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APPROACHES TO THE SYNTHESIS OF DAUNOMYCINONE

by

William Lyon Studt

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
(Chemistry)
in The University of Michigan
1973

Doctoral Committee:

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To my wife, Jane,

and our children,

Robert, Daniel and Christine

ACKNOWLEDGEMENTS

I would like to thank Professor John R. Wiseman for his guidance throughout this research. His enthusiasm for the project and personal concern for his students made these years a very pleasurable experience. I would also like to thank my entire family for the support and encouragement which they have given me.

I would like to thank the American Cancer Society for fellowship support through a grant to Dr. Wiseman, The University of Michigan, for teaching fellowship and research fellowship support, and the Sun Oil Company for summer fellowship support.

TABLE OF CONTENTS

Dedication ii

Acknowledgements iii

Introduction 1

Experimental Results and Discussion 48

Introduction to the Problem 48

Researches into the Total Synthesis of Daunomycinone 56

Experimental 130

General 130

Preparation of 5,8-Dihydro-1,4-napthohydroquinone (118) 130

Preparation of 5,8-Dihydro-1,4-napthohydroquinone Diacetate (119) 131

Preparation of 5,6,7,8-Tetrahydro-1,4-napthohydroquinone-6,7-oxide Diacetate (137) . . 131

Attempted Preparation of 5,6,7,8-Tetrahydro-6-ethynyl-7-hydroxy-1,4-napthohydroquinone Diacetate (138) 132

Preparation of 1-Chloro-5-hydroxyanthraquinone (132) 133

Preparation of Ethyl Levulinate (124) 134

Attempted Stobbe Condensation of Benzaldehyde and Ethy Levulinate (124) 134

Preparation of Ethyl 3-Carbomethoxylevulinate (146) 136

Preparation of Methyl γ-Methyl Paraconate (147) . 137

Preparation of di-tertiary-Butyl 2-(1-Hydroxy-ethyl) Succinate 137

Preparation of γ-Methyl Paraconic Acid (145) . . . 138

Preparation of 1-Hydroxy-5-methoxyanthraquinone (149) 139

Imidomethylation of 1-Chloro-5-hydroxyanthraquinone with N-methylolphthalimide (152) . . . 140

Preparation of 1-Acetoxy-4-bromo-5-chloroanthraquinone (163) 141

Preparation of 1-Hydroxy-2-chloromethyl-5-chloroanthraquinone (148) 142

Preparation of Methyl 3-Carbomethoxy Levulinate (166) 143

Preparation of Methyl 3-Acetyl-3-carbomethoxy-4-(1-hydroxy-5-chloro-2-anthraquinonyl) butyrate (168) 144

Attempted Preparation of 3-Acetyl-3-carbomethoxy-4-(1-hydroxy-5-chloro-2-anthraquinonyl) Butyrate Ethylene Ketal (169) 145

Preparation of Ethyl 3-Carbomethoxylevulinate Ethylene Ketal (170) 146

Preparation of tertiary-Butyl Bromoacetate (171). 146

Preparation of tertiary-Butyl Acetoacetate (172). 147

Preparation of di-tertiary-butyl 2-Acetyl-succinate (173) 148

Preparation of di-tertiary-Butyl 2-Acetyl-2-(1-hydroxy-5-chloro-2-anthraquinonyl) Methyl Succinate (174) 149

Preparation of Ethyl 3-(1-hydroxy-5-chloro-2-anthraquinonyl) Methyl Levulinate (175) 150

Preparation of 1-Acetamido-8-chloro-4-hydroxy-anthraquinone (181) 151

Preparation of Ethyl 3-(1-Hydroxy-4-nitro-5-chloro-2-anthraquinonyl) Methyl Levulinate (189) 152

Preparation of Ethyl 3-(1-Hydroxy-4-bromo-5-chloro-2-anthraquinonyl) Methyl Levulinate (190) 153

Preparation of di-tertiary-Butyl 2-Acetyl-2-(1-hydroxy-4-bromo-5-chloro-2-anthraquinonyl) Methyl Succinate (191) 154

Preparation of Ethyl 3-(1-Hydroxy-4-nitro-5-chloro-2-anthraquinonyl) Methyl Levulinate Ethylene Ketal (194) 155

Preparation of Ethyl 3-(1-Hydroxy-4-amino-5-chloro-2-anthraquinonyl) Methyl Levulinate Ethylene Ketal (195) 156

Preparation of Triethyl 1-(1-Hydroxy-5-Chloro-2-anthraquinonyl) Methyl-1,1,2-ethane Tricarboxylate (198) 156

Preparation of Triethyl 1-(1-Hydroxy-4-bromo-5-chloro-2-anthraquinonyl) Methyl-1,1,2-Ethane Tricarboxylate (199) 157

Attempted Potassium Hydroxide Fusion of 199 . . . 158

Attempted Sodium Hydroxide Hydrolysis of 199. . . 159

Attempted Hydrolysis of 195 160

Preparation of Leucoquinizarin (229). 161

Preparation of Triethyl 1-(1-Hydroxy-4-nitro-5-chloro-2-anthraquinonyl) Methyl-1,1,2-ethane tricarboxylate (232) 161

Appendix, NMR and IR Spectra of Selected Compounds . . 163

Bibliography 188

LIST OF FIGURES

Figure		Page
1.	Substitution patterns determining the nomenclature of the anthracyclinone subclasses.	3
2.	Numbering and ring designation in daunomycin (3)	8
3.	Comparison of visible spectra of 16, 1,6,7,11-tetrahydroxy-5,12-napthacenedione and 1,6,10,11-tetrahydroxy-5,12-napthacenedione . . .	17

INTRODUCTION

The isolation of actinomycin in 1940 by Waksam and Woodruff,[1] from the bacterium Streptomyces antibioticus, led the way to the discovery of many medicinally useful natural products which occur in the genus Streptomyces. Among these have been the tetracyclines[2] and the anthracyclines.[3] The anthracylines are a class of glycosides composed of a sugar moiety and an aglycone, or non-sugar portion, referred to in this case as an anthracyclinone.

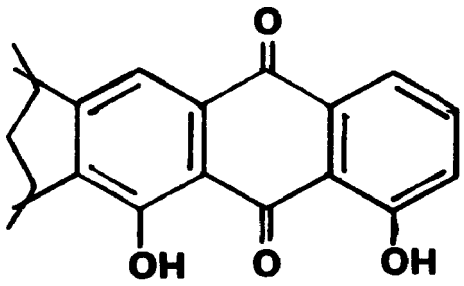
The anthracyclinones are a class of naturally occuring quinones which are found solely in the various species of the Streptomyces bacteria.[4] The anthracyclinones, of which about 30 examples are known, are characterized by a napthacenequinone carbon skeleton in which one of the four rings is usually saturated. The three remaining rings form the chromophoric portion of the system and are recognizable as substituted 9,10-anthraquinones. The presence of the anthraquinone chromophore was acknowledged by Brockmann[5] when he gave the names anthracyclinones and anthracyclines to these classes of compounds. The anthracyclinones are highly oxygenated species and differ from the naturally occurring anthraquinones, which are found primarily in fungi, by the appearance of oxygen functions only on the alpha positions of the anthraquinone nucleus.[6] The distribution of the functionality on the anthraquinone nucleus has led to the division of this class of

compounds into six subclasses,[6] as shown in Figure I.

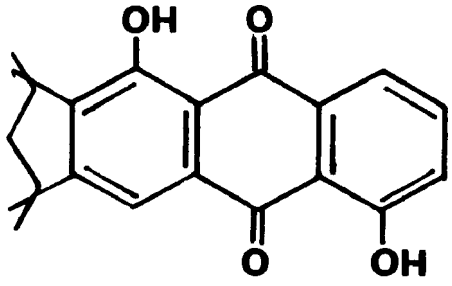
In his extensive studies of the anthracyclinones, Brockmann[3] has designated the individual members of the above subclasses with Greek letters according to their behavior on chromatography. He assigned them alphabetically in the order of increasing R_f values. Brockmann[7] has also suggested that the anthracyclinones are formed biogenetically by the acetate-malonate pathway as is described for quinones by Birch.[8]

Daunomycinone(1), the subject of this work, because of its substitution pattern is a member of the rhodomycinone subclass of the anthracyclinones. Daunomycinone occurs in nature as a glycoside, in which the amino sugar daunosamine(2) is bonded through a glycosidic link to the C-7 position of daunomycinone. The anthracycline formed by this combination of aglycone and amino sugar is variously known as daunomycin(3),[9] daunorubicin,[10] rubidomycin[11] and rubomycin C.[12]

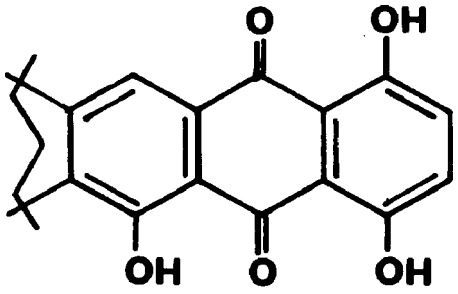
Daunomycin was discovered independently by two groups at approximately the same time. In 1962, a French group[11,13,14] from the Rhone-Poulenc Laboratories in Paris applied for a French patent on three compounds which they had isolated from the bacterium Streptomyces caeruleosubiclus. One of these materials they called rubidomycin. Shortly thereafter a series of publications, from DiMarco[9,15-19] and coworkers at Farmitalia Laboratories



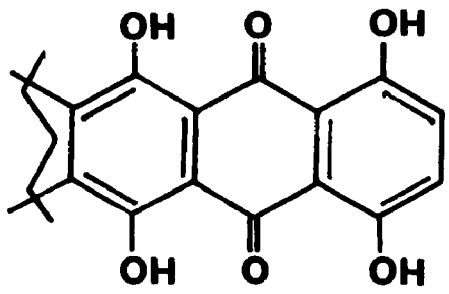
Aklavinones



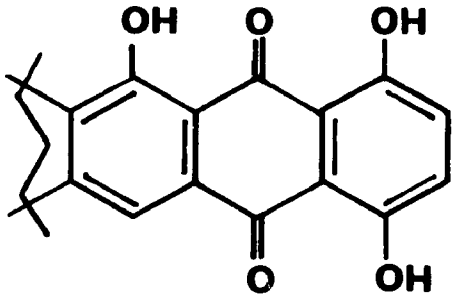
Citromycinones

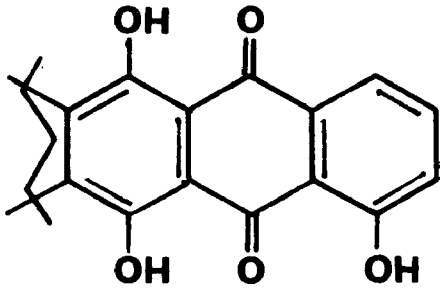


Pyrromycinones

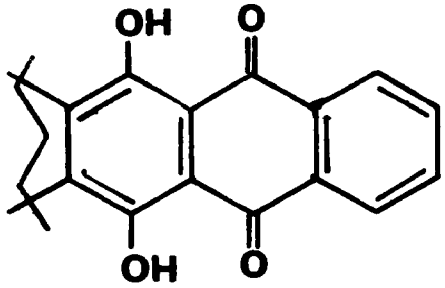


iso-Rhodomycinones



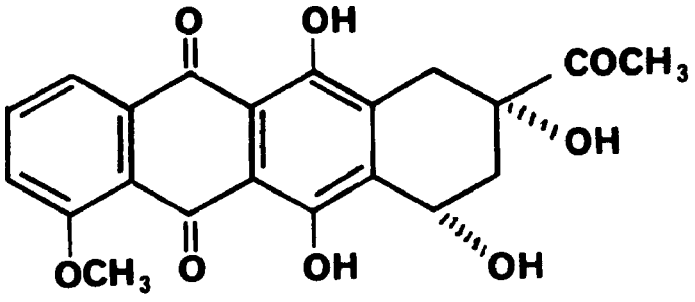


Rhodomycinones

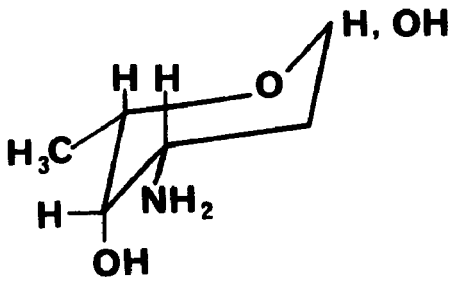


Reticulomycinones

Figure 1. Substitution patterns determining the nomenclature of the anthracyclinone subclasses.



1



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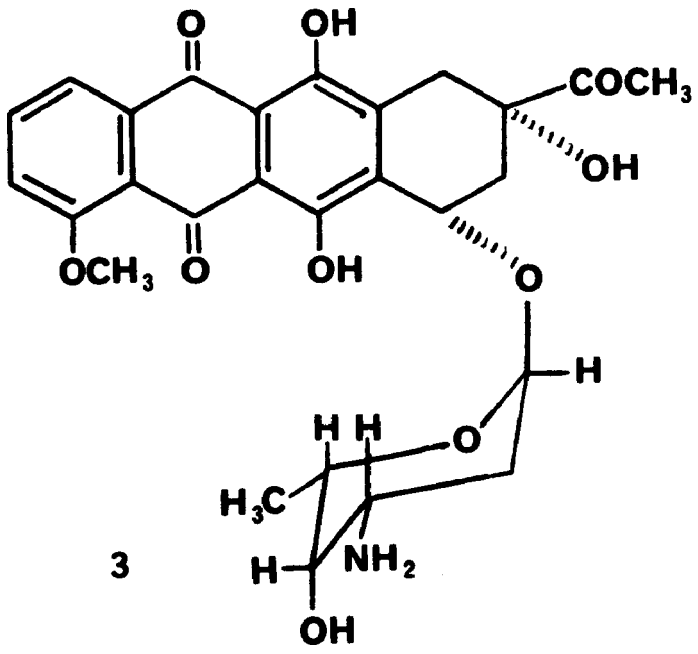


3

in Milan, Italy, described a substance called daunomycin which they had isolated from the newly characterized bacterium Streptomycis peucetius. A few years later in Russia a substance known as rubomycin, obtained from

Streptomyces antibioticus was found by chromatography to be a mixture of three compounds. The fastest moving component on thin layer chromatography became known as rubomycin C.[12,20]

DiMarco[17] and Despois[21] suggested, based on the similarity of uv and ir spectra and chromatographic behavior, that daunomycin and rubidomycin should be considered identical. It was not however until a few years later that Goodman[22] and coworkers were able to state definitely that the two antibiotics were identical. Goodman[22] noted that daunomycin, as prepared by the Italian firm, Farmitalia, was homogeneous on chromatography, whereas the rubidomycin, which was prepared by the French firm of Rhone-Poulenc, contained a small amount of the free aglycone. It was only after extensive purification of the two antibiotics and preparation of the pentabenzoate derivative of each that he could show beyond doubt, using ir, nmr, uv, chromatography and X-ray techniques that daunomycin and rubidomycin were indeed identical. At about the same time Despois[23] demonstrated the pharmacological identity of daunomycin and rubidomycin. In a 1969 review on rubidomycin[4] the identity of rubomycin C and rubidomycin was established by comparison of published spectral, physical and analytical data as well as by comparative chromatographic evaluation of the two substances.

Daunomycin(3), as it is isolated from Streptomyces peucetius, is obtained as its hydrochloride salt in thin red needles, mp 184-186°C. As an antibiotic daunomycin exhibits an inhibiting effect upon Gram-positive microorganisms.[19] However, the most promising use of daunomycin is in the areas of tumor inhibition and leukemia treatment. The early reports of DiMarco[15,18,19,23] and coworkers indicated that the effectiveness of daunomycin(3) against implanted animal tumors was very good and that clinical trials should be begun. At this same time DiMarco[24,25] also determined the effect of daunomycin on normal cells in vitro. DiMarco[19] felt that daunomycin owed its antitumor activity to its ability to complex with DNA and thereby inhibit cellular replication by the inhibition of RNA synthesis. However, Theologides [26] and coworkers have shown that the inhibition of DNA synthesis and splitting by daunomycin(3) is more efficient and perhaps has a more important effect on the replication of cells then does the inhibition of RNA synthesis. These findings have been supported by Gause[27] who has carried out a similar investigation using rubomycin C. The way in which daunomycin complexes with DNA is beyond the scope of this work. However, for those interested a thorough discussion of this phenomenon has been presented by Calendi [28] and coworkers.

The medicinal uses of daunomycin, which have been studied extensively in clinical situations, are out of context with the remainder of this work and will not be considered here. For interested readers, however, this area is well covered in Volume 20 of the "Recent Results in Cancer Research" series,[4] and in a collection of papers delivered at the "Symposium on Daunomycin and Rubidomycin" held in 1967 at Saint Louis Hospital in Paris.[28] Perhaps the areas of most clinical interest in daunomycin(3) research, acute myelocytic leukemia and myelogenous leukemia are dealt with very effectively by Boiron[29] and Bornstein,[30] respectively. The side effects and disadvantages of daunomycin treatment are covered quite well by Tan[31] and coworkers, and the pharmacokinetic properties of daunomycin in man have been the subject of a recent study by Alberts[32] and coworkers.

The intense interest in daunomycin as an antitumor and antileukemia agent necessitated the elucidation of the structure and stereochemical configuration of the antibiotic substance. The successful structure determination and stereochemical assignment for daunomycin(3) has been presented in a series of papers by Arcamone,[33-38] Despois[21] and Iwamoto.[39] The reasoning which led to the structural and stereochemical assignments follows.

Daunomycin(3) (hydrochloride salt, $C_{27}H_{29}O_{10}N \cdot HCl$, mp 188-190°C, $[\alpha]_D$ = + 253 C = 0.15 CH_3OH) undergoes a

readily reversible reduction, either chemically or polarographically (0.62 ev), indicating the presence of a quinoid type of functionality.[33] Examination of the electronic spectra of 3 indicated a very close resemblance to 1,4,5-trihydroxyanthraquinone. Mild acid hydrolysis of 3, with either 0.2N hydrochloric acid at 90°C for one hour[31] or 1N sulfuric acid at 100°C for one hour,[21] gave a red crystalline aglycone, or non-sugar moiety, called daunomycinone (1) ($C_{21}H_{18}O_8$, mp 213-214°C, $[\alpha]_D^{20°}$ + 193° C = 0.1 dioxane) and a new amino sugar daunosamine (2) (hydrochloride salt, $C_6H_{13}O_3N \cdot HCl$, mp 168°C dec, $[\alpha]_D^{20°C}$ -54.5° at equilibrium in H_2O).

Throughout the following discussion the designation of rings as A, B, C, or D and the numbering will be that which is shown in Figure 2.

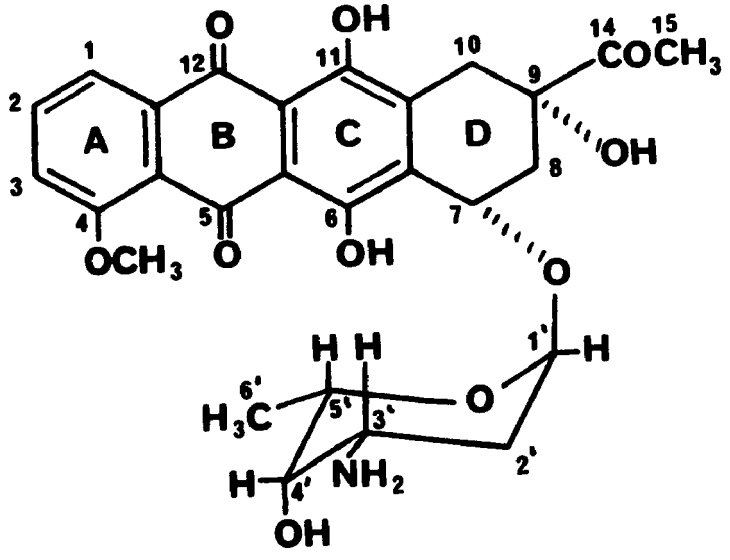
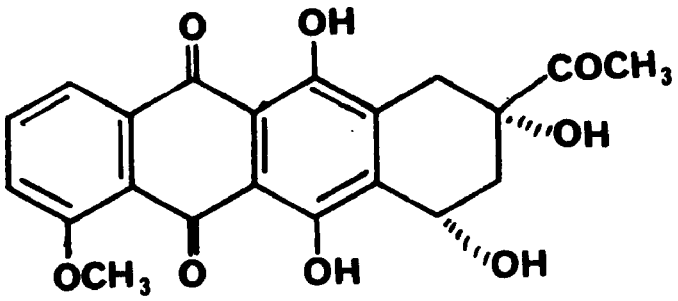
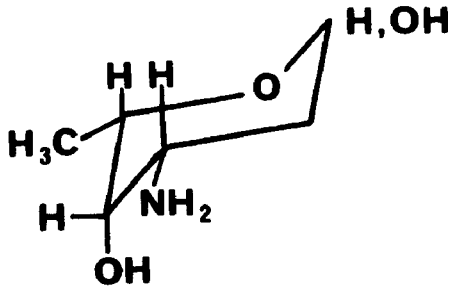


Figure 2. Numbering and ring designation in daunomycin (3).



1



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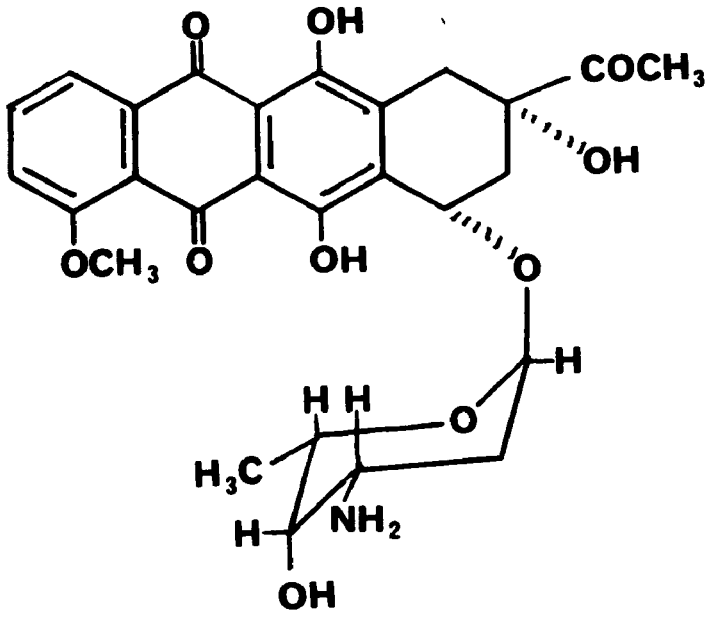
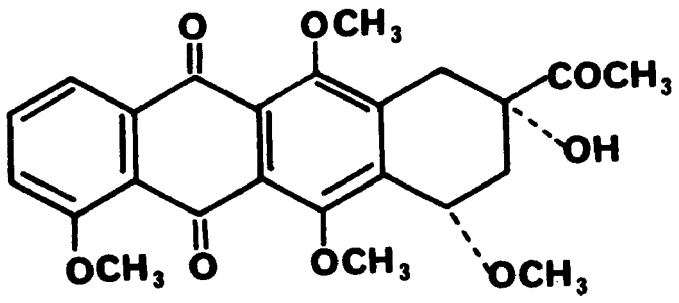


3

A preliminary spectrum[33] of 1 showed an O-CH_3 singlet at 4.04δ, an acetyl methyl type singlet 2.69δ, broad absorptions at 2.67δ(2H), 3.27δ(2H) and 7.1-7.9δ(3H) as well as a broad 1-H signal at 5.50δ which was assigned as

a hydrogen on a carbon atom bearing an hydroxy function, due to its downfield shift to 6.42δ on acetylation. When 1 was distilled from zinc dust, tetracene was formed,[33] indicating that the basic carbon skeleton of 1 was a linear tetracycle. The ir spectrum of 1 showed a carbonyl absorption at 1718 cm^{-1} which was assigned as an aliphatic methyl ketone based on the 2.69δ signal in the nmr spectrum and the facile formation of a 2,4-dinitrophenylhydrazone derivative[33] and a semicarbazone derivative (mp 236-238°C).[38] When 1 was boiled under reflux in acetone containing dimethyl sulfate and potassium carbonate a tetramethylether(4) was obtained.



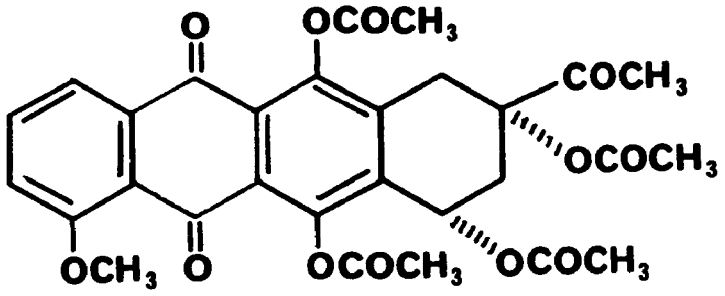
4

The nmr spectrum[38] of 4 showed one aliphatic o-methyl at 3.65δ, three aromatic o-methyls at 4.00(6H) and 3.89δ (3H), two doublets centered at 3.02δ(1H) and 3.22δ(1H)

(J = 18.5 Hz) which suggested geminal coupling on a methylene alpha to an aromatic ring and with no vicinal hydrogens. There were also two symmetrical doublets at 1.87δ(1H) and 2.42δ(1H) which were assigned as H_A and H_B of an ABX system where H_X is on a carbon atom bearing an oxygen function and appears at 4.92δ. The J_{AB} value of the ABX system was 15 Hz and suggested geminal coupling of methylene protons which as indicated by their chemical shift values are beta to an aromatic ring. There was also present in the spectrum a one proton singlet at 5.02δ which was assigned as the proton of a free hydroxyl due to its upfield shift on dilution of the sample and downfield shift when acid was added to the sample.

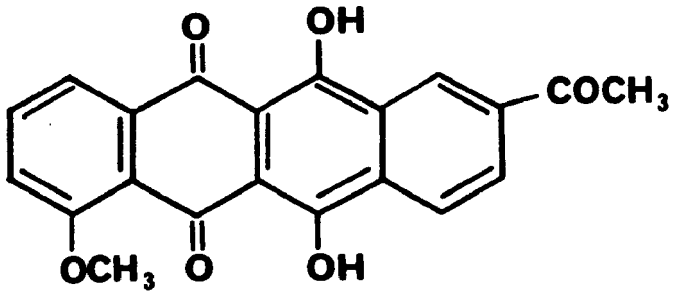
Treatment of 1 with sodium borohydride followed by sodium periodate produced acetaldehyde, which was identified by formation of its 2,4-dinitrophenylhydrazone derivative. The formation of acetaldehyde upon periodate oxidation indicated the presence in 1 of a carbon atom bearing an acetyl group and an hydroxyl function. The presence of four hydroxyls was indicated by the acetylation of 1 with acetic anhydride and pyridine which gave the tetraacetate 5.

The ir spectrum[33] of 5 showed absorptions at 1776 cm^{-1} and 1740 cm^{-1} which indicated the presence of aromatic and aliphatic acetates, respectively. Treatment of 1 with either acids or bases led to the isolation of bis-



5

anhydrodaunomycinone(6), mp 325-330°C, which had an absorption at 1765 cm^{-1} for a conjugated ketone in its ir spectrum.[33] Acetylation of 6 gave a diacetate with no

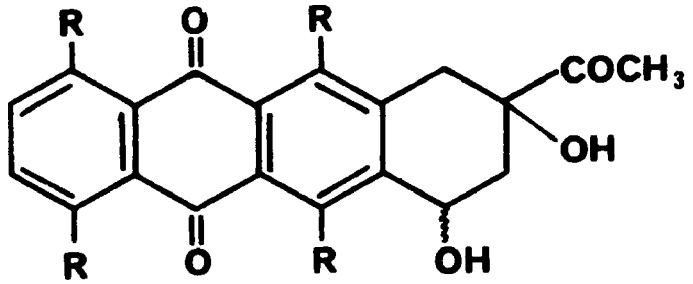


6

1740 cm^{-1} absorption in its ir spectrum and therefore no aliphatic acetates.

The foregoing information suggests a compound in which there are two phenolic hydroxyls and two aliphatic

hydroxyls one of which is on a carbon atom bearing an acetyl function. There is an aromatic methoxyl group, a methylene alpha to an aromatic ring and with no vicinal hydrogens, and a methylene unit with one alpha hydrogen which is on a carbon atom bearing an hydroxyl function. The formulated structure 7 was well substantiated and clarified by two reactions.[33] Alkaline fusion of 1 gave

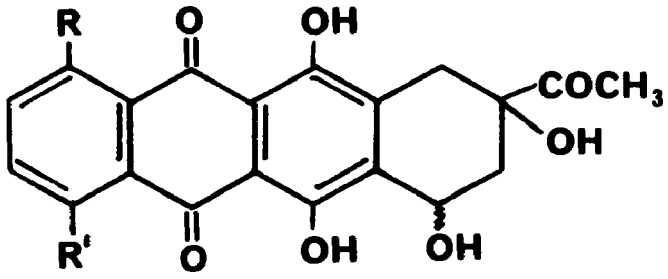


7

R = H, OCH_3, OH, OH

salicylic acid and potassium permanganate oxidation of 6 gave 1,2,4-benzene tricarboxylic acid from the D ring and 3-methoxyphthalic acid from the A ring. Based on what was known to this time, daunomycinone was assigned[33] as either 8 or 9.

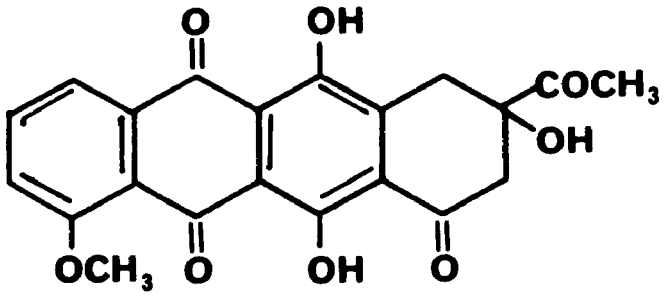
At this time the position of all the functionality was known except for the methoxyl group which was known to be at either C-1 or C-4 of the A ring. Arcamone[36,38] and Iwamoto[39] used different techniques to show that daunomycinone(1) had the structure shown for 9. When 1



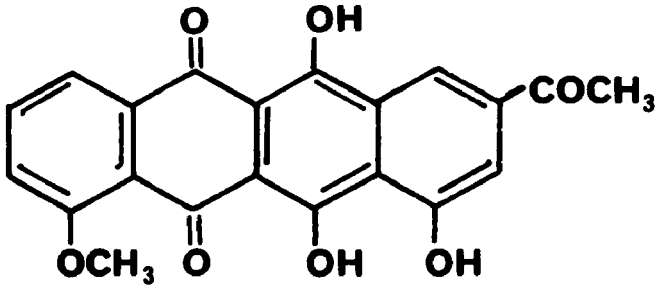
8 $R = OCH_3$, $R' = H$

9 $R = H$, $R' = OCH_3$

was oxidized with chromium trioxide in acetic acid, the diketone 10 was obtained which was smoothly aromatized to 11 on treatment with aqueous base.[33] Demethylation of 11



10



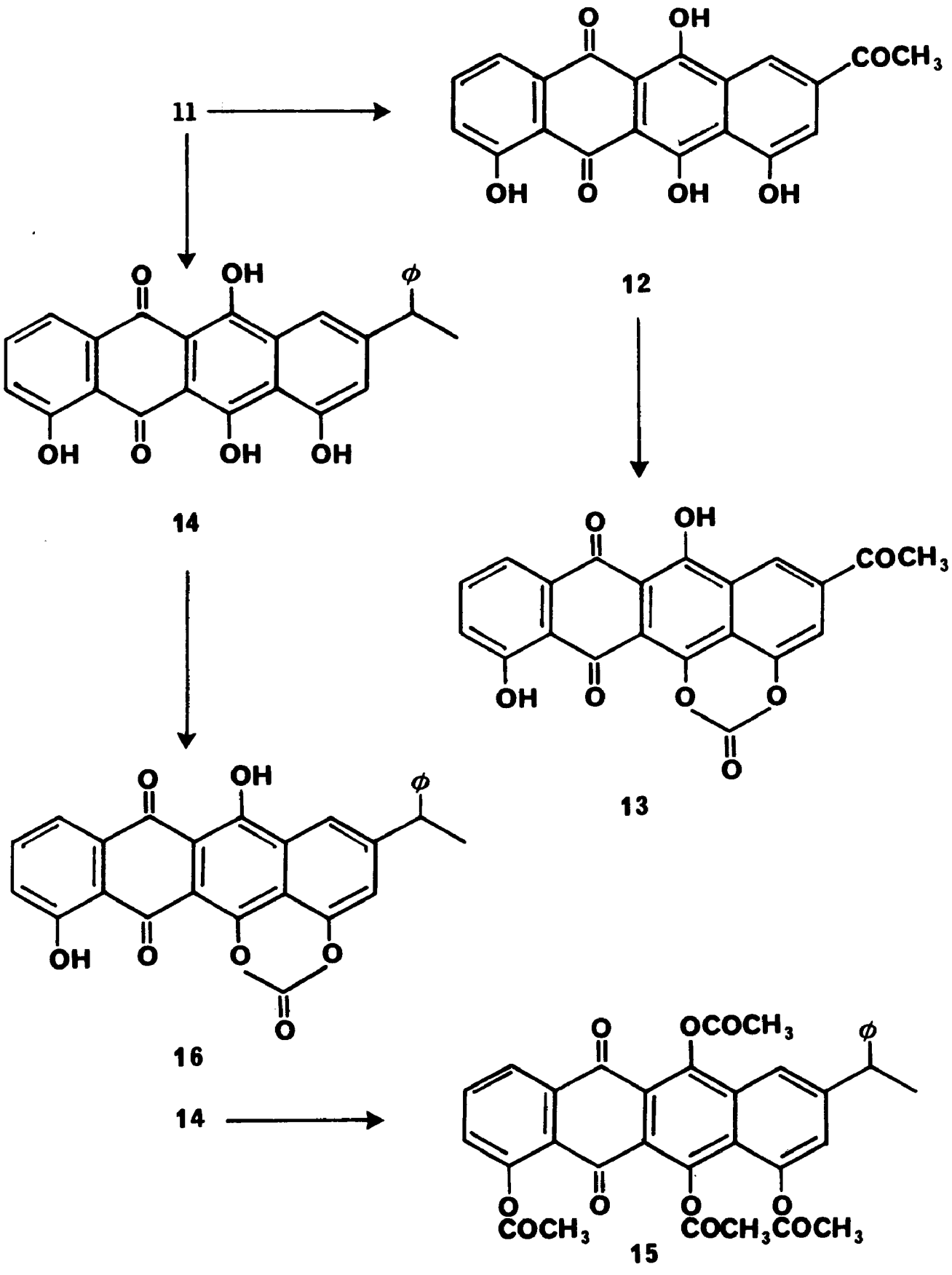
11

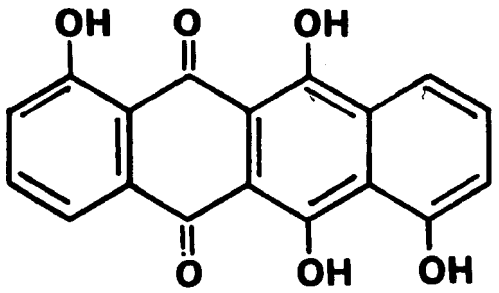
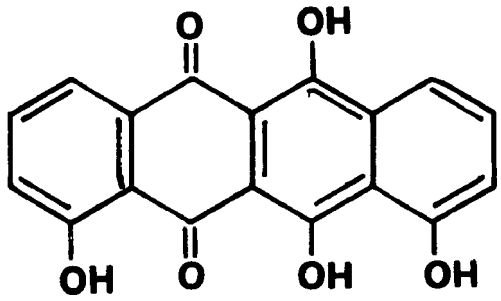
with aluminum chloride in dichloroethane gave the ketone 12 which on treatment with phosgene and pyridine followed by hydrolysis of the unwanted chloroformate esters with aqueous sodium bicarbonate gave the keto carbonate 13.[36]

The ultraviolet and visible spectra of 13 resembled those of 1,6,10,11-tetrahydroxy-5,12-napthacenedione except for a slight bathochromic shift which was caused by the presence of the keto function at C-9. However, when 11 was demethylated with aluminum chloride in benzene a Friedel-Crafts reaction with the solvent also took place and gave the tetrahydroxy compound 14. Acetylation of 14 with acetic anhydride and pyridine gave the tetraacetate 15 (mp 218-220°C) which had an absorption at 1660 cm^{-1} in its ir spectrum,[38] assigned to the unchelated quinone carbonyls. Treatment of 14 with phosgene and pyridine followed as before by hydrolyses of the chloroformate esters gave the carbonate 16.

The ir spectra of carbonates 13 and 16 showed no absorption at 1660 cm^{-1} which indicated that in each case both of the quinone carbonyls are hydrogen bonded.[36,38] A situation which requires that the two free hydroxyls be situated at C-4 and C-11. Moreover, the ultraviolet and visible spectra of 16 were found by Arcamone[38] to be identical to those of 1,6,10,11-tetrahydroxy-5,12-napthacenedione as shown in Figure 3.

Iwamoto[39] noticed that if after the 220 MHz nmr spectrum of daunomycin(3) in acetone-d_6 was recorded, the sample was warmed slightly and the spectrum rerun, there appeared two sets of absorptions for the protons of the amino sugar as well as two distinct signals for the


11
12
14
13
16
14
15

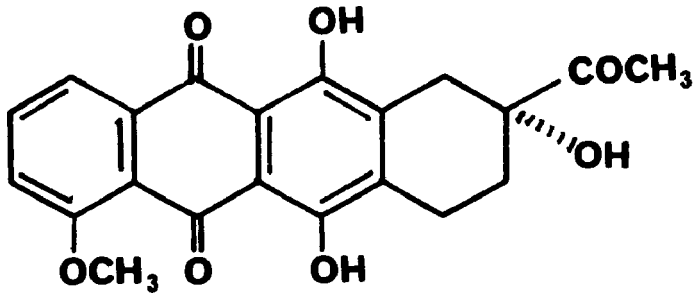
	Chloroform	DMF	Piperidine
16	482,515,554 1:2.1:2.5	566,609 1:1.1	546,590
	479,512,550 1:2.5:3.8	582,626 1:1.3	558,602
	482,515,554 1:2.1:2.5	568,609 1:1.1	546,590

17

Figure 3. Comparison of visible spectra of 16, 1,6,7,11-tetrahydroxy-5,12-napthacene-dione and 1,6,10,11-tetrahydroxy-5,12-napthacenedione, λ nm and ratio of ε.

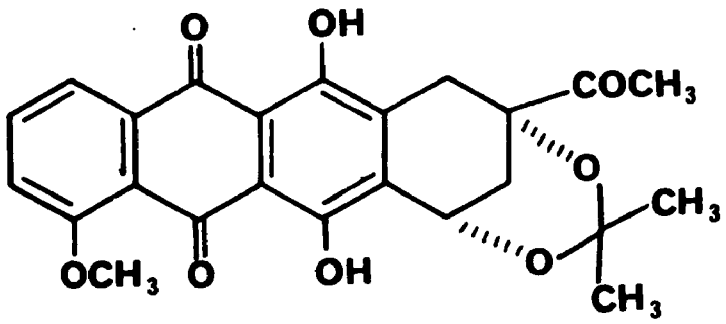
methoxyl protons. Whereas, the spectrum in acetone-d_6 before warming showed only one methoxyl absorption and one set of absorptions for the sugar moiety. This observation not only indicated conformational mobility of the sugar but also placed the methoxyl group at C-4, since a methoxyl group situated on C-1 would be too distant to be affected by changes at C-1' and/or C-7.

Two observations led to the conclusion that the glycosidic link was situated at C-7 of 1. The nmr spectrum of daunomycinone trimethylether(4) showed a signal for the hydrogen at C-7 at 4.92δ whereas in daunomycinone tetraacetate the same absorption came at 6.42δ. In daunomycin pentaacetate the hydrogen at C-7 appears at 5.07δ which indicated an ether or glycoside linkage at C-7.[33] Moreover, hydrogenation of daunomycin(3) over palladium on barium sulfate gave daunosamine(2) and 7-deoxydaunomycinone[38] (17).



17

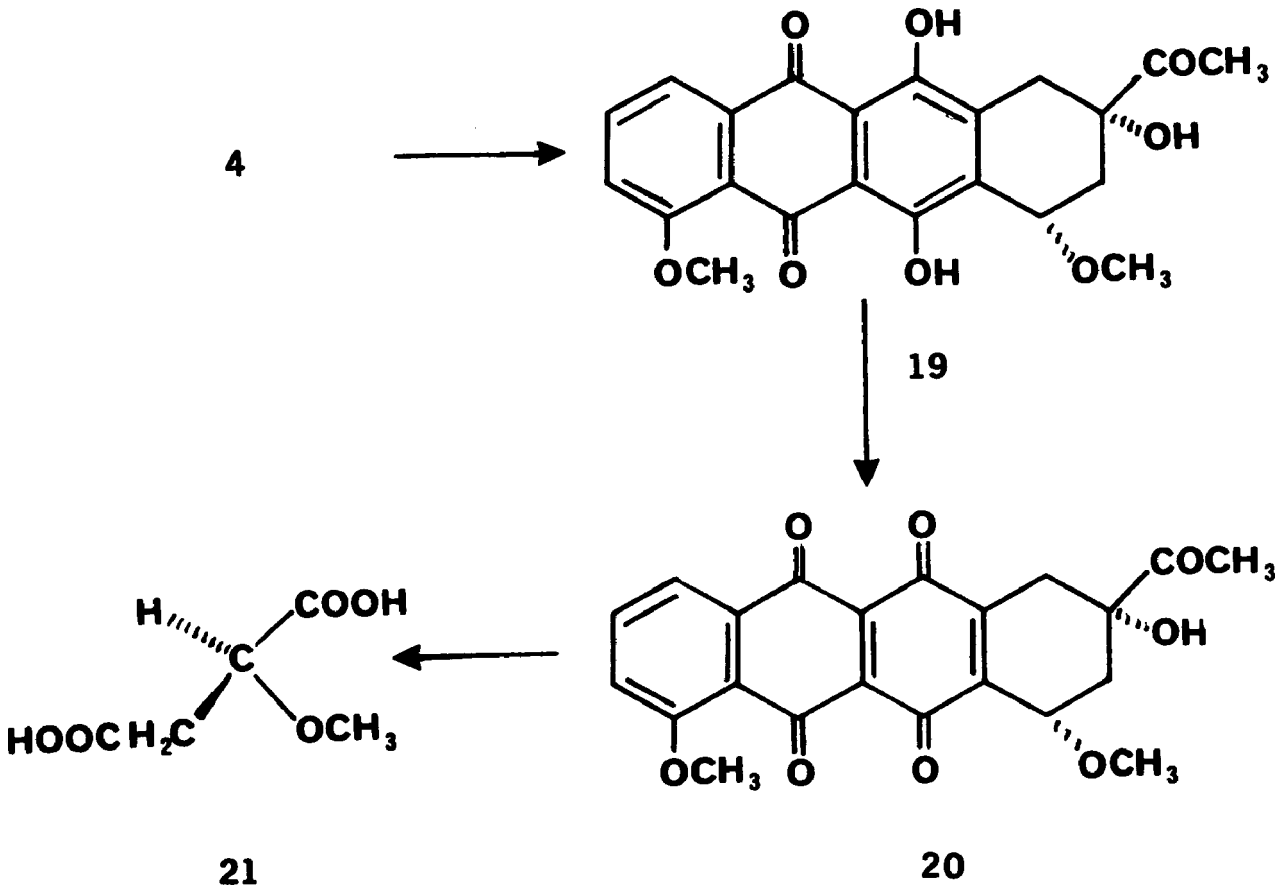
In order to determine the absolute stereochemistry at C-7 and C-9 in daunomycinone(1), Arcamone[35] treated 1 with 2,2-dimethoxypropane in the presence of p-toluenesulfonic acid and obtained the isopropylidene derivative 18, mp 224-226°C. The formation of the isopropylidene 18 proved the cis relationship of the hydroxyls at C-7 and C-9.



18

To determine the absolute configuration at C-7 and C-9, Arcamone[35] demethylated daunomycinone trimethyl ether (4) with aluminum chloride in benzene and obtained the methylether 19. Oxidation of 19 to the diquinone 20 with lead tetraacetate followed by sodium periodate potassium permanganate oxidation of 20 gave, after separation of the ether soluble acidic reaction products S(-)methoxysuccinic acid(21). The acid 21 was identified by comparison with an authentic sample prepared by the method of Fodor.[40] Therefore, the absolute configuration at C-7 was shown to be S and by reason of the cis relationship between the

hydroxyls the configuration at C-9 was also assigned as S.

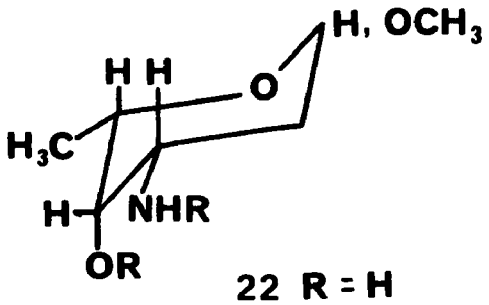


In order to show that the assymetric center at C-7 in either 1 or 3 is not affected by hydrolysis or derivatization, Iwamoto[39] compared the circular dichroism spectra of a series of compounds. It was observed that 1 and 3 have nearly identical strong CD curves, whereas 7-deoxydaunomycinone(17) exhibits only a very weak CD curve. Therefore, Iwamoto[39] considered the configuration

at C-7 to be the factor which determined the intensity and direction of the CD curve in this system. If the configuration at C-7 was epimerized completely on hydrolysis, one would expect 1 and 3 to have opposite CD curves which is not found to be the case. Moreover, if the configuration at C-7 were racemized one would expect to obtain two diasteriomeric compounds, as Marsh[41] did in a similar case to be discussed later, when 1 is treated with α-acetobromoglucose. However, Iwamoto[39] obtained only one diastereomer, 7-(tetraacetoxy-β(D)-glucopyranosyl) daunomycinone, which exhibited a CD curve which was nearly identical to that of 3.

A combination of chemical and spectral techniques was also used to determine the structure of daunosamine(2). Daunosamine(2) was found to be a reducing sugar as shown by its reaction with Tollen's and Fehling's reagents.[34] The presence of an amine function was substantiated by positive Elson-Morgan and ninhydrin tests.[34] Oxidation of 2 with periodate produced acetaldehyde identified as its 2,4-dinitrophenyl hydrazone, and 1,3-propandial which was identified by its reaction with thiobarbituric acid.[42] The presence of 1,3-propandial indicated a methylene unit at either C-2 or C-3 and acetaldehyde indicated a methyl group on an oxidizable carbon. A positive iodoform test placed the methyl group at C-5. Treatment of 2 with acetic anhydride and pyridine gave a mixture of anomeric triacetates which with the previous information indicated a

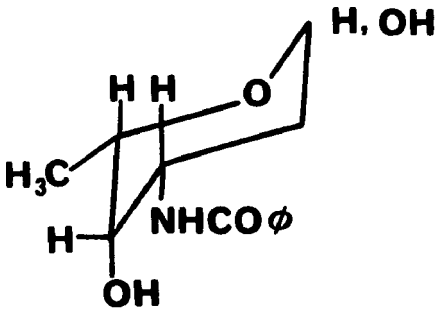
trideoxyhexose.[34] Treatment of 2 with acidic methanol gave the anomeric ethers 22 which reacted with one equivalent of sodium periodate, thus placing the methylene at C-2.[37] In a control experiment it was shown that the diacetate 23 was unreactive toward sodium periodate.



