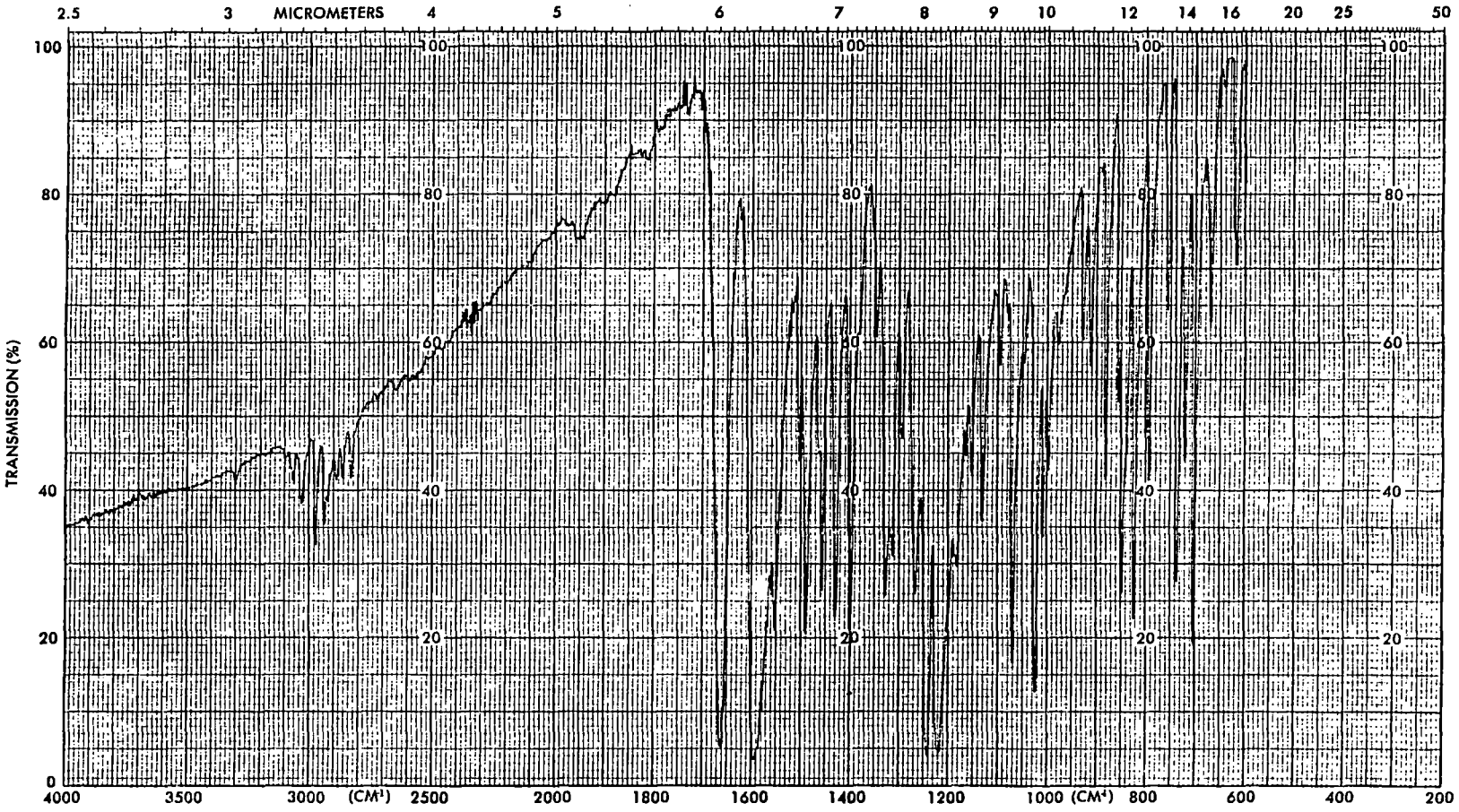
^{13}C NMR SPECTRUM OF **22**

PFT X CW _; Solvent: $CDCl_3$; SF: 25.2 MHz; WC: 500 Hz; T: ^{o}C; NT: .

Size K; PW/RF 15 µs/dB ; TO: Hz; FB: Hz; Lock: ^{2}H; D1,D5: 5 s.

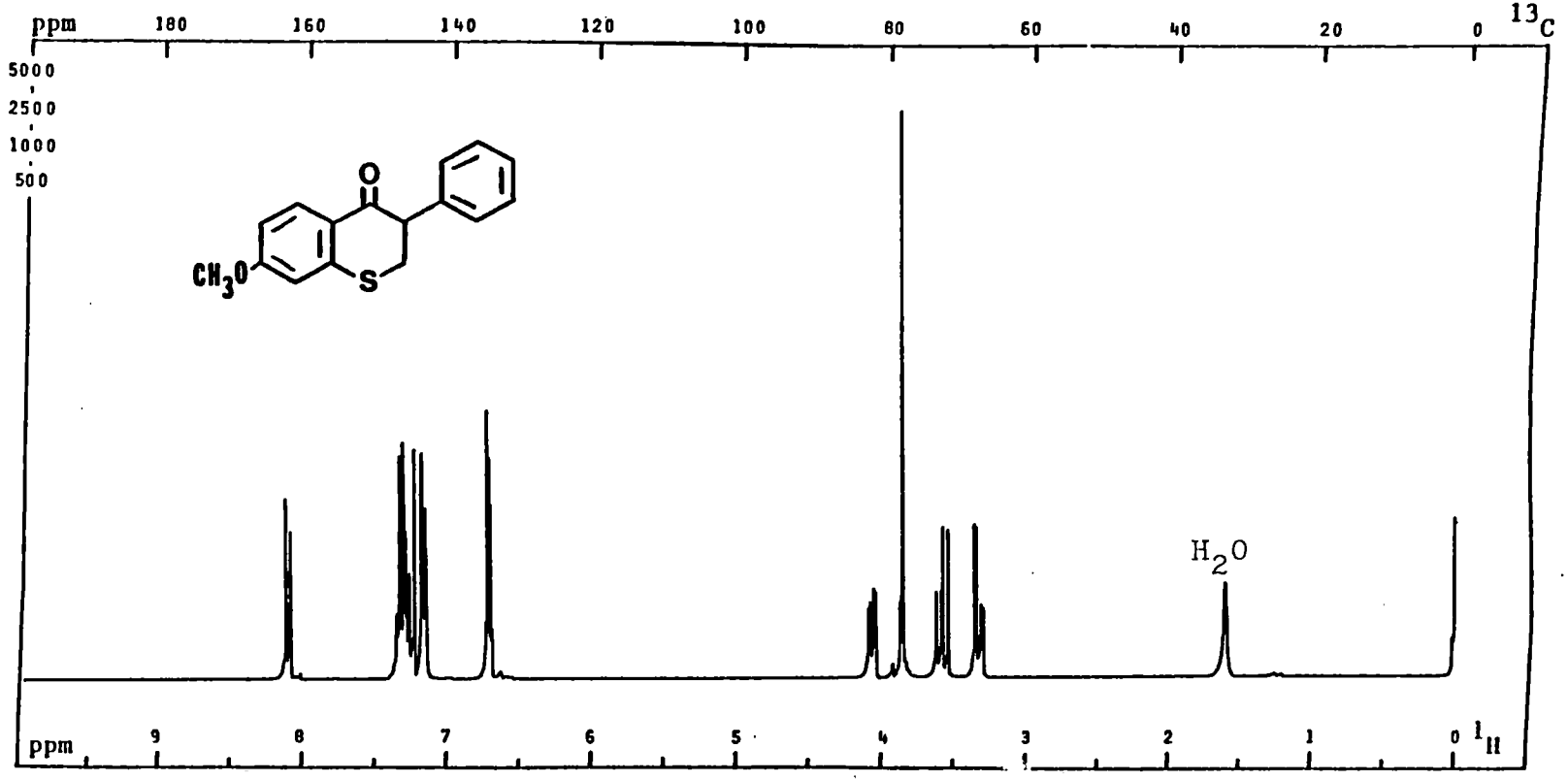
DC: (Y), N ; Gated off: A or D; Do: Hz; RF(Power); W/dB; NBW: Hz; LB: Hz.

