XANTHOCYCLINE

SYNTHESIS

by

Vilayat A Sayeed

Department of Chemistry

Submitted in Partial Fulfillment

of the Requirement for the Degree

of

Doctor of Philosophy

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A thesis submitted to the Faculty of Graduate Studies of
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To My
Parents, Brother
and
Sister

ACKNOWLEDGEMENT

The author express his sincere appreciation to Dr. J. L. Charlton for his guidance and patience during the supervision of this work.

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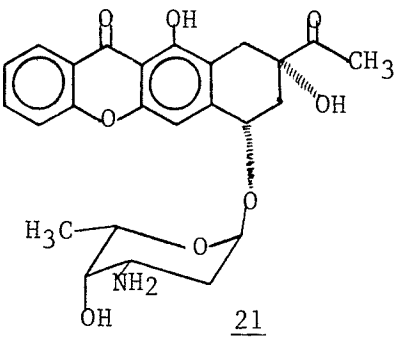
ABSTRACT

In search of analogs with reduced cardiotoxicity, a major structural modification to the existing anthracycline antibiotics is described. The structural change involves replacing the 5-carbonyl of the anthracyclines with an oxygen to produce a tetracyclic xanthone such as 21. As a first step in the complete synthesis of



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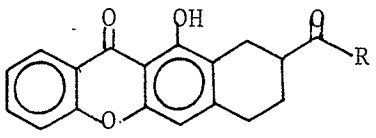
analogs such as 21, the feasible routes that could be applied to the synthesis of the basic tetracyclic carbon skeleton 22 were investigated.

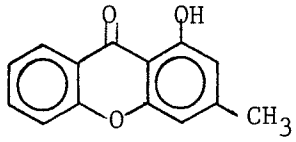


R= OCH_3 or CH_3

22

By the retroanalytical approach, three distinct synthetic routes were chosen for the synthesis of the proposed tetracyclic carbon skeleton 22. The three routes are classified as: (i) xanthone approach (ii) 6,8-Dimethoxy-1-tetralone approach and (iii) chromone approach.

In the xanthone method, an approach to the synthesis of the tetracyclic skeleton involving the condensation of the hydroxy xanthone 23, with the dibromo ester 24 is reported.



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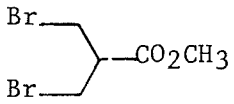

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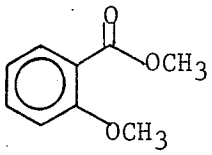
The 6,8-dimethoxy-1-tetralone methodology deals with the attempted synthesis of the precursor 26 as a prelude to condensation with 52.



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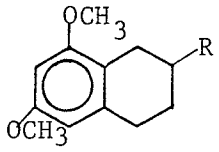

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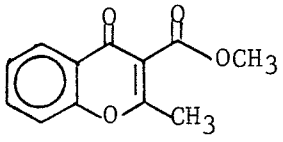
R= CO_2CH_3 or $COCH_3$

In the chromone approach the synthesis of the target molecule xanthocycline 22 (R=OCH_3) is reported starting from the precursors 27 and 28.



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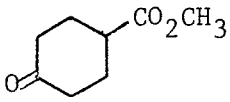

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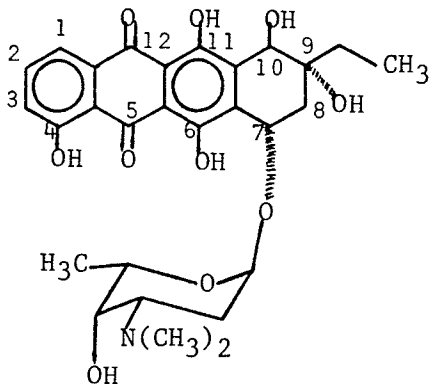
INTRODUCTION

Cancer is characterised by the abnormal uncontrolled growth of cells exhibiting varying degrees of malignancy. The uncontrolled growth can produce tumors, and cancerous cells often invade adjacent normal tissues. Cancer can be treated by a variety of drugs. A major problem associated with cancer chemotherapy is the tendency for the drugs to interfere with both normal and maligant cells. That is, while they are toxic towards cancer cells, they are usually toxic towards normal cells as well. The chemotherapeutic value of anticancer agents results from the fact that, in vivo, the normal tissues critical for the survival of the host, are less susceptible than the cancerous tissues.

The most essential requirement of a potential chemotherapeutic agent is its selective toxicity. As most of the known anticancer agents lack this vital property, the search for better drugs with selective toxicity has been approached by modifying the structure of the existing chemotherapeutic agents. This approach has led to the discovery of many compounds of clinical value and has recently been applied to anthracycline antibiotics to increase their therapeutic efficacy.

In the late 1950s a pigmented compound isolated from a strain of streptomyces sp was found to exhibit antitumor activity (1). The structure of this pigment, rhodomycin B was establish as quinone 1 by Brockmann (2). The general class of pigmented glycosides similar to 1 are now referred to as anthracyclines and the corresponding aglycones are called anthracyclinones.

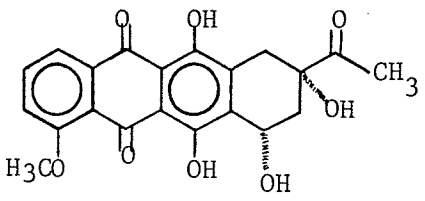
Later studies have resulted in the isolation and characterization of several anthracyclines from different streptomyces species. These compounds generally differ only in the pattern of hydroxylation on the anthracycline carbon skeleton (3).



1

In the early 1960s a new antibiotic was isolated simultaneously in the laboratories of Farmitalia, where it was given the name daunomycin, and in those of Rhone-Poulenc (4), where it was named rubidomycin. This antibiotic, now called daunorubicin (5), had important pharmacological properties superior to previously known anthracyclines.

Structure elucidation studies (6,7) concluded that daunorubicin was a glycoside of a new anthracyclinone, daunomycinone 2, with a previously unknown amino sugar daunosamine 3. Both of these moieties present important variations with respect to the known anthracyclines 1.



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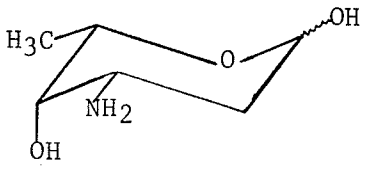

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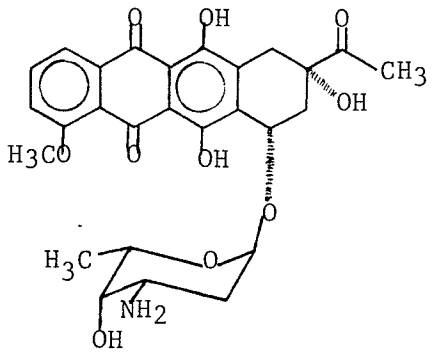
The complete structure and stereochemistry of daunorubicin 4 was established by Arcamone and coworkers (8).



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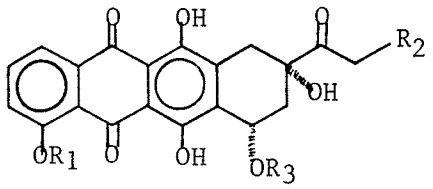
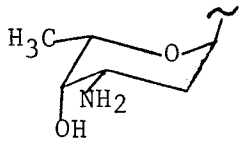
A search for other microbial analogs resulted in the isolation and characterization of doxorubicin 5 (9), and carminomycin 7 (10). It was found that the doxorubicin 5 and carminomycin 7 contained the aglycones, adriamycinone 6 and carminomycinone 8 respectively, and also contained the aminosugar daunosamine 3.

The configuration at the glycosidic carbon (C_7) of doxorubicin 5 and carminomycin 7 was reported to be the same as that of daunorubicin 4 (11,12).

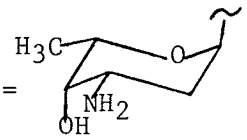


5 R_1=CH_3, R_2=OH, R_3=



6 R_1=CH_3, R_2=OH, R_3=H

7 R_1=H, R_2=H, R_3=

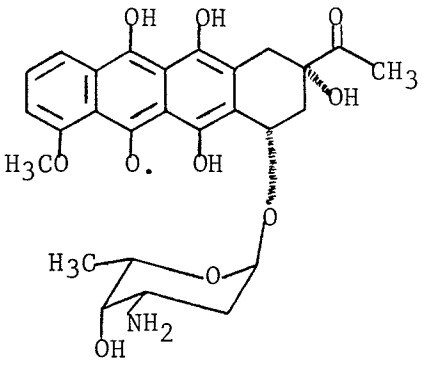


8 R_1=H, R_2=H, R_3=H

The anthracycline quinones doxorubicin(adriamycin) 5 and daunorubicin 4 are among the most promising new antitumor agents in clinical medicine at the present time and are currently in use against a range of neoplasms (13). It is widely accepted that the antineoplastic activity of these quinones stems from their ability to interact with nucleic acids (14). It has been proposed that intercalation of the anthraquinone structure between base pairs of the DNA helix occurs and leads to inhibition of DNA replication and/or RNA synthesis. The presence of the free amino group and the stereochemistry of the sugar was reported to be essential for the stabilization of the DNA binding complex (15). However, it has been suggested that other mechanisms including

the generation of free radical intermediates (16) and/or bioreductive covalent attachment to biomolecules may also be significant (17).

The clinical success of these antibiotics has been limited by: i) a severe dose related cardiotoxicity (18,19) and ii) a tendency of the anthracyclines to undergo reductive deglycosidation by both hydrolytic and reductive glycosidases to produce the inactive 7-deoxyaglycones (13 to 20). There is experimental evidence that the 6-hydroxyl of the anthracyclines plays an essential role in this reductive cleavage (21). It has been proposed that both the cardiotoxicity and cleavage of the sugar requires an initial one electron reduction of the chromophore to give a semiquinone radical 9. The subsequent generation of reactive



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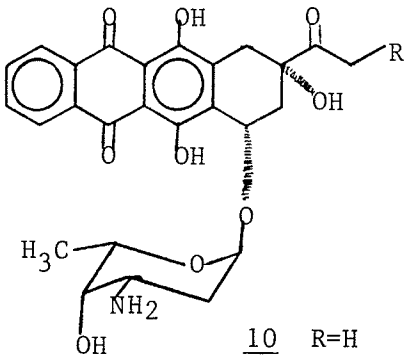
oxygen species including hydrogen peroxide, superoxide anion, and hydroxy radicals has also been suggested (16,19,22 to 24). The involvement of these reactive oxygen species in cardiotoxic effects induced by the anthracycline antibiotics may be accounted for by the low amount of the protective enzymes superoxide dismutases,

catalase and glutathione peroxidase present in heart tissue (22, 25,26). Thus the cardiac tissue damage is linked to lipid peroxidation by the above species.

To suppress this untoward effect, and to broaden the spectrum of activity (27 to 29), new analogs of the antitumor anthracyclines have been synthesized by modifying the C_9 side chain, the sugar moiety and the aglycone (30 to 35). It has recently been found that 4-demethoxydaunorubicin 10 and 4-demethoxyadriamycin 11, obtained by total synthesis of the aglycone moiety according to the procedure developed by Wong (33), exhibit even greater activity than the parent drugs (29,34,35).

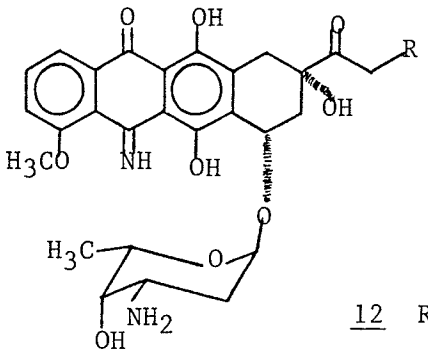


10 R=H

11 R=OH

The quinone function found in the structure of numerous antitumor agents is widely recognised as a key mediator of biochemical action (17,36,37). This is particularly true for the clinically important anthracyclines doxorubicin 5 and daunorubicin 4 (38). Despite the above evidence some modifications of the quinone function, such as in 5-iminodaunorubicin 12 (39), have led to

reduced cardiotoxic effects in certain tests (39,40) while the compounds still retain antitumor activity (39). That this effect is variable is indicated by the fact that 5-iminodoxorubicin 13 is reported to show a 10-fold decrease in antitumor potency as

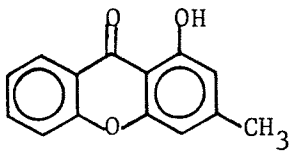


12 R=H

13 R=OH

compared to 12 (41). The reduced cardiotoxic effect observed on quinone modification (39,40), and a simultaneous reduction in capacity to generate free radicals (37,42) through cyclic reduction-reoxidation of the quinoid structure are probably connected (41).

Xanthones, another class of naturally occurring compounds are found in various plants species and microbial sources. Since their discovery in 1821 (43), nearly one hundred and fifty xanthone derivatives, with different degrees of oxidation patterns and substitutions in the side chains, have been isolated (44 to 47). In general these compounds are tricyclic 14, however compounds with the tetracyclic carbon skeleton such as 14a are also known (47).



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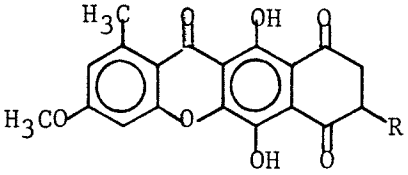


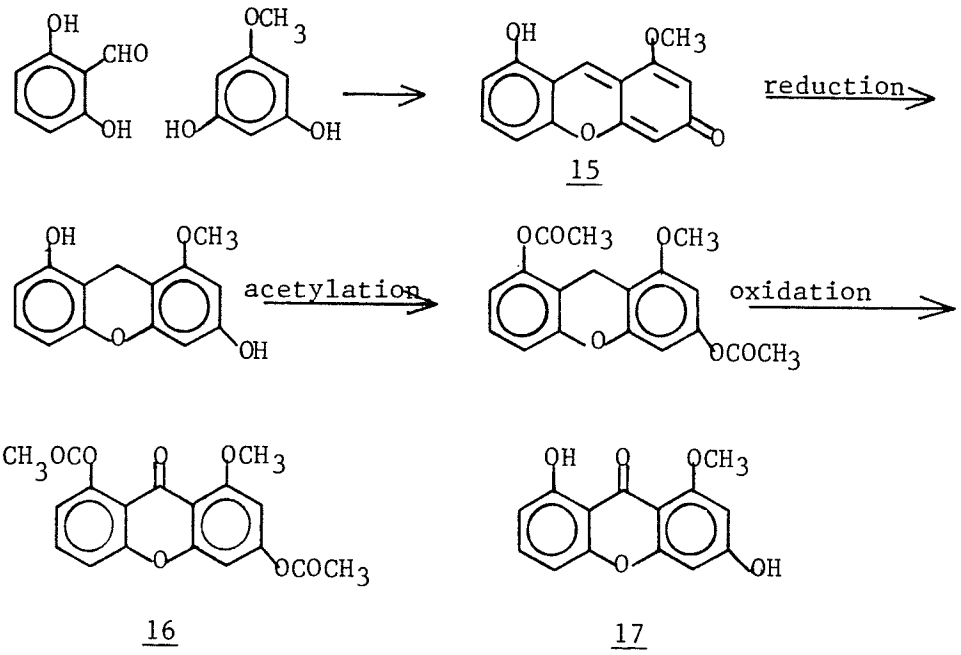
14a

These xanthones are reported to possess pharmacological and biological activity (48) over a wide spectrum. Xanthones are known to be monoamine oxidase inhibitors, cardiovascular stimulants, anticonvulsants, antitubercular agents and antipsychotics (49 to 51). Certain derivatives of 1-hydroxyxanthone are also reported to show varied inhibitory activity towards Sarcoma 180 tumor cells (52).

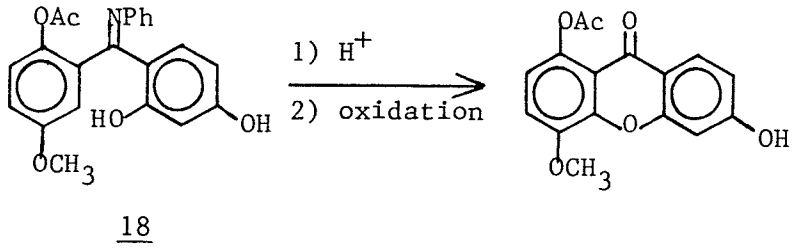
Polyoxygenated xanthones have been synthesized by a number of methods. The most extensively used approach is that of Grover, Shah and Shah (53) even though it suffers from serious limitations. Their procedure involves a condensation of o-hydroxybenzoic acids with a reactive phenol in the presence of zinc chloride and phosphorus oxychloride to produce xanthones, plus other side products, via intermediate benzophenones. A fair number of xanthones and their derivatives have been synthesized by this procedure (48).

Another synthesis of xanthones, reported by Asahina and Tanase (54,55), involves the condensation of o-hydroxybenzaldehydes with a phenol to produce 9H-xanthene-3-ones eg 15 which upon

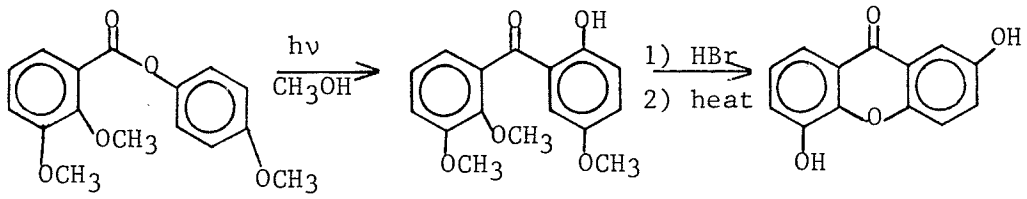
reduction and oxidation give 9H-xanthene-9-ones eg 16. 3,8-Dihydroxy-1-methoxyxanthone 17 has been synthesized by this procedure (56).



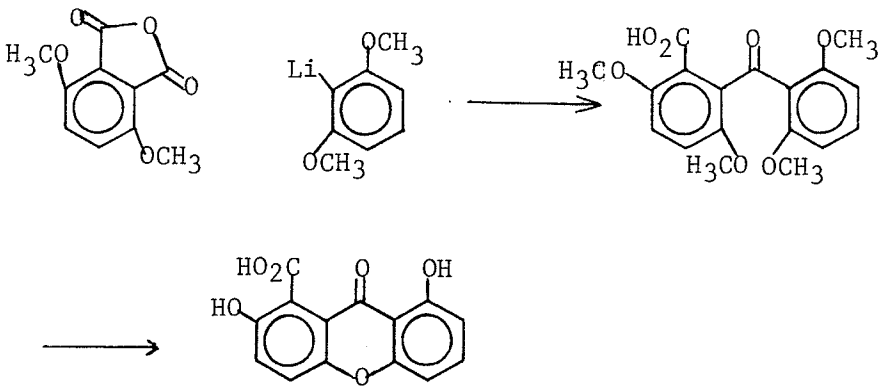
Robinson and Nishikawa (57) have synthesized xanthones through ketimine intermediates of type 18.



Xanthones have also been synthesized by the oxidation of benzophenones obtained by such methods as the photo-Fries rearrangement of aryl esters (58,59), Friedel-Crafts acylation (60),

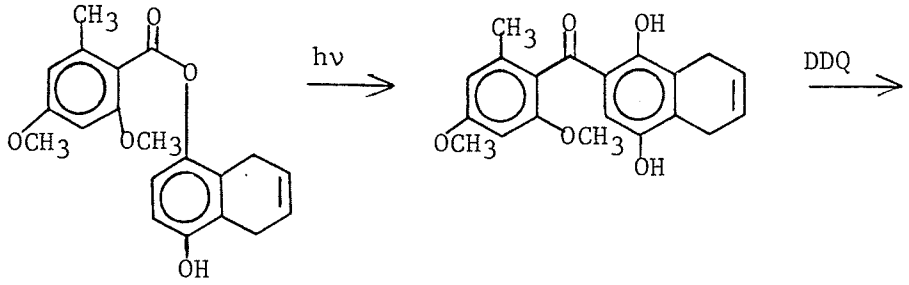


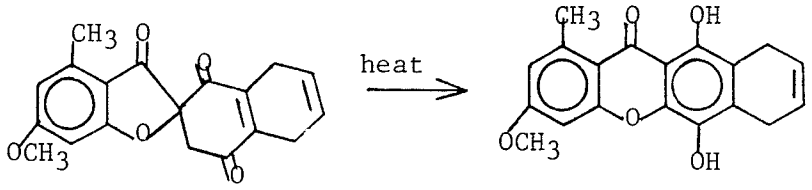
and the condensation of lithium salts of phenyl ethers with appropriately substituted benzoyl chlorides (61) and anhydrides (62).



Recently Lewis and coworkers (63) have synthesized the tetracyclic xanthone 20 by a photo-Fries rearrangement followed

by oxidation and thermal isomerization of the intermediate spirocyclohexenedione 19.





19 20

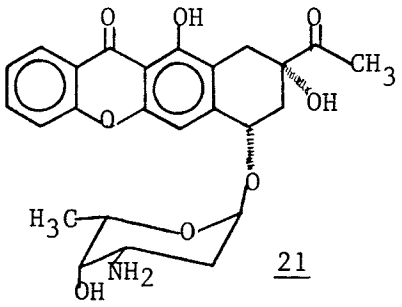
Since the discovery of the anthracycline antibiotics, several structural modifications have been introduced by various investigators, with the hope that the new analogs thus produced would have retained antitumor activity and reduced cardiotoxicity. Although the exact mechanism of the cardiotoxic effect is unknown, it is generally accepted that the process involves the quinone function and its ability to generate reactive oxygen species through a redox cycle. In considering modification to the quinone functionality of the anthracycline, a change was sought which might alter the redox character of the quinone portion of the molecule without introducing gross structural alteration. This basic idea had already met with limited success in the 5-imino

analogs. Among the other possible modifications one might envision for the quinone function, the conversion to a xanthone seemed most reasonable. This proposal is supported by the known biological properties of xanthones. That is, they are not known to be cardiotoxic and some derivatives even show mild antitumor activity.

This change in functionality should alter the reduction potential of the compound, and may reduce or eliminate the formation of the free radicals and reactive oxygen species, which are associated with cardiotoxicity. The proposed change of quinone to xanthone would not change the geometry of the molecule considerably, which is essential since the molecular shape is important to its ability to complex with DNA and initiate the antitumor effect.

Another minor modification to the anthracyclines that might prove beneficial is the removal of the 6-hydroxy group. This hydroxyl is implicated in the deglycosidation of the anthracyclines and its removal might increase the lifetime of the drug and hence increase its potency.

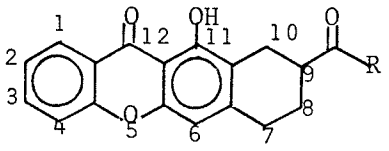
On the basis of the above, it is proposed that, by combining the xanthone and anthracycline features in an analog such as 21, one should be able to retain the antitumor activity, and the



21

geometrical requirement essential for this activity. This modified analog 21 might also show a considerable reduction in cardiotoxicity and deglycosidation, due to the absence of the quinone function and the 6-hydroxyl group.

The object of this thesis was to study the feasible synthetic routes that could be used in synthesizing the tetracyclic carbon skeleton 22 of the proposed analog 21.



R= OCH_3 or CH_3

22

In the following sections an antithetic approach is applied in order to determine possible routes to the target molecule 22. Thereafter, the actual experimental approaches to the synthesis are discussed. The general name xanthocycline is proposed for compounds having the tetracyclic xanthone skeleton such as found in 22.

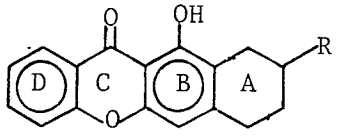
RETROSYNTHETIC ANALYSIS OF XANTHOCYCLINE

Recently a systematic retroanalytical approach has been used in designing different synthetic methodologies. The discussion given below involves the application of the retroanalytical approach to designing syntheses of the target molecule xanthocycline.

In accordance with the retroanalytical approach (64), the target molecule xanthocycline was disconnected at appropriate positions in order to systematically determine the best route and starting material for the synthesis of the molecule.

Three major disconnections (disc), at position a, b and c were considered on the tetracyclic system, to obtain distinctly different synthetic starting points.

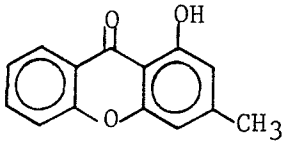
(1) Disconnection a



22

disc a

R= CO_2CH_3 or $COCH_3$



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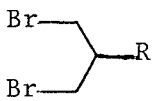

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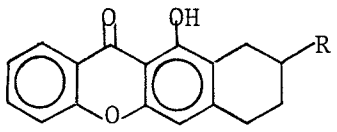
(2) Disconnection b



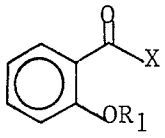
22

disc b

R_1=H or CH_3

R =CO_2CH_3 or $COCH_3$

X =Cl, H or OCH_3



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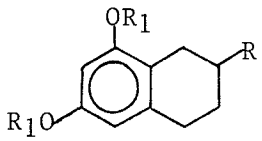
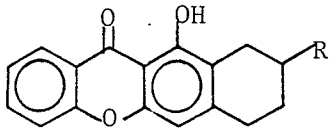


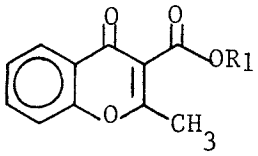
26

(3) Disconnection c

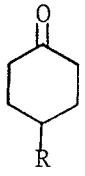


22

disc c



27 R_1= CH_3 or C_2H_5

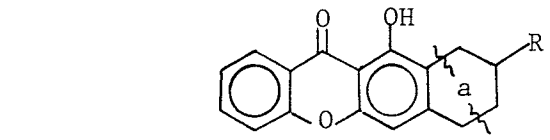


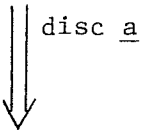
28 R=CO_2CH_3 or $COCH_3$

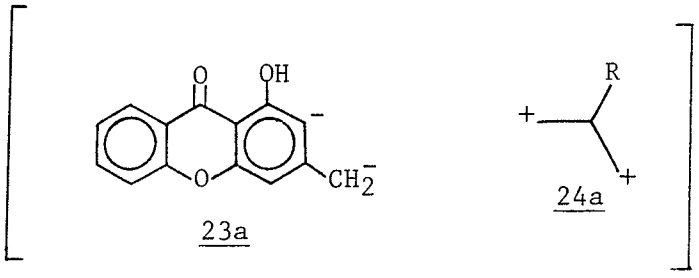
The synthetic equivalents (syn equ) 23, 24, 26, 27 and 28 were in turn related to easily accessible starting materials by further retrosynthetic analysis.

Disconnection a

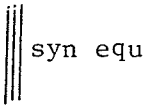
Disconnecting the tetracyclic system at position a gave synthons 23a and 24a, for which the synthetic equivalents are 23 and 24.

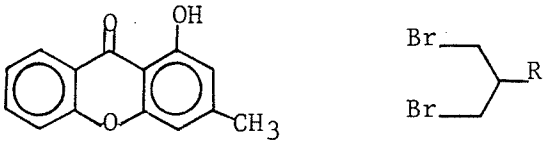






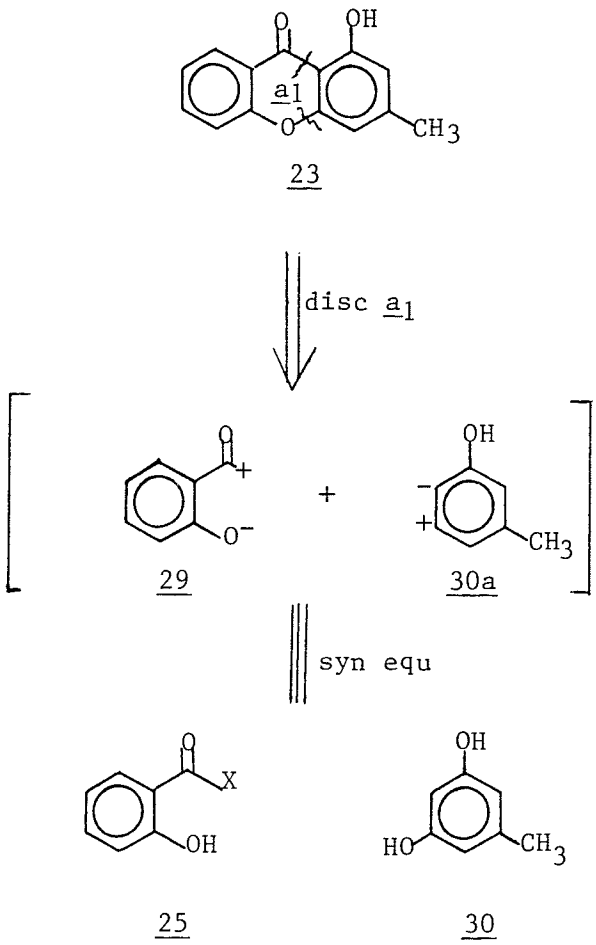
23a 24a





23 24 R=CO_2CH_3 or $COCH_3$

Disconnection of 23 at a_1 resulted in the two synthons 29 and 30a, which have synthetic equivalents 25 and 30.

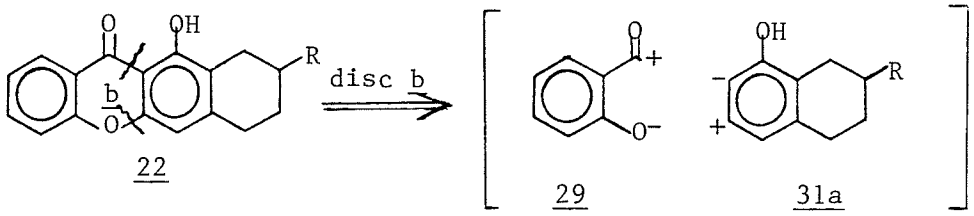


Thus, the total synthesis would require the three simple materials 24, 25, and 30.

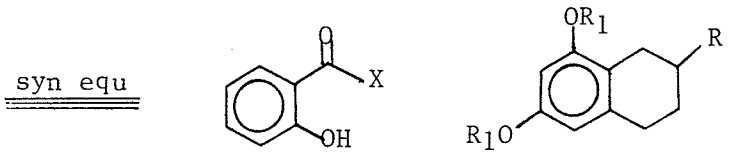
This a disconnection route will be later referred to as the xanthone approach in discussing the synthesis of the tetracyclic system.

Disconnection b

The tetracyclic system, when disconnected at position b, gave mono and bicyclic synthetic equivalents 25 and 26 via synthons 29 and 31a respectively.



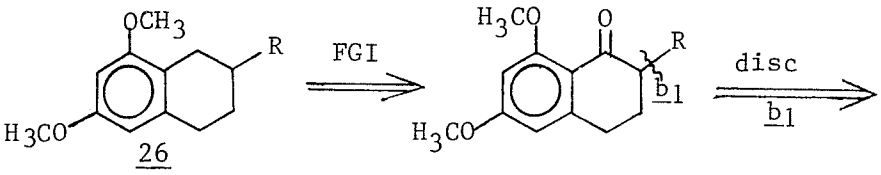
22 29 31a



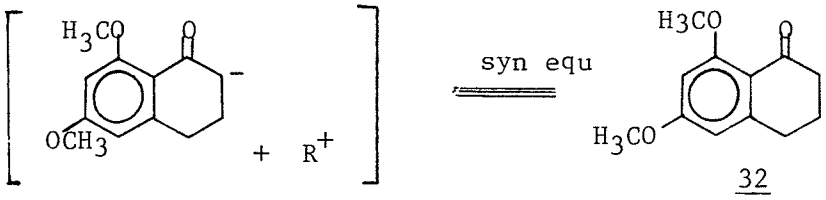
25 26 R_1=H or CH_3

R =CO_2CH_3 or $COCH_3$

A functional group interconversion (FGI) in the bicyclic compound 26, followed by a disconnection at b_1 gave 32.

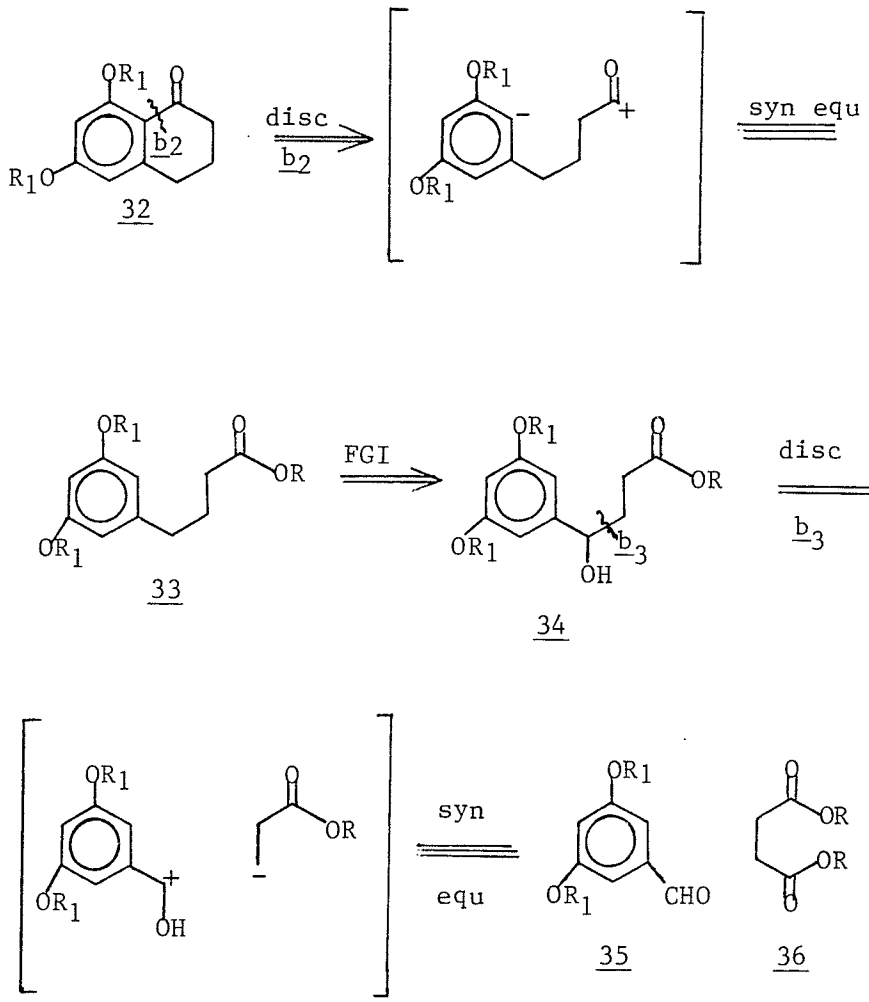


26



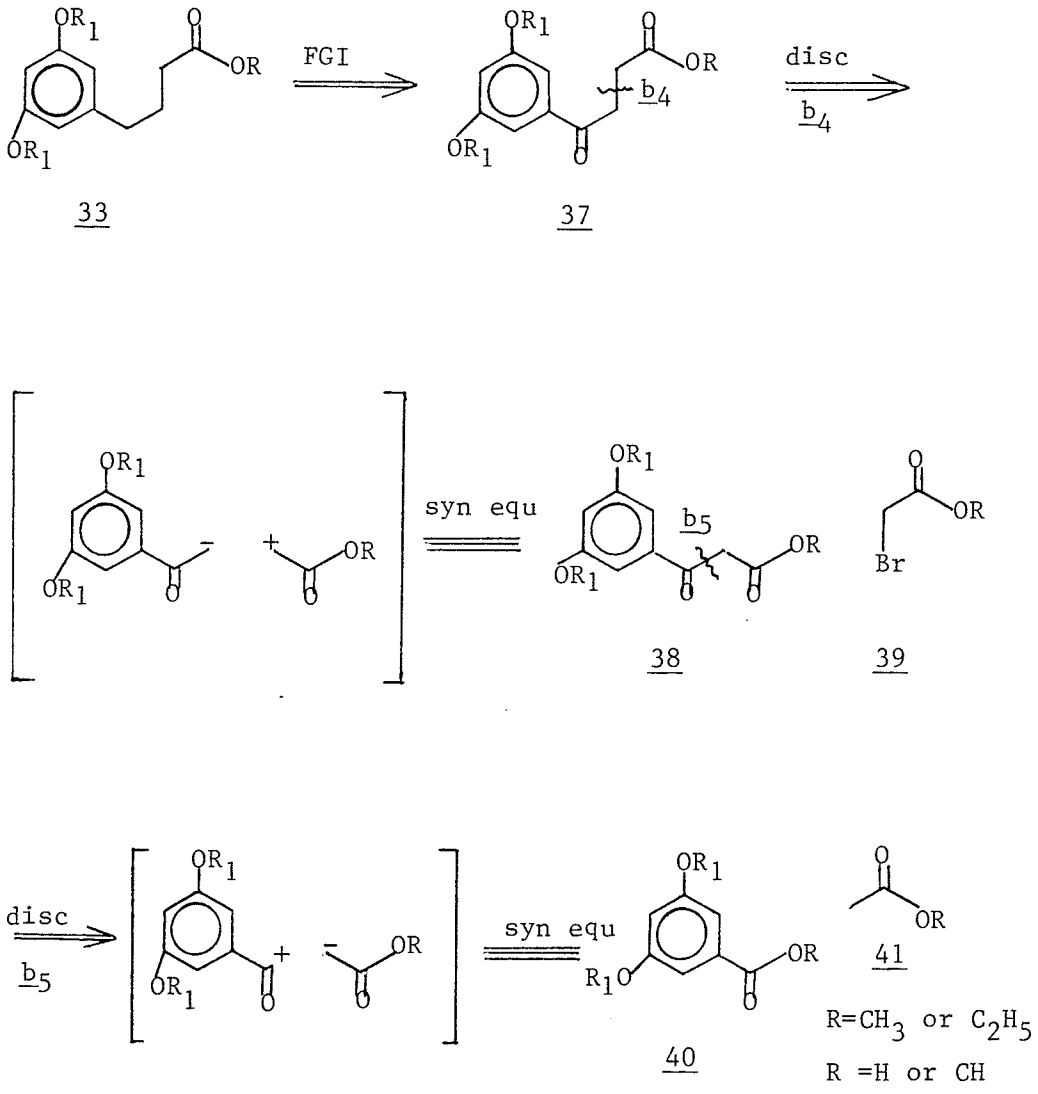
32

The bicyclic compound 32 can be further simplified, by two distinct functional group interconversions and disconnections. Disconnection of 34 at b_3, which had been obtained by a functional group interconversion of 33, gave the synthetic equivalents 35 and 36 as indicated in Scheme 1.



Scheme 1

The functional group interconversion of 33 to 37, then disconnecting 37 at b_4 and 38 at b_5, gave simple starting materials 39, 40 and 41 as shown in Scheme 2.

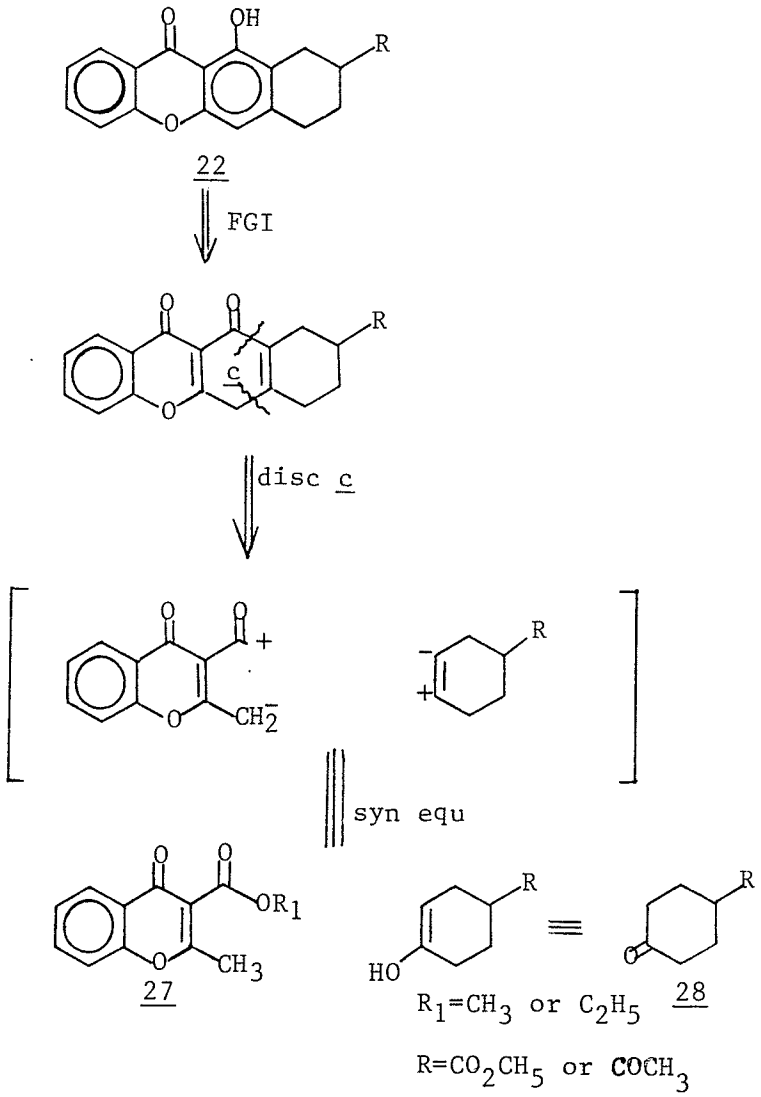


Scheme 2

The b transformation will be referred to as 6,8-dimethoxy--1-tetralone approach.

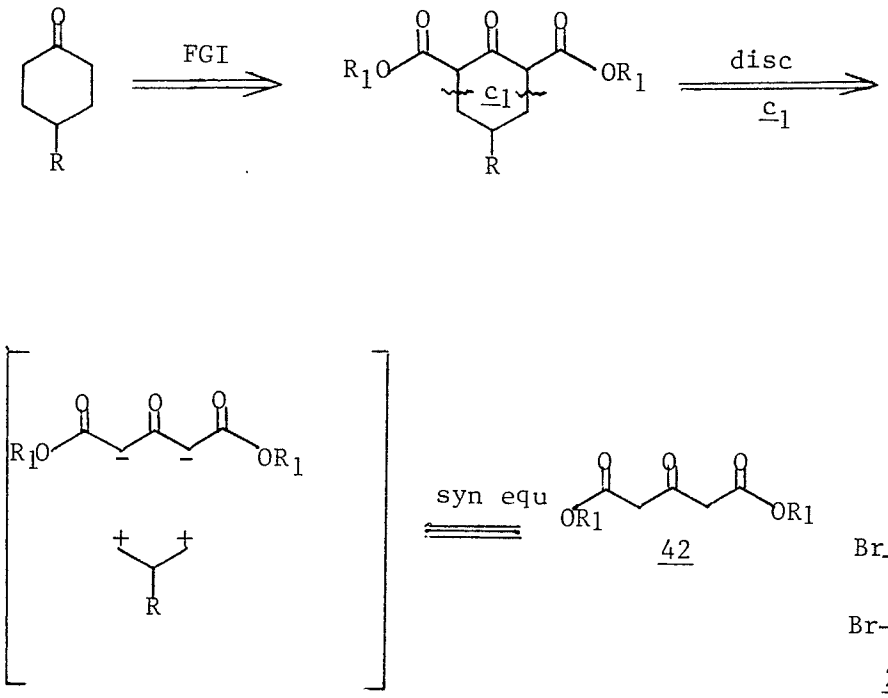
Disconnection c

Functional group interconversion of the parent molecule 22, followed by a disconnection at c, gave synthetic equivalents 27 and 28.



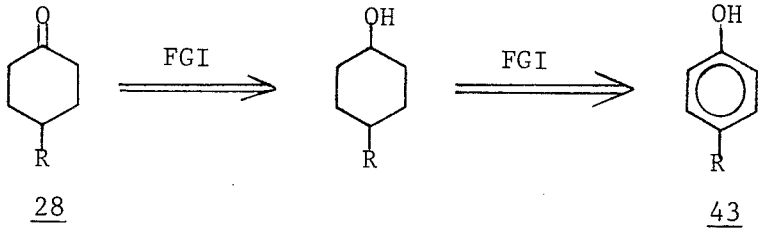
The mono and bicyclic compounds thus obtained were further simplified to readily available precursors.

Functional group interconversion of compound 28, and disconnection at c_1, led to the reagents 42 and 24 (Scheme 3).



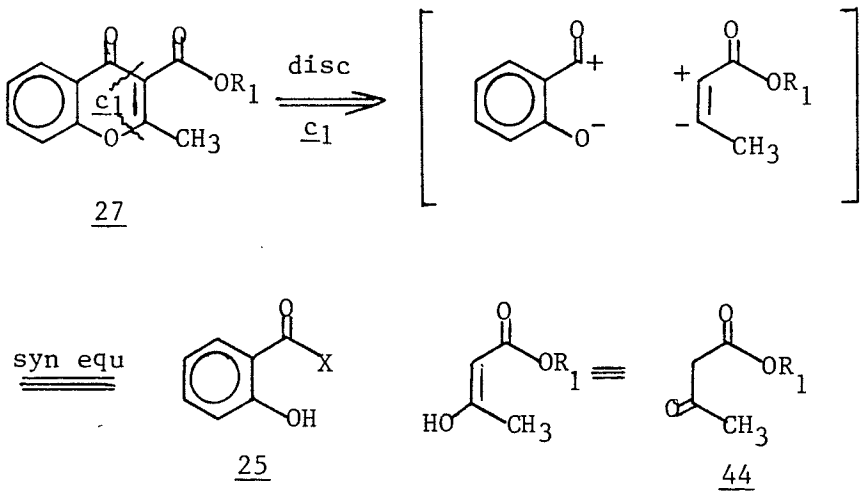
Scheme 3

Alternative functional group interconversion of compound 28 gave the phenol 43 (Scheme 4).



Scheme 4

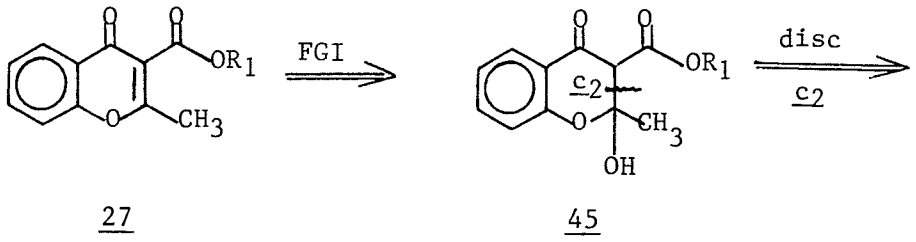
The bicyclic compound 27, obtained from disconnection of the tetracyclic system at c, was broken down to simpler compounds, as shown in Schemes 5 and 6. In Scheme 5, the disconnection of 27 at

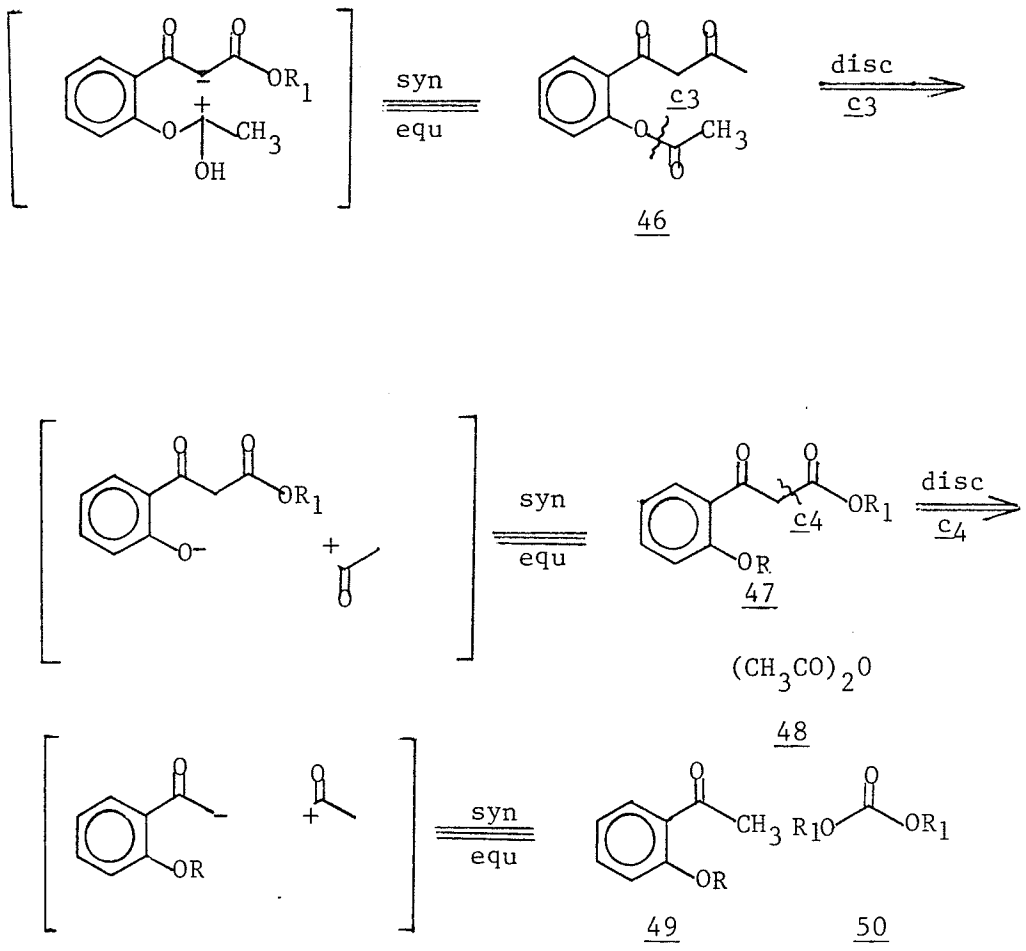


Scheme 5

$\underline{c}_1$ gives synthetic equivalents 25 and 44 as illustrated.

An alternate disconnection of 45, shown in Scheme 6 resulted in entirely different starting materials. This approach involves a functional group interconversion and a set of sequential disconnections at $\underline{c}_2$, $\underline{c}_3$ and $\underline{c}_4$ to give the starting materials 48, 49 and 50.





Scheme 6

The c disconnection will be hereafter referred to as the chromone approach.

Disconnections at other positions on the tetracyclic molecule give synthons whose synthetic equivalents are not readily available or are illogical. Thus, only the disconnections which lead to logical, and simple starting materials, are discussed in the synthesis of the target molecule, xanthocycline.

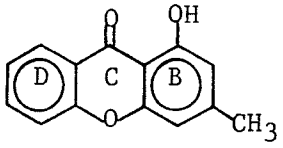
RESULTS AND DISCUSSIONS

SYNTHESIS

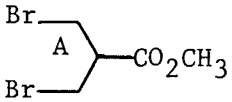
The strategies in synthesizing the target molecule follow, in the reverse sense, the pathway of the retrosynthetic analysis.

(A) The xanthone approach

This approach involved the separate synthesis of the tricyclic unit BCD and the A unit followed by the condensation of these two segments to complete the tetracyclic system.