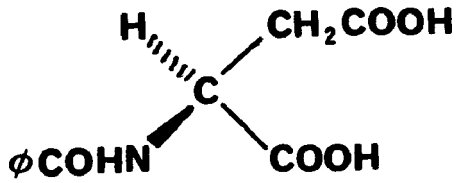
22 R = H
23 R = $COCH_3$

Arcamone[34,38] treated 2 with benzoyl chloride in aqueous sodium carbonate and obtained N-benzoyl daunosamine(24), mp 154-156°C. Oxidation of 24 with sodium periodate gave acetaldehyde and a non-volatile aldehyde which was further oxidized to N-benzoyl-L-(+)aspartic acid(25) identified by comparison with an authentic sample prepared by the method of Fischer.[43] By the convention of Cahn[44] and coworkers the formation of 25 showed the configuration at C-3 of daunosamine(2) to be S.

In the nmr spectrum[34] of 23 there was: a triplet at 4.75δ(1H, H_1, $J_{1e2e} = J_{1e2a} = 2.0$ Hz), an N-H doublet at 5.85δ(J = 8 Hz) which disappeared on treatment with D_2O,



24



25

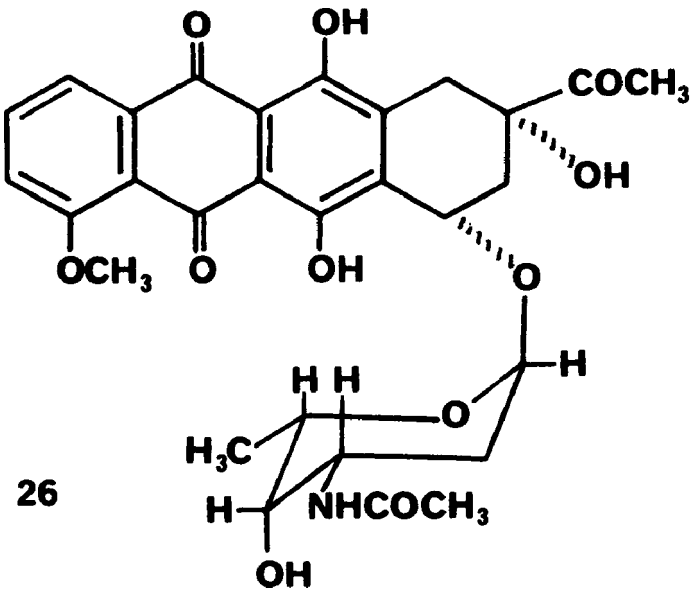
a broad absorption at 4.46δ(H_3, line width = 18-19 Hz after treatment with D_2O), a quartet 5.02δ(H_4, J = 1.5 and 2.5 Hz) and a quartet further split to an octet at 4.00δ(H_5, $J_{4,5}$ = 1.0-1.5 Hz). The small coupling constants between H_4 and H_5 (J = 1 Hz) and H_3 and H_4 (J = 2.5 Hz) indicated that neither set of protons could be diaxially oriented. Furthermore, the line width of the absorption at 4.46δ(18-19 Hz) suggested an axial orientation for H_3, since it is more than double the value calculated for an equatorial orientation of H_3. Consideration of the above J values dictated the following orientations: H_1 equatorial, H_3 axial, and H_4 equatorial. This assignment was supported by the chemical shift values of the acetyl groups. The o-acetyl signal appeared at 2.16δ in good agreement with the normal values of 2.12-2.25δ[45] for an axial acetoxy function. The N-acetyl signal

appeared at 1.91δ in good agreement with the normal values of 1.91-1.96δ[46] for an equatorial acetamido group. The methyl group at C-5 was assigned as equatorial since if the methyl group were axial then the ring would flip to the more stable conformation and the configuration at C-1 would be reversed, which is in direct disagreement with the observed J values. Since the absolute configuration at C-3 was known to be S and the relationship of all the substituents was known the absolute configuration at C-4 and C-5 could also be assigned as S.

The assigned absolute configuration of daunosamine(2) was completely substantiated by the stereospecific synthesis of 2 by Marsh[47] and the synthesis of the other enantiomorph D-daunosamine by Richardson.[48]

From previous work[33] the glycosidic linkage in daunomycin(3) was known to be at C-7 and the configuration at that carbon was known to be S. However, the configuration at C-1' remained undefined. Arcamone[36] used the 100 MHz nmr spectrum of N-acetyldaunomycin(26) (mp 180°C $[\alpha]_D$ + 228° C 0.1, chloroform) which was prepared by treatment of 3 with acetic anhydride in acetone and Iwamoto[39] used the nmr spectrum of 3 to elucidate the configuration at C-1'.

In the 100 MHz spectrum of 26 all the protons were assigned with the aid of decoupling experiments and the following absorption was noted. At 5.47δ there appears a



26

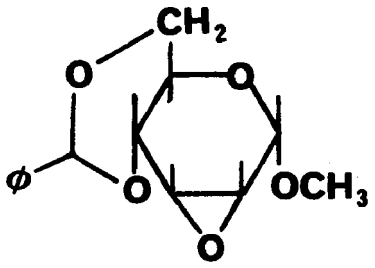
doublet-of-doublets assigned to the H-1' proton with J values of 1.5 Hz and 3.0-3.5 Hz. This absorption collapsed to a singlet on irradiation at 1.85δ where the C-2' hydrogen appears. The sum of the coupling constants of H-1' (4.5-5.0 Hz) defined an equatorial orientation for this proton since there is no possibility of any axial-axial coupling which normally yields a coupling constant on the order of 6-14 Hz.[49] The previous configuration assignments for 2 were also supported in the 100 MHz nmr spectrum. Given that the absolute configuration at C-3' was S, the orientation about C-3' and C-4' and the equatorial orientation of H-1' the glycoside linkage in 26, and therefore 3, had to be designated as an alpha linkage and the absolute configuration at C-1' as R. Therefore, the total absolute configuration of daunomycin(3) was shown to be 7(S), 9(S), 1'(R), 3'(S), 4'(S) and 5'(S).

The 220 MHz nmr spectrum of 3 not only substantiated

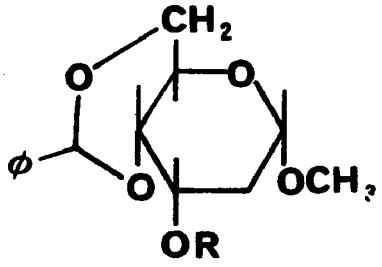
the alpha-L nature of the sugar moiety but also yielded some information about the conformation of the saturated D ring in 3. The 5.41δ signal for the C-7 proton showed coupling constants of $J_{7\text{-}8ax}$ = 5.0 Hz and $J_{7\text{-}8eq}$ = 1.5 Hz, the value of which indicated that H-7 was pseudo-equatorially oriented. When the solvent was changed from pyridine-d_5 to acetone-d_6 the $J_{7\text{-}8ax}$ decreased to 3.0 Hz which indicated an axial orientation for the glycoside oxygen and the C-9 hydroxyl group.

The value of daunomycin(3) as an antitumor agent and the challenges involved in its synthesis have generated a great deal of interest in the attainment of a workable total synthesis. The synthesis of both enantiomers of daunosamine(2) have been reported as well as some approaches to the synthesis of daunomycinone(1) and this year a total synthesis of 1 has been published.[59]

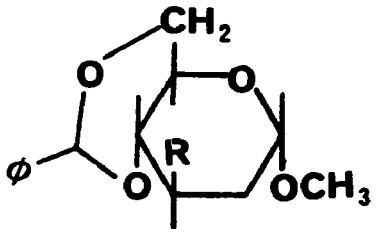
In 1965 Richardson[48] reported his synthesis of 3-benzamido-2,3,6-trideoxy-D-lyxo-hexose(27), the D enantiomorph of natural daunosamine benzamide. The synthesis began with the epoxide 28 which was reduced with lithium aluminum hydride to methyl-4,6-O-benzylidene-2-deoxy-α-D-ribo-hexopyranoside 29, which was converted to the corresponding methanesulfonate ester 30 on treatment with methanesulphonyl chloride. Treatment of 30 with sodium azide in boiling N,N-dimethylformamide gave the azido compound 31 with inverted configuration at C-3. Reduction of 31 and treatment of the resulting amine with acetic anhydride gave the acetamide 32. The benzylidene protecting group was removed with methanolic acetic acid at room temperature to give the diol 33. Selective sulfonation of the primary hydroxyl[50] with p-toluene-sulfonyl



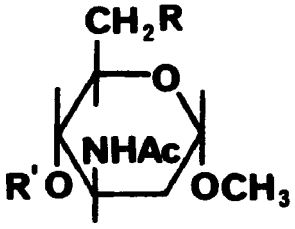
28



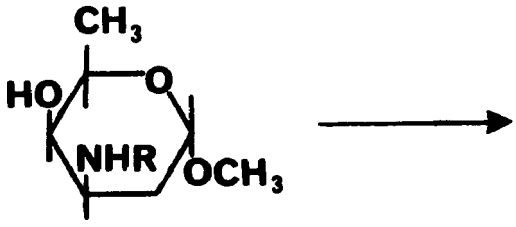
29 R = H
30 R = SO_2CH_3



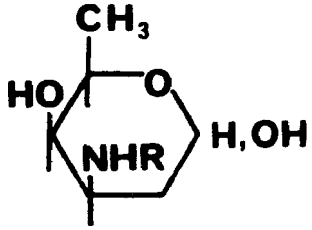
31 R = N_3
32 R = $NHCOCH_3$



33 R = OH, R' = H
34 R = TsO, R' = H
35 R = I, R' = H
36 R = R' = H
37 R = H, R' = SO_2CH_3



38 R = $COCH_3$
39 R = COϕ

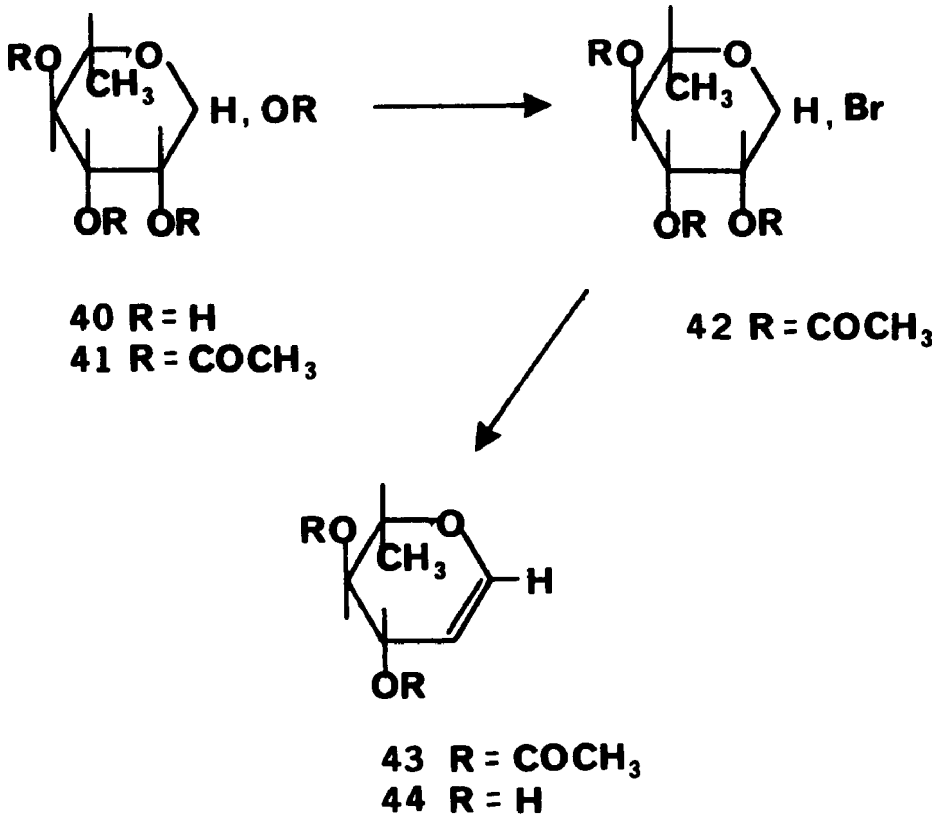


27 R = COϕ

chloride and treatment of the product 34 with sodium iodide in boiling acetone gave compound 35. Hydrogenation of 35 gave the 2,3,6-trideoxypyranoside 36. To obtain the desired amino sugar the configuration at C-4 had to be inverted. Esterification of 36 with methanesulfonyl chloride gave the mesylate 37. When 37 was heated in aqueous sodium acetate the desired compound 38 was obtained, presumably by way of an intramolecular displacement which was first described for acetamido sugars by Baker.[51] Alkaline hydrolysis of 38 followed by treatment with benzoylchloride gave the benzamide 39. Hydrolysis of 39 with aqueous acetic acid gave 27 the benzamide derivative of D-daunosamine, mp 150.5-151.5°C, $[\alpha]_D$ + 110.5° (ethanol) which was compared to the corresponding data reported by Arcamone[34] for the benzamide derivative of natural L-daunosamine, mp 154-156°C, $[\alpha]_D$ -107.5° (ethanol).

In 1967, Marsh[47] and coworkers reported the synthesis of L-daunosamine(2). The natural sugar L-rhamnose(40) was converted by the method of Iselin and Reichstein[52] to L-rhamnal(44). Treatment of 40 with acetic anhydride in pyridine gave the tetraacetate 41 which was converted to the bromotriacetate 42 on treatment with hydrogen bromide in acetic acid. Compound 42 was reduced with zinc dust to the unsaturated diacetate 43 and hydrolyzed to L-rhamnal 44 with methanolic barium hydroxide.

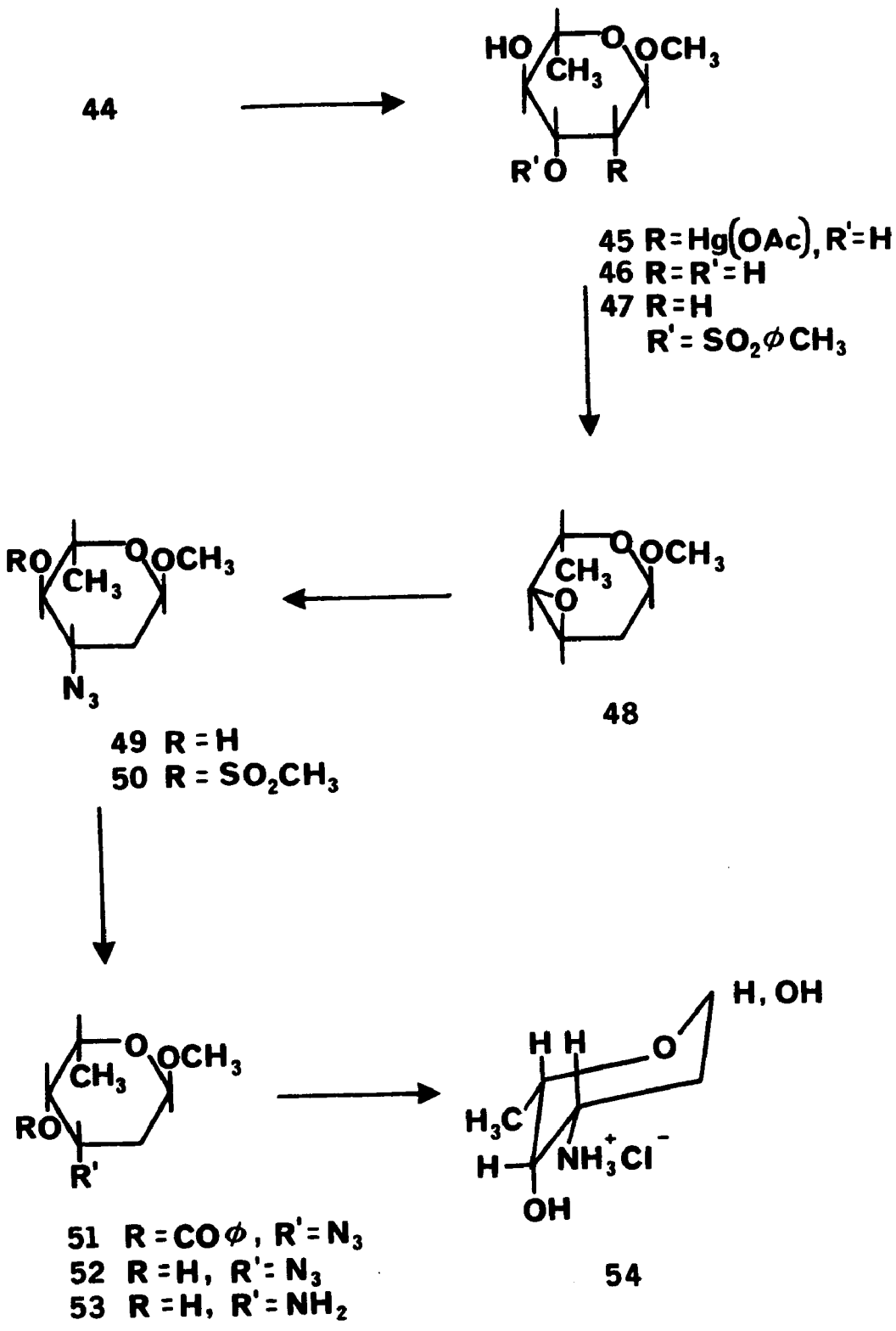
Treatment of 44 with mercuric acetate in methanol gave the organo mercurial 45 which was reduced to 46 with potassium borohydride. Treatment of 46 with p-toluenesulfonyl chloride gave primarily the monotosylate 47. When 47 was treated with sodium methoxide in methanol the epoxide 48 was obtained, which was converted to the azido



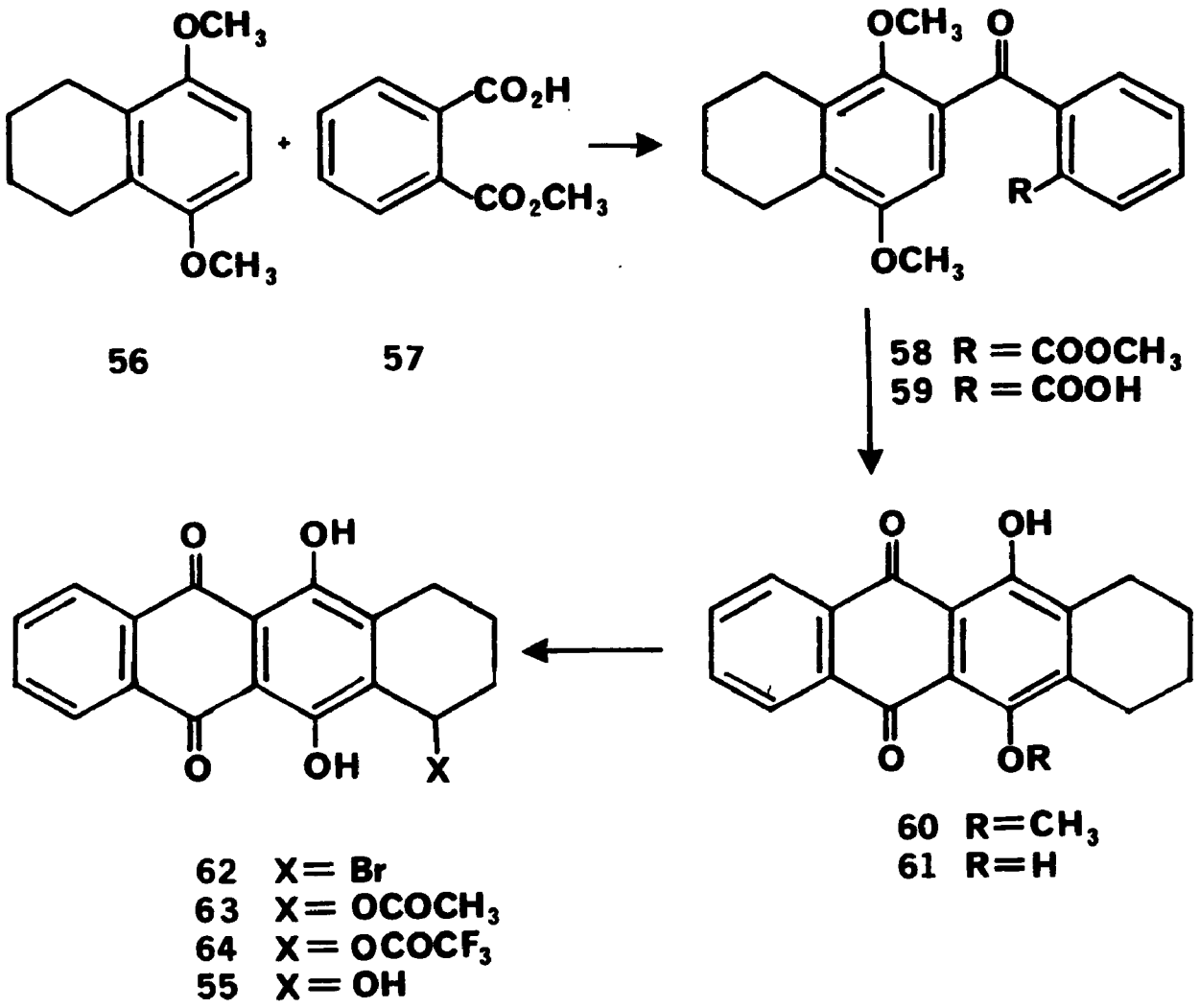
compound 49 upon addition of sodium azide. The hydroxyl group in 49 was esterified with methanesulfonyl chloride to give the methane sulfonate 50 which on solvolysis with sodium benzoate in N,N-dimethyl formamide gave the benzoate 51. Hydrolysis of 51 with sodium hydroxide in aqueous methanol gave the azido alcohol 52 which was hydrogenated to the glycoside 53. Hydrolysis of 53 was carried out in dilute hydrochloric acid and gave the hydrochloride salt of 3-amino-2,3,6-trideoxy-L-lyxo

hexose 54, which was deemed identical in all respects to an authentic sample of the natural L-daunosamine hydrochloride.

Daunomycinone(1) the aglycone portion of daunomycin (3) has presented a somewhat more formidable synthetic challenge. In 1968, Marsh[41] and coworkers reported the synthesis of a model system for 1 which they used to investigate the glycoside linkage of daunomycin(3). The synthesis of 7,8,9,10-tetrahydro-6,7,11-trihydroxy-5,12-napthacinedione(55) was accomplished by means of a stepwise condensation of 1,4-dimethoxy-5,6,7,8-tetrahydronapthalene(56) and methyl hydrogen phthalate (57). A mixture of 56 and 57 was heated at reflux in trifluoroacetic anhydride and the keto ester 58 was obtained. Saponification of 58 with potassium hydroxide in aqueous ethanol gave the corresponding acid 59. Ring closure of 59 was effected by heating in sulfuric acid and was accompanied by the cleavage of one of the methyl ether protecting groups to give the quinone 60. Demethylation of 60 with aluminum chloride in benzene gave the dihydroxy quinone 61. Benzylic bromination of 61 was accomplished with tetramethyl ammonium perbromide and gave the bromo compound 62 which was always contaminated with a small amount of the dibromide. Treatment of 62 with silver acetate gave the acetate 63 which on methanolysis gave a mixture of products. However, the trifluoroacetate 64,


44
HO
CH3
O
OCH3
R'O
R
45 R=Hg(OAc), R'=H
46 R=R'=H
47 R=H
R'=SO2φCH3
RO
CH3
O
OCH3
N3
49 R=H
50 R=SO2CH3
CH3
O
OCH3
O
48
CH3
O
OCH3
RO
R'
51 R=COφ, R'=N3
52 R=H, R'=N3
53 R=H, R'=NH2
H, OH
H H
O
H3C
H
NH3+Cl-
OH
54

prepared by dissolving 63 in trifluoroacetic acid, was easily methanolyzed with a trace of sodium methoxide in methanol to give the desired trihydroxy compound 55.

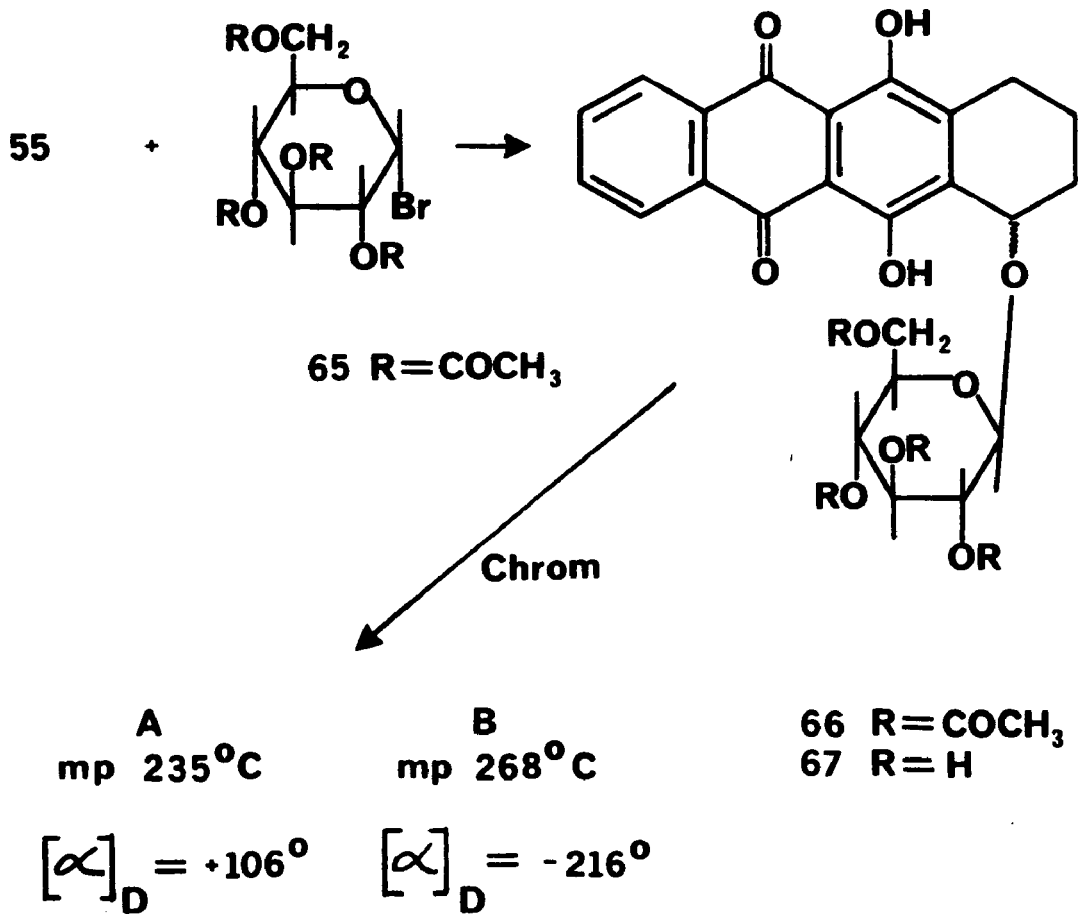


In order to study the formation of glycosides similar to daunomycin(3) Marsh[41] and coworkers prepared the C-7 beta-D-glucoside of 55. When 55 was treated with alpha-acetobromo glucose(65) in the presence of mercuric cyanide there was obtained a good yield of the tetraacetate 66. Compound 66 was assumed to be the beta anomer based on a

literature study by Lemieux[53] who suggested that in the case of alpha-acetobromoglucose reaction with an alcohol at ambient temperature gives predominantly the beta anomer of the glucoside. Methanolysis of 66 occurred quite readily when it was treated with cold methanol and a trace of sodium methoxide. The glucoside 67 which was obtained was a mixture of stereoisomers. However, the stereoisomeric tetraacetates could be readily separated by chromatography on silicic acid and then methanolyzed.

The faster moving glucoside A had a melting point of 235°C and an $[\alpha]_D$ value of +106° in dioxane. The slower moving glucoside B had a melting point of 268°C and an $[\alpha]_D$ value of -216° in dioxane. The stereoisomer A exhibited a CD curve which was almost identical to the CD curve of daunomycin(3), which indicated that A had the same configuration at C-7 as 3. Whereas the CD curve exhibited by B was opposite that of daunomycin(3). This assignment was further substantiated by the fact that when 1 was treated with alpha-acetobromoglucose there was obtained one glucoside which showed an identical nmr pattern for the acetyl methyl groups as was seen in the nmr spectrum of A and yet different from that shown in the nmr spectrum of B.

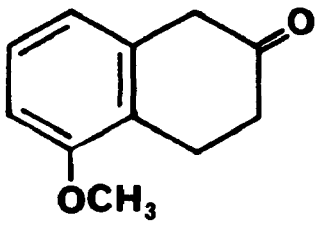
As a part of their continuing synthetic study of the anthracyclinones Horii[54,55,56] and coworkers have in a series of papers described the synthesis of bisanhydro-



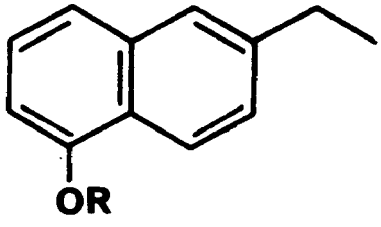
daunomycinone(6). In the synthesis of 6, Horii[55] planned the oxidation of his target molecule 8-ethyl-1,6,11-trihydroxy-5,12-napthacenedione(68) which could be prepared by the method of Brockmann[57] or by an alternate synthesis which was partially described by Horii.[54,55] Brockmann[57] treated 5-methoxy-2-tetralone(69) with ethyl magnesium bromide and obtained, after dehydration with p-toluenesulphonic acid and aromatization with palladium on char-

coal, 2-ethyl-5-methoxy napthalene(70). Demethylation of 70 with boron tribromide gave 71 which was condensed with 3-nitro phthalic anhydride (72) using boron bromide to give the acid 73. Hydrogenation of 73 over palladium on carbon gave the corresponding amine 74 which was diazotized with sodium nitrite in sulfuric acid and then heated in aqueous acid to give the dihydroxy compound 75. Bromination of 75 was accomplished using bromine in carbon disulfide and gave the bromo compound 76 which on heating at 120°C in sulfuric acid gave the desired trihydroxy quinone 68.

By acetylation of 68 in acetic anhydride and pyridine Horii[58] and coworkers prepared the triacetate 77 which upon bromination with N-bromosuccinimide in carbon tetrachloride gave the benzylic bromide 78. Solvolysis of 78 in a mixture of acetic acid and acetic anhydride containing some potassium acetate gave the tetraacetate 79. Saponification of 79 with potassium hydroxide in aqueous methanol gave the tetrahydroxy compound 80 which was methylated with dimethylsulfate and potassium carbonate in acetone to give the trimethyl ether 81. Oxidation of 81 with manganese dioxide in benzene gave the trimethoxy ketone 82. Selective demethylation of 82 with ten equivalents of boron tribromide in cold methylene chloride gave an unspecified yield of the desired bisanhydrodaunomycinone 6.

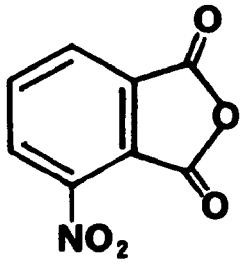


69



70 R= CH_3
71 R= H

71 +



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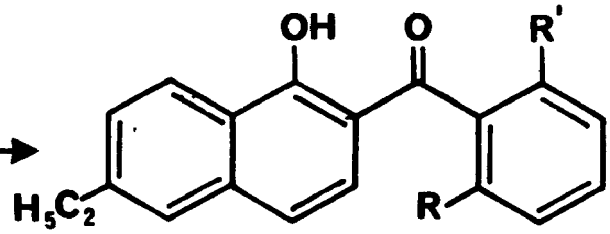
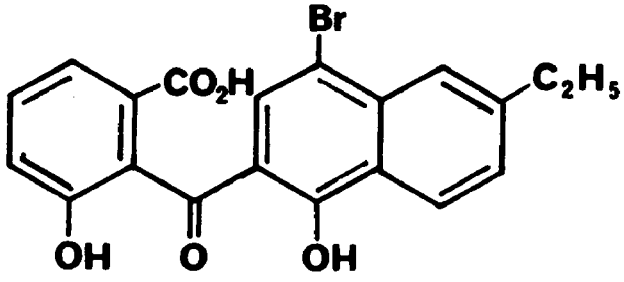
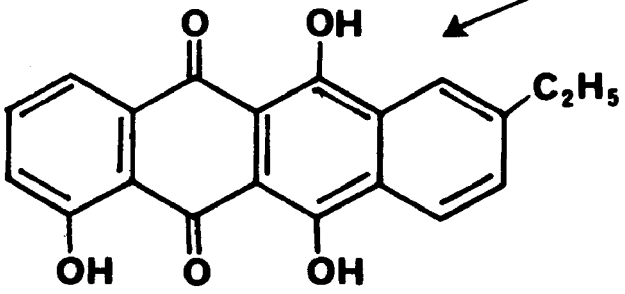


73 R=COOH, R'=NO_2
74 R=COOH, R'=NH_2
75 R=COOH, R'=OH

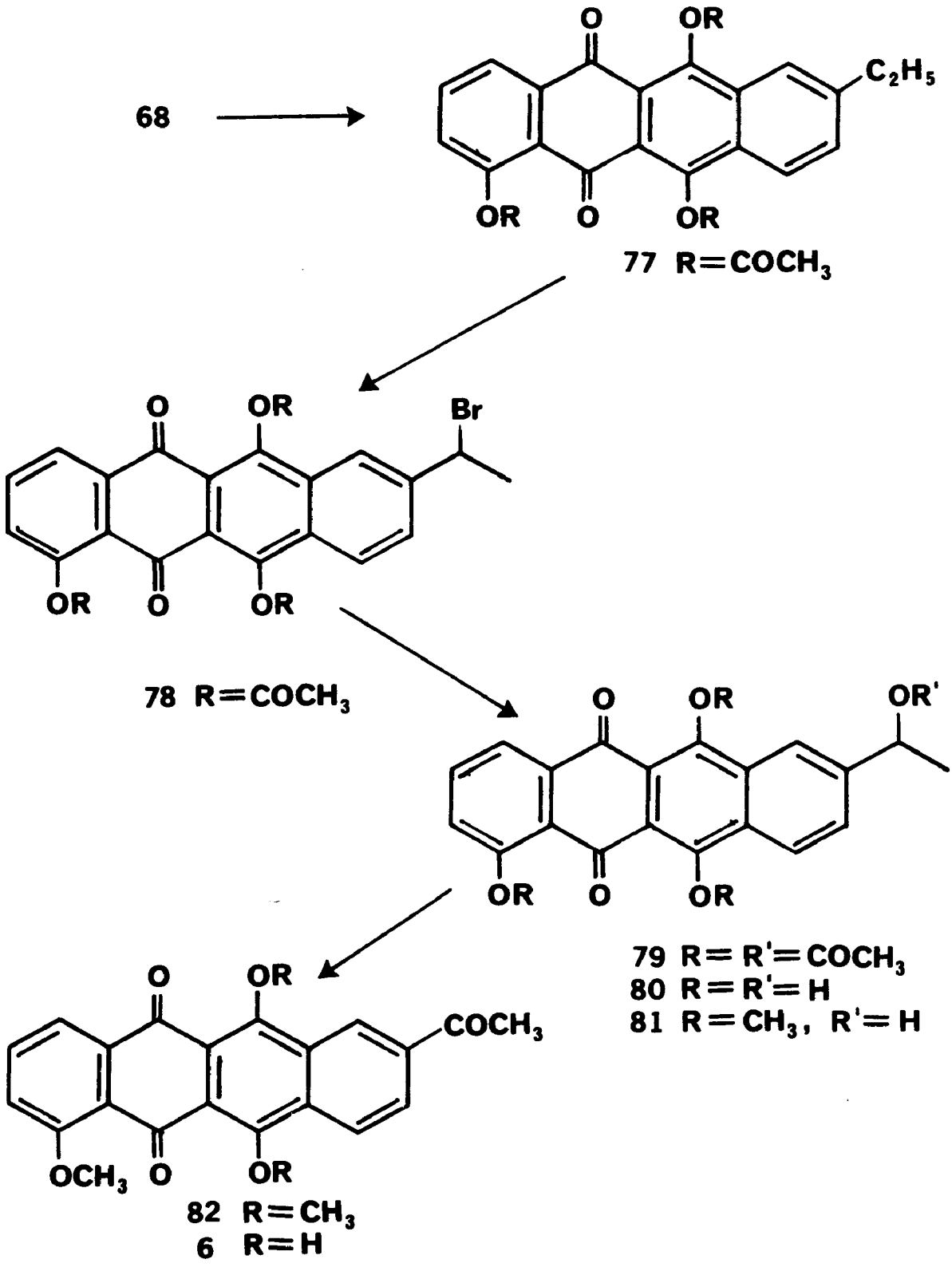
75 →



76

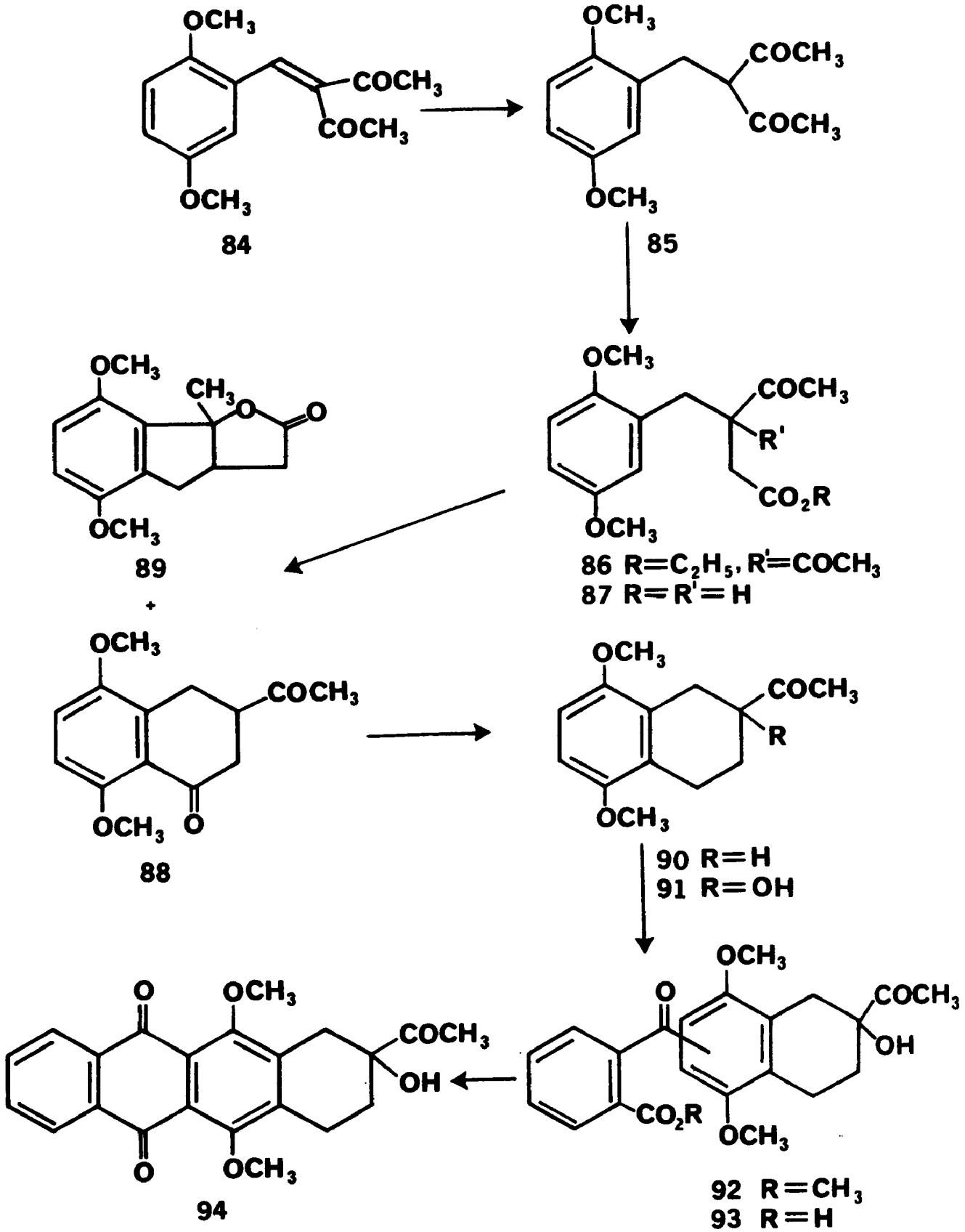


68


68
O
OR
C2H5
OR
O
OR
77 R=COCH3
O
OR
Br
OR
O
OR
78 R=COCH3
O
OR
OR'
OR
O
OR
79 R= R'=COCH3
80 R= R'=H
81 R=CH3, R'=H
O
OR
COCH3
OCH3
O
OR
82 R=CH3
6 R=H

In 1971 Wong[58] and coworkers reported the synthesis of 4-demethoxy-7-O-methyl daunomycinone(83). A mixture of 2,5-dimethoxybenzaldehyde and 2,4-pentanedione in benzene was treated with acetic acid and piperidine. The unsaturated diketone 84 which was obtained was hydrogenated over palladium on carbon to give the diketone 85. Alkylation of 85 with ethyl bromoacetate and sodium hydride in tetrahydrofuran gave the diketo ester 86 which on treatment with aqueous sodium hydroxide gave the keto acid 87. Cyclization of 87 with hydrofluoric acid gave a 12:1 ratio of the tetralone 88 and the lactone 89, which were separated by hydrolysis of the lactone 89 and extraction with aqueous base. The benzylic ketone carbonyl in 88 was removed by hydrogenolysis in acidic ethanol to give the tetralin 90. Treatment of 90 with potassium-tertiary-butoxide and oxygen in tertiary-butanol solution, followed by reduction of the intermediate hydroperoxide with zinc dust gave the hydroxy ketone 91.

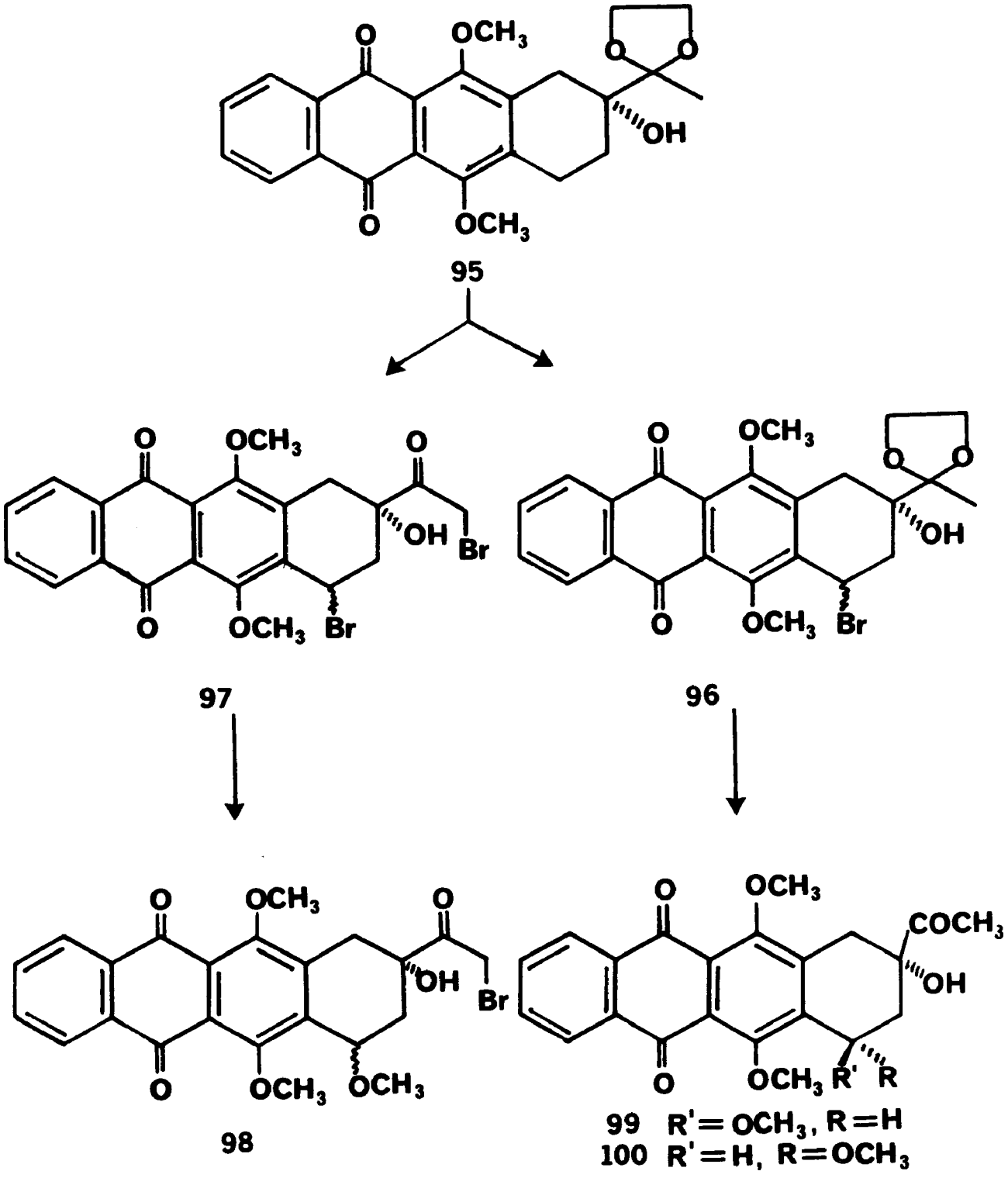
To prove that the hydroxyl group in 91 was in the tertiary position, 91 was reduced to the corresponding diol with sodium borohydride. The diol was converted to a mixture of cis and trans olefins which had only one olefinic proton. Oxidation of the olefin with osmium tetraoxide followed by oxidation of the secondary hydroxyl group with N,N-dicyclohexylcarbodiimide and dimethylsulfoxide returned the hydroxy ketone 91.