PLATE X



IR SPECTRUM OF **11**

PLATE XI



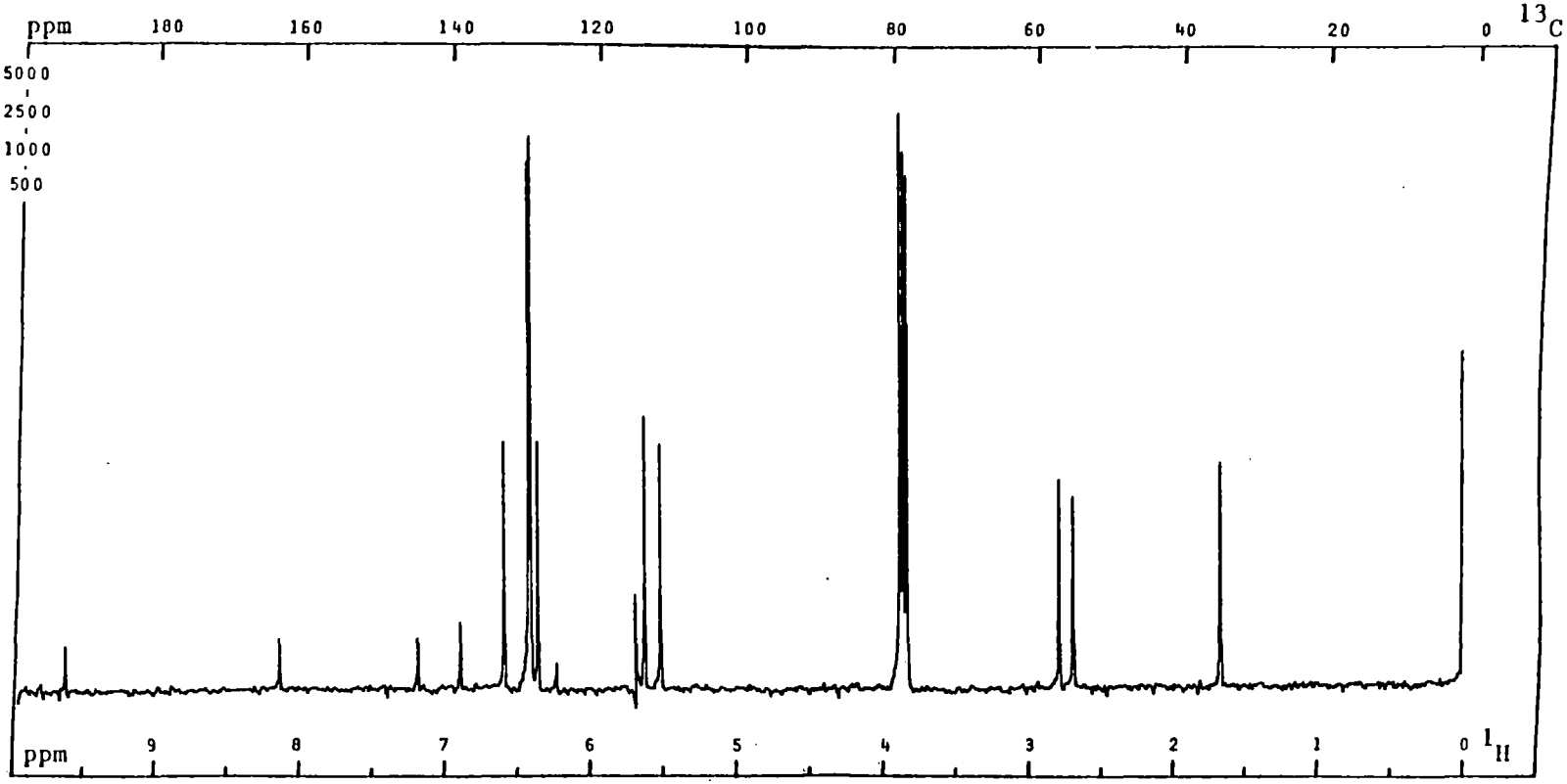
^{1}H NMR SPECTRUM OF **11**

PFT X CW _; Solvent: $CDCl_3$; SF: 299.9 MHz; WC: 500 Hz; T: ^{o}C; NT: 8 .

Size K; PW/RF 5 µs/dB ; TO: 0 Hz; FB: Hz; Lock: ^{2}H; D1,D5: 0 s.

DC: Y, N ; Gated off: A or D; Do: Hz; RF(Power); W/dB; NBW: Hz; LB: Hz.

PLATE XII



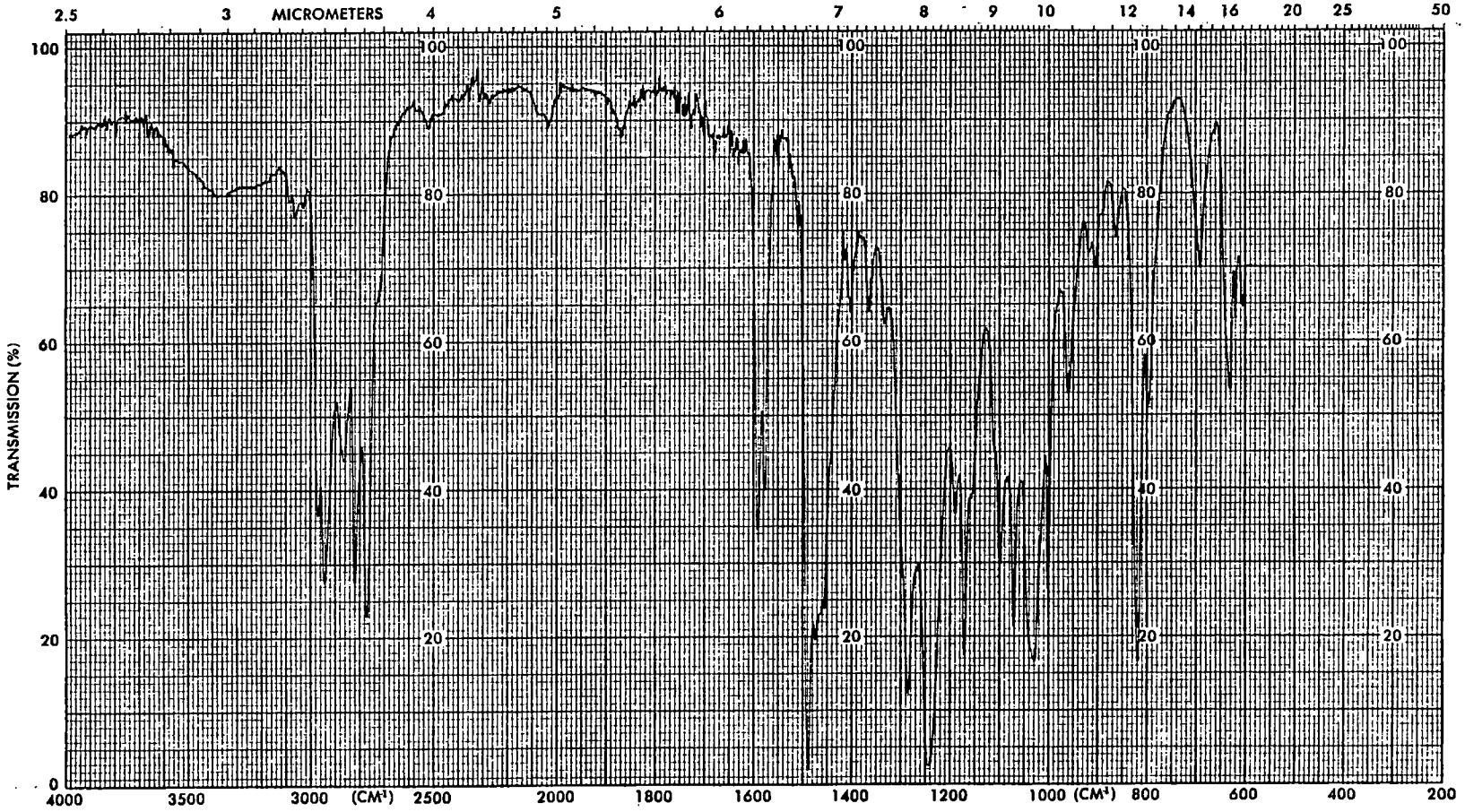
^{13}C NMR SPECTRUM OF **11**

PFT X CW _; Solvent: $CDCl_3$; SF: 75.4 MHz; WC: 500 Hz; T: ^{o}C; NT: 4000 .

Size K; PW/RF 12 µs/dB ; TO: 1000 Hz; FB: Hz; Lock: ^{2}H; D1,D5: 4.0 s.

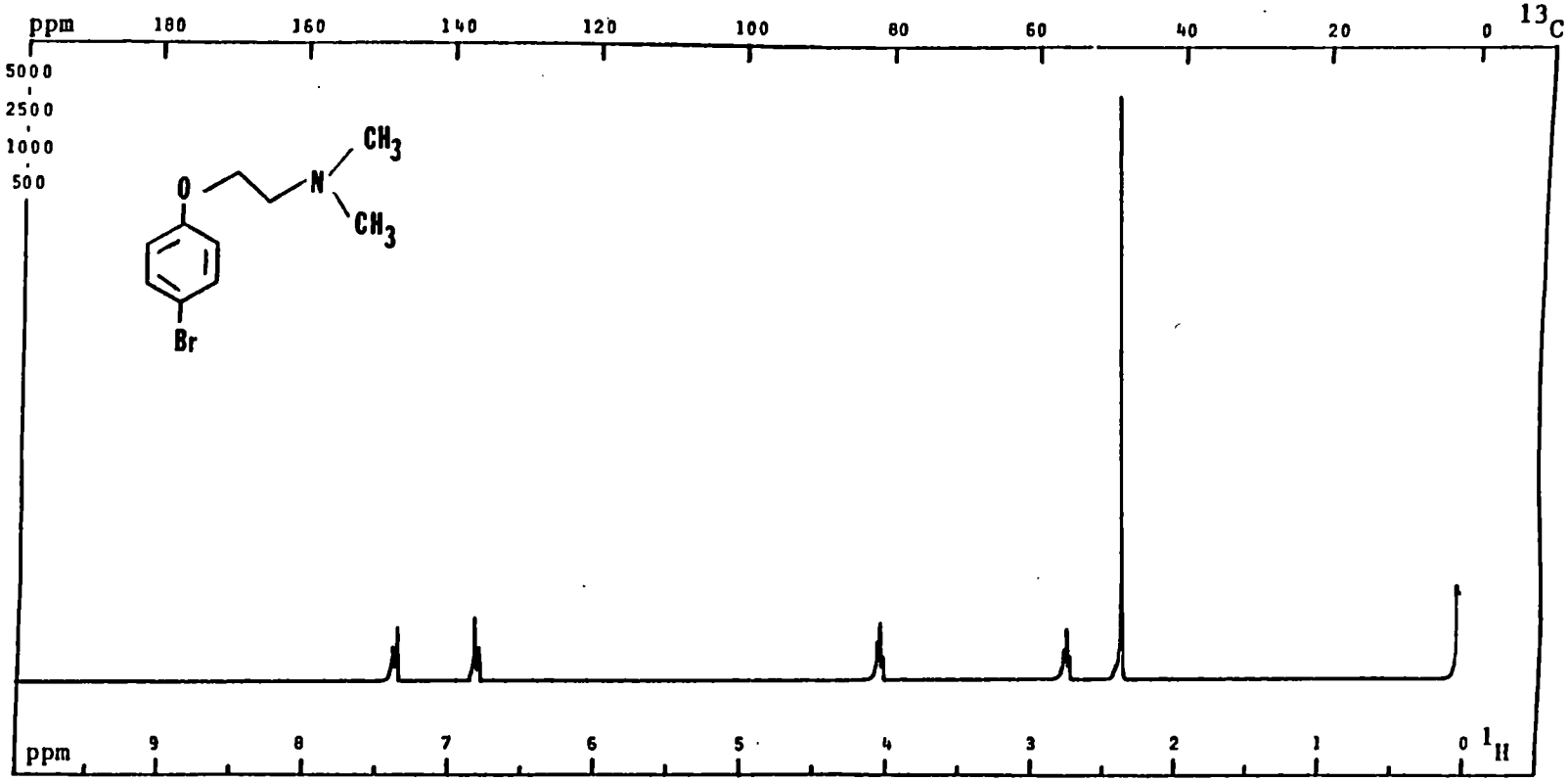
DC: (Y), N ; Gated off: A or D; Do: Hz; RF(Power); W/dB; NBW; Hz; LB; 2.0 Hz.