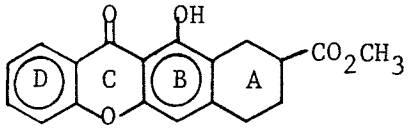


23



24

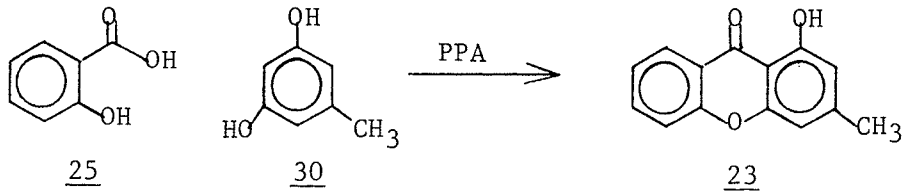
condense



22

A literature survey showed that xanthone 23, a well known natural product isolated from plants and microbial sources, had been synthesized by several methods (65). Thus, a well known procedure (66) was used for the synthesis of 1-hydroxy-3-methylxanthone 23 . This synthesis involved condensation of

salicylic acid and orcinol monohydrate in polyphosphoric acid(PPA) at 140°C for four hours to give the product in 33% yield as shown in Scheme 7. The recommended workup involved simply filtering the product from the reaction mixture after dilution with water. It was found, however, that the crude product obtained in this way



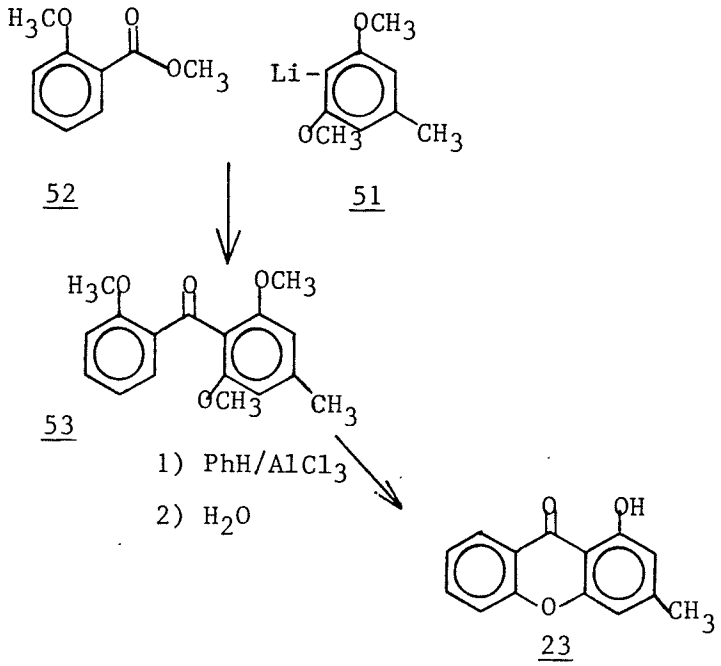
Scheme 7

contained phosphate. A second hydrolysis in refluxing water followed by filtration or extraction was therefore necessary. The product obtained in this way was then passed through a silica gel column (eluant benzene) to give pure xanthone 23 (mp 146-147°C, lit 148°C) in 30% overall yield. The compound was characterised by ir, nmr and mass spectra.

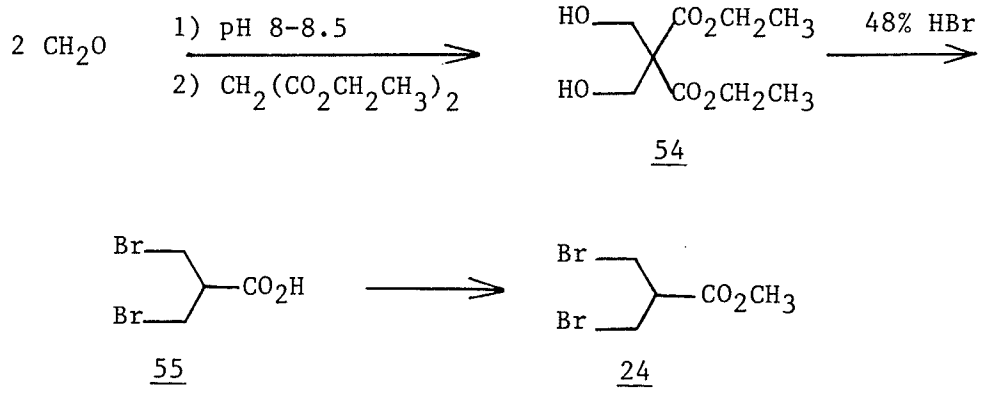
The hydroxymethylxanthone 23 was also regioselectively synthesized by condensing 2,6-dimethoxy-4-methyl phenyllithium 51 (67), with methyl anisate 52 to give 53 (68). Demethylation and cyclization of 53 in $AlCl_3$/benzene gave 23 in 59% overall yield.

The benzophenone 53 was isolated, recrystallized from benzene/hexane and characterised by its mass spectrum and elemental analysis. The two samples of xanthone 23, synthesized by the

independent routes, were identical. This correlation unambiguously established the position of the methyl and hydroxyl substituents in 23.



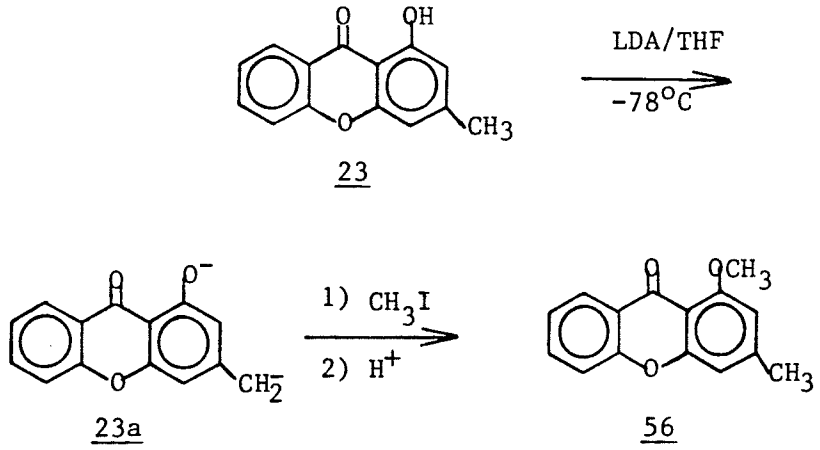
It was anticipated that the A ring of the tetracyclic xanthone could be added by condensing the xanthone 23 with methyl (β,β-dibromo)isobutyrate 24. This latter compound was obtained by the literature procedure (69) outlined in Scheme 8.



Scheme 8

Condensation of formalin with ethyl malonate at pH 8-8.5 gave diethyl bis(hydroxymethyl)malonate 54. The formation of 54 was monitored by the disappearence of absorption due to ethyl malonate in the nmr spectrum. Diethyl bis(hydroxymethyl)malonate 54 was refluxed in a 14-fold molar excess of HBr(48% in water) to give the dibromo acid 55 in 46% yield. It was found that a large excess of HBr was essential in order to obtain a pure product in good yield. Methyl (β,β-dibromo)isobutyrate 24 was prepared by refluxing the acid 55 with sulphuric acid (0.25%) in methanol. The crude yield of ester was 97%. Distillation under vacuum (bp 65-68°C/1.5 mm Hg) gave 86% of the pure dibromo ester.

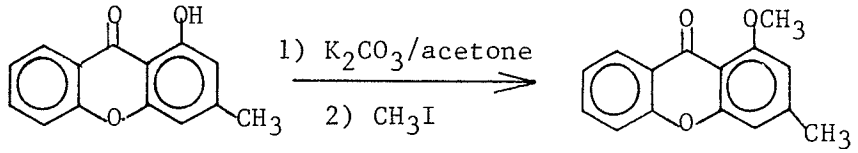
Before attempting the condensation of methyl dibromoisobutyrate 24 with the xanthone 23 several model studies were carried out using CH_3I as the alkylating agent. 1-Hydroxy-3-methylxanthone 23 was treated with freshly prepared lithium diisopropylamide (LDA) in THF at -78°C, to generate a dianion 23a (Scheme 9).



Scheme 9

Methyl iodide was then added at -78°C to the reaction mixture. The reaction mixture was warmed to room temperature, and then worked up. This resulted in the isolation of 23 with no C or O-alkylation. When the temperature was raised to reflux after the addition of methyl iodide at -78°C, O-alkylation was observed. Since preparation and alkylation of the dianion of the hydroxymethylxanthone 23 at the C_3 methyl was unsuccessful the alkylation of 1-methoxy-3-methylxanthone 56 was attempted.

The methyl ether 56 was prepared by the following sequence.

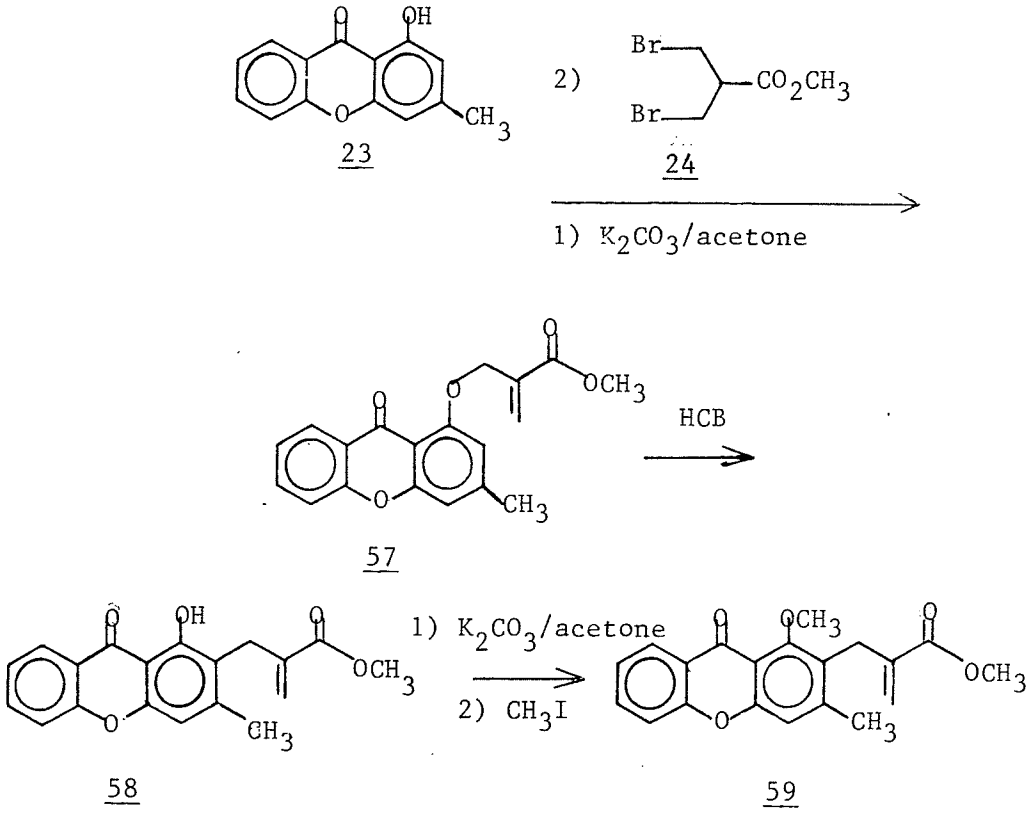


23 56

A mixture of hydroxyxanthone 23, methyl iodide and potassium carbonate was refluxed in dry acetone for 15 hours. The reaction was conveniently followed on tlc (solvent:benzene). The methoxyxanthone 56 fluoresces under uv and had a very low R_f value on the tlc. It was characterised by its nmr and mass spectra.

Considerable effort was made to alkylate the methoxyxanthone 56 by changing the reaction conditions such as temperature, counter ions (Li^+, K^+), base and solvent. Even though the solution turned dark red when the xanthone was added to the LDA, indicating the possible presence of the carbanion, no condensation with

methyl iodide was observed. In all cases only the starting material was recovered. The ease of O-alkylation of hydroxyxanthone 23, and the failure in alkylating the methoxyxanthone 56 at methyl position, led us to attempt the Claisen rearrangement of the O-alkylated xanthone 57. The following set of reactions were carried out on the hydroxyxanthone 23 to synthesize the hydroxy C-allylic xanthone 58 (Scheme 10).

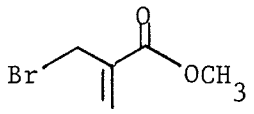


Scheme 10

The allylic ether 57 was prepared in 95% yield by refluxing a mixture of 23, 24 and potassium carbonate in dry acetone for 15 hours. C-allylicxanthone 58 was prepared in quantitative yield by

boiling the allylic ether 57 in hexachlorobutadiene (HCB) for 12 minutes. This Claisen rearrangement was easily monitored by tlc and nmr. Monitoring by tlc was facilitated by the fact that the O-alkylated xanthone 57 fluoresces under uv while the free hydroxyxanthone 58 does not. On rearrangement of 57 to 58 the nmr peak at δ 4.8 in 57 disappears and new peaks at δ 12.55, 6.25, 5.20 and 3.75 appear. These new peaks can be assigned to the phenolic proton, the vinylic protons of the acrylate and the allylic-benzylic methylene protons of compound 58. The phenolic group of compound 58 was readily methylated with methyl iodide in acetone with suspended potassium carbonate.

When one considers the alkylation of the hydroxyxanthone 23 with the dibromo ester 24, as indicated in Scheme 10, two possible mechanisms come to mind. Firstly, the hydroxyxanthone 23 may be directly alkylated by the dibromo ester 24 followed by dehydrodromination to yield 57. Alternatively the dibromo ester 24 may be dehydrobrominating to yield the bromoacrylate 60 in situ. The hydroxyxanthone 23 could then be alkylated by 60.

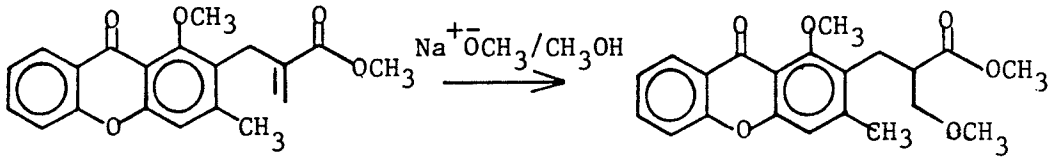


60

Some support for this latter proposal is achieved by the fact that compound 60 can readily be prepared under mild conditions. A literature search showed that methyl α-bromoacrylate 60 is an important compound both as a starting material for specifically

functionalized polymers and for use in general organic synthesis (71,72,73). The three reported procedures, including two patents (74,75), suffered from unreasonable yields, reagents or conditions. Thus, we developed a phase transfer catalysed synthesis of 60. It was found that treatment of 24 in carbon tetrachloride with aqueous sodium hydroxide (1M) and a catalytic amount of benzyltriethylammonium chloride (BTEAC) at $0^{o}C$ for one hour gave a quantitative yield of 60. The reaction was conveniently followed by running the nmr spectrum of the organic layer. Similar results were also obtained when 24 in dry acetone was refluxed with anhydrous potassium carbonate. These latter conditions are essentially identical to those used for alkylation of 23.

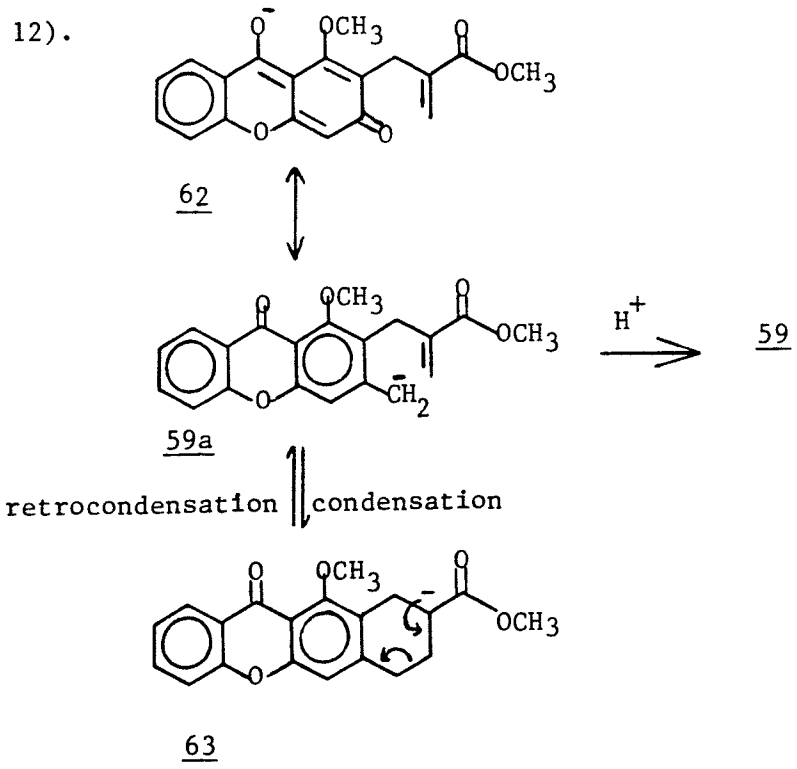
The synthesis of the tetracyclic xanthone skeleton from the C-allylic compound 59 requires the formation of a C—C bond between the aromatic methyl and the vinylic position of the ester. It was expected that strong base should catalyse this condensation. On treating the methoxy C-allylic xanthone 59 with sodium methoxide/methanol, conjugate addition of methoxide to the unsaturated ester gave 61 as the only product (Scheme 11).



59 61

Scheme 11

Compound 59 was also treated with freshly prepared LDA under nitrogen atmosphere at -78°C to generate the anion on the C_3 methyl. After the reaction mixture was stirred for 0.5 hour workup resulted in the recovery of compound 59. The deep red colour which appeared when xanthone 59 was added to the LDA solution was interpreted as an indication of the presence of the desired anion. Failure to achieve condensation between the methyl group and the α,β-unsaturated ester might be explained by an unusual stability of the anion due to delocalisation of the charge into the xanthone carbonyl to give the oxy anion 62. If the condensation were reversible the equilibrium might then favour 62 over 63 and workup would lead to recovery of the starting material 59 (Scheme 12).



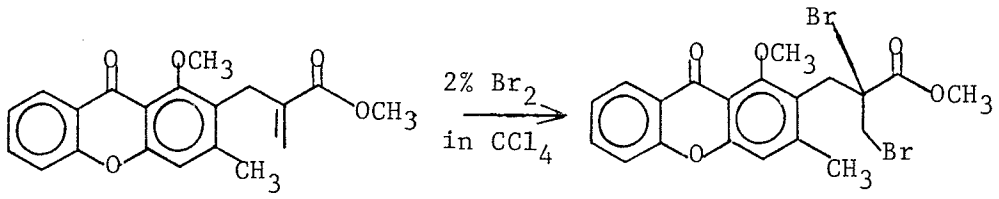
62 ⟷ 59a

63

Scheme 12

In view of the difficulties encountered we decided to introduce a leaving group into the side chain of 59. This modification should make the condensation reaction, if any, irreversible since the condensation would involve a direct alkylation rather than a Micheal addition.

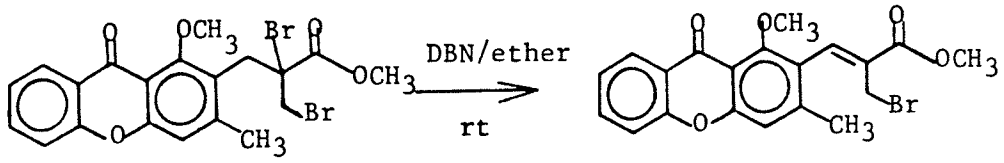
Bromine was chosen as the leaving group. The introduction of bromine was achieved as described below. The dibromo compound 64 was synthesized by treating 59 with 2% bromine in carbon tetrachloride at 40°C.



59 64

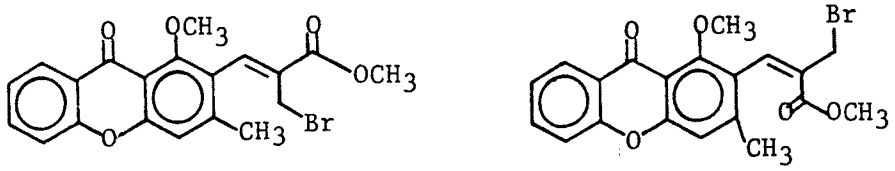
The dibromoxanthone 64 was recrystallized from CCl_4/hexane and characterised by its nmr and mass spectra and elemental analysis.

The nmr of compound 64 showed benzylic protons at δ4.25 as a quartet. The chiral carbon makes the two benzylic protons nonequivalent and coupling between these two protons gives rise to two sets of doublets which appeared as a quartet in the spectrum. The bromomethyl protons appeared as a single peak at δ 3.78. Stirring a solution of dibromoxanthone 64 with 1,5-diazabicyclo-{4.3.0}non-5-ene (DBN), in ether for 30 minutes at room temperature, gave the monobromoxanthone 65 in 90% yield.



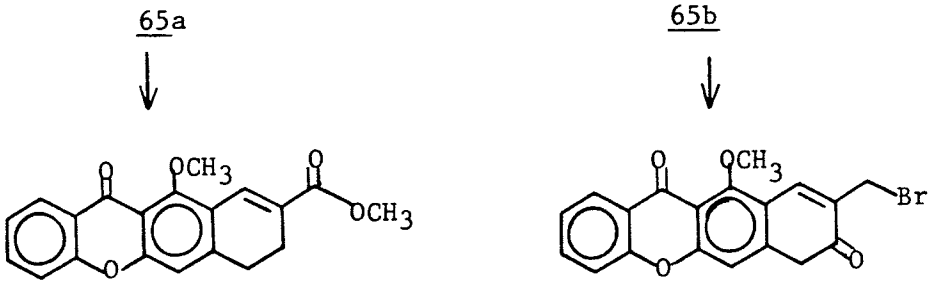
64 65

The dehydrobromination of 64 could lead to geometric isomers 65a and 65b. It appeared that the dehydrodromination of 65 gave a single compound, but it was not possible to specifically establish its stereochemistry on the basis of the spectral evidence.



65a 65b

Depending on the configuration of the monobromo compound, 65a or 65b, two products are possible from the base catalysed intramolecular condensation (Scheme 13). However, when the



Scheme 13

monobromoxanthone 65 was treated with LDA only starting material could be recovered. The most intriguing aspect of these reactions

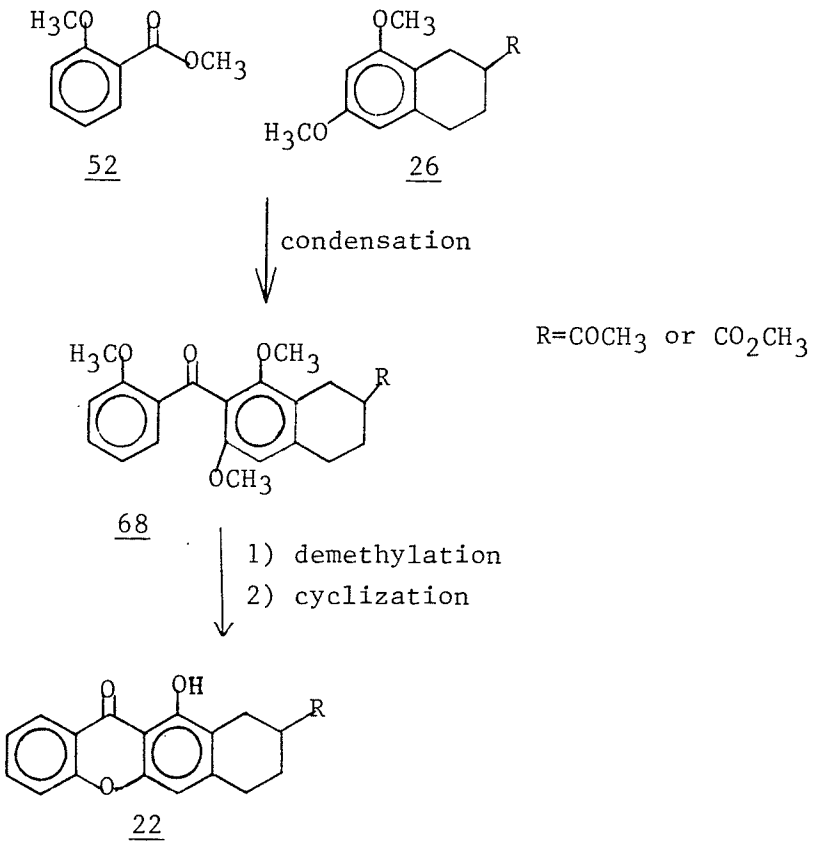
was that a blood red colour was produced on addition of methoxy-xanthones 56, 59 and 65 to the LDA solution. While the colour was initially considered to be due to the formation of the xanthone anion, no condensation was observed for any of the methoxyxanthones treated in this way.

It is known that xanthone analogs generate radical anions when treated with alkali metals (76). No evidence was found regarding xanthones reacting with alkyl lithiums or lithium amides to give radical anions. In the case of xanthone 56 an esr spectrum of a mixture of n-butyl lithium and the xanthone in THF showed the presence of a radical. Thus, the colour which appeared on addition of metal bases to xanthones and the inertness of the resulting solution to alkylation reactions could be due to the presence of a radical anion generated by electron transfer from the base.

Since successful conditions for the condensation of the C_3 methyl with the allylic side chain, required to synthesize the tetracyclic system 22 could not be achieved, the xanthone route was abandoned. At this point it was decided to look into the 6,8-dimethoxy-1-tetralone approach to the synthesis of the xanthocycline system.

(B) 6,8-Dimethoxy-1-tetralone approach

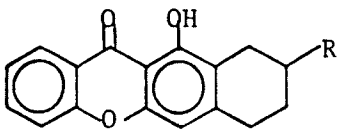
This methodology principally involves the synthesis of the AB unit 26 and condensation of this unit with methyl anisate 52 (unit D) to produce the benzophenone 68. Demethylation and cyclization of 68 would give the target molecule 22 (Scheme 14).



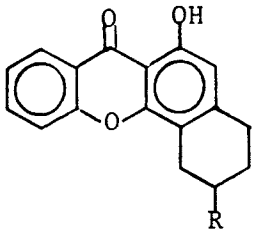
Scheme 14

The major drawback in this route is the possible nonregioselective cyclization of 68 to give linear and angular

xanthocyclines 22 and 69. However, regardless of the nonselectivity



22



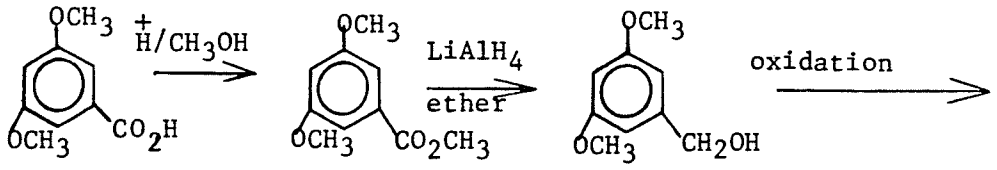
69

in this methodology, this approach to the synthesis of the target molecule was explored.

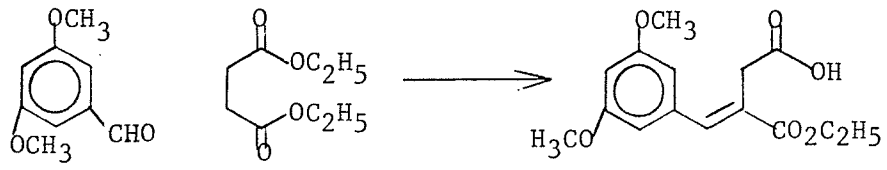
From the retrosynthetic analysis it would seem reasonable that the key intermediate 26 could be synthesized by acylation and reduction of the compound 32. The synthesis of the compound 32 was approached along two independent routes.

Route 1.

Commercially available 3,5-dimethoxybenzoic acid 70 was esterified (77) to give the ester 71. Reduction of 71 with lithium aluminum hydride gave the alcohol 72 (78) which was then oxidised to the corresponding aldehyde 35 (79). Stobbe condensation of the aldehyde 35 with diethyl succinate 36 using potassium t-butoxide in t-butyl alcohol gave 73 in 65% yield (Scheme 15).



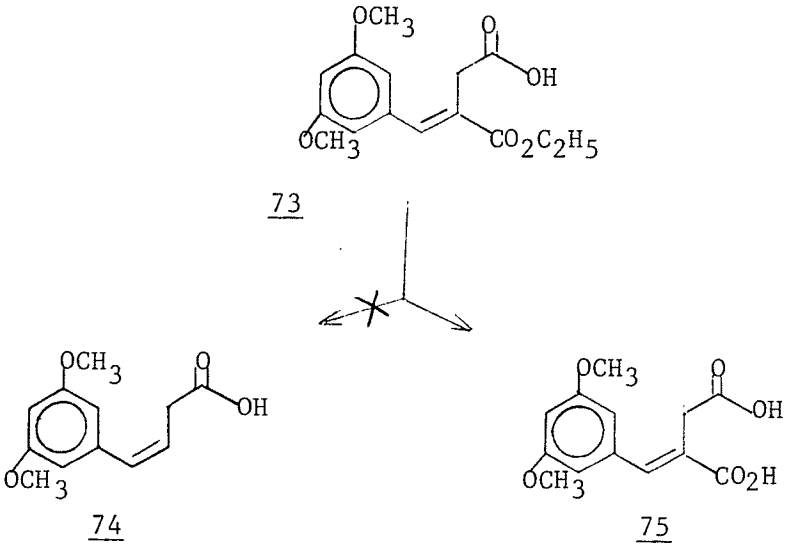
70 71 72



35 36 73

Scheme 15

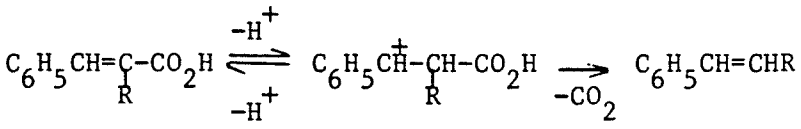
The half ester 73 was characterised by nmr, ir, and mass spectra. Attempted hydrolysis and decarboxylation of the unsaturated ester 73, in 48% HBr/CH_3COOH/H_2O (1:1:1) or pyridine/HCl (80,81), gave the diacid 75 and none of the expected mono acid 74. It has been shown (81) that the mechanism for decarboxylation of the unsaturated acids of type $C_6H_5CH{=}C(R){-}CO_2H$ 76 proceeds via a transition state involving a β carbonium ion 77. Stabilization of this carbonium ion lowers the energy of the transition state and enhances decarboxylation.



73

74 75

The intermediate carbonium ion 77 could lose a proton to regenerate the unsaturated acid 76 or cleave the C_α-COOH bond to give the

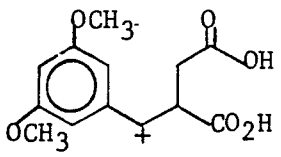


76 77 78

olefin 78. It has also been reported (81) that the presence of two electron withdrawing ortho substituents in the phenyl ring of the unsaturated acid of type 76 strongly inhibits the decarboxylation.

Thus, the total reluctance of 75, formed by the hydrolysis of 73 under the reaction conditions, to undergo decarboxylation to give 74 can be explained by the substituent effect. The two meta substituents in 75 hinder the formation of the carbonium ion 79 by increasing the energy level of the transition state. Hydrolysis of 73 in base also gave 75. The diacid 75 was characterised by nmr, ir, ^{13}C-nmr and mass spectra. The spectral data of the diacid 75 obtained by both the hydrolysis procedures were identical.

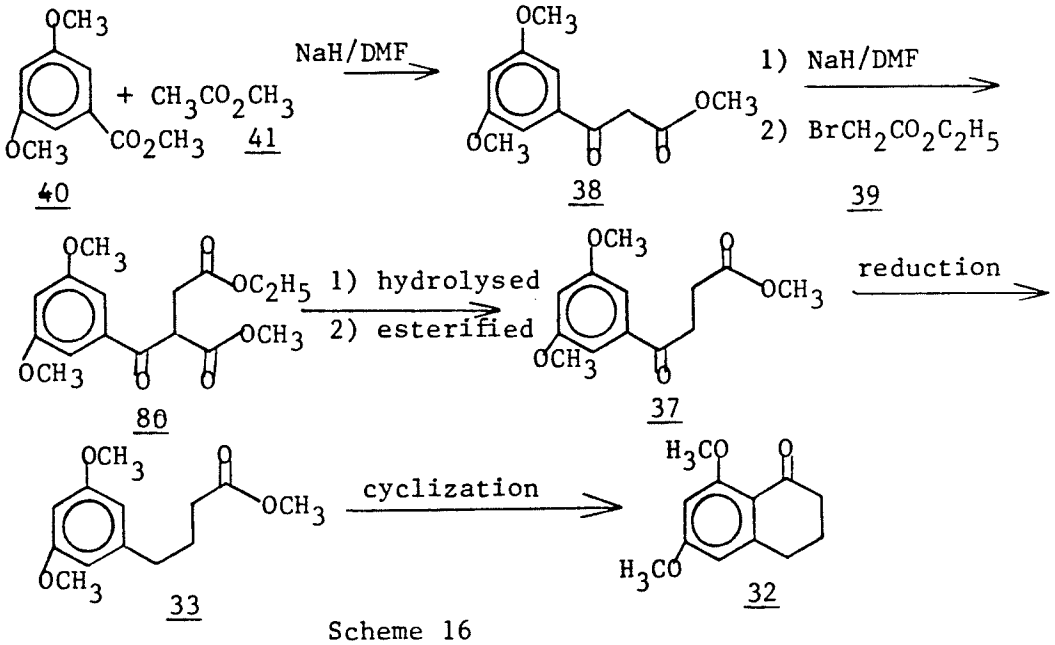
As no decarboxylation was observed in 75 the approach along route 1 was abandoned.



79

Route 2

Compound 32 was successfully synthesized by route 2 (Scheme 16)



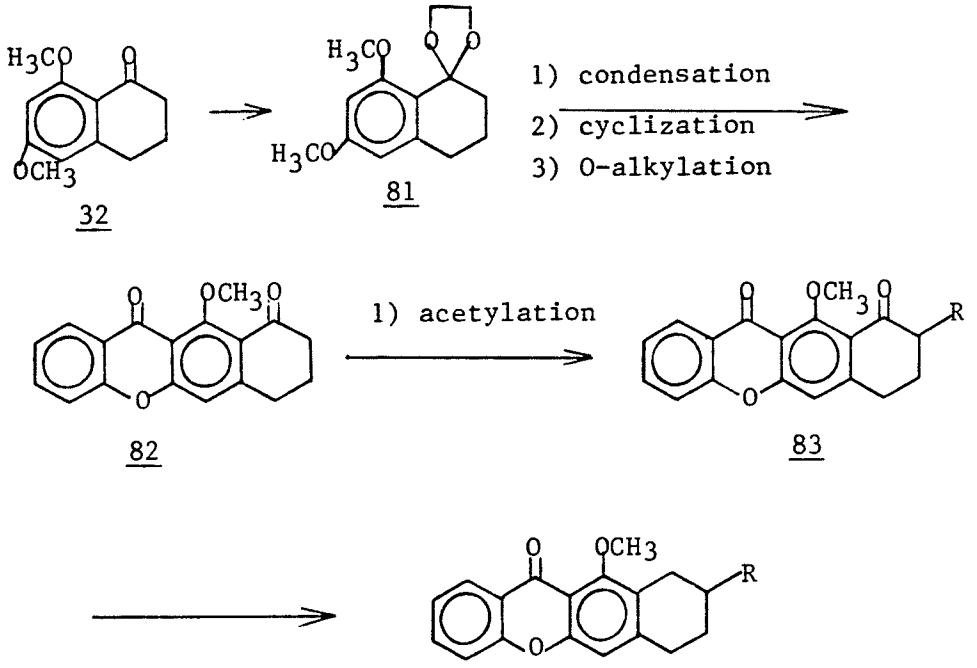
Scheme 16

This approach involved the condensation of the ester 40, in dimethylformamide (DMF) solution in the presence of sodium hydride, with methyl acetate 41. The reaction was conveniently followed on tlc (solvent:pentane/ether 2:1). The resulting product 38 was purified and identified by nmr, ir and mass spectra. Alkylation of 38 with ethyl α-bromoacetate 39 gave 80. The crude alkylated product 80 was hydrolysed and esterified to produce 37 which was recrystallized from pentane/ether (mp 57°C) and characterised by nmr, ir and mass spectra and elemental analysis.

The carbonyl group in 37 was hydrogenated in methanol with a few drops of acetic acid at atmospheric pressure using 10% palladium on charcoal as catalyst to yield 33 in quantitative yield. Heating 33 with concentrated sulphuric acid on the steam

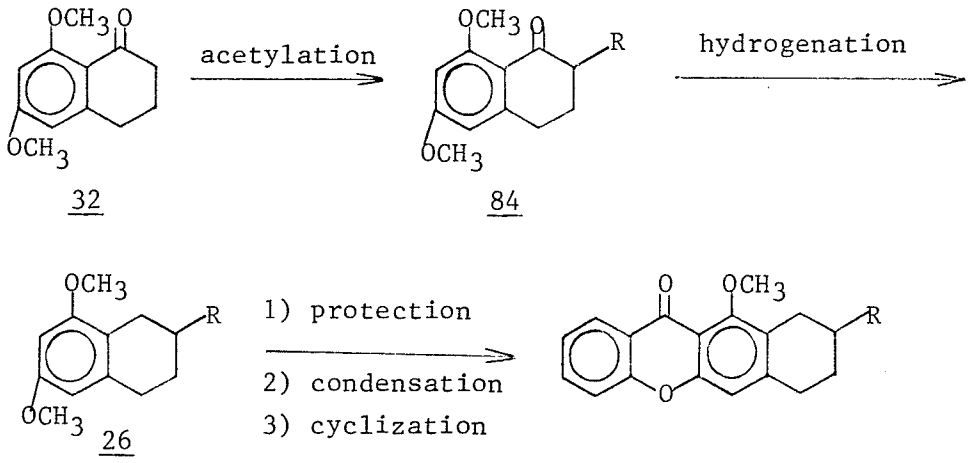
bath for 30 minutes gave 32 in quantitative yield. The compound 32 was identified by nmr, ir and mass spectra. The over-all yield of 32 starting from 40 was 87%.

From the previous experience of condensing methyl anisate with dimethoxytoluene (see page 26), it was expected that there should be no problem in condensing unit AB with unit D. However, before doing the condensation of 32 with methyl anisate it was necessary to protect the carbonyl in 32. After condensation and cyclization the carbonyl group could be regenerated to give 82. The functionality at the β position of 82 could then be introduced to give 83. Hydrogenation of the carbonyl in ring A of 83 would yield the target molecule (Scheme 17).



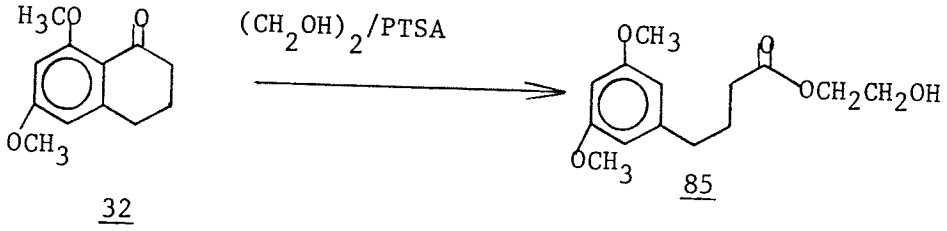
Scheme 17

The other possibility was to introduce the functionality in the bicyclic compound 32 by the synthesis of 84. Hydrogenation of the carbonyl in 84 would yield 26 and condensation of 26 with methyl anisate, followed by cyclization, would yield the target molecule 22 (Scheme 18).



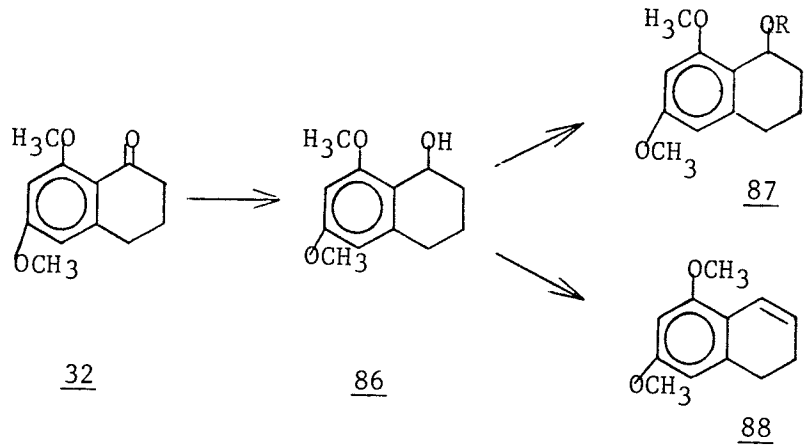
Scheme 18

Ketal formation, a common method for protecting ketones (82), was the obvious choice for protecting the carbonyl in 32. However, on treating 32 and ethylene glycol with a catalytic amount of p-toluenesulfonic acid (PTSA) in benzene to make the ketal, it was found that the tetralone ring opened under the reaction conditions to give hydroxy ester 85. No ketal could be detected in the reaction mixture. The hydroxy ester 85 was isolated and characterised by nmr, ir and mass spectra. This unusual phenomenon of giving a ring opened compound was also observed by other workers for similar compound (83). As attempts to make the ketal failed,



32 85

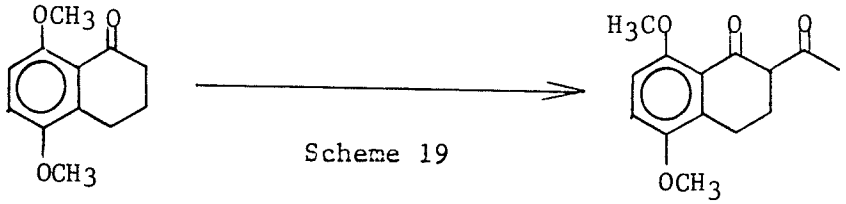
we decided to reduce the ketone 32 to alcohol 86 and the protect the alcohol by conversion to its ether (84).



32 86

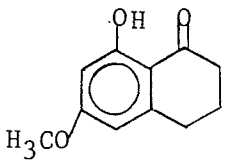
The carbonyl 32 was reduced to alcohol 86 with lithium aluminum hydride in 96% yield. Attempts to make the tetrahydropyranyl ether by stirring a mixture of 86, dihydropyran and pyridinium p-toluenesulfonate in methylene chloride at room temperature resulted in dehydration of 86 to give the alkene 88.

Acylation of 1,4-dimethoxy-1-tetralone using $BF_3/CH_3CO_2H/(CH_3CO)_2O$ was reported to give the corresponding 1,4-diketone in very high yield (90) (Scheme 19). However, in our case, the BF_3



Scheme 19

catalysed acylation of 32 at room temperature always resulted in the recovery of the starting material. On heating the reaction mixture mono demethylated product 89 was isolated but no acylation



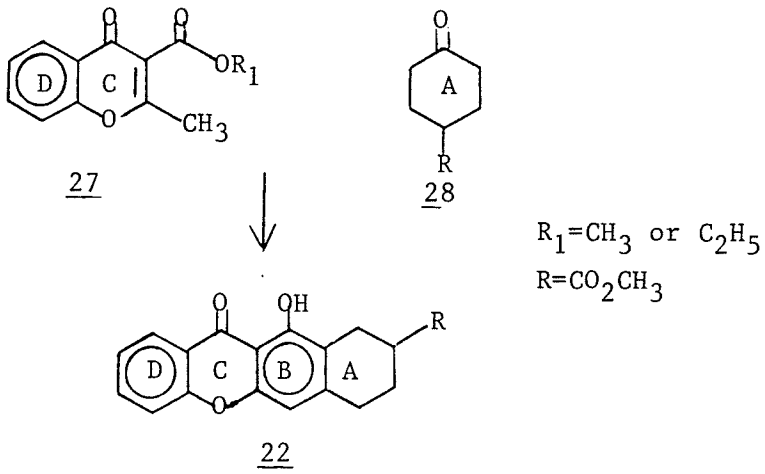
89

was observed. The compound 89 was also made by bubbling BCl_3 through a solution of 32 in methylene chloride at $0^{o}C$ for 5 minutes followed by further stirring at room temperature for 30 minutes (91). The compound 89 obtained by both the procedures were compared and characterised by nmr, ir and mass spectra. Thus, even after considerable effort on all three reported procedures, we were unable to synthesize the 1,3-diketone 84. Similar results were also observed with tetracyclic ketone 82 (92).

At this stage we terminated the tetralone approach and proceeded to study the synthesis of the target molecule by the chromone methodology.

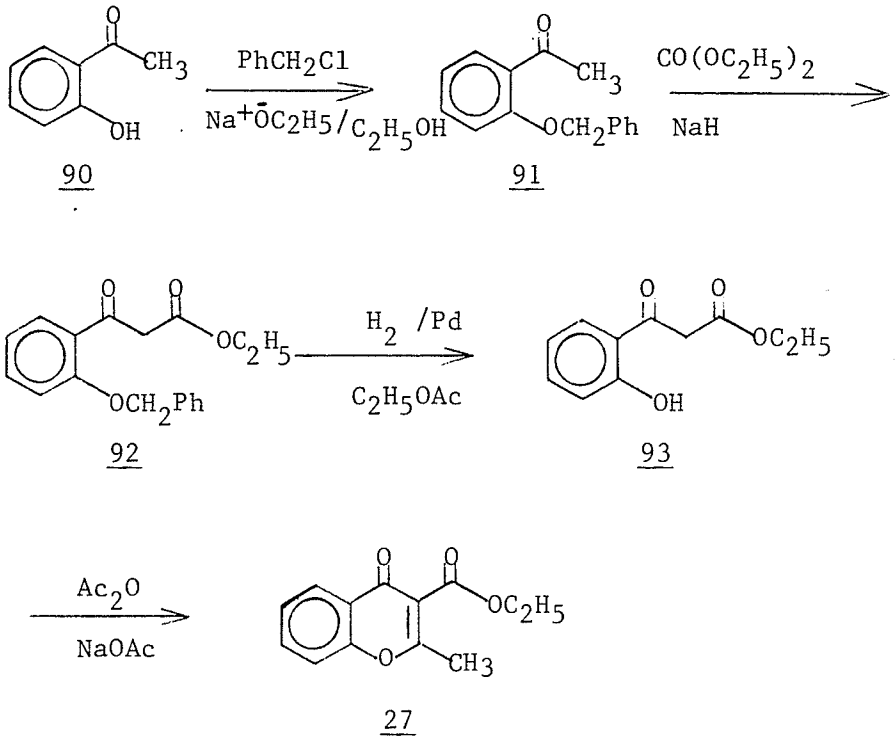
(C) Chromone approach

This approach basically involves the synthesis of the CD unit of the tetracyclic system (a chromone) and the A unit. Condensing these two molecules together gives the target molecule xanthocycline 22.



The chromone 27 was initially synthesized by a known procedure (93). The commercially available o-hydroxyacetone 90 was converted to 2-benzyloxyacetophenone 91 (94) and this product was reacted with ethyl carbonate using sodium hydride to give 92 (95). Hydrogenolysis of 92 in ethyl acetate using 5% palladium on charcoal gave 93. It was observed that the recommended solvent (95), ethyl alcohol, led to carbonyl reduction. The chromone 27 was obtained, in 35% yield by heating a mixture of 92, acetic anhydride and sodium acetate. Although a 62% yield for the analogous methyl ester was reported (93), we were unable to obtain yields of more than 35% for the step involving the conversion of 93 to 27.

Compound 27 was characterised by nmr, ir and mass spectra (Scheme 20).



Scheme 20

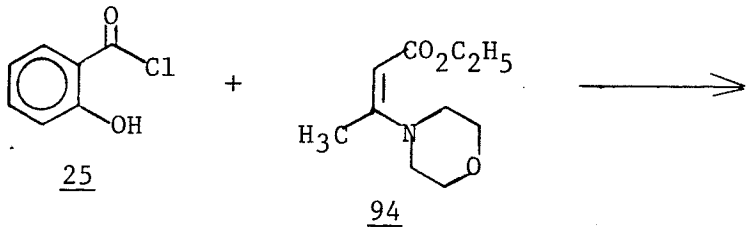
The major problem in this synthesis was the conversion of 93 to 27. Due to low yields and rather tedious procedures an alternate route to the synthesis of the chromone 27 was explored.

It seemed reasonable that a direct condensation of salicyloyl chloride with ethyl acetoacetate would yield the chromone 27. As base catalysed condensation of salicyloyl chloride and ethyl acetoacetate could cause polymerization of the acid chloride and/or rearrangement of the chromone to an hydroxy coumarin (94),

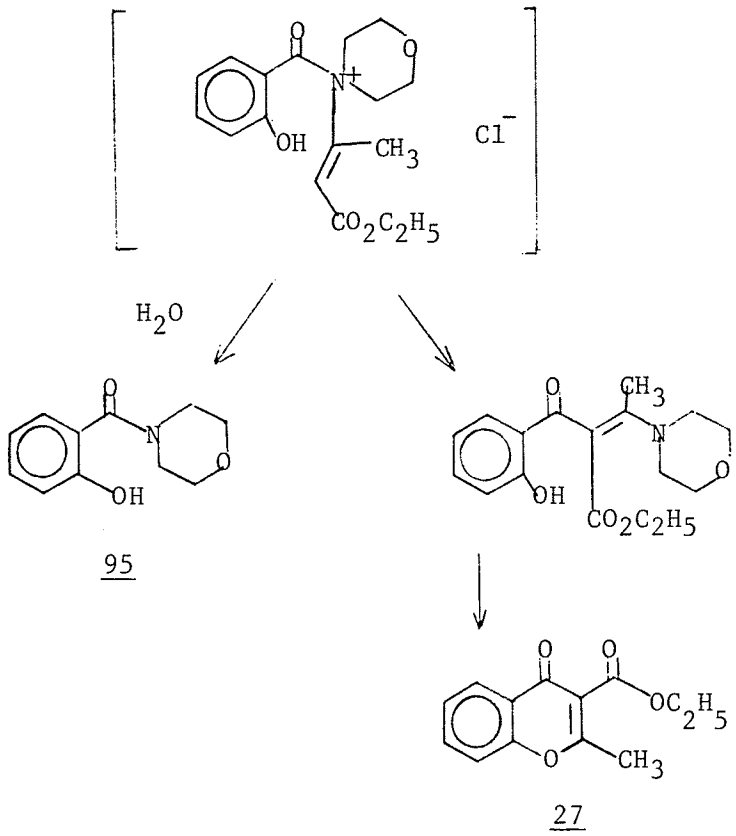
an enamine condensation was attempted.

The ethyl acetoacetate morpholine enamine 94 and salicyloyl chloride were prepared. The acid chloride was prepared in 89% yield by gently heating (40-50°C) a mixture of salicylic acid, thionyl chloride and a catalytic amount of aluminum chloride for 72 hours. Highly polymerised product and low yields of the acid chloride were observed when the mixture was heated strongly. The ethyl acetoacetate morpholine enamine was prepared in quantitative yield by refluxing a mixture of ethyl acetoacetate, morpholine and a catalytic amount of p-toluenesulfonic acid in toluene for 10 hours. The water was removed azeotropically from the reaction mixture by using a Dean-Stark trap.

The chromone 27 was prepared by adding ethyl acetoacetate morpholine enamine 94 to an ice-cold solution of salicyloyl chloride in methylene chloride and triethylamine. Immediate workup gave a quantitative yield of morpholine salicylamide 95, presumably obtained by the initial N-acylation of the enamine 94. However, when the reaction was stirred for 70 hours at room temperature, and then worked up with acid and base washing to remove the remaining amino and phenolic or enolic by-products, a 36% yield of crude chromone 27 was obtained as a deep red oil which crystallized on standing (Scheme 21).

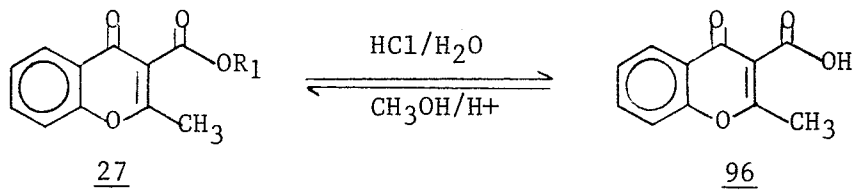


25 94



Scheme 21

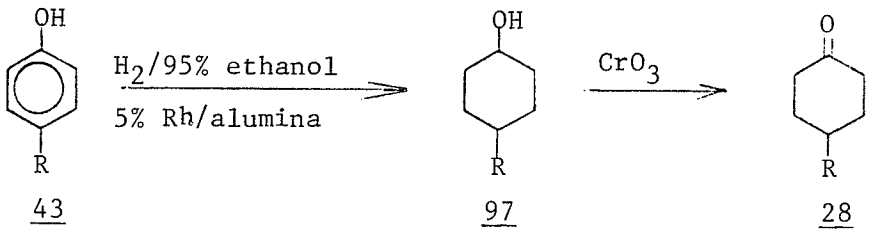
The chromone was characterised by nmr, ir and mass spectra and elemental analysis. Hydrolysis of the chromone ester 27 in HCl gave the chromone acid 96 in 47% yield as pale buff crystals which were essentially free of all impurities. The chromone acid 96 was converted to its methyl ester 27 in quantitative yield.



Recently an alternative high yield synthesis of the chromone ester 27 from o-fluorobenzoyl chloride has been reported (96).

Synthesis of unit A

A literature survey revealed that the monocyclic compound 28 (unit A) could be synthesized by two procedures (97,98). The simplest of these procedures involves reduction of methyl p-hydroxybenzoate followed by oxidation of the alcohol to the ketone (97).