OCH3
COCH3
COCH3
OCH3
84
85
CH3
O
O
89
+
88
R'
CO2R
86 R=C2H5, R'=COCH3
87 R=R'=H
R
90 R=H
91 R=OH
OH
92 R=CH3
93 R=H
94

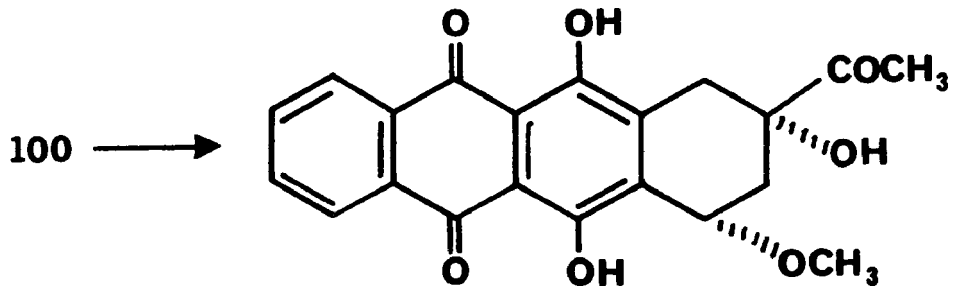
Condensation of methyl hydrogen phthalate and 91 in trifluoroacetic anhydride gave the mixture of esters 92. Hydrolysis of 92 with sodium hydroxide gave the corresponding acids 93 which without purification were cyclized with hydrofluoric acid to give 6,11-dimethoxy-8-acetyl-7,8,9,10-tetrahydro-5,12-napthacenedione 94.

Bromination of the hydroxy ketone 94 gave a mixture of products which included bromination at both benzylic positions as well as at the acetyl methyl. However, treatment of 94 with ethylene glycol and p-toluenesulfonic acid gave the ketal 95 which showed some selectivity towards bromination. Bromination of 95 with N-bromosuccinimide in refluxing carbon tetrachloride gave the unstable bromo ketal 96 and the dibromo ketone 97. The mixture of 96 and 97 was heated under reflux in methanol and the product mixture, after hydrolysis of the ketal, was separated by chromatography on silica to give three compounds 98 and the diasteriomers 99 and 100. The assignment of structures 98→100 was made solely on the position of the hydroxyl proton in the nmr spectra, with it being assumed that hydrogen bonding to the C-7-O-methyl in 98 and 100 gives rise to the absorption above 5δ whereas the free hydroxyl in 99 appears below 4δ. Demethylation of 100 with aluminum chloride in benzene gave the desired 4-dimethoxy-7-O-methyldaunomycinone(83).

In the replacement of bromine at C-7 with a methoxyl group the authors[58] suggested that the presence of only

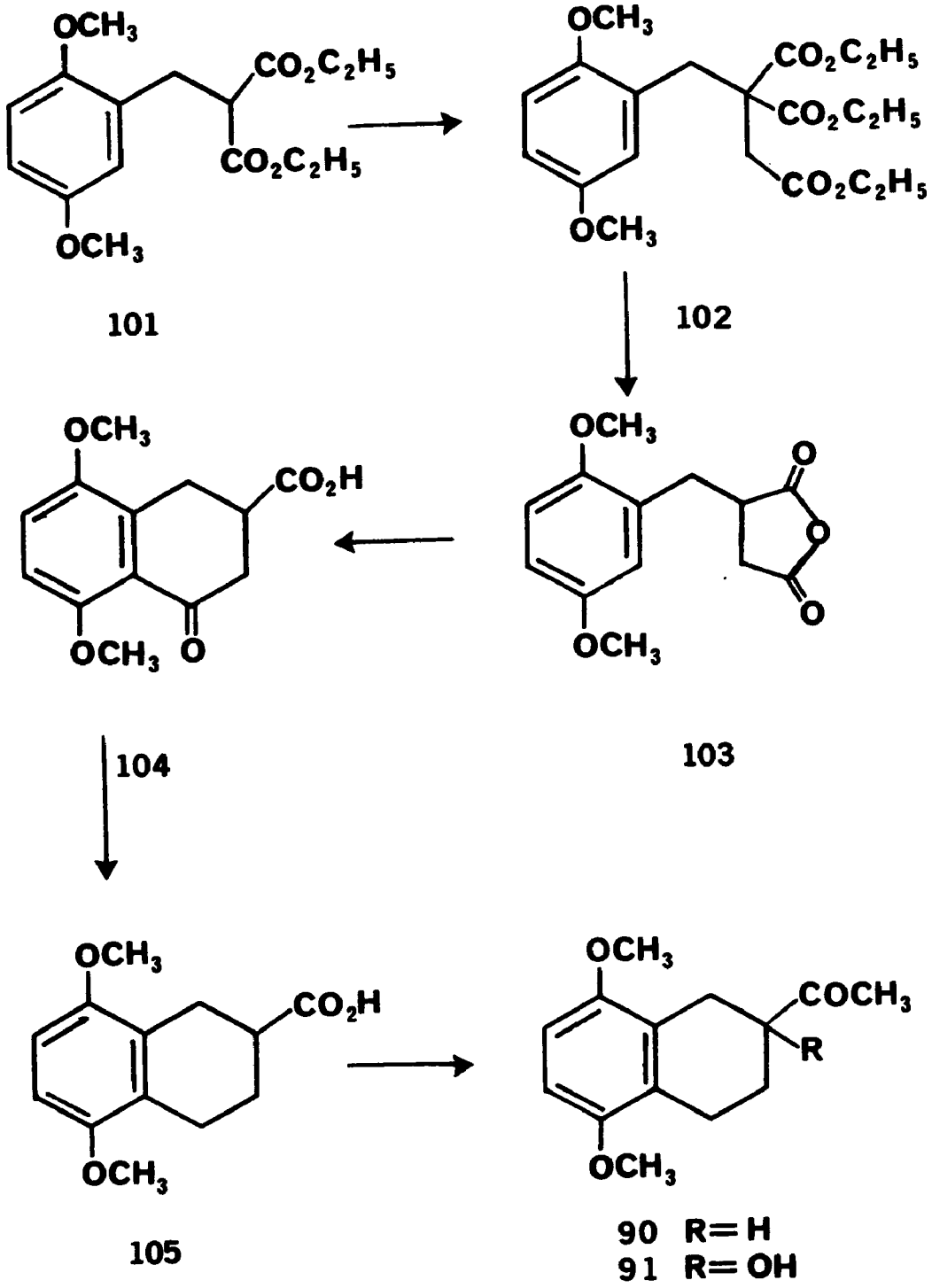

95
97
96
98
99 R'= OCH3, R=H
100 R'=H, R=OCH3

98, and not its enantiomorph, as well as an almost 2:1 ratio in favor of 100 over 99 could be accounted for by a "partially stereospecific S_N1 process." Where the stereospecificity of the attack by methanol is due to shielding of one face of the cationic center by either the methyl ketone function or the bromomethyl ketone.



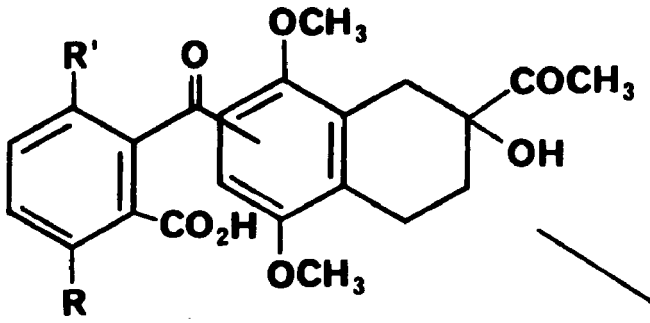
83

In 1973 Wong[59] and coworkers, extending their previous results, reported the total synthesis of daunomycinone(1). The synthesis of the key intermediate 91 in the previous synthetic sequence was improved by replacing 2,4-pentanedione with diethylmalonate. Therefore, condensation of diethyl malonate and 2,5-dimethoxy benzaldehyde followed by hydrogenation gave the diester 101. Alkylation of 101 with ethyl bromoacetate and sodium hydride gave the triester 102 which was hydrolyzed and the resultant diacid treated with acetic anhydride to give the anhydride 103. The anhydride 103 was cyclized

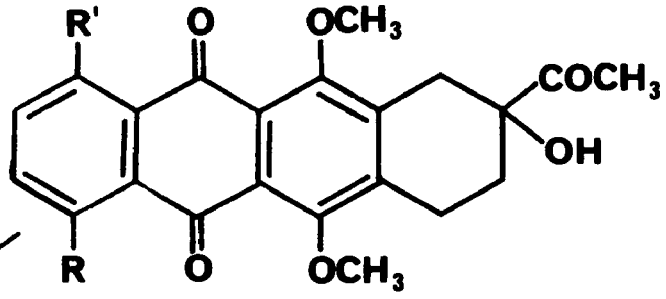

OCH3
CO2C2H5
CO2C2H5
OCH3
101
102
CO2H
O
103
104
105
COCH3
R
90 R=H
91 R=OH

with hydrofluoric acid and the resulting keto acid 104 was hydrogenolized in acidic ethanol to give the acid 105. Treatment of 105 with methyl lithium gave the ketone 90 which was converted as before to 91.

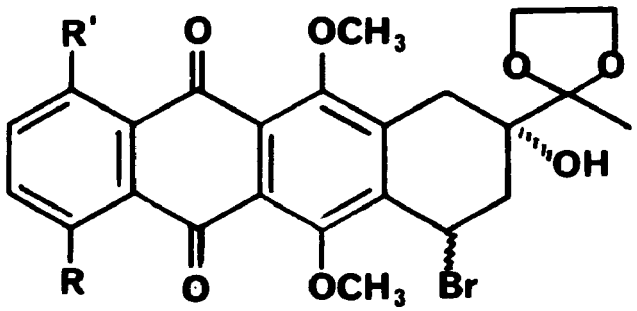
When 91 was condensed in trifluoroacetic anhydride with the isomeric monomethyl esters of 3-acetoxy phthalic acid and the reaction product saponified, a mixture of acids 106 was obtained. The mixture 106 was cyclized with hydrofloric acid and the crude product methylated with dimethylsulfate and potassium carbonate to give an inseparable mixture of the two isomers 107 and 108. Preparation of the ethylene ketals of 107 and 108 followed by benzylic bromination with N-bromosuccinimide in carbon tetrachloride gave the bromo ketals 109 and 110. The mixture of 109 and 110 was heated at reflux in methanol and after chromatography two mixtures of epimeric tetramethyl ethers 111 and 112 were obtained. Hydrolysis of the ketal 112 gave a separable mixture of ketones, daunomycinone trimethyl ether 4 and its enantiomorph 113 in a ratio of 1:1. Demethylation of 4 with aluminum chloride in benzene gave 19. Lead tetraacetate oxidation of 19 gave the unstable diquinone 114 which without isolation was methylated with dimethyl sulfate and potassium carbonate and reduced to 7-O-methyldaunomycinone(115). Dissolution of 115 in trifluoroacetic acid at room temperature gave the trifluoroacetate 116 which on treatment



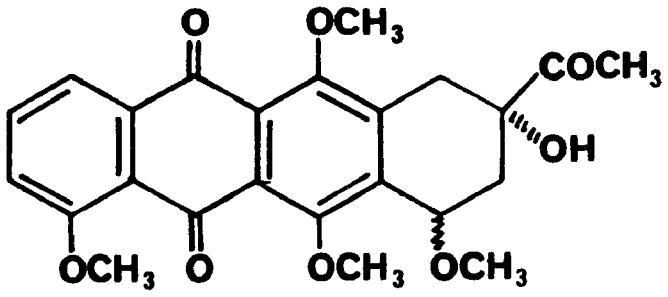
106 R' or R=OCOCH$_3$



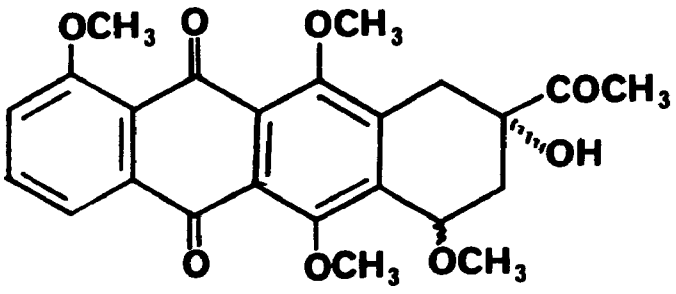
107 R'= OCH$_3$, R = H
108 R'= H, R = OCH$_3$



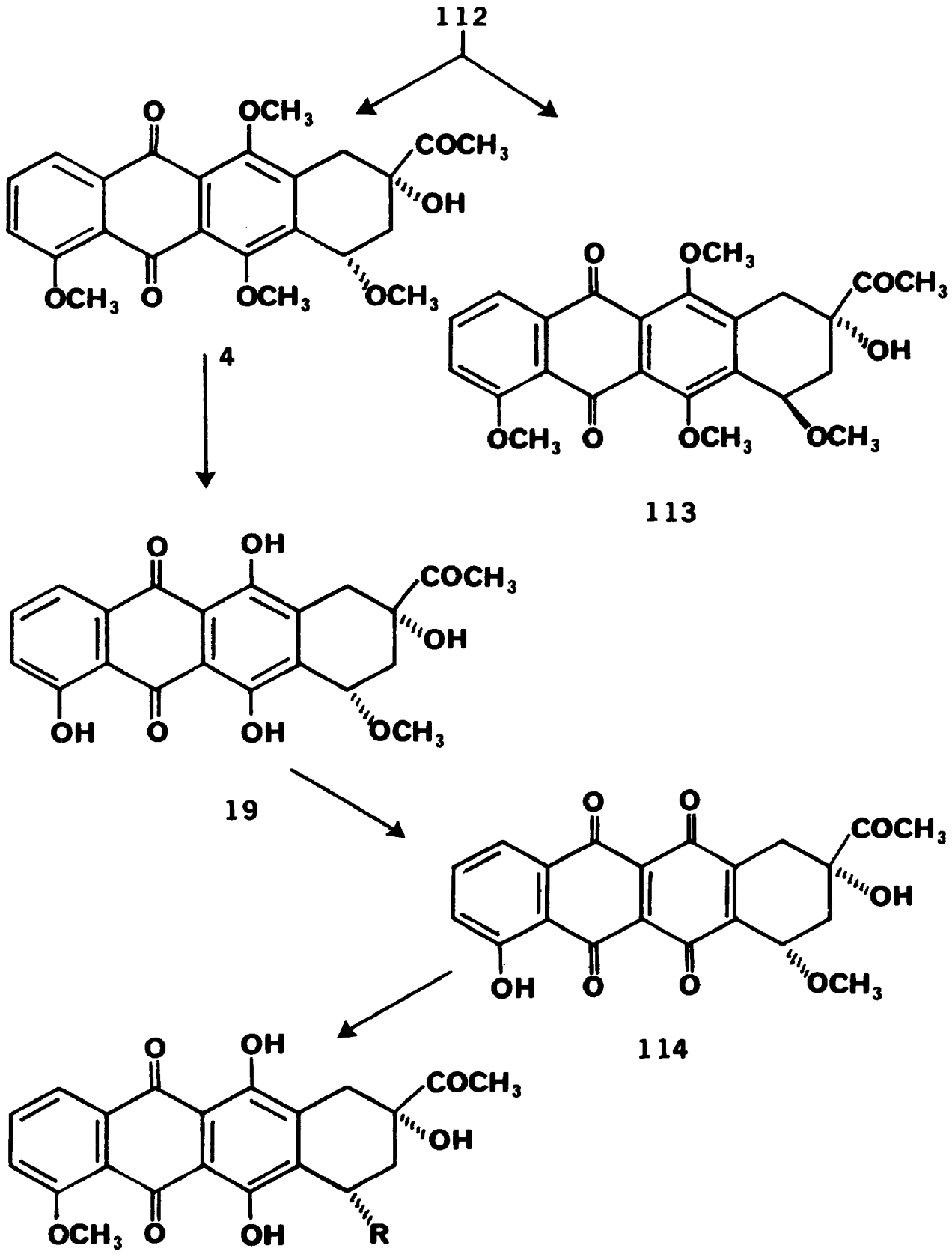
109 R'= OCH$_3$, R = H
110 R'= H, R = OCH$_3$



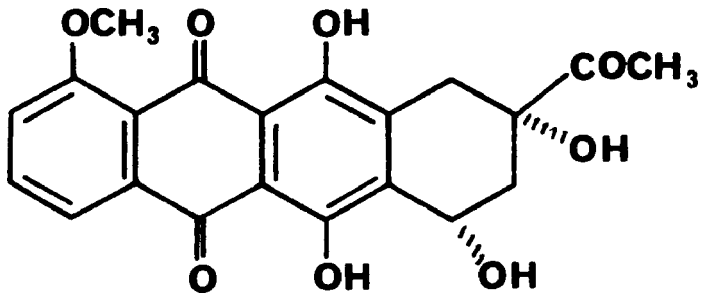
112



111


112
4
113
19
114
115 R= OCH3; 116 R= OCOCF3; 1 R= OH

with ammonium hydroxide in boiling acetone gave daunomycinone 1, identical to naturally derived material. Similar treatment of 111 gave isodaunomycinone(117), mp 216-218°C.



117

EXPERIMENTAL RESULTS AND DISCUSSION

Introduction to the Problem

At the time this work was begun no attempts at the total synthesis of daunomycin(3) or daunomycinone(1) had appeared in the literature. However, the stereospecific synthesis of daunosamine(2)[47] had been achieved and there was strong precedence[41] for the glycoside forming reaction which would be required to combine daunomycinone(1) and daunosamine(2) in a site selective and stereospecific manner. Therefore, the total synthesis of daunomycinone(1) would lead to the total synthesis of the naturally occurring antibiotic.

The medicinal value of daunomycin(3) makes it necessary to have a reasonable source of the material available. For this reason a synthesis, by which the antibiotic could be obtained in quantity and at reasonable expense on a commercial scale, might be beneficial as a supplement to natural material. Also, it is hoped that the successful synthetic pathway might lend itself well to the preparation of analogs of daunomycin(3) which might be of still greater medicinal value.

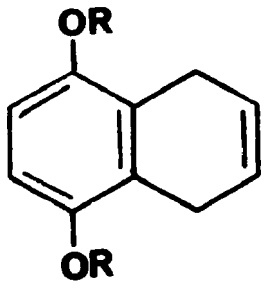
In addition to the above a total stereospecific synthesis of daunomycinone(1) would constitute the final confirmative step in the structure proof of the natural product. The problem then becomes one of discovering a workable synthetic scheme for the preparation of daunomycinone(1) and

verifying its condensation with daunosamine(2).

During the course of this work four approaches to the synthesis of the primary target daunomycinone(1) have been investigated.

Approach I.

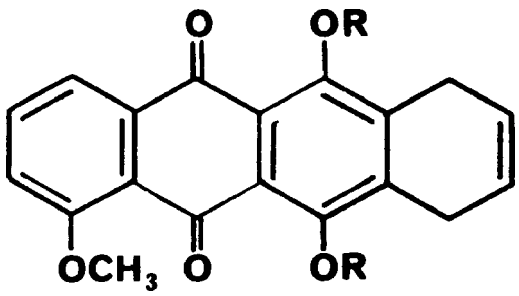
The first synthetic approach to daunomycinone(1) which was formulated involved the preparation of a precursor for the C and D rings. The intermediate napthalene derivative was to be condensed with a phthalic acid derivative by a two-step procedure which had been used in several previous instances.[60a-c] An attractive precursor for the C and D rings would be 1,4-dihydroxy-5,8-dihydronapthalene (118), its diacetate 119 or its dimethyl ether 120. The first two compounds have been prepared previously by Fieser[61] and the dimethyl ether 120 has been prepared by a Russian group.[62]



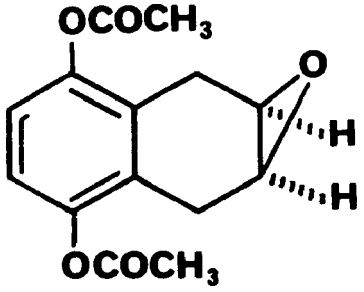
118 R=H; 119 R=$COCH_3$; 120 R=CH_3

It was planned that 119 or 120 would be condensed with 3-methoxy phthalic anhydride and the resulting dihydro-

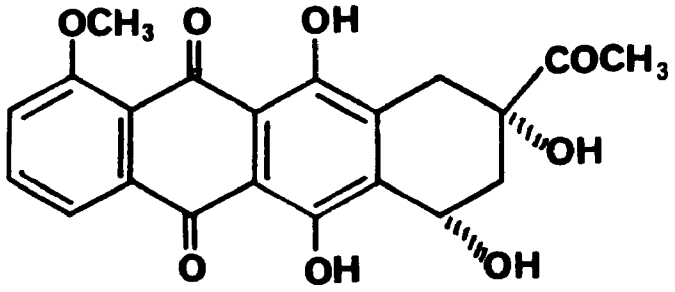
napthacenedione 121 would be functionalized by elaboration of the 8,9-double bond. In order to study the reactions of 121 the less complicated diacetate 119 was used as a model. The double bond in 119 was to be epoxidized to give the new epoxide 122. Nucleophilic opening of the oxirane ring in 121 with a C_2 fragment would give a mixture of two isomers one of which would be further converted to daunomycinone (1) and the other to isodaunomycinone (117).



121 R=$COCH_3$ or CH_3



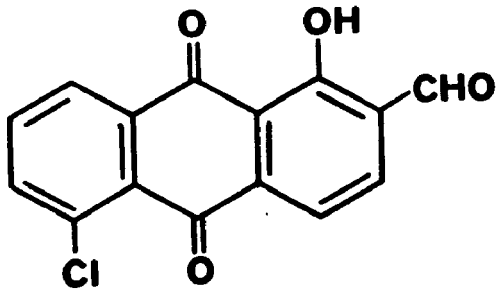
122



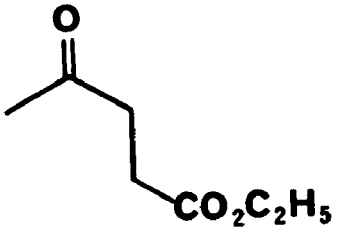
117

Approach II.

The second synthetic scheme to be investigated involved a modified Stobbe[63] condensation between an anthraquinone aldehyde such as 123 and ethyl levulinate (124).

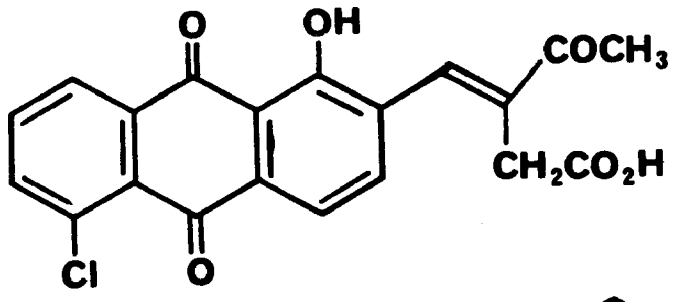


123

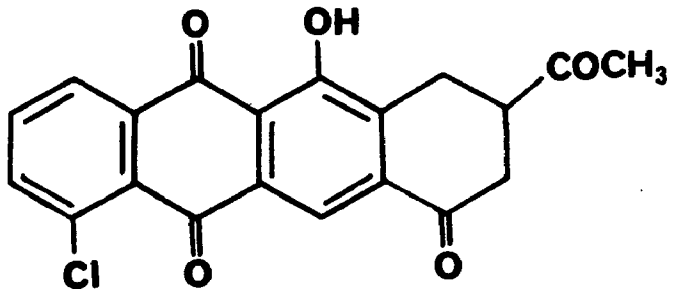


124

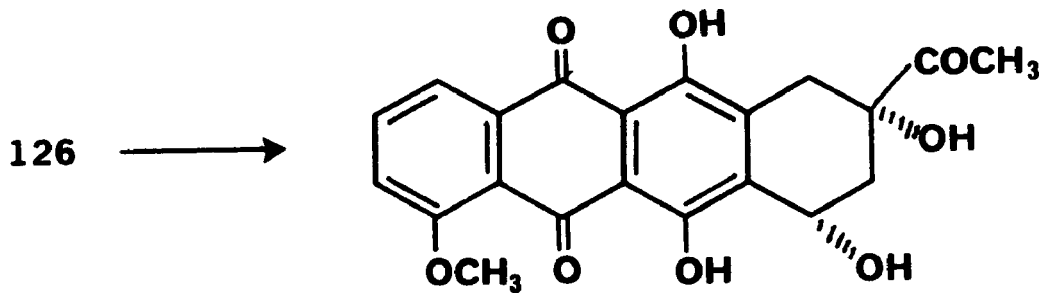
It was felt that the hypothetical product 125 of the above condensation could be hydrogenated and cyclized to a suitable tetracyclic precursor 126 of daunomycinone(1).



125



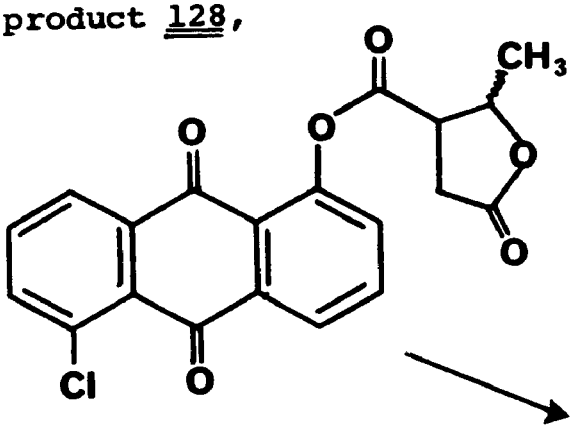
126



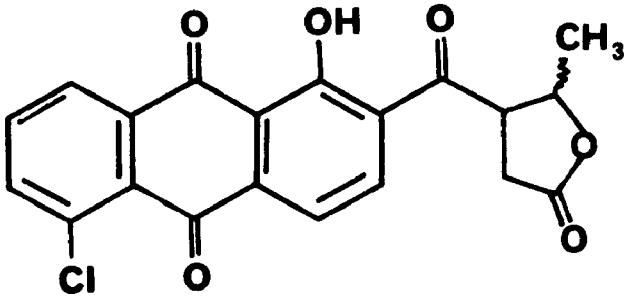
1

Approach III.

The third proposed pathway, like the second, was designed to eliminate isomers which would lead to isodaunomycinone (117). A Fries[64] rearrangement of the lactone ester 127 should give primarily the ortho substitution product 128,



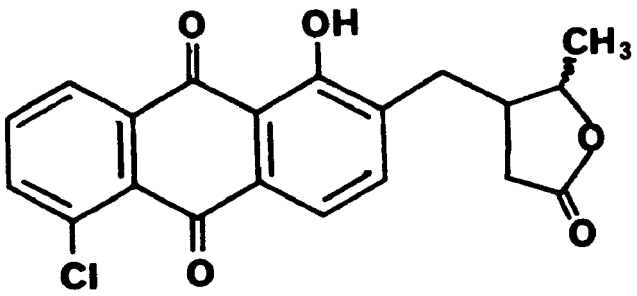
127



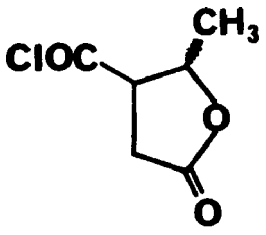
128

from which the ketone carbonyl could be removed by reduction to give 129. The preparation of 127 would depend on the

synthesis of the acid chloride 130. Oxidation of 129 to

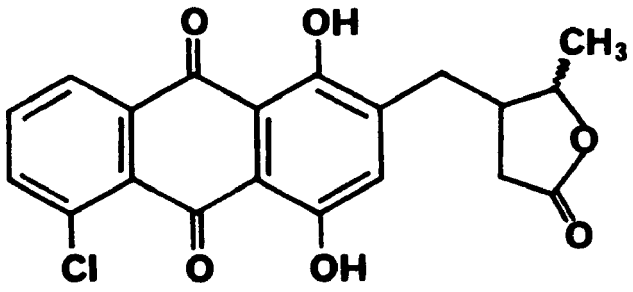


129



130

give the 1,4-dihydroxy compound 131 followed by cyclization would give a napthacenedione with functionality which could be manipulated to give the desired daunomycinone(1).

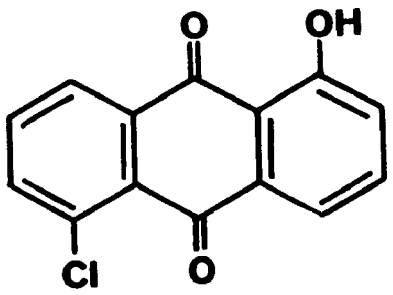


131

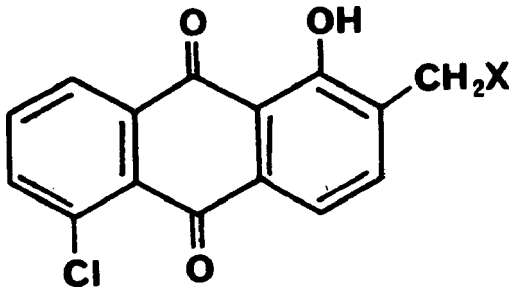
Approach IV.

The fourth and most extensively investigated approach involved the functionalization of 1-chloro-5-hydroxyanthraquinone (132) at the six position to give a compound such as

133 which could be used as an alkylating agent. The keto

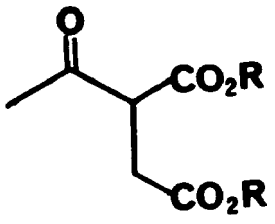


132

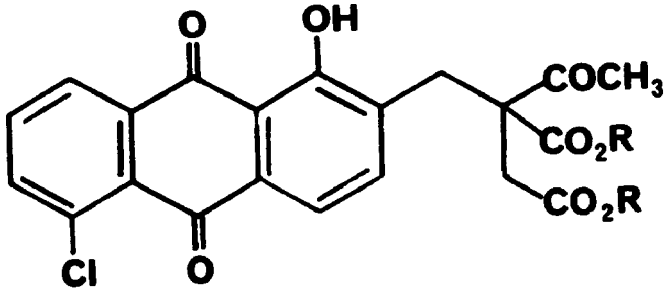


133 X=Cl or $\overset{+}{N}R_3$

ester 134 contains all the carbon atoms and functionality required to construct the D-ring of daunomycinone(1) and would be a good candidate for alkylation with 133.



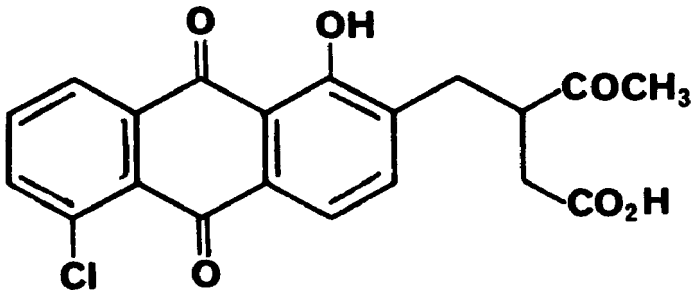
134



135

The product 135 of the above alkylation could be oxidized to the dihydroxy compound corresponding to 131. Alternatively, hydrolysis of the esters and monodecarboxylation would give

the keto acid 136. Cyclization of 136 would give a 5,12-

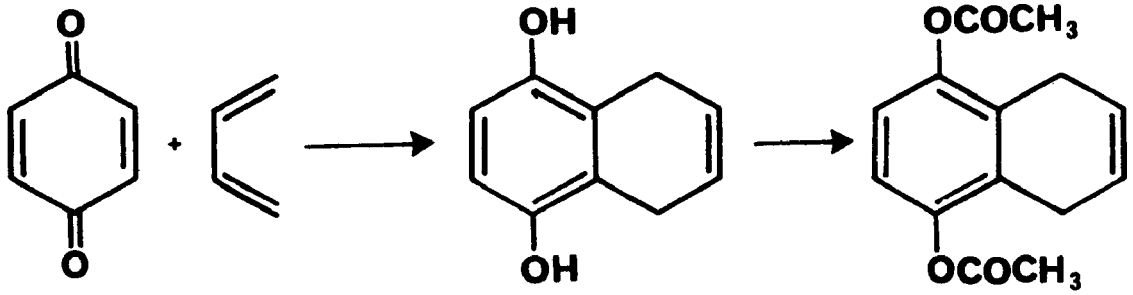


136

napthacenedione suitable for elaboration to daunomycinone(1). Replacement of the chlorine atom at C-4 with a methoxyl group would be accomplished by a nucleophilic substitution reaction[65,66] which has been used in the preparation of other methoxyanthraquinones.

RESEARCHES INTO THE TOTAL SYNTHESIS OF DAUNOMYCINONE

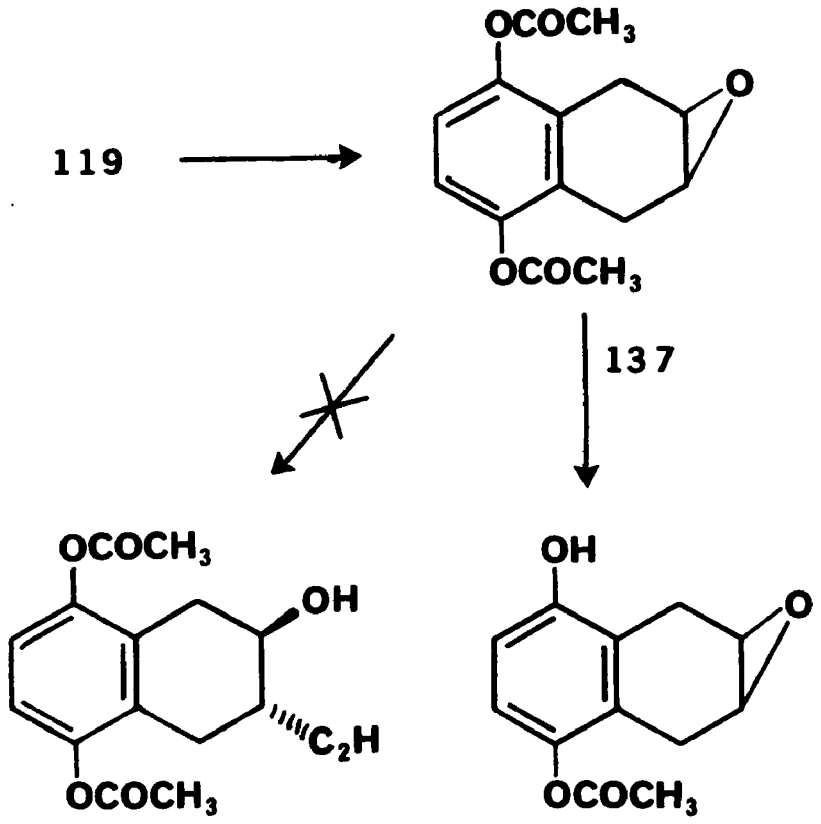
In pursuing the first proposed synthetic pathway, 5,8-dihydro-1,4-napthohydroquinone diacetate (119) was prepared in 79% overall yield by the method of Fieser.[61] 1,4-Benzoquinone and excess butadiene were mixed in acetic acid in a pressure bath and kept at 20-30°C for approximately 50 hours. Treatment of the crude reaction product with a mixture of hydrochloric acid and stannous chloride gave 5,8-dihydro-1,4-napthohydroquinone (118) mp 208-209.5°C. Acetylation of 118 in acetic anhydride and pyridine gave the diacetate 119 mp 123-124°C.



118 119

The diacetate 119 was epoxidized following an experimental procedure adopted from McEuen.[67] The diacetate 119 dissolved in methylene chloride was treated with a 40% solution of peracetic acid in acetic acid; and after work-up and purification by recrystallization a 63% yield of the heretofore unknown 5,6,7,8-tetrahydro-1,4-napthohydro-

quinone-6,7-oxide diacetate 137, mp 162-163°C, was obtained. The nmr spectrum of 137 indicates a fairly symmetrical molecule with a sharp six proton singlet at 2.30δ for the acetate methyls, two broadened singlets of two protons each at 2.98δ and 3.22δ for the benzylic protons, a two proton broad singlet at 3.45δ for the oxirane ring protons,

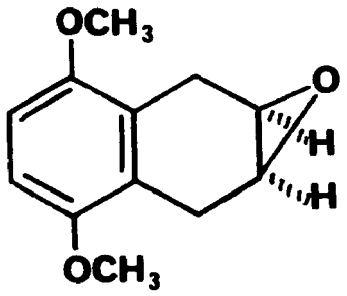


138 139

and a sharp two proton singlet at 6.95δ for the aromatic protons. The mass spectrum of 137 is interesting in that it shows a very large peak at m/e 261 corresponding to the loss of one hydrogen atom and the formation of a fairly stable cation.

It was hoped that in order to functionalize what was to become the D-ring of daunomycinone(1) the oxirane ring in 137 could be opened with either sodium acetylide[68] or an alkyl copper reagent[69] acting as a nucleophile. However, when 137 was treated with excess sodium acetylide in liquid ammonia none of the desired alkyne (138) could be found. The only product isolated (42%) was 5,6,7,8-tetrahydro-1,4-napthohydroquinone-6,7-oxide monoacetate (139). The nmr spectrum of 139 was almost identical to that of 137 except for the loss of one acetyl methyl and a doublet of doublets (J = 7Hz) centered at 6.58δ and 6.82δ for the two nonequivalent aromatic protons. The loss of one acetyl group was also indicated by the mass spectrum of 139 which had a molecular ion at m/e 220. The oxirane ring opening was obviously going to require something other than simple addition of acetylide ion. However, before the addition of alkyl copper reagents to either 137 or the corresponding dimethyl ether 140 could be attempted, this synthetic route was abandoned. A co-worker[70] was experiencing difficulty in attempted condensations of 119 and 120 with either phthalicanhydride or methyl hydrogen phthalate, a reaction which was essential to this synthetic plan. We felt that

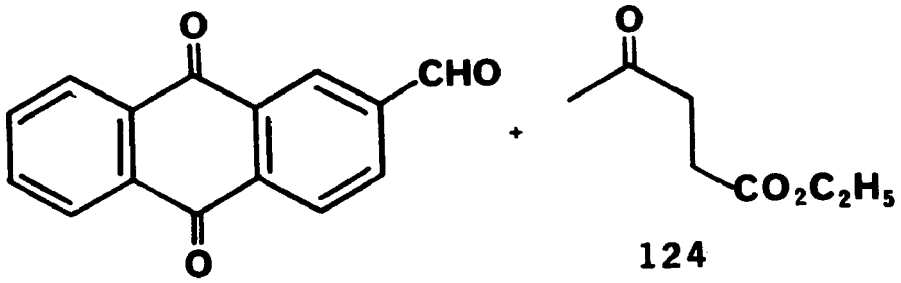
our synthesis could not tolerate any low yield reactions because we planned to use it as a model for the preparation of analogs of daunomycin(3).



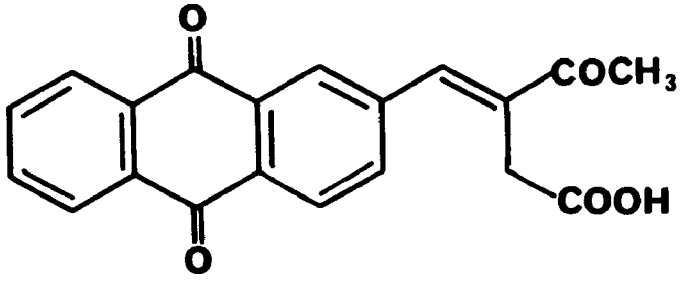
140

To investigate the second proposed synthetic scheme for the synthesis of daunomycinone(1) a properly substituted anthraquinone would have to be prepared. Anthraquinyl-2-aldehydes had been shown[71] to undergo a Claisen condensation with compounds containing an activated methylene. It therefore seemed reasonable to plan a modified Stobbe[63] condensation as is shown below for 2-anthraquinonal and ethyl levulinate (124) to give the unsaturated keto acid 141.

A literature search indicated that 1-amino-5-chloranthraquinone (142), which is commercially available, would provide the most useful substitution pattern for the preparation of a suitable aldehyde. The amine function can be used in many ways to further functionalize what is to



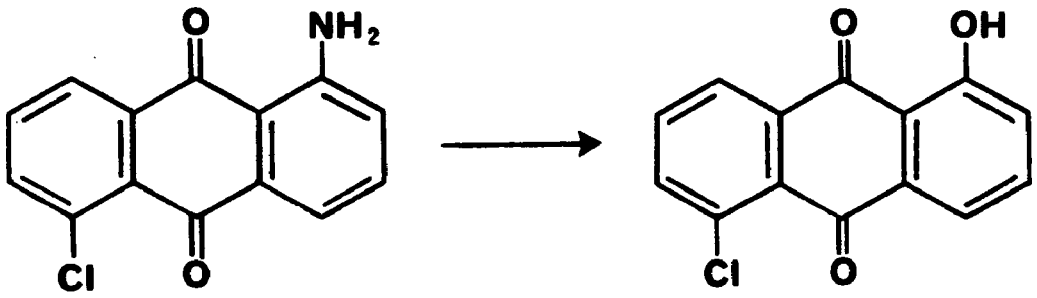
124



141

become the C-ring of daunomycinone(1). Furthermore, the halogen functionality not only provides a means for the introduction of methoxyl[65,66] but also acts to deactivate what is to become the A-ring towards electrophilic substitution. Also, the 1,5-orientation of the two groups provides the selectivity required to eliminate the formation

of the A-ring isomer isodaunomycinone(117).



142 132

The conversion of 142 to 1-chloro-5-hydroxyanthraquinone (132) was planned and it was hoped that the C-6 position of 132 could be functionalized as Marschalk[72] and coworkers had done in the case of 1-hydroxyanthraquinone. Several methods were applied to the preparation of 132. It was hoped that an acid catalyzed hydrolysis which had been used[73] in the case of some other aromatic amines would be successful. However, when 142 was placed in a combustion tube with dilute sulfuric acid and heated at 200°C for more than 8 hours the only material recovered was 54% of the starting material which was easily identified by tlc and its ir spectrum.

The Bucherer[74] reaction seemed well suited to the conversion of 142 to 132 and the procedure of Friez-David[75] and coworkers was attempted. When 142 in aqueous ethanol was heated at reflux for 27 hours in the presence of sodium

bisulfite, there was a 98% recovery of the starting material which was identified by tlc.

The conversion of 142 to 132 might be accomplished by diazotization and an adaption of two procedures[76,77] for the diazotization of aminoanthraquinones did indeed afford some of the desired product. When 142 was dissolved in cold sulfuric acid and treated with sodium nitrite, a mixture of 132 and 142 was obtained and could be separated by an extraction technique involving aqueous methanol and potassium hydroxide. However, when the sulfuric acid solution was heated at 120-130°C for two hours and then poured into water, a relatively pure product containing none of the amine was obtained. After recrystallization from acetic acid 132 had a melting point of 220.5-222°C, in good agreement with that reported by Green.[77] The product, however, was always contaminated with another compound which showed very similar behavior on tlc and was never characterized.

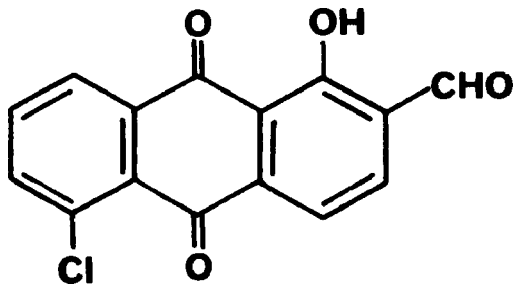
A later procedure[66] for the diazotization of aminoanthraquinones, which was used in the preparation of naturally occurring dyestuffs, proved to be the best method. Diazotization of 142 in cold sulfuric acid as before was followed by treatment with acetic acid and thin crushed ice. The cold diazonium ion suspension was then added to boiling 50% sulfuric acid and the product was purified by recrystallization from aqueous acetone. This procedure gave an 87% yield of dark gold needles of 132, mp 223-224°C, which could be submitted for analytical analysis without further purification.

The spectra of 132 provide some very useful diagnostic tools which can be used to study the reactions of 132. The ir spectrum of 132 shows two distinct absorptions for the quinone carbonyls; the C-10 hydrogen bonded carbonyl appears at 1640 cm^{-1} and the C-9 free carbonyl appears at 1675 cm^{-1}. The nmr spectrum of 132 includes two one proton doublet-of-doublets absorptions, one at 7.38δ (J = 2Hz and 7Hz) assigned as the C-6 proton ortho to hydroxyl, and one at 8.45δ (J = 2Hz and 7Hz) assigned to the C-4 proton which is para to chlorine and very useful in determining effects on the chlorine bearing ring. The mass spectrum of 132 contains a P + 2 peak at m/e 260 which is 35% of the intensity of the parent ion at m/e 258 and is indicative of one chlorine atom per molecule.

While the conditions for the preparation of 132 were being worked out, the condensation of ethyl levulinate with benzaldehyde was attempted. Ethyl levulinate (124) was prepared by esterification of commercial levulinic acid and in repeated experiments was mixed with benzaldehyde, sodium hydride and a trace of ethanol in dry benzene following a general procedure for the Stobbe[63] condensation. A waxy crystalline solid was obtained whose nmr spectrum was quite different from the starting materials but which did not contain any signals that could be attributed to a methyl ketone function. The absence of a methyl group yet acidic character implies that the condensation was kinetically controlled and involved the acyl methyl instead of

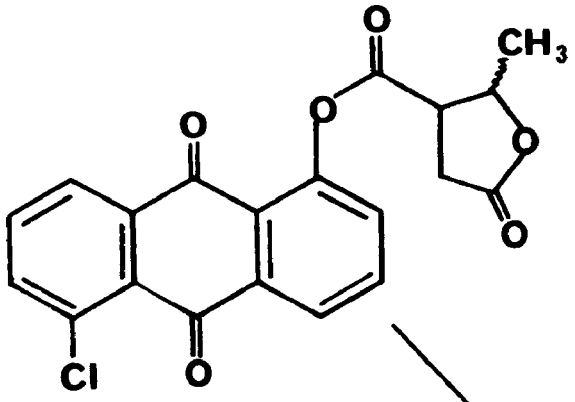
the methylene.

The results of the above condensation and the difficulties anticipated in the preparation of an aldehyde such as 143 prompted us to look for other synthetic routes to daunomycinone(1).

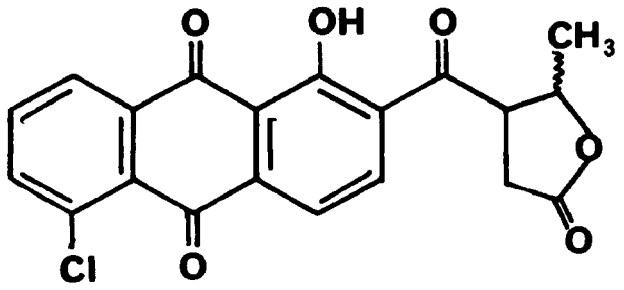


143

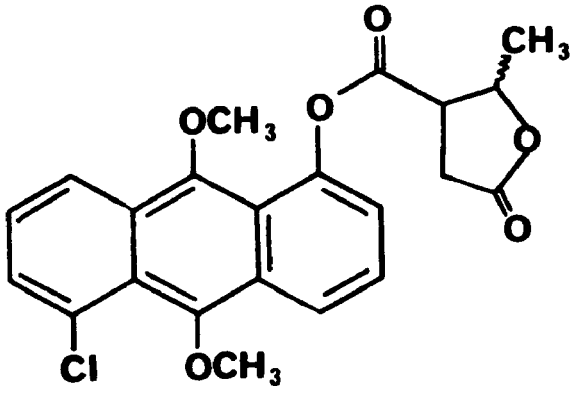
From the limited number of examples which were available in the literature, it appeared that the placement of an aliphatic side chain specifically at the C-6 position of 132 would be a synthetic challenge. The Lewis acid catalyzed or photolytic Fries rearrangement[64] appeared to be a reasonable possibility and therefore a synthesis of the lactone ester 127 was formulated. The Fries reaction is known to be quite dependent on reaction temperature, solvent and substituents on the phenol portion.[78] However, it was felt that if the rearrangement of 127 to 128 was hindered by the quinone functionality, a reduced species such as 144 could be photolytically rearranged.