PLATE XIII



IR SPECTRUM OF **25**

PLATE XIV



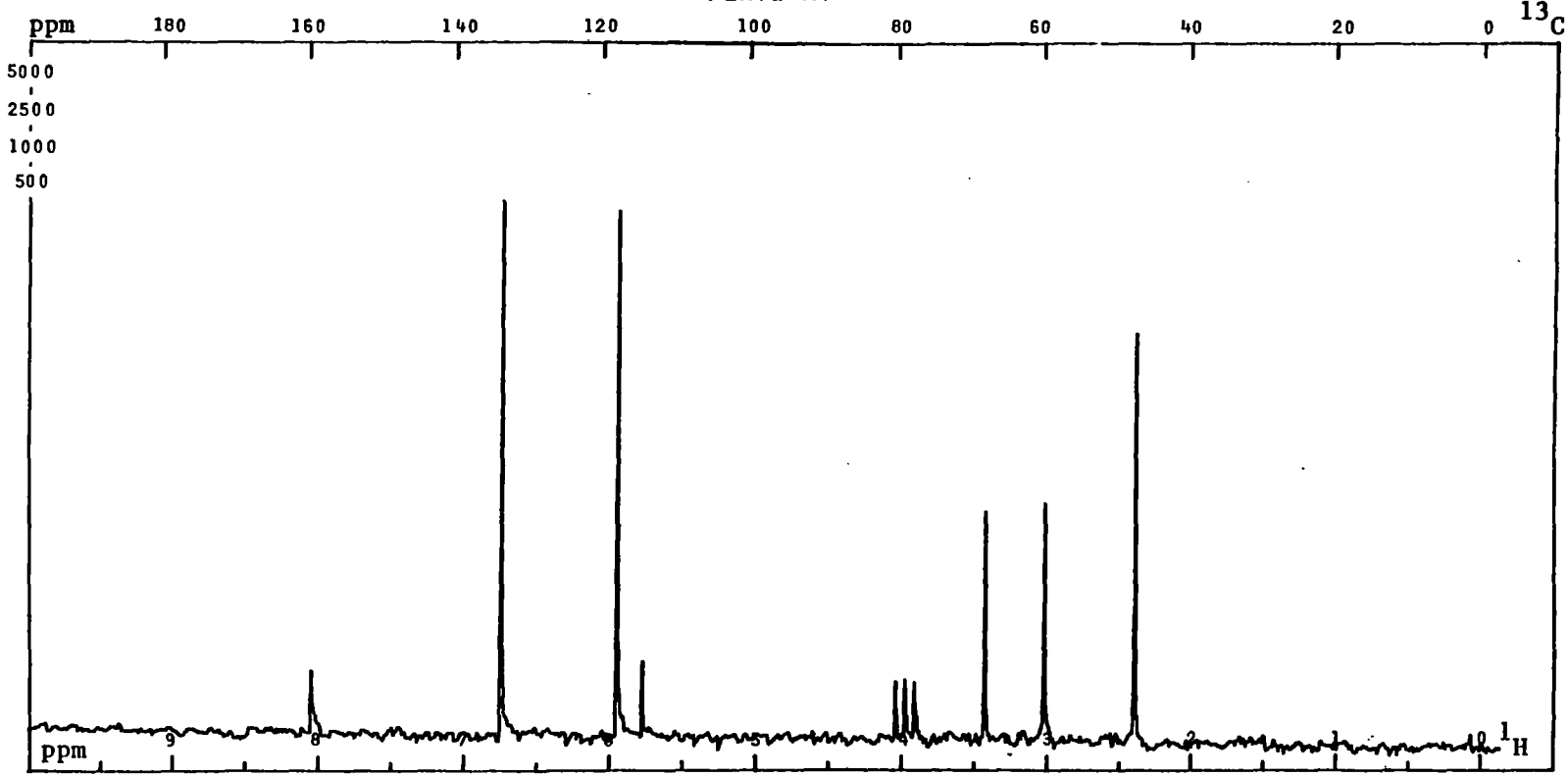
^{1}H NMR SPECTRUM OF **25**

PFT X CW _; Solvent: $CDCl_3$; SF: 299.9 MHz; WC: 500 Hz; T: ^{0}C; NT: 8 .

Size K; PW/RF 5 µs/dB ; TO: 0 Hz; FB: Hz; Lock: ^{2}H; D1,D5: 0 s.

DC: Y, N ; Gated off: A or D; Do: Hz; RF(Power); W/dB; NBW: Hz; LB: Hz.

PLATE XV



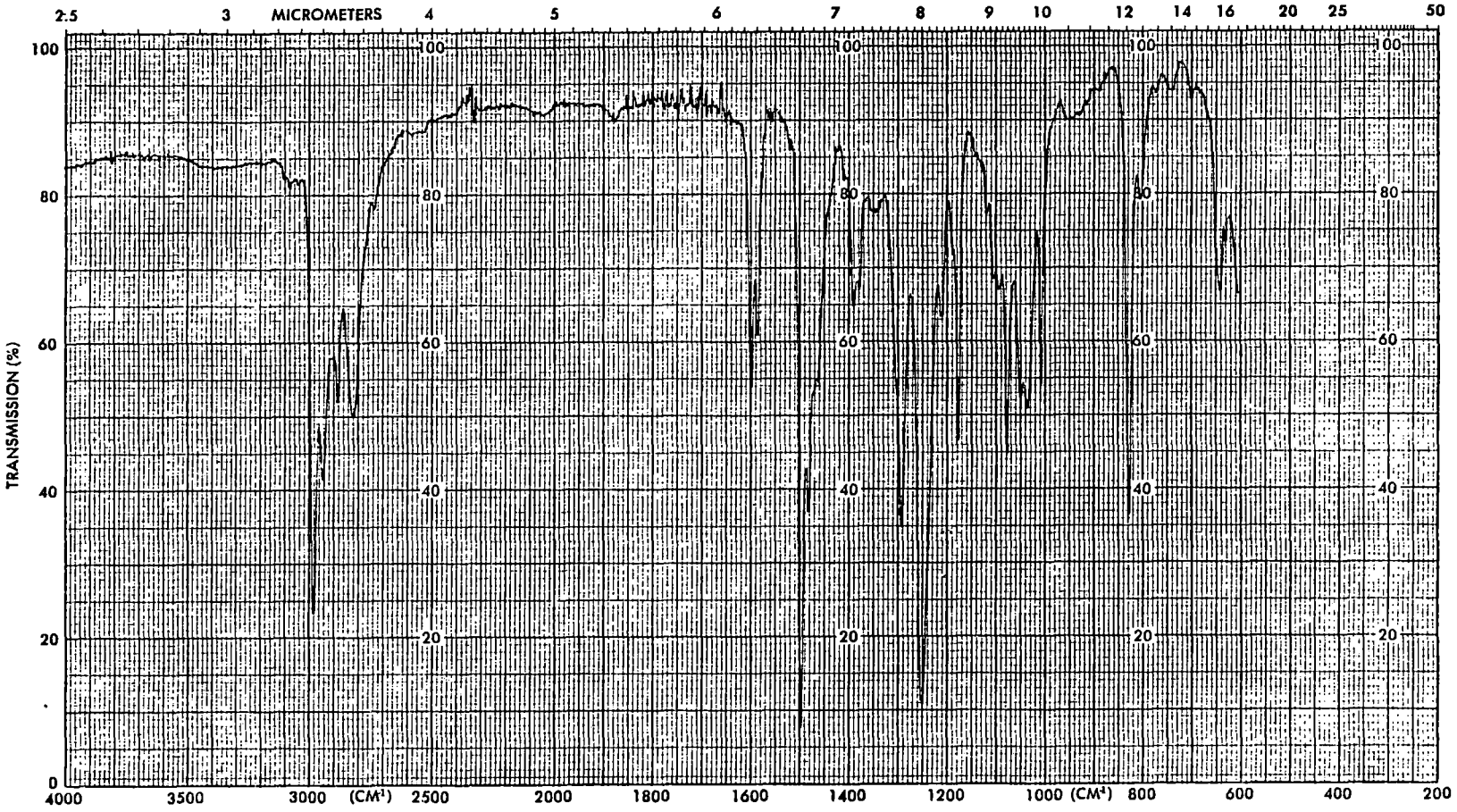
^{13}C NMR SPECTRUM OF **25**

PFT X CW _; Solvent: $CDCl_3$; SF: 25.2 MHz; WC: 500 Hz; T: ^{0}C; NT: .