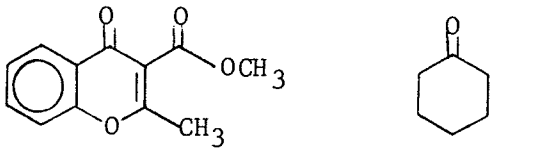
43 97 28

$R=CO_2CH_3$

Thus, commercially available methyl p-hydroxybenzoate 43, in 95% ethyl alcohol, was hydrogenated at 45 psi in the presence of a catalytic amount of 5% rhodium on alumina for 96 hours to give 4-carbomethoxy cyclohexanol 97 in 97% yield. The alcohol 97 in ether, was oxidised with aqueous chromic acid to its corresponding ketoester 28 in 46% yield. The ketoester 28 was identified by nmr, ir and mass spectra.

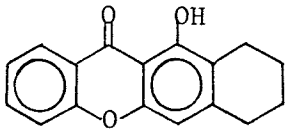
Before condensing the chromone 27 with the ketoester 28 to synthesize the target molecule (xanthocycline), a model reaction

using the more readily available cyclohexanone was attempted. Thus, the conditions developed in this model synthesis could be used to synthesize the target molecule.



27 98

condensation

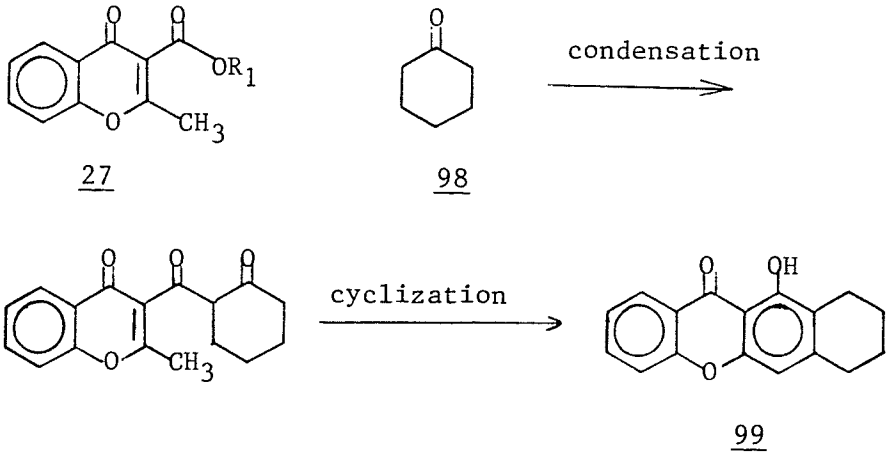


99

There are two possible routes for synthesis of the tetracyclic system 99 from the chromone and cyclohexanone.

Route 1

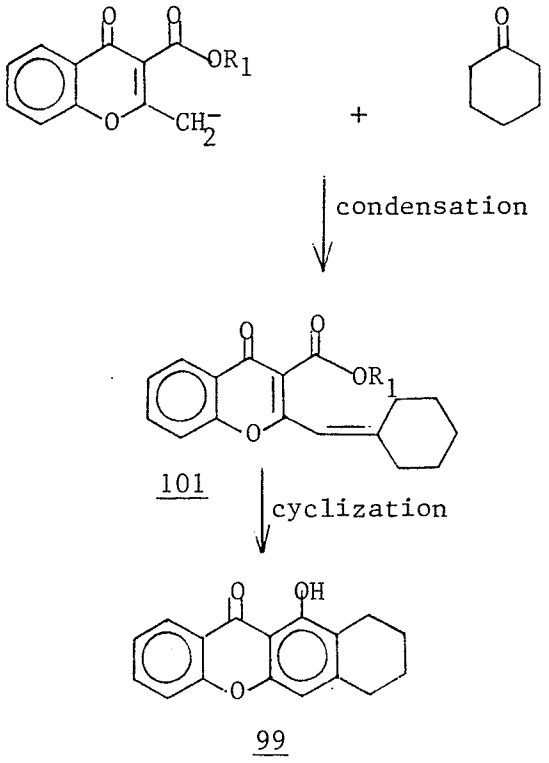
Condensation of cyclohexanone 98 at position 3 of the chromone 27, followed by cyclization, would yield the compound 99 (Scheme 22).



Scheme 22

Route 2

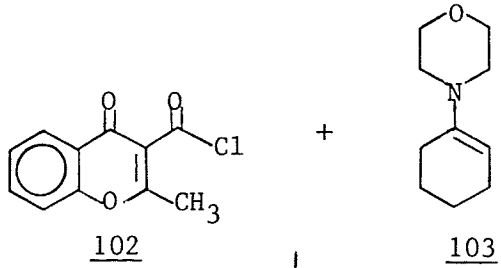
Condensation at the 2-methyl group of the chromone 27, by generating an anion at this center, followed by cyclization, would also give the tetracyclic system 99 (Scheme 23).



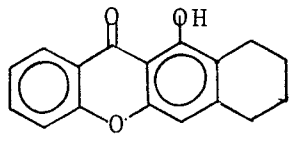
Scheme 23

The basic outline of Scheme 22 was explored in the following sequence of reactions. The chromone acid chloride 102 was synthesized by refluxing the chromone acid 96 with thionyl chloride in chloroform. Condensation of the chromone acid chloride 102 with cyclohexanone morpholine enamine 103, in methylene chloride using triethylamine as an acid scavenger, gave the tetracyclic

system 99 in 3% yield, after chromatography of the reaction mixture. This reaction evidently involves acylation at the vinylic carbon of the enamine followed by in situ cyclization.



102 103

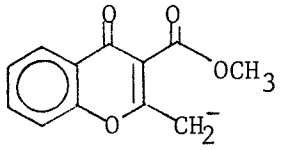


99

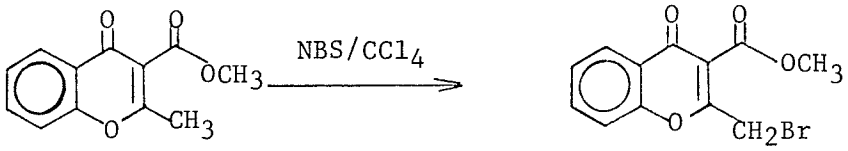
All efforts to increase the yield of the tetracyclic system 99 by changing the reaction conditions were unsuccessful. The major product of the reaction was always the chromonic acid and/or the chromone amide. Aromatic acid chlorides normally acylate enamines at carbon, however, in our case of chromone acid chloride 102 the major reaction observed was at the nitrogen centre. It appeared that the basic premise of Scheme 22 was sound but limited by the efficiency of the acylation reaction.

Thus, we decided to investigate the possibility of condensation at the 2-methyl group of the chromone (Scheme 23). The anion at this center should be stabilized by delocalization of the charge into the two carbonyls and a reactivity similar to that of

the malonate anion could be expected. The 2-methyl chromone ester



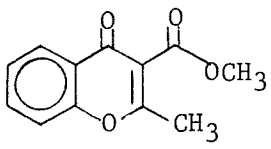
27 was converted in 82% yield based on recovered starting material, to 2-monobromomethyl chromone ester 104 by treatment with N-bromosuccinimide (NBS) in carbon tetrachloride. Allowing the bromination to go to completion resulted in the formation of a mixture containing dibromo, monobromo and methylchromone. The reaction was usually worked up at approximately 75% completion and before the formation of the dibromo compound became significant. Attempted condensation of monobromo chromone 104 with cyclohexanone under Reformatsky and Wittig conditions resulted only in the reduction of 104 to 27.



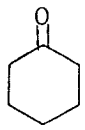
27 104

Several attempts were made to condense the chromone 27 with cyclohexanone under conditions suitable for malonic ester condensation involving non-nucleophilic bases, such as potassium carbonate

1,4-diazbicyclo{2,2,2}octane (DABCO), and 1,5-diazobicyclo{4,3,0}-non-5-ene (DBN). In all of the above attempts the starting material was recovered. However, when the condensation was attempted in potassium t-butoxide in t-butyl alcohol/dimethoxyethane (DME) the spiro-lactone 105 was obtained in high yield.

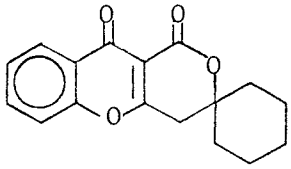


27



98

potassium t-butyl oxide
t-butyl alcohol/DME

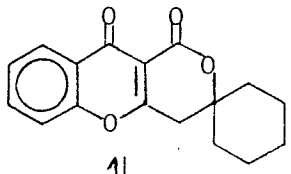


105

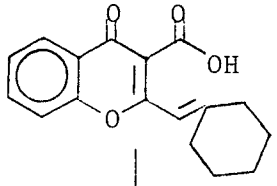
Initially the reaction was carried out for 20 minutes at room temperature but only a very complex mixture of products was observed. When the reaction was repeated and followed on tlc it was found that no starting material was left after one minute. Therefore the reaction mixture was quenched immediately with aqueous acid and the product was isolated in nearly quantitative yield. It appears that the product formed was unstable under the reaction conditions. The product was identified as spirolactone 105. The structure of 105 was established by nmr, ir and mass spectra and elemental analysis.

It was found that the spirolactone 105 had a very low R_f value on tlc. It was suspected that this low mobility of the lactone 105 on silica gel could be due to the fact that the lactone was in equilibrium with its corresponding acid 106. By treating the spirolactone 105 in methanol with diazomethane in diethyl ether it was possible to trap the acid 106 as its methyl ester 107.

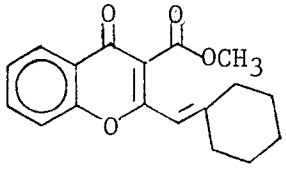
105



106

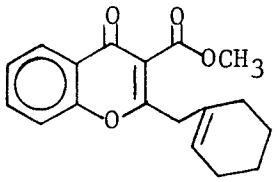


107



The cyclohexylidine chromone ester 107 was also synthesized by treating the spirolactone 105 in dry acetone with K_2CO_3/CH_3I. It was also observed that when the spirolactone 105 was treated with dry HCL in methanol the unconjugated cyclohexenyl chromone ester 108 was obtained. Treating the conjugated ester 107 in benzene with a catalytic amount of p-toluenesulfonic acid also gave the unconjugated ester 108. The unconjugated ester was not fully

characterised but its nmr and mass spectra were consistent with the proposed structure. Apparently the unconjugated ester 108 is thermodynamically more stable than the conjugated ester 107. The isomerization of the double bond in 107 to give 108 under acid condition led to the proposal that the tetracyclic system 99 could be synthesized by the intramolecular acylation of the double bond. Treating the spirolactone 105 in toluene with

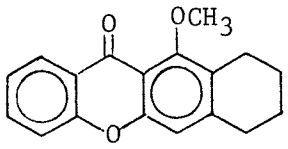


108

polyphosphoric acid for one hour at 170°C gave the tetracyclic system 99 in 41% yield. The tetracyclic system 99 was also synthesized by treating the spirolactone 105 in toluene with phosphorous pentoxide (47% yield) or in neat trifluoromethane sulfonic acid (triflic acid) (49% yield). No reaction was observed with hydrofluoric acid as the spirolactone was recovered from the reaction mixture. In the case of phosphorous pentoxide the workup involved an acid hydrolysis to hydrolyse the phosphate complex of the product. The cyclization using triflic acid was the preferred method.

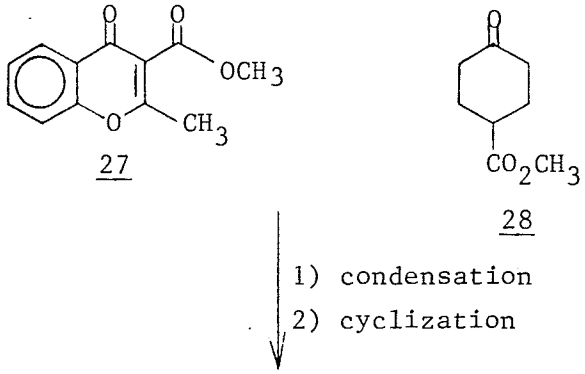
The nmr, tlc and mass spectrum of the xanthocycline 99 obtained by both the enamine/acid chloride and cyclohexanone/chromone procedures were compared and found to be identical.

The hydroxyxanthone 99 was converted to its methyl ether 109 and the elemental analysis of both 99 and 109 was obtained.



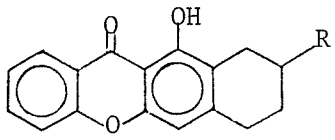
109

Having found the optimum conditions for the synthesis of the tetracyclic system 99 the condensation of the methylchromone ester 27 with 4-carbomethoxy cyclohexanone 28 was attempted as a method to synthesize the target molecule 22.



27 28

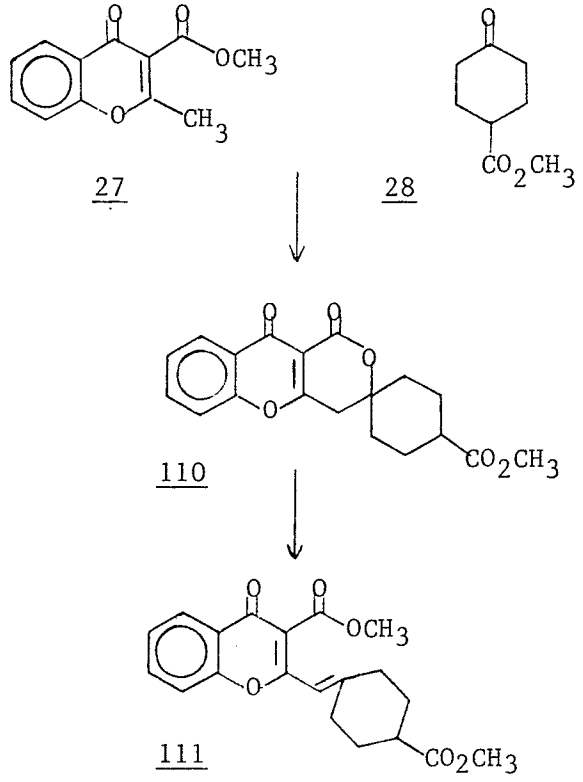
1) condensation
2) cyclization



22

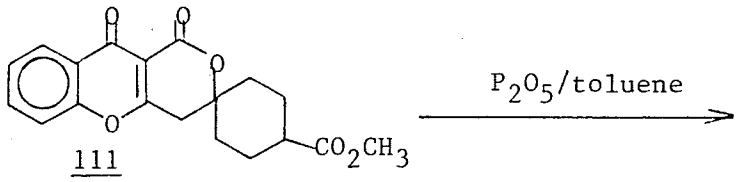
The carbomethoxy spirolactone 110 was prepared by treating a mixture of 28 and 27 in DME with potassium t-butoxide in t-butyl alcohol for one minute. The carbomethoxy spirolactone was characterised by nmr, ir and mass spectra as well as elemental analysis. The corresponding carbomethoxy cyclohexylidine chromone

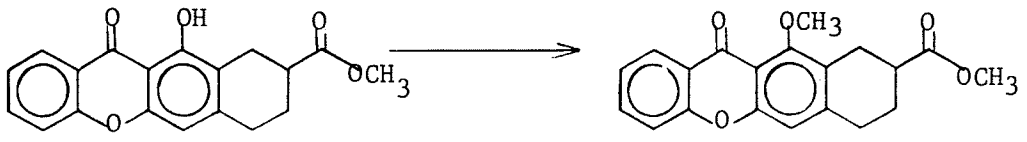
ester 111 was prepared by treating the carbomethoxy spirolactone 110



in methanol with diazomethane in diethyl ether.

In the case of the carbomethoxy spirolactone 110, the intramolecular acylation to synthesize the target molecule could not be catalysed by triflic acid. However, the target molecule was obtained when the carbomethoxy spirolactone 110 in toluene was treated with phosphorous pentoxide (yield 52%).





22 22a

The carbomethoxy hydroxyxanthocycline 22 was identified by nmr and mass spectra. The carbomethoxy hydroxyxanthocycline 22 was converted to its methyl ether 22a by treating with K_2CO_3/CH_3I in acetone.

The carbomethoxy methoxyxanthocycline 22a was characterised by nmr, ir and mass spectra and elemental analysis. Thus the target molecule 22 was successfully synthesized by the chromone approach in an overall yield of 24% starting from chromone ester 27.

CONCLUSIONS

Three synthetic routes were studied for the synthesis of the target molecule 22. In the xanthone approach, the allylic side chain was introduced regioselectively on the C_2 position of xanthone 23 by a Claisen rearrangement. However, the formation of the tetracyclic system by ring closing the C_3 methyl to the allylic side chain in 59 was thwarted by the apparent formation of a radical ion on addition of the base to xanthone. The formation of the radical presumably occurs exclusively, relative to the anion at the C_3 methyl. Thus it seems reasonable, that if the problem of radical formation could be overcome the cyclization at the C_3 methyl would proceed. One possible solution would be to convert the xanthone to its pyrylium cation with $BF_4^- \overset{+}{O}(C_2H_5)_3$ and then attempt to activate the methyl by proton abstraction using a nonnucleophilic base.

The 6,8-dimethoxy-1-tetralone approach is limited by the number of steps required to synthesize the bicyclic precursor 32. As well, there is the possibility that even with the appropriate AB precursor 26 the final condensation -cyclization would lead to an angularly fused tetracyclic system.

The target molecule was sucessfully synthesized by the chromone approach. The major problem of condensing unit A with unit CD was overcome by using potassium t-butyl oxide in t-butyl alcohol. The compound 22 was regioselectively synthesized in an over-all yield of 24% involving only two steps from the chromone.

Preliminary studies have shown that the position 6 of 22

is highly susceptible to bromination. This indicates that it should be possible to access the 6-hydroxyl derivative by an appropriate oxidation technique. This would provide a regioselective route to compounds which are even more structurally analogous to adriamycin and daunorubicin.

EXPERIMENTAL

GENERAL

Mass spectra were recorded on a Finnigan 1015 Mass spectrometer. Only the molecular ion and major fragments of diagnostic value are reported. Nuclear magnetic resonance (nmr) spectra were obtained on a Varian EM360 or Bruker WH 90 DS spectrometer. Unless otherwise stated, deuteriochloroform ($CDCl_3$) was used as the solvent with tetramethylsilane (TMS) as the internal reference. The chemical shifts are reported as δ values in ppm relative to TMS=0. Infrared spectra were recorded on a Perkin-Elmer model 700 instrument. ^{13}C-Nuclear magnetic resonance spectra were recorded on a Bruker WH 90 DS spectrometer. The electron spin resonance spectrum was recorded on Varian E-3 EPR spectrometer. Selected IR and NMR spectra, referenced in the experimental by NMR # and IR #, can be found at the end of the experimental section.

Melting points were determined on a Fisher-John melting point apparatus and are uncorrected.

Thin layer chromatography (tlc) was carried out on Camag Kieselgel DSF-5. Column chromatography was carried on silica gel, Merck 60, 230-400 mesh, using the flash chromatography technique (99).

Elemental analysis were performed by Guelph Chemical Laboratories Ltd. Guelph, Ontario, CANADA.

PART 1

XANTHONE APPROACH

(A) Xanthone approach

1-Hydroxy-3-methyl-9H-xanthene-9-one 23

(1-Hydroxy-3-methylxanthone 23) Method A

Salicylic acid (24.0g, 0.173 mole), orcinol monohydrate (24.0g, 0.170 mole) and 200g of polyphosphoric acid were stirred together and heated to 140°C ± 10°C (oil bath temperature) for 4 hours. The mixture was cooled in an ice bath, ice cold water was added to make the volume 500 ml and the whole solution was stirred for 0.5 hour. The crystals thus obtained were filtered off and washed with water. The filter cake was suspended in 500 ml of water and heated to 90°C (steam bath) with stirring for 0.5 hour. The suspension was cooled and extracted with $CHCl_3$ (3x200 ml). The organic extract was dried ($MgSO_4$) and evaporated to give yellow crystals. Chromatography on a silica gel column (eluant:benzene) gave 11.5g (30%) of the pure compound.

ms: m/e (relative intensity) 226(100), 197(40)

nmr δ: 12.25(s,1H), 8.3-7.3(m,4H), 6.7(s,1H), 6.6(s,1H), 2.35(s,3H) (NMR 1)

ir (CH_2Cl_2) ν: 1645 cm^{-1} (IR 1)

mp: 147°C (reported mp: 148°C)

Synthesis of 1-Hydroxy-3-methylxanthone 23 (Method B)

3,5-Dimethoxytoluene 51

Orcinol monohydrate (10.0g, 0.07 mole) and potassium

hydroxide (11.5g, 0.293 mole) were dissolved in 100 ml of water. The mixture was cooled in an ice bath and dimethyl sulphate (35 ml, 0.21 mole) was added through a dropping funnel over 30 minutes. After the addition, the mixture was refluxed with stirring for 3 hours. The solution was cooled, extracted with chloroform (3x100 ml) and the combined organic extracts were washed with 5% KOH (2x50 ml), then water, dried ($MgSO_4$) and evaporated to give a yellow oil 9.5g (89%).

Methyl o-methoxybenzoate 52

o-Methoxybenzoic acid (10.0g, 0.065 mole), dry methanol (200 ml) and 0.5 ml of sulphuric acid was cooled and the methanol evaporated under vacuum. The residue was dissolved in chloroform (100 ml), washed with 10% aqueous sodium bicarbonate solution (2x50 ml), then water, dried ($MgSO_4$) and evaporated to give 10.0g (93%) of crystalline product.

nmr (CCl_4) δ: 7.55-6.5(m,4H), 3.56(d,6H)

2,2,5 Trimethoxy-3-methylbenzophenone 53

A solution of 2,6-dimethoxy-4-methylphenyllithium in dry ether was prepared by treating 3,5-dimethoxytoluene (2.0g, 0.013 mole) in dry ether (15 ml) under nitrogen with 20 ml of t-butyl lithium (1M) in pentane. To a vigorously stirred solution of methyl anisate (2.5g, 0.15 mole) in dry ether (20 ml) under

nitrogen at 0°C. The above solution of phenyllithium reagent was added, through a dropping funnel over 5 minutes. After the addition, the mixture was stirred at room temperature for one hour. The solution was then poured into 6N HCl (50 ml). The two layers were separated, the aqueous layer was extracted with more ether (3x100 ml) and the combined organic extracts were washed with water , dried ($MgSO_4$) and evaporated to give 1.75g (47%) of crude product.

Recrystallization from benzene/hexane gave a white crystalline compound.

ms: m/e (relative intensity) 286(7.5), 255(18.5), 179(92), 165(33), 135(100)

nmr δ: 7.8-6.8(m,4H), 6.4(s,2H), 3.78(s,3H), 3.70(s,6H) 2.4(s,3H) (NMR 2)

ir ($CHCl_3$) ν: 1760 cm^{-1} (IR 2)

mp: 143°C

analysis: calculated for $C_{17}H_{18}O_4$: C, 71.32; H, 6.29
found: C, 71.07; H, 6.33

1-Hydroxy-3-methylxanthone 23

2,2,5-Trimethoxy-3-methylbenzophenone 53 (2.0g, 0.007 mole) and aluminum chloride (3g) in 100 ml of benzene were refluxed for 5 hours. After cooling the benzene was removed in vacuum and aqueous acid (1N, 40 ml) was added. The solution was the refluxed for 45 minutes. The cooled solution was extracted with chloroform

(3x50 ml) and the combined organic extracts were washed with water, dried ($MgSO_4$) and evaporated to give yellow crystals 1.3g (82%) with spectral data (nmr and mass spectra and melting point) identical to those obtained by procedure (A).

1-Methoxy-3-methylxanthone 56

1-Hydroxy-3-methylxanthone 23 (4.0g, 0.018 mole), anhydrous potassium carbonate (6.0g, 0.043 mole), and 150 ml of dry acetone (freshly distilled) were stirred for 10 minutes. Dimethyl sulphate (10.0 ml, 0.059 mole) was added to the above mixture through a dropping funnel over 5 minutes. The solution was stirred at room temperature for 40 minutes and then heated under reflux for 18 hours. The cooled solution was poured into water (50 ml), extracted with $CHCl_3$ (3x50 ml). The combined organic extracts were washed with water, dried ($MgSO_4$) and evaporated to give 4.3g of crude product. The crude product in 10 ml of hot benzene was applied to a column of silica gel which was then eluted with benzene and benzene/ether (1:1) to give 4.1g (97%) of pure product.

ms: m/e (relative intensity) 240(87.5), 225(25), 211(100), 194(75)

nmr δ: 8.4-7.0(m,4H), 6.78(s,1H), 6.5(s,1H), 4.0(s,3H), 2.45(s,3H) (NMR 3)

General preparation of lithium diisopropylamide (LDA) in dry THF

To a well stirred solution of diisopropylamine in dry tetrahydrofuran (THF) at -78°C under nitrogen atmosphere was added, equal moles of n-butyllithium in pentane through a syringe. The mixture was stirred for 10 minutes at -78°C before using.

Attempted C-methyl alkylation of 1-hydroxy-3-methylxanthone

1-Hydroxy-3-methylxanthone 23 (0.50g, 0.002 mole) in 10 ml of dry THF was added dropwise under nitrogen to a freshly prepared solution of LDA (0.01 mole) in THF (15 ml) at -78°C. The mixture was stirred for 10 minutes at -78°C, then CH_3I (0.5 ml) in 5 ml of dry THF was added dropwise under nitrogen with stirring over 5 minutes. The mixture was stirred at -78°C for 30 minutes and then at reflux for one hour. The reaction was followed on tlc (developing solvent:benzene). The solution was cooled, poured into 10% HCl and extracted with $CHCl_3$ (3x20 ml). The combined organic extracts were washed with water, dried ($MgSO_4$) and evaporated to give 0.46g of crude material. Two compounds were indicated by tlc. These were separated on a silica gel column (eluant:10% ether/benzene). Compounds A and B were obtained in decreasing order of R_f value.

Compound A was identical (nmr, mass spectrum) to the starting material.

Compound B was identified (nmr, mass spectrum) as 1-methoxy-3-methylxanthone 56.

Attempted C-methyl alkylation of 1-methoxy-3-methylxanthone

(1) With lithium diisopropylamide (LDA)

1-methoxy-3-methylxanthone 56 (0.5g, 0.002 mole) was subjected to the same experimental conditions as described above with 1-hydroxy-3-methylxanthone 23. The recovered material was identical (nmr, mass spectrum) to the starting 1-methoxy-3-methyl-xanthone.

(2) With triphenylmethyl lithium

A solution of triphenylmethyl lithium was prepared by treating triphenyl methane (160mg, 0.6 mmole) in dry THF (10 ml) under nitrogen at $0^{o}C$ with 0.6 ml n-butyllithium (1M) in pentane. After the red mixture had stirred for 10 minutes, the 1-methoxy -3-methylxanthone 56 (150mg, 0.6 mmole) in THF (10 ml) was added dropwise under nitrogen with stirring over 5 minutes. The mixture was stirred for a further 10 minutes and CH_3I (0.2 ml) was added dropwise. On addition of CH_3I the colour changed from red to pale yellow. The mixture was stirred for an additional 40 minutes at $0^{o}C$. The mixture poured into water (20 ml), extracted with ether (3x20 ml) and the combined extracts were washed with water, dried ($MgSO_4$) and evaporated to give 300mg of crude crystalline material. The crude material was purified by chromatography on a silica gel column (eluant:ether/benzene (1:2)).

Compounds A and B were obtained in decreasing order of R_f value.

Compound A was identified (nmr, mass spectrum) as triphenyl methane.

Compound B was identified (nmr, mass spectrum) as 1-methoxy-3-methylxanthone 56.

Diethyl bis(hydroxymethyl)malonate 54

Formalin (380g, 40% formaldehyde, 5 moles) and 4 drops of BDH universal pH indicator were cooled (0-5°C), 10% sodium hydroxide solution was added and the pH was adjusted to 8-8.5. Ethyl malonate (200g, 1.25 moles) was added dropwise to the above solution over a period of 2 hours with stirring. The pH of the solution was maintained at 8-8.5 throughout the addition of ethyl malonate. The mixture was stirred at room temperature for 5 hours, diluted with brine (500 ml) and extracted with ether (6x300 ml). The combined organic extracts were washed with water (2x500 ml), dried ($MgSO_4$) and evaporated to give 260g of crude product. The reaction was followed by the disappearance of the methylene in ethyl malonate in the nmr spectrum.

nmr (CCl_4) δ: 4.45-3.9(m,10H), 1.3(t,6H) (NMR 4)

β,β-Dibromoisobutyric acid 55

Diethyl bis(hydroxymethyl)malonate, 54 (150g, 0.681 mole) and 1500 ml (13 moles) of 48% hydrobromic acid were heated (126-128°C) until ethyl bromide and hydrobromic acid distilled

off and the volume was reduced to approximately 300 ml (5 hours). The mixture was cooled for 1.5 hours in an ice bath. The crystals obtained were filtered on a sintered glass funnel, washed with ice cold water and suction dried to give 71g of product. The distillate and the filtrate were combined and used for a second reaction (100g of diethyl bis(hydroxymethyl)malonate). The sequence of distillation and crystallization was repeated to obtain a futher 61g of dibromo acid 55. The combined yield of β,β-dibromoisobutyric acid was 132g (45%).

ms: m/e (relative intensity) 248(11), 246(11), 244(11), 201(5), 199(3), 167(100), 165(100), 153(72), 152(72), 121(33), 119(33), 85(84)

nmr δ: 12.55(s,1H), 3.80(s,2H), 3.7(s,2H), 3.4-3.1(m,1H) (NMR 5)

Methyl(β,β-dibromo)isobutyrate 24

β,β-Dibromoisobutyric acid 55 (132g, 0.536 mole), dry methanol (1 litre) and 0.5 ml of H_2SO_4 (16N) were refluxed together for 15 hours. The solution was cooled and evaporated in vacuum to 300 ml. The residue was taken up in $CHCl_3$ (500 ml) and washed with water (200 ml), dried ($MgSO_4$) and evaporated to give 135g (97%) of crude product. The crude was distilled, bp 65-68°C (1.5 mm Hg), to give 118g (86%) of pure product.

nmr δ: 3.78(s,4H), 3.7(s,3H), 3.2(t,1H) (NMR 6)

Methyl β-bromomethylacrylate 60

Methyl (β,β-dibromo)isobutyrate 24 (10g, 0.038 mole), in carbon tetrachloride (50 ml) was treated, with aqueous sodium hydroxide (50 ml, 1M) and a catalytic amount of benzyltriethylammonium chloride (BTEAC, 50mg), at $0^{o}C$ for one hour. The organic layer was separated, washed with water, dried ($MgSO_4$), and evaporated to give 6.4g (94%) of methyl β-bromomethacrylate. The reaction was followed by nmr of the organic layer.

nmr (CCl_4) δ: 6.33(s,1H), 5.95(s,1H), 4.15(s,2H), 3.82(s,3H) (NMR 7)

1-(2-Carbomethoxyalloxy)-3-methyl-9H-xanthene-9-one 57

1-Hydroxy-3-methylxanthone 23 (4.0g, 0.18 mole), anhydrous potassium carbonate, (6.0g, 0.043 mole) and 150 ml of dry acetone (freshly distilled) were stirred for 10 minutes. Methyl β,β-dibromoisobutyrate 24 (5.0g, 0.019 mole) in 5 ml of dry acetone was added to the above mixture through a dropping funnel over 5 minutes, then refluxed for 15 hours. The solution was cooled, filtered and evaporated to give 5.6g of crude product. Recrystallization from carbon tetrachloride/cyclohexane gave 5.45g (95%) of off white crystals.

ms: m/e 324(m^+)

nmr δ: 8.35-7.2(m,4H), 6.8(s,2H), 6.6(s,2H), 4.8(s,2H), 3.85(s,3H), 2.4(s,3H) (NMR 8)

ir ($CHCl_3$) ν: 1645 cm^{-1}, 1715 cm^{-1} (IR 3)

1-Hydroxy-2-(2-carbomethoxyallyl)-3-methyl-9H-xanthene-9-one 58 (1-Hydroxy-2-C-allylic-3-methylxanthone)

1-(2-Carbomethoxyalloxy)-3-methyl-9H-xanthene-9-one 57 (5.0g, 0.015 mole) and hexachlorobutadiene (50 ml) were refluxed for 10 minutes. The solution was cooled and hexane added. Further cooling and scratching resulted in the crystallization of the product. The crystals obtained were filtered and dried under suction to give 4.8g (96%) of product. The same result could be accomplished by passing the cooled reaction mixture through a column of silica gel made in hexane and eluting first with hexane and then with benzene.

ms: m/e (relative intensity) 324(7.5), 293(4.5), 265(100), 239(15), 226(10)

nmr δ: 12.55(s,1H), 8.42-7.25(m,4H), 6.85(s,1H), 6.25(s,1H), 5.2(s,1H), 3.9(s,3H), 3.75(s,2H), 2.35(s,3H) (NMR 9)

ir ($CHCl_3$) ν: 1640 cm^{-1}, 1720 cm^{-1} (IR 4)

mp: 153°C

analysis: calculated for $C_{19}O_5H_{16}$: C, 70.37; H, 4.94
found: C, 70.36; H, 4.98

1-Methoxy-2-(2-carbomethoxyallyl)-3-methyl-9H-xanthene-9-one 59 (1-Methoxy-2-C-allylic-3-methylxanthone)

1-Hydroxy-2-C-allylic-3-methylxanthone 58 (5.0g, 0.015 mole), anhydrous potassium carbonate (5.0g, 0.036 mole) and 150 ml of dry acetone were stirred for 10 minutes. To this solution was

added methyl iodide (6.0g, 0.042 mole) over 2 minutes. After the addition, the mixture was refluxed with stirring for 15 hours. The reaction was cooled, filtered and evaporated to give 5.1g (98%) of white crystalline product.

ms: m/e (relative intensity) 338(50), 323(33), 307(66), 279(100), 239(83)

nmr δ: 8.4-8.27(d,1H), 7.7-7.35(m,3H), 7.15(s,1H), 6.2(s,1H), 5.15(s,1H), 3.9(s,3H), 3.85(s,3H), 3.77(s,2H), 2.35(s,3H) (NMR 10)

mp: 123°C

analysis: calculated for $C_{20}H_{19}O_5$: C, 71.00; H, 5.62
found: C, 71.02; H, 5.36

1-Methoxy-2-(3-methoxy-2-carbomethoxypropyl)-3-methyl-9H-xanthene-9-one 61

1-Methoxy-2-C-allylic-3-methylxanthone 59 (50mg, 0.15 m mole), in 2 ml of dry methanol, was added at room temperature over a period of 2 minutes, to a freshly prepared solution of sodium methoxide. The mixture was refluxed with stirring for one hour. The solution was cooled, poured into 10% HCl and extracted with $CHCl_3$ (3x20 ml). The combined organic extracts were washed with water, dried ($MgSO_4$) and evaporated to give 40 mg of crude material. The tlc of the crude product indicated the presence of two compounds. These were separated by chromatography

on a silica gel column (eluant:pentane/ether 1:1). Compound A and B were obtained in decreasing order of R_f value.

Compound A (7mg) was identical to starting material.

Compound B: 20mg (42% based on recovered starting material).

ms: m/e (relative intensity) 370(18), 325(52), 253(100), 239(96)

nmr δ 8.35-8.25(d,1H), 7.7-7.28(m,3H), 7.1(s,1H), 3.9(s,3H), 3.6(s,3H), 3.5(m,2H), 3.3(s,3H), 3.0(s,3H), 2.5(s,3H) (NMR 11)

1-Methoxy-2-(2,3-dibromo-2-carbomethoxypropyl)-3-methyl-9H-xanthene-9-one 64

1-Methoxy-2-C-allylic-3-methylxanthone 59 (1.0g, 0.003 mole) and carbon tetrachloride (30 ml) was warmed to 40°C with stirring for 5 minutes. Bromine (2% in CCl_4, 40 ml, 0.005 mole) was added to the above solution (1 ml every 2 minutes). The mixture was kept warm (40°C) during the addition. After the addition, the solution was stirred for an additional 10 minutes at 40°C. The solution was cooled and evaporated in vacuum yielding 1.35g (92%) of crude product. Recrystallization from CCl_4/hexane gave white crystals. The reaction was followed on tlc (developing solvent: pentane/ether 1:1).

ms: m/e (relative intensity) 500(1), 498(1), 496(1), 471(2), 469(2), 467(2), 419(20), 417(20), 387(4), 385(4), 338(8), 279(12), 253(100)

nmr δ: 8.84-8.82(bd,1H), 7.78-7.38(m,3H), 7.18(s,1H), 4.25(q,2H), 3.98(s,3H), 3.85(s,3H), 3.78(s,2H), 2.53(s,3H) (NMR 12)

ir ($CHCl_3$) ν: 1660 cm^{-1}, 1740 cm^{-1} (IR 5)

mp: 126°C

analysis: calculated for $C_{20}H_{19}O_5Br_2$: C, 48.19; H, 3.81
found: C, 48.13; H, 3.60

1-Methoxy-2-(3-bromo-2-carbomethoxypropyl)-3-methyl -9H-xanthene-9-one 65

1-Methoxy-2-(2,3-dibromo-2-carbomethoxypropyl)-3-methyl -9H-xanthene-9-one 64 (1.0g, 0.002 mole) was dissolved in 100 ml of ether. 1,5-Diazabicyclo{4.3.0}non-5-ene (DBN) (2.5 ml, large excess) was added to the above solution. The mixture was stirred at room temperature for 30 minutes. Hydrochloric acid (50 ml, 2N) was added and the organic layer was separated and washed with HCl (2N, 2x30 ml). The aqueous layers were re-extracted with ether. The combined ether extracts were washed with water, dried ($MgSO_4$) and evaporated to give 0.75g (90%) of product. The reaction was followed on tlc (developing solvent:pentane/ether 1:1). Recrystallization from cyclohexane gave white crystals.

ms: m/e (relative intensity) 418(5), 416(5), 387(5), 385(5), 359(10), 357(10), 321(40), 307(100), 277(70), 263(40), 239(90)

nmr δ: 8.35-8.2(d,1H), 7.65-7.3(m,4H), 7.15(s,1H), 3.9(s,5H),
3.7(s,3H), 2.6(s,3H) (NMR 13)

ir ($CHCl_3$) ν: 1660 cm^{-1}, 1720 cm^{-1} (IR 6)

mp: 138°C

PART II

6,8-DIMETHOXY-1-TETRALONE APPROACH

(B) 6,8-Dimethoxy-1-tetralone approach

Methyl 3,5-Dimethoxybenzoate 71

3,5-Dimethoxybenzoic acid 70 (50g, 0.27 mole), dry methanol (one liter) and sulphuric acid (0.5 ml) were refluxed for 15 hours. The solution was cooled and evaporated under reduced pressure to a small volume (200 ml). The residue was taken up in chloroform and washed with aqueous sodium bicarbonate (10%). The aqueous layer was re-extracted and the combined organic extracts were washed with water, dried ($MgSO_4$) and evaporated to give 51g (95%) of product.

ms: m/e 196(m^+)

3,5-Dimethoxybenzyl alcohol 72

Methyl 3,5-Dimethoxybenzoate 71 (30g, 0.15 mole) in dry ether (100 ml) was added dropwise to a mixture of $LiAlH_4$ (4g, 0.1 mole) in 200 ml of dry ether over a period of 15 minutes. The mixture was stirred at room temperature for 30 minutes. Excess of hydride was destroyed by adding 0.5% aqueous potassium hydroxide solution. The two layers were separated and the aqueous layer was extracted with ether (3x100 ml). The combined organic extract was washed with water, dried ($MgSO_4$) and evaporated to give 24.6g (96%) of crystalline product. The reaction was followed on tlc (developing solvent:benzene).

ms: m/e 168(m^+)

nmr δ: 6.5-6.35(m,3H), 4.65(d,2H), 3.8(s,6H), 2.35(s,1H)

When a drop of D_2O was added to the nmr sample the peak at δ 2.35 disappeared.

3,5-Dimethoxybenzaldehyde 35

Chromium trioxide (16g, 0.16 mole) in 2N H_2SO_4 (200 ml) was added dropwise to a cooled (0-5°C) solution of 3,5-dimethoxybenzyl alcohol (20g, 0.12 mole) in 200 ml of ether. After the addition, the solution was stirred at room temperature for 30 minutes. The layers were separated and the aqueous layer was extracted with ether (2x50 ml). The combined organic extracts were successively washed with 10% sodium bicarbonate (2x50 ml) and then with water, dried ($MgSO_4$) and evaporated to give 14.3g (72%) of product. The reaction was followed on tlc (developing solvent:ether).

ms: m/e 166(m^+)

nmr δ: 9.9(s,1H), 7.03(d,2H), 6.75-6(m,1H), 3.85(s,6H)

(NMR 14)

3-Carboethoxy-4-(3',5'-dimethoxyphenyl)-3-butenoic acid 73

3,5-Dimethoxybenzaldehyde 35 (10g, 0.06 mole) and diethyl succinate (10.5g, 0.062 mole) in 20 ml of dry tert-butyl alcohol were added dropwise to a freshly prepared solution of potassium t-butoxide (2.5g, of potassium in 50 ml of t-butyl alcohol) over a period of 30 minutes with stirring under nitrogen atmosphere and

then refluxed for 30 minutes. The solution was cooled, poured into 10% HCl (100 ml) and extracted with ether (3x100 ml). The combined ethereal solutions were extracted with 1N ammonium hydroxide. The ammonium hydroxide solution was acidified and extracted with ether (3x100 ml). The combined organic extracts were washed with water, dried ($MgSO_4$) and evaporated to give 11.5g (65%) of product.

ms: m/e (relative intensity) 294(40),249(10), 248(20), 220(20), 204(10), 176(80), 175(100), 161(40)

nmr δ: 9.0(bs,1H), 7.83(s,1H),6.5(s,3H), 4.3(q,2H), 3.75(s,6H), 3.57(s,2H), 1.3(t,3H) (NMR 15)

ir (nujol) ν: 1715 cm^{-1}, 1725 cm^{-1}, 2710-3400 cm^{-1}

When D_2O was added to nmr sample the peak at δ 9.0 disappeared.

3-Carboxy-4-(3',5'-dimethoxyphenyl)-3-butenoic acid 75

3-Carboethoxy-4-(3',5'-dimethoxyphenyl)-3-butanoic acid 73 (5.0g, 0.017 mole) was taken up in potassium hydroxide (100 ml, 2N) and heated to 70°C with stirring for 1.5 hours. The solution was cooled, acidified with hydrochloric acid (2N) and extracted with ether (3x100 ml). The combined organic extracts were washed with water, dried ($MgSO_4$) and evaporated to give 4.1g (91%) of product. Recrystallization with $CHCl_3$/ether gave colourless crystals.

ms: m/e (relative intensity) 266(54), 248(90), 220(81), 205(72), 175(100), 161(72)

nmr (acetone-d_6) δ: 9.4(bs,2H), 7.97(s,1H), 6.7-6.5(m,3H), 3.85(s,6H), 3.6(s,2H) (NMR 16)

When D_2O was added to nmr sample the peak at δ 9.4 disappeared.

^{13}C-nmr (acetone-d_6)

line	δ (ppm)
1	172.5
2	168.8
3	161.9
4	142.1
5	137.9
6	128.0
7	107.7
8	101.8
9	55.7
10	34.1

Attempted decarboxylation of 3-carboxy-4-(3',5'-dimethoxyphenyl)-3-butanoic acid

(i) HBr (48%)/CH_3CO_2H/water

3-Carboxy-4-(3',5'-dimethoxyphenyl)-3-butanoic acid 75 (0.50g, 0.0018 mole), hydrobromic acid (HBr 20 ml), acetic acid (20 ml) and water (5 ml) were stirred at room temperature for one hour. The reaction mixture was extracted with ether (3x50 ml). The combined organic extracts were washed with water, dried ($MgSO_4$) and evaporated to give 0.46g of material. The recovered material was identical (nmr, and mass spectra) to the diacid 75.

(ii) HBr (48%)/CH_3CO_2H/water at reflux temperature

3-Carboxy-4-(3',5'-dimethoxyphenyl)-3-butanoic acid 75

(0.50g, 0.0018 mole), HBr (48%, 20 ml), CH_3CO_2H (20 ml) and water (5 ml) were refluxed for 3 hours with stirring. The solution was cooled, then extracted with ether, dried ($MgSO_4$) and evaporated to give 0.45g of material. The recovered material was identical (nmr and mass spectra) to the diacid 75.

(iii) Pyridine/HCl at 100°C

3-Carboxy-4-(3',5'-dimethoxyphenyl)-3-butanoic acid 75

(0.50g, 0.0018 mole), pyridine (50 ml) and HCl (1 ml) were heated to 100°C for 12 hours. The solution was cooled, then extracted with ether (3x50 ml). The combined organic extracts were washed with 10% HCl (2x25 ml), then water, dried ($MgSO_4$) and evaporated to give 0.41g of material. The recovered material was identical (nmr and mass spectra) to the diacid 75.

Methyl (3,5-Dimethoxybenzoyl)acetate 38

Methyl acetate (4.2 ml, 0.052 mole) in dry N,N-dimethylformamide (10 ml) was added dropwise under nitrogen atmosphere to a heated (45°-50°C) mixture of methyl 3,5-dimethoxybenzoate (10.0g, 0.051 mole) and sodium hydride (3g, 50% in oil) in 100 ml of N,N-dimethylformamide over a period of 15 minutes with stirring. The mixture was stirred at (45°-50°C) for 0.5 hour, then at 100°C for one hour. The solution was cooled, poured into HCl (100 ml,1N)

and extracted with chloroform (3x50 ml). The combined organic extracts were washed with 5% sodium bicarbonate solution (3x50 ml), then washed with water, dried ($MgSO_4$) and evaporated to give 12.5g of oily crude product. The tlc of the crude product (developing solvent:pentane/ether 2:1) indicated some unreacted starting material was still present. The crude mixture was washed with hexane (to remove oil from sodium hydride) and then chromatographed on silica gel (eluant:pentane/ether 2:1) to obtain 9.6g (79%) of the pure methyl (3,5-Dimethoxybenzoyl)acetate.

ms: m/e (relative intensity) 238(33), 206(19), 165(100), 137(33)

nmr δ: 7.0(s,1H), 6.95(s,1H), 6.6(m,1H), 3.95(s,2H), 3.7(s,6H), 3.65(s,3H) (NMR 17)

ir ($CHCl_3$) ν: 1685 cm^{-1}, 1740 cm^{-1} (IR 7)

Ethyl 3-carbomethoxy-3-(3',5'-dimethoxybenzoyl)propionate 80

Ethyl α-bromoacetate (4.3 ml, 0.038 mole) in N,N-dimethylformamide (10 ml) was added under nitrogen atmosphere to a heated (45-50°C) mixture of methyl (3,5-dimethoxbenzoyl)acetate 38 (9.0g, 0.037 mole) and sodium hydride (2g, 50% in oil) in 100 ml of N,N-dimethylformamide over a period of 5 minutes with stirring. The mixture was stirred for one hour. The solution was cooled, then 10% HCl added (100 ml) and resulting mixture was extracted with $CHCl_3$ (3x75 ml). The combined organic extracts were washed

with water, dried ($MgSO_4$) and evaporated to give 11.5g of crude oil.

ms: m/e (relative intensity) 324(6), 279(4), 247(3), 219(6), 179(40), 165(100), 137(25)

3-(3',5'-Dimethoxybenzoyl)propionic acid

Ethyl 3-carbomethoxy(3',5'-dimethylbenzoyl)propionate 80 (11.5g,0.035 mole) was taken up in a mixture of glacial acetic acid/12N hydrochloric acid (100 ml, 1:1) and refluxed with stirring for 3 hours. The solution was cooled and extracted with $CHCl_3$ (3x100 ml). The combined organic extracts were washed with 10% sodium bicarbonate (4x50 ml). The chloroform extracts were washed with water, dried ($MgSO_4$) and evaporated to give 8.0g (95%) of product.

ms: m/e (relative intensity) 238(16), 196(16), 165(100), 151(33)

Methyl 3-(3',5'-dimethoxybenzoyl)propionate 37

3-(3',5'-Dimethoxybenzoyl)propionic acid (8.0g, 0.034 mole), dry methanol (500 ml) and H_2SO_4 (16N, 0.25 ml) were refluxed for 15 hours. The solution was cooled and evaporated under reduced pressure to a small volume (50 ml). The residue was worked up by $CHCl_3$/water extraction. The crude ester was obtained in 100% yield and recrystallized from pentane/ether.

ms: m/e (relative intensity) 252(7), 221(5), 193(2), 165(100), 137(40)

nmr δ: 7.15(m,2H), 6.7(bs,1H), 3.85(s,6H), 3.7(s,3H), 3.35-2.7(m,4H) (NMR 18)

ir ($CHCl_3$) ν: 1695 cm^{-1}, 1740 cm^{-1} (IR 8)

analysis: calculated for $C_{13}H_{16}O_5$: C, 61.90; H, 6.35
found C, 61.65; H, 6.59

Methyl 4-(3',5'-dimethoxyphenyl)butanoate 33

Methyl 3-(3',5'-dimethoxybenzoyl)propionate 37 (8.0g, 0.032 mole), dry methanol (400 ml, freshly distilled from Mg metal), 5% palladium/carbon (200mg) and HCl (12N, 0.25 ml) were stirred under a hydrogen atmosphere at room temperature for 15 hours. The solution was filtered and evaporated to a small volume (50 ml). The residue was worked up by $CHCl_3$/water extraction. The reduced product was obtained in 95% yield.

ms: m/e (relative intensity) 238(64), 207(33), 170(16), 165(100), 151(95)

nmr δ: 6.4(s,3H), 3.8(s,6H), 3.7(s,3H), 2.65-1.95(m,6H) (NMR 19)

ir (neat) ν: 1745 cm^{-1} (IR 9)

6,8-Dimethoxy-1-tetralone 32

Methyl 4-(3',5'-dimethoxyphenyl)butanoate 33 (5.0g, 0.021 mole) was taken up in sulphuric acid (50 ml, 16N) and heated on a steam bath for 20 minutes with stirring. The solution was cooled, poured onto ice (200g) and extracted with $CHCl_3$ (4x50 ml). The

combined organic extracts were washed with 10% sodium bicarbonate (3x50 ml), then water, dried ($MgSO_4$) and evaporated to give 4.1g (95%) of 6,8-dimethoxy-1-tetralone.

ms: m/e (relative intensity) 206(100), 178(98), 149(42), 135(39)

nmr δ: 6.35(s,2H), 3.9(s,3H), 3.85(s,3H), 3.0-1.9(m,6H) (NMR 20)

ir (neat) ν: 1680 cm^{-1} (IR 10)

Attempts to protect the carbonyl of 6,8-Dimethoxy-1-tetralone

(i) Ethylene glycol/p-toluenesulfonic acid/benzene

6,8-Dimethoxy-1-tetralone 32 (0.50g, 0.0024 mole) ethylene glycol (freshly distilled), p-toluenesulfonic acid (20mg) and 100 ml of benzene were refluxed (using a Dean-Strak trap) for 3 hours with stirring. The solution was cooled and washed with 5% sodium bicarbonate (2x25 ml), then water, dried ($MgSO_4$) and evaporated to give 0.52g of crude material. The crude product was separated on a silica gel column (eluant:benzene/ether 1:1). The compounds were obtained in decreasing order of R_f value.

Compound A was identified (nmr, ir and mass spectra) as 2-hydroxyethyl 4-(3',5'-dimethoxyphenyl)butanoate 85

ms: m/e (relative intensity) 268(23), 207(38), 165(69), 151(100)

nmr δ: 6.4(s,3H), 4.3-3.6(m,4H), 3.8(s,6H), 2.7-1.95(m,7H) (NMR 21)

ir ($CHCl_3$) ν: 1740 cm^{-1}, 3500 cm^{-1} (IR 11)

Compound B was identical (nmr, ir and mass spectra) to 6,8-dimethoxy-1-tetralone.

(ii) Morpholine/p-toluenesufonic acid/benzene

6,8-Dimethoxy-1-tetralone 32 (0.50g, 0.0024 mole), morpholine (1 ml, large excess), p-toluenesufonic acid (20 ml) and 100 ml of benzene were refluxed (using a Dean-Stark trap) for 12 hours with stirring. The solution was cooled, washed with water, dried ($MgSO_4$) and evaporated to give 0.48g of product material.

The recovered material was identical (nmr, ir and mass spectra) to 6,8-dimethoxy-1-tetralone.