127



128



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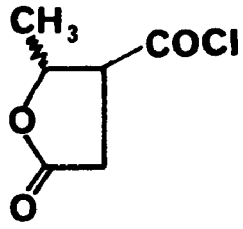


130

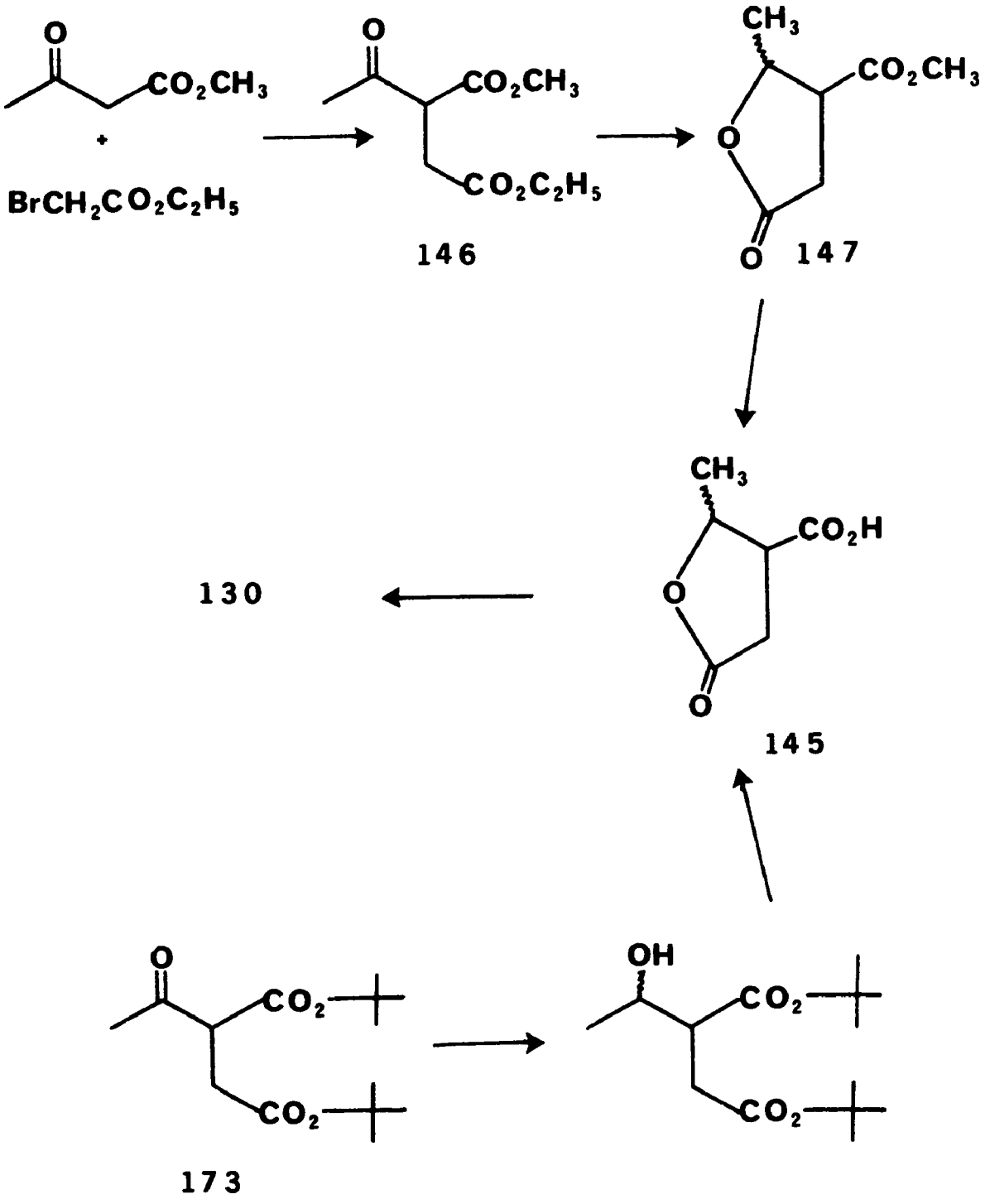
The synthesis of 127 would require the preparation of γ-methyl paraconyl chloride (130). A literature search revealed only one synthesis of γ-methyl paraconic acid (145). In 1889, Fittig[79] condensed the disodium salt of succinic acid with acetaldehyde in refluxing acetic anhydride for several days and obtained 145 in a 15-16% yield. He reported two different melting points of 79-80°C and 84-85°C for 145. In 1913, Barbier[80] reported the preparation of γ-methyl paraconyl chloride (130), bp 142°C at 10 mm of Hg by treatment of 145 with thionyl chloride. He also reported the preparation of methyl γ-methyl paraconate (147), bp 145-160°C at 11 mm of Hg by treatment of 130 with methanol. Methyl paraconic acid (145) was also mentioned in two kinetic studies[81] one of which gave the melting point as 84-85°C.[81a]

It appeared that 145 could be best prepared by an altogether new synthesis. Alkylation of methyl acetoacetate in N,N-dimethylformamide with ethyl bromoacetate and sodium hydride gave, after fractional distillation of the crude product, a 51.6% yield of methyl ethyl 2-aceto succinate (146), bp 78-81°C at 0.25 mm of Hg. The nmr spectrum of 146 shows very clean signals for the methyl ester (3.60δ), the acetyl methyl (2.17δ) and the ethyl ester (1.15δ, τ, 3H, J = Hz; 3.95δ, q, 2H, J = 6Hz) indicating that no ester exchange had taken place. To complete the spectrum the C-2 methine appears at 3.79δ as a triplet (J = 8 Hz) and the C-3 methylene is at 2.61δ as a doublet (J = 8Hz). Acid or

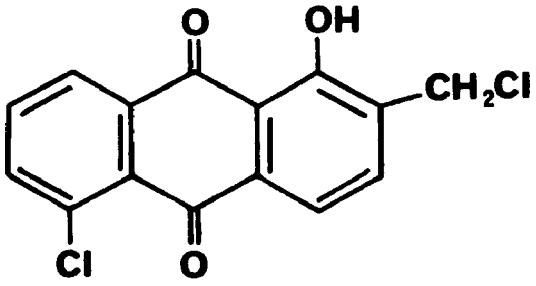
base catalyzed hydrolysis of 146, followed by sodium borohydride reduction, gave the desired acid 145 in varying yields.

However, reduction of 146 to the corresponding alcohol with sodium borohydride in methanol, followed by acidification of the reaction mixture and removal of most of the methanol by distillation gave, after an extractive workup with ether, a 93% yield of the methyl ester 147, bp 78-84°C at 0.10 mm of Hg. Hydrolysis of 147 with potassium hydroxide in ethanol followed by acidification and azeotropic removal of the ethanol with excess benzene gave a benzene solution of 145. The acid 145, mp 85-86°C, could be obtained in 88-90% yield by cooling and addition of petroleum ether.

The overall yield of 40-42% of 145 from ethyl bromoacetate could undoubtedly be increased by optimizing the reaction conditions for the formation of 146. It was discovered later when di-t-butyl 2-acetoacetate (173) was prepared that the acid 145 could be made in two simple steps from this diester. Reduction of 173 to the corresponding alcohol with sodium borohydride in methanol followed by hydrolysis of the esters with p-toluenesulfonic acid in benzene gave 145 in nearly quantitative yield from 173. It was also discovered that the acid could be purified by sublimation at 78-80°C and 0.025 mm of Hg.

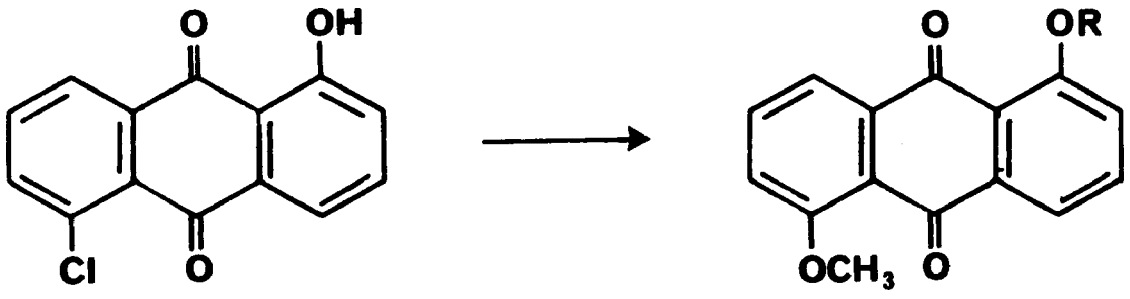

O
CO2CH3
+
BrCH2CO2C2H5
O
CO2CH3
CO2C2H5
146
CH3
CO2CH3
O
O
147
CH3
CO2H
O
O
145
130
O
CO2
CO2
173
OH
CO2
CO2

However, the discovery of an effective new method for the preparation of 1-hydroxy-5-chloro-2-chloromethylanthraquinone (148) and the low yields which could be expected from the Fries rearrangement prompted us to abandon this synthetic approach.



148

Before going too far into the investigation of the use of 132 as a starting material for the preparation of daunomycinone (1) it was decided that the nucleophilic substitution reaction which was planned for the conversion of 132 to 1-hydroxy-5-methoxyanthraquinone (149) should be tested.



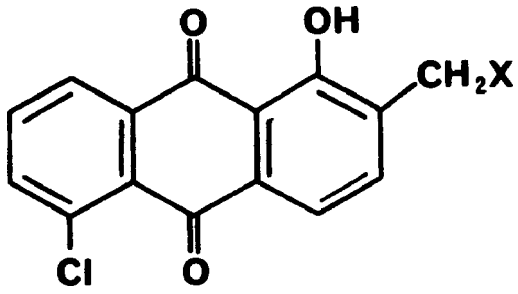
132

149 R=H
150 R=COCH3

When 1-chloro-5-hydroxyanthraquinone (132) was heated for 70 hours under reflux in dry methanol in the presence of a large excess of sodium methoxide and a catalytic amount of cuprous oxide, a 3:1 mixture of 149 and 132 was obtained. Acetylation of the crude product gave a more easily separable mixture which after chromatography on silica gel gave a 62% yield of the acetate 150, mp 161-162°C. Acetate 150 could be quantitatively hydrolyzed to the desired product 149, mp 182-183°C. The nmr spectrum of 149 shows a three proton singlet at 4.05δ as well as a rather symmetrical six proton aromatic multiplet centered at 7.75δ.

The success of the above reaction substantiated our previous idea that 132 would be a useful starting material for the synthesis of daunomycinone (1). Moreover, it was believed at that time that this replacement reaction could be carried out at any of several places along the route of our newly proposed synthetic pathway. To further investigate this proposed synthesis the first problem was to find a method for the preparation of an anthraquinone such as 133. The "X" functionality in 133 could be anything like a tetraalkyl ammonium ion, halogen atom or oxygen function which could be easily removed for the formation of a new carbon-carbon bond at that position.

Consideration of the problem and the findings of Marschalk[72] suggested the use of a Mannich[82] reaction for the preparation of 133 where X = NR_2. The general procedures[83] from several previous Mannich reactions on



133

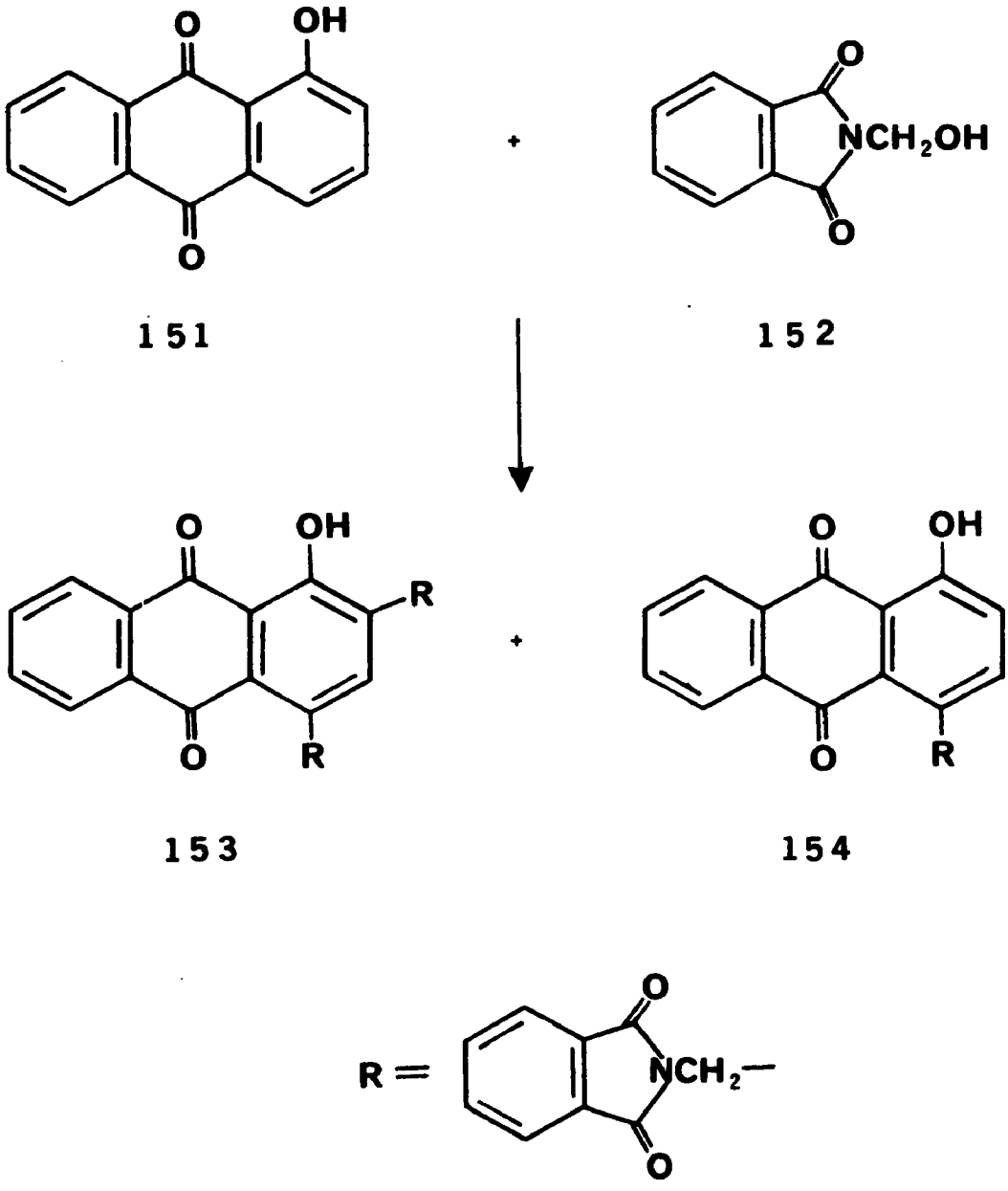
variously substituted phenols were followed. A mixture of 132 and 37% formalin was heated at 100°C for 3.5 hours in 25% aqueous morpholine. After an extractive workup and removal of excess morpholine at the vacuum pump there was an 87% recovery of the starting material as shown by tlc and ir.

In a similar experiment, 132 was ground to a fine powder and mixed with two equivalents of paraformaldehyde. The resulting powder was heated in eight equivalents of morpholine at 100°C for 3 hours. After workup 89% of the starting material was recovered. This procedure was repeated twice, once with a catalytic amount of acetic acid added, and the second time with a mixture of acetic acid and phosphoric acid added. In both cases the starting material was returned in high yield, 85 and 87%, respectively. Shortly after it was concluded that the Mannich reaction would not be applicable to this system a report

of similar findings appeared in the literature. A Russian group[84] reported that 1-hydroxyanthraquinone, 1,4-dihydroxy anthraquinone and 1,2,3-trihydroxyanthraquinone were unreactive towards mixtures of secondary amines and paraformaldehyde.

The Tscherniac-Einhorn reaction[85] is a powerful method for the preparation of amidomethyl and imidomethyl aromatic compounds and appeared to be a good choice after the failure of the Mannich reaction. The applicability to this system was shown by de Diesbach[86] in 1928 when he reported his results on the amidomethylation of 1-hydroxyanthraquinone (151). He found that treatment of 151 with 2 to 3 equivalents of N-methylolphthalimide (152) in concentrated sulfuric acid produced a mixture of compounds. The major product was the 2,4-diphthalylimidomethyl compound 153. The minor product was found to be 4-phthalylimidomethyl compound 154.

It was of interest to us to discover what the distribution of products would be if 132 was treated with only one equivalent of 152. One might expect either a mixture of the two possible monosubstitution products or only one isomer corresponding to 154. N-Methylolphthalimide (152) was prepared in very good yield by the method of Buc.[87] Stoichiometric quantities of 1-chloro-5-hydroxyanthraquinone (132) and 152 were dissolved in sulfuric acid and kept at approximately 60°C for 2-3 hours. After dilution with water there was obtained a mixture of three compounds

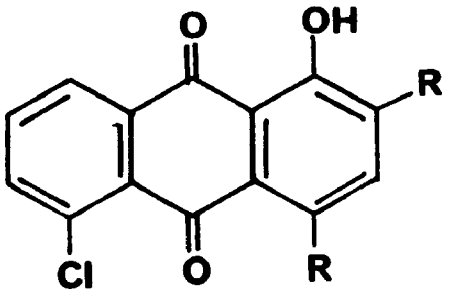


as shown by the presence of three spots on tlc. The more rapidly moving spot was equivalent in all solvent systems to the starting material 132. Trituration of the crude product with acetone gave an insoluble solid (155) and an acetone solution. The acetone solution showed only a very faint spot on tlc corresponding to the slowest moving spot

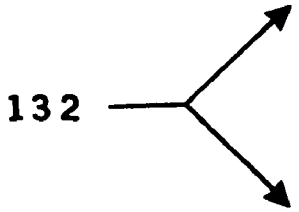
of the crude product. The solid could be recrystallized from acetic acid and gave a 27% yield of the di-substituted material 155, mp 316-320°C with decomposition. Removal of the acetone under vacuum and recrystallization of the residue from a mixture of chloroform and ethanol gave the major product 156, mp 256-257°C.

The minor product 155 was assumed to be the 2,4-diphthalimidomethyl derivative based on two observations. The first is the similarity of 155 to 153 (mp 295°C) in terms of melting point and solubility behavior. The second is the presence of a very intense band in the ir spectrum at 1710 cm^{-1} and a less intense band at 1785 cm^{-1} which are attributable to the phthalimido carbonyls. The major product 156 (42.5%) is a mono-substituted product as shown by the nmr spectrum of its acetate (157), mp 239-240°C. The spectrum shows a nine proton aromatic multiplet from 7.20δ to 8.00δ, a two proton singlet at 5.39δ for the methylene and a three proton singlet at 2.42δ for the acetate. The monosubstituted product 156 was judged to be the para-substituted isomer, shown below, on the basis of its non-identity with the product obtained when 148 was treated with phthalimide in the presence of a base.

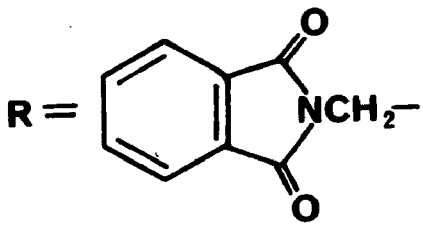
The absence of any C-2 substituted product probably indicates that the first addition is specific for the C-4 position. However, even though the amidomethylation gives the wrong product the reaction might still be of use if a blocking substituent could be placed at the C-4 position



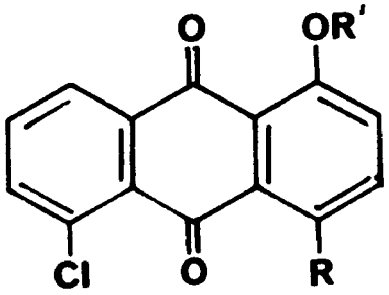
155



132



R =

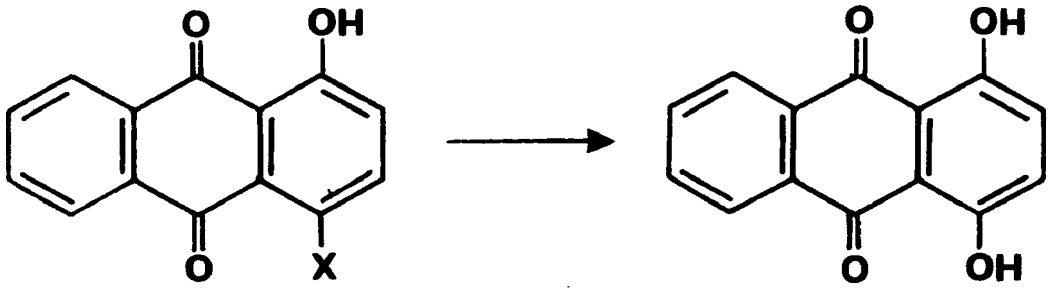


156 R′ = H
157 R′ = COCH$_3$

and later converted to an hydroxyl function. With regard to the choice of a blocking substituent the following two reactions reported in the literature were of particular interest.

It was reported[76] that on heating in concentrated sulfuric acid in the presence of excess boric acid, 1-

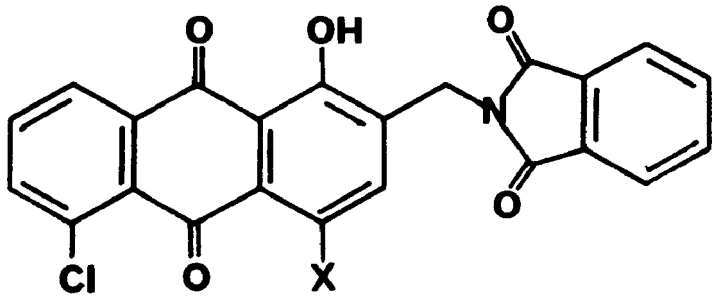
hydroxy-4-chloroanthraquinone (158) could be converted in good yield to quinizarin (159). It was also reported[88] that high temperature acid hydrolysis in a pressure vessel of 1-amino-4-hydroxyanthraquinone (160) gave a quinzarin (159).



158 X = Cl
160 X = NH_2

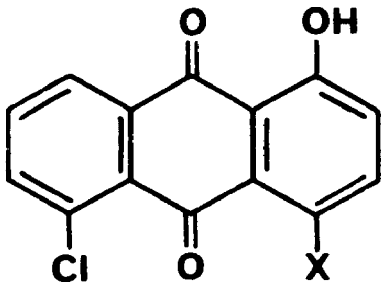
159

The availability of these conversions suggested the possibility of bromination or nitration of 132 followed by amidomethylation to give the desired substitution pattern as shown in compounds 161 and 162.



161 X = Br
162 X = NO_2

Bromination of 132 was carried out by the method of Fries[89] after other more conventional methods had failed. A solution of 132 and excess sodium acetate in acetic acid at 100°C was treated with a stoichiometric amount of bromine in acetic acid. After 5 to 10 minutes the product was precipitated by addition of the reaction mixture to water. Recrystallization from aqueous acetone gave an 88% yield of the monobromo compound 163, mp 242-243°C.



163=X Br
164=X NO_2

Nitration of 132 was accomplished following the method of Gattermann.[90] A mixture of 132 and excess boric acid was heated in concentrated sulfuric acid to form the borate ester of 132 and then the mixture was cooled to room temperature. Treatment of the cooled solution with a mixture of nitric and sulfuric acids followed by pouring the reaction mixture into ice water gave an 88-93% yield of 1-hydroxy-4-nitro-5-chloroanthraquinone (164), mp 255-256°C, which was contaminated by a small amount of the

dinitro product. The structure of 164 was later verified by its conversion to quinizarin (159) on treatment with sodium dithionite in hot aqueous sodium hydroxide.

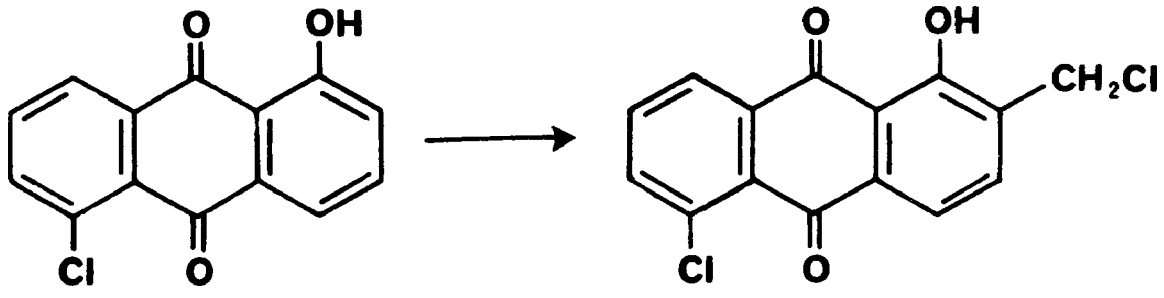
Use of the nitration reaction was attractive but attempts to amidomethylate 164 with 152 under various conditions failed completely. However, the bromination-amidomethylation route appeared more promising due to the difference in reactivity which 163 and 164 should show towards amidomethylation. Before this route was investigated further two discoveries caused it to be abandoned. The first was the chloromethylation of 132 to give 1-hydroxy-2-chloromethyl-5-chloroanthraquinone (148). The second was difficulty in removal of the phthaloyl group from 156.

Of the two general methods for the cleavage of phthalimides base catalyzed hydrolysis was not attempted because it was felt that the hydrolysis would be complicated by the elimination of phthalimide. Therefore, the use of hydrazine[91] as a cleavage reagent was attempted. However, when 156 was treated with hydrazine in boiling ethanol only a 9% yield of acid soluble material was obtained. The remainder of the colored material was obtained as a mixture of 2 or 3 compounds which were not identified.

The success of the amidomethylation reaction prompted us to try another method of alkylation. The chloromethylation[92] reaction which has been used for the preparation

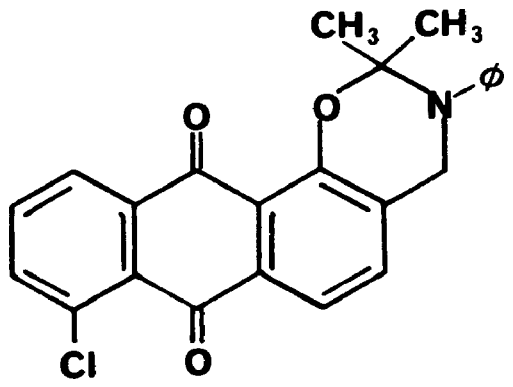
of many aromatic chloromethyl compounds was considered. However, 132 was thought to be too unreactive to be affected by the normal Blanc[93] conditions of hydrochloric acid and formaldehyde. In 1963, Taylor and Davis[94] reported the chloromethylation in high yield of an unreactive phenol using aluminum chloride with chloromethyl methyl ether as the solvent [caution before using chloromethyl methyl ether consult Organic Reactions, 19, 422 (1972)].

Taylor and Davis[94] suggested the use of one equivalent of Lewis acid catalyst for each oxygen atom in the substrate in order to obtain an homogeneous reaction mixture. When 132 was suspended in cold chloromethyl methyl ether and treated rapidly with 3.3 equivalents of anhydrous aluminum chloride powder, a 70% yield of pure 1-hydroxy-2-chloromethyl-5-chloroanthraquinone (148), mp 204-205°C, was obtained.



132 148

The nmr spectrum of 148 consisted of four signals. A two proton singlet at 4.78δ which was assigned to the benzylic methylene, a four proton aromatic multiplet centered at 7.85δ, a one proton doublet-of-doublets at 8.38δ (J = 2Hz and 7Hz) for the C-4 proton and a phenolic proton singlet at 12.80δ were observed. The absence of an absorption at 7.38δ indicated the ortho relationship of the hydroxyl and chloromethyl groups. This assignment was substantiated by the formation of 165 on treatment of 148 with a mixture of aniline and acetone in the presence of acid.



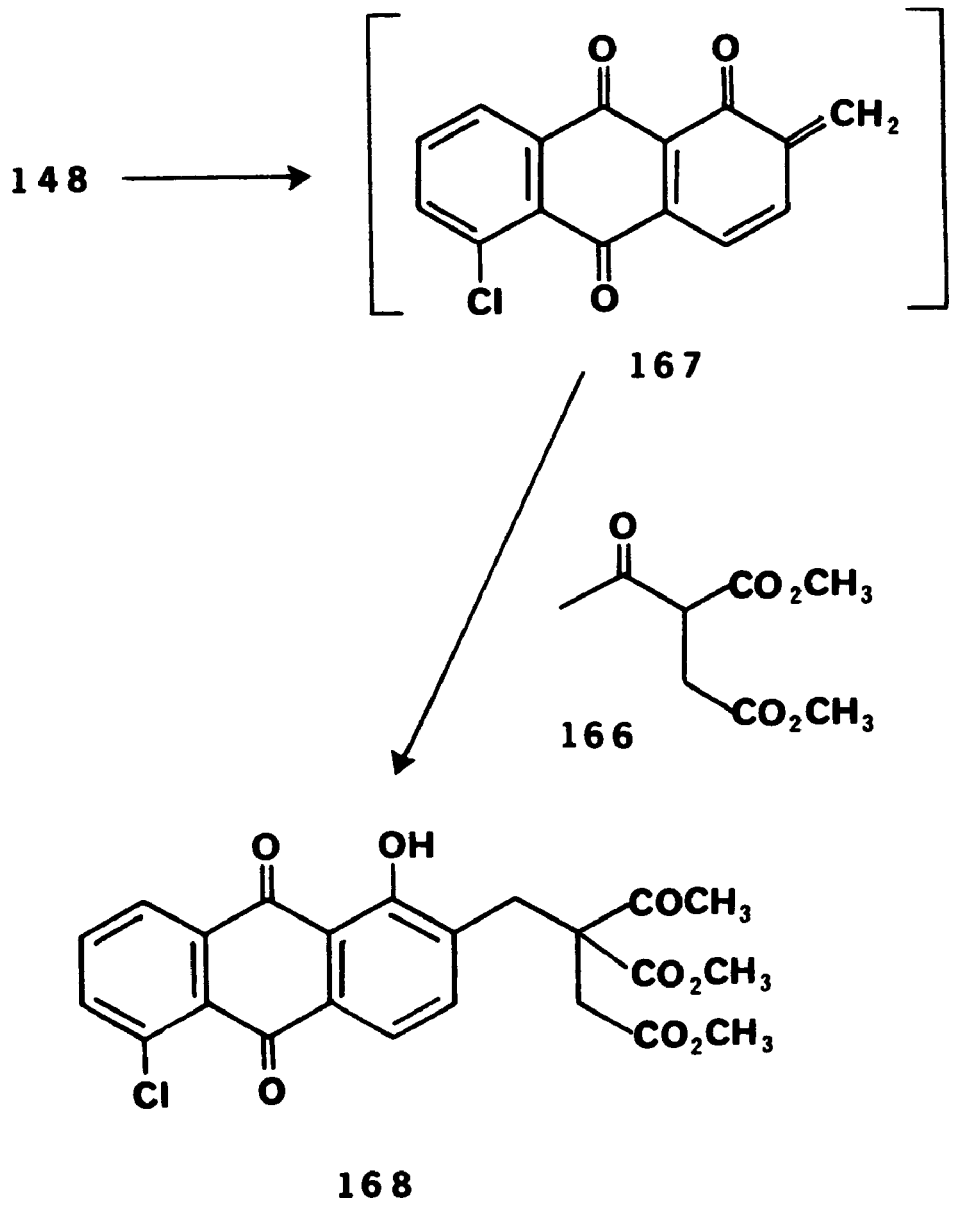
165

The ir spectrum of 165 showed no hydrogen bonded carbonyl and the nmr spectrum showed a six proton singlet at 1.25δ. The mass spectrum of 148 was quite simple showing a P + 2 peak at m/e 308 which is 71% of the intensity of the parent ion (m/e 306) and a base peak at m/e 271 which is attributed to the loss of the benzylic chlorine atom.

Although 148 is quite stable thermally in the pure state, it decomposed rapidly when heated in solution, especially in the presence of basic materials. This caused the preparation of derivatives such as the acetate or methyl ether to be quite difficult.

The proposed use of 148 was as an alkylating agent. The ketodiester 146 had been prepared earlier in this work and appeared to be well suited for alkylation by 148. However, it was felt that the mixed diester (146) might unnecessarily complicate the spectra of the desired product. To alleviate this problem the corresponding dimethyl ester 166, bp 94-97°C at 1.5 mm of Hg, was prepared by alkylation of methylacetoacetate with methylbromoacetate. The nmr spectrum of 166 was very straightforward. It contained a three proton singlet at 2.28δ for the acetyl methyl, a two proton doublet-of-doublets (J = 1.5Hz and 6Hz) at 2.95δ, a one proton triplet at 4.02δ and two three proton singlets at 3.71δ and 3.80δ. It was speculated that the alkylation would occur by elimination of hydrogen chloride to give the intermediate 167 which could undergo a Michael addition of the enolate of 166 to give the desired product.

When the enolate anion of 166 was prepared in benzene and treated with a solution of 148 in the same solvent, a 75% yield of methyl 3-acetyl-3-carbomethoxy-4-(1-hydroxy-5-chloro-2-anthraquinonyl)butyrate (168), mp 179-180°C, was obtained. The position of alkylation on 166 was easily determined by analysis of the nmr spectrum of 168. In the



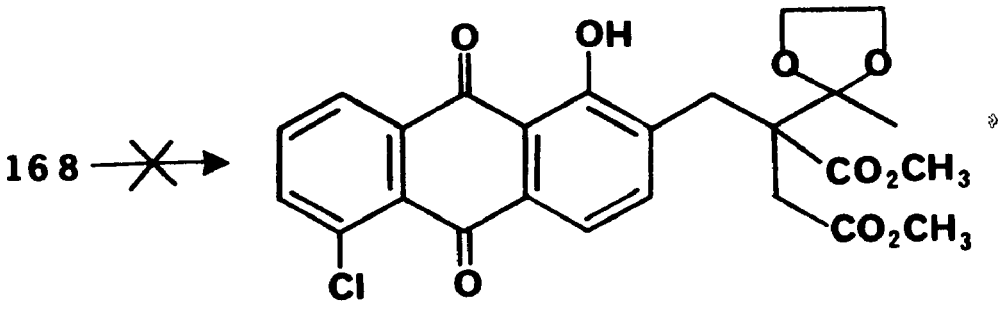
168

spectrum of 168 there was no signal at 4.02δ and the C-2 methylene protons had collapsed to a two proton singlet at 2.90δ. Also obvious in the spectrum was the shift of the benzylic methylene protons to 3.52δ from 4.78δ in 148. These absorptions along with a three proton acetyl methyl singlet at 2.38δ allow no other structure than that shown for 168.

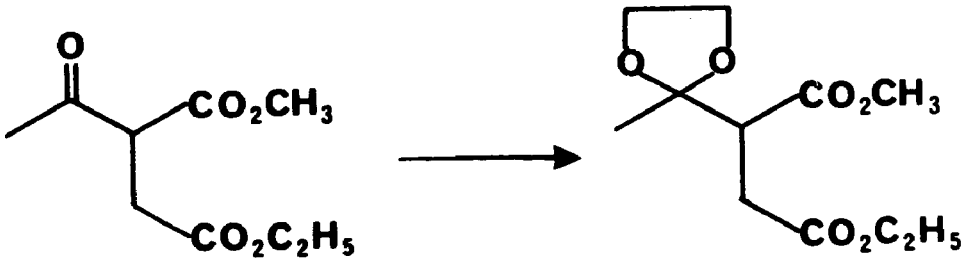
Hydrolysis of 168 to the keto acid 136 was attempted by heating the diester 168 at reflux in 5% methanolic potassium hydroxide for three hours. After acidification of the reaction mixture there was obtained a dark tan solid which had no aliphatic hydrogen absorptions in its nmr spectrum. It was felt that perhaps a reverse of the previous alkylation reaction was occurring and that protection of the ketone function in 168, as the ketal 169, might eliminate this problem. However, when 168 was treated with ethylene glycol and para-toluenesulfonic acid in refluxing benzene, with a Dean-Stark trap for the removal of water, there was obtained after 12 hours a quantitative return of the starting material as shown by tlc and nmr. The resistance of 168 toward ketal formation must be due to steric factors about the ketone carbonyl since identical treatment of 146 for 4 hours gave a 98% yield of ethyl 3-carbomethoxylevulinate ethylene ketal (170).

The nmr of 170 was conclusive for the structure shown: besides the methyl and ethyl ester signals there appears a three proton singlet at 1.30δ, a two proton multiplet at 2.52δ, a one proton quartet (J_a = 8Hz and J_b = 4.5Hz) at 3.09δ and a four proton singlet at 3.93δ.

The failure of the diester 168 to undergo hydrolysis made it necessary to find another precursor to the keto acid 136. Since the alkylation reaction which gave 168 had worked so well the preparation of an acetosuccinate diester, like 166, with ester groups which could be easily cleaved



169



146 170

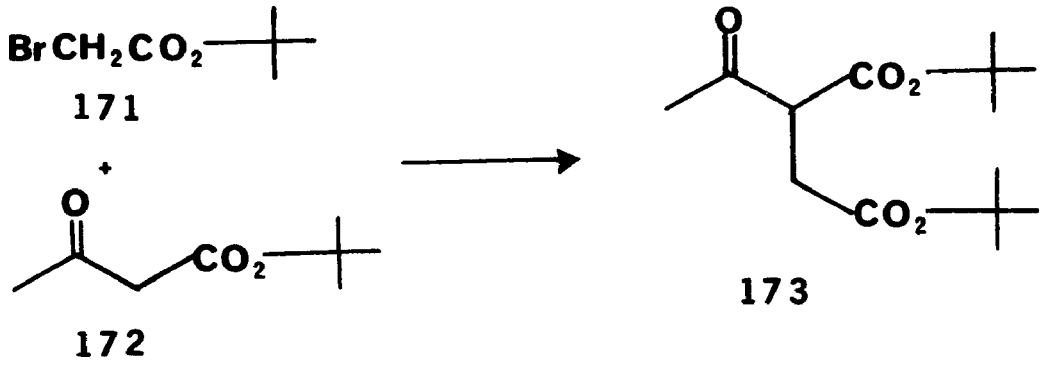
would be very beneficial. The tertiary-butyl ester group is known[95] to be quite stable towards basic reaction conditions and yet can be cleaved very easily by mild acid treatment.

Tertiary-butyl bromoacetate (171) was prepared in 58% yield from technical bromoacetic acid by the method of

Johnson.[96] The clear lacrymatory liquid was collected from a fractional distillation at 69-70°C and 18 mm of Hg. The nmr spectrum of 171 showed two signals, a nine proton singlet at 1.45δ and a two proton singlet at 3.66δ.

Tertiary-butyl acetoacetate (172) was prepared in 71% yield from diketene and tertiary-butyl alcohol by the method of Sandberg.[97] The clear liquid was obtained from a fractional distillation of the crude reaction mixture over a one degree range of 82-83°C at 1.6 mm of Hg. The ir spectrum of 172 shows distinct ester and ketone carbonyl absorptions at 1735 and 1708 cm^{-1}, respectively. The nmr spectrum of 172 has a nine proton singlet at 1.43δ, a three proton singlet at 2.21δ for the acetyl methyl group and a two proton singlet at 3.38δ for the methylene.

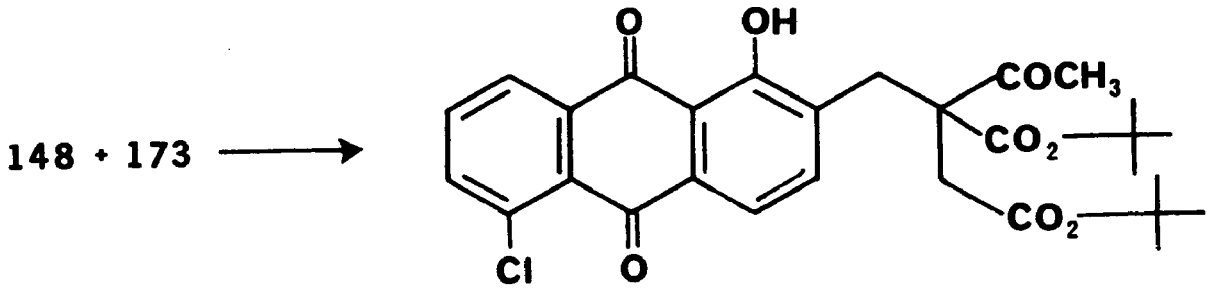
Alkylation of the enolate anion of tertiary-butyl-acetoacetate (172) in N,N-dimethylformamide with tertiary-butyl bromoacetate (171) gave the hitherto unknown di-tertiary-butyl 2-acetylsuccinate (173) in 83% yield, bp 91-93°C at 0.015 mm of Hg. In the distillation, 33% of the tertiary-butyl acetoacetate was recovered. The nmr spectrum of 173 showed two nine proton singlets at 1.40δ and 1.42δ, a three proton singlet for the acetyl methyl at 2.22δ, a two proton doublet-of-doublets at 2.60δ with J_a = 8Hz and J_b = 2Hz for the C-3 methylene protons and a one proton triplet at 3.70δ with J = 8Hz for the methine proton. The ir spectrum of 173 had a very intense carbonyl absorption centered at 1710 cm^{-1} for the combined carbonyls



as well as absorptions at 1392 cm^{-1} and 1370 cm^{-1}, indicative of the tertiary-butyl groups. Not too surprisingly, the molecular ion is missing in the mass spectrum of 173, but a peak at m/e 216 corresponding to loss of isobutylene and a very strong base peak at m/e 57 for the tertiary-butyl cation are present. A perfect elemental analysis for 173 was obtained without further purification.

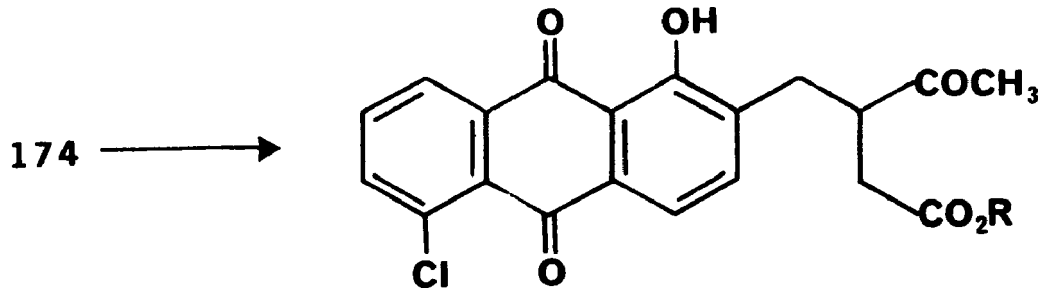
With the successful preparation of 173 its alkylation with 148 was planned. The enolate anion of di-tertiary-butyl acetosuccinate (173) was formed by treatment with sodium hydride in N,N-dimethylformamide. To the solution of the enolate anion there was added a solution of 5-chloro-1-hydroxy-2-chloromethyl anthraquinone (148) in N,N-dimethylformamide. After stirring at approximately 50°C for 2.5 hours the reaction mixture was neutralized by pouring it into a large volume of 1% aqueous acetic acid. An extractive workup and chromatography of the crude product

gave a 70% yield of di-tertiary-butyl 2-acetyl-2-(1-hydroxy-5-chloro-2-anthraquinonyl)methyl succinate (174) as a dark gold semisolid which crystallized completely on standing. The melting point of 174 was indefinite with gas evolution and decomposition beginning at 162-165°C.



174

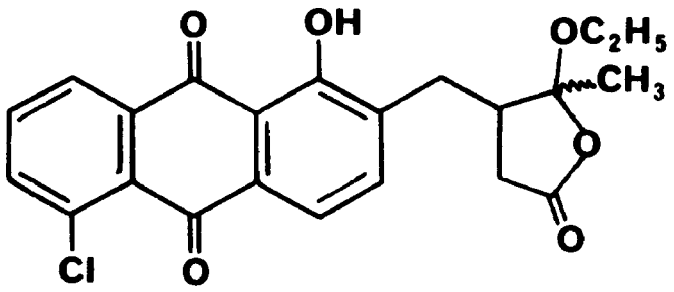
The conversion of the diester 174 to the desired keto acid 136, mp 212-213°C, was accomplished very cleanly under acidic conditions following the procedure of Puterbaugh[98] and coworkers. However, due to the physical characteristics of 136 it was found necessary to adapt the procedure to give the keto ester 175. The diester 174 in benzene under reflux was treated with a catalytic amount of para-toluenesulfonic acid. After isobutylene and carbon dioxide evolution had ceased the benzene was removed by azeotropic distillation with excess ethanol. After cooling of the residual ethanol solution an 87% yield of the desired keto ester 175 in fine golden yellow plates, mp 133.5-



136 R=H

175 R=C_2H_5

134.5°C was obtained. The nmr and ir confirmed that 175 is the ketoester shown and not the isomeric lactone 176.

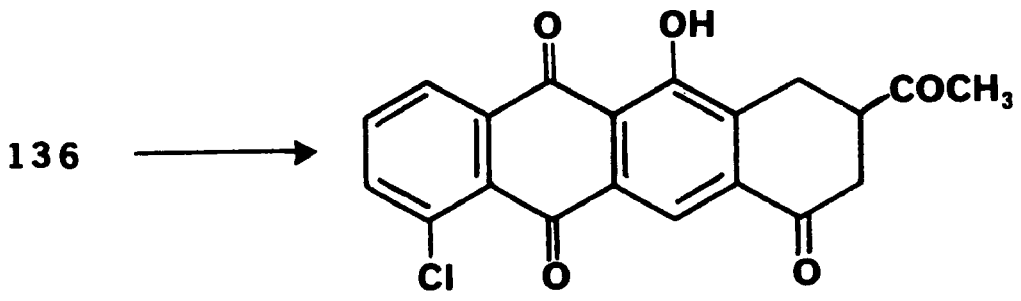


176

The nmr spectrum of 175 shows an acetyl methyl absorption at 2.27δ which is at lower field than would be expected for the methyl group in 176. The ir spectrum of 175 shows a combined ester and ketone carbonyl absorption at 1712 cm^{-1} indicative of the structure 175 and incon-

sistent with the expected value for lactone 176.