Size K; PW/RF 15 µs/dB ; TO: Hz; FB: Hz; Lock: ^{2}H; Delay: 4.0 s.

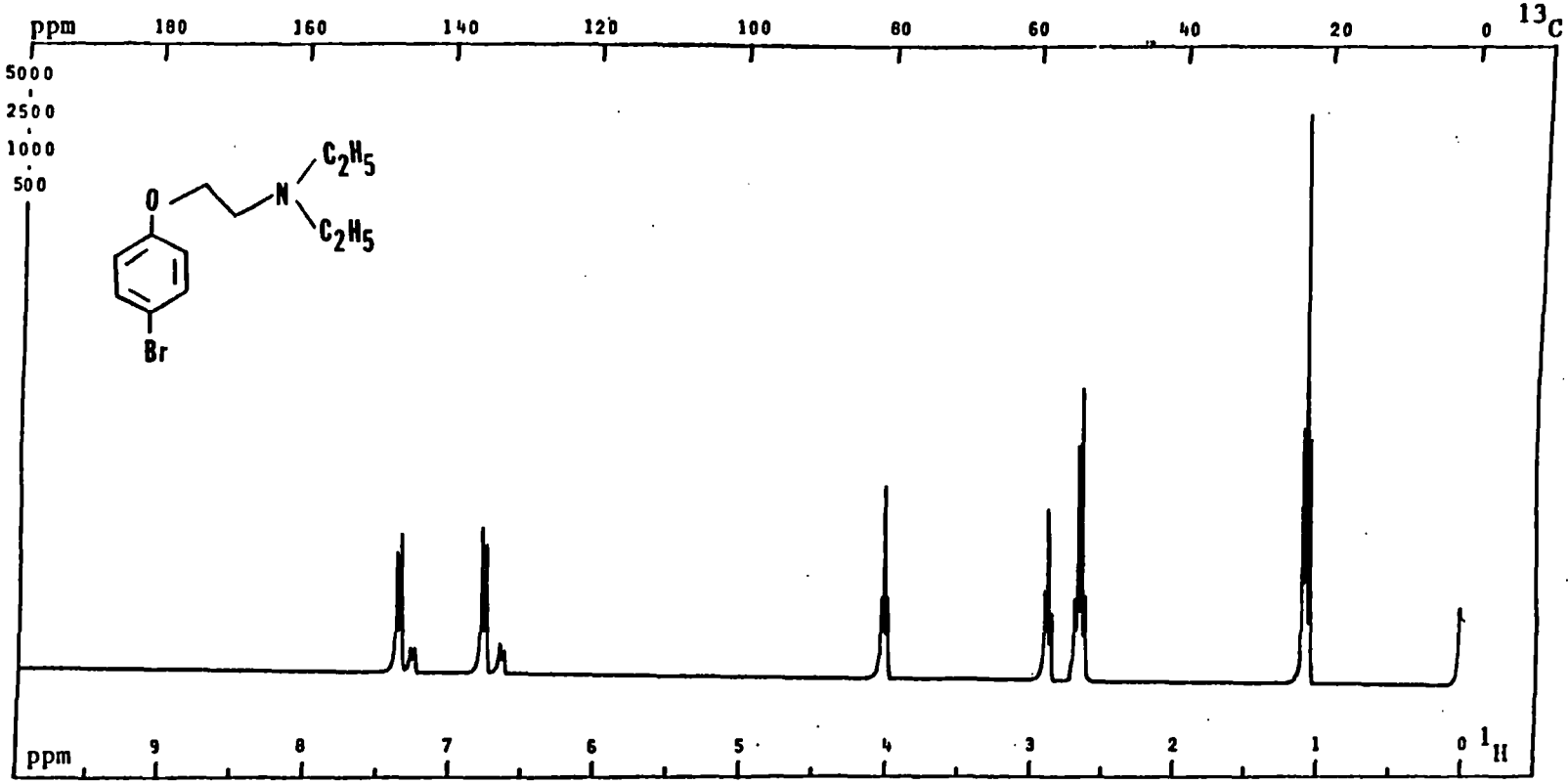
DC: (Y), N ; Gated off: Offset; Hz; RF: W/dB; NBW; Hz; LB; .

PLATE XVI



IR SPECTRUM OF **26**

PLATE XVII



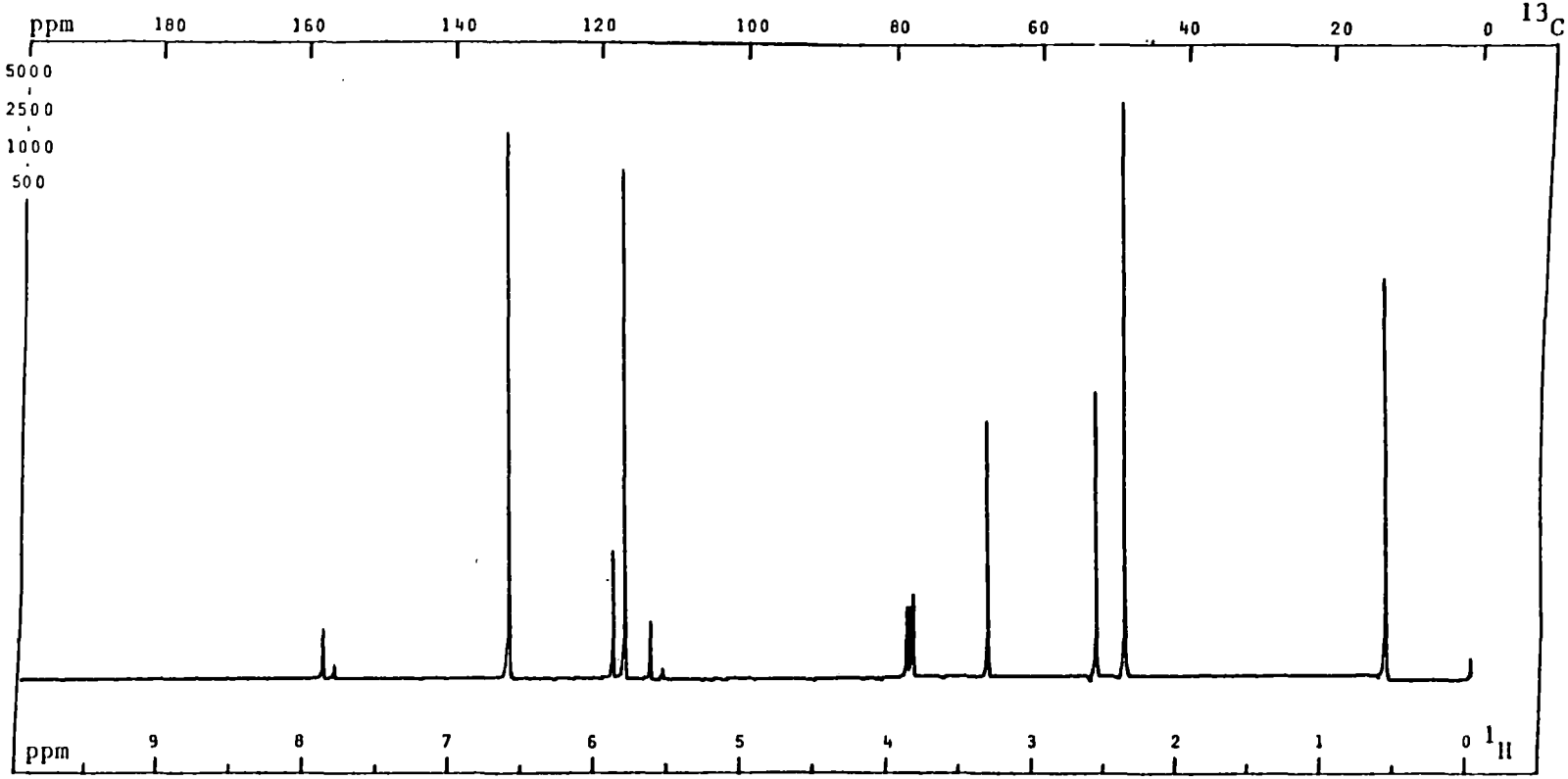
^{1}H NMR SPECTRUM OF **26**

PFT X CW _; Solvent: $CDCl_3$; SF: 299.9 MHz; WC: 500 Hz; T: ^{0}C; NT: 16 .

Size K; PW/RF 5 µs/dB ; TO: 0 Hz; FB: Hz; Lock: ^{2}H; D1,D5: 0.5 s.

DC: Y, N ; Gated off: A or D; Do: Hz; RF(Power); W/dB; NBW: Hz; LB: Hz.