1-Hydroxy-6,8-dimethoxytetralin 86

6,8-Dimethoxy-1-tetralone 32 (1g, 0.005 mole) in 50 ml of dry ether was reduced using $LiAlH_4$ (excess) in the usual way to 1-hydroxy-6,8-dimethoxytetralin.

ms: m/e 208(m^+), 190(m^+-H_2O)

nmr δ: 6.25(bs,2H), 5.0-4.85(m,1H), 3.75(s,3H), 3.7(s,3H), 3.0(s,1H), 2.8-2.6(m,2H), 1.95-1.7(m,4H) (NMR 22)

ir (neat) ν: 3450-3600 cm^{-1} (IR 12)

Attempt to prepare the tetrahydropyranyl ether of 1-hydroxy-6,8-dimethoxytetralin

(i) Dihydropyran/pyridinium-p-toluene sulfonate/CH_2Cl_2

6,8-Dimethoxy-3,4-dihydronaphthalene 88

1-Hydroxy-6,8-dimethoxytetralin 86 (0.2g, 0.9 m mole), dihydropyran (0.2 ml), pyridinium-p-toluene sulfonate (2mg) and 30 ml of dry methylene chloride were stirred at room temperature for one hour. The solution was washed with water, dried ($MgSO_4$) and evaporated to give 0.19mg of 6,8-dimethoxy-3,4-dihydronaphthalene.

ms: m/e 190(m^+)

nmr δ: 6.87-6.7(d,1H), 6.3(s,2H), 6.0-5.75(m,1H), 3.8(s,6H), 2.9-2.6(m,2H), 2.45-2.1(m,2H) (NMR 23)

ir (neat) ν: 1620 cm^{-1} (IR 13)

The multiplet at δ 6.0-5.75 appeared as a doublet when the protons at δ 2.45-2.1 were decoupled.(NMR 24)

6-Methoxy-8-hydroxy-1-tetralone 89

6,8-Dimethoxy-1-tetralone 32 (0.2g, 0.9 m mole) in 30 ml of dry methylene chloride was cooled to 0-5°C and boron trichloride was bubbled through the solution for 5 minutes. The flask was stoppered and stirred at room temperature fo 30 minutes. The solution was poured into cold water, dried ($MgSO_4$) and evaporated to give 0.19g of crude product. The reaction was followed on tlc (developing solvent:ether).

ms: m/e 182(m^+)

nmr δ: 12.6(s,1H), 6.25(s,2H), 3.8(s,3H), 2.95-2.5(m,4H), 2.25-1.9(m,2H) (NMR 25)

Attempts to acylate the C_2 position of 6,8-Dimethoxy-1-tetralone

(i) $BF_3/(CH_3CO)_2O$ complex

6,8-Dimethoxy-1-tetralone 32 (0.50g, 0.0024 mole), acetic anhydride (1.3g, 5 moles excess) and 30 ml of CH_2Cl_2 were cooled (0-5°C) and gaseous boron trifluoride added over a period of 2 hours with constant stirring. The mixture was stirred for 30 minutes at room temperature. The mixture was then poured into cold water, the organic layer was then separated, washed with water, dried ($MgSO_4$) and evaporated to give the oily product. The reaction was followed on tlc (developing solvent:ethyl acetate). The recovered material was subjected to a high vacuum to remove excess acetic anhydride. The residual material was identical (nmr, ir and mass spectra) to 6,8-Dimethoxy-1-tetralone.

(ii) $BF_3/CH_3CO_2H/(CH_3CO)_2O$ complex

The reaction of 6,8-Dimethoxy-1-tetralone 32 (o.50g, 0.0024 mole) with acetic acid (5 mole excess), acetic anhydride (5 mole excess) 30 ml of CH_2Cl_2 and BF_3 gas was carried out under the conditions described in the above experiment. The recovered material was identical (nmr, ir and mass spectra) to 23.

(iii) $NaH/CH_3CO_2CH_3$/benzene

Sodium hydride (150mg, 50% in oil) was added under nitrogen atmosphere to a solution of 6,8-dimethoxy-1-tetralone 32 (0.50g, 0.0024 mole) in 50 ml of dry benzene. The mixture was heated (40-45°C) with stirring over a period of 10 minutes. Methyl acetate (0.5g, 0.006 mole) in 5 ml of dry benzene was added dropwise under nitrogen over a period of 3 minutes with stirring. The mixture was further stirred at (40-45°C) for 3 hours. The cooled solution was washed with water, dried ($MgSO_4$) and evaporated to yield 0.45g of material. The recovered material was identical (nmr, ir and mass spectra) to 6,8-dimethoxy-1-tetralone.

PART III

CHROMONE APPROACH

(C) Chromone approach

o-Benzyloxyacetophenone 91

Benzyl chloride (150g, 1.18 moles) was added dropwise to a solution of o-hydroxyacetophenone (136g , 1.0 mole) in sodium ethoxide (23g of sodium in 600 ml of dry ethanol) over a period of 20 minutes. The mixture was then refluxed for 5 hours. The solution was cooled, filtered and evaporated to 200 ml. The residue was taken up in ether, washed with water, dried ($MgSO_4$) and evaporated to give 200g of crude product. Distillation of the crude product gave 192g (85%) of pure product.

ms: m/e (relative intensity) 226(29), 211(14), 183(20), 121(100)

nmr (CCl_4) δ: 7.8-6.8(m.9H), 5.1(s,2), 2.5(s,3H) (NMR 26)

Ethyl (o-Benzyloxybenzoyl)acetate 92

A mixture of diethyl carbonate (250 ml, 2.2 moles) and sodium hydride (20g, 50% in oil dispersion) was heated to 80°C under nitrogen. o-Benzyloxyacetophenone 91 (49.7g, 0.22 mole) was added with stirring over 20 minutes. The mixture was cooled, diluted with dry ether, filtered and evaporated in vacuum. The crude product was filtered through silica gel (eluant:chloroform) to give 34.6g (61%) of pure product.

ms: m/e (relative intensity) 298(2), 280(15), 252(2), 210(22), 120(100)

nmr δ: 8.0-7.8(d,1H), 7.4-6.7(m,8H), 5.15(s,2H), 4.1(m,4H), 1.15(t,3H) (NMR 27)

Ethyl (2-hydroxybenzoyl)acetate, (Ethyl salicyloylacetate) 93

Ethyl (2-benzyloxybenzoyl)acetate 92 (5.0g, 0.017 mole) and 5% palladium on charcoal (400mg) were mixed in ethyl acetate (200 ml, freshly distilled) and hydrogenated at atmospheric pressure for 20 hours. The solution was filtered and evaporated in vacuum to give 3.6g (96%) of the product.

ms: m/e (relative intensity) 208(33), 163(100), 146(17), 121(98), 120(98)

Ethyl 2-methyl-4-oxo-4H-1-benzopyran-3-carboxylate 27 (Ethyl 2-methylchromone-3-carboxylate) Method A

Ethyl salicyloylacetate 93 (6.0g, 0.029 mole), acetic anhydride (40 ml) and sodium acetate (2.5g, anhydrous) were heated to 105°C with stirring for 3 hours. The solution was cooled, diluted with benzene and filtered. The resulting filtrate was stirred for 2 hours with water (100 ml). The organic layer was dried ($MgSO_4$) and evaporated to give 3.0g of crude product. The crude product was chromatographed through a silica gel column (eluant:benzene/ether 9:1) to give 1.9g (32%) of the pure ester.

ms: m/e (relative intensity) 232(7), 207(16), 187(71), 160(100), 121(89), 120(71)

nmr δ: 8.2-8.0(d,1H), 7.8-7.17(m,3H), 4.42(q,2H), 2.5(s,3H), 1.42(t,3H) (NMR 28)

ir (nujol) ν: 1640 cm^{-1}, 1725 cm^{-1} (IR 14)

mp: 63-65°C

Salicyloyl chloride 25

Salicylic acid (276g, 2 moles), freshly distilled thionyl chloride, (143 ml, 2 moles) and a catalytic amount of aluminum chloride (100mg) were heated with stirring at a gentle reflux in two liters of petroleum-ether (40-50°C) for 72 hours. When the mixture was cooled the polymerised acid chloride settled in the bottom of the flask. The clear upper solution was decanted and evaporated under pressure without excessive heating to give 281g (90%) of acid chloride which was used without further purification.

Ethyl 3-morpholino-2-butenoate 94

Ethyl acetoacetate (200g, 1.5 moles), morpholine (140g, 1.6 moles) and a catalytic amount of p-toluenesulfonic acid (100mg) in one liter of toluene were refluxed, using a Dean-Stark trap, for 10 hours. Water (30 ml) was removed azeotropically from the reaction mixture. The solution was cooled and evaporated to give the product in quantitative yield. The crude product was used without further purification.

Ethyl 2-methyl-4-oxo-4H-1-benzopyran-3-carboxylate 27
(Ethyl 2-methylchromone-3-carboxylate) Method B

Salicyloyl chloride 25 (164g, 1.0 mole) in dry methylene chloride (400 ml) was added dropwise to a cooled (0-5°C) solution of ethyl 3-morpholino-2-butenoate 94 (200g, 2.2 moles) in one liter of methylene chloride over a period of one hour with stirring. The mixture was stirred at room temperature for 70 hours, then refluxed for 3 hours. The cooled solution was washed successively with one liter each of 1.5N hydrochloric acid (4 times), and 2.5N potassium hydroxide (4 times). The organic phase was then washed with water, dried ($MgSO_4$) and evaporated in vacuum to give 84g, (36%) of a deep red oil which crystallized on standing. A sample was purified by sublimation under high vacuum giving white crystals. (see procedure A for nmr, ir and mass spectra).

analysis: calculated for $C_{13}H_{12}O_4$: C, 67.24; H, 5.21
found: C, 67.45; H, 5.29

2-Methyl-4-oxo-4H-1-benzopyran-3-carboxylic acid 96
(2-Methylchromone-3-carboxylic acid)

The crude ethyl 2-methylchromone-3-carboxylate 27 (84g, 0.362 mole) was taken up in hydrochloric acid (500 ml, 12N) and heated to a gentle reflux for 1.5 hours. This solution was poured onto ice (500g) and extracted into chloroform. The product was then extracted from chloroform into saturated aqueous sodium bicarbonate. Acidification of the bicarbonate solution and filtration

gave 35g (47%) of pale buff crystals. Recrystallization from 2-propanol gave pale yellow crystals.

ms: m/e (relative intensity) 204(12), 189(7), 186(6), 160(29), 121(49), 120(100), 92(48)

nmr δ: 14.33(broad,1H), 8.2-8.1(d,1H), 8.0-7.2(m,3H), 3.05(s,3H) (NMR 29)

Methyl 2-methyl-4-oxo-4H-1-benzopyran-3-carboxylate 27 (Methyl 2-methylchromone-3-carboxylate)

2-Methylchromone carboxylic acid 96 (35.0g, 0.171 mole) anhydrous methanol (500 ml) and 0.5 ml of sulphuric acid (16N) were refluxed for 15 hours. The solvent was removed in vacuum and the residue was dissolved in chloroform, washed with 5% aqueous bicarbonate,dried ($MgSO_4$) and evaporated to give 37.2g (99%) of ester.

ms: m/e (relative intensity) 218(16), 203(53), 160(63), 121(100), 120(79)

nmr δ: 8.35-8.25(d,1H), 7.8-7.28(m,3H), 3.96(s,3H), 2.55(s,3H) (NMR 30)

4-Carbomethoxycyclohexanol 97

Methyl p-hydroxybenzoate 43 (20.0g, 0.131 mole) and 5% rhodium on alumina (400mg) were mixed in 95% ethanol (150 ml) and hydrogenated at 45 psi with stirring at room temperature for 96 hours. The solution was filtered and ethanol was evaporated to a small volume (50 ml). The residue was taken up in ether (300 ml)

and washed with aqueous sodium hydroxide (5%, 2x50 ml), then water, dried ($MgSO_4$) and evaporated in vacuum to give 20.0g (97%) of product.

ir (neat) ν: 1745 cm^{-1}, 3800-3200 cm^{-1}

Methyl 4-oxocyclohexane carboxylate 28

Aqueous chromic acid (20g, CrO_3 in 200 ml of 25% H_2SO_4) was added dropwise to a cooled (0-5°C) solution of 4-carbomethoxy cyclohexanol 97 (36.0g, 0.23 mole) in 250 ml of ether over a period of 40 minutes with stirring. The mixture was stirred at room temperature for 4 hours. The organic layer was separated and the aqueous layer was washed with ether (2x100 ml). The combined organic extracts were washed with aqueous potassium carbonate (5%, 2x200 ml), and then with water, dried ($MgSO_4$) and evaporated to give 16.5% (46%) of product.

ms: m/e (relative intensity) 156(22), 128(17), 125(21), 100(100)

nmr δ: 3.72(s,3H), 3.0-1.9(m,9H) (NMR 31)

ir ($CHCl_3$) ν: 1730 cm^{-1}, 1685 cm^{-1}

2-Methylchromone-3-carboxylic acid chloride 102

The title compound was prepared by refluxing 2-methylchromone -3-carboxylic acid 96 (16g, 0.07 mole) in an excess of thionyl chloride (40 ml) and chloroform (200 ml) for 15 hours. The solution was evaporated in vacuum to dryness to give a yellow brown

crystalline material which was used without further purification.

ms: m/e (relative intensity) 224(3), 222(5), 187(100), 161(54)

nmr δ: 8.3-8.15(d,1H), 7.9-7.2(m,3H), 2.56(s,3H) (NMR 32)

1-Hydroxy-2,3-cyclohexanoxanthene-9-one 99 (Method A)

A solution of the 2-methylchromone-3-carboxylic acid chloride 102 (1.52g, 0.007 mole) in chloroform (20 ml) was added dropwise to cooled ($0^{o}C$) solution of 1-morpholinocyclohex-1-ene (5.84g, 0.035 mole) in chloroform (30 ml) with stirring. The mixture was refluxed for 45 hours. The solution was cooled and washed with water, then dried ($MgSO_4$) and evaporated to yield an oil. Chromatography on silica gel (eluant:benzene /ether 95/5) gave 45mg (3%) of a crystalline early fraction.

(For properties see method C).

Methyl 2-bromomethylchromone-3-carboxylate 104

A mixture of methyl 2-methylchromone-3-carboxylate 27 (5.0g, 0.023 mole), N-bromosuccinimide (NBS) (4.2g, 0.024 mole) and dry carbon tetrachloride (50 ml) were refluxed until most of the methylchromone reacted (followed the reaction on tlc eluant: benzene/15% ether). The R_f value of the bromomethylchromone was greater than that of the methylchromone.

The following compounds were obtained in decreasing order of R_f value.

Compound A (5.6g, 82%) was identified as methyl 2-bromomethylchromone-3-carboxylate.

ms: m/e (relative intensity) 298(50), 296(50), 266(100), 264(100), 217(87), 120(76)

nmr δ: 8.2-8.1(d,1H), 8.0-7.2(m,3H), 4.5(s,2H), 4.0(s,3H) (NMR 33)

Compound B was identical (nmr and mass spectra) to the methyl 2-methylchromone-3-carboxylate.

It was observed that refluxing after most of the methylchromone had reacted resulted in the formation of a mixture containing the dibromo, the monobromo and the non brominated chromone.

Spectral data for Methyl 2,2-dibromomethylchromone-3-carboxylate 104a

ms:m/e (relative intensity) 378(9), 376(19), 374(9), 346(50), 344(100), 342(50), 298(18), 296(18), 216(31), 201(68), 187(41)

nmr δ: 8.27-8.15(d,1H), 8.0-7.27(m,3H), 7.0(s,1H), 4.0(s,3H) (NMR 34)

Attempts to condense methyl 2-bromomethylchromone-3-carboxylate with cyclohexanone

(i) Zinc/I_2/Benzene

A solution of methyl 2-bromomethylchromone-3-carboxylate 104 (0.50g, 0.0016 mole), and cyclohexanone (2g, 0.02 mole) in 20 ml of dry benzene was added dropwise to granulated zinc (0.5g), and

iodine (small crystal), in 20 ml of benzene with stirring under nitrogen atmosphere. The mixture was refluxed for 2 hours. The solution was cooled, benzene was decanted and 10% sulphuric acid was added to the solution and stirred for 10 minutes at room temperature. The organic layer was separated, washed with water, dried ($MgSO_4$) and evaporated in vacuum to give an oil. Chromatography on silica gel (eluant: 15% ether/benzene) gave two compounds. Compounds A and B were obtained in decreasing order of R_f value.

Compound A was identified as cyclohexanone.

Compound B, a crystalline material (0.3g), was identical (nmr and mass spectra) to methyl 2-methylchromone-3-carboxylate.

(ii) $P(C_6H_5)_3/NaH/CH_2Cl_2$

To a well stirred solution of methyl 2-bromomethylchromone--3-carboxylate 104 (0.50g, 0.0016 mole) in 50 ml of dry methylene chloride under nitrogen atmosphere, was added triphenylphosphine (0.5g). The mixture was refluxed for 2 hours, cooled and sodium hydride (50mg) was added followed by cyclohexanone 0.5 ml. The solution was then mildly refluxed for two hours, cooled, washed with hydrochloric acid (1.5N), then water, dried ($MgSO_4$) and evaporated in vacuum to give an oil. Excess cyclohexanone was removed at high vacuum to give a crystalline material. The recovered material was identical (nmr and mass spectra) to methyl 2-methylchromone-3-carboxylate.

Spirolactone 105

To a solution of methyl 2-methylchromone-3-carboxylate 27 (0.50g, 0.0017 mole) and cyclohexanone (0.83g, 0.0085 mole) in dimethoxyethane (DME) (5 ml) was added a solution of potassium t-butoxide in t-butyl alcohol (15g of 0.11M). The solution was stirred for one minute at room temperature, poured into 200 ml of 2N HCl and extracted into chloroform. The combined extracts were dried ($MgSO_4$) and evaporated in vacuum to yield an orange solid 0.63g (96%). Recrystallization from acetone gave white crystals.

ms: m/e (relative intensity) 284(20), 261(28), 228(57), 213(48), 204(48), 200(100)

nmr δ: 8.40-8.15(d,1H), 7.85-7.25(m,3H), 3.08(s,2H), 2.2-1.1(m,10H) (NMR 35)

ir ($CHCl_3$) ν: 1740 cm^{-1}, 1655 cm^{-1} (IR 15)

mp: 164-165.5°C

analysis: calculated for $C_{17}H_{16}O_4$: C, 71.81; H, 5.67

found: C, 72.14; H, 5.89

Cyclohexylidenechromone ester 107

(Methyl 2-cyclohexylidenemethylchromone-3-carboxylate)

(i) Diazomethane

To a solution of the spirolactone 105 (0.50g, 0.0017 mole) in methanol (10 ml) was added an excess of diazomethane in ether

(75 ml). The mixture was stirred at room temperature for 48 hours, washed with dilute HCl, dried ($MgSO_4$) and evaporated to give a yellow oil (0.58g). Chromatography on silica gel (eluant: benzene/ether 60/40) gave pale yellow crystals (0.27g, 52%). Recrystallization from 2-propanol gave white crystals.

ms: m/e (relative intensity) 298(45), 266(71), 255(45), 251(49),238(57), 225(67), 121(100)

nmr δ: 8.32-8.15(d,1H), 7.9-7.2(m,3H), 6.13(s,1H), 3.93(s,3H), 2.9-2.5(m,2H), 2.45-2.1(m,2H), 2.0-1.3(m,6H) (NMR 36)

ir ($CHCl_3$) ν: 1735 cm^{-1}, 1640 cm^{-1}

(ii) K_2CO_3/CH_3I/acetone

To a solution of the spirolactone 105 (0.124g, 0.0004 mole) in dry acetone (10 ml), anhydrous potassium carbonate (0.1g) and methyl iodide (0.226g, 0.0016 mole) were added sequentially. The mixture was stirred at room temperature for 72 hours then poured into dilute hydrochloric acid and extracted with chloroform. The combined extracts were washed with water, dried ($MgSO_4$) and evaporated in vacuum to give yellow crystalline material. The spectral data of the compound obtained were identical to those for cyclohexylidenechromone ester 107.

1-Hydroxy-2,3-cyclohexanoxanthene-9-one 99 (Method B)

To a solution of the spirolactone 105 (1.48g, 0.0052 mole) in toluene (100 ml), was added phosphorous pentoxide (20g). The

mixture was refluxed with stirring for 3 hours. The toluene was decanted and a slurry of 2N hydrochloric acid in crushed ice was added to the residue. The toluene was returned back to the flask and the mixture was gently heated without a reflux condensor until all of the toluene had distilled off. The remaining aqueous solution was cooled and extracted with chloroform, the combined organic extracts were washed with water, dried ($MgSO_4$) and evaporated to give crystalline material. Chromatography on silica gel (eluant:benzene) gave (0.533g, 38%) of crystalline product. Recrystallization from ethanol gave yellow crystals. (For properties see method C).

1-Hydroxy-2,3-cyclohexanoxanthene-9-one 99 (Method C)

The spirolactone 105 (80mg, 0.003 mole) in trifluoromethane sulfonic acid (4 ml) was heated at 100-110°C (oil bath temperature) with stirring for 42 hours. The mixture was cooled and poured into cold water (40 ml) and extracted with chloroform. The organic layer was washed with water, dried ($MgSO_4$) and evaporated to give crystalline material. Chromatography on a silica gel column (eluant:benzene) gave (32mg, 43%) yellow crystals.

ms: m/e (relative intensity) 266(100), 265(38), 251(55), 238(37)

nmr δ: 12.63(s,1H), 8.4-8.2(d,1H), 7.9-7.15(m,3H), 6.65(s,1H), 3.0-2.5(m,4H), 2.0-1.55(m,4H) (NMR 37)

ir ($CHCl_3$) ν: 1650 cm^{-1} (IR 16)

mp: 199.5-201.5°C

analysis: calculated for $C_{17}H_{14}O_3$: C, 76.67; H, 5.30

found: C, 76.73; H, 5.45

1-Methoxy-2,3-cyclohexanoxanthene-9-one 109

A mixture of 1-hydroxy-2,3-cyclohexanoxanthene-9-one 99 (0.50g, 0.0018 mole), anhydrous potassium carbonate (0.5g) and methyl iodide (0.7g) in dry acetone (30 ml) was refluxed for 18 hours. The solution was filtered and evaporated to give (0.51g, 97%) of product. Recrystallization from isopropyl alcohol gave off-white crystals.

ms: m/e (relative intensity) 280(100), 265(71), 236(71), 139(90)

nmr δ: 8.4-8.2(d,1H), 8.0-7.1(m,3H), 6.95(s,1H), 3.93(s,3H), 3.0-2.65(m,4H), 1.95-1.65(m,4H) (NMR 38)

ir ($CHCl_3$) ν: 1665 cm^{-1}

mp: 148-149°C

analysis: calculated for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75

found: C, 76.88; H, 5.75

Carbomethoxy spirolactone 110

To a solution of methyl 2-methylchromone-3-carboxylate 27 (1.09g, 0.005 mole) and methyl-4-oxocyclohexane carboxylate 28 (3.44g, 0.02 mole) in dimethoxyethane (7 ml), was added 0.1M

potassium t-butoxide in t-butyl alcohol (55g). The mixture was stirred for one minute at room temperature, poured into 2N HCl (300 ml) and extracted into chloroform (3x50 ml). The combined organic extracts were washed with water, dried ($MgSO_4$) and evaporated to give an oily residue which contained an excess of methyl 4-oxocyclohexanecarboxylate 28. The product crystallized out of the oil on standing in a refrigerator for 12 hours. The crystals were filtered and washed with hexane under suction. Recrystallization from CCl_4/isopropyl alcohol/hexane gave brown crystals (0.81g, 47%). Further recrystallization from isopropyl alcohol gave white crystals.

ms: m/e (relative intensity) 324(15), 311(7), 265(32), 241(100), 186(62)

nmr δ: 8.36-8.25(d,1H), 7.92-7.33(m,3H), 3.7(s,3H), 3.05(s,2H), 2.85-1.55(m,9H) (NMR 39)

ir ($CHCl_3$) ν: 1742 cm^{-1}, 1665 cm^{-1} (IR 17)

mp: 153.5-154.5°C

analysis: calculated for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30
found: 66.44; H, 5.57

Carbomethoxy cyclohexylidenechromone ester 111

To a solution of carbomethoxy spirolactone 110 (50mg, 0.15 m mole) in methanol (15 ml) was added an excess of diazomethane in ether (30 ml). The mixture was stirred at room temperature for 4 hours, and evaporated in vacuum to give a yellow oil (0.5g).

Chromatography on silica gel (eluant:benzene/hexane 3/1) gave yellow crystals (0.31g, 60%).

ms: m/e 356(m^+)

nmr δ: 8.3-8.1(d,1H), 7.9-7.23(m,3H), 6.16(s,1H), 3.92(s,3H), 3.7(s,3H), 2.85-1.56(m,9H) (NMR 40)

ir ($CHCl_3$) ν: 1725 cm^{-1}, 1640 cm^{-1} (IR 18)

Carbomethoxy hydroxyxanthocycline 22

To a solution of the carbomethoxy spirolactone 110 (1.17g, 0.0034 mole) in toluene (100 ml) was added phosphorous pentoxide (10g). The mixture was heated with stirring at 130°C (oil bath temperature) for 2 hours. The toluene was decanted and a slurry of 2N hydrochloric acid in crushed ice was added to the residue. The toluene was returned to the flask and the mixture was gently heated without a reflux condensor until all of the toluene had distilled off. The aqueous solution was cooled and extracted with chloroform, the combined organic extracts were washed with aqueous bicarbonate (5%), then water, dried ($MgSO_4$) and evaporated to yield 0.565g of material. The crude product was chromatographed on silica gel (eluant:benzene/ether 60/40) to give 0.277g of yellow crystals. Recrystallization, with some difficulty, from ethanol gave pale yellow crystals.

ms: m/e (relative intensity) 324(55), 265(100), 249(14), 238(24)

nmr δ: 12.97(s,1H), 8.34-8.21(d,1H), 7.9-7.33(m,3H), 6.7(s,1H), 3.85(s,3H), 3.1-1.50(m,7H) (NMR 41)

ir ($CHCl_3$) ν: 1730 cm^{-1}, 1640 cm^{-1} (IR 19)

mp: 160-164°C

Carbomethoxy methoxyxanthocycline 22a

To a solution of the carbomethoxy hydroxyxanthocycline 22 (100mg, 0.3 m mole) in dry acetone (25 ml) was added potassium carbonate (400mg) followed by methyl iodide (2 ml). The mixture was refluxed for 48 hours. The solution was cooled, filtered and the acetone evaporated in vacuum. The residue was taken up in chloroform, washed with 1N hydrochloric acid, then water, dried ($MgSO_4$) and evaporated to yield 90mg (86%) of yellow crystals. Recrystallization was achieved from isopropyl alcohol/cyclohexanae.

ms: m/e (relative intensity) 388(88), 323(100), 309(70), 279(82)

nmr δ: 8.4-8.2(d,1H), 7.9-7.3(m,3H), 7.05(s,1H), 3.96(s,3H), 3.77(s,3H), 3.1-1.95(m,7H) (NMR 42)

ir ($CHCl_3$) ν: 1740 cm^{-1}, 1670 cm^{-1}

mp: 155-156°C

analysis: calculated for $C_{20}H_{18}O_5$: C, 71.01; H, 5.32

found: C, 70.84; H, 5.64

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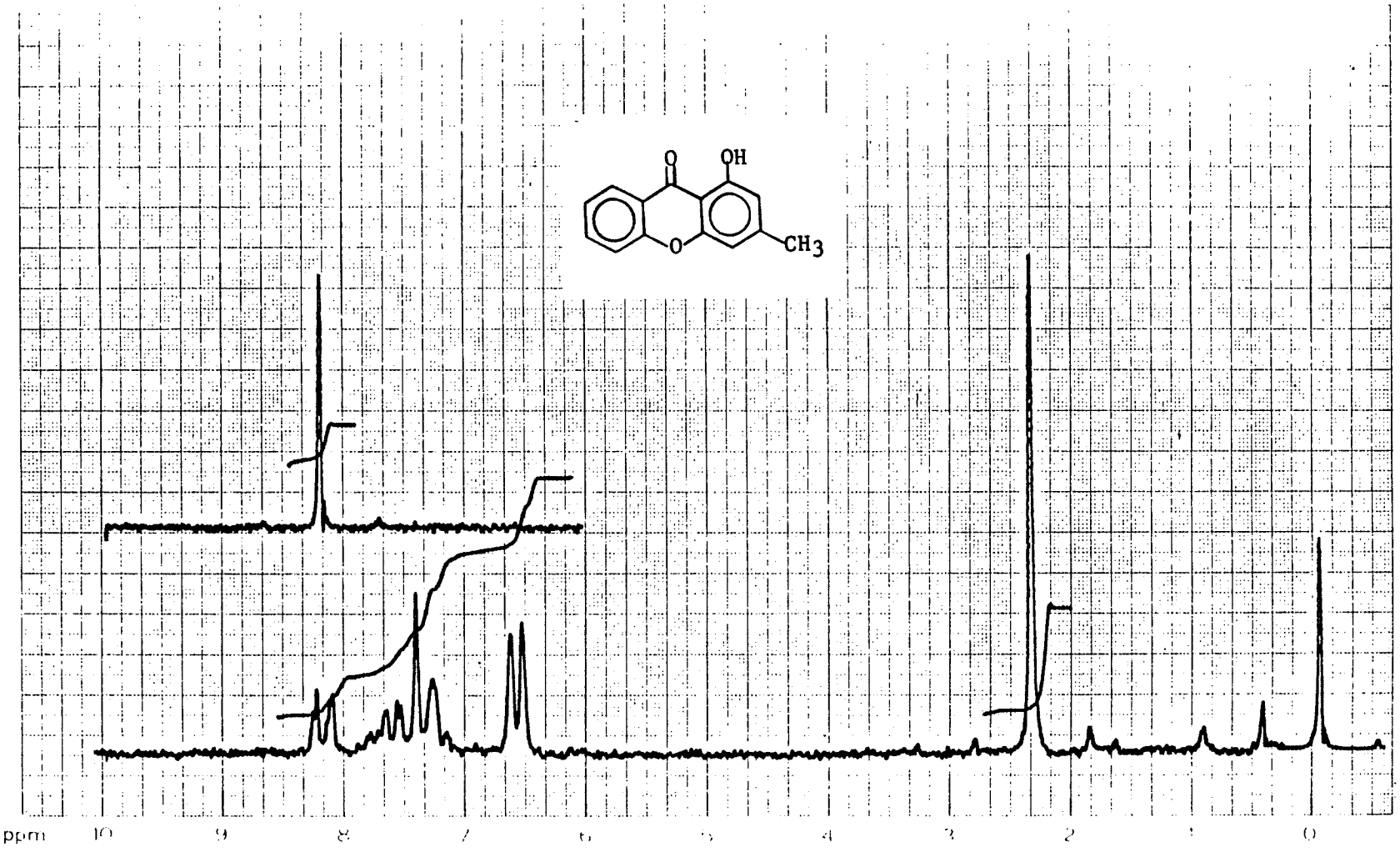
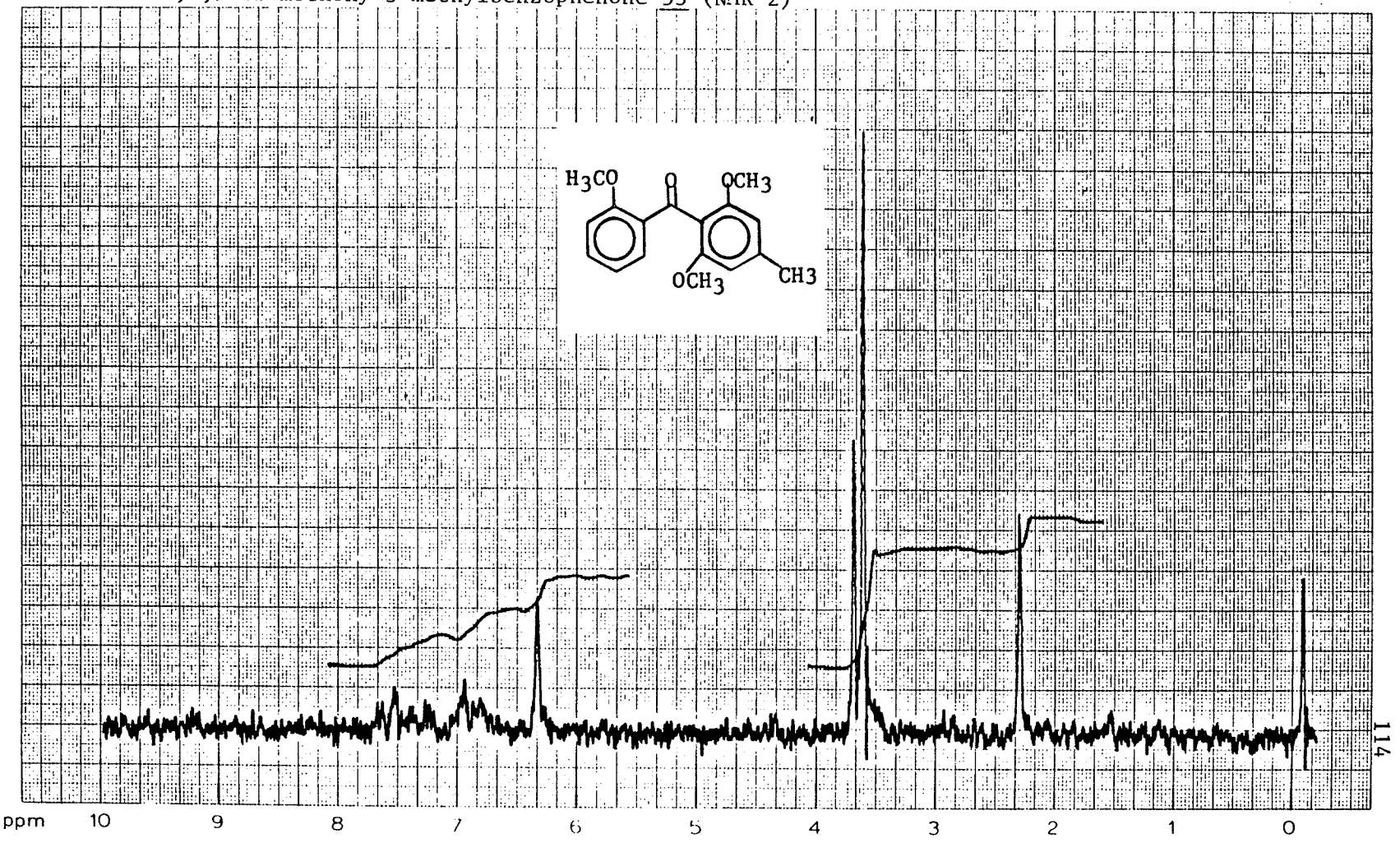
1-Hydroxy-3-methylxanthone 23 (NMR 1)



2',2,5 Trimethoxy-3-methylbenzophenone 53 (NMR 2)



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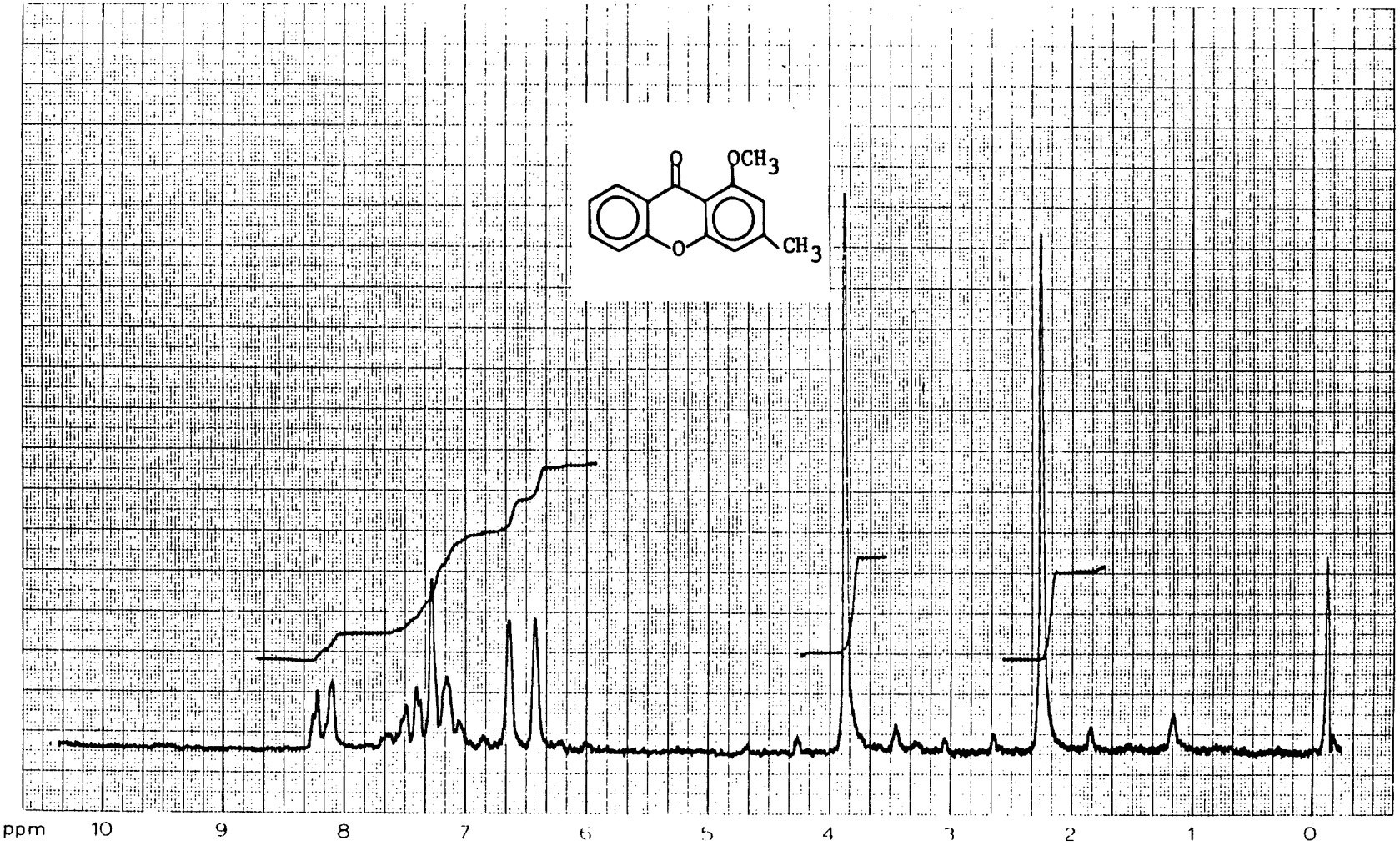
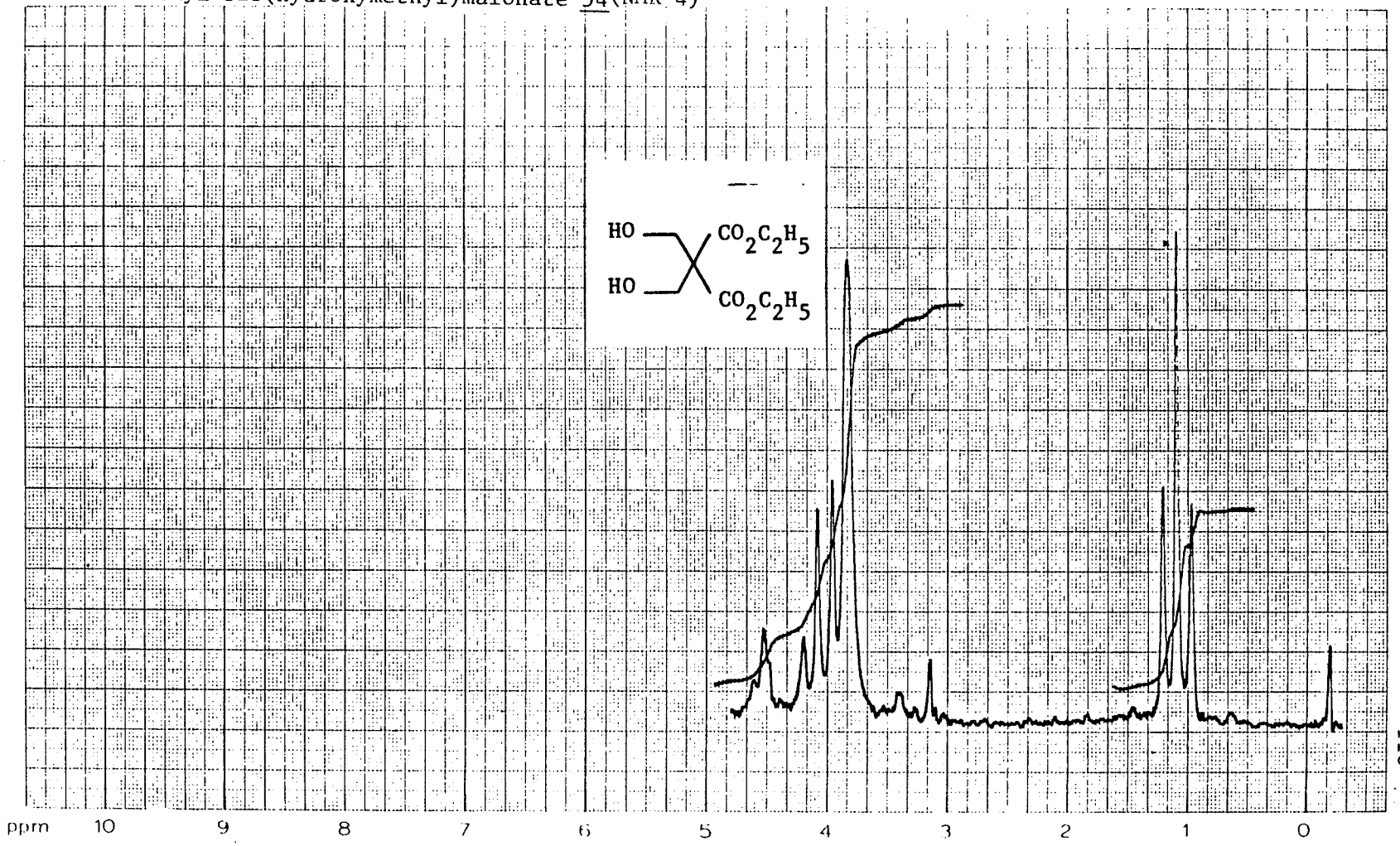
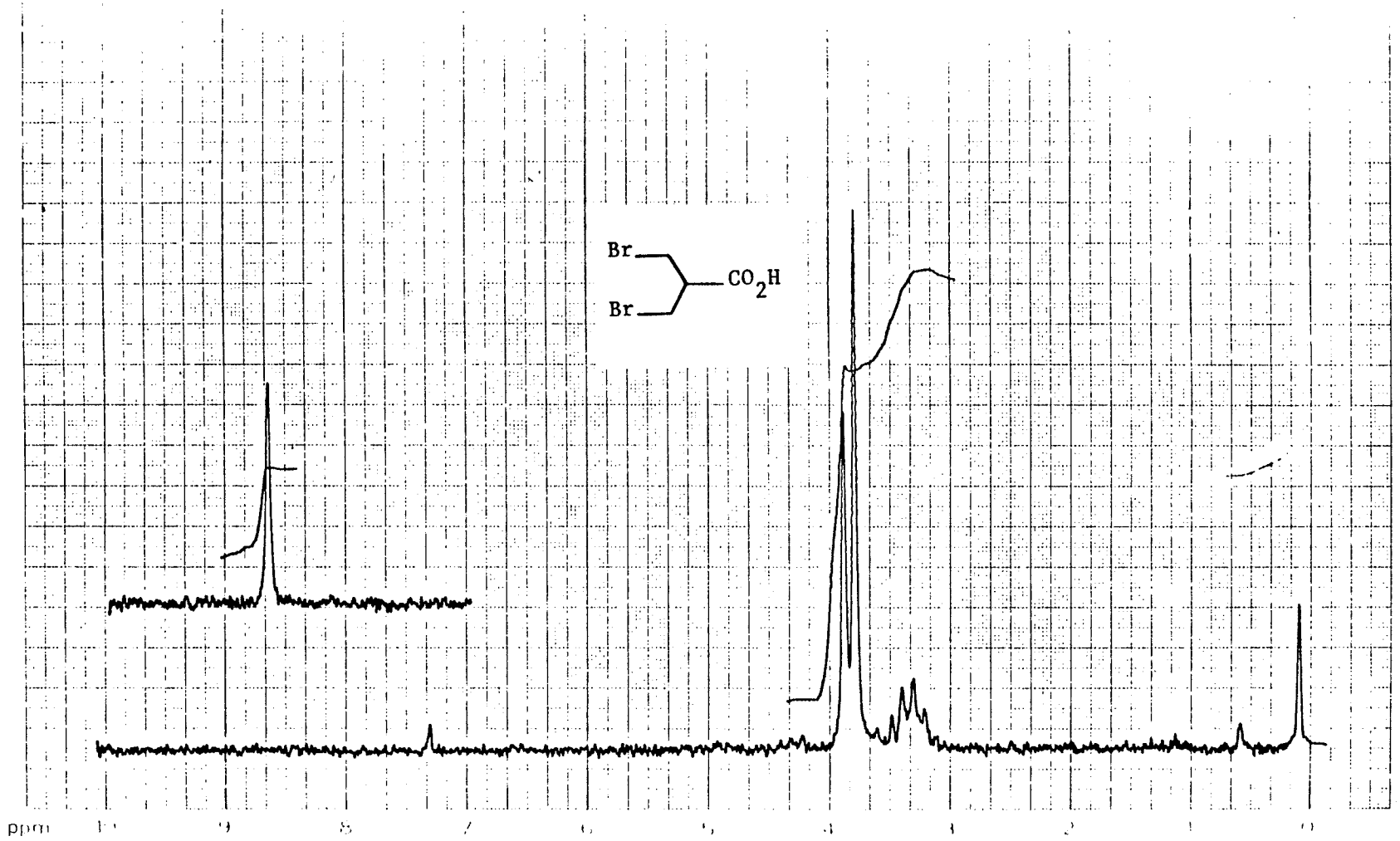


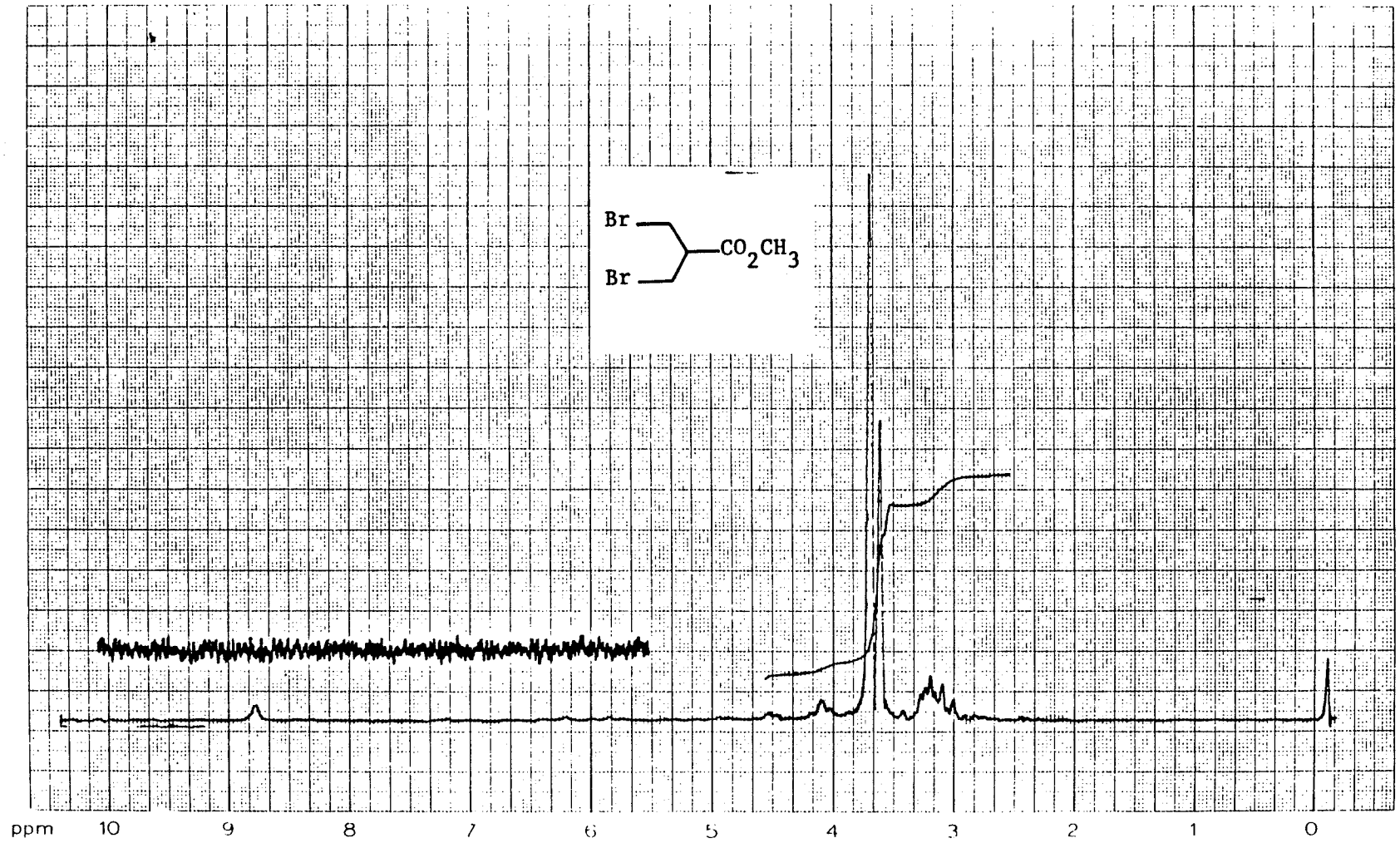
Diethyl bis(hydroxymethyl)malonate 54(NMR 4)



β,β-Dibromoisobutyric acid 55 (NMR 5)



Methyl(β,β-dibromo)isobutyrate 24 (NMR 6)