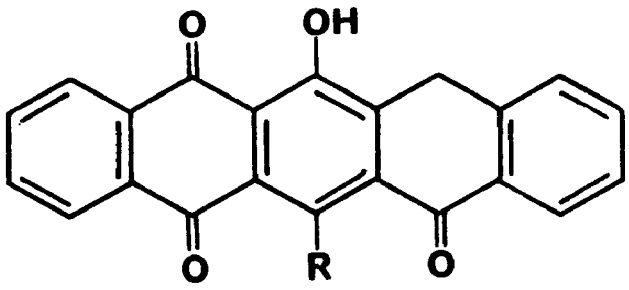
It was expected that either the acid 136 or the ester 175 could be caused to undergo a ring closure reaction to give the tetrahydronapthacenedione 177.



177

When 136 was heated in sulfuric acid or polyphosphoric acid following the procedures of Marsh[41] and Snyder[99] at various temperatures from 80-140°C, almost quantitative returns of the starting material were obtained. The product was identified by tlc and conversion to the ester 175.

Marschalk[72] prepared the pentacene quinones 178 and 179 by an intra molecular condensation using a fused mixture of aluminum chloride and sodium chloride. However, when Marschalk's conditions were repeated exactly using the acid 136, the starting material was recovered along with some tar. Decreasing the reaction temperature and lengthening the reaction time gave no new products.



178 R=H

179 R=OH

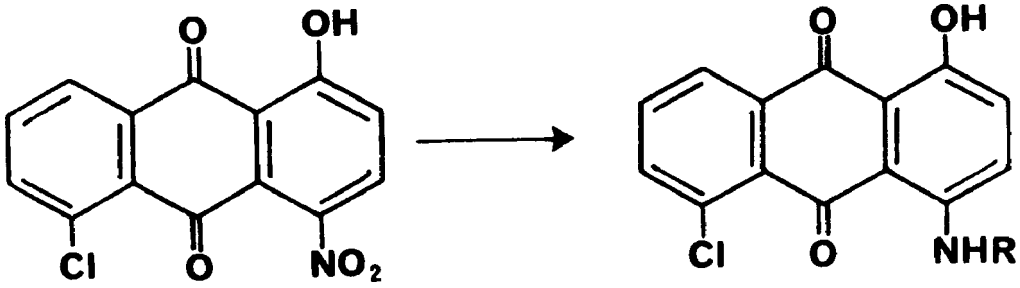
It was felt that the ring closure reaction would be more favorable if an activating substituent such as hydroxyl could be placed at the C-4 position of 136. To accomplish this functionalization several different methods were attempted.

Following a procedure[100] for the oxidation of phenols to quinones the hydroxyanthraquinone 132 was dissolved in a mixture of acetic acid and sulfuric acid and treated with hydrogen peroxide. At room temperature or on warming there was no reaction involving 132 as shown by tlc. Likewise the Elb's persulfate oxidation[101] of 132 using potassium persulfate in aqueous base gave no reaction. In an attempt to discover a stronger oxidizing agent Fremy's salt, potassium nitrosodisulfonate, was prepared by the method of Singh.[102] Following a literature procedure[103] for oxidation with Fremy's salt the keto ester 175 was treated with potassium nitrosodisulfonate and potassium monohydrogen

phosphate in a mixture of N,N-dimethylformamide and water. In repeated trials the starting material was recovered quantitatively. Increasing the percentage of N,N-dimethylformamide to retain homogeneity of the reaction mixture throughout the course of the reaction as well as increasing the reaction temperature gave the same result.

To increase the possibility of success the oxidation of substituted derivatives of 132 was attempted. A procedure[104] for the conversion of para-halogenohydroxy aromatic compounds to the corresponding quinones was attempted. When 1-hydroxy-4-bromo-5-chloroanthraquinone (163) was dissolved in glacial acetic acid and treated with an aqueous solution of chromium trioxide, the desired conversion was not effected even on warming.

In order to make the substrate even more reactive toward oxidation, the reduction of 1-hydroxy-4-nitro-5-chloroanthraquinone (164) to the corresponding amine (180) was investigated. Following the literature procedure[105] for the reduction of nitroanthraquinones 164 was treated with aqueous sodium sulfide at the reflux temperature. The amine 180, mp 168.5-170°C, was obtained as shown by the amine stretching bands at 3450 cm^{-1} and 3300 cm^{-1} in the ir spectrum. However, the product was always contaminated with a small amount of starting material and other dark colored compounds from which it was not easily separable. It should be noted that the basicity of aminoanthraquinones in general is low enough that they cannot be extracted



164

180 R = H

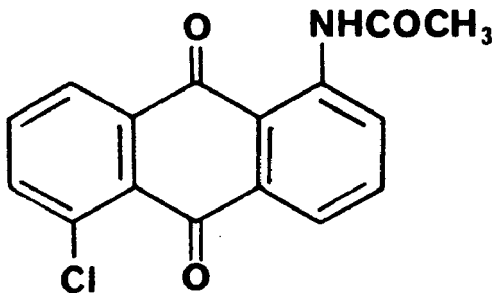
181 R = $COCH_3$

into and are not soluble in dilute aqueous acid.

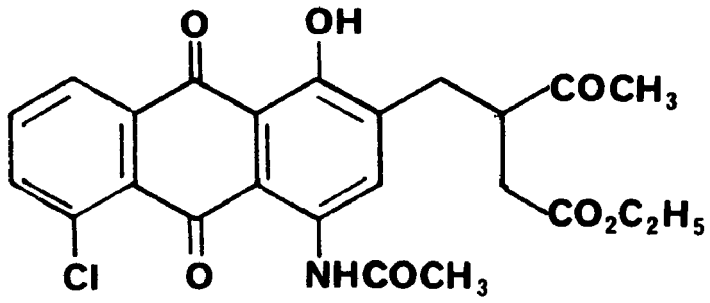
In an attempt to improve the conversion of the nitro compound 164 to the amine 180 the phenylhydrazine reduction of aromatic nitro groups[106] was attempted. When 164 was treated with three equivalents of phenyl hydrazine in refluxing dioxane there was obtained a dark red solid which showed a single spot on tlc with a greater R_f value than the starting material. The nmr spectrum of the product includes three aliphatic singlets at 1.85δ (2H), 2.05δ(2H) and 2.22δ(1H) which remained in a constant proportion with the eight proton aromatic multiplet centered at 7.10δ after extraction and chromatography. The product was not identified because it was felt to be of no use in this synthesis and because at the same time a catalytic hydrogenation was found to be successful for this conversion.

Following a general procedure[107] for the hydrogenation of aromatic nitro compounds, 5-chloro-1-hydroxy-4-

nitroanthraquinone (164) was dissolved in ethyl acetate and hydrogenated at atmospheric pressure over 5% palladium on carbon. Filtration to remove the catalyst and total evaporation of the solvent gave a dark solid (180) which was quite insoluble in most organic solvents. Treatment of 180 with acetic anhydride gave 4-acetamido-5-chloro-1-hydroxyanthraquinone (181). The ir spectrum of 181 shows acetamide carbonyl and nitrogen hydrogen bending absorptions at 1695 cm^{-1} and 1375 cm^{-1}, respectively, as well as an hydrogen bonded quinone carbonyl absorption at 1635 cm^{-1}. The nmr spectrum of 181 shows a three proton singlet at 2.32δ and a broad one-proton absorption at 11.80δ accounting for the four acetamide protons. The C-3 and C-2 protons appear as two one-proton doublets with J = 9Hz at 7.22δ and 8.95δ, respectively. The downfield shift of the C-3 proton is due to the deshielding effect of the acetamide carbonyl which is held fairly stationary by hydrogen bonding of the amide proton with the C-10 carbonyl. The shift value of the C-2 proton was assigned by comparison with the spectra of 1-acetamido-5-chloroanthraquinone (182) and the keto ester 183 where the same proton appears at 9.05δ as a doublet-of-doublets (J = 8Hz and 2Hz) and at 8.90δ as a singlet, respectively. The remainder of the nmr spectrum of 181 shows a two proton multiplet at 7.80δ, a one proton doublet-of-doublets at 8.28δ (J = 7Hz and 2Hz) and a one proton singlet at 12.95δ for the phenolic proton.



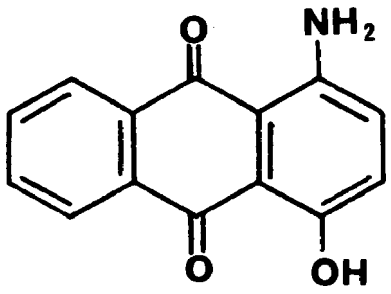
182



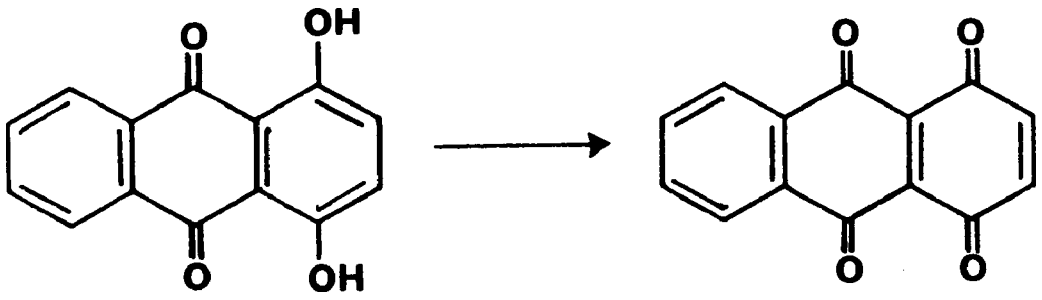
183

With a good method for the preparation of the desired amino anthraquinones available an attempt was made to discover a technique for their oxidation to the corresponding diquinones. Although there have been no reports in the literature concerning the conversion of para-aminohydroxyanthraquinones to diquinones by oxidation, it was felt that this type of reaction should be attempted. Following a general procedure described by Harmon,[108] 180 was dissolved in glacial acetic acid and treated with a solution of sodium dichromate in aqueous sulfuric acid. At room temperature there was no reaction as shown by tlc, and on increasing the temperature tar formation began to occur. Similar treatment of the 1-amino-4-hydroxyanthraquinone (184) gave the same result.

The oxidation of quinizarin (159) and its derivatives to the corresponding diquinones using lead tetraacetate was developed as a general method by Dimroth.[109]

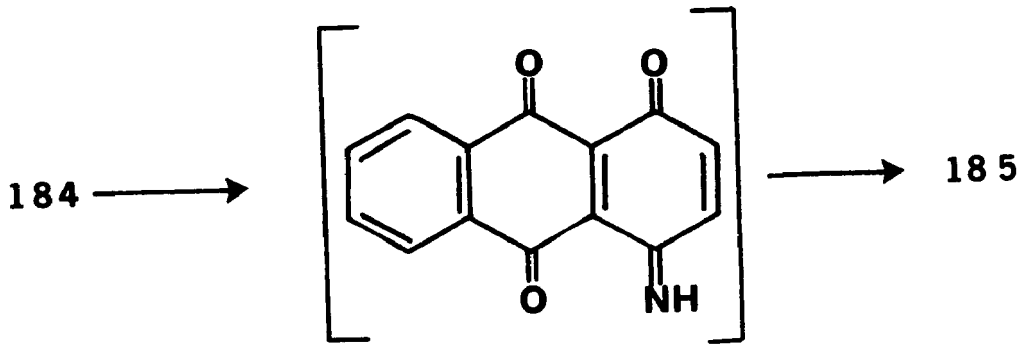


184



159 185

It was hoped that the method of Dimroth could be extended to compounds such as 180 or 184 to give the diquinones either directly or by hydrolysis of an intermediate quinone imine such as 186. When 180 was dissolved in glacial acetic acid and treated with lead tetraacetate followed by quenching with water the only material which could be dissolved in organic solvents gave a light tan spot that was com-



186

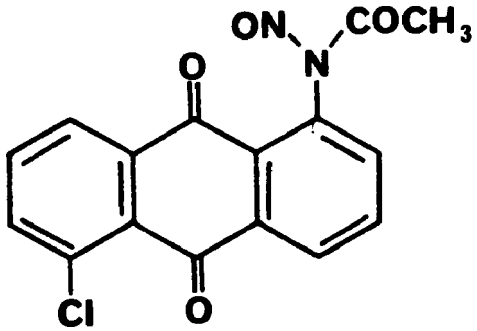
pletely immobile on tlc. When the oxidation reaction was quenched by pouring it into 50% aqueous sulfuric acid the same result was observed.

Failure of the oxidation procedures prompted us to attempt some other methods. A report[110] in the literature indicated that nitro groups on the peri or alpha position of an anthraquinone nucleus could be converted to hydroxyl groups on fusion with potassium acetate and a trace of acetic acid. However, when 164 was placed in a combustion tube with potassium acetate and a small amount of acetic acid and the tube heated at 175°C for two hours, there was obtained after acetylation of the crude product a 66% recovery of 1-acetoxy-4-nitro-5-chloroanthraquinone (187) as shown by the nmr, ir and mass spectra.

White reported[111] in 1955 that N-alkyl acetamides could be nitrosated and rearranged on heating in acetic acid solution to the corresponding acetates with the loss

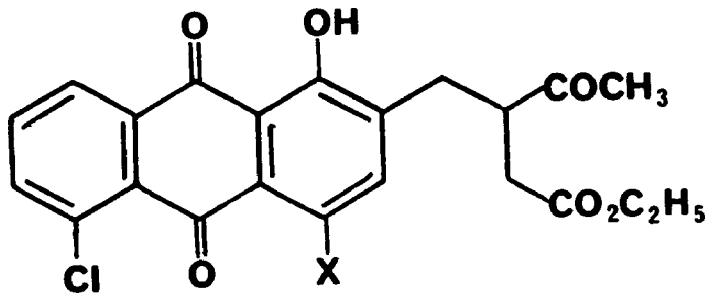
of nitrogen. Later it was reported[112] that N-aryl amides on nitrosation and heating in aromatic organic solvents gave biaryls. It was of interest to us to determine the outcome of a similar reaction involving 1-acetamido-5-chloroanthraquinone (182) in acetic acid.

Nitrosylsulfuric acid was prepared by the method of Ahmad[112] and coworkers. When 182 was dissolved in a mixture of acetic anhydride and acetic acid along with sodium acetate and phosphorus pentoxide and treated with nitrosylsulfuric acid a new spot appeared on tlc. After a few minutes tlc indicated almost complete conversion of 182 to a lighter colored product which was assumed to be the N-nitrosoamide 188. However, when the reaction mixture was heated to boiling, cooled and quenched with water, there was obtained a dark solid which on preparative thin layer chromatography gave six compounds none of which were identified.



188

During the time that the previous work was being carried out, the bromo and nitro derivatives of 175 and the bromo derivative of 174 were prepared. When 175 was dissolved in cold concentrated sulfuric acid and treated with a mixture of nitric acid and sulfuric acid, there was obtained after addition of the reaction mixture to ice water a golden yellow solid. The crude product was recrystallized from aqueous acetone to give a 77% yield of ethyl 3-(1-hydroxy-4-nitro-5-chloro-2-antraquinonyl)methyl levulinate (189), mp 147-148°C.



175 X=H
189 X=NO_2
190 X=Br

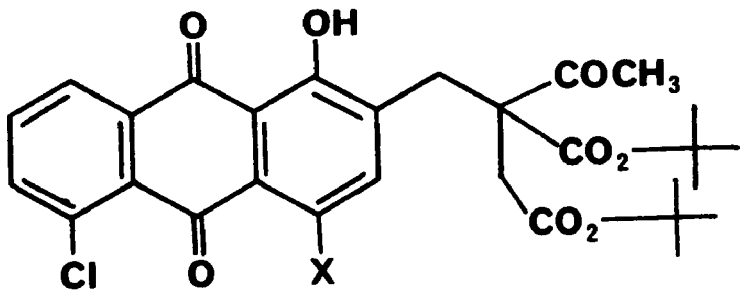
When care was not taken to keep the workup and reaction mixture ice-cold, hydrolysis of the ester became a problem. Even at low temperature some hydrolysis occurred as shown by a peak in the mass spectrum of 189 at m/e 431 which is 50% of the intensity of the parent ion at m/e 459. The P-28 peak normally occurs in similar anthraquinones due to the loss of carbon monoxide, but it is generally seen to be 35-40% of the parent ion. The presence of a

small percentage of the acid corresponding to 189 was also evident from the elemental analysis. The nmr spectrum of 189 is almost identical to that of 175 except for a change in the chemical shift and pattern of the aromatic multiplet at 7.62δ to 8.05δ.

When 175 and sodium acetate were combined in hot acetic acid and treated with bromine, an 86% yield of the desired bromo compound 190 was obtained as a single pure compound as shown by tlc. The nmr and ir spectra of 190 were essentially identical to those of 175 except for a slight downfield shift and change in pattern of the aromatic multiplet at 7.50δ to 7.95δ.

When 174 was treated with bromine and sodium acetate at 80°C in acetic acid, an 84% yield of the desired bromo compound 191 was obtained, mp 167-170°C, with gas evolution and decomposition. The mass spectrum of 191 has a parent ion at m/e 620 and a peak at m/e 622 which is 141% of the intensity of the parent ion. A pattern which is indicative of one bromine and one chlorine in the molecule. The nmr and ir spectra of 191 are almost identical to those of 174.

It was decided that the acid hydrolysis of 190 as discussed previously for compounds 161 and 163 should be attempted. When 190 was placed in a combustion tube with boric acid and 90% sulfuric acid and heated at 160°C for 3 hours there was obtained approximately a 30% yield of a dark red brown solid which was immobile on tlc. Attempts to esterify and acetylate the crude product were unsuccess-

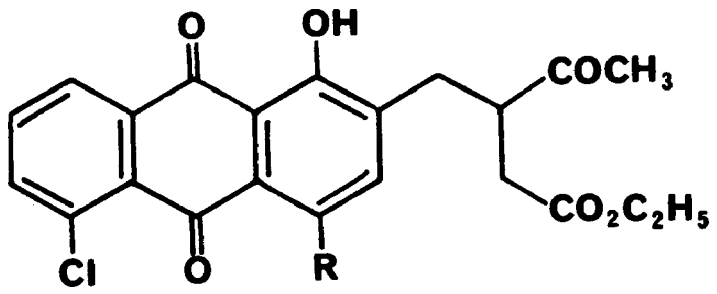


174 X=H

191 X=Br

ful. It was felt that the reaction conditions were too harsh and so the preparation and hydrolysis of the amine 192 were planned.

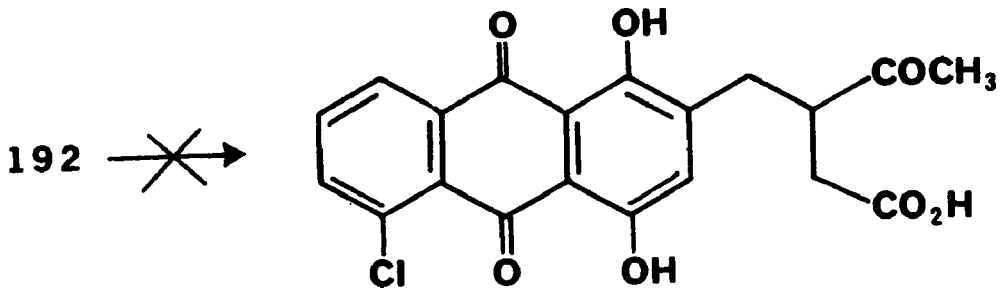
Following the procedure established for the preparation of 180, 189 was hydrogenated in ethyl acetate over palladium on carbon to give a high yield of the amine 192 which could not be completely purified.



189 R=NO_2

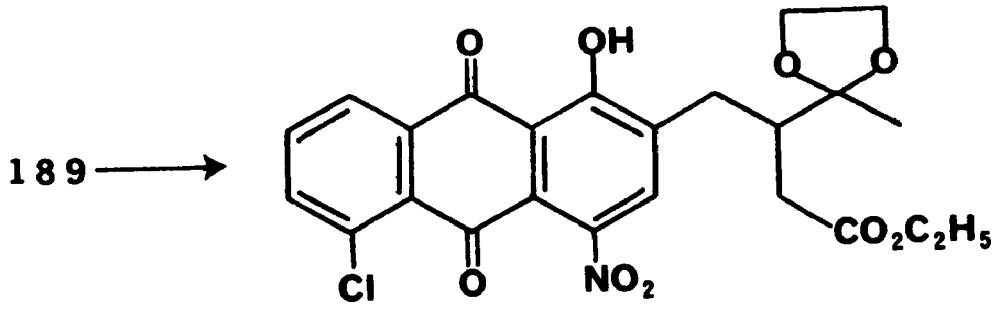
192 R=NH_2

The presence of the amine group was shown in the ir spectrum of 192 which had amine stretching absorptions at 3500 cm^{-1} and 3320 cm^{-1} and no free quinone carbonyl or nitro group absorptions. Attempts to recrystallize or chromatograph 192 resulted only in the loss of material. Moreover, an attempt to hydrolyze 192 to the corresponding dihydroxy compound 193 in 20% hydrochloric acid at 200°C gave only a tarry mass from which nothing could be extracted with organic solvents.



193

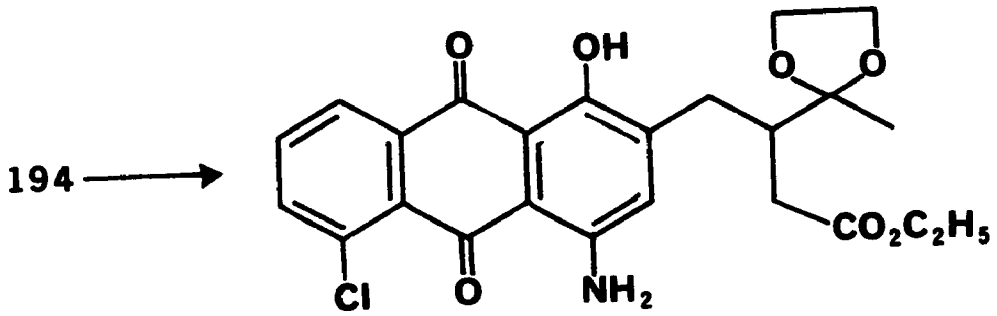
In an attempt to simplify the diverse functionality in 189 and 192, the ketone was converted to the ethylene ketal. Treatment of 189 in benzene with excess ethylene glycol and a trace of para-toluenesulfonic acid gave an essentially quantitative yield of the ethylene ketal 194, mp 119-120°C. The ir spectrum of 194 shows only ester and quinone carbonyls at 1735 cm^{-1}, 1680 cm^{-1} and 1635 cm^{-1} as well as absorptions at 1540 cm^{-1} and 1345 cm^{-1} for the nitro group. The nmr spectrum of 194 is definitive for



194

the given structure with a three proton singlet at 1.40δ for the methyl group alpha to the ketal and a four proton singlet at 3.97δ for the ethylene ketal methylenes. The mass spectrum of 194 also indicates the desired ketal with a base peak at m/e 87 for the 2-methyl-1,3-dioxolane cation.

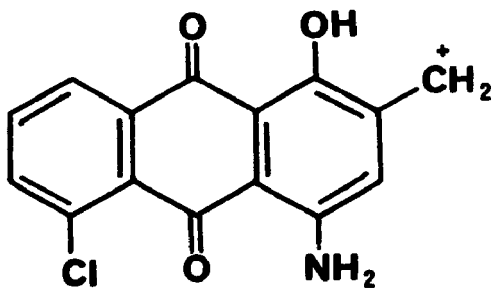
Hydrogenation of 194 in ethyl acetate for 15 minutes over palladium on carbon gave, after filtration to remove the catalyst, drying and evaporation of the solvent, a 95% yield of the desired amine ketal 195.



195

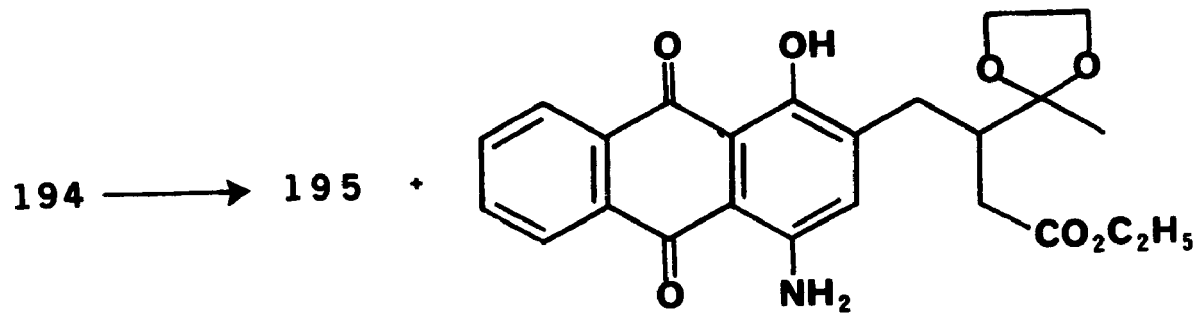
Thin layer chromatography of the crude product showed only one purple spot and a small amount of immobile brown material. Therefore, the crude product was chromatographed on a column of silica gel and all the purple material was recovered.

The ir spectrum of 195 shows amine stretching absorptions at 3475 cm^{-1} and 3300 cm^{-1} as well as ester and quinone carbonyls at 1740 cm^{-1} and 1635 cm^{-1}, respectively. The nmr spectrum of 195 shows besides the ethyl ester and ethylene ketal signals a five proton multiplet from 2.20δ to 3.30δ, a broad two proton absorption for the amine protons at 6.0 to 6.5δ, a one proton aromatic singlet at 7.38δ, a two proton aromatic multiplet at 7.40 to 7.82δ, a slightly less than one proton doublet-of-doublets at 8.38δ (J_a = 2Hz, J_b = 8Hz) and a one proton phenolic singlet at 13.95δ. The mass spectrum of 195 has a peak at m/e 475 which is 38% of the intensity of the molecular ion at m/e 473. Also prominent in the spectrum are the base peak at m/e 87 and a peak at m/e 286 which is attributable to the cationic fragment 196.



196

A seemingly anomolous peak in the mass spectrum of 195 appears at m/e 439. The m/e 439 peak is attributed to the amino ketal 197 which must be formed during the hydrogenation of 194. A comparison of the intensity of the m/e 439 and m/e 473 peaks indicates that as much as 20% of the hydrogenation product may be the dechloro compound 197.

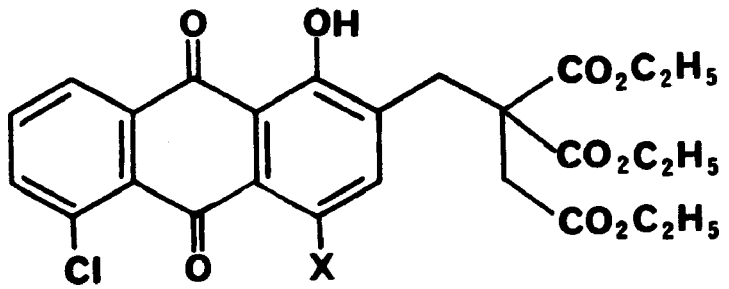


197

However, all attempts to separate the two amines 195 and 197 on tlc were unsuccessful. The presence of 197 is also confirmed by a peak at m/e 242 which appears to be the dechloro analog of 196.

The failure of the acid hydrolysis of 192 prompted us to prepare another compound similar to 192. It was felt that replacement of the ketone or protected ketone function in compounds such as 192 with an ester group would give a substrate which could be manipulated under acidic conditions. Triethyl 1,1,2-ethane tricarboxylate was chosen as a substitute for di-tertiary-butyl 2-acetylsuccinate (173).

The enolate anion of triethyl 1,1,2-ethane tricarboxylate prepared with sodium hydride in N,N-dimethylformamide was alkylated with 5-chloro-1-hydroxy-2-chloromethylantraquinone (148) to give the triester 198 in 62% yield after recrystallization, mp 108-109°C. The nmr spectrum of 198 shows two overlapping triplets accounting for a total of nine protons at 1.30δ (J = 7.5Hz), two singlets for two protons each at 2.93δ and 3.62δ, two overlapping quartets for six protons at 4.29δ (J = 7.5Hz), a four proton aromatic multiplet from 7.35 to 7.80δ, a one proton doublet of doublets at 8.32δ (J_a = 6Hz and J_b = 2Hz) and a one proton phenolic singlet at 12.72δ. The ir spectrum of 198 shows a single strong ester carbonyl stretch at 1730 cm^{-1} and quinone carbonyls at 1675 cm^{-1} and 1640 cm^{-1}. The molecular ion appears at m/e 516 in the mass spectrum and the product gave a perfect elemental analysis after one recrystallization.

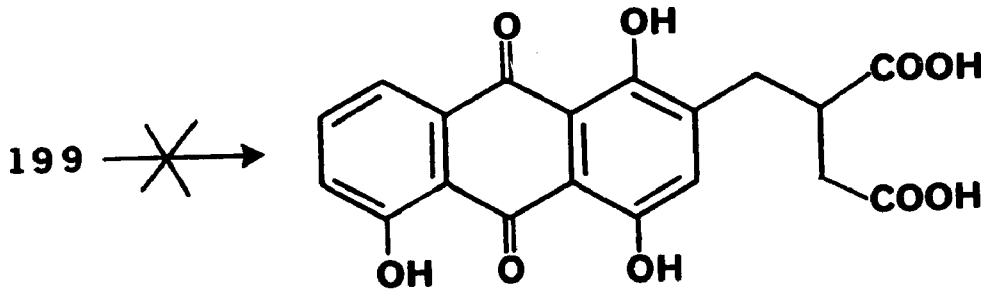


198 X=H

199 X=Br

Bromination of 198 with bromine in hot acetic acid in the presence of sodium acetate gave the bromotriester 199 in 89% yield, mp 140-141°C. The nmr spectrum of 199 was essentially identical to that of 198 except for a change in the aromatic multiplet to three protons. The mass spectrum of 199 shows a peak at m/e 596 which is 130% of the intensity of the parent ion at m/e 594, a pattern indicative of the presence of one bromine and one chlorine in the molecule.

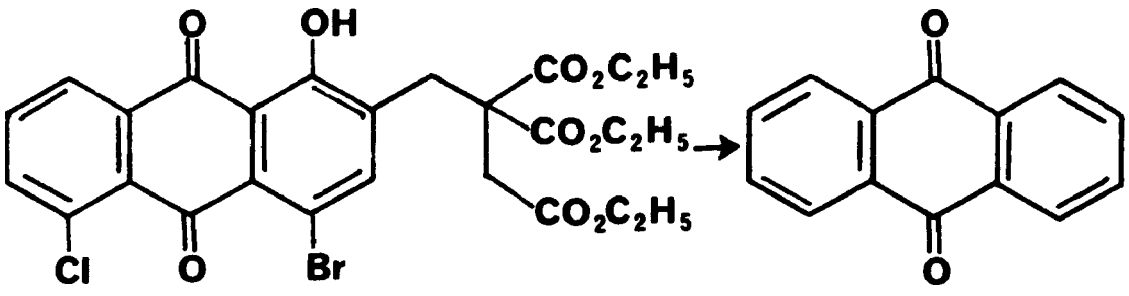
The fusion of substituted anthraquinones with alkali metal hydroxides has been used as a method for the preparation of hydroxyanthraquinones.[113] Therefore, it was hoped that the fusion of 199 with potassium hydroxide would give the corresponding trihydroxy compound 200.



200

When 199 was heated at 280°C in a stainless steel reaction vessel with a large excess of potassium hydroxide and a trace of water, a dark red melt was formed. After two hours a fine white crystalline compound (201) sublimed

out of the reaction mixture and was collected by condensation on a watch glass. After enough of 201 had collected for identification, the reaction mixture was allowed to cool and was taken up in a large volume of water. Acidification of the dark red solution and extraction with methylene chloride gave after drying and evaporation of the solvent a dark solid. Chromatography of the dark solid on a silica tlc plate gave eight or nine colored spots. The white solid 201 was identified as anthraquinone by its melting point, sublimes at 283-284°C, and mass spectrum which showed a molecular ion at m/e 208. The nmr and ir spectra of 201 were also completely consistent with the assigned structure. The conversion of 199 to anthraquinone (201) on alkaline fusion is not easy to explain, but it appears from the darkening of the stainless steel that some iron from the reaction vessel may have entered into the reaction as a reducing agent.

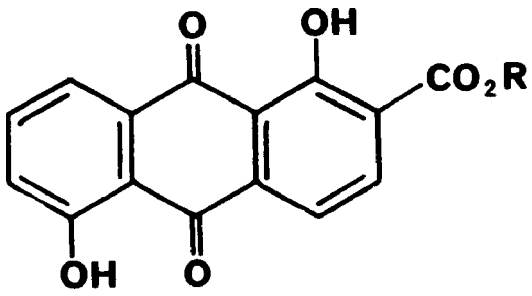


199 201

In order to carry out the same reaction under milder conditions, an alkaline hydrolysis of 199 was investigated. The procedure of Gumprecht[114] for the conversion of aromatic bromo compounds to the corresponding phenols by alkaline hydrolysis was followed. After boiling 199 in 10% aqueous sodium hydroxide in the presence of copper and copper-bronze under reflux for 68 hours, an approximate 50% yield of a dark red powder (202), mp 220-223°C was obtained. The unknown compound 202 was extremely insoluble in all solvents and completely immobile on tlc. Esterification of 202 with ethanol and acid followed by preparative thin layer chromatography gave the monoester 203, mp 166-168°C as the major product.

The mass spectrum of 203 shows a molecular ion at m/e 312 with no isotope peak at m/e 314. The molecular ion at m/e 312 and a fragmentation peak at m/e 267 for the loss of C_2H_5O radical suggest 1,5-dihydroxy-2-carboethoxyanthraquinone as the structure of the monoester 203. This assignment is in good agreement with the ir spectrum which shows absorptions for an aromatic ester at 1725 cm^{-1} and hydrogen bonded quinone carbonyls at 1635 cm^{-1}.

The nmr spectrum of 203 substantiates completely the assigned structure and led to the placement of the hydroxyls at C-1 and C-5. There is a three proton triplet at 1.25δ (J = 7Hz), a two proton quartet at 4.42δ (J = 7Hz) and two quite different phenolic proton singlets at 12.20δ and 13.25δ. The aromatic region is definitive for the substi-

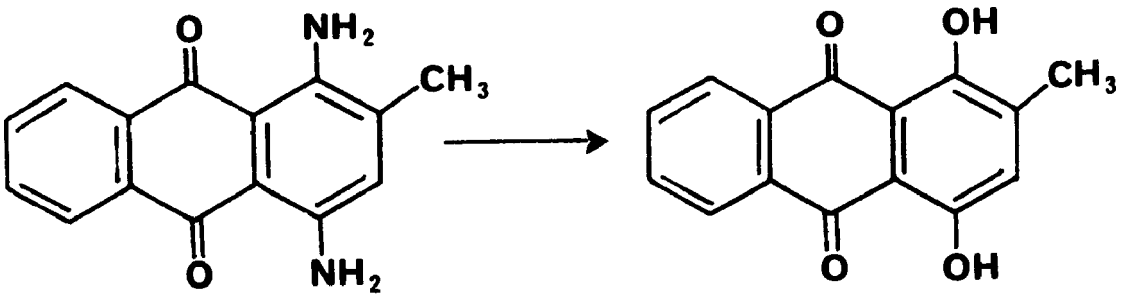


202 R = H

203 R = C_2H_5

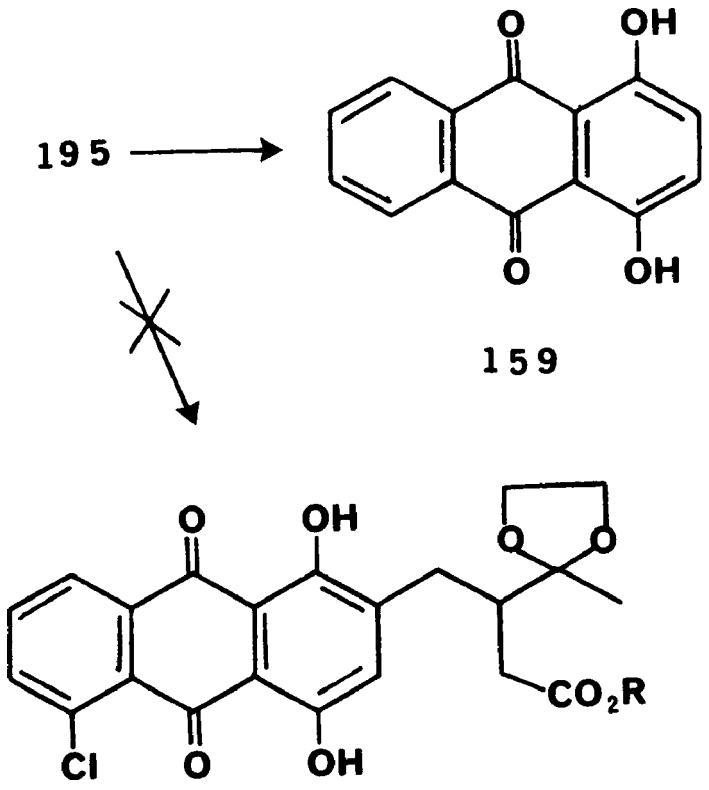
tution pattern in 203. There is a one proton doublet-of-doublets at 7.38δ (J_a = 6.5Hz and J_b = 2Hz) which is indicative of a proton ortho to an hydroxyl group and ortho and meta to two other protons. There is also a one proton doublet at 8.30δ (J = 8Hz) indicative of a proton ortho to both an ester function and one other proton.

The formation of 203 like that of 201 was hard to explain and was not understood until some further work was done on the reactions of the amino ester 195. The acid hydrolysis of 195 would undoubtedly give no better results than did the hydrolysis of 192. However, Yates and Peters[115] had developed a reductive hydrolysis method for the preparation of 2-methylquinzarin (204) from 1,4-diamino-2-methylanthraquinone (205) which seemed applicable to our problem. However, when 195 was heated at 90-95°C in 1.5% aqueous sodium hydroxide with excess sodium dithionite, neither the desired dihydroxy compound 206 or the corresponding acid



204 205

207 could be found. The crude product was recrystallized from ethanol and showed only one red-orange spot on tlc.



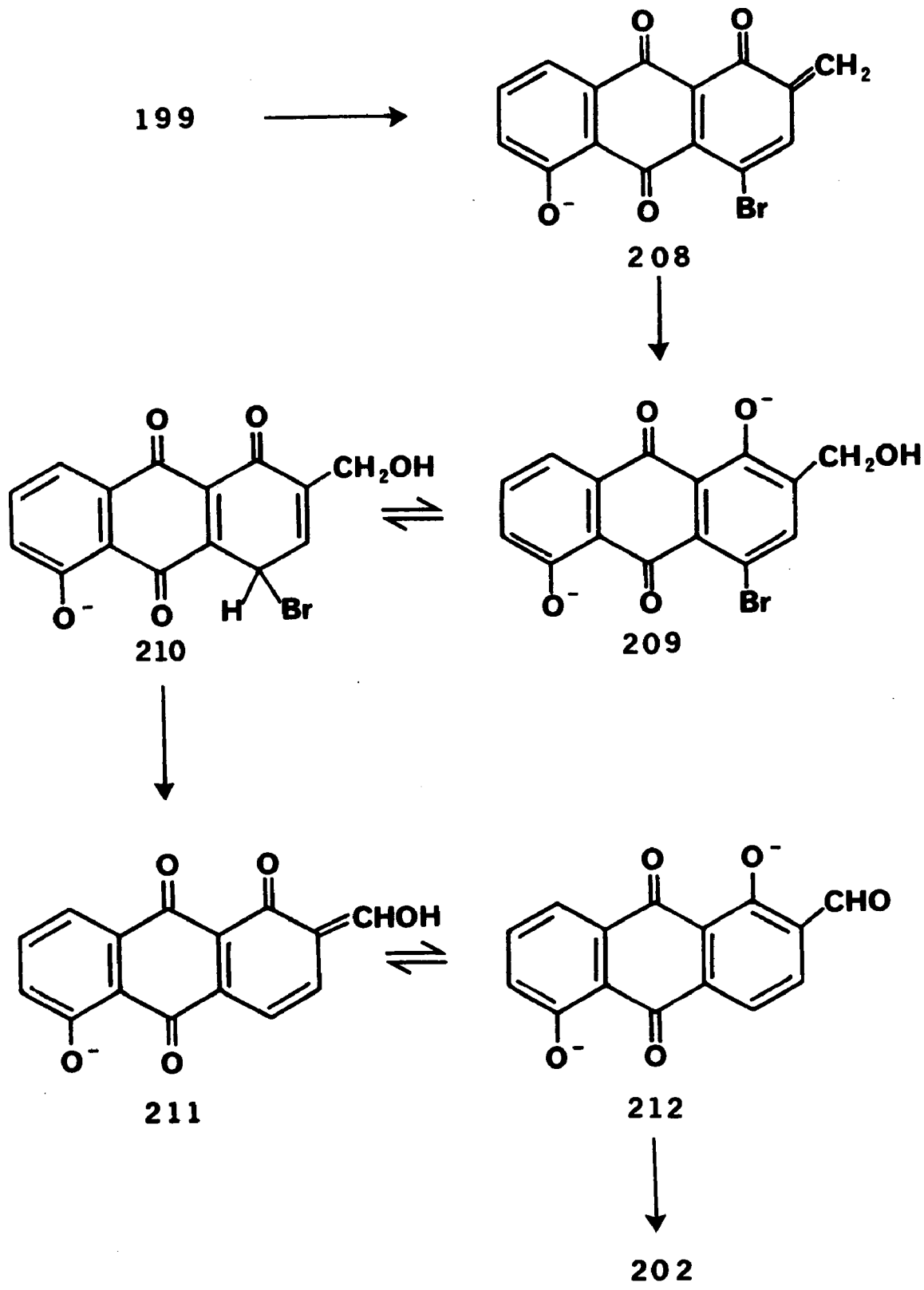
159

206 R=C_2H_5

207 R=H

The nmr spectrum showed a two proton singlet at 7.35δ, two doublet-of-doublets absorptions for two protons each at 7.85δ and 8.40δ (J_a = 7Hz and J_b = 2.5Hz) and a two proton phenolic singlet at 12.90δ, identical to the nmr spectrum of quinzarin (159). The ir spectrum showed no ester or ketone carbonyls but only a hydrogen bonded quinone carbonyl at 1640 cm^{-1}. The mass spectrum showed a molecular ion at m/e 240 indicative of quinzarin (159). Moreover, a comparative tlc experiment involving the product of the above reaction and authentic quinizarin (159) showed the two to be identical. The product was obtained in 84% yield. When the same reaction was attempted at 70-75°C or in refluxing aqueous ethanol with potassium carbonate as the base, the amine group was still present in the product as shown by ir.

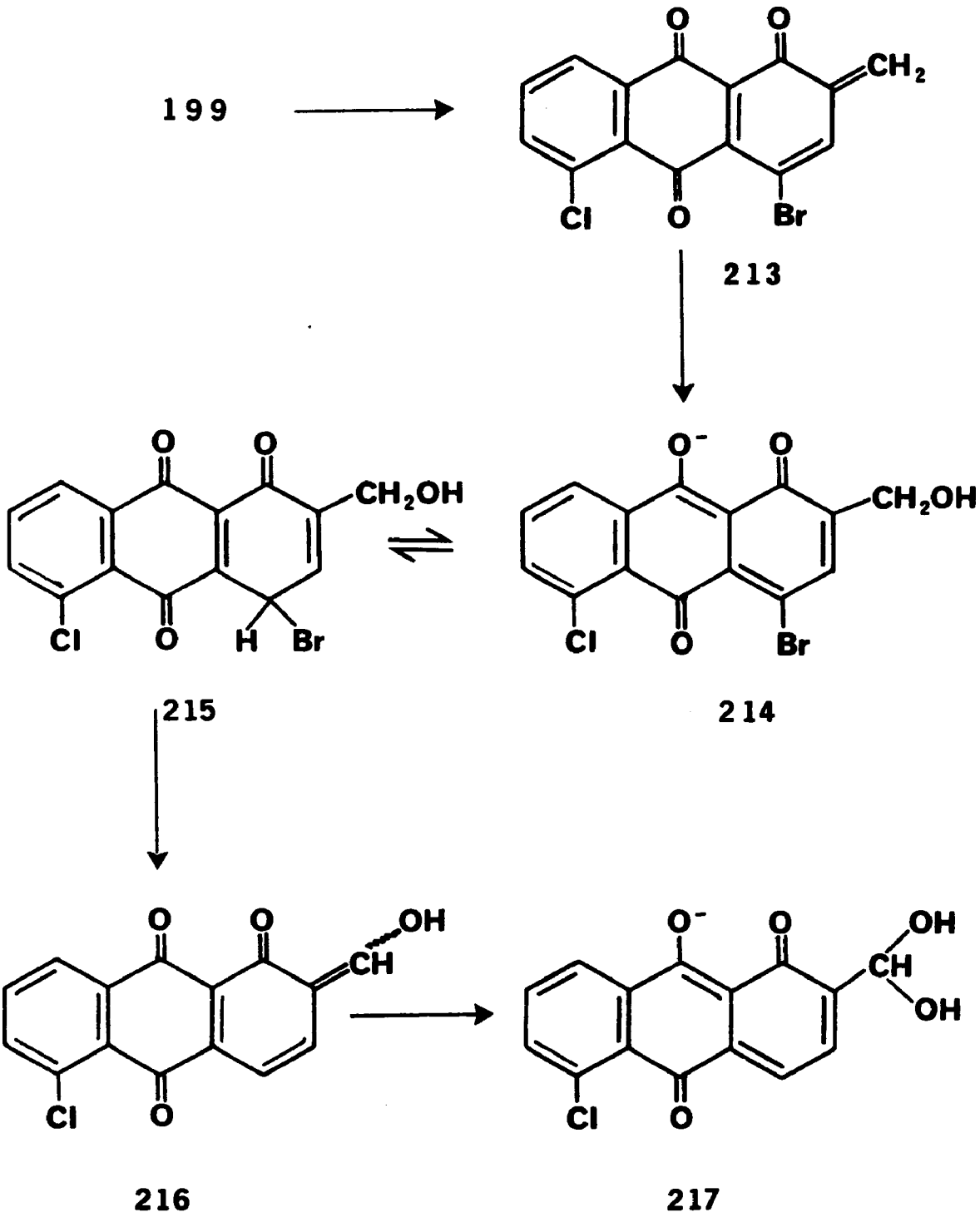
It appears that the reactions of 195 and 199 with base in the presence of a reducing agent are similar. The case of the alkaline hydrolysis of 199 is perhaps the simplest and should be discussed first. The replacement of the chlorine atom with an hydroxyl group follows the normal path for nucleophilic substitution on an anthraquinone system. A reverse of the alkylation reaction would cleave the side chain beta to the anthraquinone nucleus and give the intermediate 208. Michael addition of hydroxide ion to the methylene quinone of 208 would give the intermediate 209. Tautomerization of 209 to 210 followed by base catalyzed elimination of hydrogen bromide would give the new methylene quinone 211 which is a tautomer of


199
208
209
210
211
212
202
CH2
Br
CH2OH
H
CHOH
CHO
O
O-

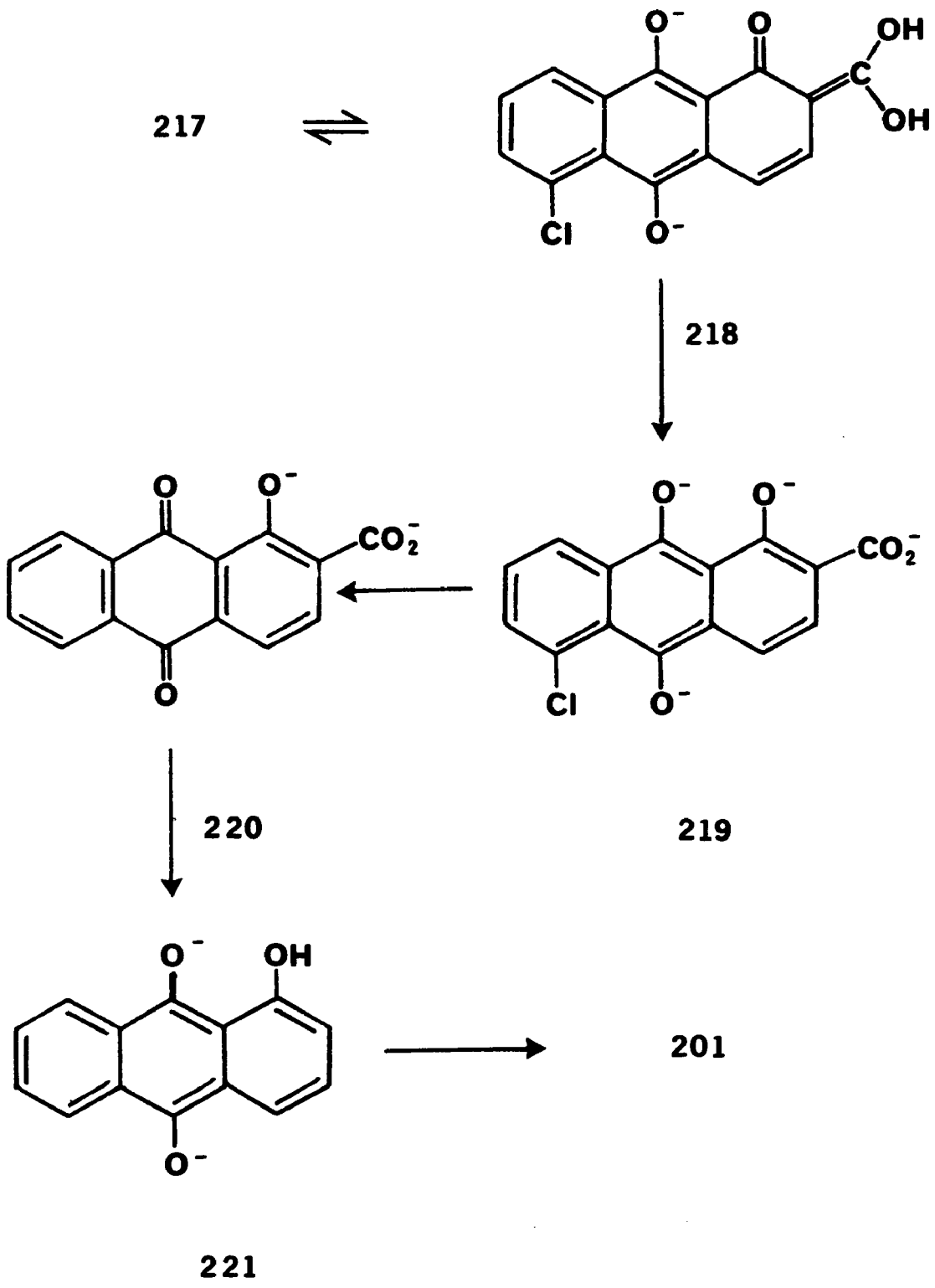
the aldehyde 212. Air oxidation of the aldehyde 212 would give the observed product 1,5-dihydroxy-2-anthraquinone carboxylic acid (202).