PLATE XVIII



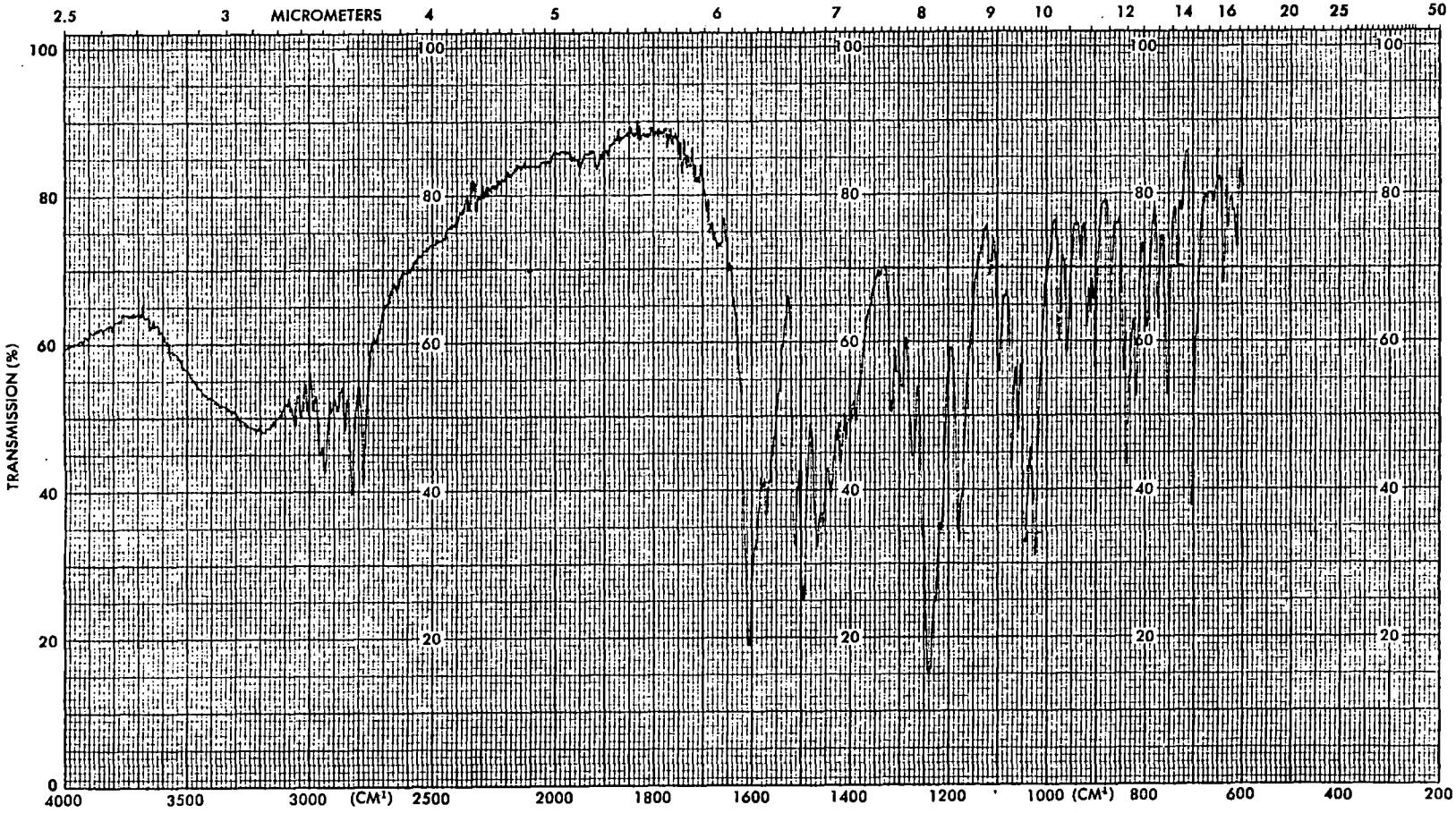
^{13}C NMR SPECTRUM OF **26**

PFT X CW _; Solvent: $CDCl_3$; SF: 75.4 MHz; WC: 500 Hz; T: ^{o}C; NT: 4092 .

Size K; PW/RF 14 µs/dB ; TO: 0 Hz; FB: Hz; Lock: ^{2}H; D1,D5: 4.0 s.

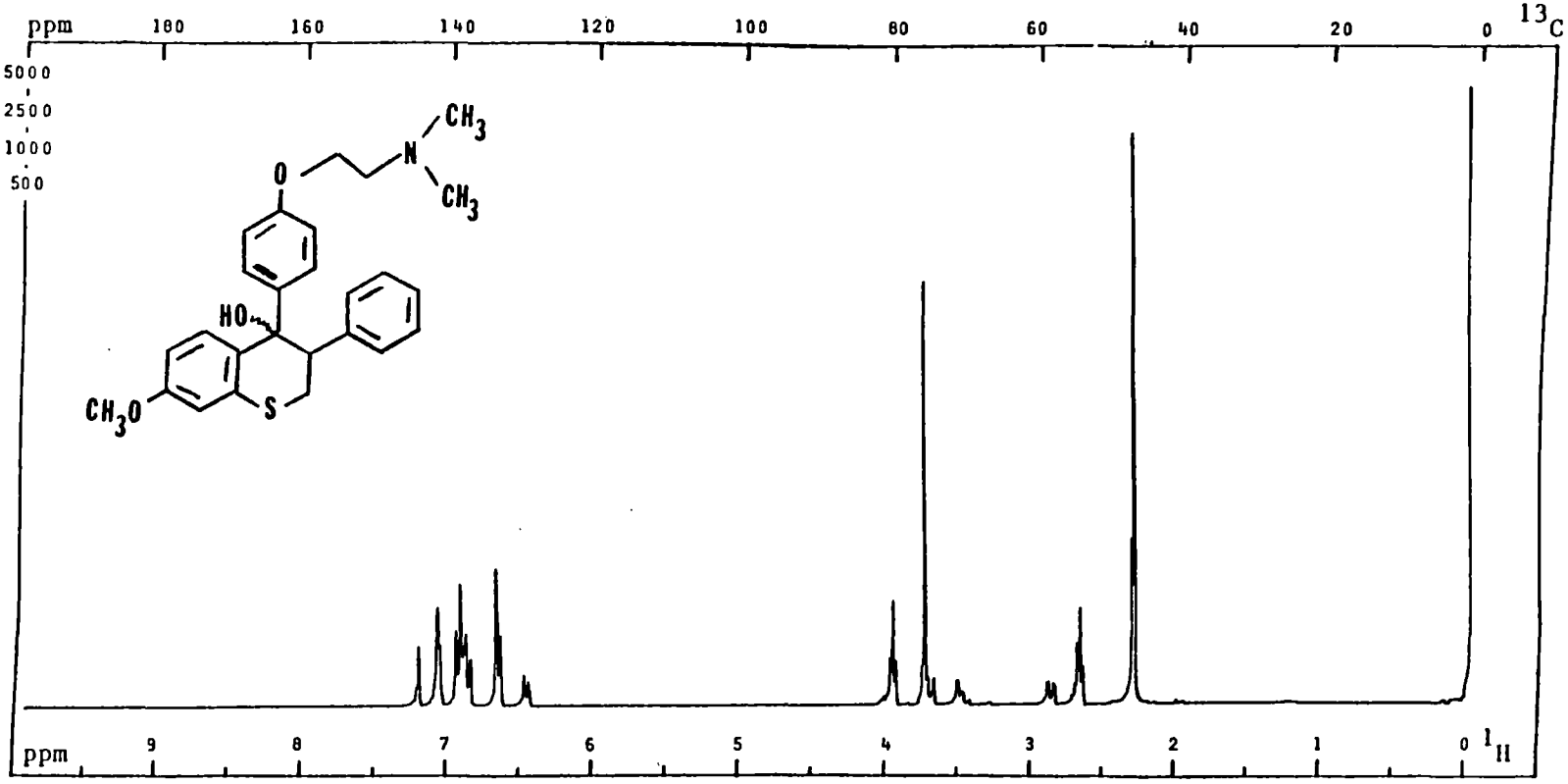
DC: (Y), N ; Gated off: A or D; Do: Hz; RF(Power); W/dB; NBW; Hz; LB; 2.0 Hz.