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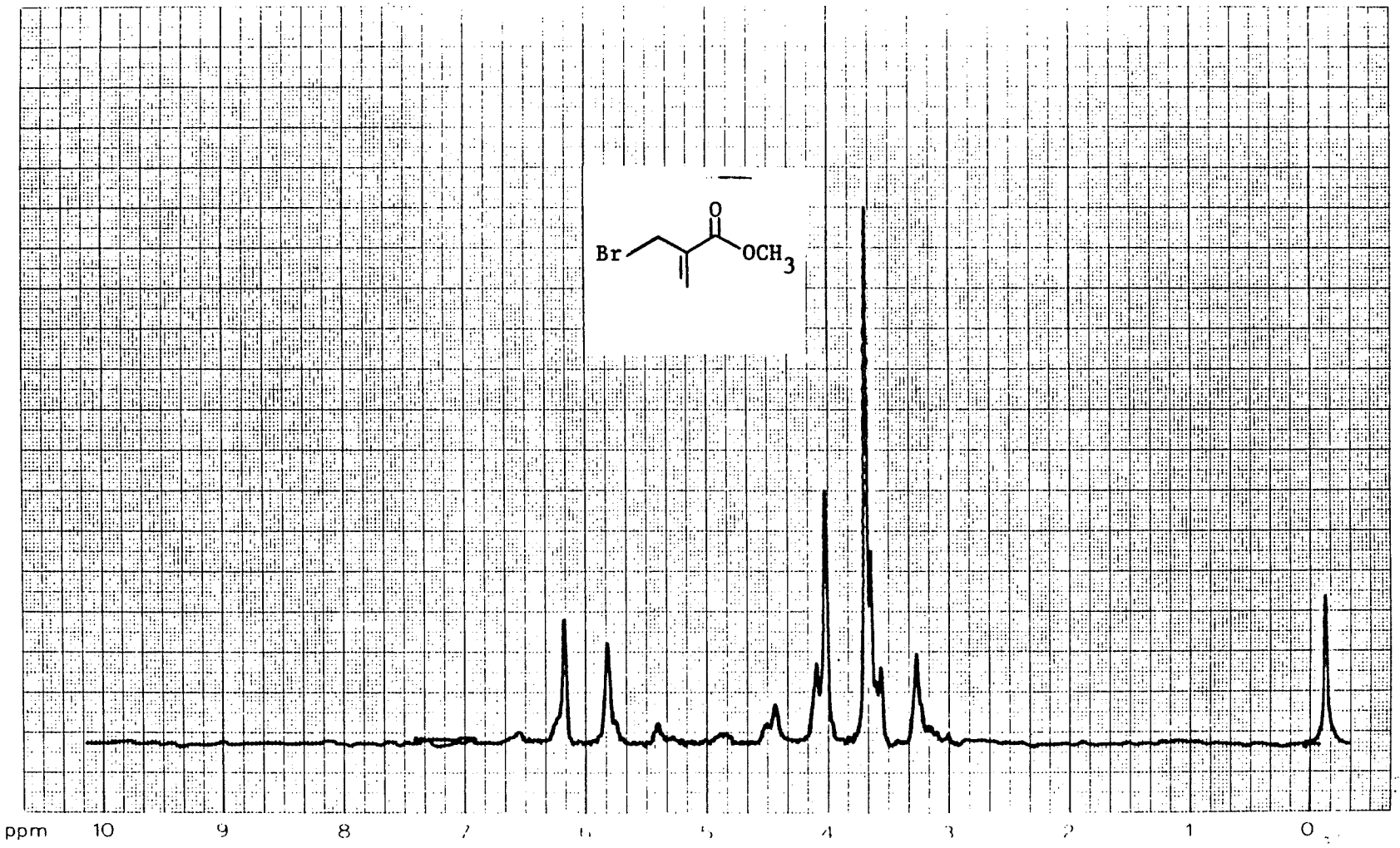
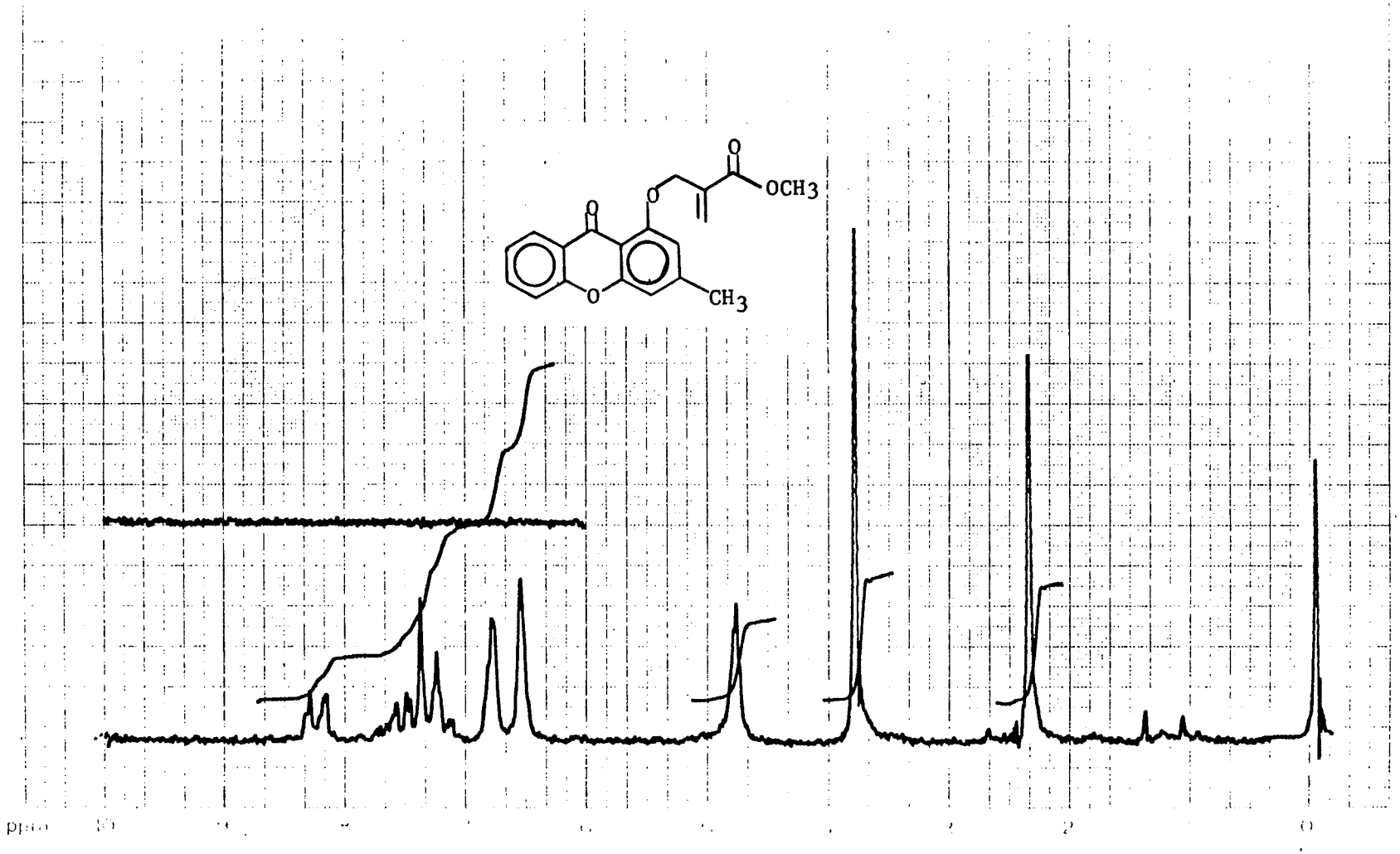
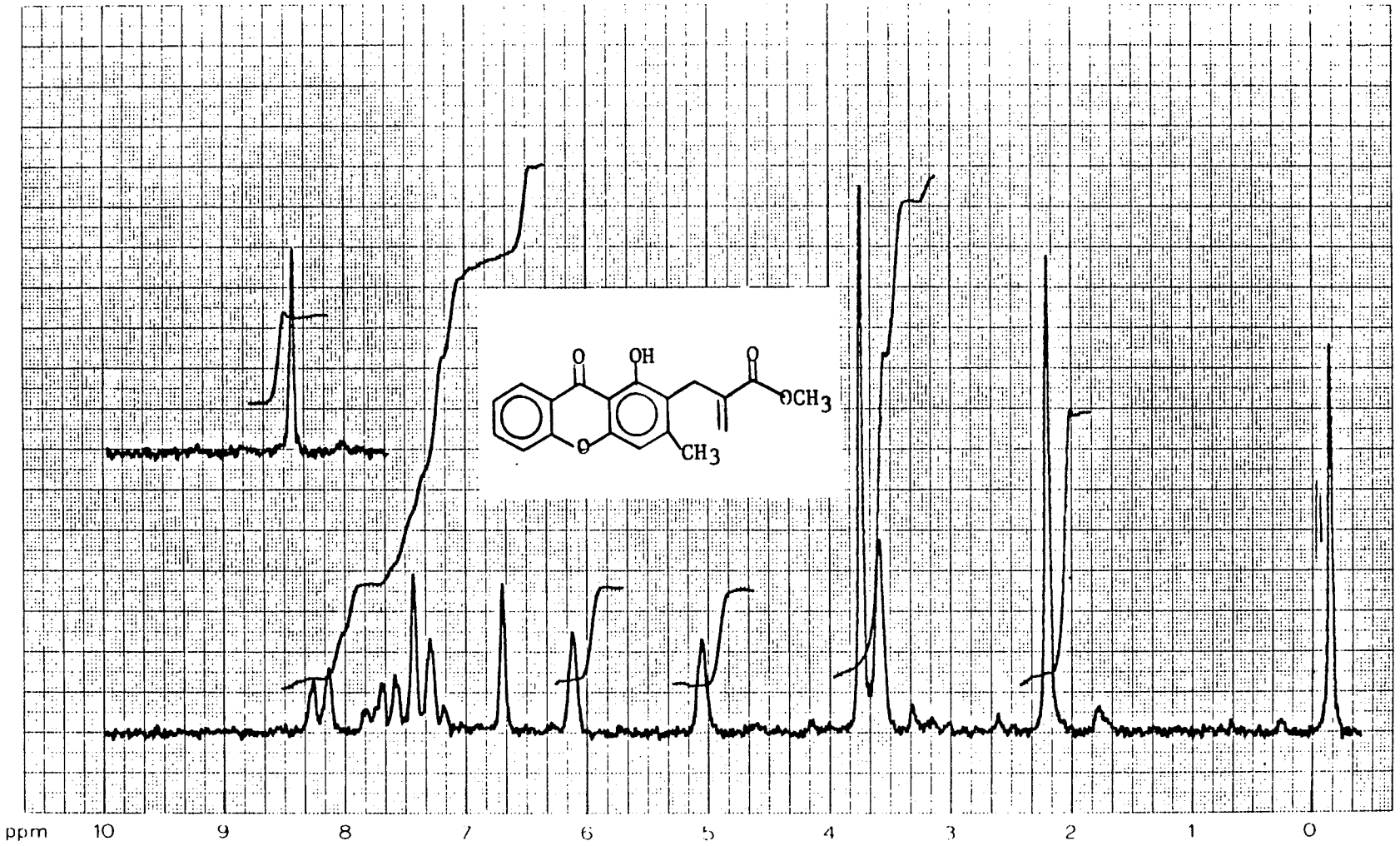


1-(2-Carbomethoxyalloxy)-3-methyl-9H-xanthene-9-one 57 (NMR 8)



1-Hydroxy-2-C-allylic-3-methylxanthone 58 (NMR 9)



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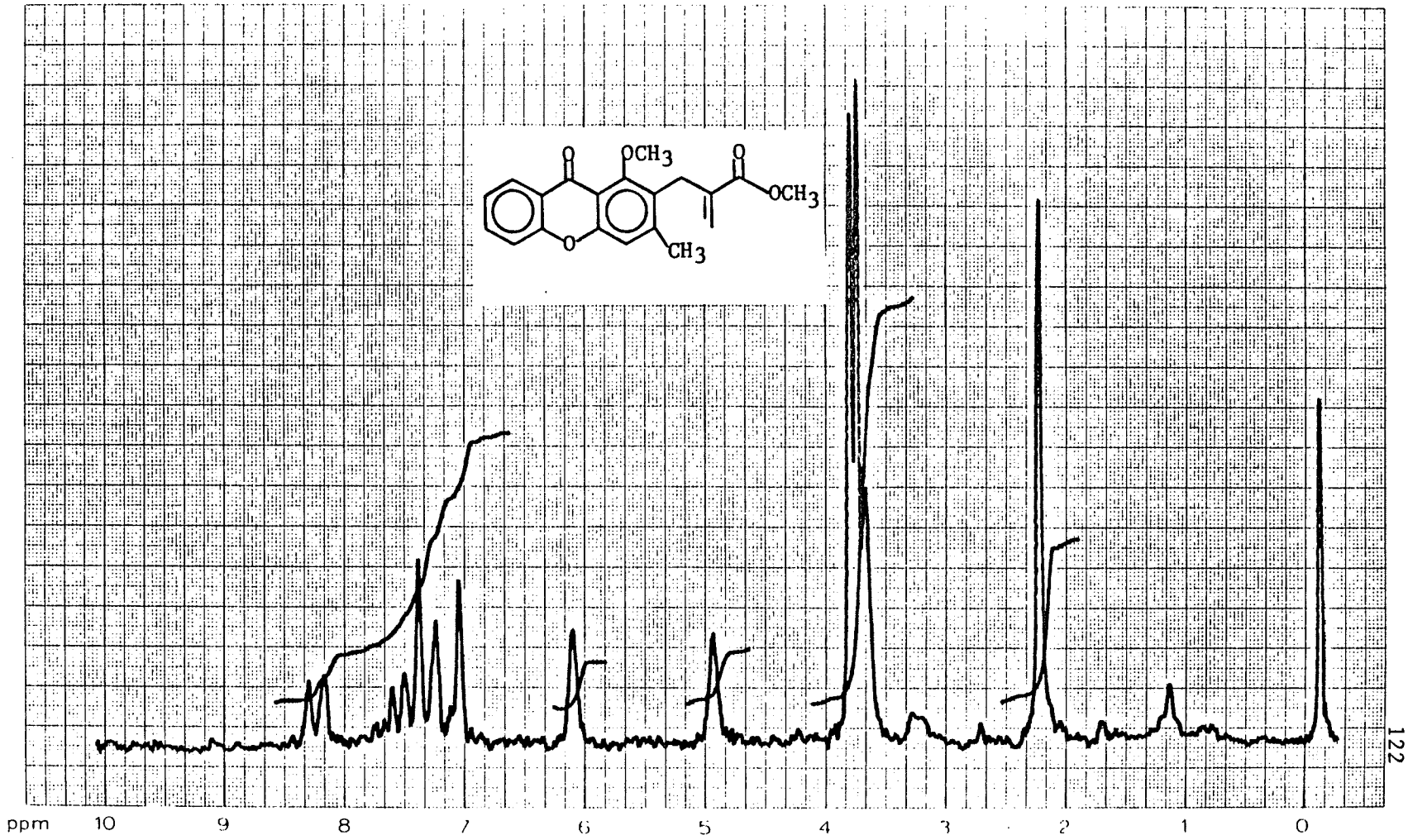
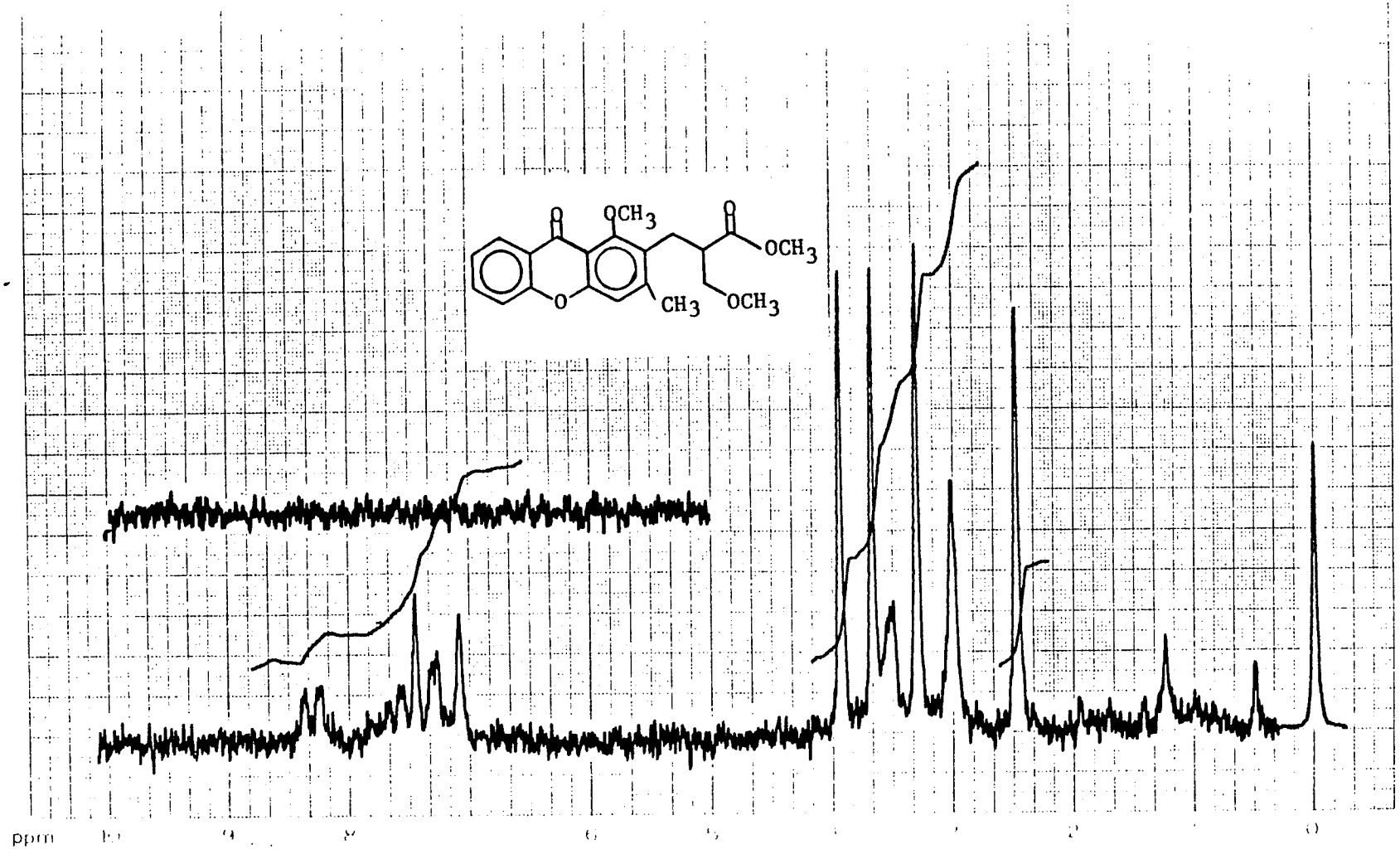
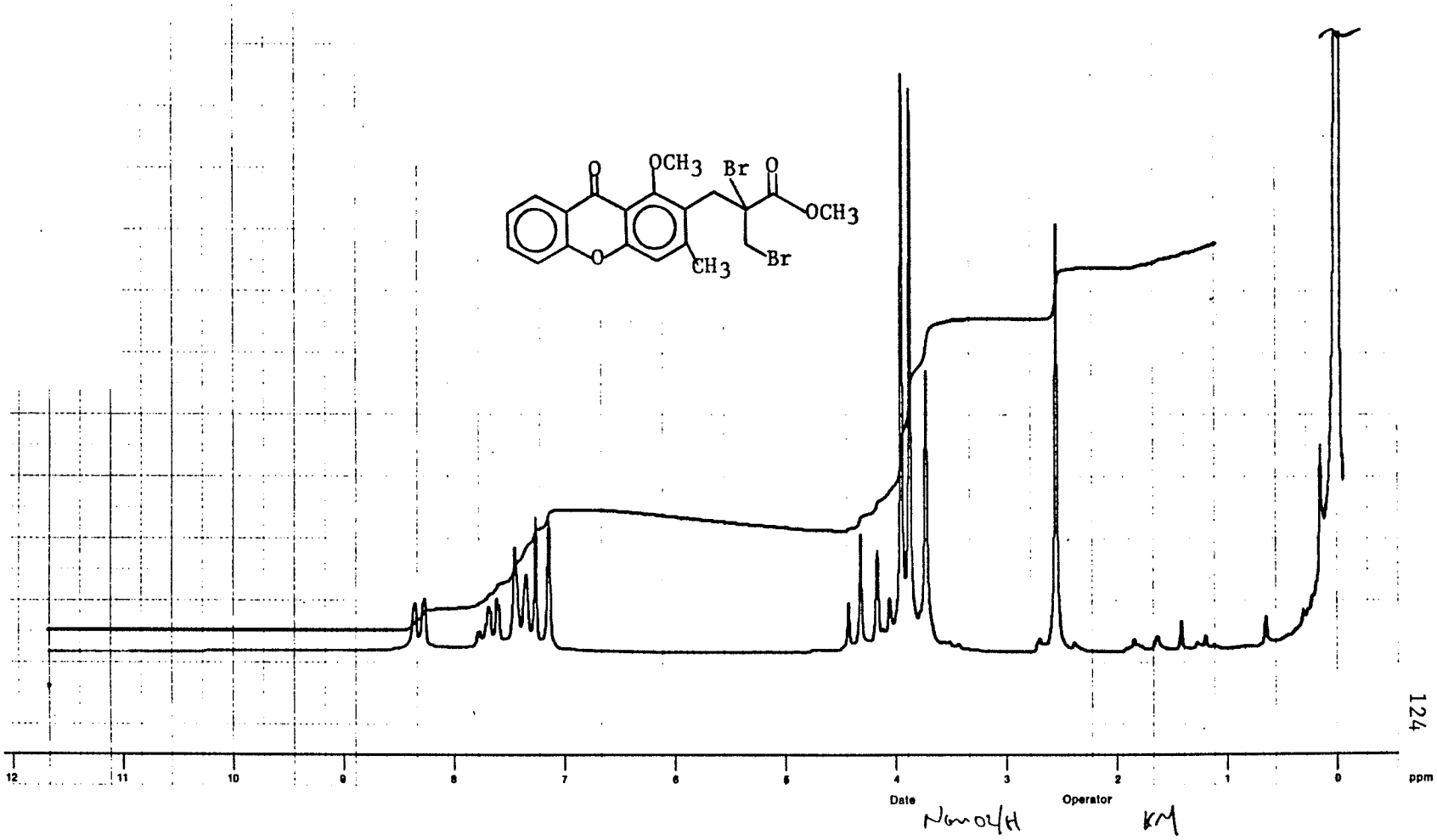


1-Methoxy-2-(3-methoxy-2-carbomethoxypropyl)-3-methyl-9H-xanthene-9-one 61 (NMR 11)



1-Methoxy-2-(2,3-dibromo-2-carbomethoxypropyl)-3-methyl-9H-xanthene-9-one 64 (NMR 12)



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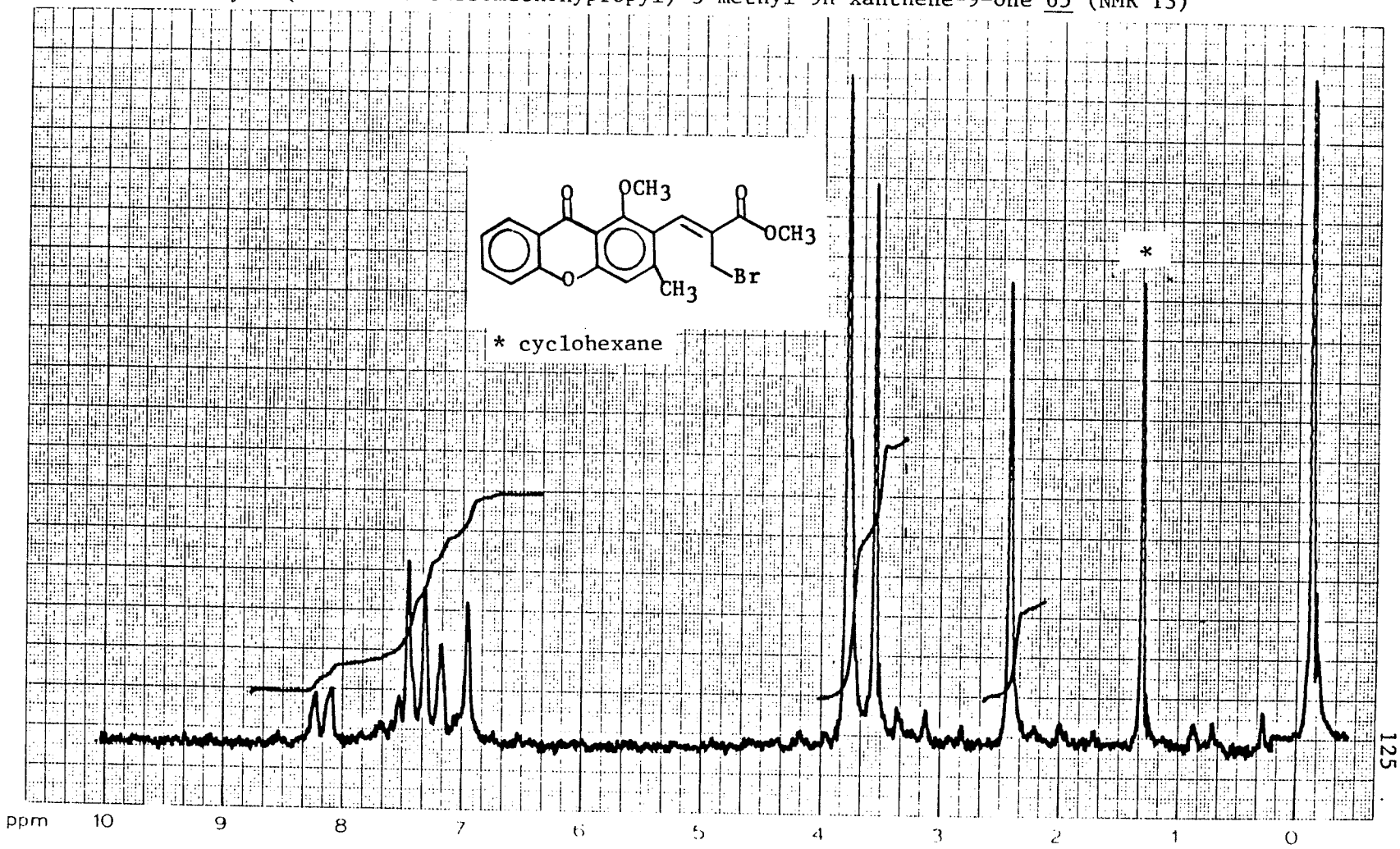
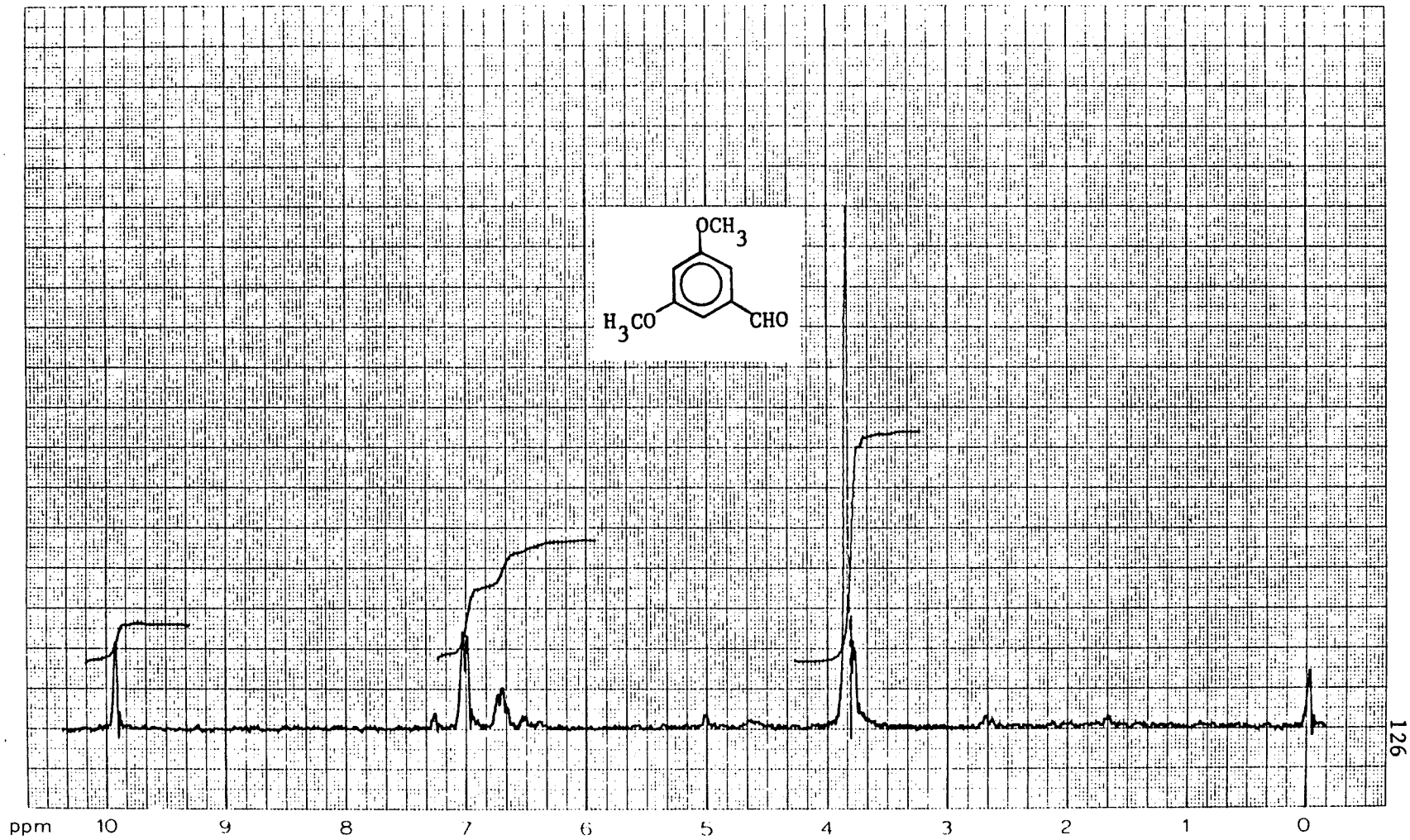
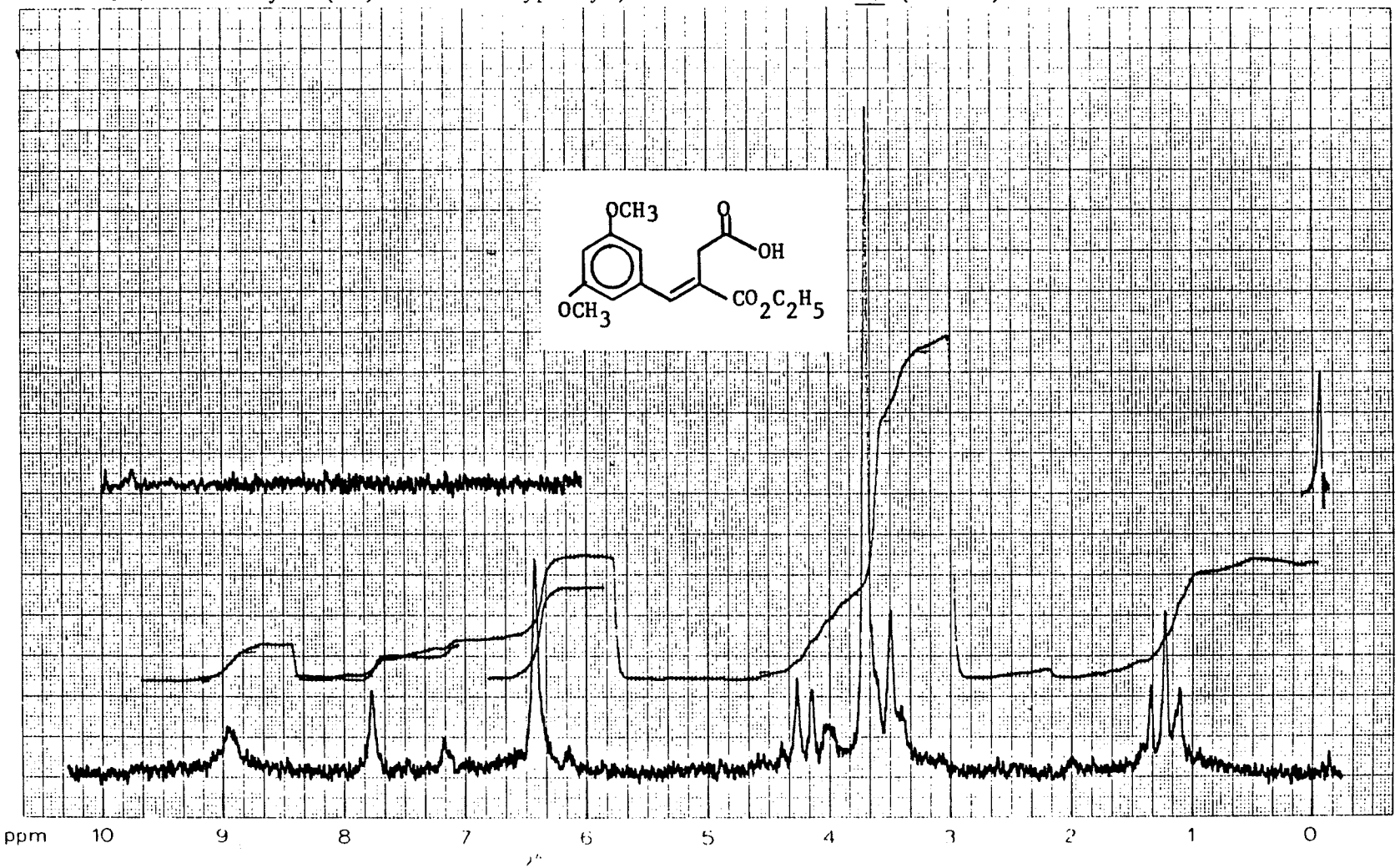


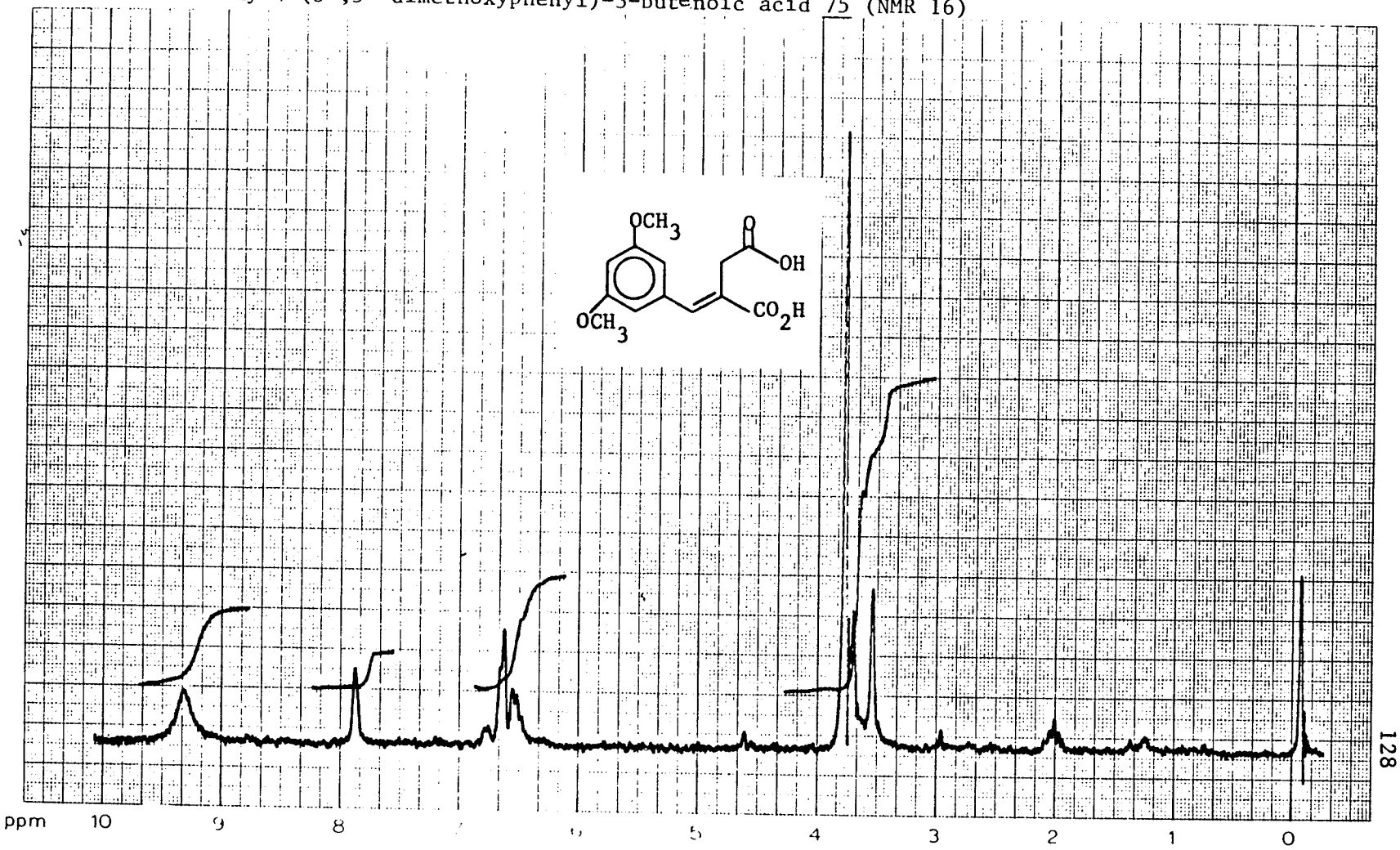
3,5-Dimethoxybenzaldehyde 35 (NMR 14)



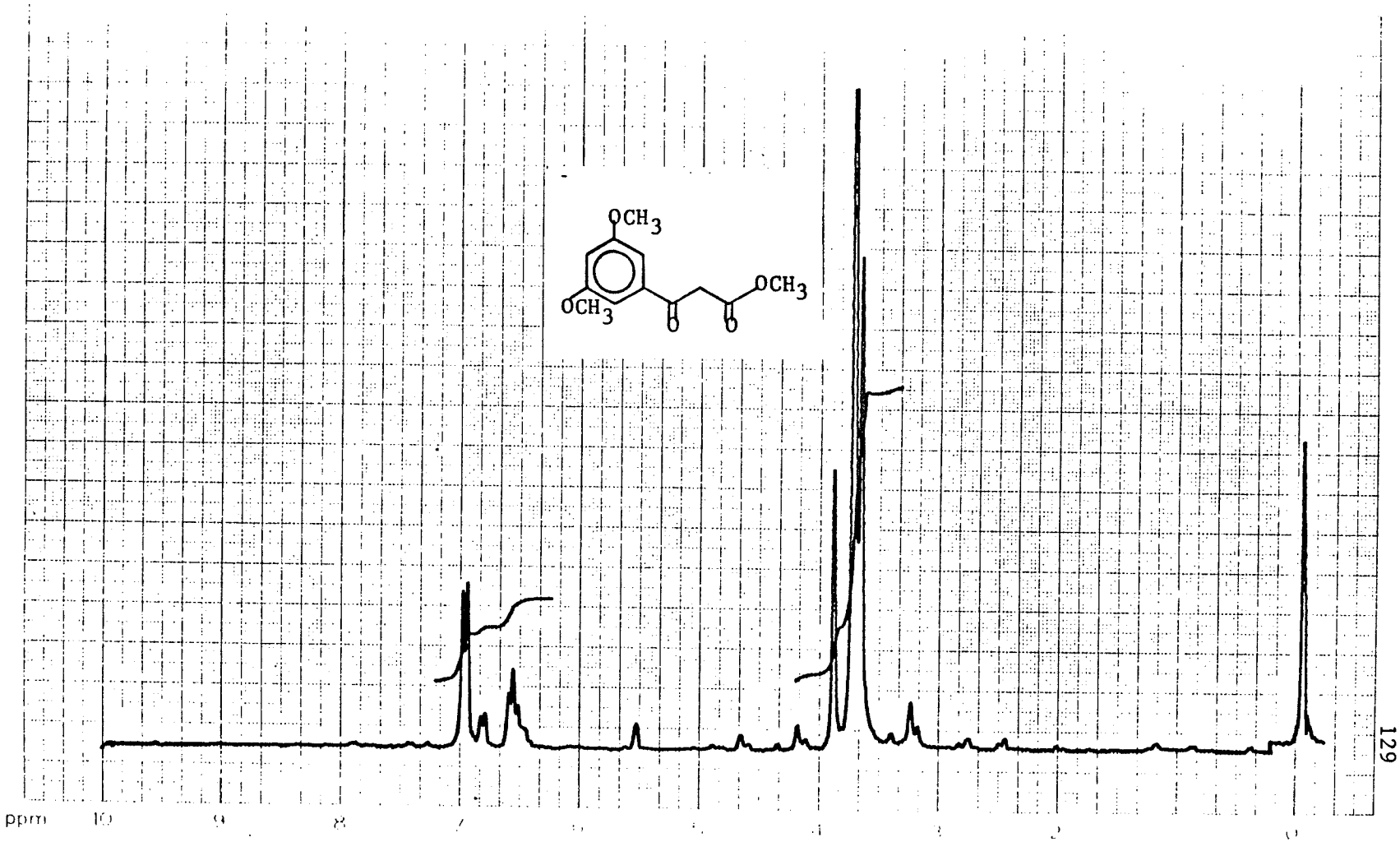
3-Carboethoxy-4-(3',5'-dimethoxyphenyl)-3-butenoic acid 73 (NMR 15)



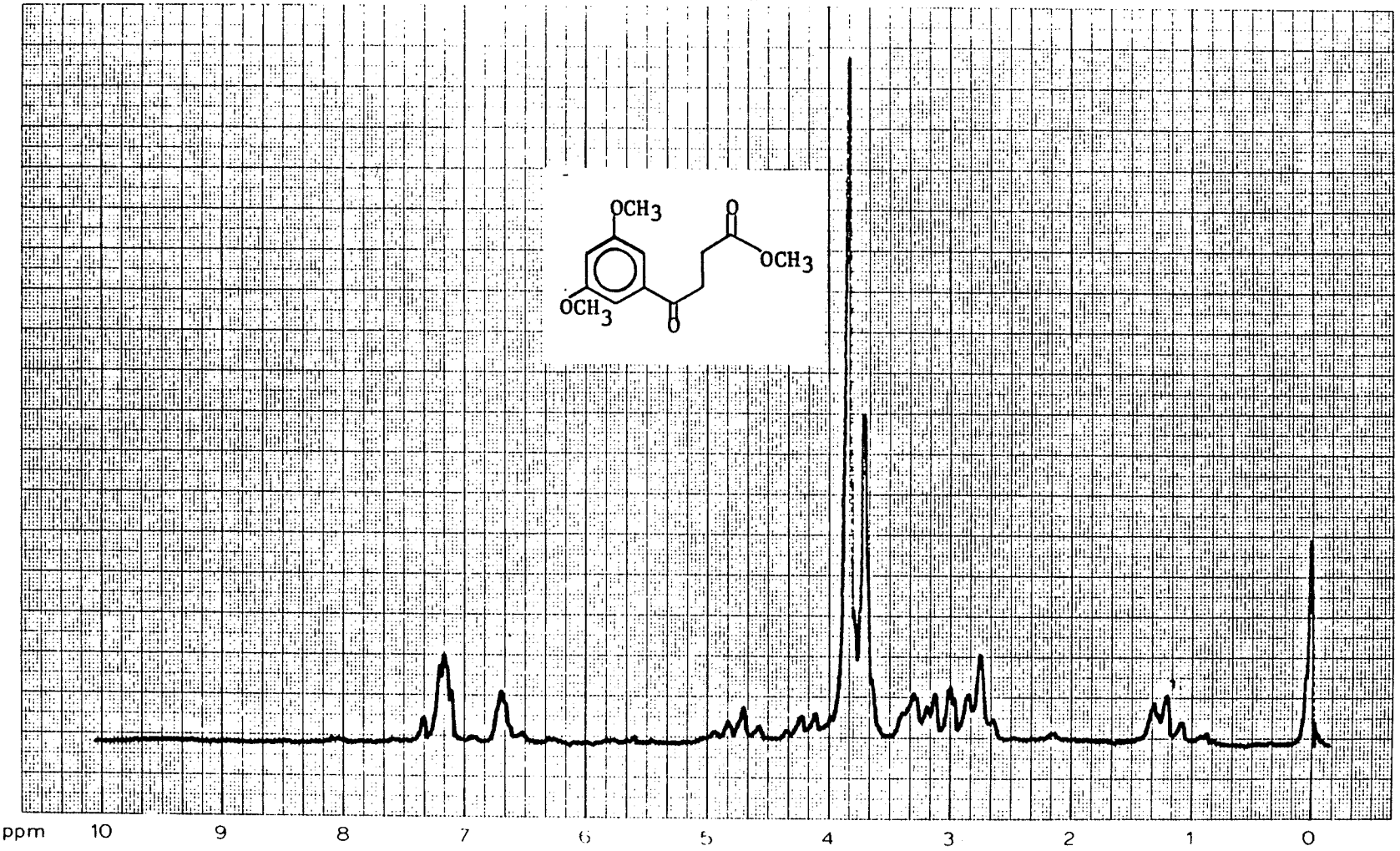
3-Carboxy-4-(3',5'-dimethoxyphenyl)-3-butenoic acid 75 (NMR 16)



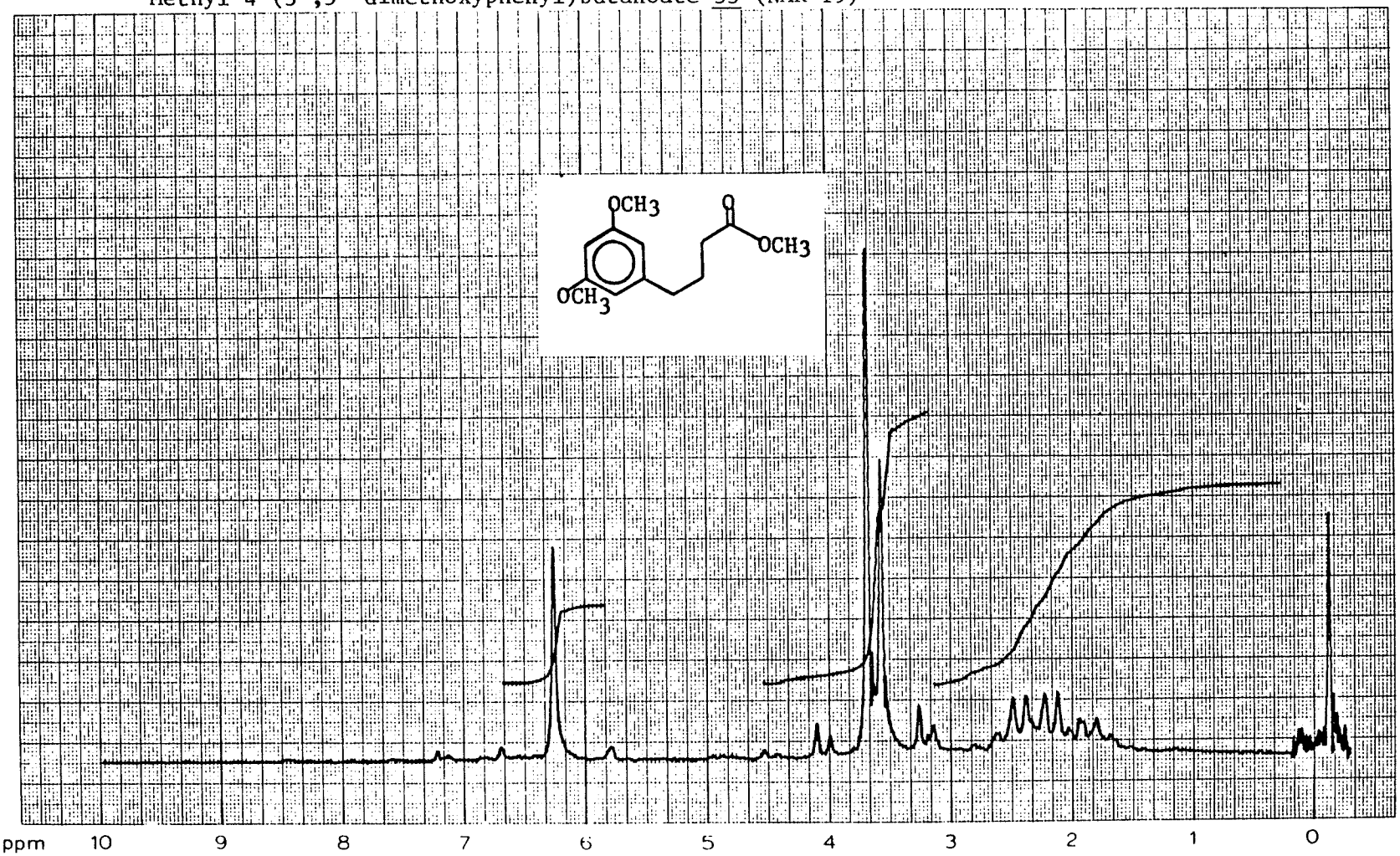
Methyl(3,5-Dimethoxybenzoyl)acetate 38 (NMR 17)



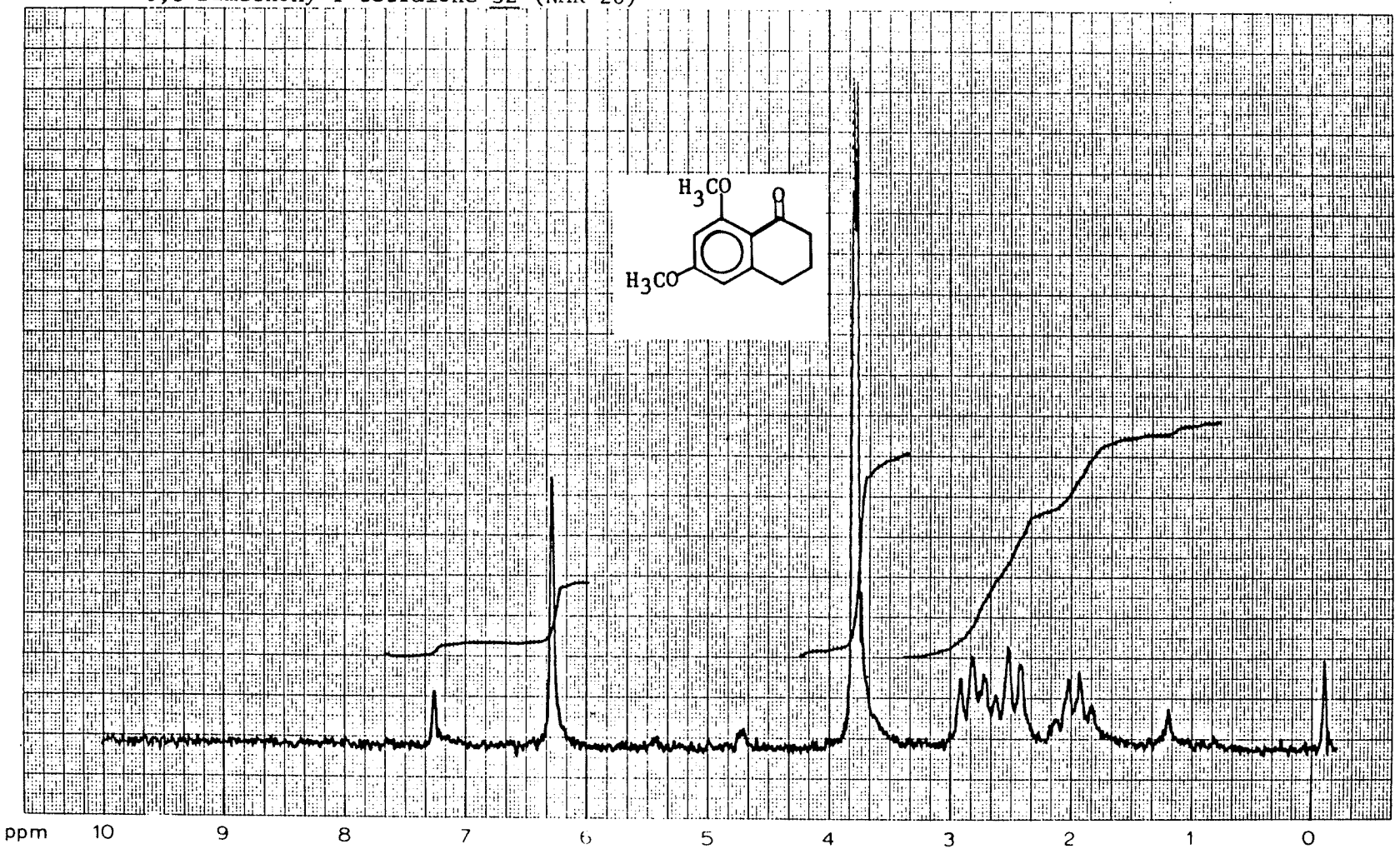
Methyl 3-(3',5'-dimethoxybenzoyl)propionate 37 (NMR 18)