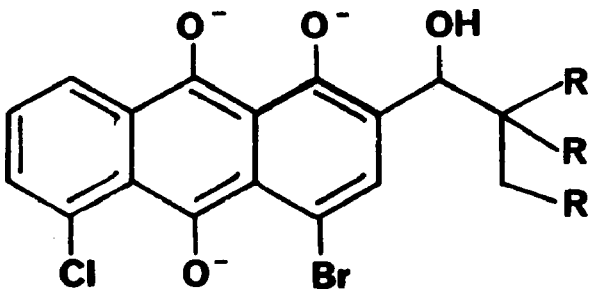
The potassium hydroxide fusion of 199 in the presence of iron might be likened to the distillation of a compound from zinc dust. Alternatively a stepwise mechanism as shown below might be envisioned. A dealkylation reaction would give 213 which could undergo Michael addition of hydroxide ion to give 214. Tautomerization of 214 to its keto form 215 followed by base catalyzed elimination of hydrogen bromide gives the methylene quinone 216. Michael addition of hydroxide to 216 gives the acetal 217 which on enolization would give the enolic acid 218. Tautomerization to the acid 219 gives the reduced form which can eliminate chloride ion to give the quinone 220. Reduction of 220 by iron or a concommitant oxidation of some other organic material followed by decarboxylation would give the reduced form 221. Elimination of water from 221 gives the observed product anthraquinone (201).

As an alternative to the dealkylation reaction the aliphatic side chain could be lost by a reverse of the Marshalk reaction.[72] The reverse of the Marshalk elimination reaction on 199 would give the alcohol 222. Tautomerization of 222 and a reverse of the Claisen condensation would give anthracene 223. Further reduction of 223 would give the observed anthraquinone (201).

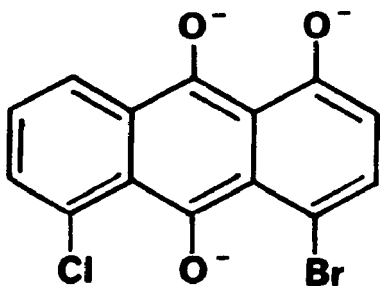

199
O
O
CH2
Cl
O
Br
213
CH2OH
Cl
O
H
Br
O-
CH2OH
Cl
O
Br
215
214
OH
CH
Cl
O
O-
OH
CH
OH
Cl
O

216 217


217
218
219
220
221
201
OH
Cl
CO2-



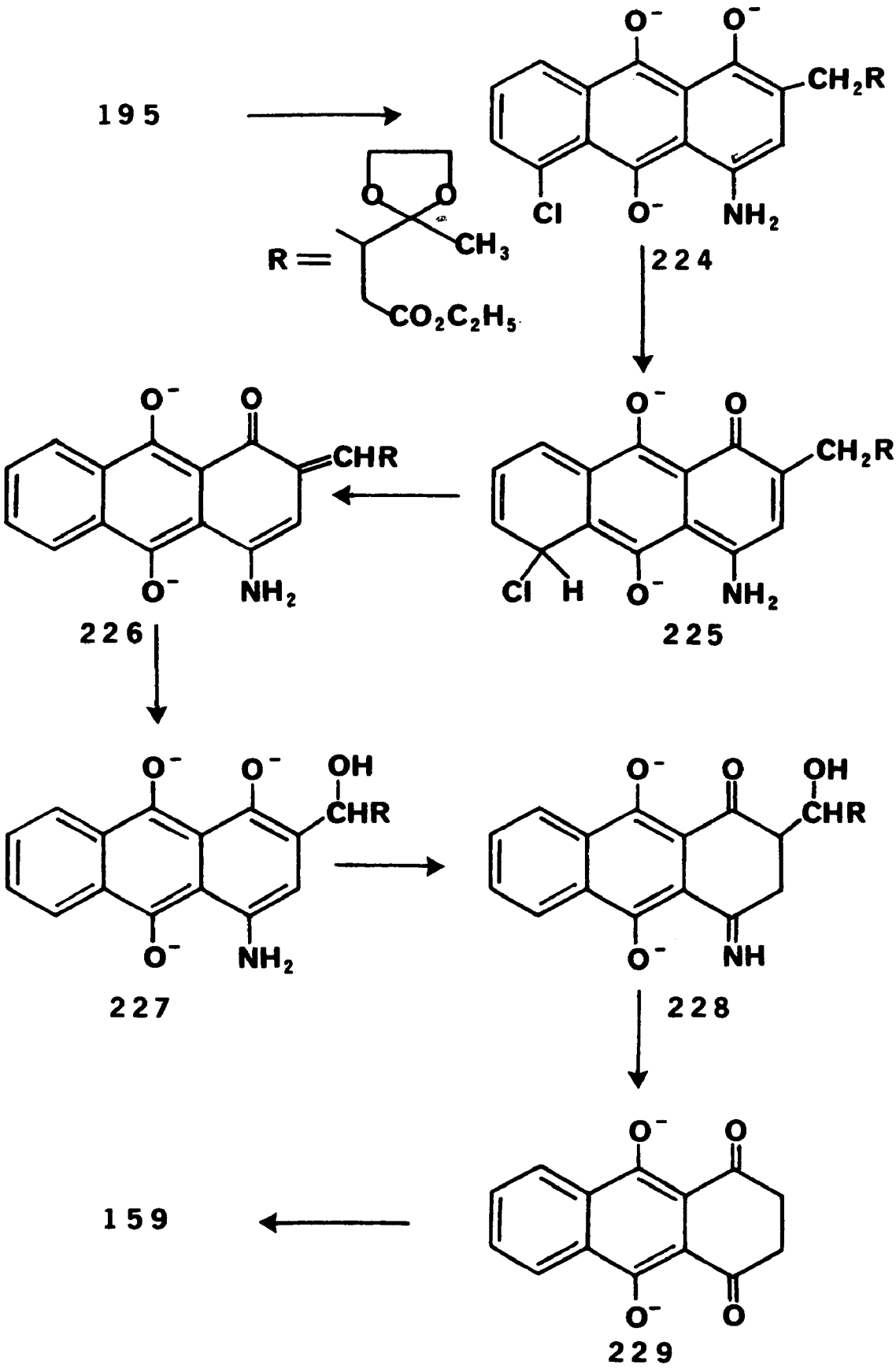
222 R= $CO_2C_2H_5$



223

The conversion of 195 to quinizarin (159) presents a slightly different problem than the two cases just discussed. The ketal function in 195 inhibits any dealkylation reaction as was suggested previously. However, in this case the reaction is being run under strongly reducing conditions and the immediate color change on addition of sodium dithionite indicates reduction of 195 to 224 is probably the first step. Tautomerization of 224 to the dianion 225 could lead to a base catalyzed elimination of hydrogen chloride to give 226. Addition of hydroxide ion to 226 in a Michael fashion would give the reduced system 227 which after tautomerization to 228 could undergo a reverse aldol condensation and hydrolysis of the imine to give the dianion of leucoquinizarin (229). Air oxidation of 229 gives the observed product quinizarin (159).

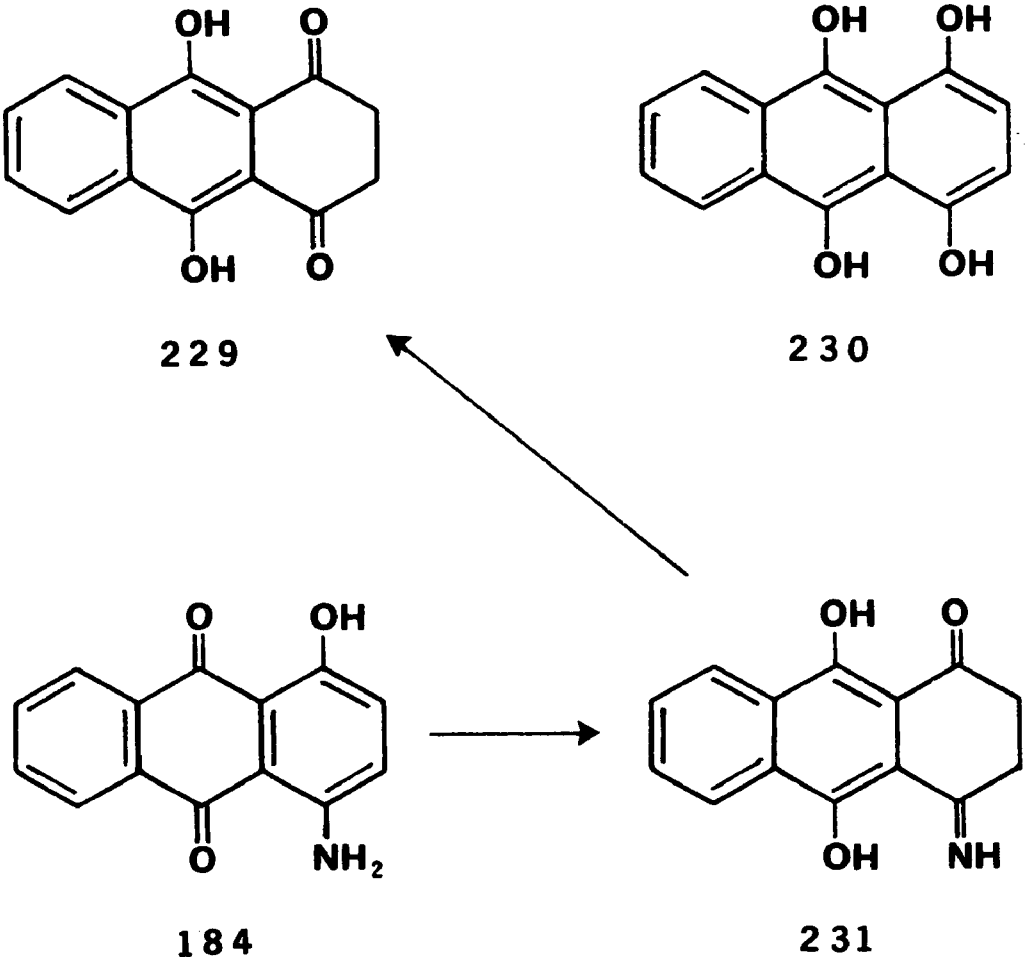
It was apparent that reactions involving strongly basic conditions or base in the presence of a reducing agent were potentially poor reactions. This was also


195
R =
CH3
CO2C2H5
CH2R
Cl
NH2
224
CHR
226
Cl
H
225
OH
227
NH
228
159
229

demonstrated when treatment of 199 with excess sodium methoxide in refluxing methanol for 60 hours gave a variety of products for which the nmr spectrum of the mixture showed far too many aromatic protons with respect to the aliphatic protons.

It was believed that reduction under acidic conditions would give the desired conversion of an amine to an hydroxyl without the loss of other substituents. Primarily because treatment of quinizarin (159) in boiling acetic acid with zinc dust by the method of Zahn[116] gives a 51% yield of leucoquinizarin (229), mp 153.5-154.5°C. The nmr spectrum of 229 shows a four proton singlet at 3.05δ for the C-2 and C-3 methylenes, a two proton doublet-of-doublets at 7.72δ (J_a = 6.5Hz, J_b = 3Hz), a doublet-of-doublets for two protons at 8.40δ (J_a = 6.5Hz, J_b = 3Hz) and a two proton singlet at 13.65δ. The mass spectrum of 229 has a molecular ion at m/e 242 which is also the base peak. The P + 1 peak which is 16% of the intensity of the parent ion agrees well with the suggested formula of $C_{14}H_{20}O_4$.

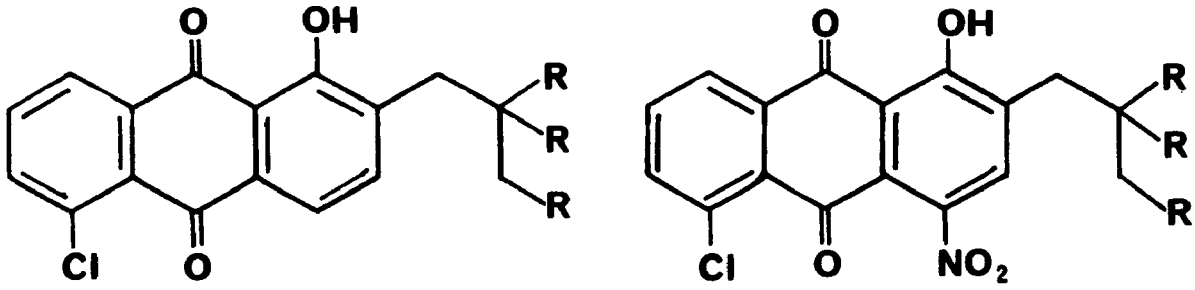
By comparison of nmr spectra at various temperatures and in different solvents, Sterk[117] concluded that leucoquinizarin (229) exists completely in the form shown with no discernable amount of the tetrahydroxy form 230. This fact encouraged us to think that reduction of compounds such as 1-amino-4-hydroxyanthraquinone (184) would lead to the keto imine 231 which could be easily hydrolyzed to 229 with aqueous acid.



However, when 184 in boiling acetic acid was treated with zinc dust and the product reoxidized, an almost quantitative return of the starting material was obtained. The same result was obtained when 70% aqueous acetic acid was used as the solvent. However, when mineral acids or sulfuric acid was added, tlc of the product showed besides

the starting material a brown immobile spot.

Even though the acid hydrolysis of 184 in the presence of a reducing agent appeared to be unsuccessful, it was felt that this reaction should at least be tried on a more complicated system. Nitration of 198 in cold concentrated sulfuric acid with a mixture of nitric and sulfuric acids gave the desired nitro compound 232 in 93% yield, mp 188.5-189.5°C.



198 $R = CO_2CH_2CH_3$ 232

The nmr spectrum of 232 was essentially identical to that of 198 except for a downfield shift of the aromatic multiplet to 7.82δ and a decrease in its intensity to three protons. The ir spectrum of 232 has a strong ester carbonyl stretch at 1730 cm^{-1}, quinone carbonyls at 1682 cm^{-1} and 1645 cm^{-1} and nitro group absorptions at 1545 cm^{-1} and 1345 cm^{-1}. The mass spectrum of 232 has a molecular ion peak at m/e 561 and a P + 2 isotope peak of 39% at m/e 563.

Treatment of 232 in hot 90% aqueous acetic acid with zinc dust gave, after 108 hours, a yellow solution which

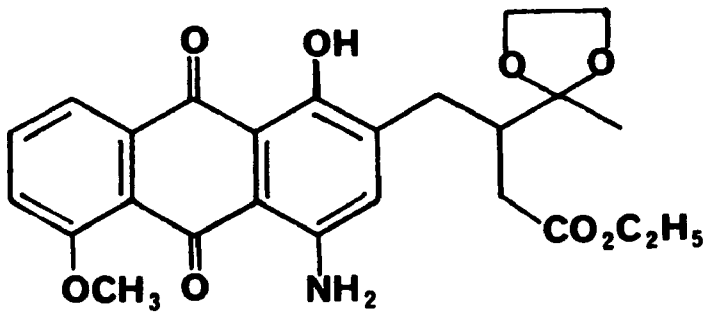
showed a single spot on tlc. Oxidation of the crude product back to the quinone (233) gave a product which was identical to the product obtained upon hydrogenation of 232. The failure of the hydrolysis was substantiated by the ir spectrum of 233 which showed amine stretching absorptions at 2480 cm^{-1} and 3300 cm^{-1}.

Our failure to obtain any tetracyclic compound which could be converted to daunomycinone (1) was discouraging but the possibility of changes in the synthetic plan was still present. The reductive hydrolysis of an aminoanthraquinone is a good method for the preparation of the desired hydroxy compounds and this reaction might be applicable at some other point in the synthesis. Moreover, it was felt that replacement of the chlorine substituent with a methoxyl group at some stage of the synthesis before the catalytic hydrogenation or the reductive hydrolysis might give the desired reaction without loss of the aliphatic side chain.

In order to investigate the possibility of using a compound such as 234 as a substrate for the reductive hydrolysis reaction, other methods of attaching the aliphatic side chain were studied.

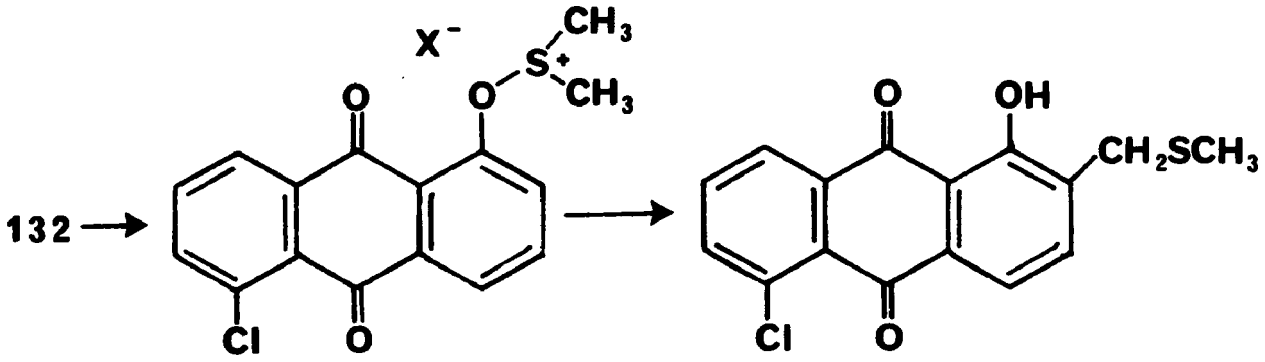
As expected, chloromethylation of 1-hydroxy-5-methoxyanthraquinone (149) by the method of Taylor and Davis[94] led to the complete demethylation of the starting material as shown by nmr.

In search of a milder method for introduction of a useful substituent onto the C-2 position of 149, the thio-



234

methylation reaction of Olofson[118] was examined. In order to study this reaction, 1-chloro-5-hydroxyanthraquinone (132) was used as a model, and it was felt that if the intermediate sulfoxonium cation 235 could be formed, its base catalyzed rearrangement to the desired product 236 would be particularly favorable.

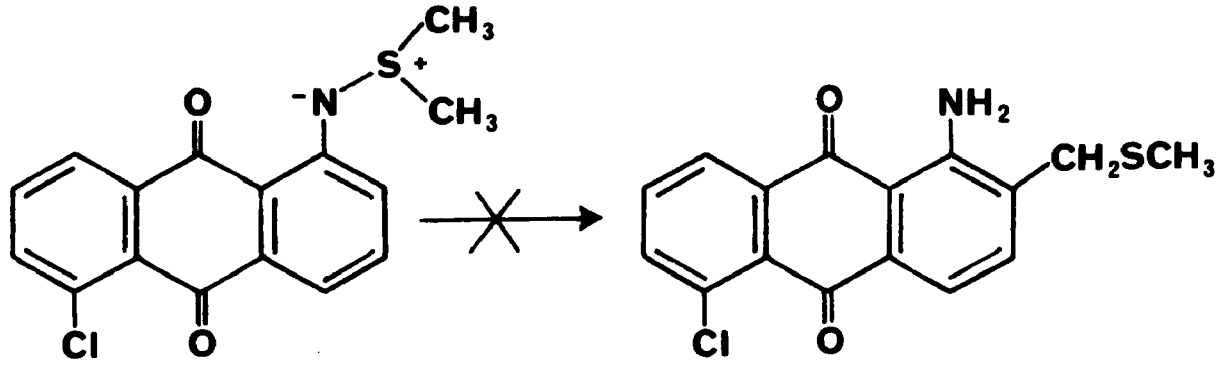


235 236

However, when 132 was treated with N,N-dicyclohexyl carbodiimide and pyridinium trifluoroacetate in either a mixture

of benzene and dimethyl sulfoxide or in neat dimethylsulfoxide, no reaction involving 132 took place as shown by tlc.

Another reaction which appeared even more promising was the alkylation reaction reported recently by Gassman.[119] The method of Teeter[120] was followed for the preparation of tertiary-butyl hypochlorite. Treatment of 1-amino-5-chloroanthraquinone (142) in cold methylene chloride with tertiary-butyl hypochlorite and triethylamine followed by a large excess of methyl sulfide gave a single new spot on tlc which was unchanged after either warming the reaction mixture to room temperature or the addition of more triethylamine. The nmr spectrum of the orange product showed a six proton singlet at 2.80δ and a six proton aromatic multiplet at 7.0-8.4δ. The chemical shift of the singlet suggests the structure shown for the stable intermediate 237. The intermediate 237 is analagous to the sulfilimine

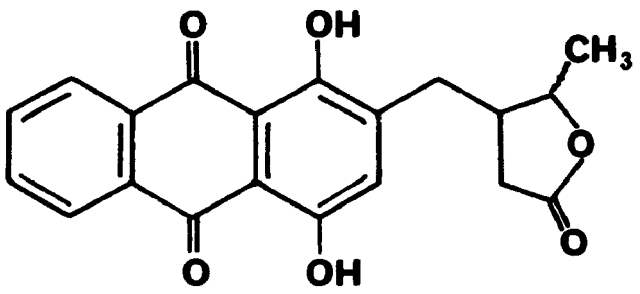


237 238

proposed by Gassman[119] and might be rearranged to the desired product 238 on treatment with strong base. How-

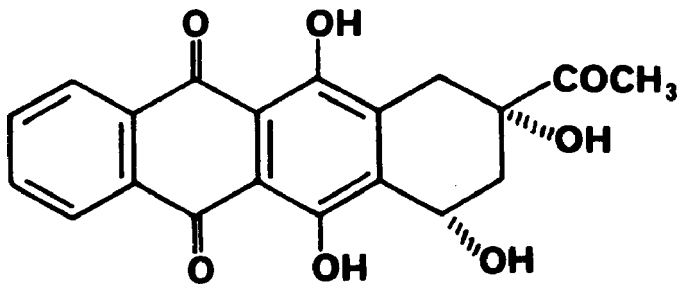
ever, when 237 was dissolved in tertiary-butyl alcohol and treated with a slight excess of potassium tertiary-butoxide, a dark red brown solution was obtained. After stirring overnight at room temperature, tlc of the reaction mixture showed only one orange spot which had a smaller R_f value than did 237. The nmr spectrum of the product showed only aromatic protons and was identical to the nmr spectrum of 1-amino-5-chloroanthraquinone (142). A comparative tlc experiment using the product and authentic 142 showed the two to be identical. As confirmative proof of this assignment, the ir spectrum of the product was taken and shown to be identical to that of 142 with the very characteristic five band pattern of carbonyls, amine bending and aromatic stretching absorptions at 1675, 1635, 1605, 1580 and 1545 cm^{-1}. Further work on this reaction might provide the desired product 238.

In addition to the above work, an attempt was made to prepare the dihydroxy compound 239 which could be used as a model to study the ring closure reaction that was planned in the synthesis of daunomycinone (1).



239

Moreover, 239 would be an important intermediate in the synthesis of 4-demethoxydaunomycinone (240).

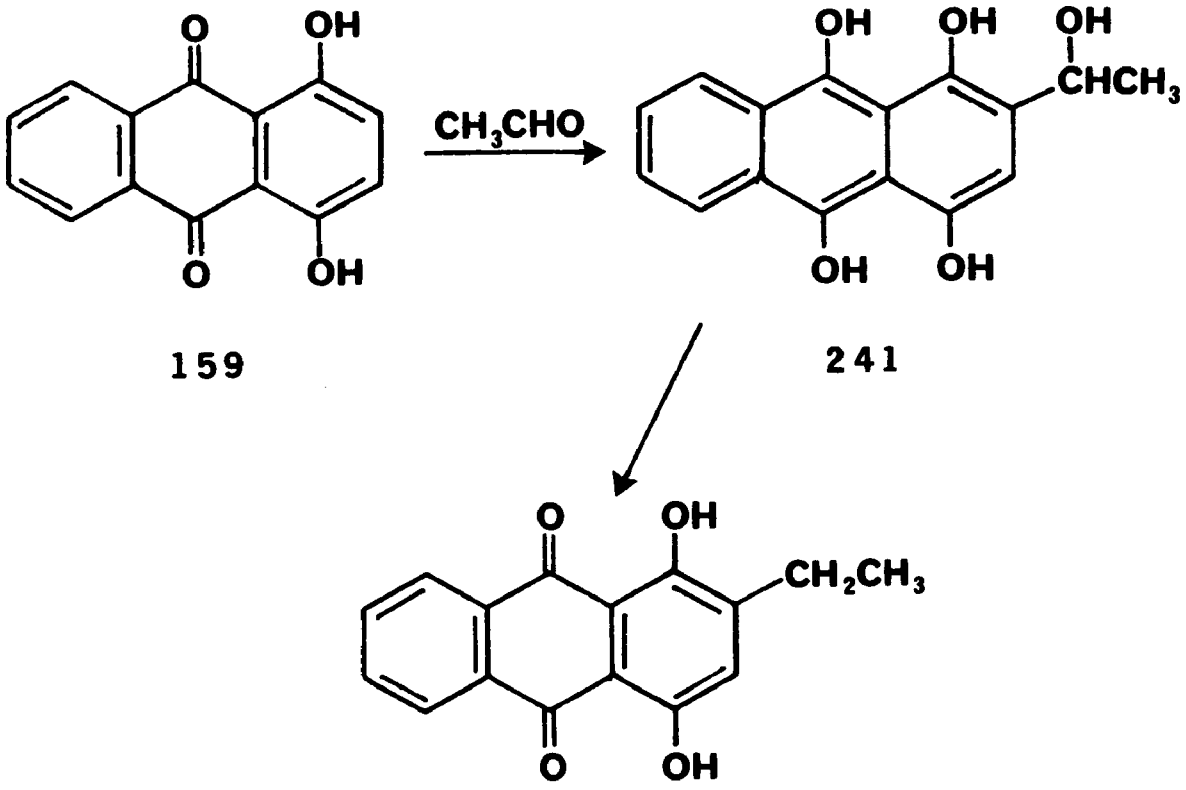


240

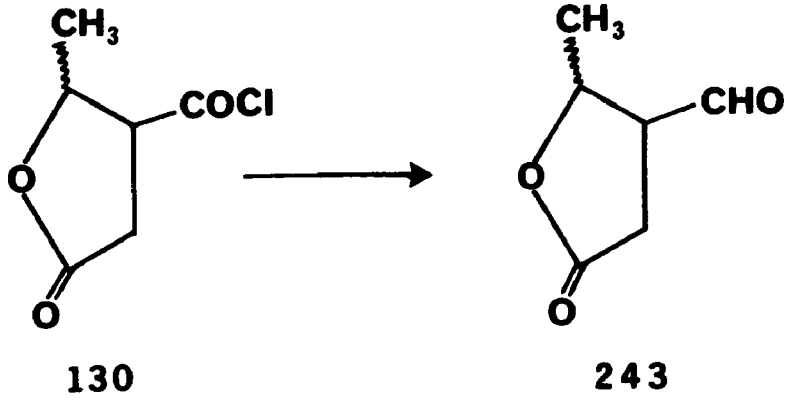
In agreement with the report cited earlier,[84] the alkylation of quinizarin (159) under the conditions of the Mannich reaction was unsuccessful. Likewise, amidomethylation and chloromethylation which were used for the alkylation of 132 were unsuccessful when the alkylation of quinizarin (159) was attempted. In all of these reactions, quinizarin (159) was returned unchanged in 90-100% yield as shown by nmr, ir and tlc.

The failure of these methods of alkylation prompted us to attempt a Marshalk[72] alkylation of quinizarin (159). Marshalk reported[72] that the condensation of hydroxyanthraquinones with aldehydes in the presence of weak base and sodium dithionite gave alkyl hydroxy anthraquinones as shown below for 159 and acetaldehyde.

To apply this reaction to our problem, the condensation of 159 and the aldehyde lactone 243 was planned. The acid

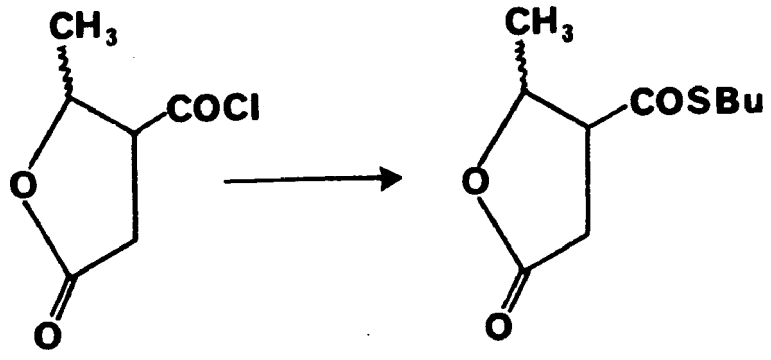


chloride 130 had been prepared earlier and therefore its conversion to the desired aldehyde 243 was planned.



It was felt that the conditions of the Rosenmund reduction[121] would be too severe to give a good yield of the desired aldehyde. Alternatively, tri-tertiary-butoxy-aluminohydride was prepared by the method of Brown[122] and was added to a solution of 130 in cold diglyme. The only material which could be recovered was the starting material 130. The tri-tertiary-butoxyaluminohydride was checked by carrying out the reduction of benzoyl chloride to benzaldehyde and perhaps it should be noted that Brown[122] obtained significantly lower yields of straight chain aliphatic aldehydes than he did with aromatic aldehydes.

Another method that was attempted was the Raney-nickel desulfurization of thiol esters.[123] The n-butanethiol ester of 145 was prepared by treating a benzene solution of 130 and pyridine with n-butanethiol. The thiol ester 244, bp 100°C at 1.0 mm of Hg, was obtained in high yield by vacuum distillation of the crude product.



130 244

The ir spectrum of 244 has lactone and thiol ester carbonyls at 1760 cm^{-1} and 1660 cm^{-1}, respectively. The nmr spectrum of 244 shows, a three proton triplet at 0.90δ (J = 6Hz), a three proton doublet and a two proton multiplet at 1.35δ ($J_{doub.}$ = 6.5Hz), a four proton multiplet centered at 2.90δ, a one proton A_2B pattern at 3.60δ and a one proton A_3B pattern at 4.82δ (J_a = 6.5Hz).

Raney-nickel was prepared by the method of Monzingo[124] and stirred with 244 in acetone. After one hour at the reflux temperature, nmr and ir spectra of the crude reaction product indicated only the starting material 244 although only 78% of the initial amount of 244 could be accounted for. Repeated attempts with fresh Raney-nickel led only to greater losses of material. Although 244 may have been lost by absorption onto the catalyst surface, it is possible that traces of residual base on the catalyst caused decomposition of 244 or any of the aldehyde 243 which was formed. Even though other routes to 243 were available, the possibility that 243 would be unstable under the conditions of the Marshalk reaction[72] caused us to abandon this synthetic plan.

The behavior of the compounds discussed in this work has raised several interesting questions concerning the chemistry and reactivity of these molecules. Furthermore, a workable totally stereospecific synthesis of daunomycinone has yet to be achieved. However, it is hoped that the

insights gained during the course of this work can be used in the accomplishment of such a synthesis.

EXPERIMENTAL

General. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Varian Associates T-60 spectrometer. Infrared spectra were recorded on Perkin-Elmer 237 and 457 spectrophotometers. Mass spectra were obtained on an Associated Electronics Instrument MS-902 mass spectrometer by Mr. Forrest MacKellar and Mrs. Margaret Johnson. Analyses were by Spang Microanalytical Laboratory, Ann Arbor, Michigan.

Preparation of 5,8-Dihydro-1,4-napthohydroquinone (118)--Method of L. F. Fieser.

Into a 1-ℓ thick-walled glass vessel was placed 109.1 g (1 mole) of 1,4-benzoquinone and 500 ml of acetic acid. The suspension was cooled in an ice bath until the solvent just began to crystallize and 65 g (1.2 mole) of 1,3-butadiene was added. The reaction vessel was sealed and kept in the dark at 5-10°C for 9 hours, then at room temperature for 46 hours. The solution was filtered through a bed of Norit and heated on a steam bath for 20 minutes. A mixture of 500 ml water, 100 ml concentrated hydrochloric acid and 15 g of stannous chloride was added, and after 15 minutes the solution was cooled. In two crops there was obtained 150.4 g (84.4%) of the desired product, mp 208-209.5°C (lit.[61] mp 208-209°C).

nmr (DMSO-d_6): δ 1.95(S,2); 3.10(S,4); 5.78(S,2); 6.40(S,2).

Preparation of 5,8-Dihydro-1,4-napthohydroquinone Diacetate (119).--A solution of 28.00 g (173 mmoles) of 118, 200 ml of acetic anhydride and 200 ml of pyridine in a 1-ℓ Erlenmeyer flask was heated at 70-75°C for 30 minutes. Water (250 ml) was added and the solution was cooled. The product was collected on a filter and was washed with aqueous acetic acid and water. Total yield 39.4 g (94%), mp 123-124°C (lit.[61] mp 123-124°C).

nmr (CCl_4): δ 2.23(S,6); 3.18(S,4); 5.81(S,2); 6.83(S,2).

Preparation of 5,6,7,8-Tetrahydro-1,4-napthohydroquinone-6,7-oxide Diacetate (137).--Into a 200 ml three-necked flask, equipped with mechanical stirrer, condenser, and addition funnel, was placed a mixture of 840 mg (6.10 mmoles) of potassium carbonate, 1.80 g (7.70 mmoles) of 5,8-dihydro-1,4-napthahydroquinone diacetate and 75 ml of methylene chloride. The reaction mixture was cooled to 20°C, and a solution of 2.20 g (11.6 mmoles) of 40% peracetic acid in acetic acid, 220 mg of sodium acetate and 25 ml of methylene chloride was added over a period of 30 minutes. The reaction mixture was stirred for 17 hours, the precipitated salts were collected and washed with methylene chloride and the combined filtrate and wash sol-

vent were evaporated to an oil. The oil was dissolved in 100 ml of ethyl ether, the ether was washed successively with water and a saturated sodium chloride solution and was dried over magnesium sulfate. The dried ether solution was boiled down to 50 ml and cooled in an ice bath to give 724 mg of white crystalline material, mp 162-163°C. Further concentration of the mother liquor and cooling gave 483 mg of identical material, total yield 63%.

nmr($CDCl_3$): δ 2.30(S,6); 2.98(S,2); 3.22(S,2); 3.45(S,2); 6.95(S,2).

ir($CHCl_3$): 1760, 1235, 915 and 835 cm^{-1}.

Mass spectrum: m/e 262(M^+), 261(M-H), 178(base).

Anal. Calcd for $C_{14}H_{14}O_5$: C, 64.12; H, 5.38.

Found: C, 64.18; H, 5.44.

Attempted Preparation of 5,6,7,8-Tetrahydro-6-ethynyl-7-hydroxy-1,4-napthohydroquinone diacetate (138).--A 25 ml three-necked flask, equipped with condenser, addition funnel and gas inlet tube, was charged with 70 mg (3 mg-atm) of metallic sodium and was placed in a Dry Ice-acetone bath. Gaseous ammonia was introduced into the flask until the liquid level had reached 10 ml. Acetylene, which had been passed successively through sulfuric acid and an empty gas washing bottle, was bubbled into the mixture until the blue color was completely discharged. A solution of 300 mg (1.18 mmoles) of 5,6,7,8-tetrahydro-6,7-oxide-1,4-napthohydroquinone in 5 ml of tetrahydrofuran was added and the

reaction mixture was stirred by passing acetylene through it for 30 minutes. The Dry Ice-acetone bath was removed and 210 mg (4.0 mmoles) of ammonium chloride was added. The ammonia was allowed to evaporate and the residue was dissolved in methylene chloride. The methylene chloride solution was washed successively with water and a saturated sodium chloride solution, dried over sodium sulfate and evaporated. A tan solid, 110 mg (0.50 mmoles, 42%) of 5,6,7,8-tetrahydro-6,7-oxide-1,4-napthohydroquinone monoacetate, mp 152-153°C, was obtained.

nmr($CDCl_3$): δ 2.18(S,3); 2.7-3.2(m,4); 3.40(S,2); 5.25(bs,1); 6.58(d, 1, J = 7Hz); 6.82(d, 1, J = 7Hz).

ir($CHCl_3$): 3580, 3320, 1745, 1230, 895 and 824 cm^{-1}.

Mass spectrum: m/e 220 (M^+), 178(base).

Preparation of 1-Chloro-5-hydroxyanthraquinone (132).--Into a 500 ml round-bottomed flask was placed 170 ml of concentrated sulfuric acid and 10.00 g (38.9 mmoles) of 1-amino-5-chloroanthraquinone (Pfaltz and Bauer). After solution was complete the flask was cooled in an ice bath to 0-5°C, and a mixture of 3.01 g (44.0 mmoles) of sodium nitrite in 20 ml of concentrated sulfuric acid was added in small portions with vigorous stirring. The reaction mixture was stirred at 0-5°C for 1 hour, and 100 ml of glacial acetic acid was added. The dark red solution was stirred for 15 minutes more and poured over 500 g of crushed ice. The

resulting tan suspension was slowly added to 700 ml of boiling 50% sulfuric acid contained in a 3-ℓ three-necked flask equipped with stirrer, condenser and 1-ℓ addition funnel. After the addition was complete the mixture was boiled gently under reflux for 30 minutes, diluted to 2.5 ℓ and cooled to room temperature. The yellow-tan solid was collected on a bed of Celite and washed with a large amount of water. The filter cake was recrystallized from aqueous acetone and gave three crops of gold needles, mp 223-224°C (lit.[77] 220.5-222°C), total yield 8.71 g (87%).

nmr($CDCl_3$): δ 7.38(q, 1, J_a = 2Hz, J_b = 7Hz); 7.80(m,4); 8.35(q, 1, J_a = 2Hz, J_b = 7Hz); 12.40(s,1).

ir($CHCl_3$): 3600-3000, 1675, 1640 and 1265 cm^{-1}.

Mass spectrum: m/e 258(M^+), 260(M+2, 35% of M^+).

Anal. Calcd for $C_{14}H_7ClO_3$
C, 65.01; H, 2.73; Cl, 13.71.
Found: C, 64.91; H, 2.79; Cl, 13.71.

Preparation of Ethyl Levulinate (124).--A 250 ml round bottom flask, equipped with a condenser and Dean-Stark trap was charged with 6.99 g (6.0 mmoles) of practical grade levulinic acid, 60 ml of absolute ethanol, 40 ml of benzene and a trace of sulfuric acid. The mixture was heated under reflux for one hour and then poured into a separatory funnel containing 5% aqueous sodium bicarbonate. The layers were separated and the aqueous layer was

extracted twice with additional benzene. The combined organic layers were dried over sodium sulfate and evaporated to a faintly yellow oil. Vacuum distillation of the crude product gave 5.31 g (3.7 mmoles, 67%) of ethyl levulinate (124), bp 95-98°C at 20 mm of Hg (lit. 93-94°C at 18 mm of Hg).

nmr(CCl_4): δ 1.05(τ, 3, J = 7Hz); 1.93(S,3); 2.38(m,4); 3.85(q, 2, J = 7Hz).

ir(CCl_4): 1725 cm^{-1}.

Attempted Stobbe Condensation of 124 and Benzaldehyde.--A 50 ml three-necked flask equipped with condenser, addition funnel, stirrer and nitrogen bubbler was charged with 420 mg (10 mmoles) of a 57% suspension of sodium hydride in mineral oil, 7.0 ml of dry benzene and a drop of absolute ethanol. To the stirred suspension was added 530 mg (5 mmoles) of benzaldehyde and then 1.73 g (12 mmoles) of ethyl levulinate (124) in 12 ml of dry benzene. The mixture was stirred for one hour and then washed with two portions of 10% aqueous sodium bicarbonate. The combined aqueous layers were acidified with dilute hydrochloric acid and extracted three times with ether. The combined ether extracts were washed with a saturated sodium chloride solution, dried over sodium sulfate and evaporated to a waxy crystalline solid, 748 mg (73% of theoretical).

nmr($CDCl_3$): δ 6.9-7.6(m, 6); 8.08(dd, 1, J_a = 8Hz, J_b = 2.5Hz); 8.79(bs, 1).

ir($CHCl_3$): 1700 cm^{-1}.

Preparation of Ethyl 3-carbomethoxylevulinate (146).--A 1-ℓ three-necked flask equipped with condenser, nitrogen bubbler, stirrer and addition funnel was charged with 14.40 g (342 mmoles) of a 57% mineral oil dispersion of sodium hydride. The mineral oil was removed by washing with three 75-ml portions of dry pentane, and the dry sodium hydride was suspended in 200 ml of dimethylformamide. There was added, at such a rate that heating and hydrogen evolution were not excessive, a solution of 39.85 g (342 mmoles) of methyl acetoacetate in 50 ml of dimethylformamide. After the addition was complete the mixture was stirred for 20 minutes. To the clear solution there was added dropwise a solution of 42.38 g (254 mmoles) of ethyl bromoacetate in 60 ml of dimethylformamide. The mixture was stirred for 30 minutes and then poured into a separatory funnel containing 800 ml of benzene and 800 ml of 1% acetic acid. The organic layer was separated, washed with water and a saturated solution of sodium chloride, dried over sodium sulfate and evaporated to a thick oil. Vacuum distillation of the crude reaction product gave 26.43 g (51.6%) of the desired keto diester, bp 78-81°C/0.25 mm Hg.

nmr(CCl_4): δ 1.15(τ, 3, J = Hz); 2.17(S,3); 2.61(d, 2, J = 8Hz); 3.60(S,3); 3.79(τ, 1, J = 8Hz); 3.95(q, 2, J = 6Hz).

ir(CCl_4): 1730 cm^{-1}.

Mass spectrum: m/e 202(M^+), 43(base).

Preparation of Methyl γ-Methyl Paraconate (147).--Into a 25-ml Erlenmeyer flask was placed 250 mg (1.24 mmoles) of ethyl 3-carbomethoxylevulinate and 10 ml of methanol. The solution was cooled to 10-15°C and 38 mg (1.0 mmoles) of sodium borohydride was added with swirling. After being stirred for 20 min the mixture was warmed to room temperature and acidified to pH = 4 with 10% hydrochloric acid. The methanol was removed on the rotary evaporator, and the residue was taken up in ether. The ether was washed with a saturated sodium chloride solution and dried over sodium sulfate. Complete removal of the ether by evaporation gave a clear liquid (164 mg, 1.15 mmoles, 93%), bp 80-83°C at 0.1 mm of Hg (lit.[80] bp 145-160°C at 11 mm of Hg).

nmr($CDCl_3$): δ 1.35(d, 3, J = 6Hz); 2.70(m, 2); 3.78(S, 3); 3.50(m, 1); 4.85(m, 1).

ir($CHCl_3$): 1795 and 1740 cm^{-1}.

Mass spectrum: m/e 158(M^+), 143($M-CH_3$), 59(base).