PLATE XIX



IR SPECTRUM OF **13A**

PLATE XX



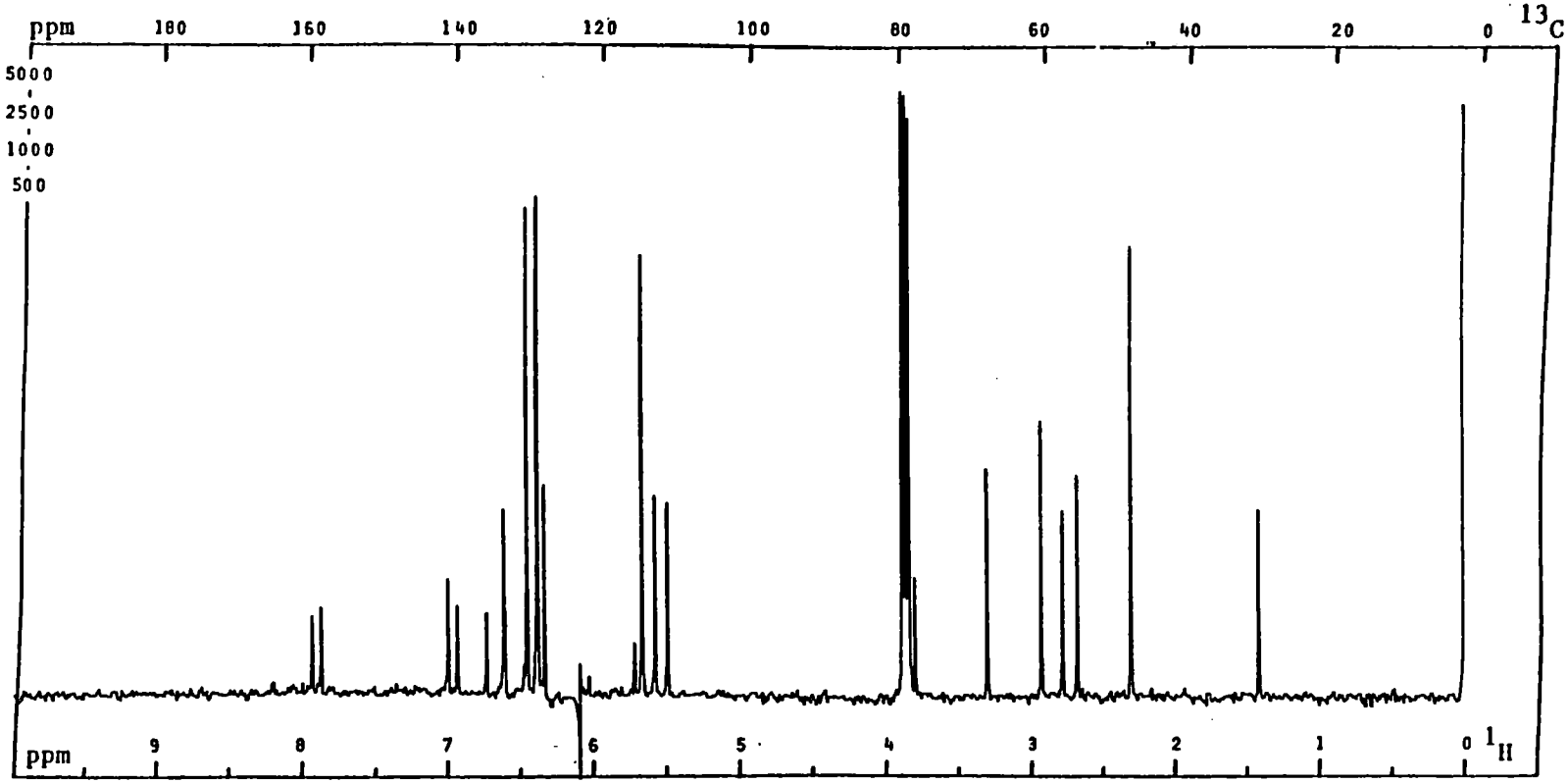
^{1}H NMR SPECTRUM OF **13A**

PFT X CW _; Solvent: $CDCl_3$; SF: 299.9 MHz; WC: 500 Hz; T: ^{o}C; NT: 24 .

Size K; PW/RF 5 µs/dB ; TO: 0 Hz; FB: Hz; Lock: ^{2}H; D1,D5: 0.50 s.

DC: Y, N ; Gated off: A or D; Do: Hz; RF(Power); W/dB; NBW: Hz; LB: Hz.

PLATE XXI



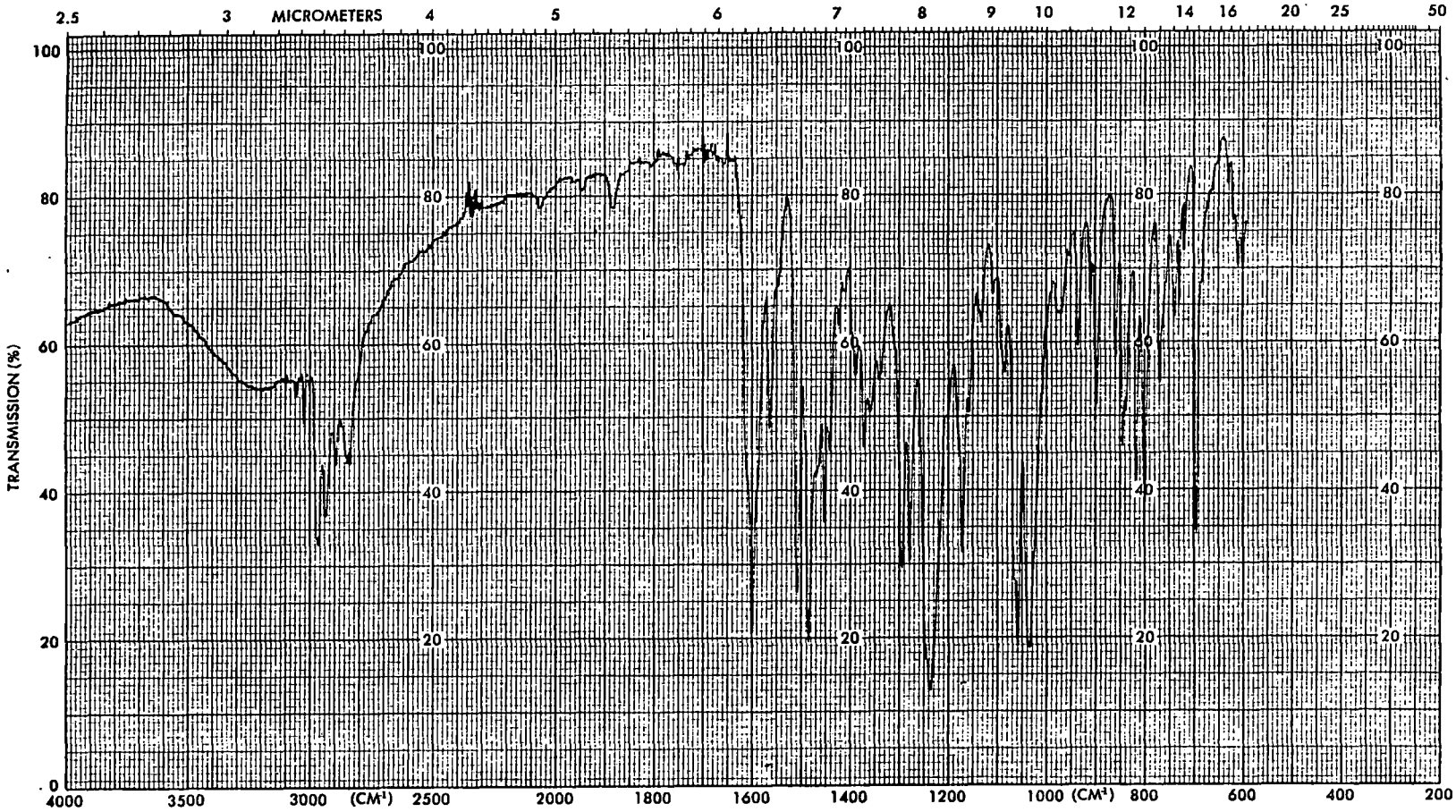
^{13}C NMR SPECTRUM OF **13A**

PFT X CW _; Solvent: $CDCl_3$; SF: 75.4 MHz; WC: 500 Hz; T: ^{o}C; NT: 12272 .

Size K; PW/RF 14 µs/dB ; TO: 1600 Hz; FB: Hz; Lock: ^{2}H; D1,D5: 4.0 s.

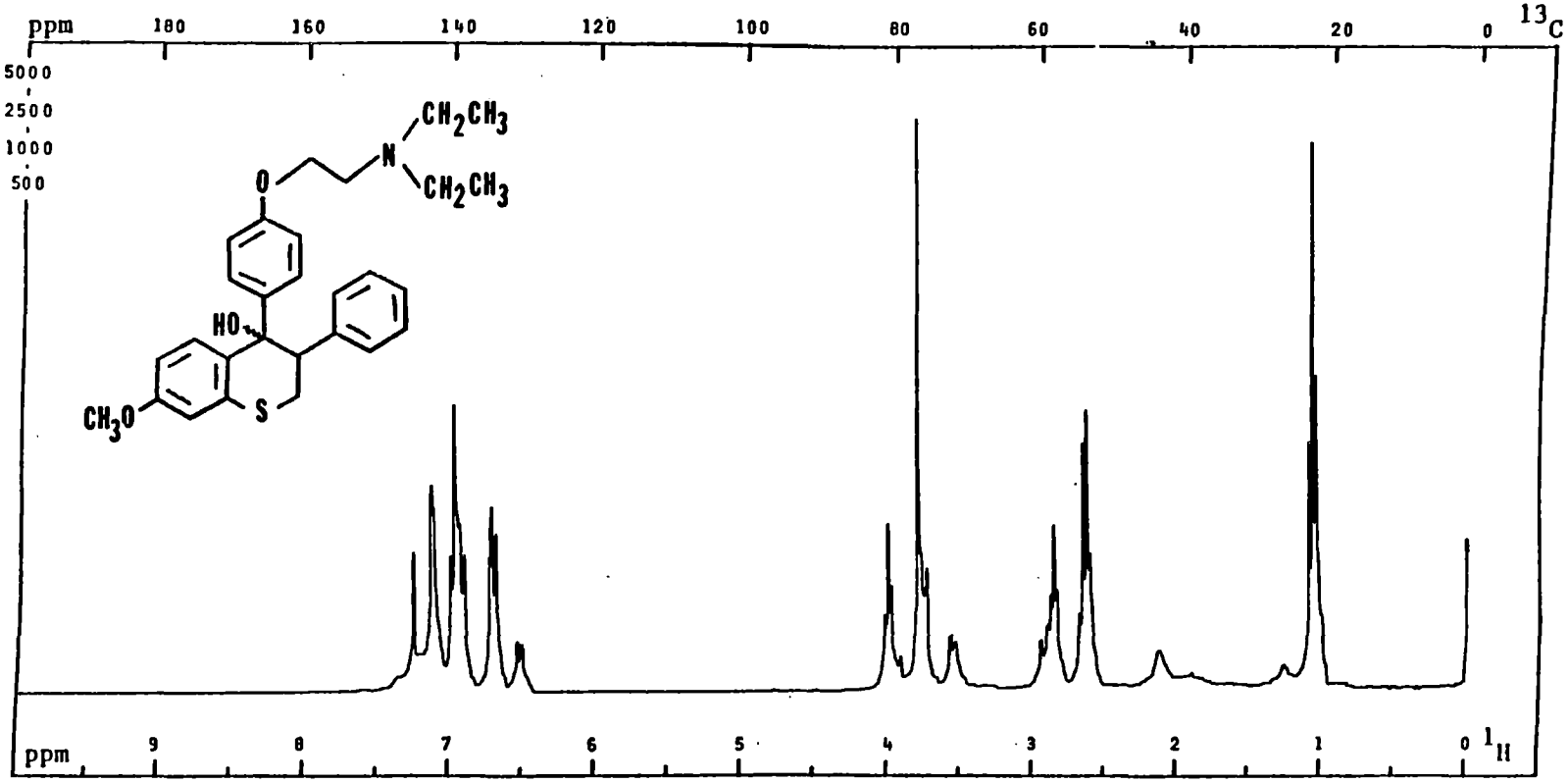
DC: (Y), N ; Gated off: A or D; Do: Hz; RF(Power); W/dB; NBW; Hz; LB; 3.0 Hz.