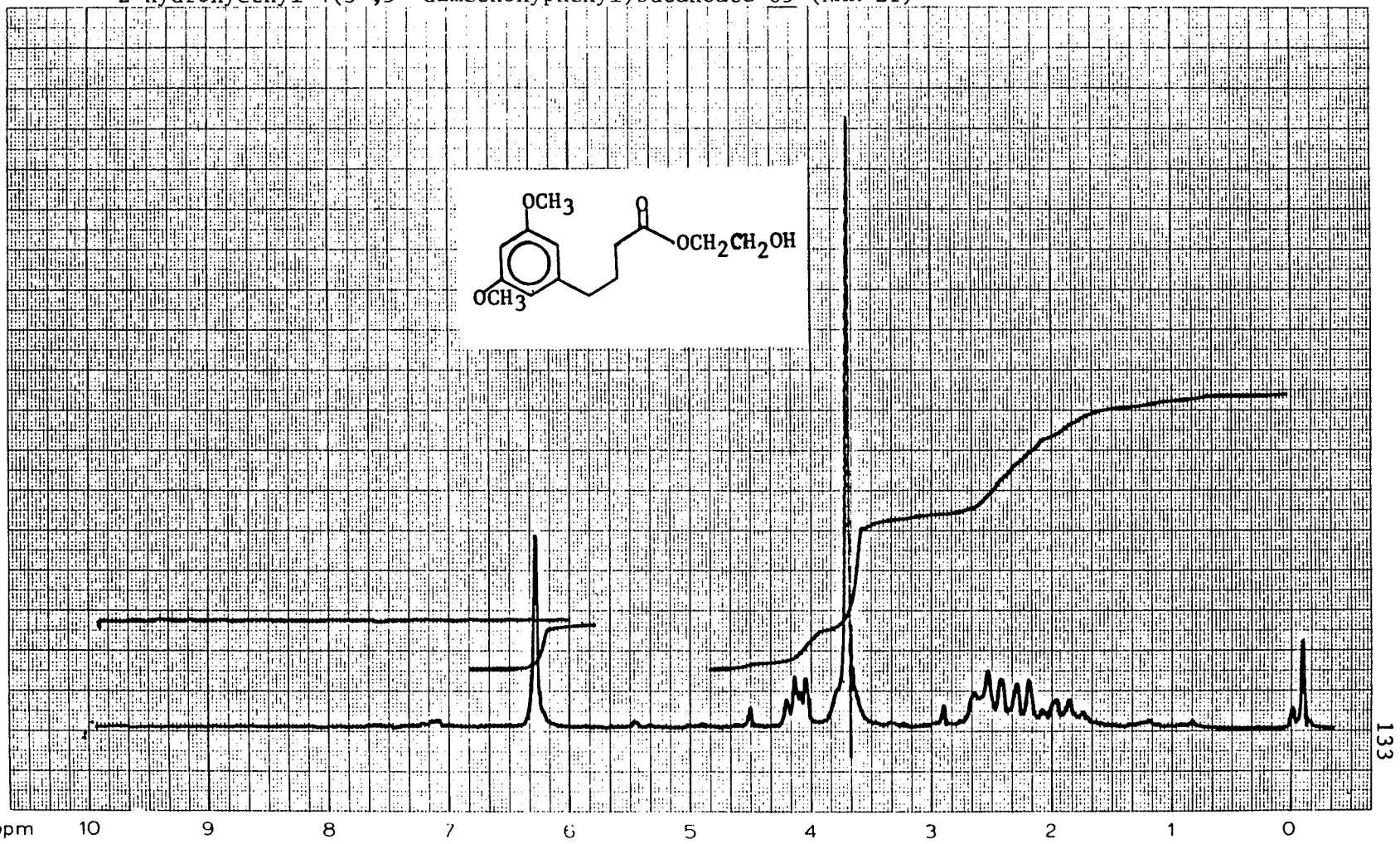
Methyl 4-(3',5'-dimethoxyphenyl)butanoate 33 (NMR 19)



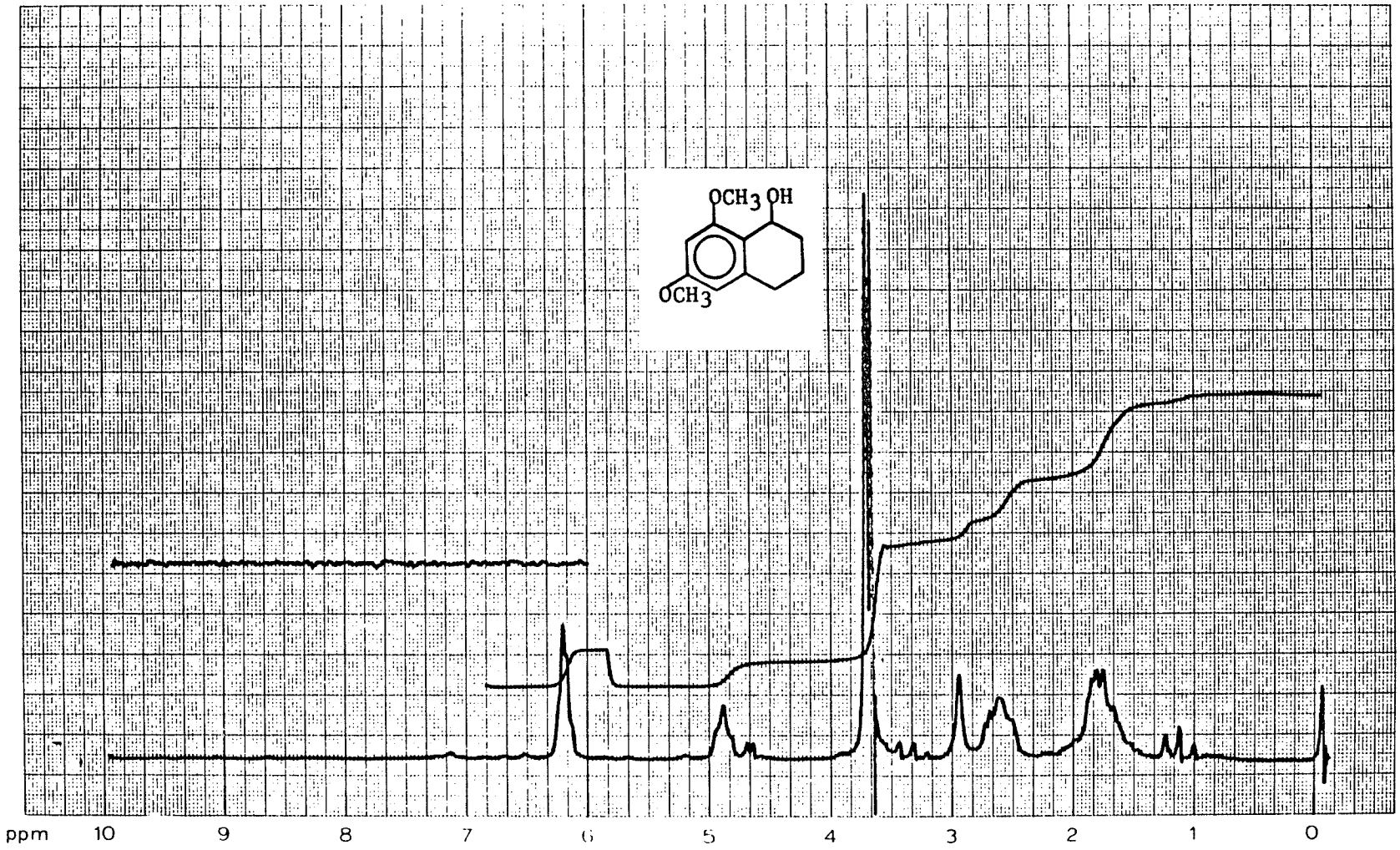
6,8-Dimethoxy-1-tetralone 32 (NMR 20)



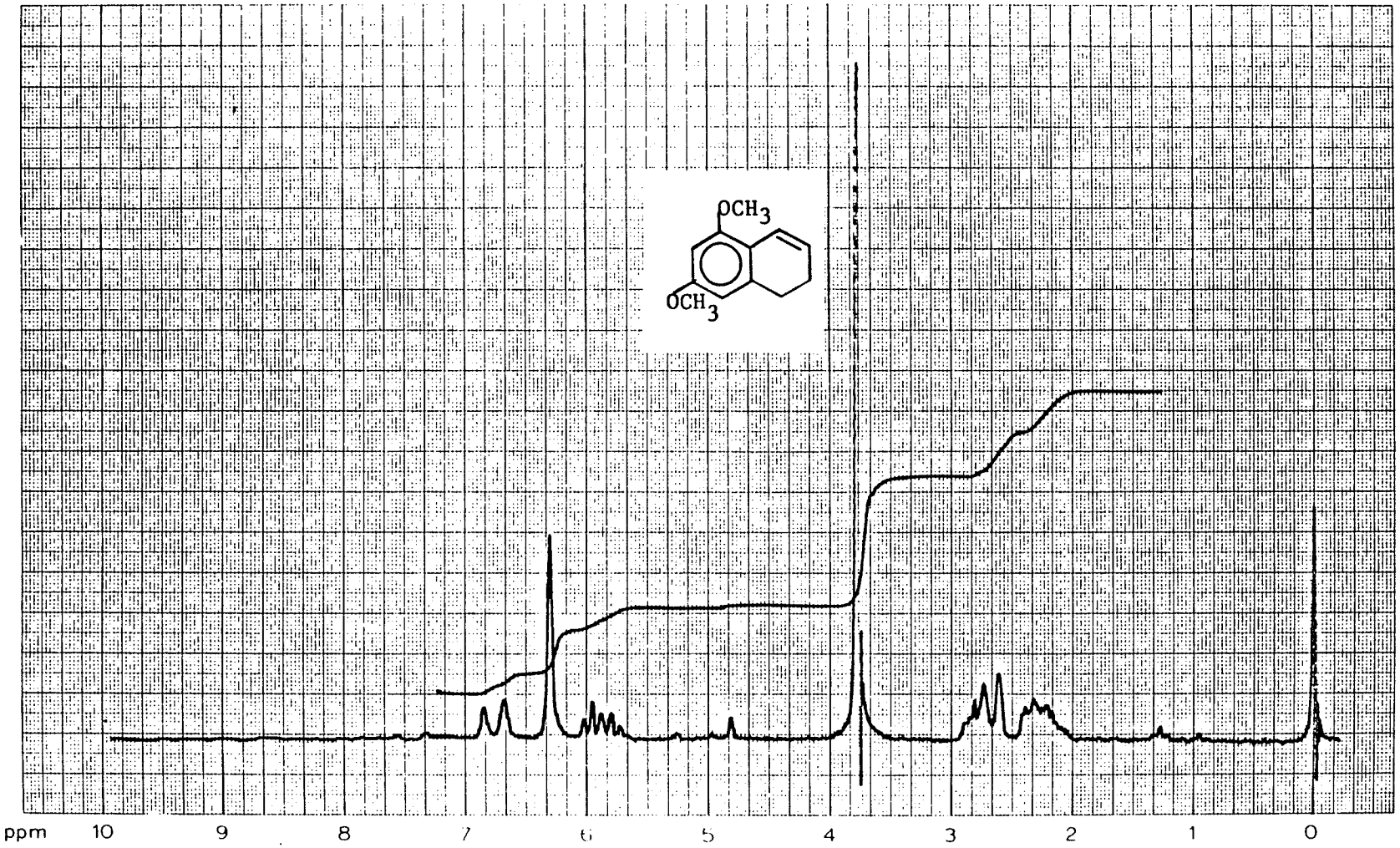
2-hydroxyethyl 4(3',5'-dimethoxyphenyl)butanoate 85 (NMR 21)



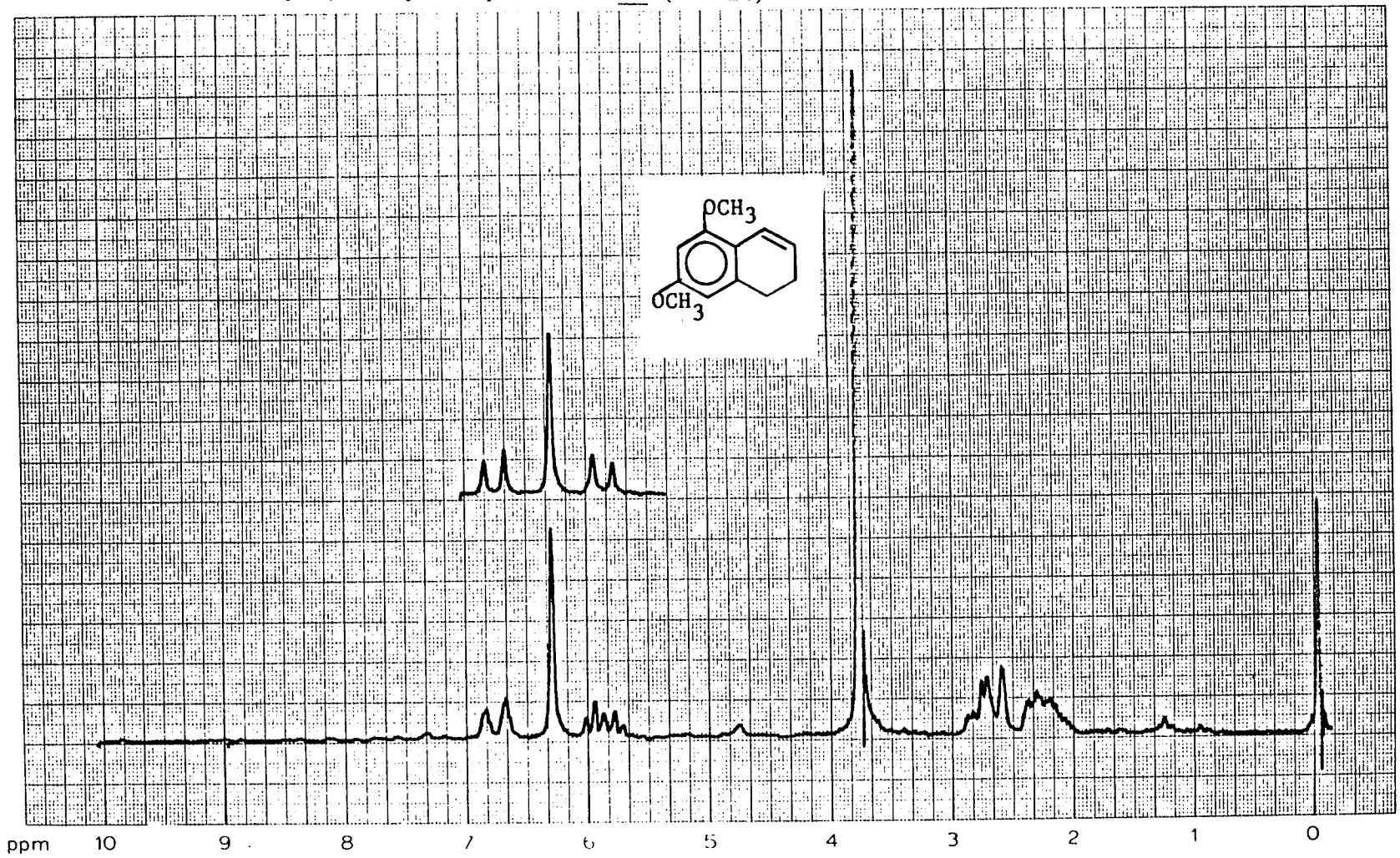
1-Hydroxy-6,8-dimethoxytetralin 86 (NMR 22)



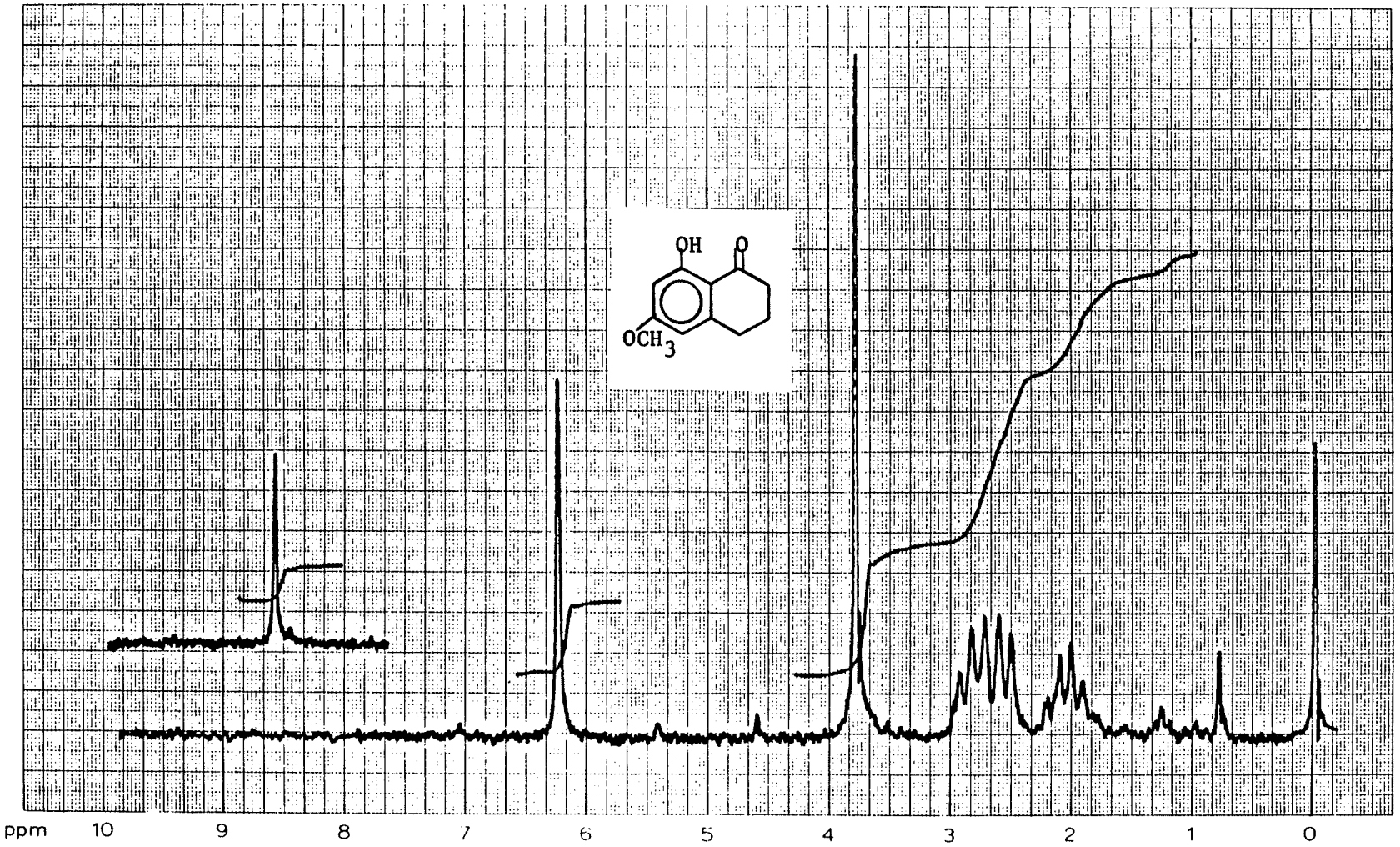
6,8-Dimethoxy-3,4-dihydronaphthalene 88 (NMR 23)



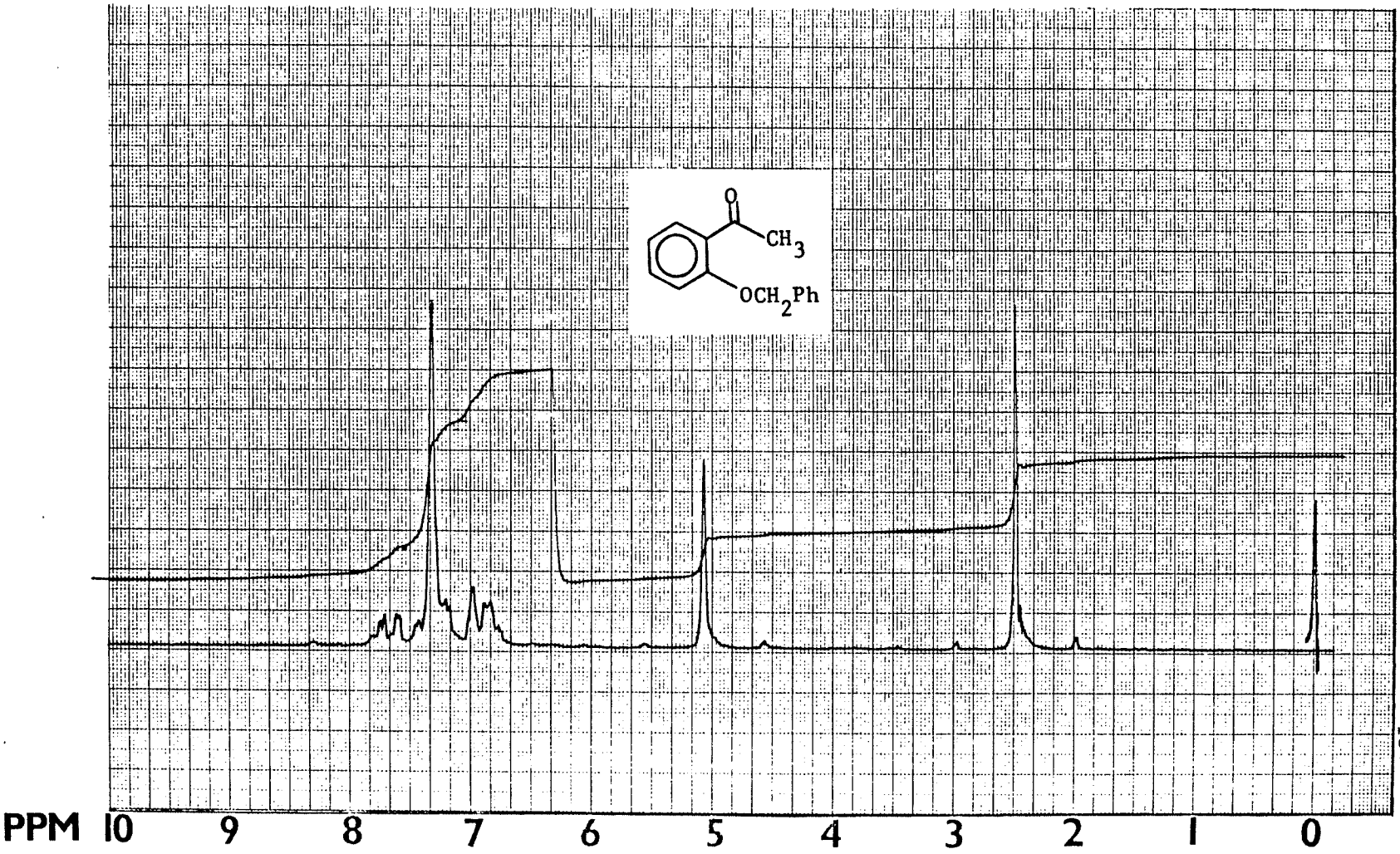
6,8-Dimethoxy-3,4-dihydronaphthalene 88 (NMR 24)



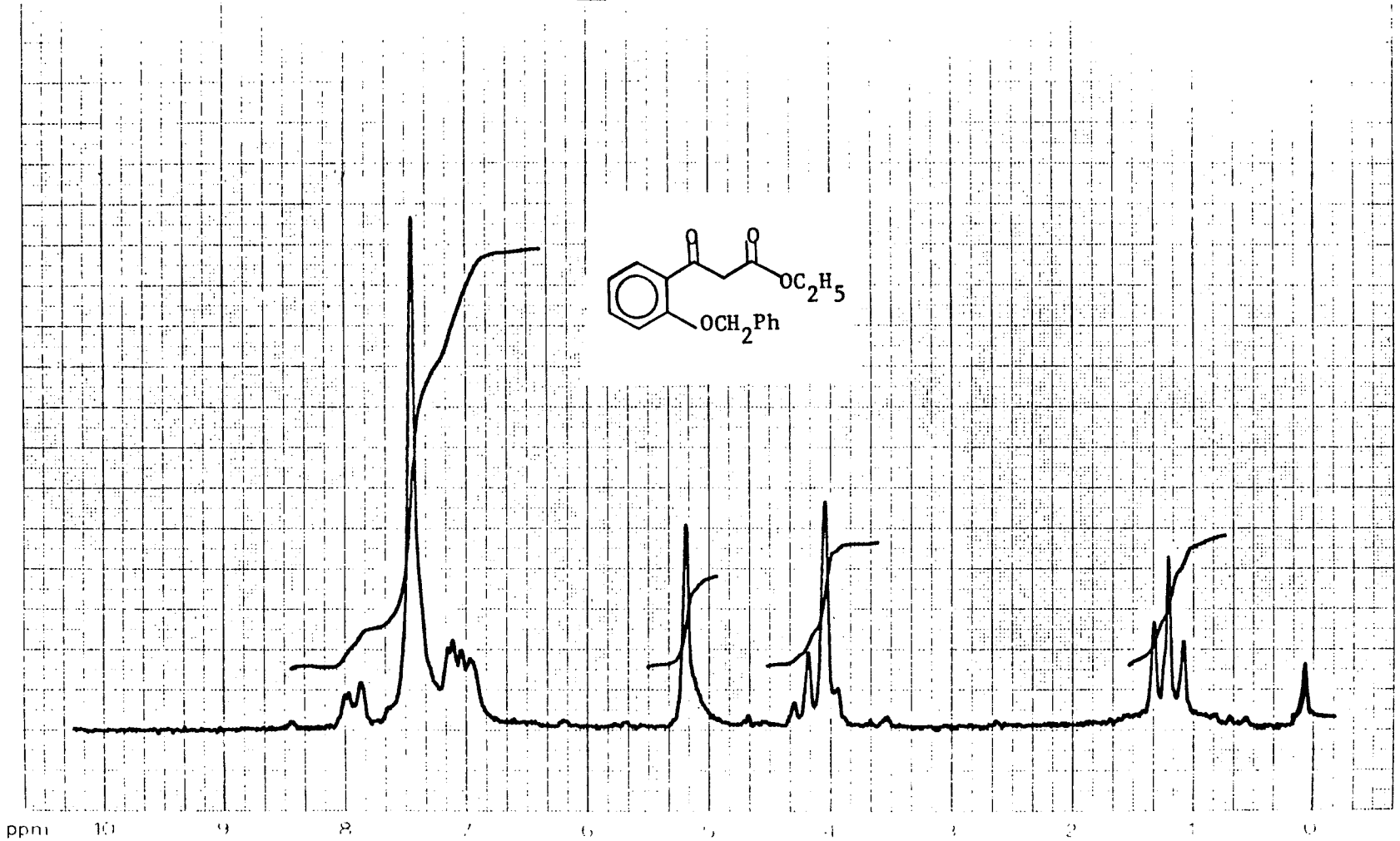
6-Methoxy-8-hydroxy-1-tetralone 89 (NMR 25)



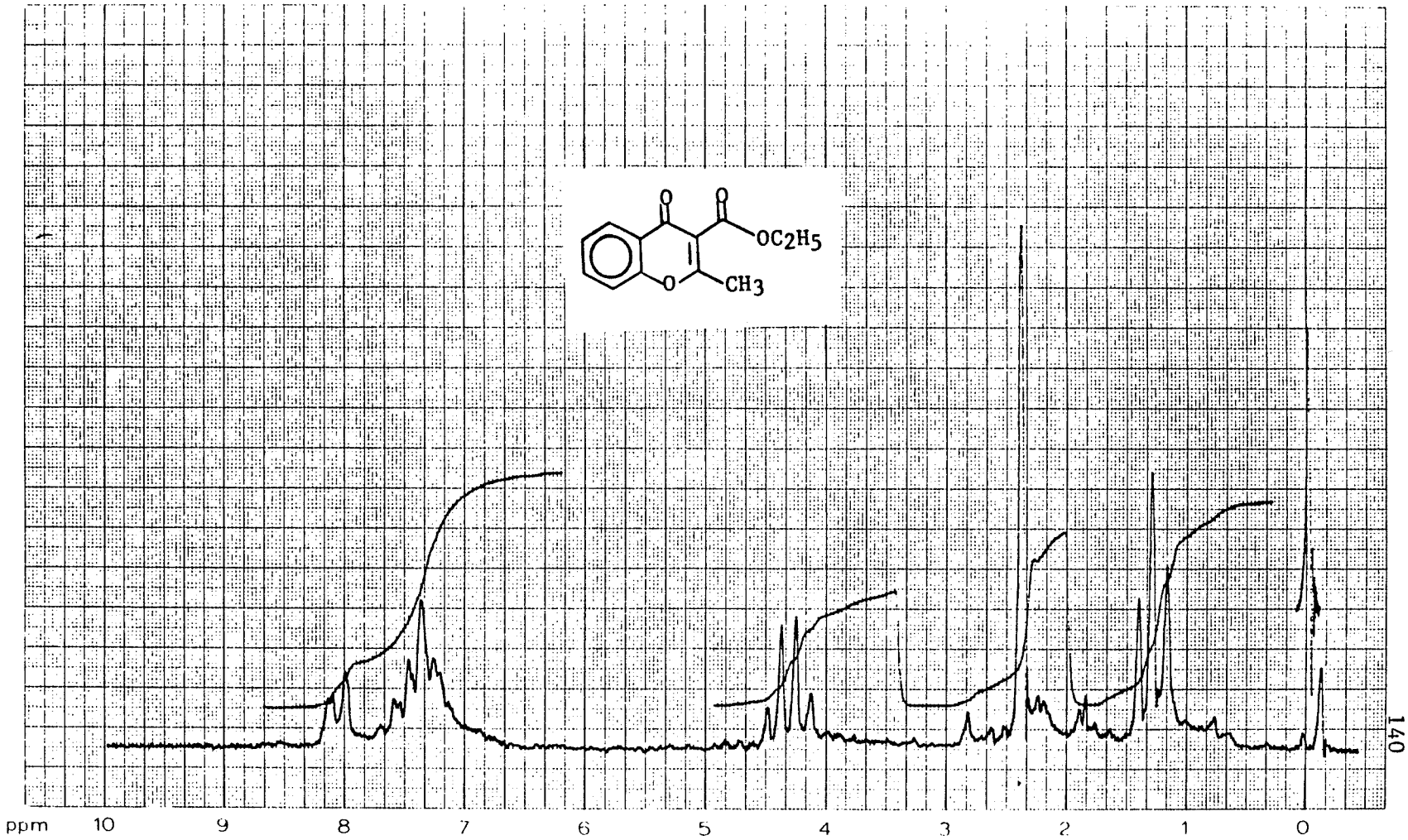
o-Benzyloxyacetophenone 91 (NMR 26)



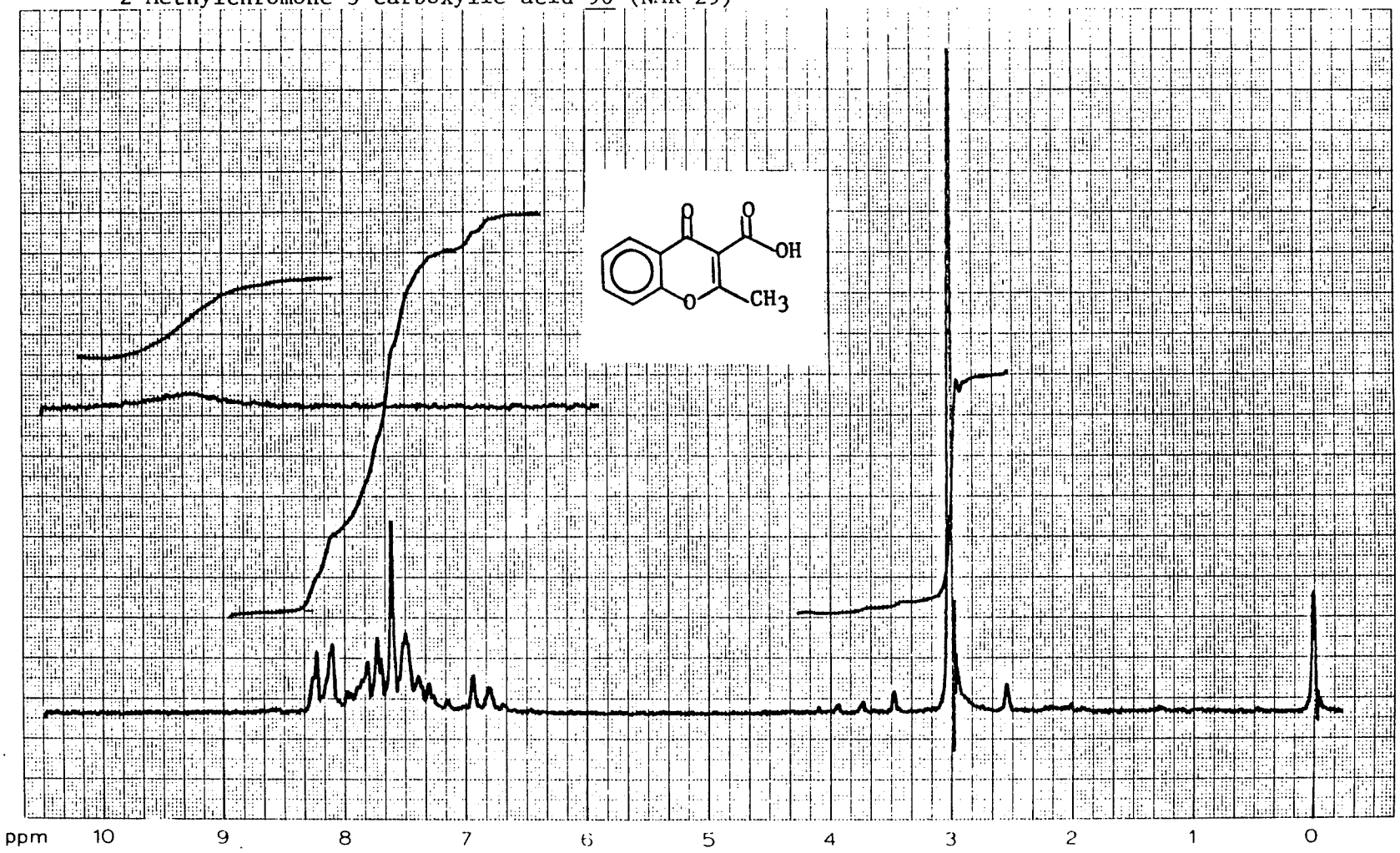
Ethyl (o-Benzyloxybenzoly)acetate 92 (NMR 27)



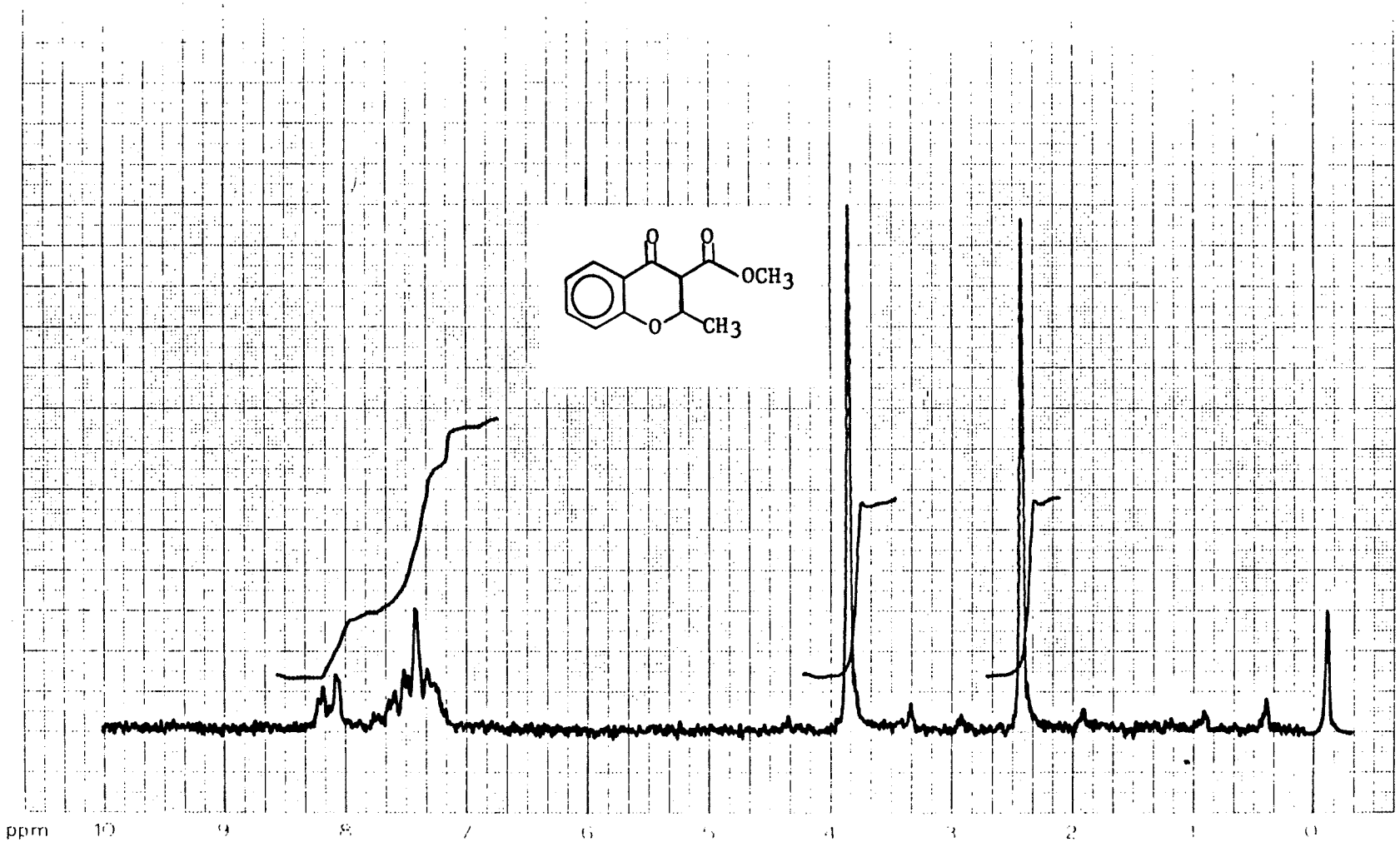
Ethyl 2-methylchromone-3-carboxylate 27 (NMR 28)



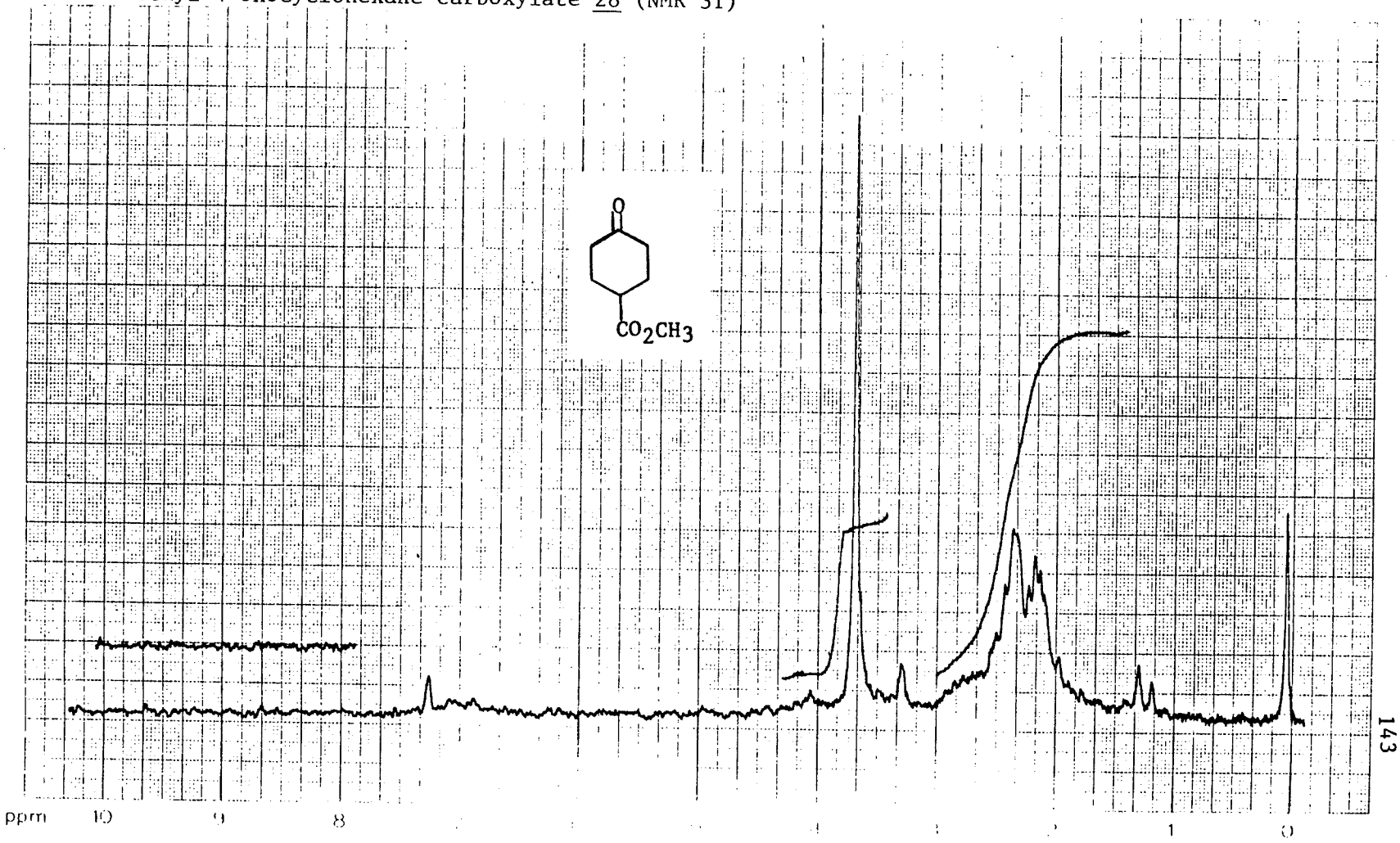
2-Methylchromone-3-carboxylic acid 96 (NMR 29)



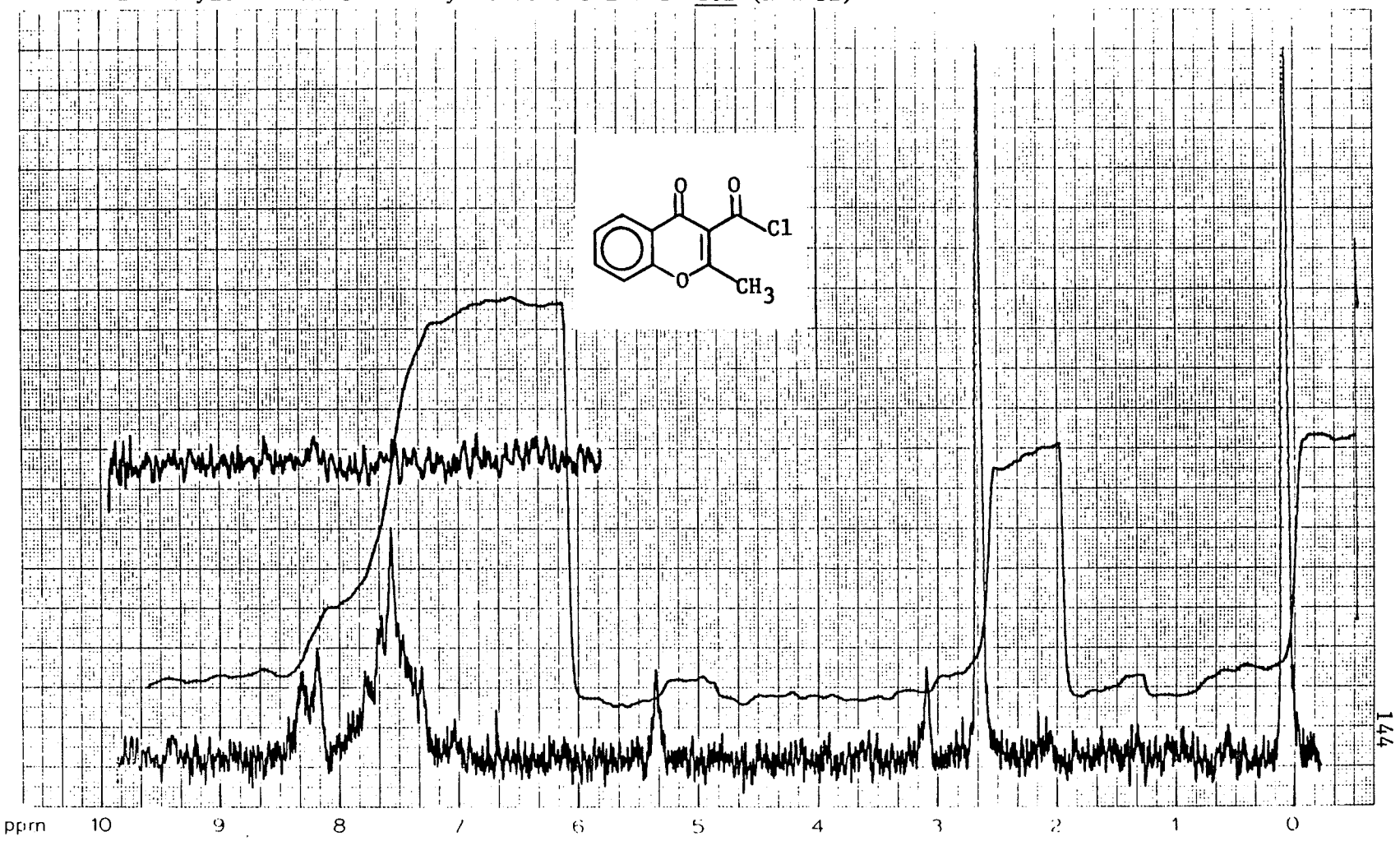
Methyl 2-methylchromone-3-carboxylate 27 (NMR 30)



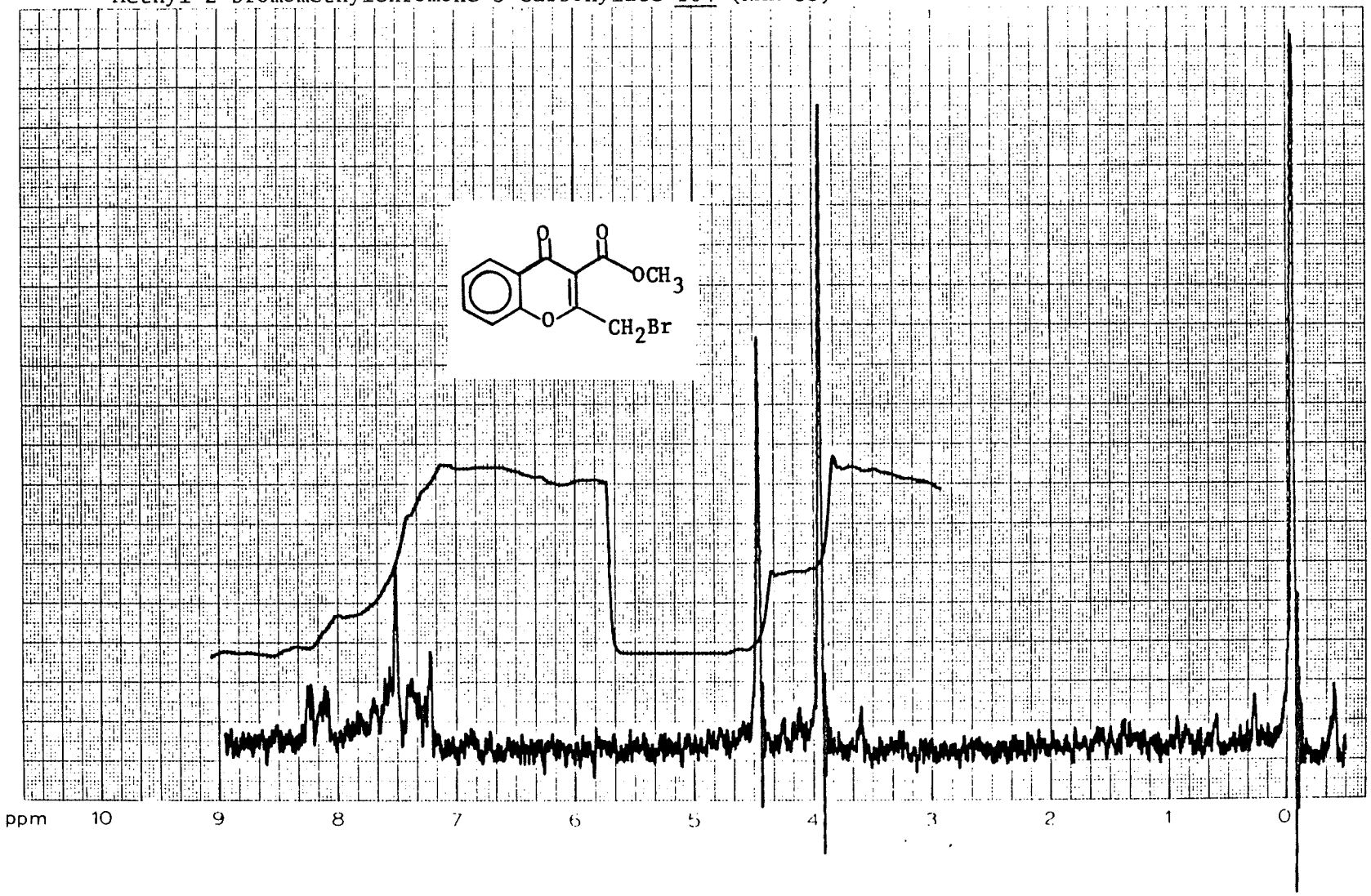
Methyl 4-oxocyclohexane carboxylate 28 (NMR 31)



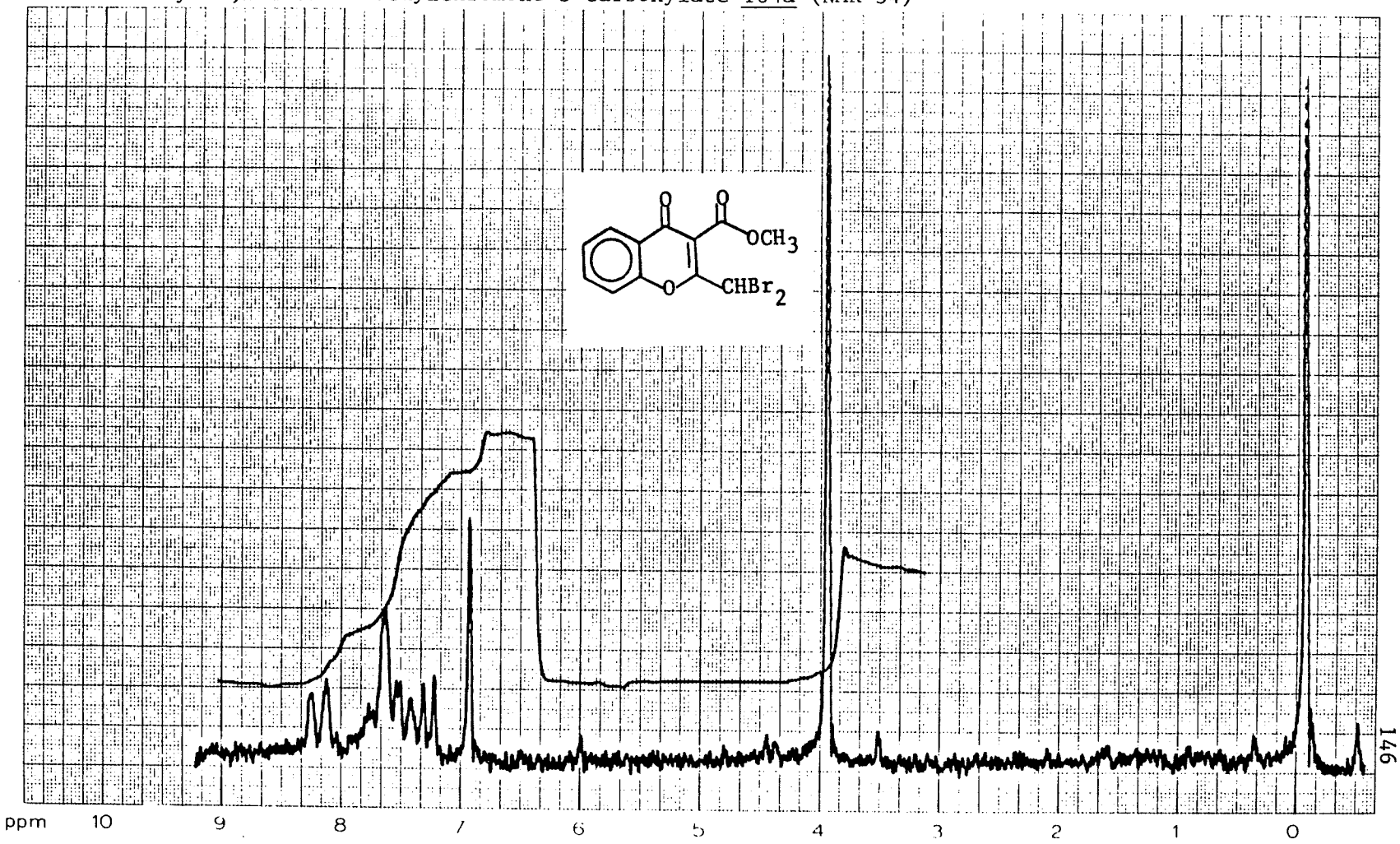
2-Methylchromone-3-carboxylic acid chloride 102 (NMR 32)