Preparation of di-Tertiary-butyl 2-(1-Hydroxyethyl)Succinate.--A 50-ml Erlenmeyer flask was charged with 1.08 g (3.82 mmoles) of di-tertiary-butyl 2-acetylsuccinate (173) and 20 ml of methanol. The solution was cooled to 15°C and 85 mg (2.2 mmoles) of sodium borohydride was added. The mixture was stirred for 20 minutes and 15 ml of water was added. The mixture was heated on a steam bath for 20 minutes and poured into a separatory funnel containing 70 ml of water and 60 ml of ethyl ether. The layers were sepa-

rated and the aqueous layer was washed twice with ether. The combined ether extracts were washed with a saturated sodium chloride solution and dried over sodium sulfate. Complete evaporation of the ether gave 971 mg (3.54 mmoles, 90%) of the desired alcohol, contaminated by a small amount of 3-carbo-6-butoxy-γ-valerolactone, as shown by a weak peak at 1785 cm^{-1} in the infrared spectrum.

nmr(CCl_4): δ 1.12(d, 3, J = 6.5Hz); 1.45(S,18); 2.40-2.80(m,3); 2.52(S,1) 4.01(m,1).

ir(CCl_4): 3500, 1730, 1395 and 1370 cm^{-1}.

Preparation of γ-Methyl Paraconic Acid (145).--A 100-ml round-bottomed flask equipped with a condenser and a Dean-Stark trap was charged with 861 mg (3.14 mmoles) of di-tertiary-butyl 2(1-hydroxyethyl) succinate, 50 ml of benzene and 25 mg of para-toluenesulfonic acid monohydrate. The mixture was boiled for 70 hours. The reaction mixture was placed in a separatory funnel with 50 ml benzene, 50 ml of saturated sodium chloride solution and 5 ml of 1% sodium acetate solution. The benzene solution was separated, dried and concentrated and the product crystallized, 339.1 mg (3.04 mmoles, 97%), mp 86-87°C (lit.[79] mp 84-85°C).

nmr($CDCl_3$): δ 1.42(d, 3, J = 7Hz); 2.80(dd, 2, J_a = 8Hz, J_b = 4Hz); 3.48(m, 1); 4.90(dd, 1, J_a = 6Hz, J_b = 1Hz); 8.53(bs, 1).

ir($CHCl_3$): 3400 to 2800 cm^{-1}, 1780 and 1730 cm^{-1}.

Anal. Calcd for $C_6H_8O_4$: C, 50.00; H, 5.59.
C, 49.82; H, 5.52.

Preparation of 1-Hydroxy-5-methoxyanthraquinone (149).--Into a 50-ml round-bottomed flask, equipped with condenser and nitrogen bubbler, was placed, in the following order, 280.5 mg (1.09 mmoles) of 1-chloro-5-hydroxyanthraquinone, 62.6 mg (0.79 mmoles) of cuprous oxide, 20 ml of dry methanol (distilled from magnesium methoxide) and 900.6 mg (16.7 mmoles) of sodium methoxide. The dark red mixture was then boiled with reflux under an atmosphere of dry nitrogen. After 70 hours the mixture was dissolved in 300 ml of water and filtered to remove the suspended cuprous oxide. Acidification of the filtrate with 10% hydrochloric acid and extraction with ethyl ether gave, after drying and evaporation of the ether, 216.2 mg of a 3:1 mixture of the methyl ether 149 and 132.

The reaction product was heated at 80-90°C in a mixture of 10 ml of acetic anhydride and 3 ml of pyridine. Water (20 ml) was added and the solution was cooled. The tan precipitate was collected on a filter and washed with water. Preparative thin layer chromatography of the mixture of acetates on silica gel, using 1:1 benzene chloroform as the eluent, gave two bands. Extraction from the silica with chloroform gave 168 mg (0.68 mmoles, 62%) of the desired methyl ether 150, mp 161-162°C.

Treatment of 150 with 5% methanolic potassium hydrox-

ide and acidification of the red solution with aqueous acetic acid gave, after cooling and crystallization, 1-hydroxy-5-methoxyanthraquinone (149), mp 182-183°C.

nmr($CDCl_3$): δ 4.05(S, 3); 7.75(m, 6); 12.43(S, 1).

ir($CHCl_3$): 1670 and 1635 cm^{-1}.

Mass spectrum: m/e 254(M^+).

Acetate 150:

nmr($CDCl_3$): δ 2.45(S, 3); 4.02(S,3); 7.75(m, 6).

ir($CHCl_3$): 1775 and 1680 cm^{-1}.

Mass spectrum: m/e 296(M^+), 254(base).

Anal. Calcd for $C_{17}H_{12}O_5$: C, 68.92; H, 4.08.

Found: C, 68.86; H, 4.28.

Imidomethylation of 1-Chloro-5-hydroxyanthraquinone (132) with N-methylolphthalimide (152).--To a 125-ml Erlenmeyer flask charged with 60 ml of concentrated sulfuric acid and 1.9684 g (7.56 mmoles) of 1-chloro-5-hydroxyanthraquinone (132) was added slowly 1.3588 g (7.62 mmoles) of N-methylolphtalimide (152) with swirling. After solution was complete the mixture was placed on a steam bath and kept at about 60°C for 2 hours. The warm solution was poured into 250 ml of water and the tan precipitate collected by filtration. The crude product was triturated with boiling acetone and filtered while hot. The solid residue was recrystallized from acetic acid to give 1.221 g (2.04 mmoles, 27%) of the disubstituted product 155, mp 316-320°C. The acetone solution was evaporated and the residue was recrystallized from

a mixture of chloroform and ethanol to give 1.395 g (3.22 mmoles, 42.5%) of the monosubstituted product 156, mp 256-257°C.

Into a 125 ml Erlenmeyer flask charged with 20 ml of acetic anhydride and 10 ml of pyridine was placed 1.395 g (3.22 mmoles) of 156. The dark red mixture was heated on a steam bath for one hour and poured into a large volume of ice water. After all the excess acetic anhydride was destroyed the solid was collected by vacuum filtration and washed with a large amount of water. The crude product was recrystallized from aqueous acetone to give 1.275 g (2.68 mmoles, 83%) of the acetate 157, mp 239-240°C.

155

ir(nujol): 1785, 1710, 1670, 1630 cm^{-1}.

156

ir(nujol): 1780, 1720, 1675, 1645 cm^{-1}.

157

ir($CHCl_3$): 1770, 1720, 1675 cm^{-1}.

nmr($CDCl_3$): δ 2.42(S, 3); 5.39(S, 2); 7.35(dd, 1, J_a = 2.5Hz, J_b = 5Hz); 7.40-8.30(m, 8).

Preparation of 1-Acetoxy-4-bromo-5-chloroanthraquinone (163).--A 10-ml Erlenmeyer flask was charged with 2.5 ml acetic acid, 124 mg of sodium acetate and 157.6 mg (0.62 mmoles) of 132. The mixture was warmed to 80°C and a mixture of 0.28 ml (5.1 mmoles) of bromine in 0.32 ml of acetic acid was added dropwise with swirling. After 3 to 4

minutes the reaction mixture was allowed to cool to room temperature and the crystallized solid was collected by vacuum filtration. The crude product was dissolved in a mixture of 3 ml of acetic anhydride and 2 ml of pyridine and heated on a steam bath for 20 minutes. The excess acetic anhydride was decomposed with water and the precipitated solid was collected on a filter and washed with dilute hydrochloric acid, dilute sodium bicarbonate solution and water. Air drying gave 208.4 mg (0.55 mmoles, 89%) of 1-acetoxy-4-bromo-5-chloroanthraquinone, mp 244-245°C.

nmr($CDCl_3$): δ 7.65(dd, 4, J_a = 7Hz, J_b = 3Hz); 8.20(dd, 4, J_a = 7Hz, J_b = 3Hz).

ir($CHCl_3$): 1770 and 1680 cm^{-1}.

Preparation of 1-Hydroxy-2-chloromethyl-5-chloroanthraquinone (148).--Into a 500-ml three-necked flask equipped with condenser, stirrer, nitrogen inlet and potassium hydroxide acid trap was placed 10.00 g (38.8 mmoles) of 1-chloro-5-hydroxyanthraquinone. The reaction vessel was placed in an ice bath, 125 ml of freshly distilled chloromethylmethyl ether (caution see Org. Rxn. Vol. 19, p. 422) was added and the golden suspension was stirred for 15 minutes. There was added, all at once with vigorous stirring, 16.50 g (124 mmoles) of powdered anhydrous aluminum chloride. The solution was stirred for 30 minutes at 0-5°C, and the flask was placed in an oil bath and heated at 45 ± 5°C for 2 hours. The reaction mixture was poured

directly into a mixture of 2.5 kg of crushed ice and 500 ml of water. The red suspension was allowed to digest with occasional stirring for 2-3 hours and the tan solid was collected on a cake of Celite, washed with water and air dried. The crude product was dissolved in methylene chloride, filtered through a column of Celite and recrystallized, to give 8.34 g (70%) of golden plates, mp - 204-205°C.

nmr($CDCl_3$): δ 4.78(S, 2); 7.85(m, 4); 8.38(q, 1, J_a = 2Hz, J_b = 7Hz); 12.80(S,1).

ir($CHCl_3$): 3600-3000 cm^{-1}, 1680, 1650 and 1270 cm^{-1}.

Mass spectrum: m/e 306(M^+), 308(71% of M^+), 271(base).

Anal. Calcd for $C_{15}H_8Cl_2O_3$: C, 58.66; H, 2.63; Cl, 23.09.

Found: C, 58.45; H, 2.72; Cl, 23.08.

Preparation of Methyl 3-Carbomethoxylevulinate (166).-- Into a 500-ml three-necked flask equipped with stirrer, condenser, addition funnel and nitrogen inlet was placed 10.66 g (197 mmoles) of sodium methoxide and 80 ml of dry dimethylformamide. To the stirred suspension at 5°C was added a solution of 23.74 g (204 mmoles) of methyl acetoacetate in 40 ml of dry dimethylformamide. The mixture was stirred for 15 minutes, and a solution of 24.66 g (160 mmoles) of methyl bromoacetate in 50 ml of dimethylformamide was added dropwise over a period of 30 minutes. The mixture was stirred and allowed to warm to room temperature

over 45 minutes. The reaction mixture was poured into a separatory funnel containing 400 ml of ethyl ether and 300 ml of water. The organic layer was washed successively with two portions of water and two portions of a saturated sodium chloride solution, dried over sodium sulfate, and evaporated to give a yellow viscous liquid. Vacuum distillation gave the desired diester, (166), 9.78 g (32.5%), bp 94-97°C at 1.5 mm of Hg.

nmr(CCl_4): δ 2.28(S, 3); 2.95(dd, 2, J_a = 6Hz, J_b = 1.5Hz); 3.71(S, 3); 3.80(S, 3); 4.02(τ, 1, J = 6Hz).

ir(CCl_4): 1730 cm^{-1}.

Mass spectrum: m/e 188(M^+), 43(base).

Preparation of Methyl 3-Acetyl-3-carbomethoxy-4-(1-hydroxy-5-chloro-2-anthraquinonyl)butyrate (168).--Into a 100-ml three-necked flask equipped with condenser, addition funnel, stirrer and nitrogen inlet was placed 263.9 mg (4.70 mmoles) of sodium methoxide and 10 ml of benzene (distilled from sodium). The flask was cooled to 10° and a solution of 547.2 mg (2.91 mmoles) of methyl 3-carbomethoxy levulinate in 5 ml of benzene was added dropwise. The solution was stirred for 20 minutes, and a mixture of 586.4 mg (1.92 mmoles) of 1-hydroxy-2-chloromethyl-5-chloroanthraquinone in 35 ml of benzene was added in one portion. The mixture was stirred for 45 minutes and poured into a separatory funnel along with 200 ml of 2% aqueous hydrochloric acid

and 150 ml benzene. The organic layer was separated, washed with a saturated sodium chloride solution, and dried over sodium sulfate. Evaporation of the benzene gave a dark red oil which was recrystallized from benzene-petroleum ether giving 666.5 mg (75%) of crystalline 168, mp 179-180°C.

nmr($CDCl_3$): δ 2.38(S, 3); 2.90(S, 2); 3.52(bs, 2); 3.64(S,3); 3.77(S, 3); 7.69(m, 4); 8.21(m, 1), 12.78(S, 1).

ir($CHCl_3$): 1730, 1675 and 1640 cm^{-1}.

Mass spectrum: m/e 458(M^+), 460(37% of M^+).

Anal. Calcd for $C_{23}H_{19}ClO_8$: C, 60.21; H, 4.17; Cl, 7.73.

Found: C, 60.23; H, 4.24; Cl, 7.80.

Attempted Preparation of Methyl 3-Acetyl-3-carbomethoxy-4-(1-hydroxy-5-chloro-2-anthraquinyl)butyrate Ethylene Ketal (169).--Into a 50-ml round-bottomed flask equipped with condenser, stirrer and Dean-Stark trap was placed 205.5 mg (0.45 mmoles) of methyl 3-aceto-3-carbomethoxy-4-(1-hydroxy-5-chloro-2-anthraquinyl)butyrate, 30 ml of benzene, 5 ml of ethylene glycol and 25 mg of para-toluenesulfonic acid monohydrate. The mixture was boiled under reflux for 3 hours and poured into a separatory funnel with 70 ml benzene and 100 ml of 2% sodium bicarbonate. The organic layer was separated and washed successively with water and a satura-

ted sodium chloride solution. The benzene solution was dried over sodium sulfate and evaporated to give 207 mg (100%) of the starting material.

nmr($CDCl_3$): δ 2.38(S, 3); 2.90(S, 2); 3.52(bs, 2); 3.64(S, 3); 3.77(S, 3); 7.69(m, 4); 8.21(m, 1); 12.70(S, 1).

Preparation of Ethyl 3-Carbomethoxy Levulinate Ethylene Ketal (170).--Into a 100-ml round-bottomed flask equipped with condenser and Dean-Stark trap was placed 4.05 g (20 mmoles) of ethyl 3-carbomethoxy levulinate, 100 mg of para-toluenesulfonic acid monohydrate, 70 ml of benzene and 4 ml of ethylene glycol. The mixture was boiled under reflux for 4 hours and poured into a separatory funnel containing 100 ml benzene and 60 ml of 2% aqueous sodium bicarbonate. The organic layer was separated and washed successively with two portions of water and one portion of saturated sodium chloride solution. The benzene solution was dried over sodium sulfate and evaporated to a clear viscous liquid, 4.83 g (19.6 mmoles, 98%).

nmr($CDCl_3$): δ 1.22(τ, 3, J = 6.5Hz); 1.30(S, 3); 2.52(m, 2); 3.09(q, 1, J_a = 8, J_b = 4.5Hz); 3.70(S, 3); 3.93(S, 4); 4.10(q, J = 6.5Hz).

Preparation of tertiary-Butyl Bromoacetate (171)--Method of W. S. Johnson.[96]--Into a 500-ml heavy-walled glass pressure vessel was placed 67.00 g (0.48 mole) of bromoacetic

acid, 120 ml of ethyl ether and 15 ml of concentrated sulfuric acid. The bottle was cooled in a Dry Ice-acetone bath and 105 ml (approximately 1.3 mole) of liquid isobutylene was added. The reaction vessel was stoppered and placed on a Parr shaker. The reaction vessel was shaken for 4.5 hours at room temperature, and cooled in a Dry Ice-acetone bath. The contents were poured into a 1-ℓ separatory funnel containing a mixture of 250 ml of water, 70 g of sodium hydroxide and 250 g of crushed ice. The mixture was shaken until the ice melted, and the layers were separated. The aqueous layer was washed twice more with 100 ml portions of ethyl ether, and the combined ether extracts were dried over potassium carbonate. After filtration of the drying agent the ether was removed by flash distillation and the crude product was distilled under vacuum (caution lacrymator), to give 54.22 g (0.28 mole, 58%), of ester 171, bp 69-70°C at 18mm of Hg.

nmr(CCl_4): δ 1.45(S, 9); 3.66(S, 2).

ir(CCl_4): 1732, 1394 and 1373 cm^{-1}.

Preparation of tertiary-Butyl Acetoacetate (172)--Method of Rune Sandberg.[97]--A 500-ml three-necked flask equipped with stirrer, addition funnel and Claisen adapter with condenser and thermometer was charged with 79.0 g (1.07 mole) of tert-butyl alcohol and heated to 80-85°C. Anhydrous sodium acetate, 400 mg (4.9 mmoles) was added and with stirring 200 ml (approximately 1.14 mole) of a 50%

solution of diketene in acetone was added over a period of 2.5 hours. During the addition and for an additional 45 minutes the temperature was maintained at 70-75°C. The mixture was transferred to a 500-ml round-bottomed flask and distilled under vacuum immediately, giving 120 g (0.76 mole, 71%) of 172, bp 82-83°C at 1.6 mm of Hg.

nmr(CCl_4): δ 1.43(S, 9); 2.21(S, 3); 3.38(S, 2).

ir($CHCl_3$): 1735, 1708, 1395 and 1374 cm^{-1}.

Preparation of di-tertiary-Butyl 2-Acetylsuccinate (173).-- Into a 500-ml three-necked flask equipped with stirrer, addition funnel, condenser and nitrogen bubbler was placed 11.61 g (215 mmoles) of sodium methoxide. The reaction flask was cooled to less than 5°C in an ice bath and 60 ml of dry N,N-dimethylformamide (distilled from calcium oxide) and then a solution of 33.98 g (215 mmoles) of 172 in 120 ml of dry N,N-dimethylformamide were added. The solution was stirred and a solution of 21.45 g (110 mmoles) of 171 in 50 ml of dry N,N-dimethylformamide was added dropwise over the course of 30 minutes. The ice bath was replaced with an oil bath and the reaction mixture was heated to 50°C over the course of one hour. The suspension was poured into a separatory funnel containing 600 ml of benzene and 900 ml of 1% aqueous acetic acid. The organic layer was separated and washed successively with three portions of water and one portion of a saturated sodium chloride solution. The solution was dried over sodium sulfate and

evaporated to a faintly yellow oil. Vacuum distillation gave a 33% (11.33 g) recovery of tertiary-butyl acetoacetate and 24.95 g (91.0 mmoles, 83%) of the desired diester 173, bp 91-93°C at 0.015 mm of Hg.

nmr(CCl_4): δ 1.40(S, 9); 1.42(S, 9); 2.22(S, 3); 2.60(dd, 2, J_a = 8Hz, J_b = 2Hz); 3.70(τ, 1, J = 8Hz).

ir(CCl_4): 1710, 1392, 1370 and 1150 cm^{-1}.

Mass spectrum: m/e 216 ($M-C_4H_8$), 57(base).

Anal. Calcd for $C_{14}H_{24}O_5$: C, 61.74; H, 8.88.
Found: C, 61.63; H, 8.83.

Preparation of di-tertiary-Butyl 2-Acetyl-2-(1-hydroxy-5-chloro-2-anthraquinonyl)Methyl Succinate (174).--A well dried 500-ml three-necked flask equipped with condenser, stirrer, addition funnel and nitrogen bubbler was charged with 1.10 g (25 mmoles) of a 57% mineral oil dispersion of sodium hydride. The mineral oil was removed by washing with two 20 ml portions of dry pentane, and the sodium hydride was suspended in 10 ml of dry N,N-dimethylformamide. The reaction flask was placed in an ice bath, and a mixture of 3.131 g (11.5 mmoles) of di-tertiary-butyl 2-acetosuccinate (173) in 15 ml of dry N,N-dimethylformamide was added dropwise. After hydrogen evolution had ceased a warm (40-50°C) solution of 3.433 g (11.1 mmoles) of 1-hydroxy-2-chloromethyl-5-chloroanthraquinone (148) in 100 ml of dry N,N-dimethylformamide was added as rapidly as possible. The

purple solution was heated to 50°C for 2.5 hours, and then poured into a 2-ℓ separatory funnel containing 850 ml of chloroform and 850 ml of 1% aqueous acetic acid. The organic layer was separated and washed successively with five portions of water and one portion of a saturated sodium chloride solution. The chloroform solution was dried over sodium sulfate and evaporated to a thick red oil. The product was purified by chromatography on a column of silica gel (60 g) using 7:3 chloroform-pentane as the eluent. Evaporation of the solvent gave 4.23 g (7.80 mmoles, 70%) of a dark gold semi-solid which crystallized on standing. The melting point was indefinite with gas evolution beginning at 162-165°C.

nmr($CDCl_3$): δ 1.45(S, 18); 2.34(S, 3); 2.75(d, 2, J = Hz); 3.53(bs, 2); 7.70(m, 4); 8.30(q, 1, J_a = Hz, J_b = Hz); 12.70(S, 1).

ir($CHCl_3$): 1720, 1675, 1640, 1395, 1370 and 1260 cm^{-1}.

Mass spectrum: m/e 542(M^+), 544(38% of M^+), 431(base).

Anal. Calcd for $C_{29}H_{31}ClO_8$: C, 64.15; H, 5.75; Cl, 6.47.

Found: C, 64.03; H, 5.71; Cl, 6.53.

Preparation of Ethyl 3-(1-Hydroxy-5-chloro-2-anthraquinonyl) Methyl Levulinate (175).--Into a 250-ml round-bottomed flask equipped with stirring bar, condenser and nitrogen bubbler was placed 2.00 g (3.70 mmoles) of di-tertiary-butyl 2-acetyl-2-(1-hydroxy-5-chloro-2-anthraquinylmethyl)succi-

nate (174), 150 ml of benzene and 120 mg of para-toluenesulfonic acid monohydrate. The mixture was boiled under reflux until the gas evolution ceased (1 hour). The red solution was added to 200 ml of absolute ethanol and the volume reduced to about one-third by boiling. Recrystallization of the desired ester from the ethanol gave 1.337 g (3.25 mmoles, 87%) of 175, mp 133.5-134.5°C.

nmr($CDCl_3$): δ 1.20(τ, 3, J = 7Hz); 2.27(S, 3); 2.40-3.30(m, 4); 3.50(m, 1); 4.10(q, 2, J = 7Hz); 7.42-7.90(m, 4); 8.34(q, 1, J_a = 6Hz, J_b = 2Hz); 12.80(S, 1).

ir($CHCl_3$): 1712, 1675 and 1635 cm^{-1}.

Mass spectrum: m/e 414(M^+), 416(37% of M^+), 271(base).

Anal. Calcd for $C_{22}H_{19}ClO_6$: C, 63.70; H, 4.62; Cl, 8.55.

Found: C, 63.60; H, 4.59; Cl, 8.67.

Preparation of 1-Acetamido-8-Chloro-4-hydroxyanthraquinone (181).--A 125-ml hydrogenation flask was charged with 106.5 mg (0.35 mmole) of 164, 25 ml of ethyl acetate and 20 mg of 5% palladium on carbon. The flask was placed on an atmospheric hydrogenation apparatus and stirred for 15 minutes at which time 25 ml of hydrogen had been taken up. The dark red solution was filtered to remove the catalyst and evaporated to a gummy residue. The residue was treated with 10 ml of warm acetic anhydride and after 10 minutes

enough water was added to destroy the excess acetic anhydride. The mixture was poured into a separatory funnel containing water and chloroform and the organic layer was separated. The chloroform solution was washed successively with dilute sodium bicarbonate and water and dried over sodium sulfate. Thin layer chromatography of the solution showed only one spot and evaporation of the solvent gave 97 mg (0.31 mmole, 89%) of 181, mp 198-199°C.

nmr($CDCl_3$): δ 2.32(S, 3); 7.22(d, 1, J = 9Hz), 7.60-7.90(m, 2); 8.35(dd, 1, J_a = 7Hz, J_b = 2Hz); 8.95(d, 1, J = 9Hz); 11.80(bs, 1); 12.98(S, 1).

ir($CHCl_3$): 1695, 1635 and 1575 cm^{-1}.

Preparation of Ethyl 3-(1-Hydroxy-4-nitro-5-chloro-2-anthraquinonyl) Methyl Levulinate (189).--A 250-ml Erlenmeyer flask was charged with 60 ml of concentrated sulfuric acid and cooled to 0-5°C in an ice bath. To the cold acid was added 760 mg (1.84 mmole) of ethyl 3-(1-hydroxy-5-chloro-2-anthraquinylmethyl) levulinate (175). After the solution became homogeneous, a cold mixture of 3.0 ml of concentrated nitric acid (70-73%) and 9.0 ml of concentrated sulfuric acid was added with vigorous stirring. The mixture was stirred for 5 minutes and poured into a mixture of 400 g of crushed ice and 300 ml of water. The tan solid was collected on a bed of Celite and washed with a large amount of cold water. The filter cake was recrystallized from 90% aqueous acetone, 705.3 mg (1.42 mmole, 77%),

mp 147-148°C.

nmr($CDCl_3$): δ 1.22(τ, 3, J = 7Hz); 2.25(S, 3); 2.32-3.15(m, 4); 3.30(m, 1); 4.05(q, 2, J = 7Hz); 7.62-8.05(m, 3); 8.32(q, 1, J_a = 6Hz, J_b = 2Hz); 13.36(S, 1).

ir($CHCl_3$): 1715, 1685, 1642, 1540 and 1345 cm^{-1}.

Mass spectrum: m/e 459(M^+), 461(37.5% of M^+), 296(base).

Anal. Calcd for $C_{22}H_{18}ClNO_8$:
C, 57.46; H, 3.94; Cl, 7.71; N, 3.05.
Found: C, 56.73; H, 4.07; Cl, 8.49; N, 3.37.

Preparation of Ethyl 3-(1-Hydroxy-4-bromo-5-chloro-2-anthraquinonyl)methyl Levulinate (190).--A 10-ml Erlenmeyer flask was charged with 76.7 mg (0.18 mmole) of 175, 53.0 mg (0.65 mmole) of sodium acetate and 2 ml of glacial acetic acid. The flask was placed in a hot water bath at 85°C and 0.5 ml of water was added. With swirling 0.05 ml of a 47% solution of bromine in acetic acid (0.44 mmole of bromine) was added and the mixture was kept at 85°C for 5 minutes. The reaction mixture was poured into a separatory funnel containing water and chloroform and the organic layer was separated. The chloroform solution was washed three times with 5% aqueous sodium bicarbonate, once with water, and dried over sodium sulfate. Evaporation of the chloroform gave 77.2 mg (0.15 mmole, 86%) of 190, mp 176-177°C, which showed a single spot on tlc.

nmr($CDCl_3$): δ 1.20(τ, 3, J = 6.5Hz); 2.28(S, 3); 2.50-3.70(m, 5); 4.15(q, 2, J = 6.5Hz); 7.60-7.90 (m, 3); 8.25(dd, 1, J_a = 7Hz, J_b = 2Hz); 13.30 (S, 1).

ir($CHCl_3$): 1730, 1715, 1680 and 1640 cm^{-1}.

Preparation of di-tertiary-Butyl 2-Acetyl-2-(1-hydroxy-4-bromo-5-chloro-2-anthraquinonyl)methyl Succinate (191).--A 50-ml Erlenmeyer flask was charged with 162 mg (0.30 mmole) of di-tertiary-butyl 2-acetyl-2-(1-hydroxy-5-chloro-2-anthraquinonyl)methyl succinate (174), 10 ml of glacial acetic acid and 200 mg of sodium acetate. The mixture was heated to 80°C and a solution of 145 mg (0.91 mmole) of bromine in 2 ml of glacial acetic acid was added with stirring. The mixture was stirred for 5 min and 15 ml of water was added. The solid was collected on a filter, washed with water and air dried. Recrystallization from petroleum ether (bp 90-100°C), yielded 157 mg (0.25 mmole, 84%) of 191, mp 167-170°C, decomposition with gas evolution.

nmr($CDCl_3$): δ 1.45(S, 9); 1.50(S, 9); 2.38(S, 3); 2.81(S, 2); 3.57(S, 2); 7.40-8.35(m, 4); 13.20 (S, 1).

ir($CHCl_3$): 1735, 1720, 1675, and 1635 cm^{-1}.

Mass spectrum: m/e 620(M^+), 622(141% of M^+), 57(base).

Preparation of Ethyl 3-(1-Hydroxy-4-nitro-5-chloro-2-anthraquinonyl)methyl Levulinate Ethylene Ketal (194).--A 250-ml round-bottomed flask, equipped with condenser, nitrogen bubbler and Dean-Stark trap was charged with 645 mg (1.41 mmole) of ethyl 3-(1-hydroxy-4-nitro-5-chloro-2-anthraquinyl methyl) levulinate (189), 120 ml of benzene, 90 mg of para-toluenesulfonic acid monohydrate and 4 ml of ethylene glycol. The mixture was boiled under reflux for 20 hours and poured into a separatory funnel containing 200 ml of benzene and 200 ml of 1% aqueous sodium bicarbonate. The organic layer was separated and washed successively with three 200 ml portions of water and one 200 ml portion of a saturated sodium chloride solution. The golden solution was dried over sodium sulfate and evaporated to give 673 mg (94%) of the desired ester ketal 194, mp 119-121°C. The nmr spectrum of 194 indicated that 9% of the material had been transesterified with ethylene glycol.

nmr($CDCl_3$): δ 1.18(τ, 3, J = 7Hz); 1.40(S, 3); 2.20-3.40(m, 5); 3.97(S, 4); 3.99(τ, 2, J = 7Hz); 7.60-8.0(m, 3); 8.25(dd, 1, J_a = 6Hz, J_b = 2Hz); 13.15(S, 1).

ir($CHCl_3$): 1725, 1680, 1635, 1540 and 1345 cm^{-1}.

Mass spectrum: m/e 503(M^+), 505(40% of M^+), 87(base).

Preparation of Ethyl 3-(1-Hydroxy-4-amino-5-chloro-2-anthraquinyl)methyl Levulinate Ethylene Ketal (195).--A 125-ml hydrogenation flask was charged with 190 mg (0.38 mmole) of 194, 30 mg of 5% Pd/c and 30 ml of ethyl acetate. The mixture was stirred on the atmospheric hydrogenation apparatus for 15 minutes. The purple solution was dried by the addition of sodium sulfate and filtered. The filtrate was evaporated to give 170 mg (95%) of an inseparable mixture of 195 and ethyl 3-(1-hydroxy-4-amino-2-anthraquinonyl)-methyl levulinate ethylene ketal (197).

nmr($CDCl_3$): δ 1.25(τ, 3, J = 6Hz); 1.42(S, 3); 2.20-2.80(m, 4); 3.0-3.3(m, 1); 4.05(S over q, 6); 6.0-6.6(bs, 2); 7.38(S, 1); 7.4-7.8(m, 2); 8.35 (dd, 1, J_a = 2Hz, J_b = 7Hz); 13.45 (S, 1).

ir($CHCl_3$): 3475, 3300, 1740, 1635 cm^{-1}.

Mass spectrum: m/e 473(P^+), 475(38% of P^+), 439(25% of 473), 87(base).

Preparation of Triethyl 1-(1-Hydroxy-5-chloro-2-anthraquinonyl)methyl-1,1,2-ethane Tricarboxylate (198).--A 500-ml three-necked flask equipped with stirrer, condenser, nitrogen inlet and addition funnel was charged with 300 mg (12.5 mmoles) of sodium hydride, and the flask was cooled in an ice bath to 5°C. With stirring a solution of 1.23 g (5.0 mmoles) of triethyl-1,1,2-ethane tricarboxylate in 100 ml of dry N,N-dimethylformamide was added in small portions. When the hydrogen evolution had ceased, a mixture

of 1.50 g (4.90 mmoles) of 1-hydroxy-2-chloromethyl-5-chloroanthraquinone (148) and 100 ml of dry N,N-dimethylformamide was added as rapidly as possible. The purple reaction mixture was allowed to warm to room temperature over the course of 30 minutes and was poured into 1.2 ℓ of 2% hydrochloric acid. The yellow solid was collected and washed with cold water. Recrystallization from 75% aqueous ethanol gave the desired triester 198, 1.64 g (62%), mp 108-109°C.

nmr($CDCl_3$): δ 1.30(τ, 9, J = 7.5Hz); 2.93(S, 2); 3.62(S, 2); 4.29(q, 6, J = 7.5Hz); 7.35-7.80 (m, 4); 8.32(dd, 1, J_a = 6Hz, J_b = 2Hz); 12.72 (S, 1).

ir($CHCl_3$): 1730, 1675 and 1640 cm^{-1}.

Mass spectrum: m/3 516(M^+), 518(40% of M^+, 397(base).

Anal. Calcd for $C_{26}H_{25}ClO_9$:

C, 60.41; H, 4.87; Cl, 6.86.

Found: C, 60.39; H, 4.82; Cl, 6.88.

Preparation of Triethyl 1-(1-Hydroxy-4-bromo-5-chloro-2-anthraquinonyl)methyl-1,1,2-ethane Tricarboxylate (199).--A 125-ml Erlenmeyer flask was charged with 4.922 g (9.5 mmoles) of 198, 35 ml of acetic acid and 1.0 g of sodium acetate. The mixture was heated to 100°C, and a mixture of 0.55 ml (10 mmoles) of bromine in 2 ml of acetic acid was added with swirling. The mixture was heated for an additional 10 minutes and poured into 250 ml of water. The

solid was collected on a bed of Celite and recrystallized from 80% aqueous acetone, giving 5.063 g (0.85 mmoles, 89%) of 199, mp 140-141°C.

nmr($CDCl_3$); δ 1.25(τ, 9, J = 7Hz); 2.90(S, 2); 3.52(S, 2); 4.22(q, 6, J = 7Hz); 7.65(m, 3); 8.18(m, 1); 13.15(S, 1).

ir($CHCl_3$): 1730, 1680 and 1640 cm^{-1}.

Mass spectrum: m/e 594(M^+), 596(130% of M^+), 416(base).

Attempted fusion of 199 with potassium Hydroxide.--Into a 125-ml stainless steel beaker was placed 20 g of potassium hydroxide, 3 ml of water and 1.096 g (1.85 mmoles) of 199. The beaker was covered with a watch glass, and the mixture was heated at 280°C for 2 hours. A fine white crystalline compound sublimed out of the reaction mixture and collected on the watch glass. The sublimed material was shown to be anthraquinone (201), mp 283-284°C. The dark red melt was allowed to cool and was dissolved in 600 ml of water. The aqueous solution was filtered and acidified with dilute hydrochloric acid. The resulting suspension was extracted with methylene chloride and the methylene chloride solution was washed with water and dried over sodium sulfate. Thin layer chromatography of the dried solution showed at least eight separate spots and separation of the compounds was not attempted.

201

nmr($CDCl_3$): δ 7.60(m, 2); 8.15(m, 2).

Mass spectrum: m/e 208(M^+, base), 180(loss of CO).

Attempted Sodium Hydroxide Hydrolysis of 199.--A 250-ml round-bottomed flask was charged with 1.50 g of cuprous oxide, 0.50 g of copper-bronze, 150 ml of 10% aqueous sodium hydroxide and 1.00 g (1.68 mmoles) of 199. The mixture was heated at reflux under an atmosphere of nitrogen for 68 hours and then was filtered through a sintered glass funnel while still hot. The solution was acidified with 15% hydrochloric acid and the copious tan precipitate was collected by vacuum filtration and washed with water. The filter cake was triturated with 400 ml of hot methanol and the resulting suspension was filtered. The volume of methanol was reduced by boiling and addition of water caused the precipitation of a red powder. The solid was collected by filtration and dried to give 356 mg (75%) of a material which was immobile on tlc. The crude material was esterified in a boiling mixture of 11 ml of absolute ethanol, 12 ml of benzene and 1 ml of sulfuric acid. After 14 hours under reflux the mixture was poured into a separatory funnel containing ether and 5% sodium bicarbonate. The ether layer was separated, washed with water, dried over sodium sulfate and evaporated to give 292 mg of a dark tan solid. Preparative thin layer chromatography on two silica plates using chloroform as the eluent gave three bands of material as well as an immobile brown band. The two products with the highest R_f values were minute traces

of unidentified materials. The third band contained 243 mg (0.78 mmole, 47% from 199) of 2-carboethoxy-1,5-dihydroxyanthraquinone (203), mp 166-168°C.

nmr($CDCl_3$): δ 1.25(τ, 3, J = 7Hz); 4.42(q, 2, J = 7Hz); 7.38(dd, 1, J_a = 6.5Hz, J_b = 2Hz); 7.60-8.0(m, 3); 8.30(d, 1, J = 8Hz); 12.20(S, 1); 13.25(S, 1).

ir($CHCl_3$): 1725 and 1635 cm^{-1}.

Mass spectrum: m/e 312 (M^+), m/e 267($M-C_2H_5O$).

Attempted Hydrolysis of 195.--A 25-ml round-bottomed flask fitted with a condenser and nitrogen bubbler was charged with 170 mg (0.36 mmole) of 195, 10 ml of 1.5% aqueous sodium hydroxide and 400 mg (2.30 mmoles) of practical sodium dithionite. The mixture was heated at 90-95°C for 20 minutes and an additional 0.1 ml of 25% aqueous sodium hydroxide and 100 mg (0.57 mmoles) of sodium dithionite were added. The mixture was heated for an additional 30 minutes, tlc showed one colored spot and some dark immobile material. The solution was aerated for 1 hour, which caused no change on tlc, and then acidified with acetic acid. The aqueous suspension was extracted with chloroform and the resultant chloroform solution was dried and evaporated to give a red solid. The solid was dissolved in 2% ethanolic sulfuric acid and boiled for 30 minutes in an attempt to esterify any carboxylic acid present. After neutralization with aqueous potassium carbonate and crystallization, 74 mg (0.31 mmole, 85%) of quinizarin (159)

was obtained.

nmr($CDCl_3$): δ 7.35(S, 2); 7.85(dd, 2, J_a = 7Hz, J_b = 2.5Hz); 8.40δ(dd, 2, J_a = 7Hz, J_b = 2.5Hz); 12.90(S, 2).

ir($CHCl_3$): 1640 cm^{-1}.

Mass spectrum: m/e 240(M^+, base).

Preparation of Leucoquinizarin (229).--A 500-ml Erlenmeyer flask was charged with 150 ml of glacial acetic acid and 10.00 g (41.0 mmoles) of technical quinizarin (159). The solution was heated to boiling and 12.0 g (185 mg-atoms) of zinc dust was added in small portions over the course of 30 minutes. The hot solution was filtered into 400 ml of water, and the precipitate was collected on a filter. Recrystallization of the filter cake from ethanol gave 5.82 g (24 mmoles, 59%) of 229, mp 153.5-154.5°C.

nmr($CDCl_3$): δ 3.05(S, 4); 7.72(dd, 2, J_a = 6.5 Hz, J_b = 3Hz); 8.40(dd, 2, J_a = 6.5Hz, J_b = 3Hz); 13.65(S, 2).

ir($CHCl_3$): 1640 cm^{-1}.

Mass spectrum: m/e 242(M^+), 243(16% of M^+).

Preparation of Triethyl 1-(1-Hydroxy-4-nitro-5-chloro-2-anthraquinonyl)methyl-1,1,2-ethanetricarboxylate (232).--A 50-ml Erlenmeyer flask was placed in an ice bath and charged with 200 mg (0.39 mmole) of 198 and 20 ml of cold concentrated sulfuric acid. The solution was stirred for 15

minutes and a mixture of 0.75 ml of concentrated nitric acid (70.3%) and 2.0 ml of concentrated sulfuric acid was added dropwise. The solution was stirred for 5 minutes and poured into a mixture of 50 ml of water and 50 g of crushed ice. The solid was collected on a filter and washed with a large amount of water. Recrystallization of the crude product from 90% aqueous acetone gave 204 mg (0.37 mmole, 93%) of 232, mp 188.5-189.5°C.

nmr($CDCl_3$): δ 1.22(τ, 9, J = 7Hz); 2.93(S, 2); 3.60 (S, 2); 4.20(q, 6, J - 7Hz); 7.82(m, 3); 8.35 (dd, 1, J_a = 6.5Hz, J_b = 2Hz); 13.10(S, 1).

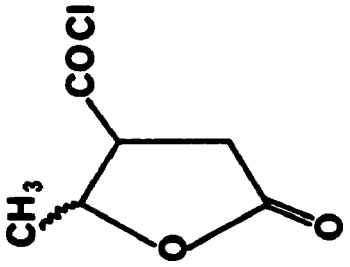
ir($CHCl_3$): 1730, 1680, 1645, 1545 and 1345 cm^{-1}.

Mass spectrum: m/e 561(M^+), 563(39% of M^+), 361(base).