PLATE XXII



IR SPECTRUM OF **13B**

PLATE XXIII



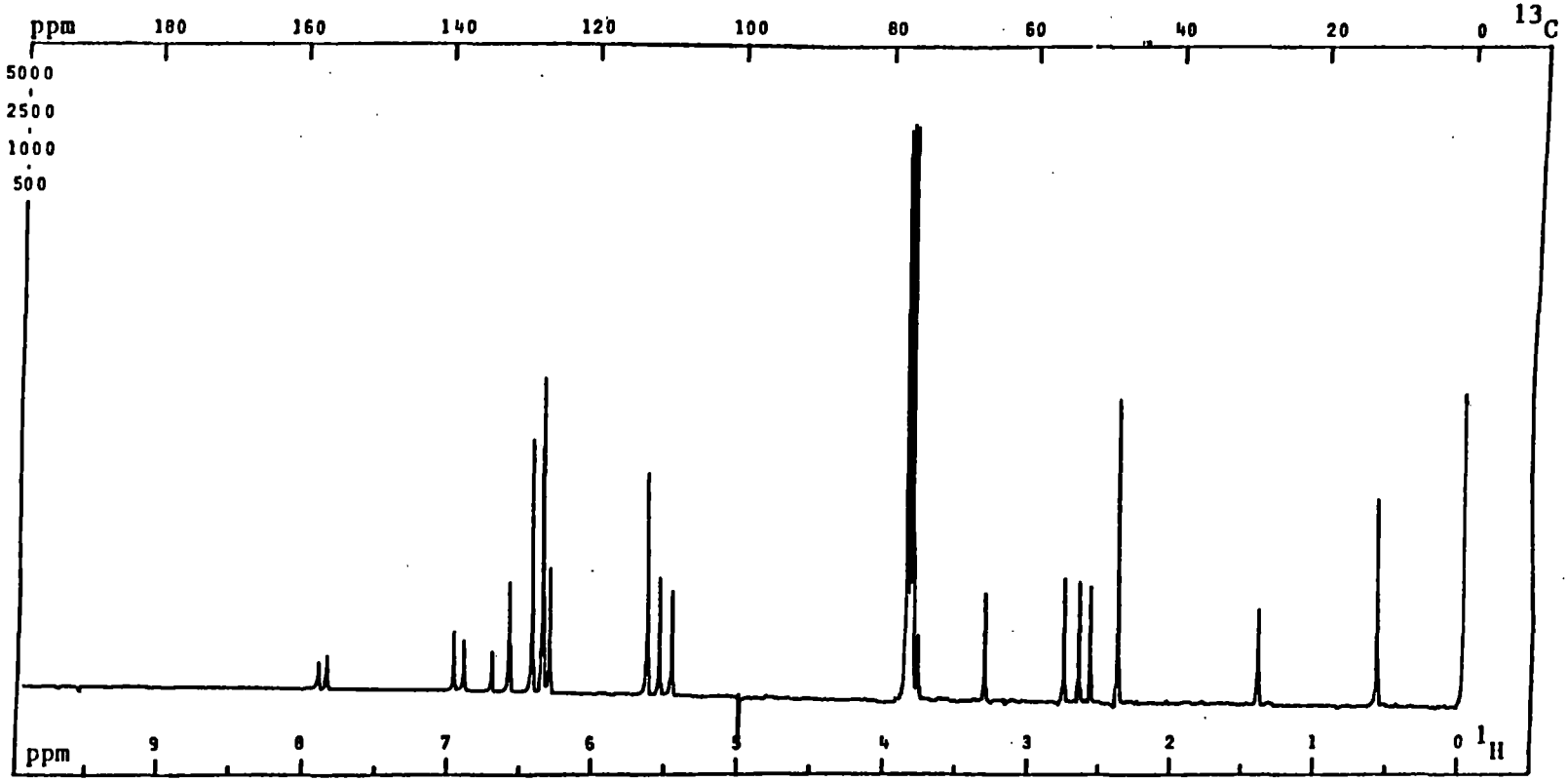
^{1}H NMR SPECTRUM OF **13B**

PFT X CW _; Solvent: $CDCl_3$; SF: 299.9 MHz; WC: 500 Hz; T: ^{o}C; NT: 32 .

Size K; PW/RF 5 µs/dB ; TO: 100 Hz; FB: Hz; Lock: ^{2}H; D1,D5: 0.50 s.

DC: Y, N ; Gated off: A or D; Do: Hz; RF(Power); W/dB; NBW: Hz; LB; Hz.

PLATE XXIV



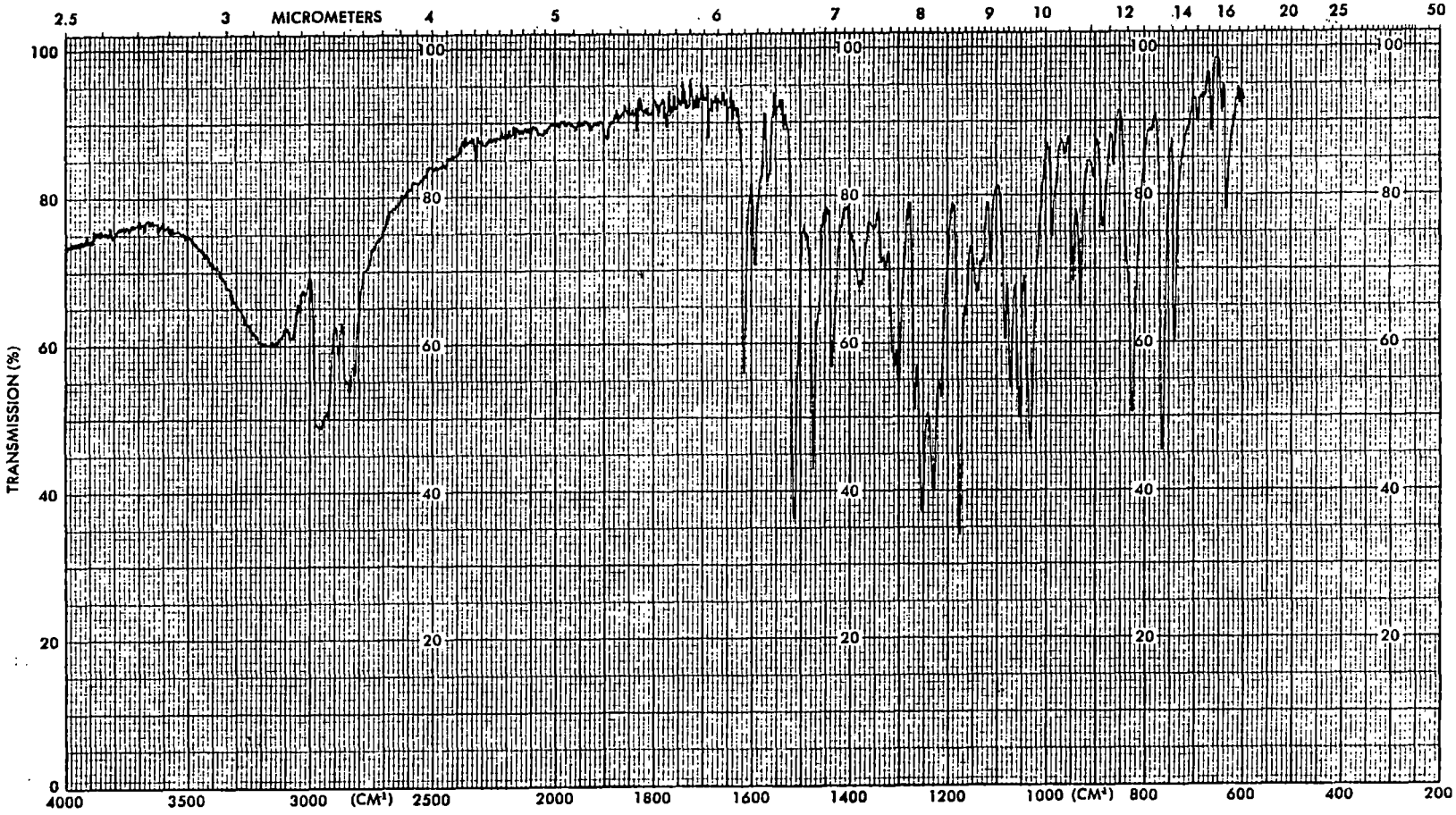
^{13}C NMR SPECTRUM OF **13B**

PFT X CW _; Solvent: $CDCl_3$; SF: 75.4 MHz; WC: 500 Hz; T: ^{o}C; NT: 12272 .