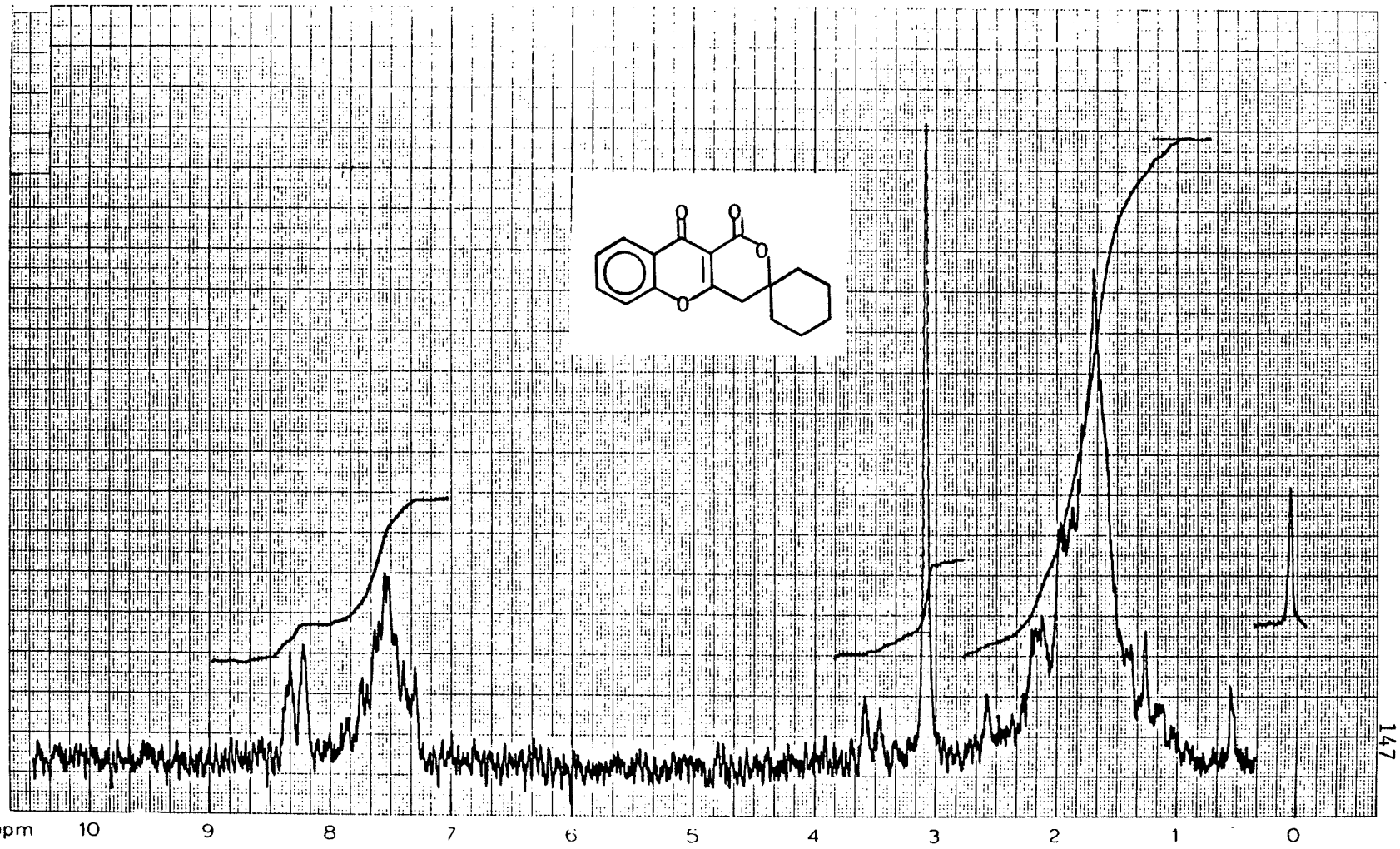
Methyl 2-bromomethylchromone-3-carboxylate 104 (NMR 33)



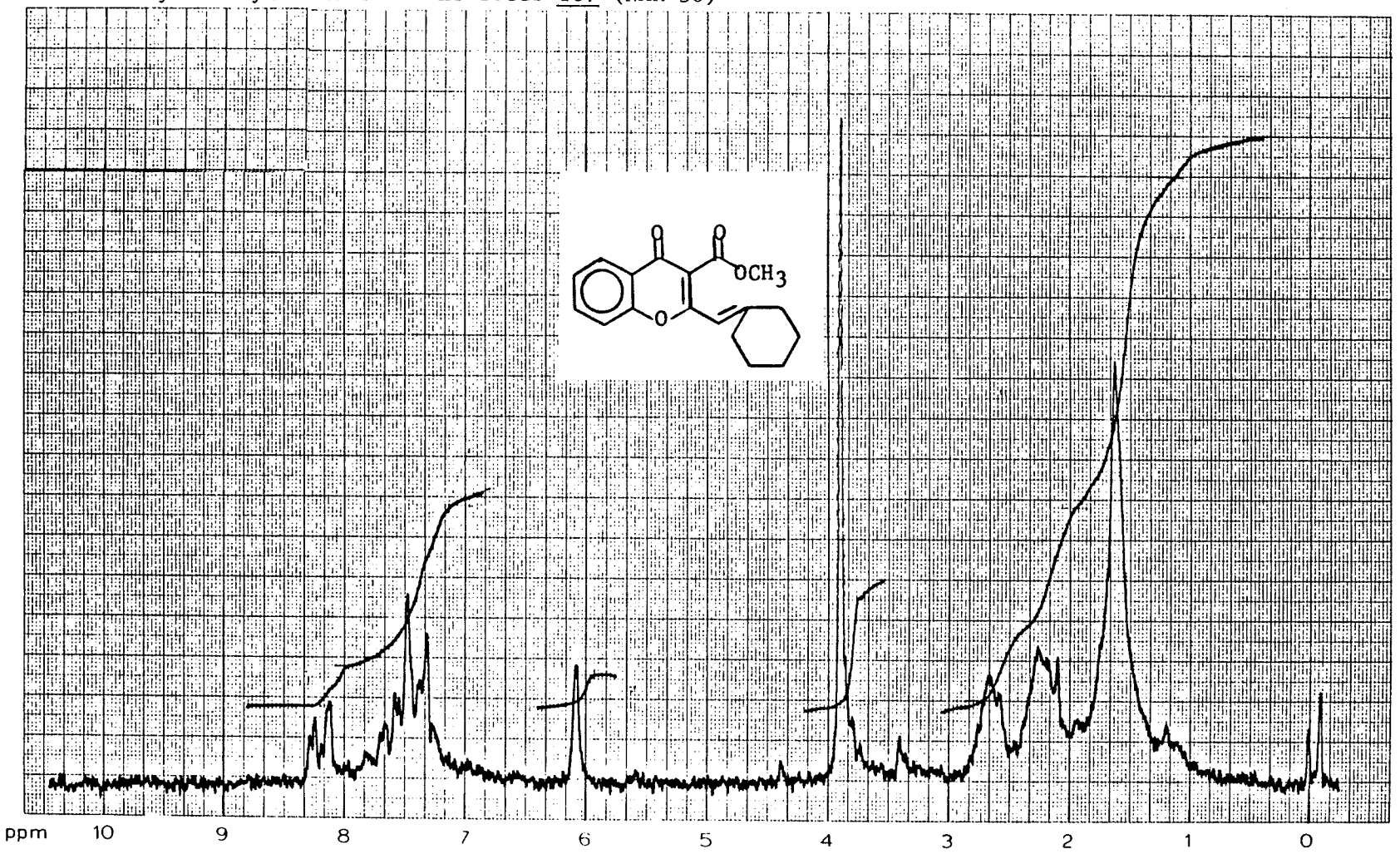
Methyl 2,2-dibromomethylchromone-3-carboxylate 104a (NMR 34)



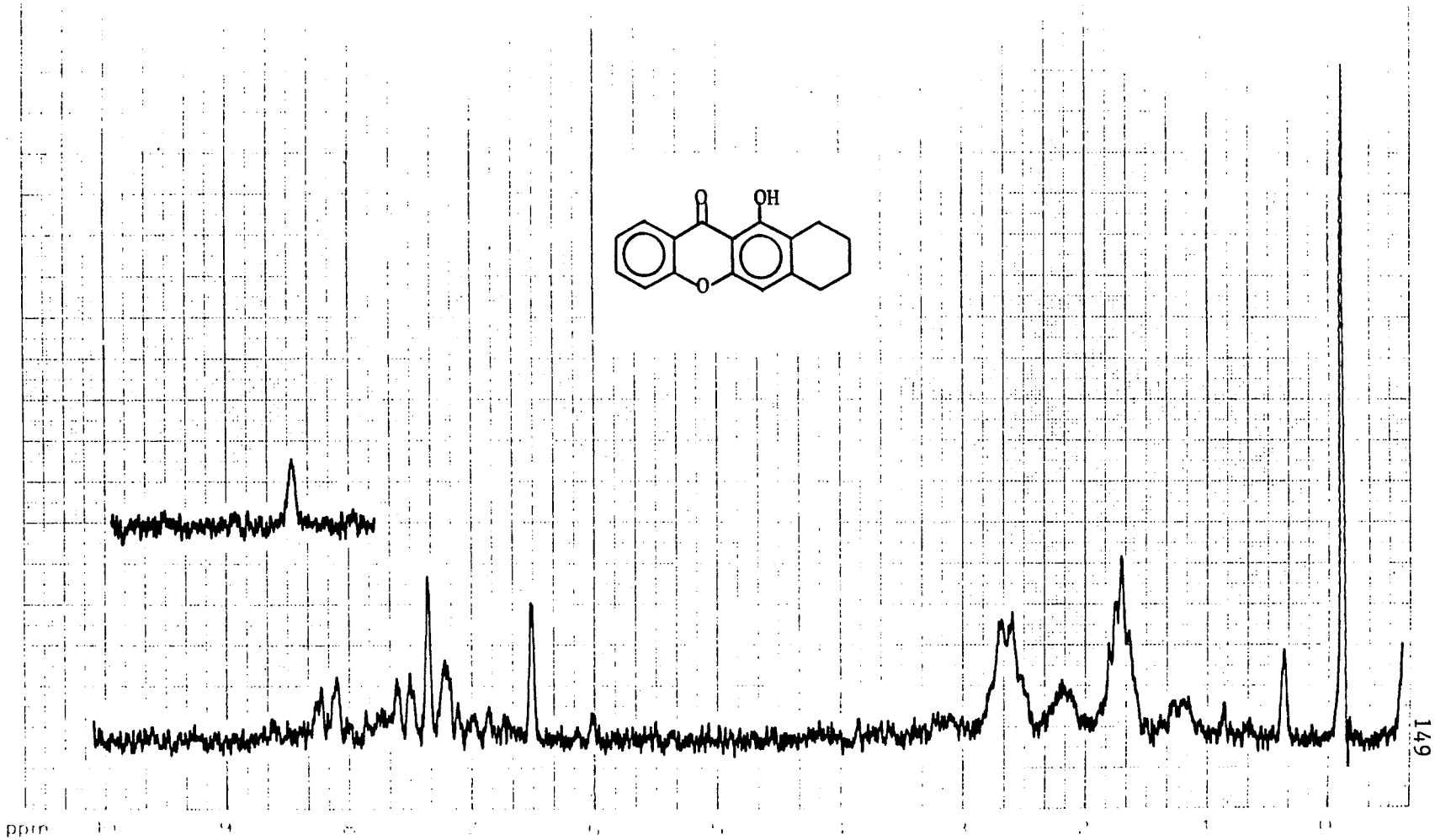
Spirolactone 105 (NMR 35)



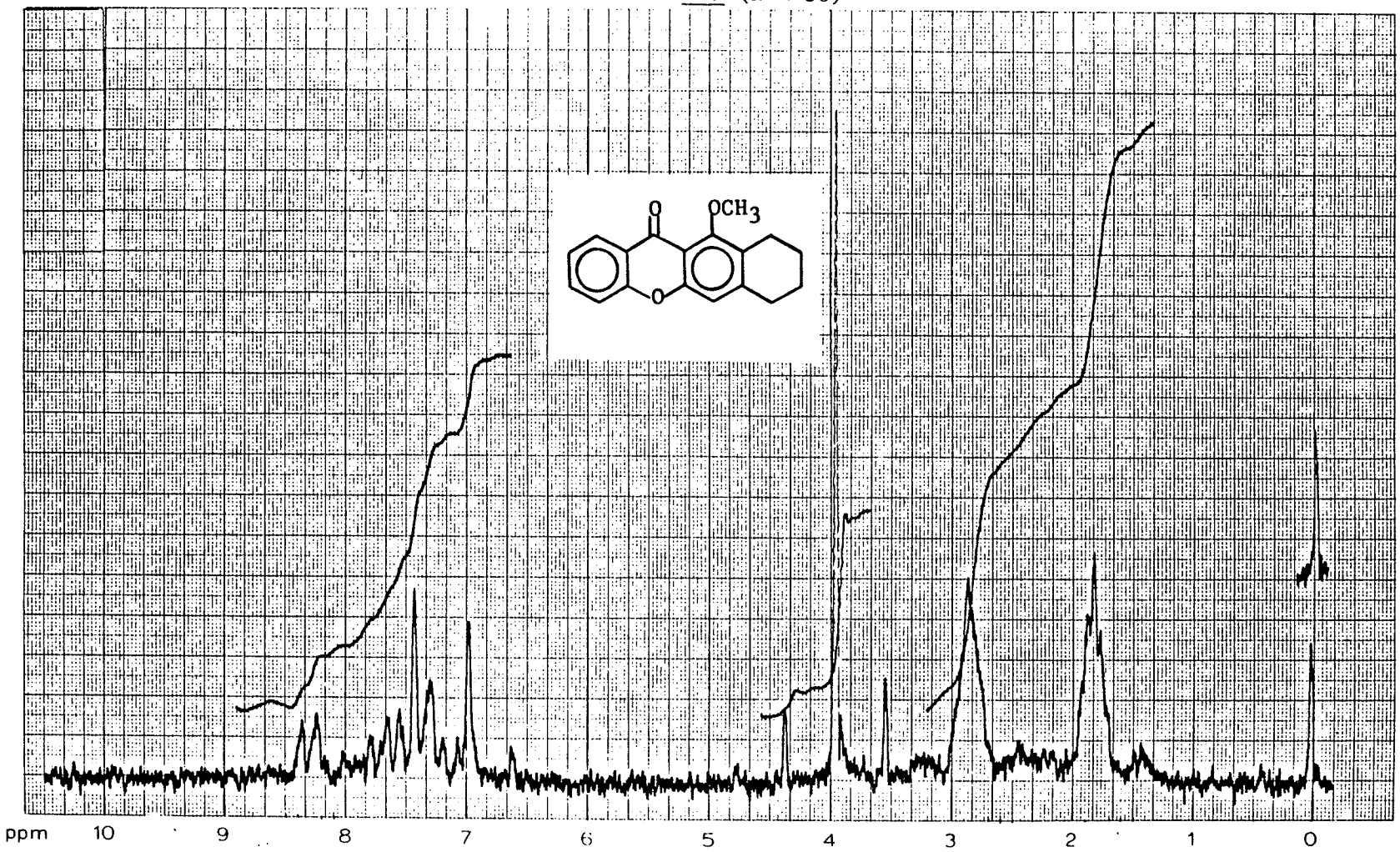
Cyclohexylidene chromone ester 107 (NMR 36)



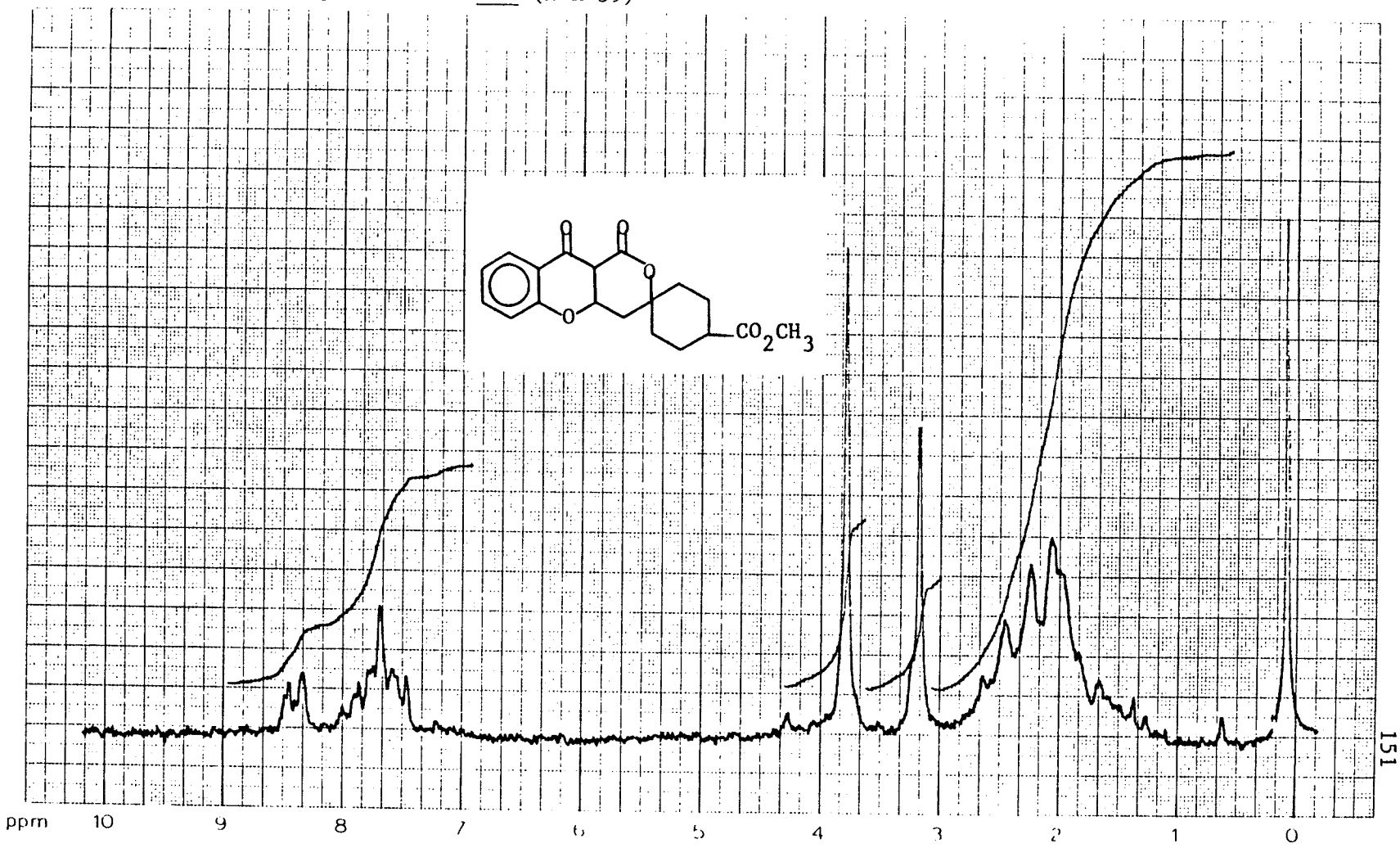
1-Hydroxy-2,3-cyclohexanoxanthene-9-one 99 (NMR 37)



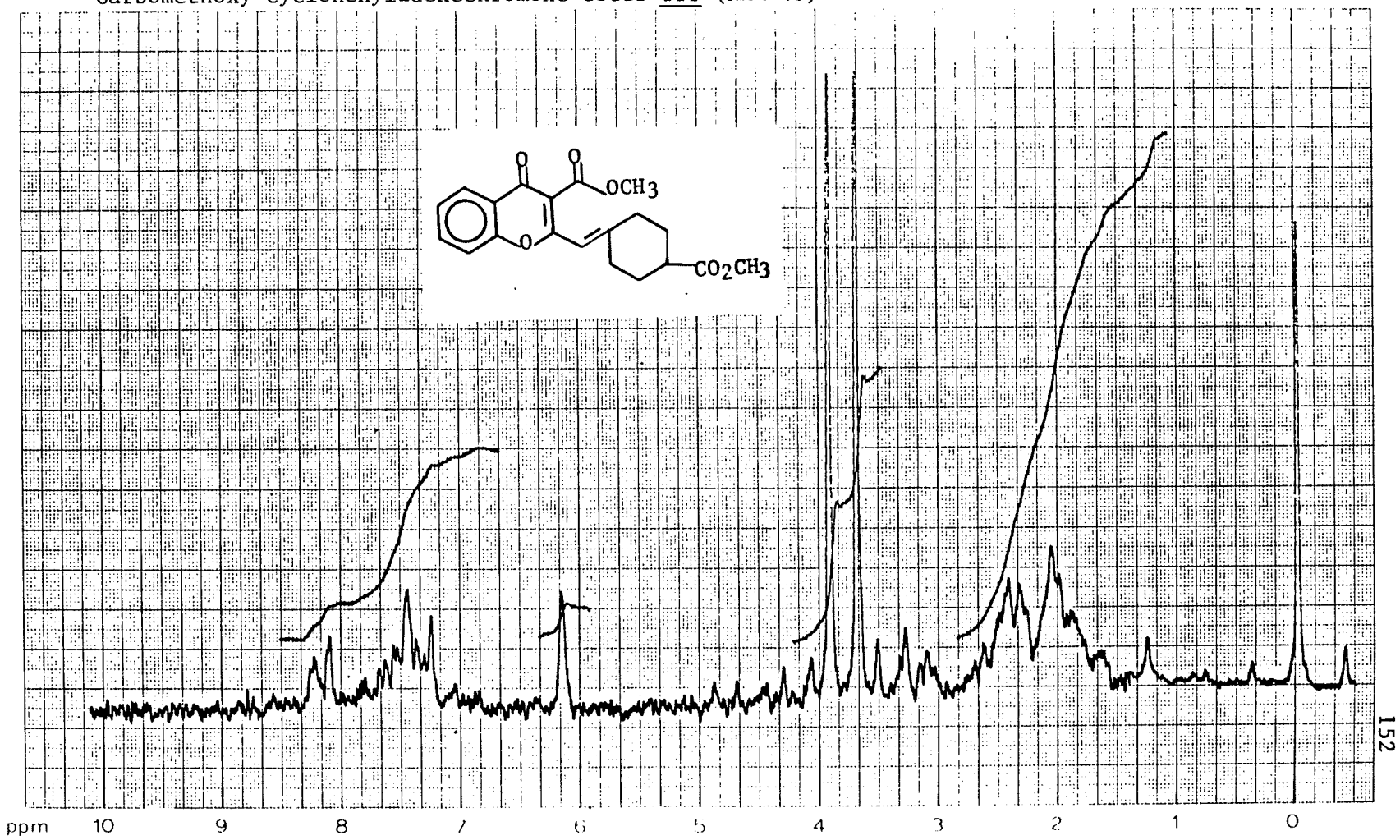
1-Methoxy-2,3-cyclohexanoxanthene-9-one 109 (NMR 38)



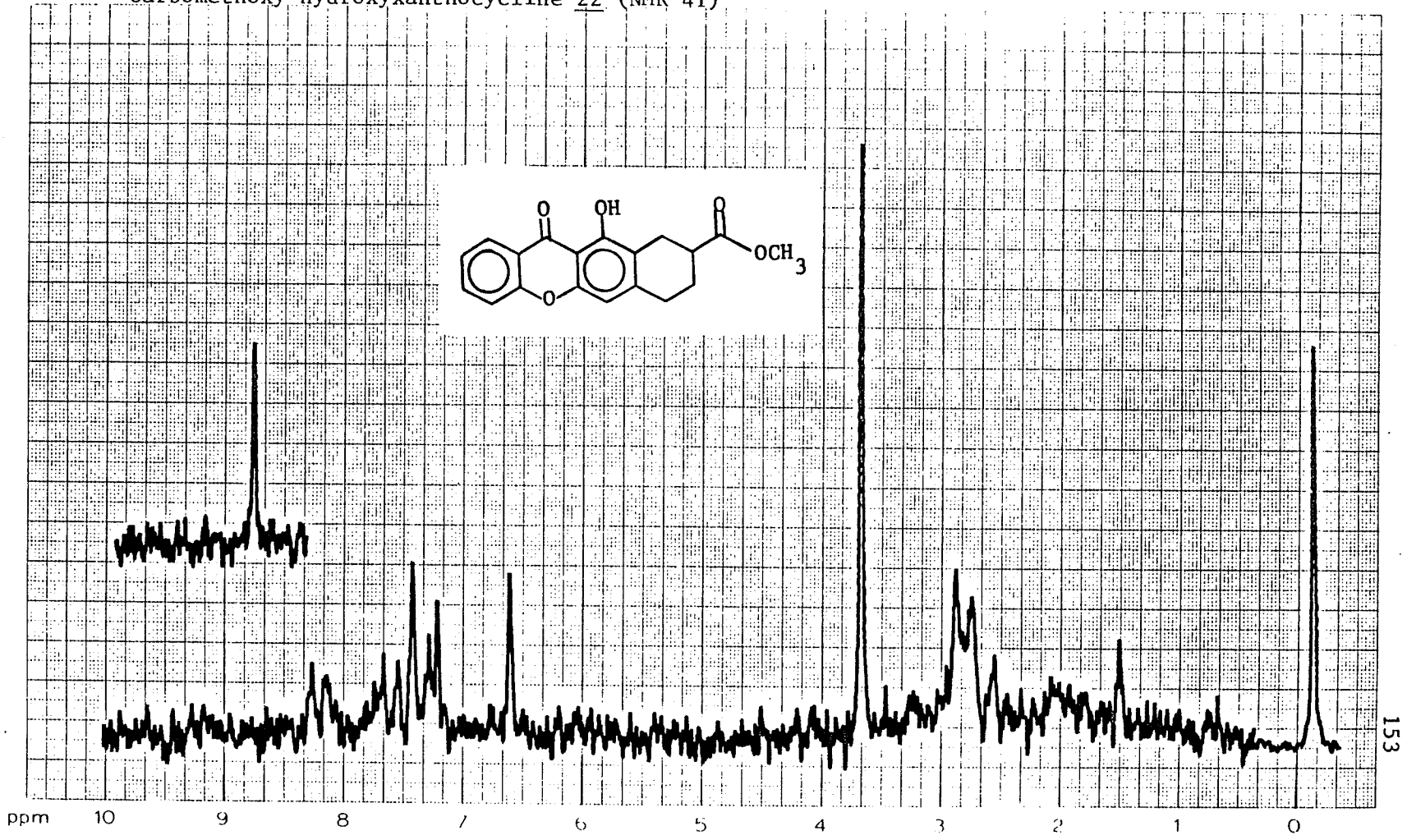
Carbomethoxy spirolactone 110 (NMR 39)



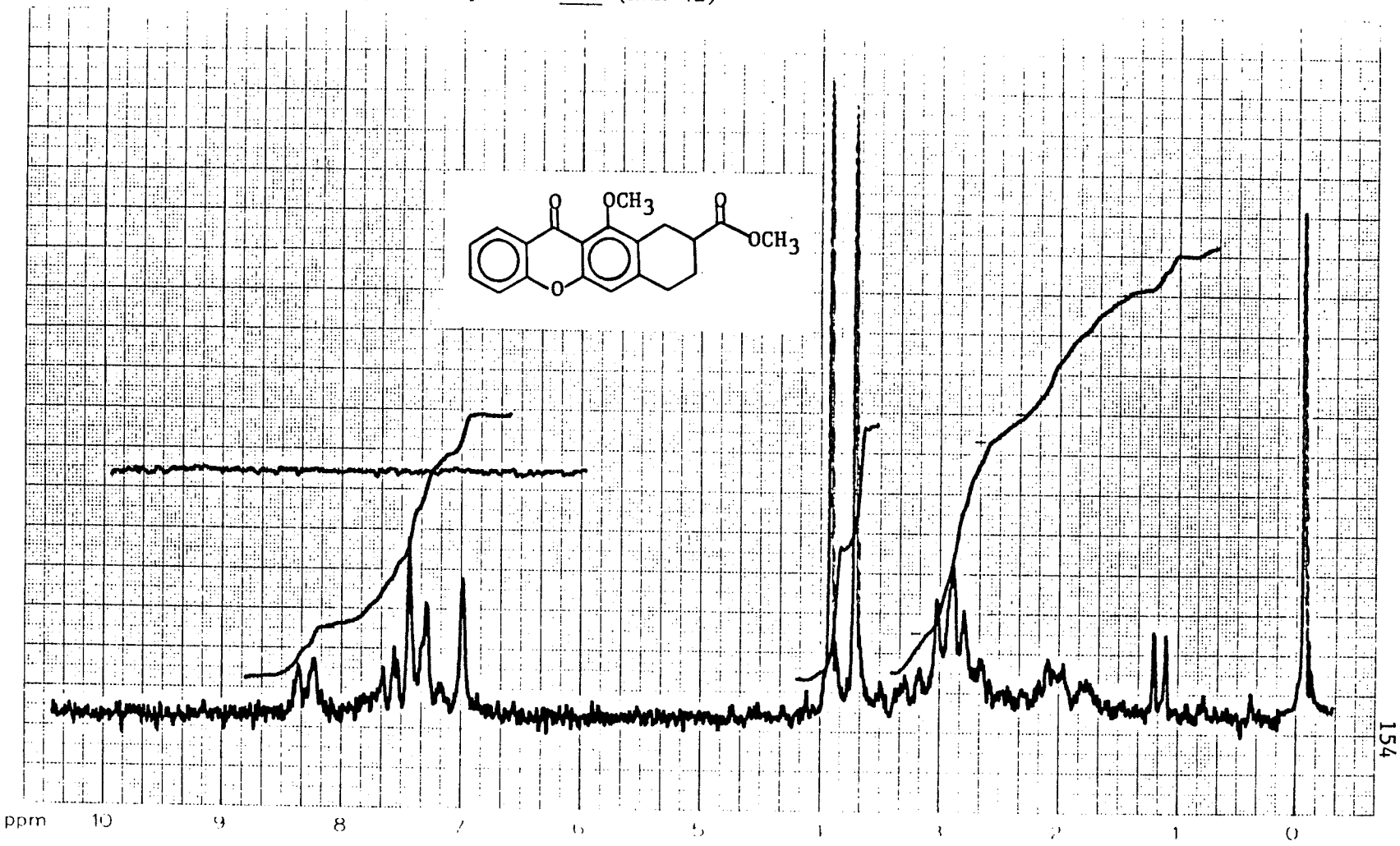
Carbomethoxy cyclohexylidenechromone ester 111 (NMR 40)

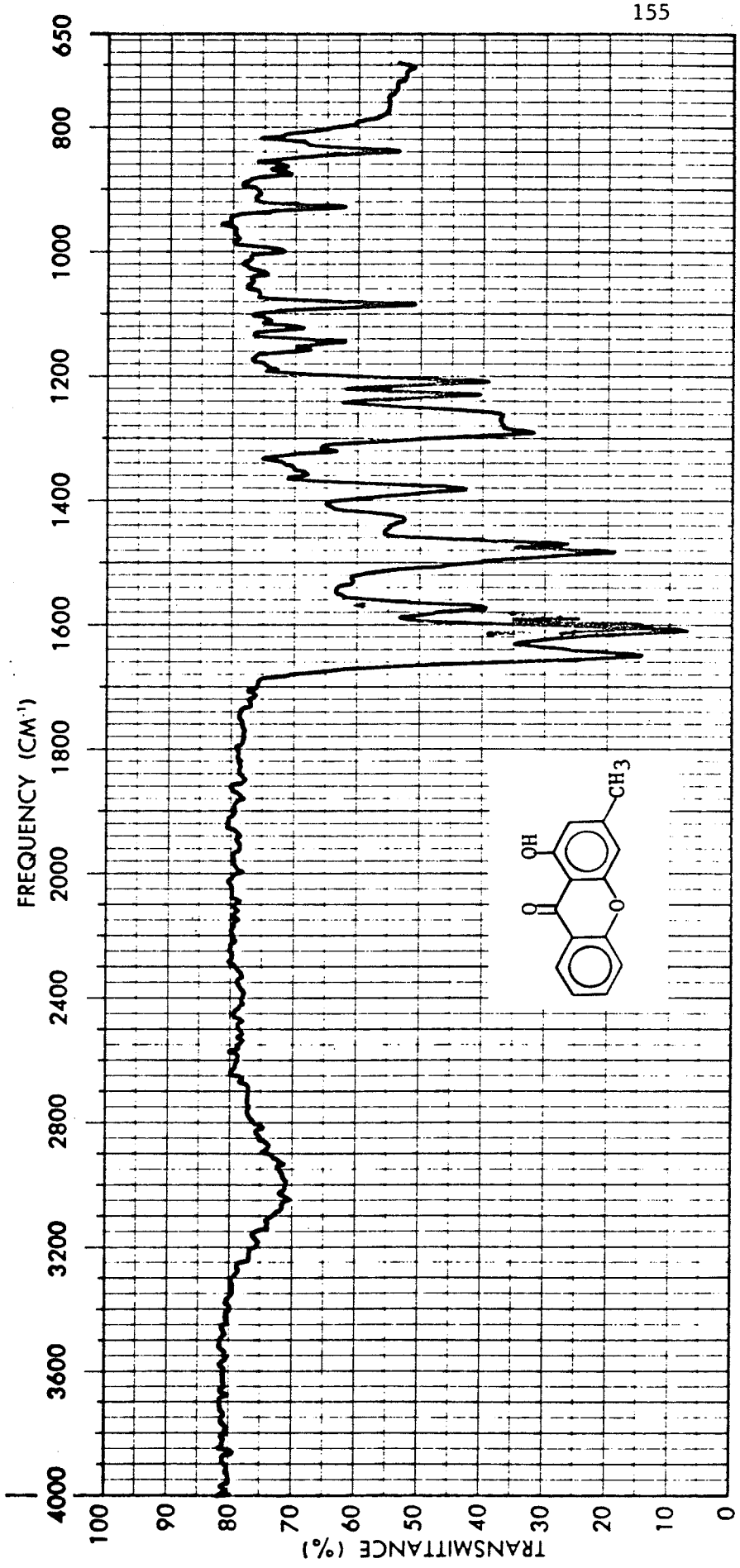


Carbomethoxy hydroxyxanthocycline 22 (NMR 41)



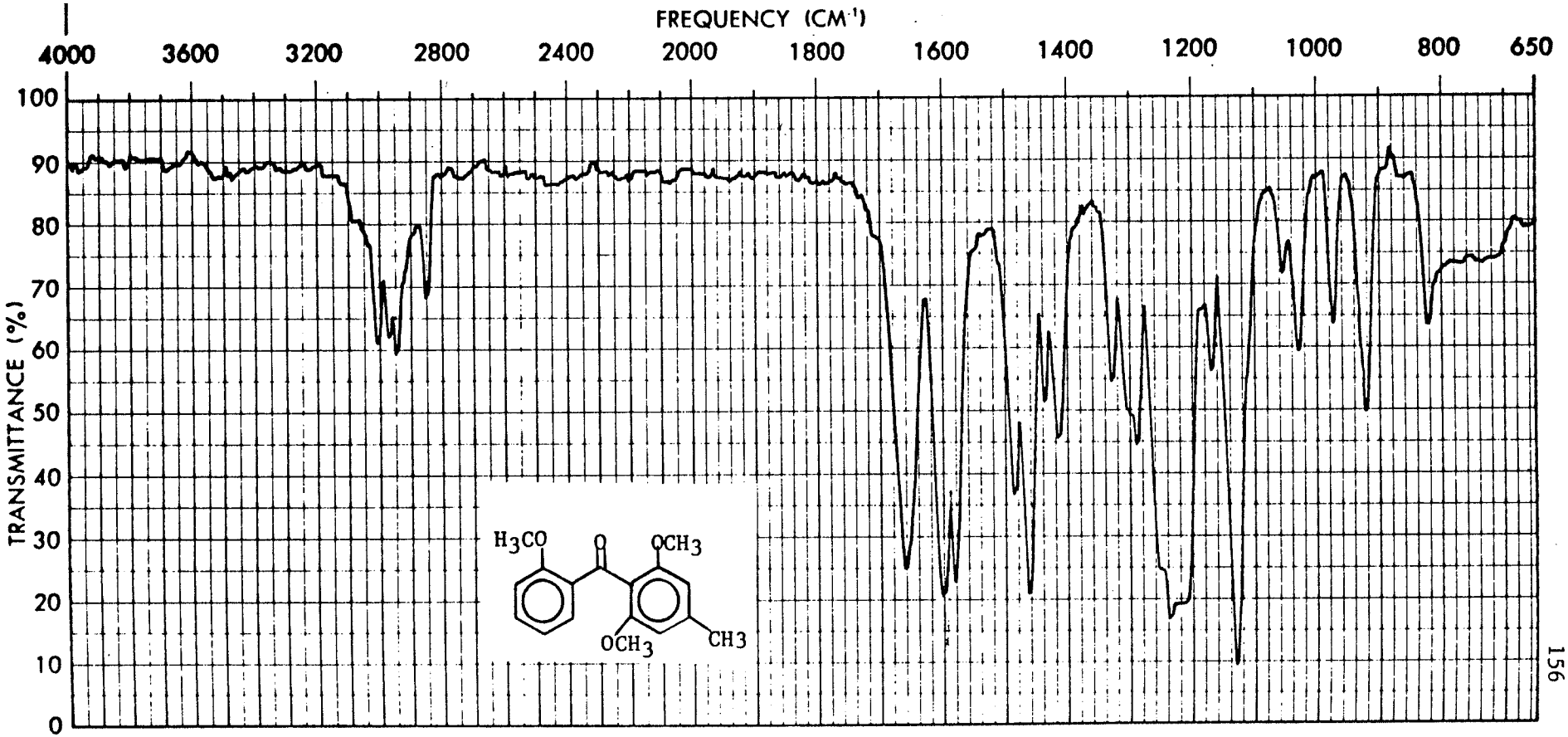
Carbomethoxy methoxyxanthocycline 22a (NMR 42)



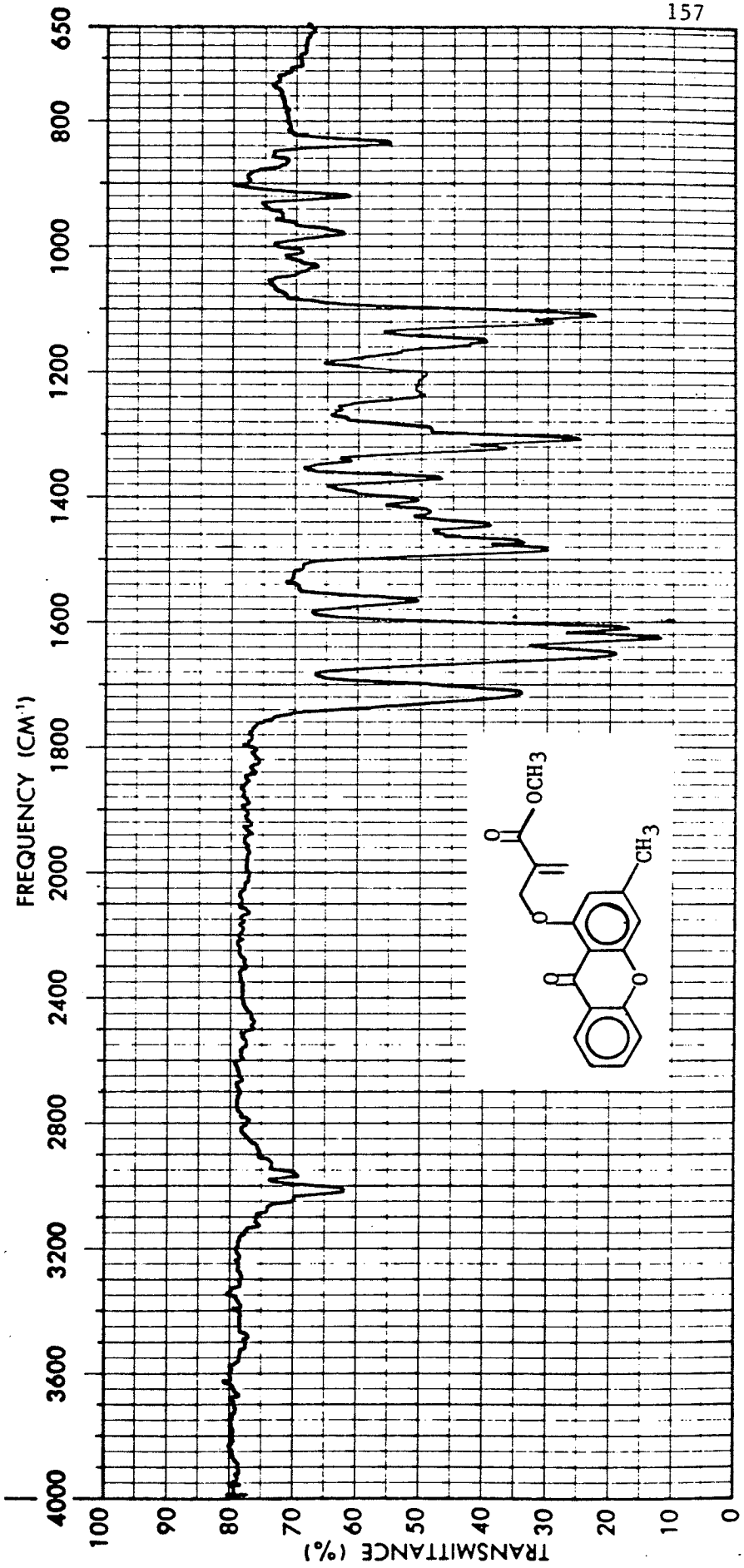


1-Hydroxy-3-methylxanthone 23 (IR 1)

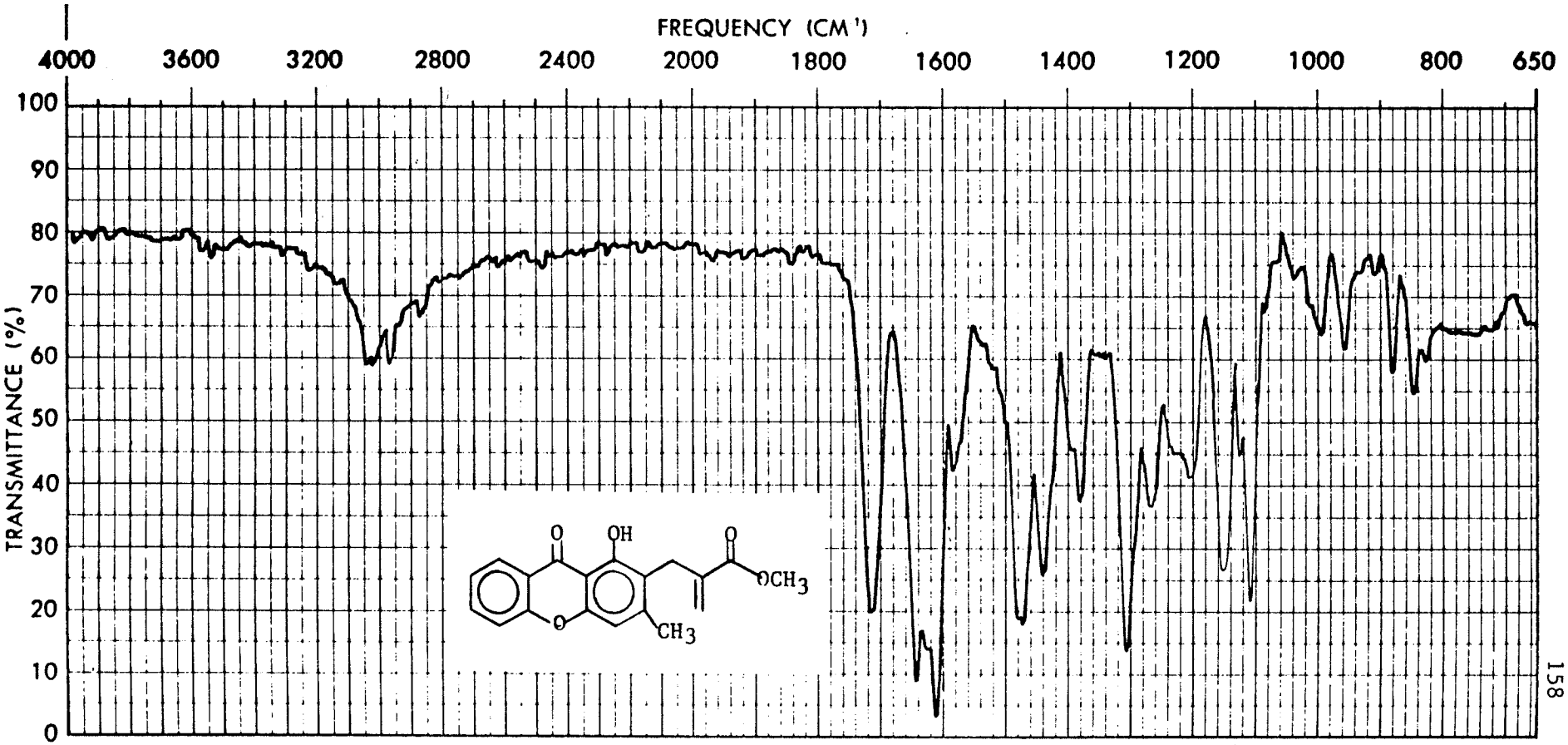
2',2,5 Trimethoxy-3-methylbenzophenone 53 (IR 2)



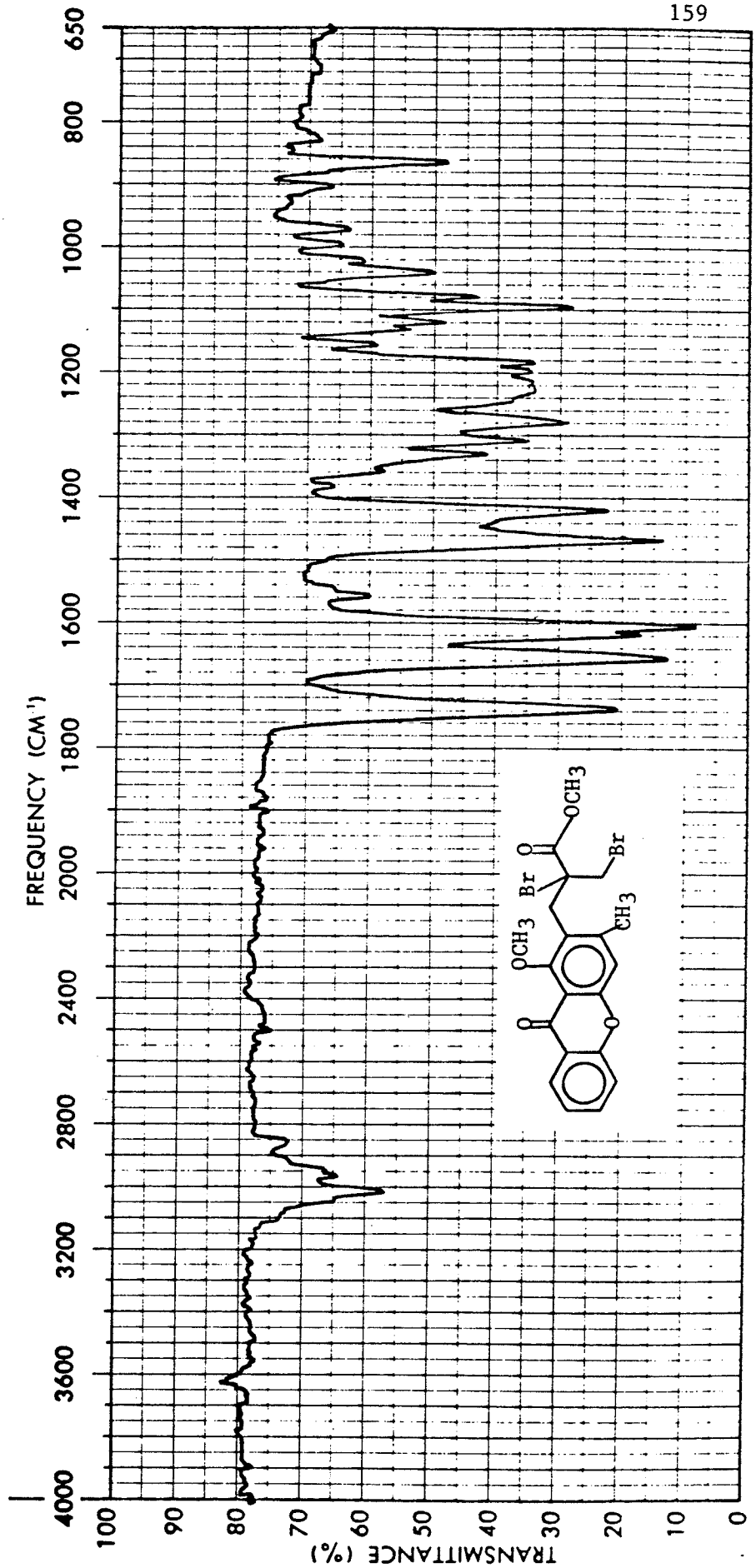
1-(2-Carbomethoxyalloxy)-3-methyl-9H-xanthene-9-one 57 (IR 3)



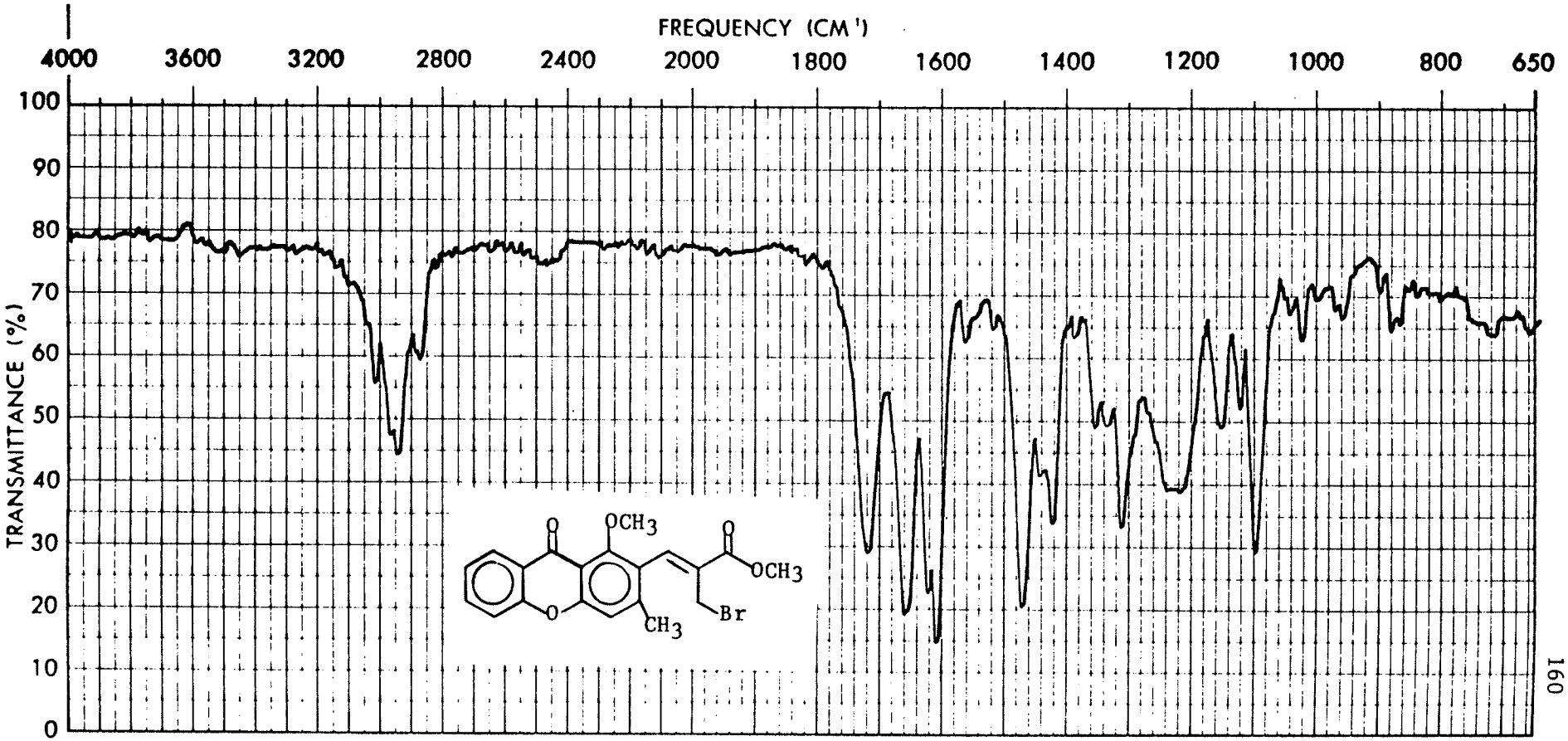
1-Hydroxy-2-C-allylic-3-methylxanthone 58 (IR 4)



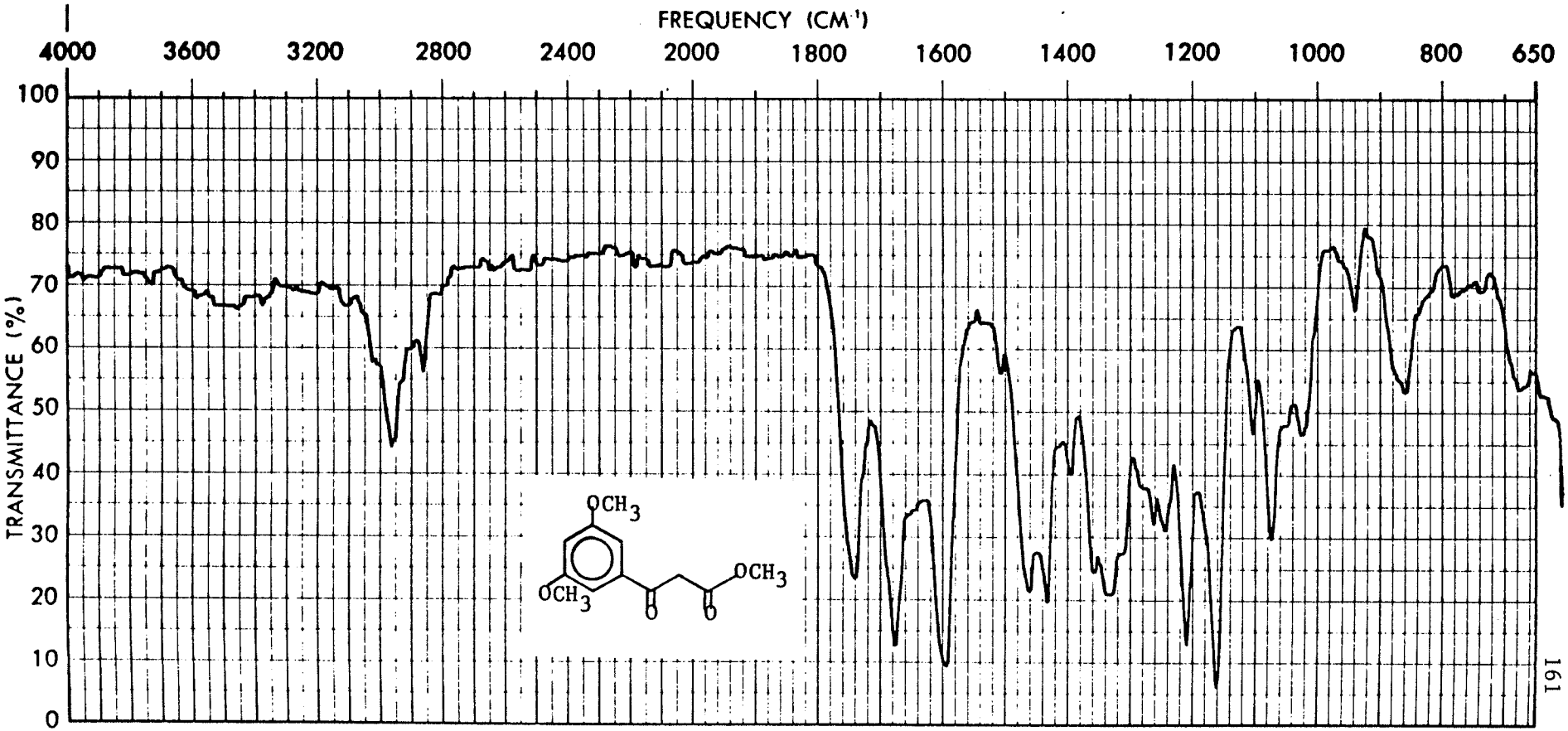
1-Methoxy-2-(2,3-dibromo-2-carbomethoxypropyl)-3-methyl-9H-xanthene-9-one 64 (IR 5)



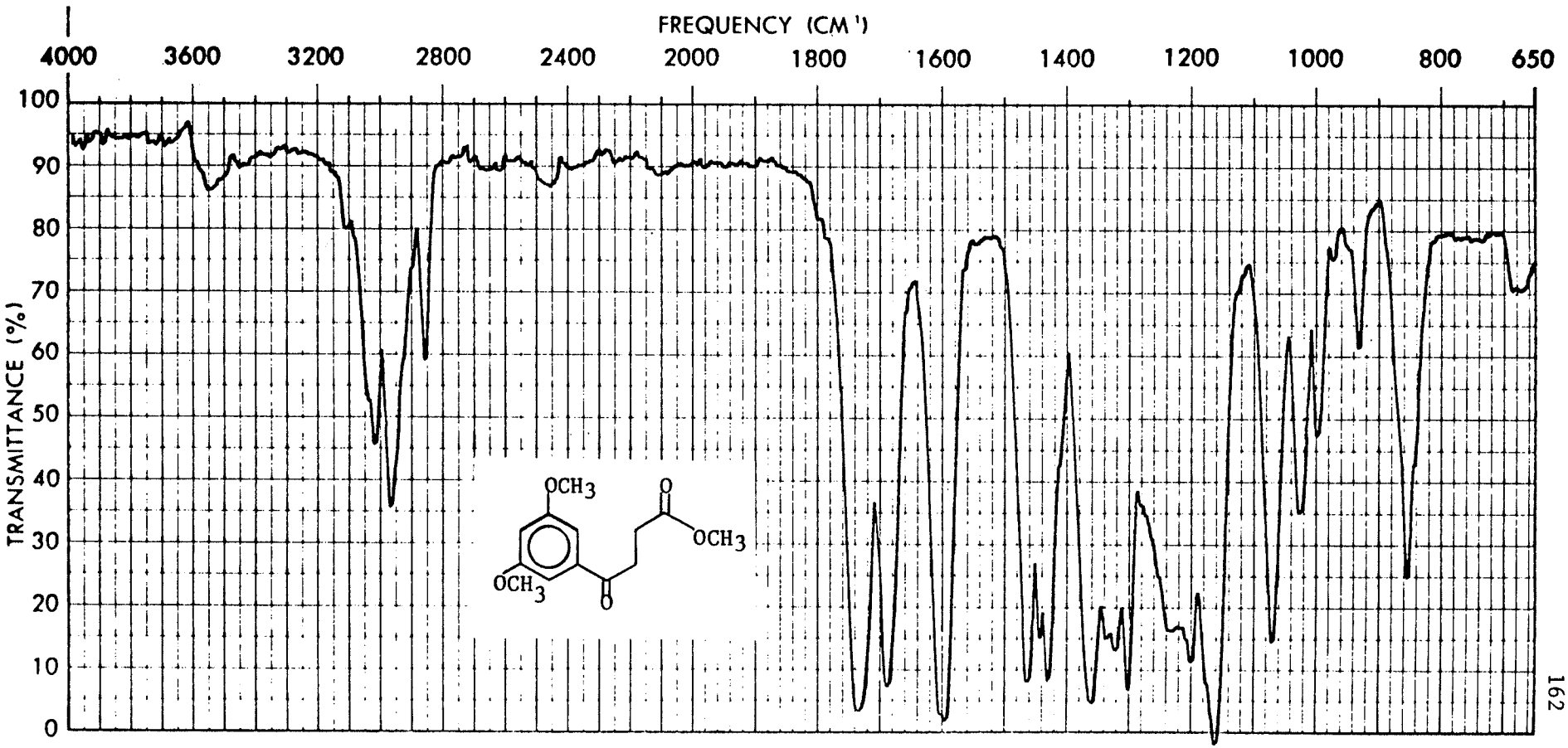
1-Methoxy-2-(3-bromo-2-carbomethoxypropyl)-3-methyl-9H-xanthene-9-one 65 (IR 6)



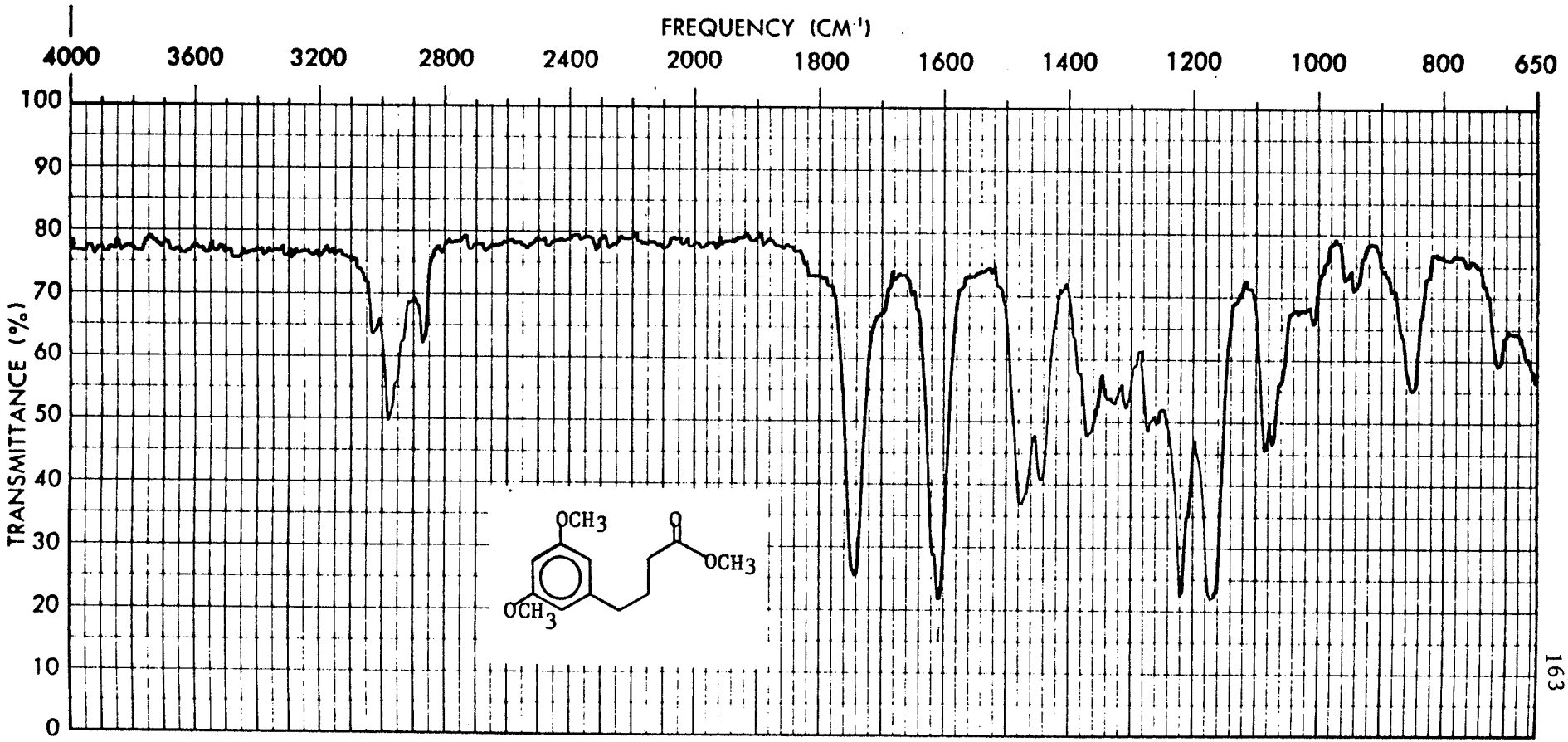
Methyl (3,5-Dimethoxybenzoyl)acetate 38 (IR 7)



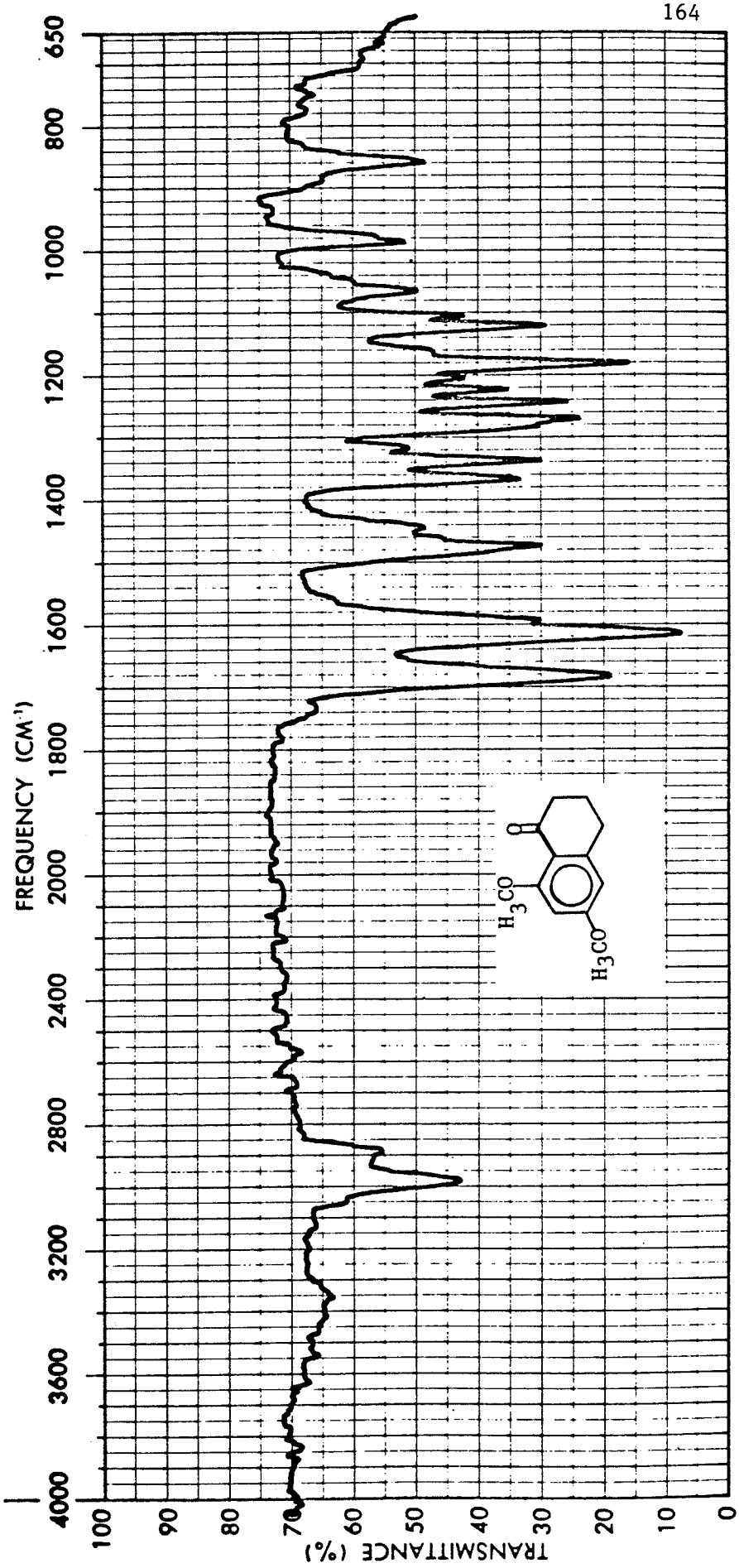
Methyl 3-(3',5'-dimethoxybenzoyl)propionate 37 (IR 8)



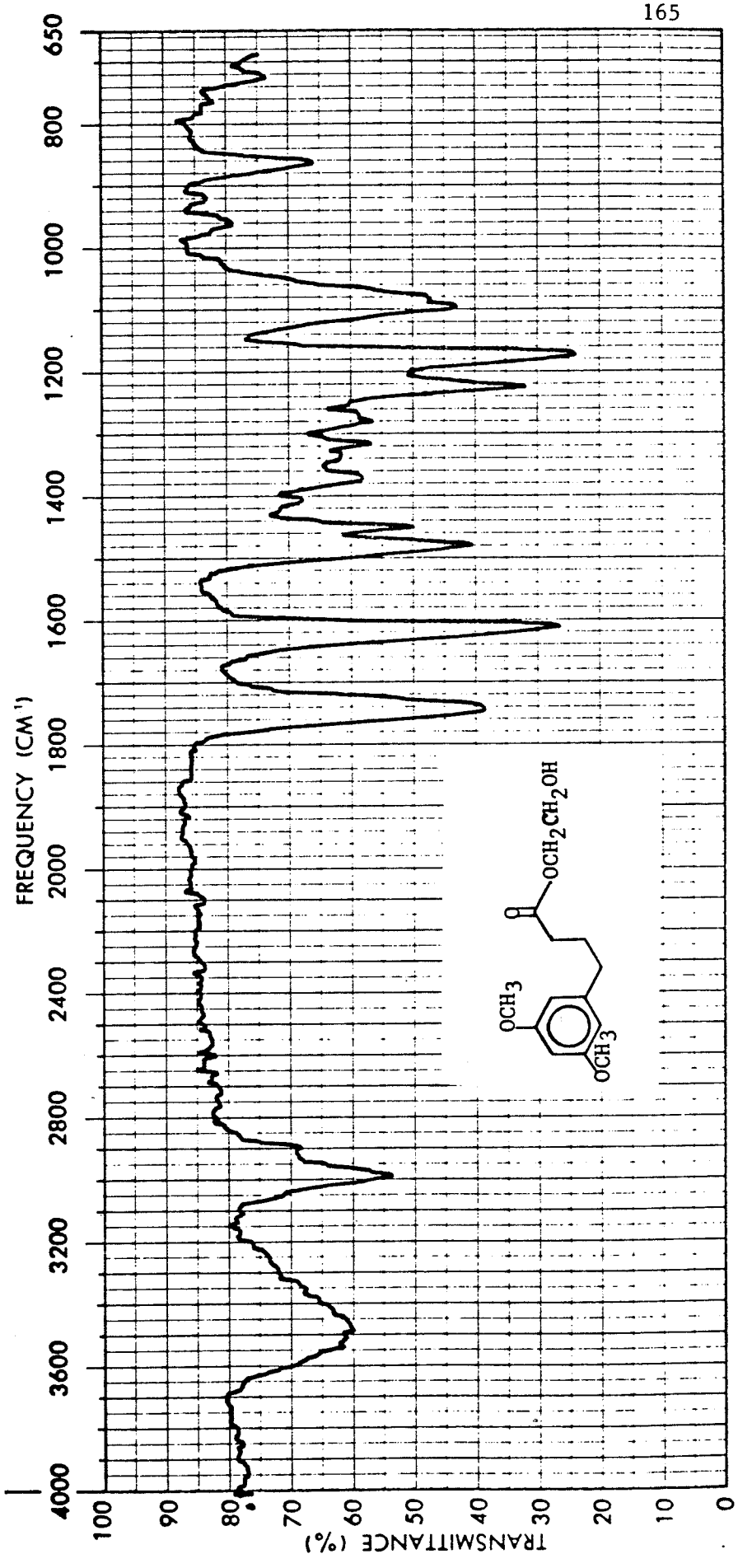
Methyl 4-(3',5'-dimethoxyphenyl)butanoate 33 (IR 9)



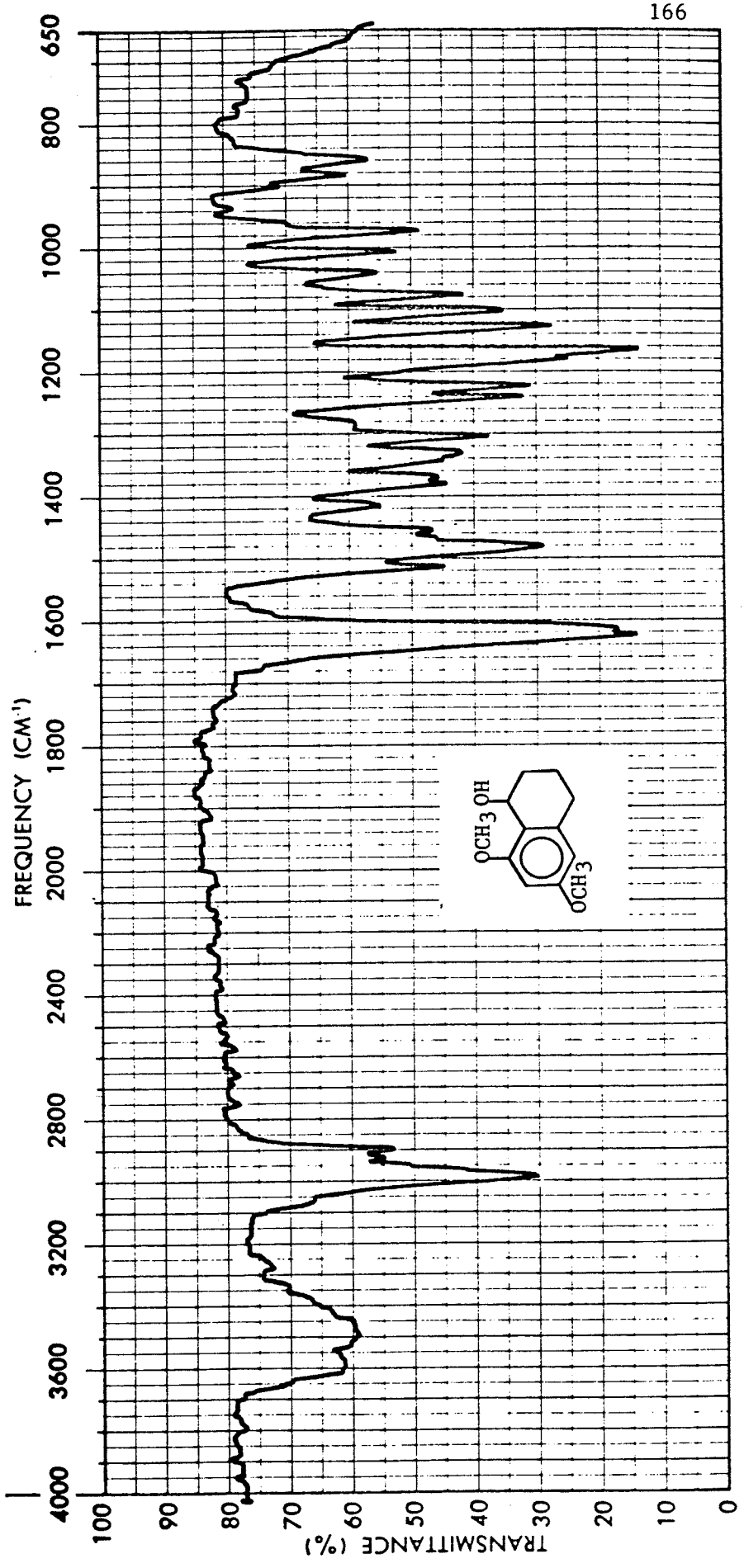
6,8-Dimethoxy-1-tetralone 32 (IR 10)



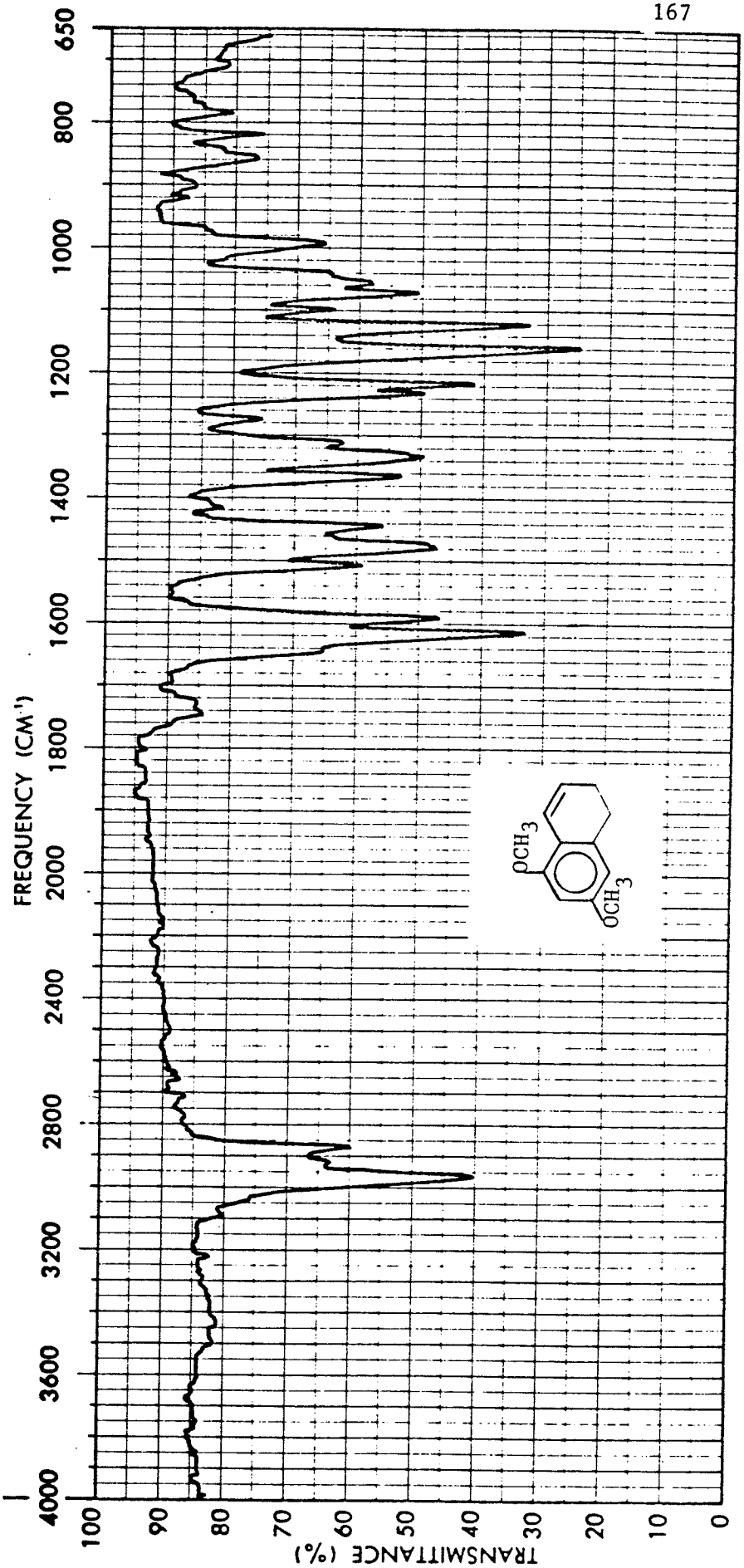
2-hydroxyethyl 4-(3',5'-dimethoxyphenyl)butanoate 85 (IR 11)



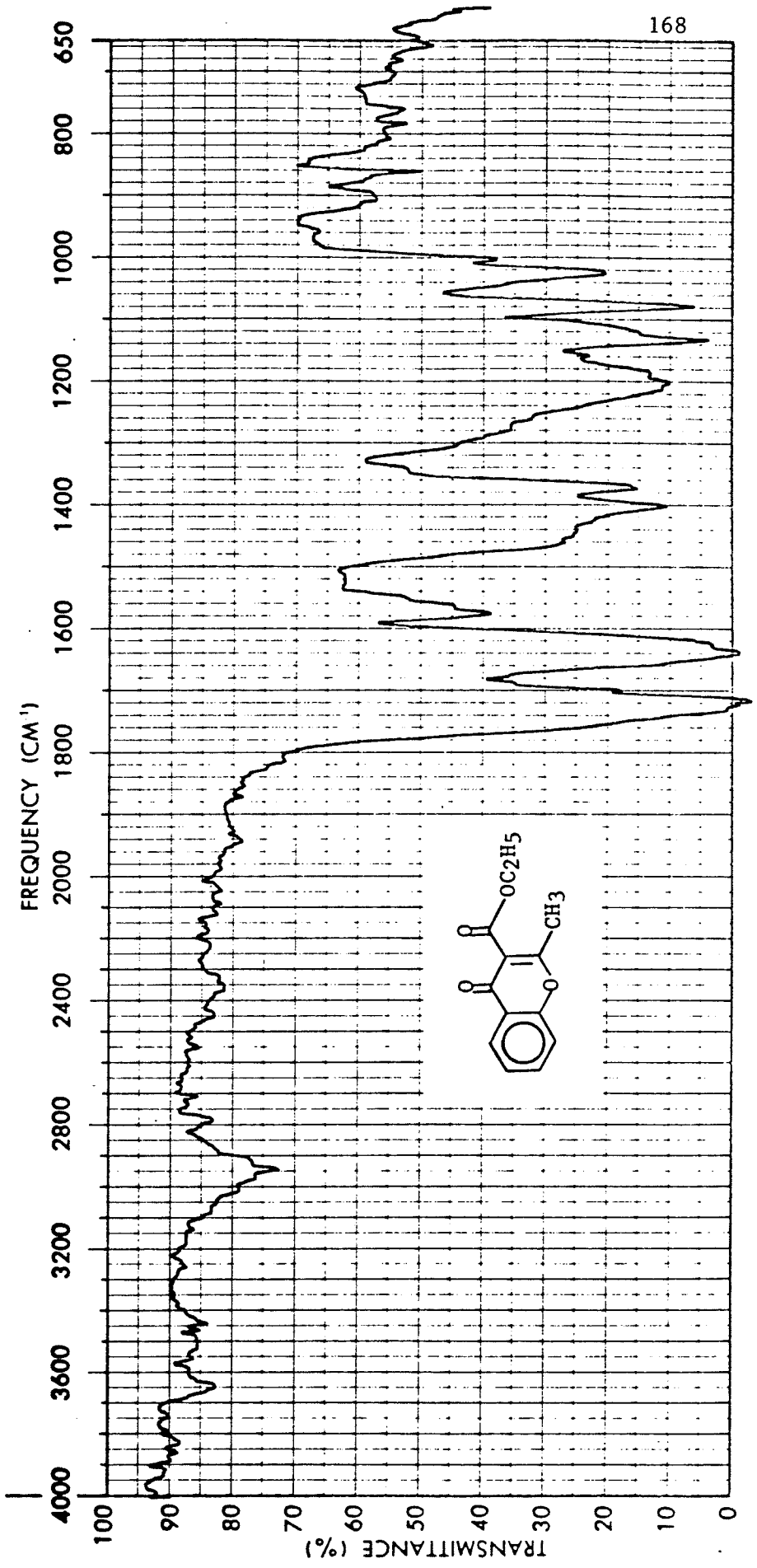
1-Hydroxy-6,8-dimethoxytetralin 86 (IR 12)

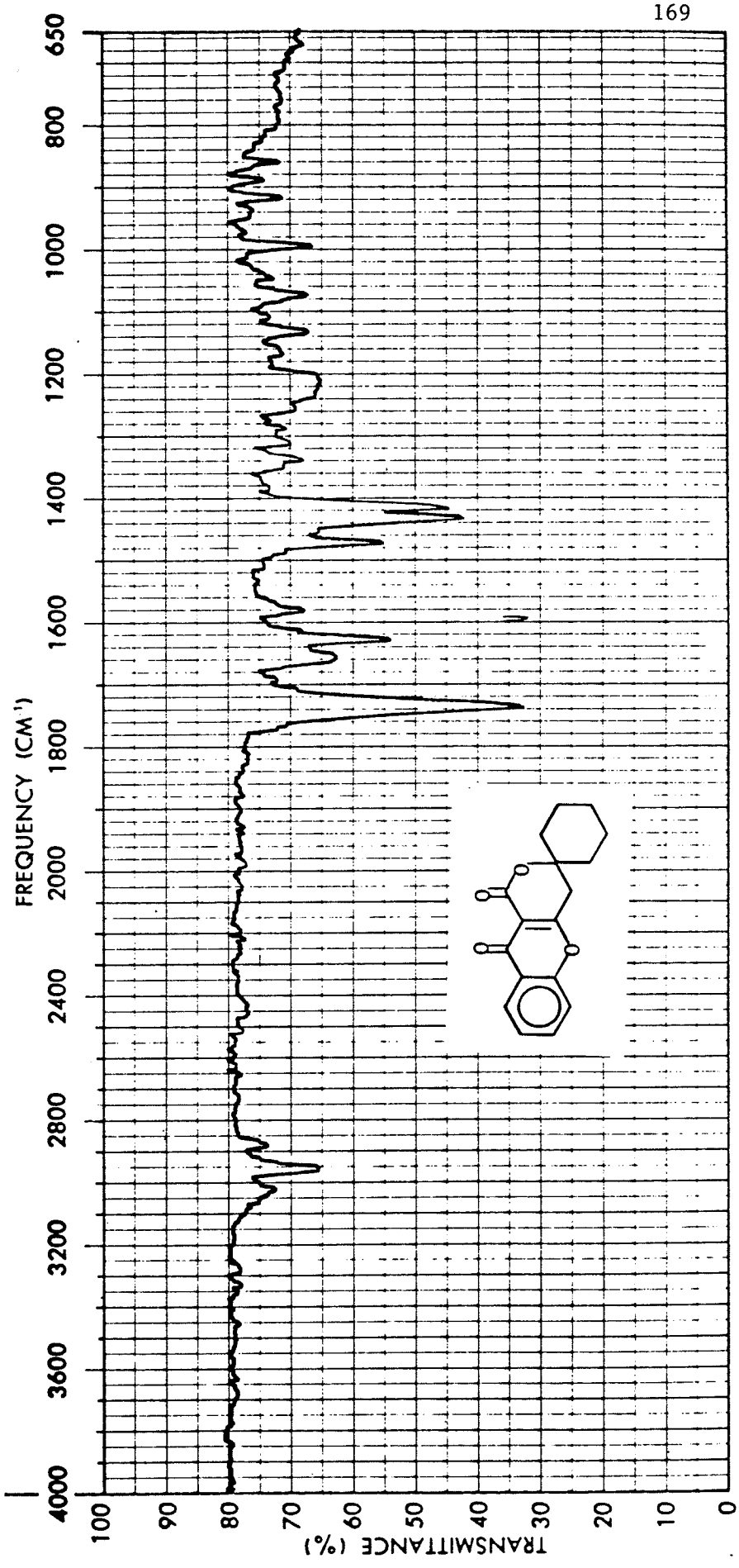


6,8-Dimethoxy-3,4-dihydroxynaphthalene 88 (IR 13)



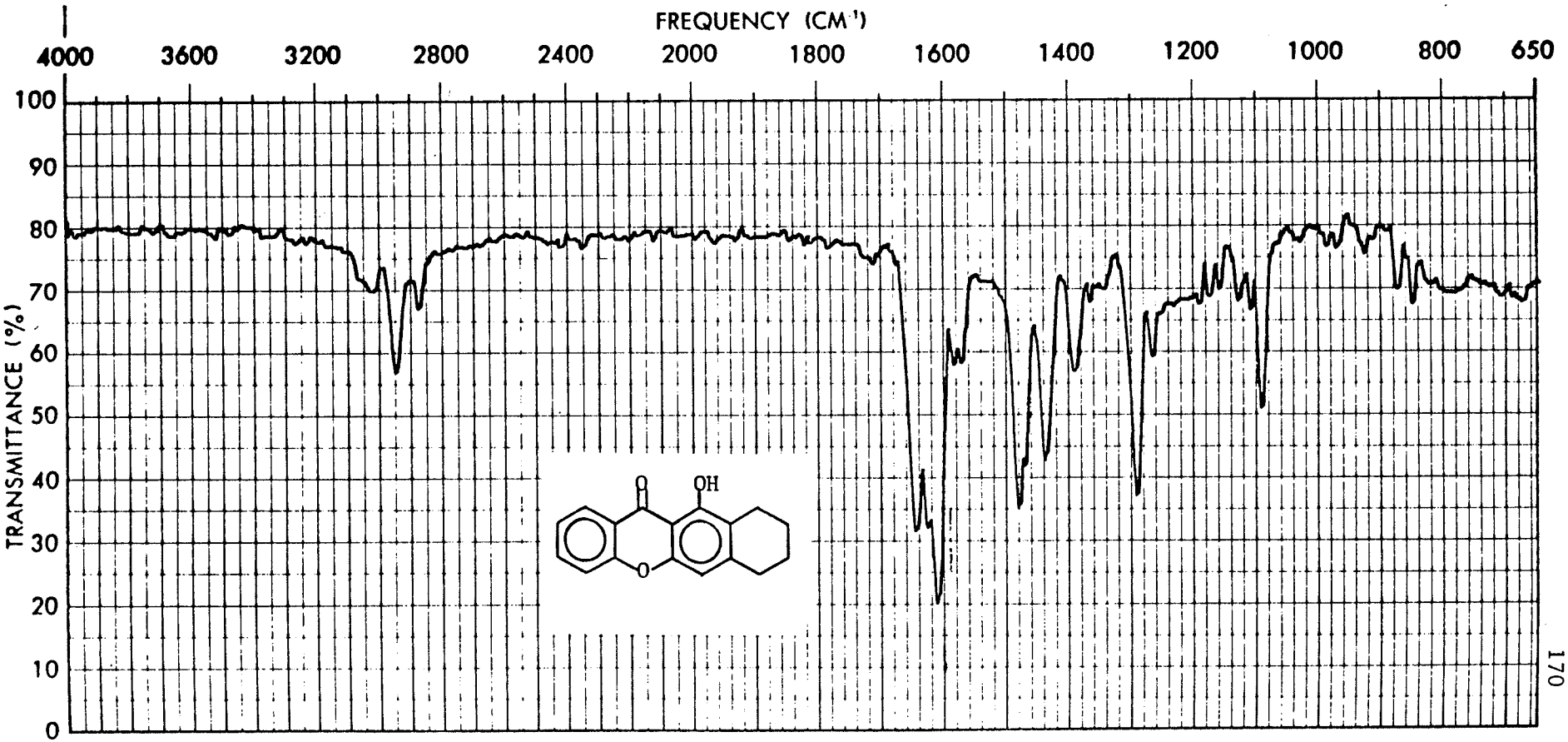
Ethyl 2-methylchromone-3-carboxylate 27 (IR 14)



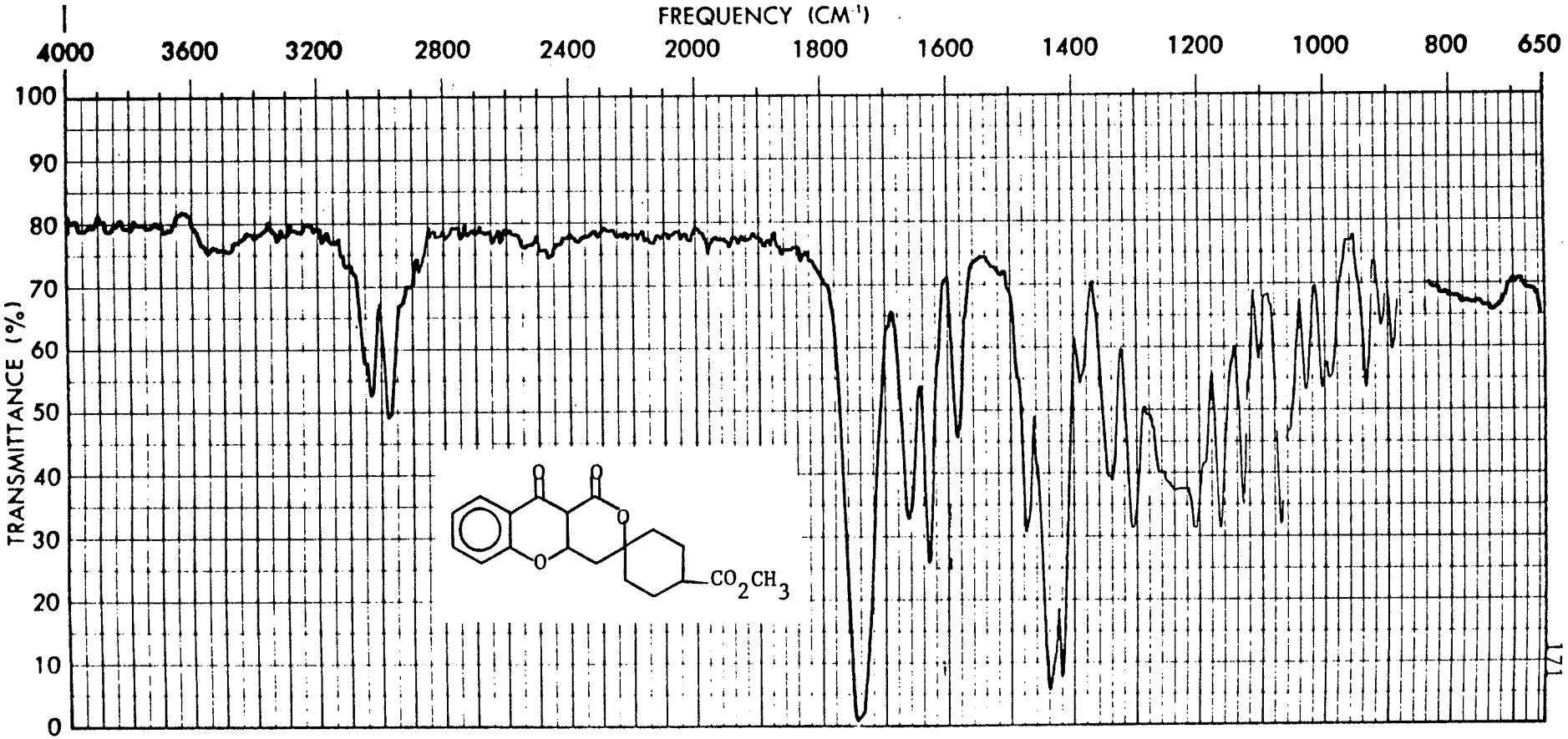


Spirolactone 105 (IR 15)

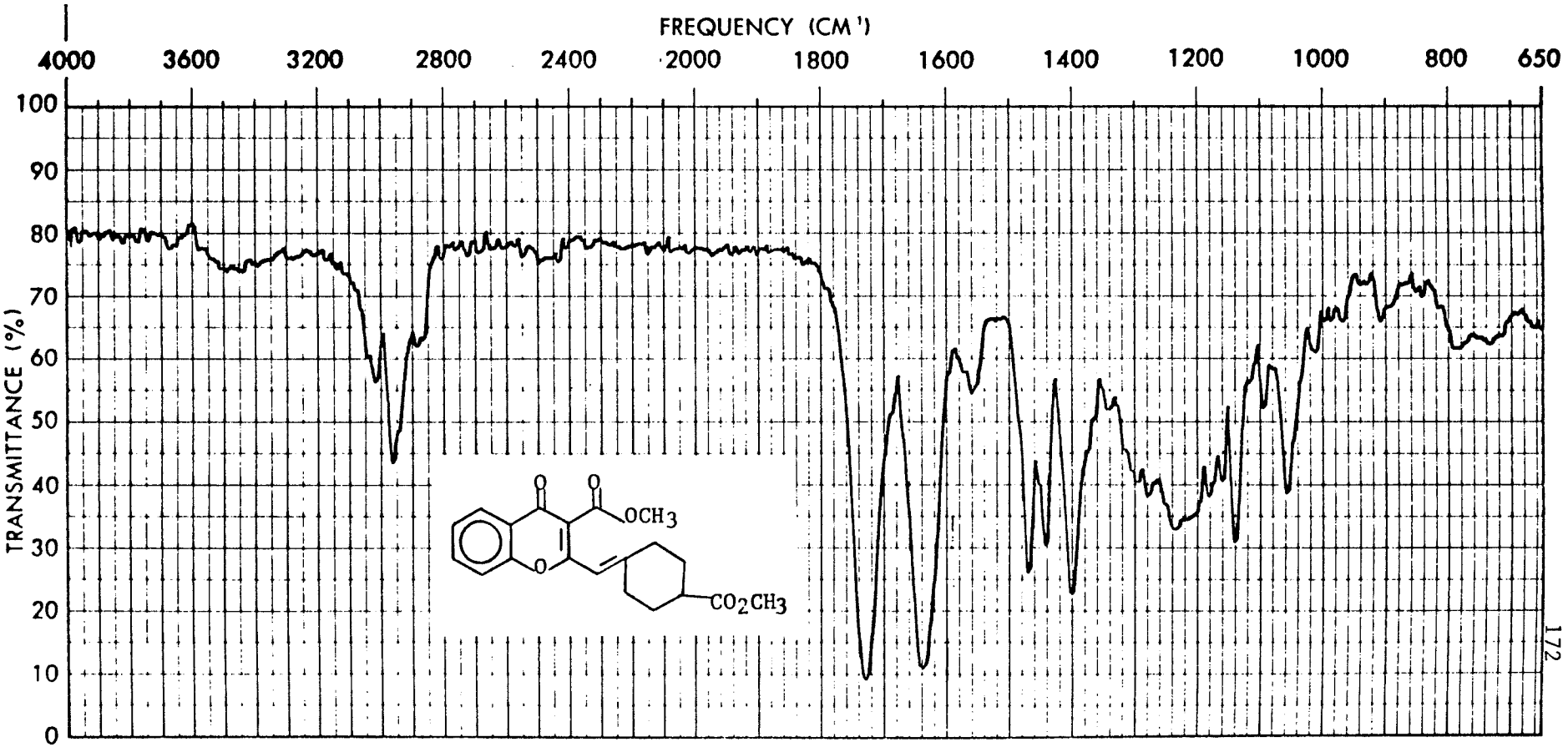
1-Hydroxy-2,3-cyclohexanoxanthene-9-one 99 (IR 16)



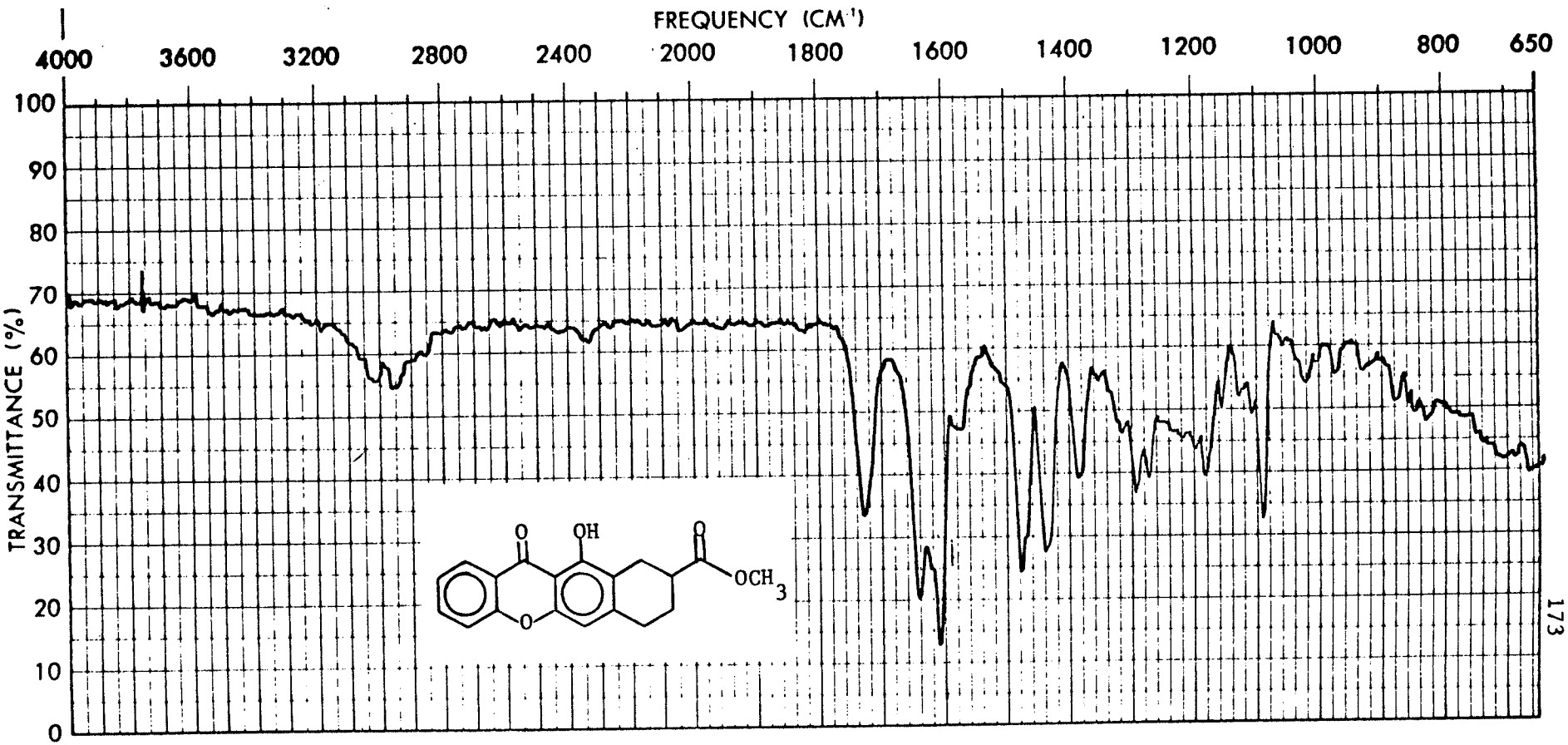
Carbomethoxy spirolactone 110 (IR 17)



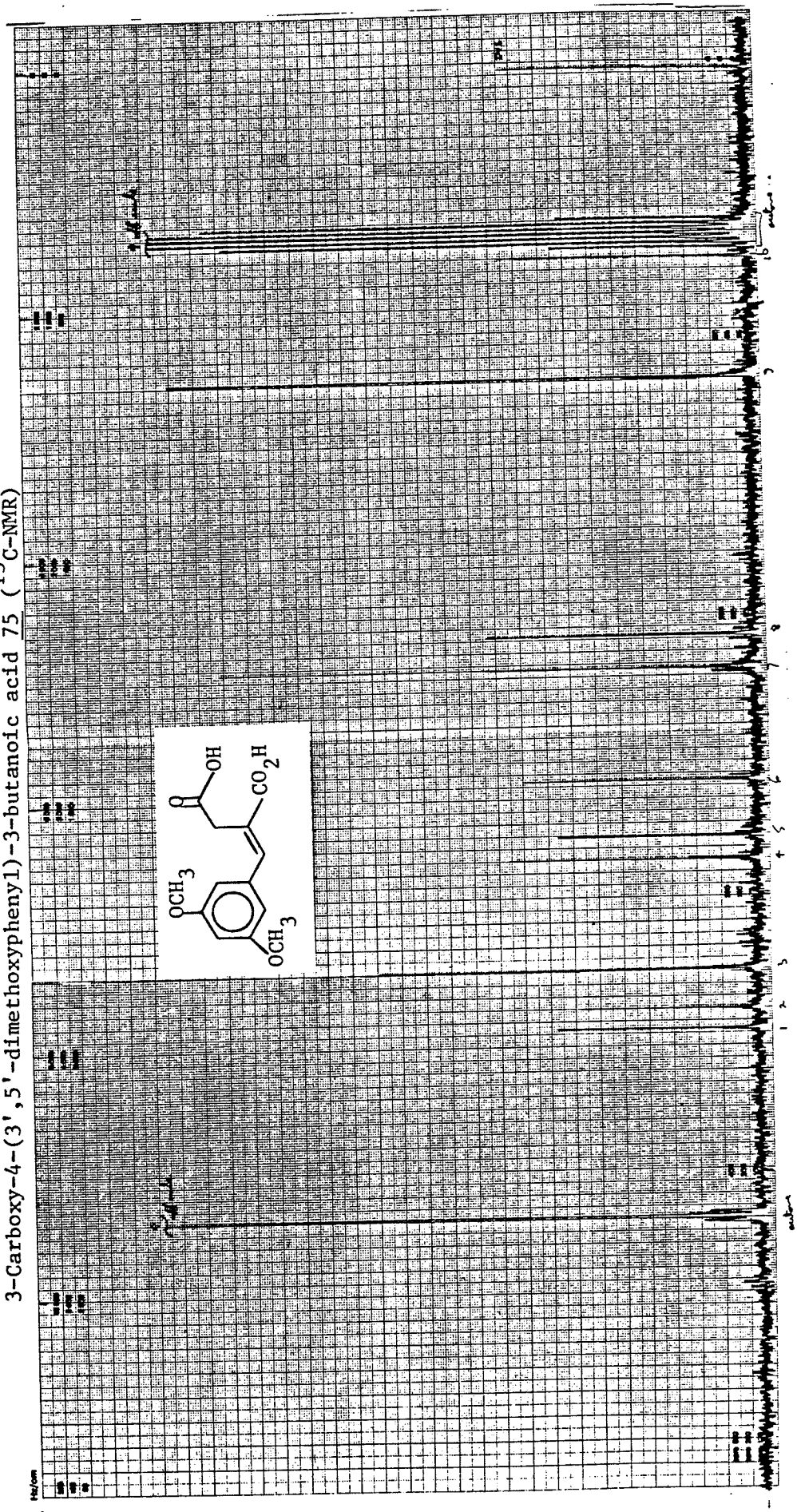
Carbomethoxy cyclohexylidenechromone ester 111 (IR 18)



Carbomethoxy hydroxyxanthocycline 22 (IR 19)



3-Carboxy-4-(3',5'-dimethoxyphenyl)-3-butanoic acid 75 (^{13}C-NMR)



1-Methoxy-3-methylxanthone 56 (ESR)