Size K; PW/RF 14 µs/dB ; TO: 0 Hz; FB: Hz; Lock: ^{2}H; D1,D5: 4.0 s.

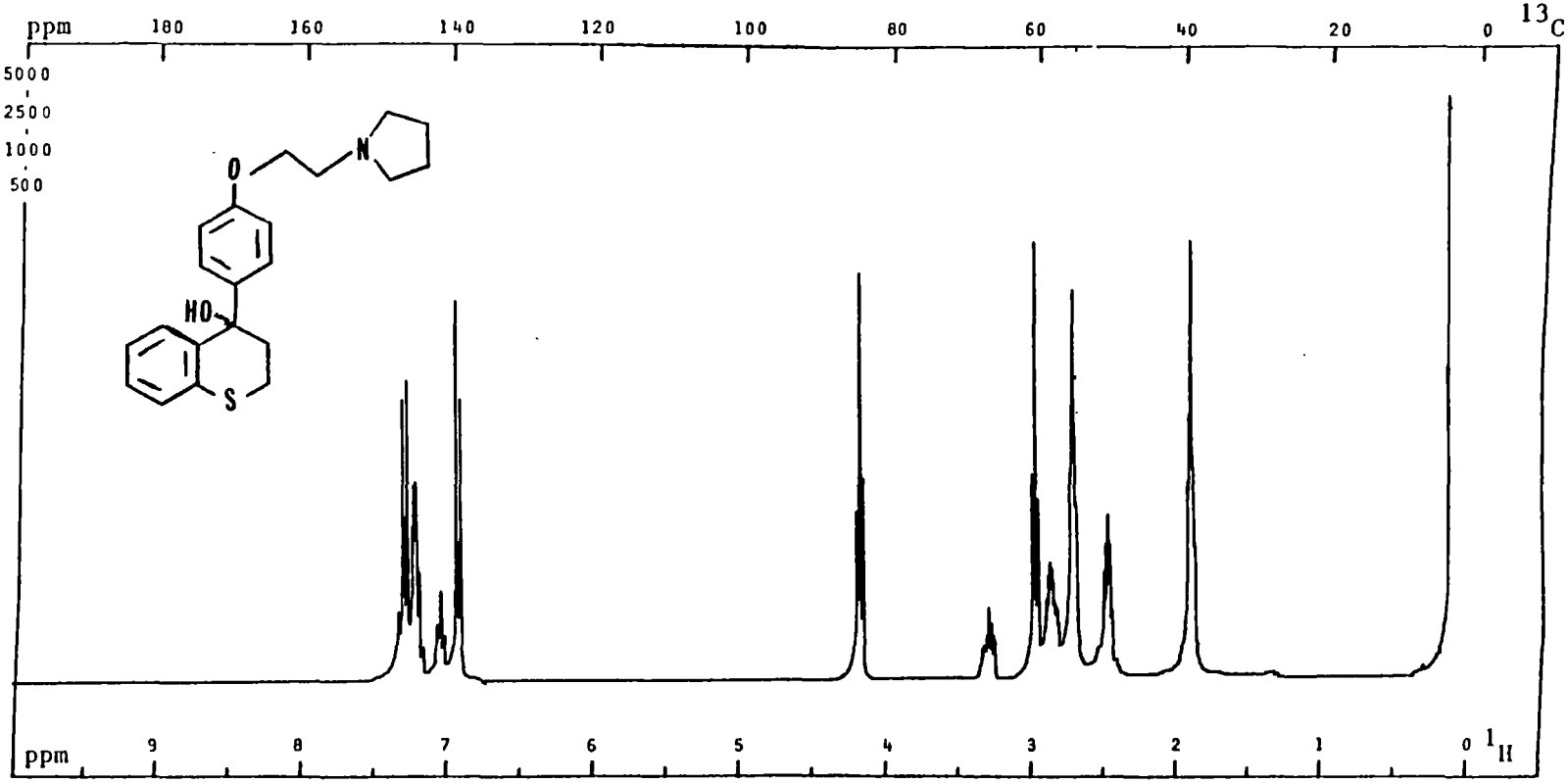
DC: (Y), N ; Gated off: A or D; Do: Hz; RF(Power); W/dB; NBW: Hz; LB: 2.0 Hz.

PLATE XXV



IR SPECTRUM OF **14**

PLATE XXVI



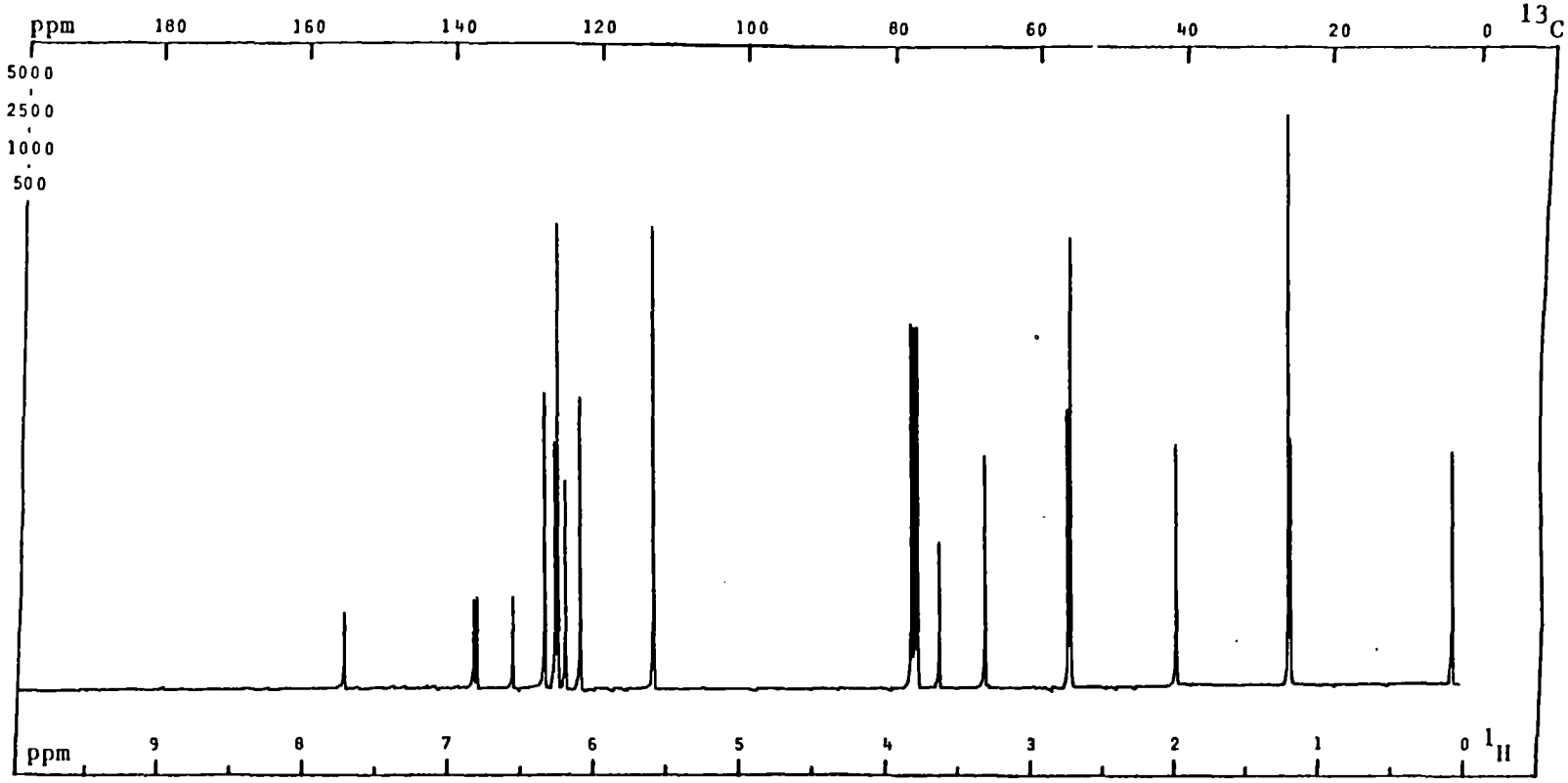
^{1}H NMR SPECTRUM OF **14**

PFT X CW _; Solvent: $CDCl_3$; SF: 299.9 MHz; WC: 500 Hz; T: ^{o}C; NT: 16 .

Size K; PW/RF 5 µs/dB ; TO: 0 Hz; FB: Hz; Lock: ^{2}H; D1,D5: 0.50 s.

DC: Y, N ; Gated off: A or D; Do: Hz; RF(Power); W/dB; NBW: Hz; LB: Hz.

PLATE XXVII



^{13}C NMR SPECTRUM OF **14**

PFT X CW _; Solvent: $CDCl_3$; SF: 75.4 MHz; WC: 500 Hz; T: ^{o}C; NT: 1228 .

Size K; PW/RF 12 µs/dB ; TO: 1000 Hz; FB: Hz; Lock: ^{2}H; D1,D5: 4.0 s.

DC: (Y), N ; Gated off: A or D; Do: Hz; RF(Power); W/dB; NBW; Hz; LB; 2.0 Hz.

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