APPENDIX

NMR AND IR SPECTRA OF SELECTED COMPOUNDS*

* These spectra were obtained by tracing the originals with a pantograph. NMR insets are at 360 Hz offset.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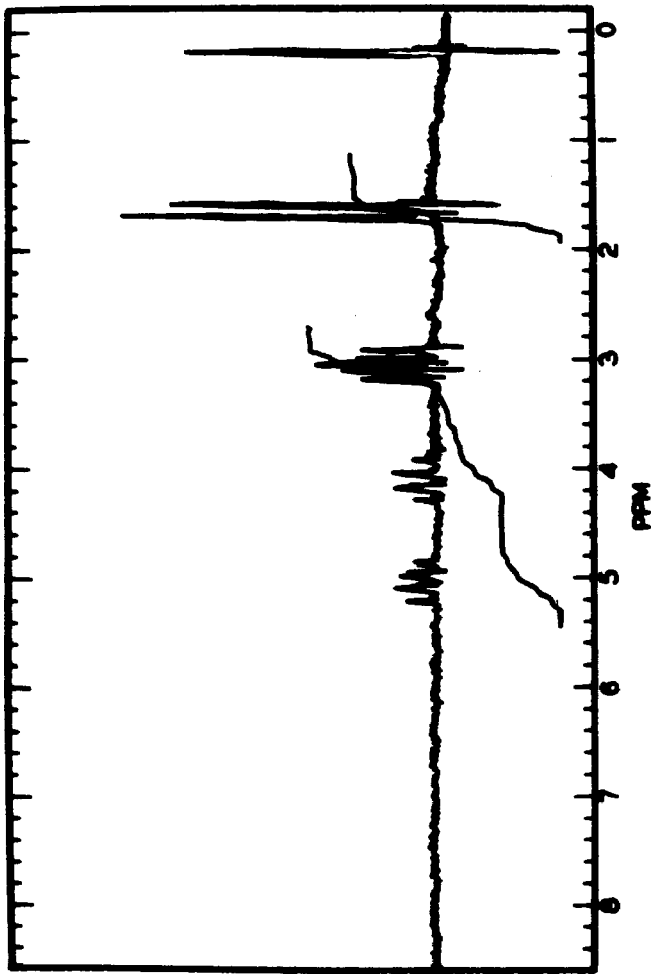
CH3
O
O

130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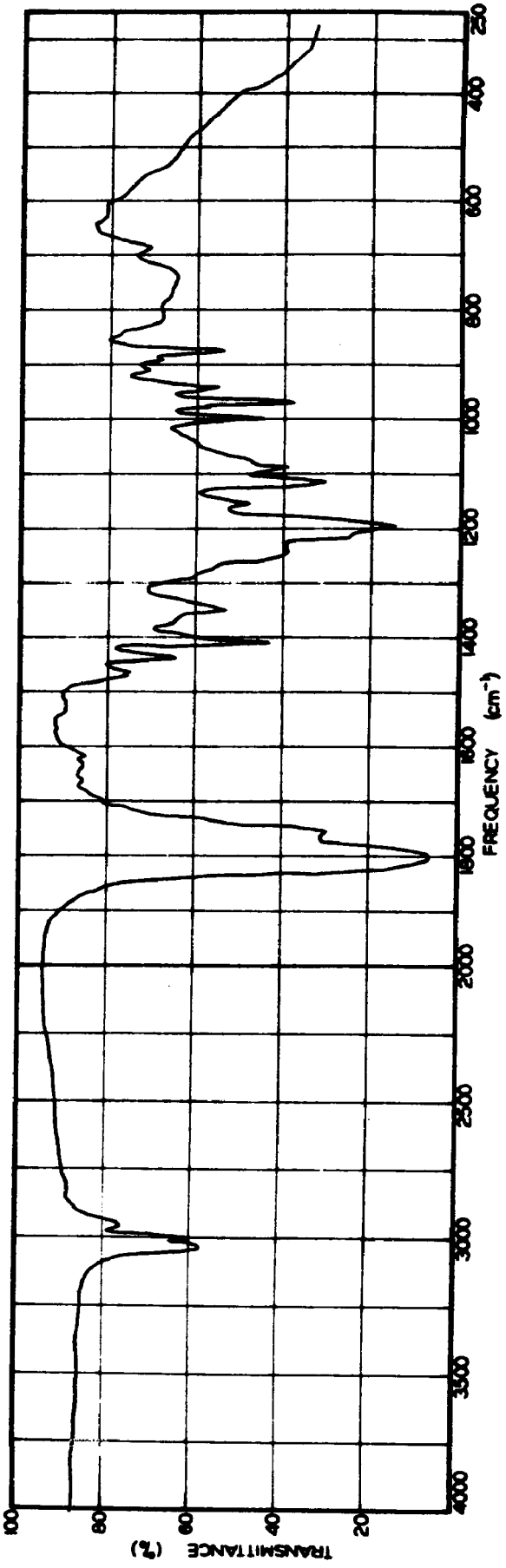
1
2
3
4
5
6
7
8
PPM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80
60
40
20
TRANSMITTANCE (%)
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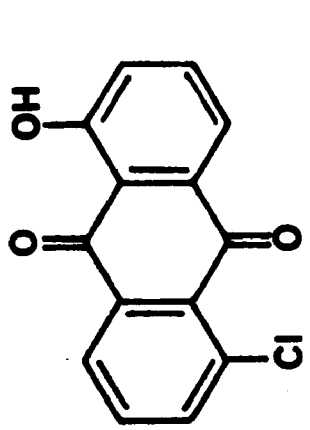
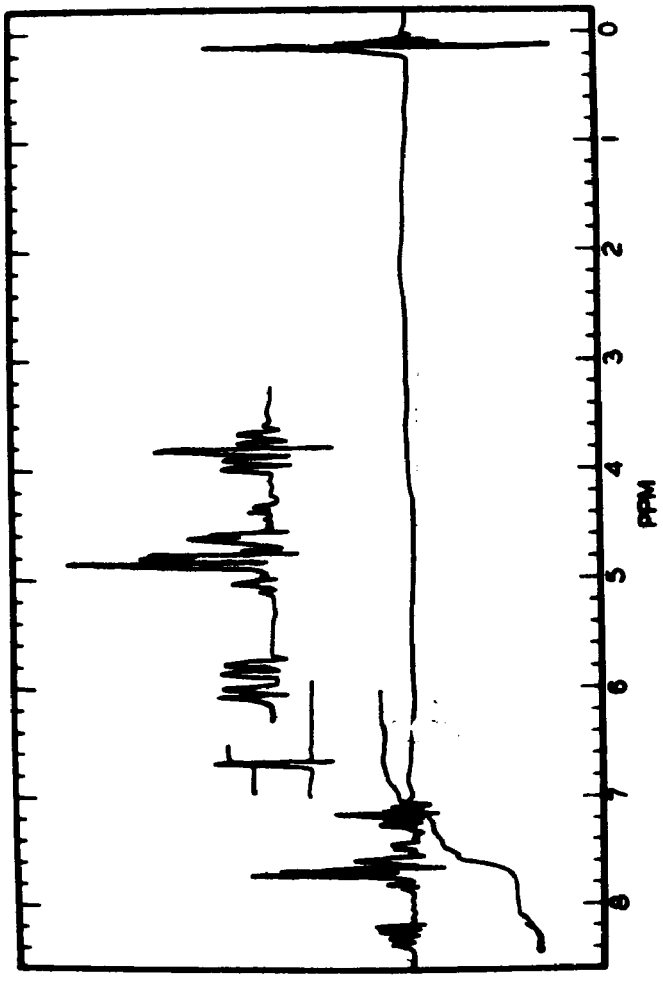
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400
250
FREQUENCY (cm⁻¹)


OH
O
O
Cl

132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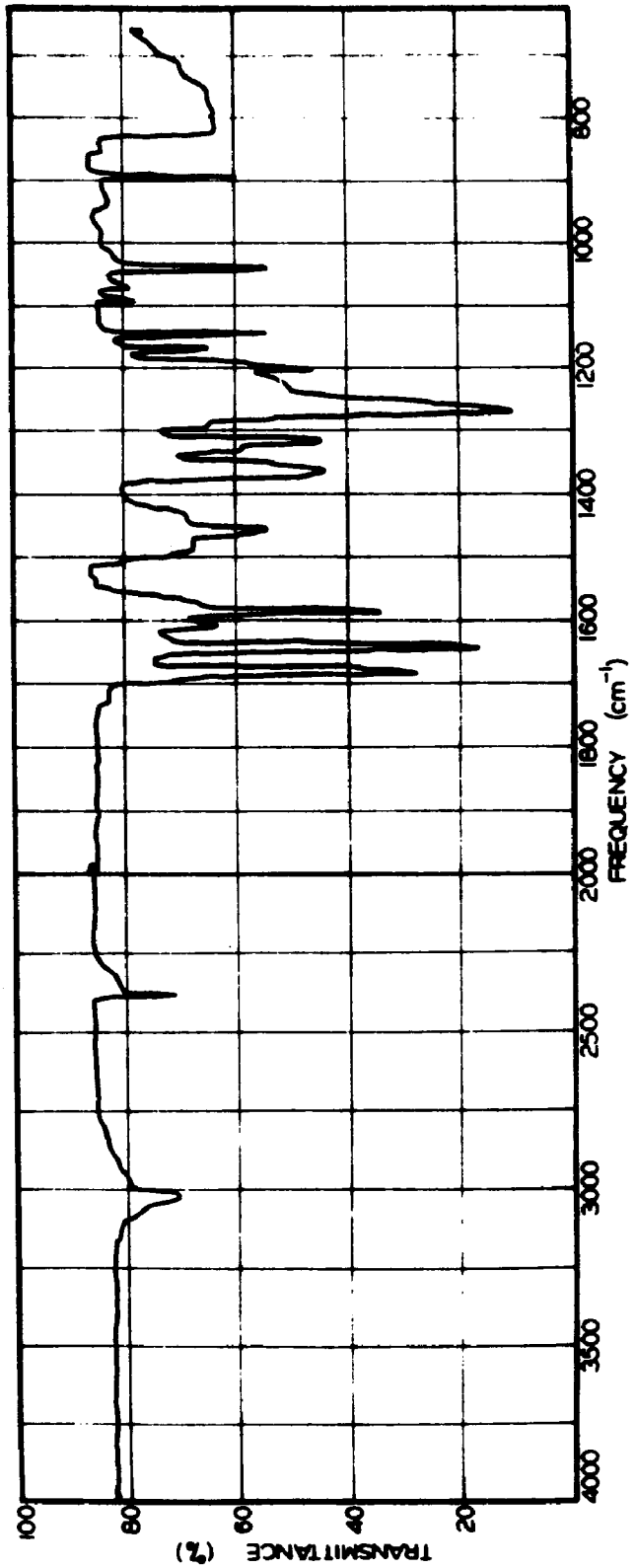
1
2
3
4
5
6
7
8
PPM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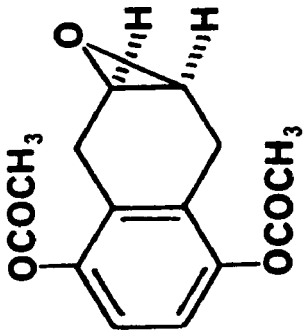
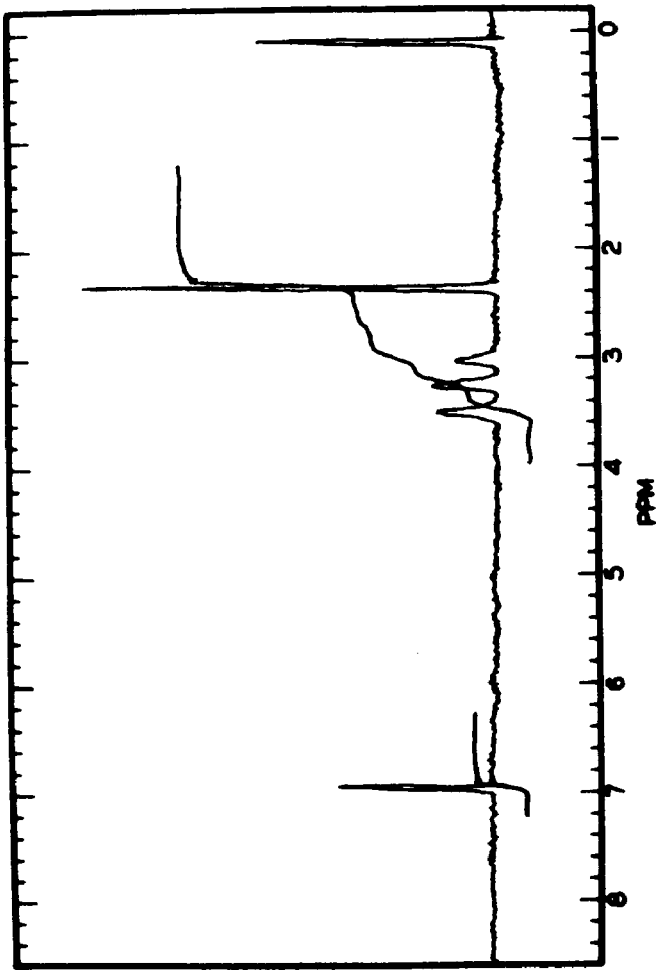
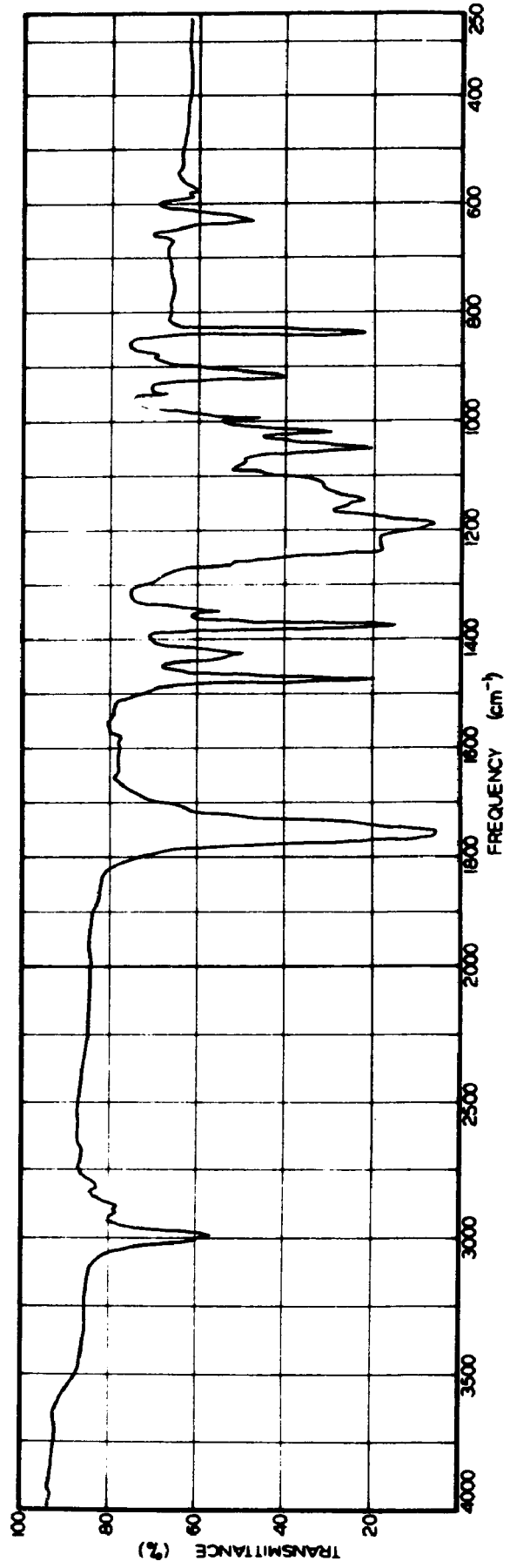
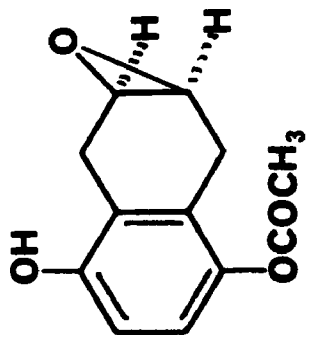
80
60
40
20
TRANSMITTANCE (%)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
FREQUENCY (cm⁻¹)


O
H
H
OCOCH3
OCOCH3

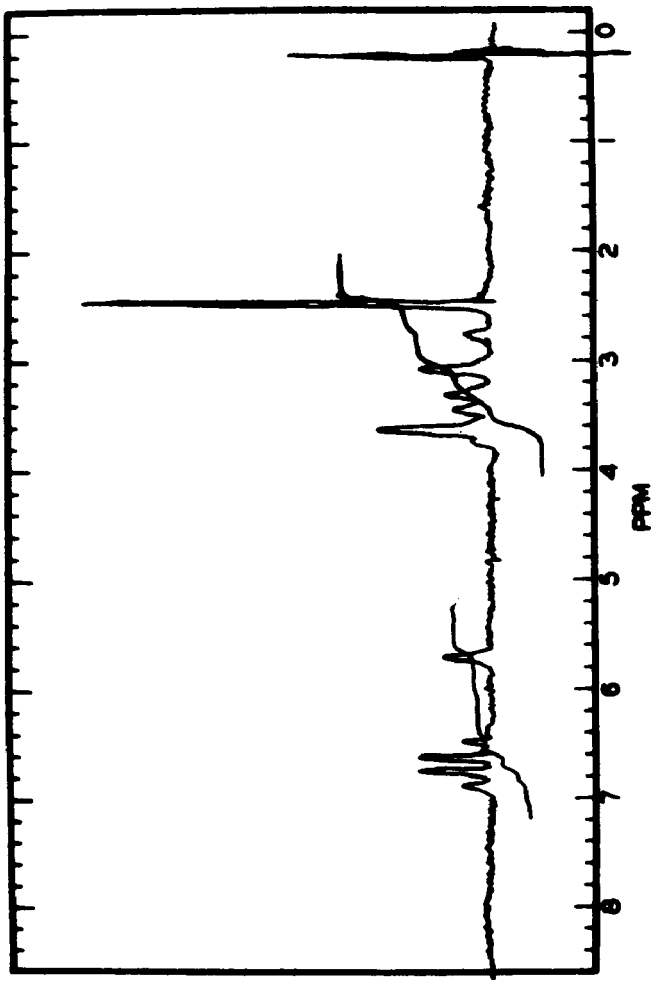
137

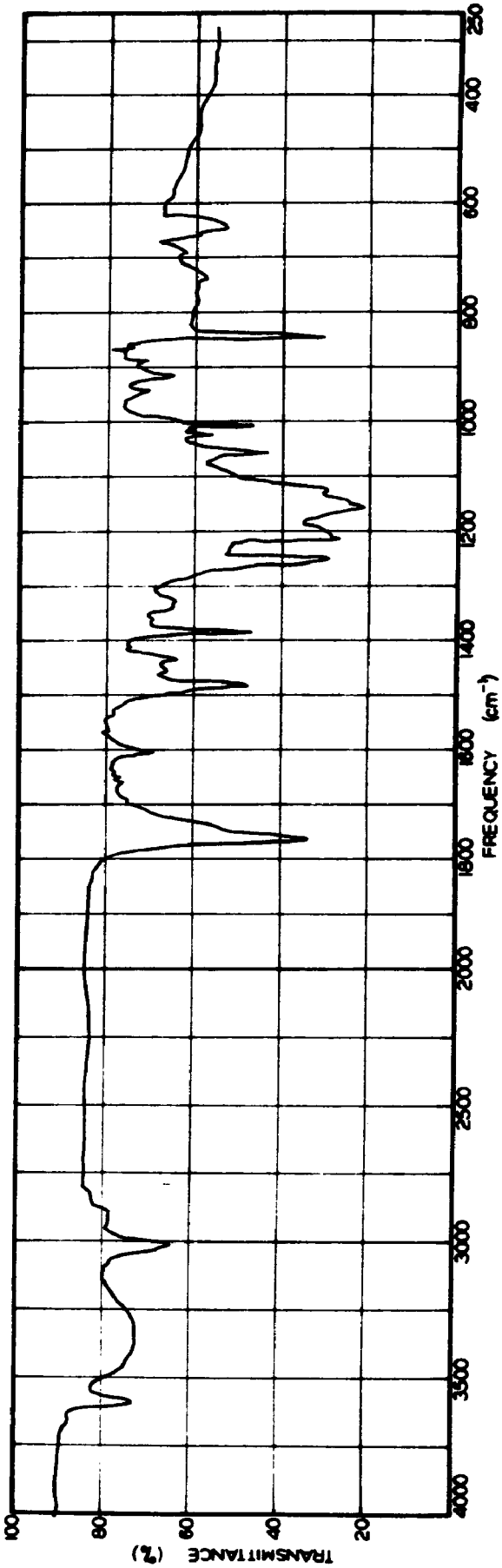

0
1
2
3
4
5
6
7
8
PPM

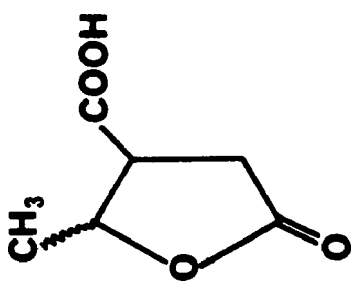

100
80
60
40
20
TRANSMITTANCE (%)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400
250
FREQUENCY (cm⁻¹)


O
H
H
OH
OCOCH3

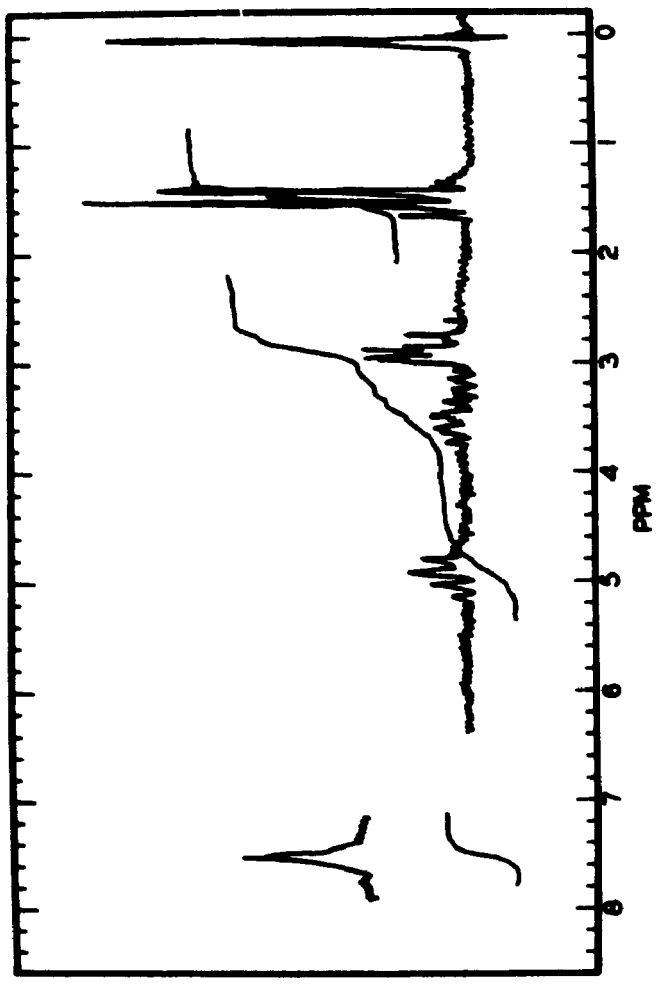
139

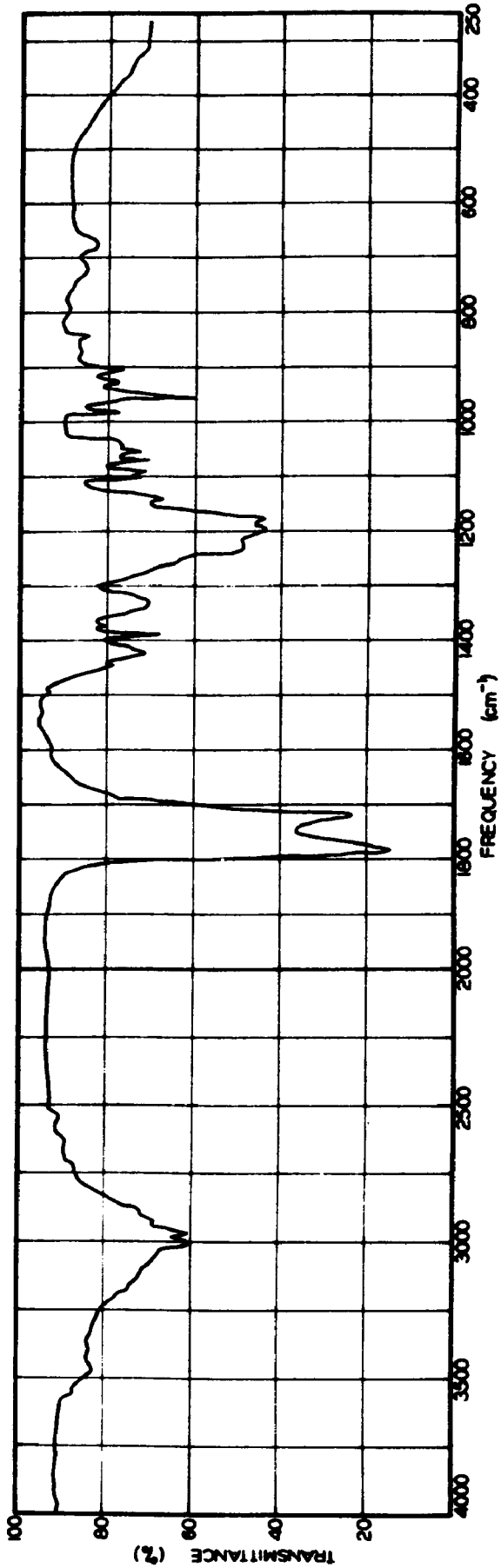

0
1
2
3
4
5
6
7
8
PPM

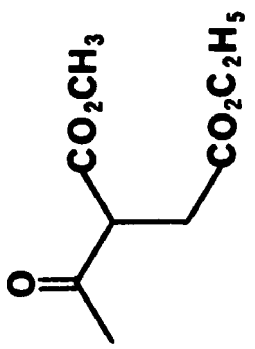

100
80
60
40
20
TRANSMITTANCE (%)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400
250
FREQUENCY (cm⁻¹)


COOH
CH3
O
O

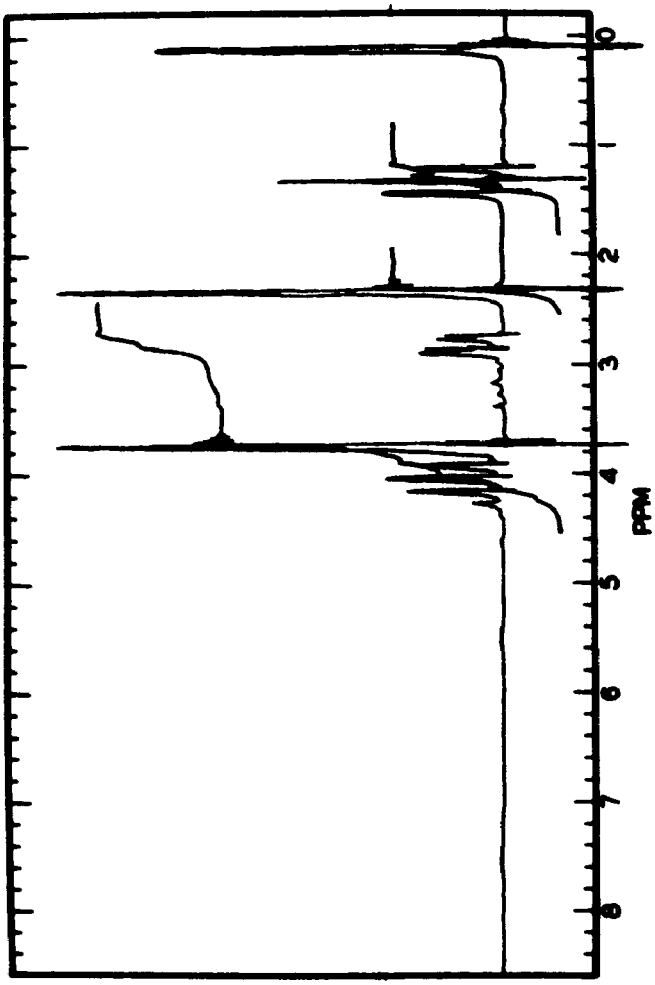
145

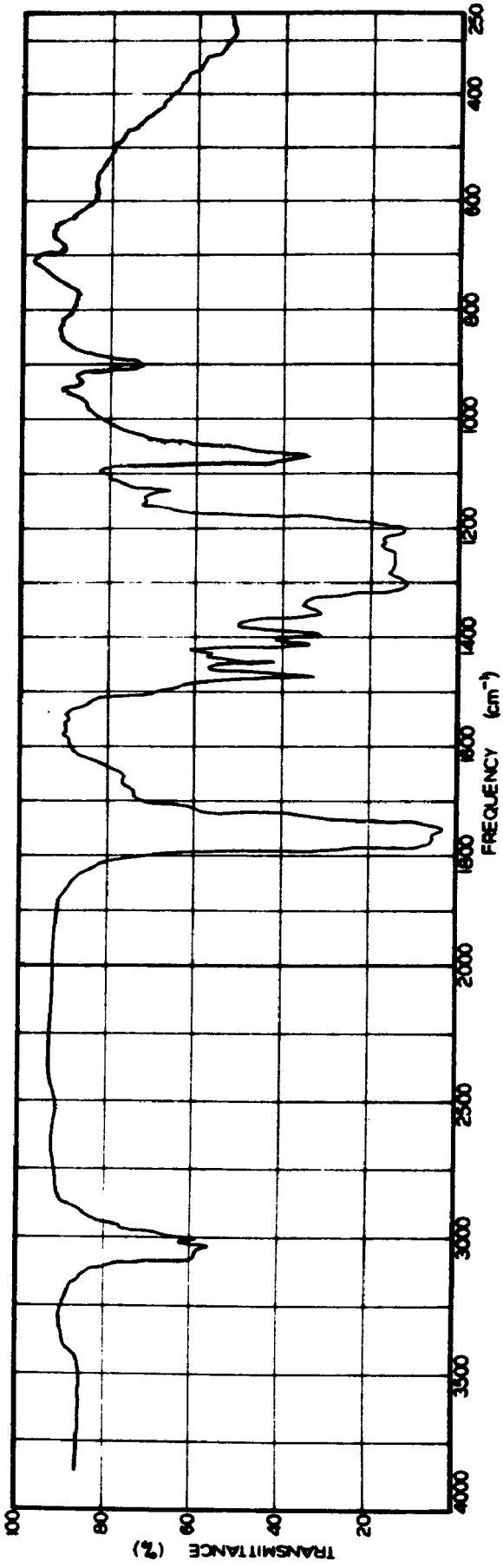

PPM
0
1
2
3
4
5
6
7
8

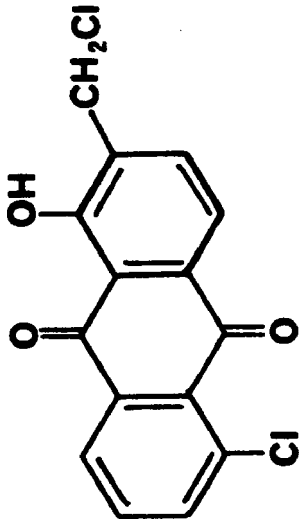

TRANSMITTANCE (%)
100
80
60
40
20
FREQUENCY (cm⁻¹)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400
250


CO2CH3
CO2C2H5
O

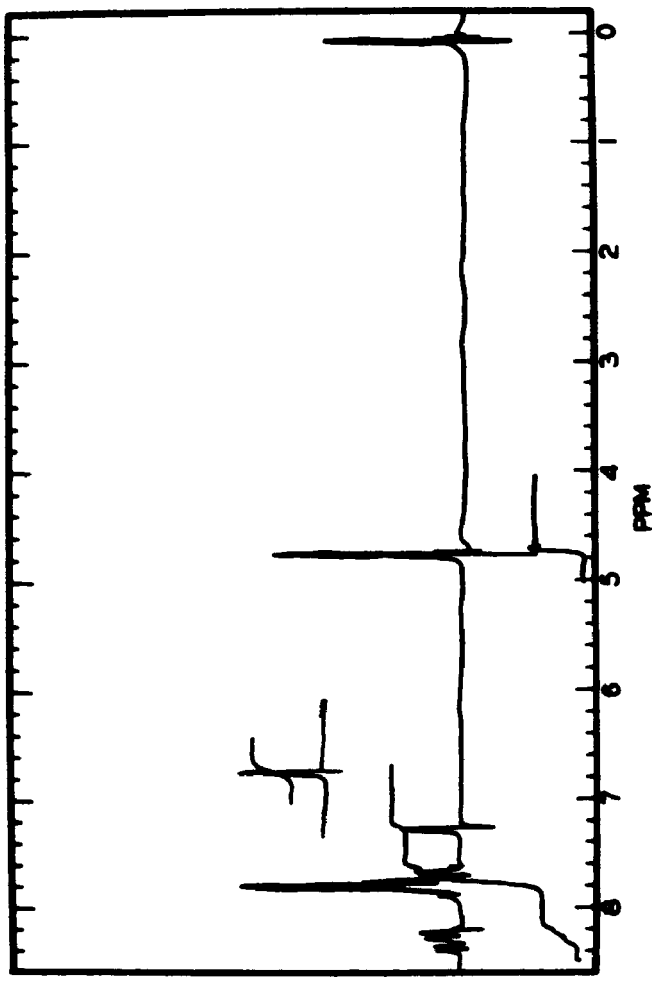
146

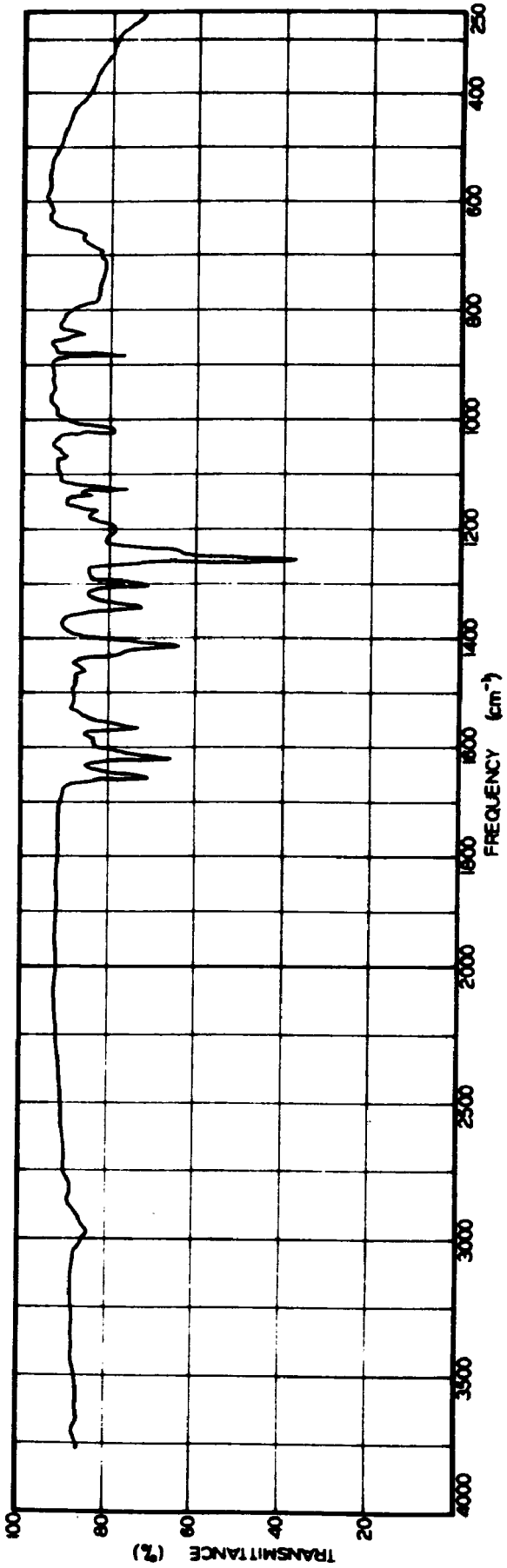

0
1
2
3
4
5
6
7
8
PPM

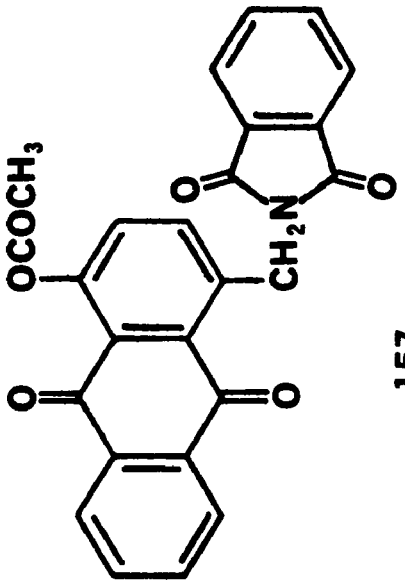

100
80
60
40
20
TRANSMITTANCE (%)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400
250
FREQUENCY (cm⁻¹)


CH2Cl
OH
O
O
Cl

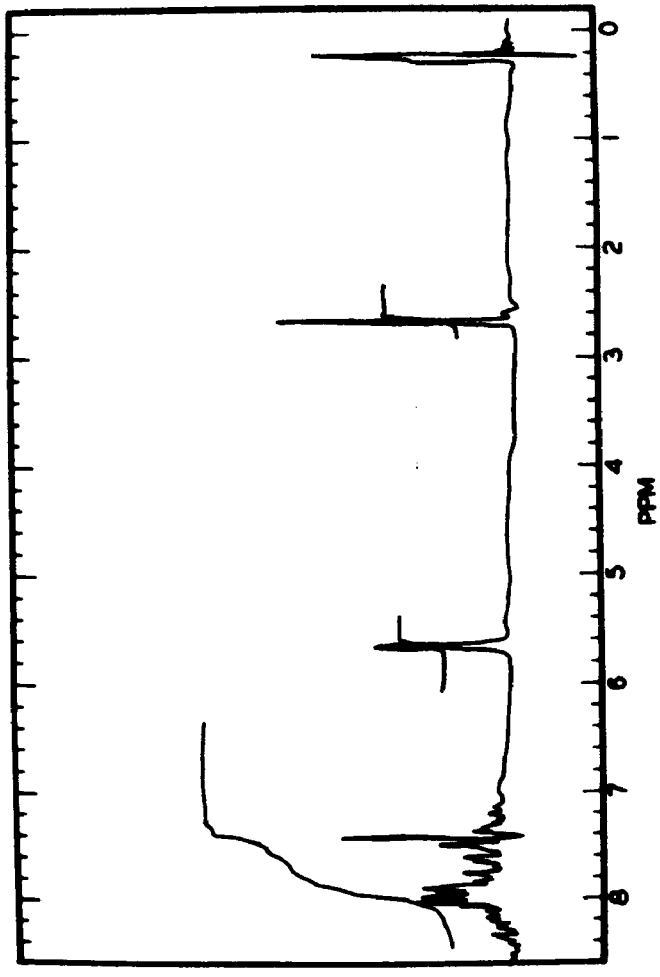
148

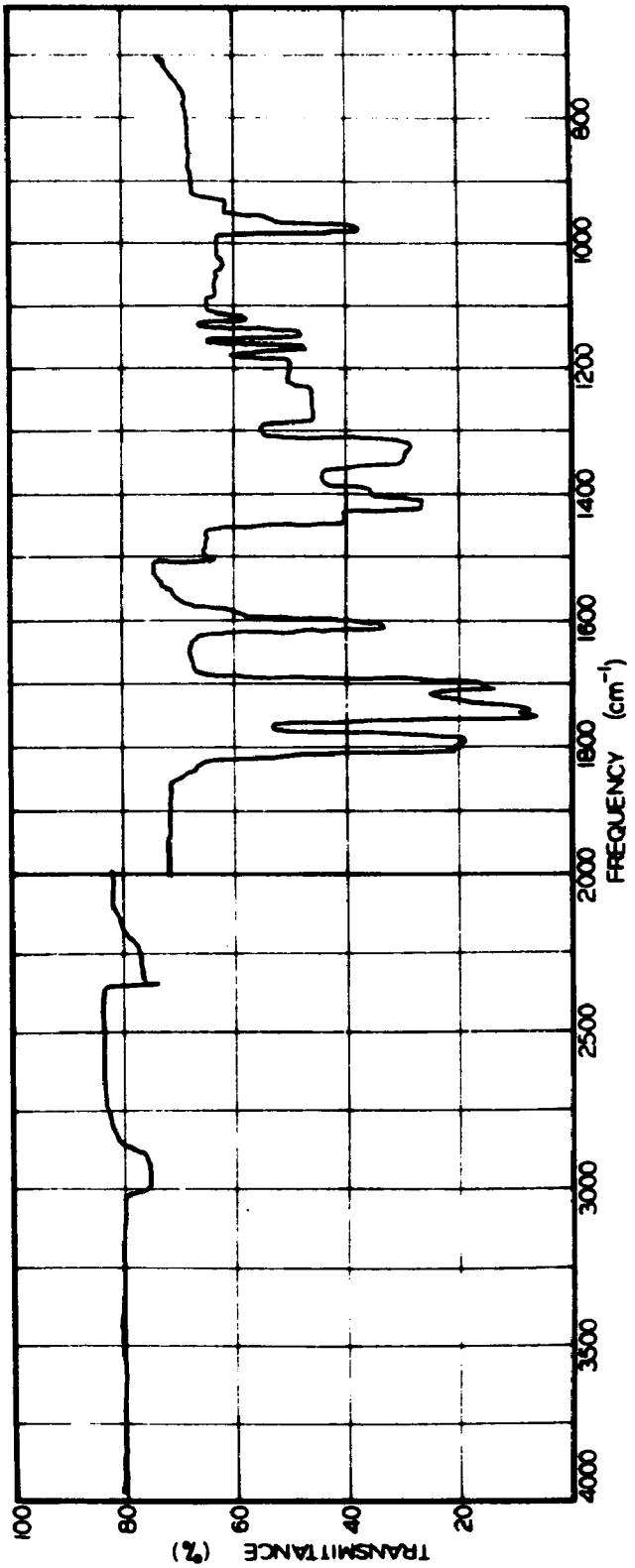

0
1
2
3
4
5
6
7
8
PPM

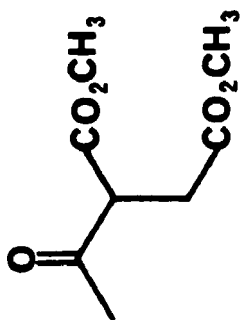

100
80
60
40
20
TRANSMITTANCE (%)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400
250
FREQUENCY (cm⁻¹)


OCOCH3
CH2N
O
O
O
O

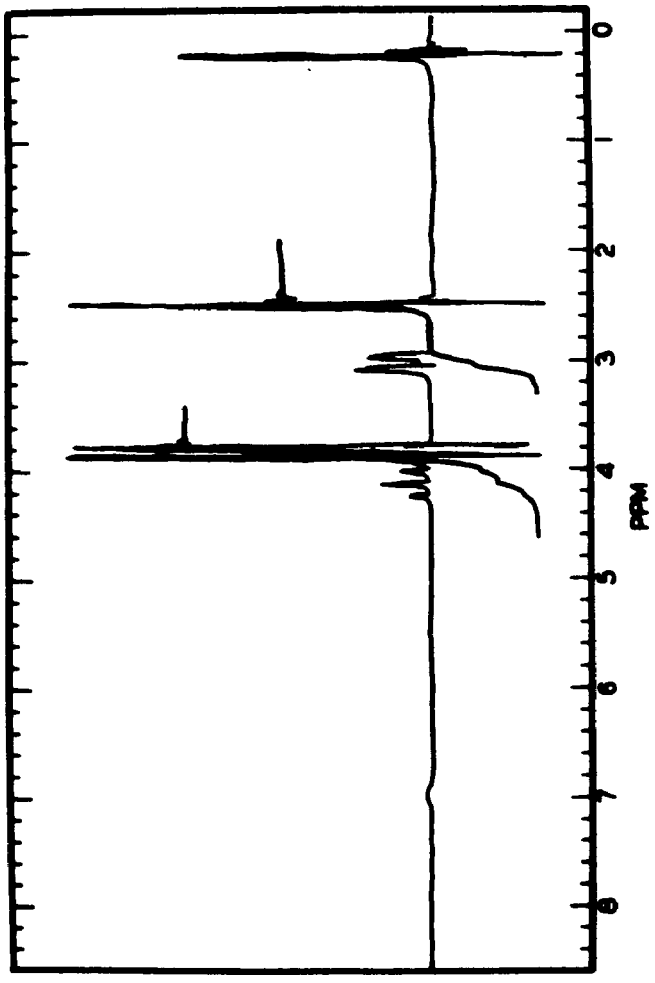
157

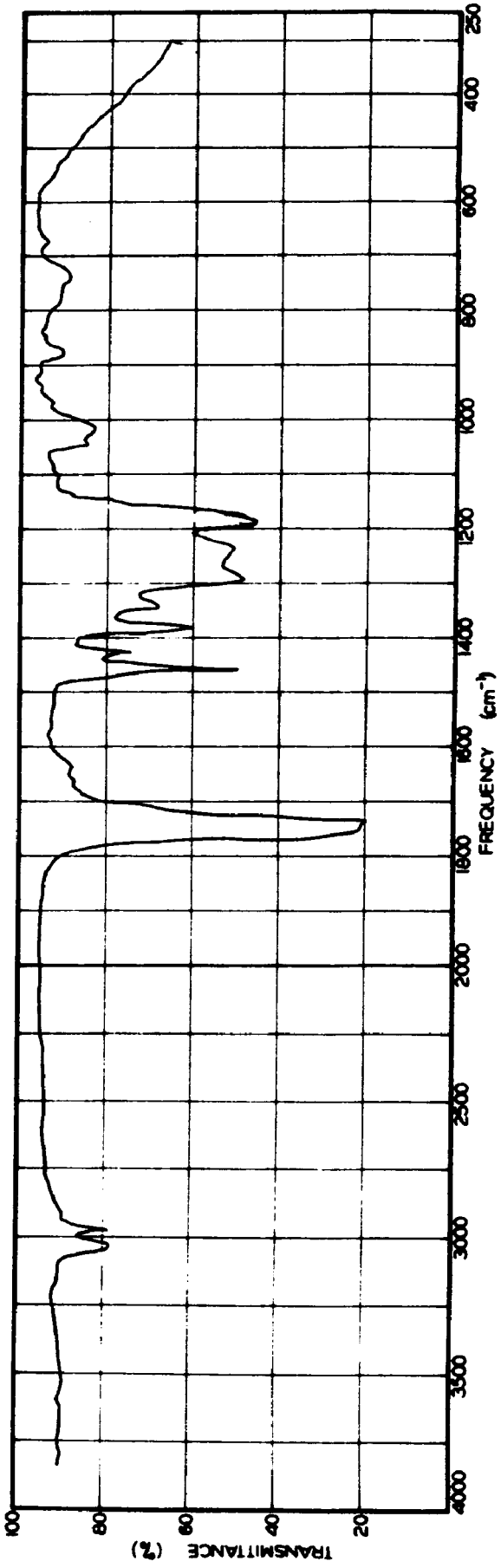

0
1
2
3
4
5
6
7
8
PPM

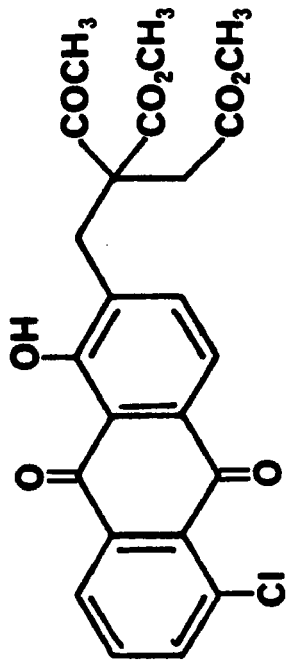

100
80
60
40
20
TRANSMITTANCE (%)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
FREQUENCY (cm⁻¹)


CO2CH3
CO2CH3
O

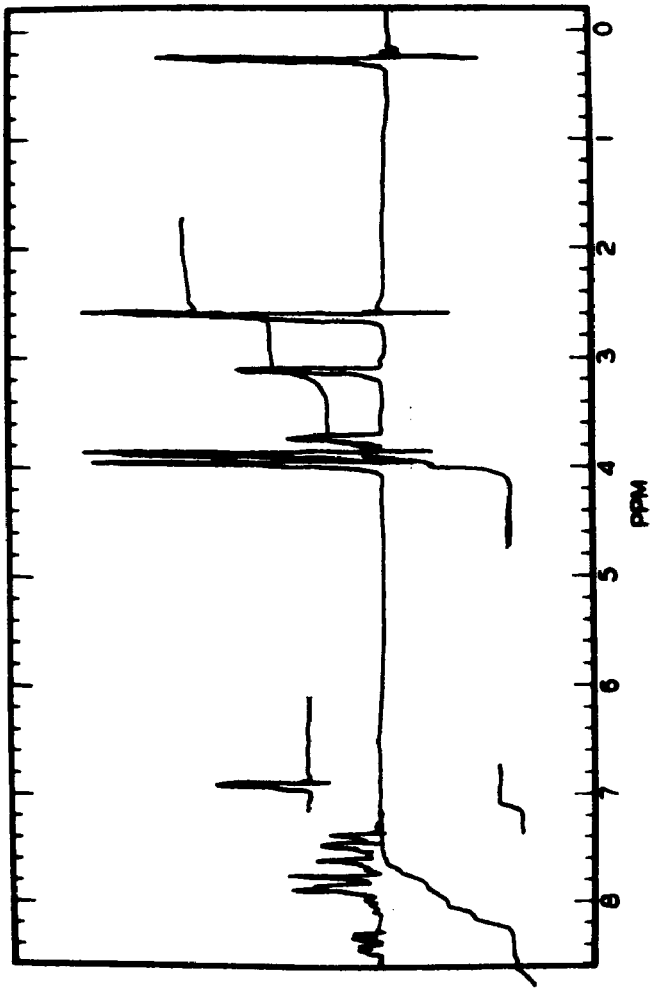
166

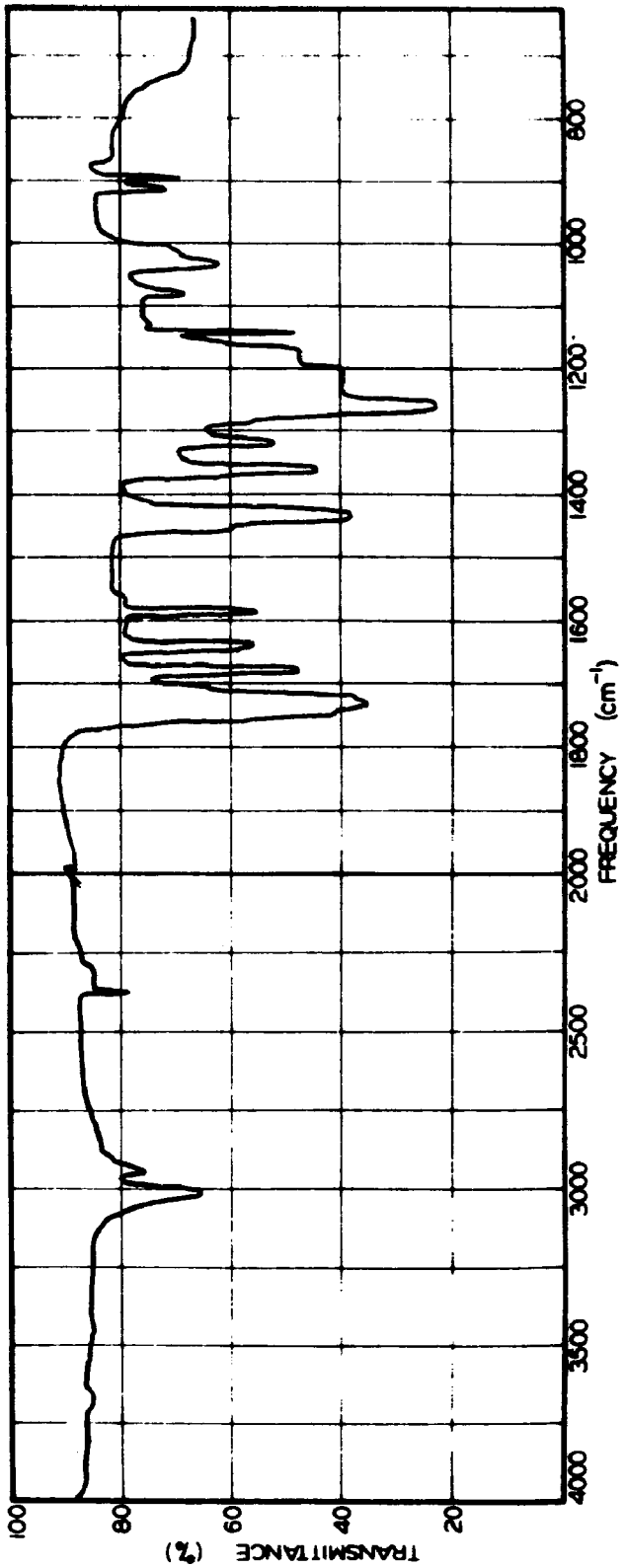

0
1
2
3
4
5
6
7
8
PPM

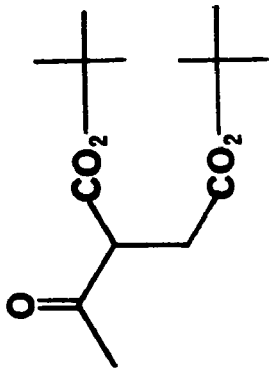

100
80
60
40
20
TRANSMITTANCE (%)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400
250
FREQUENCY (cm⁻¹)


COCH3
CO2CH3
CO2CH3
OH
O
O
Cl

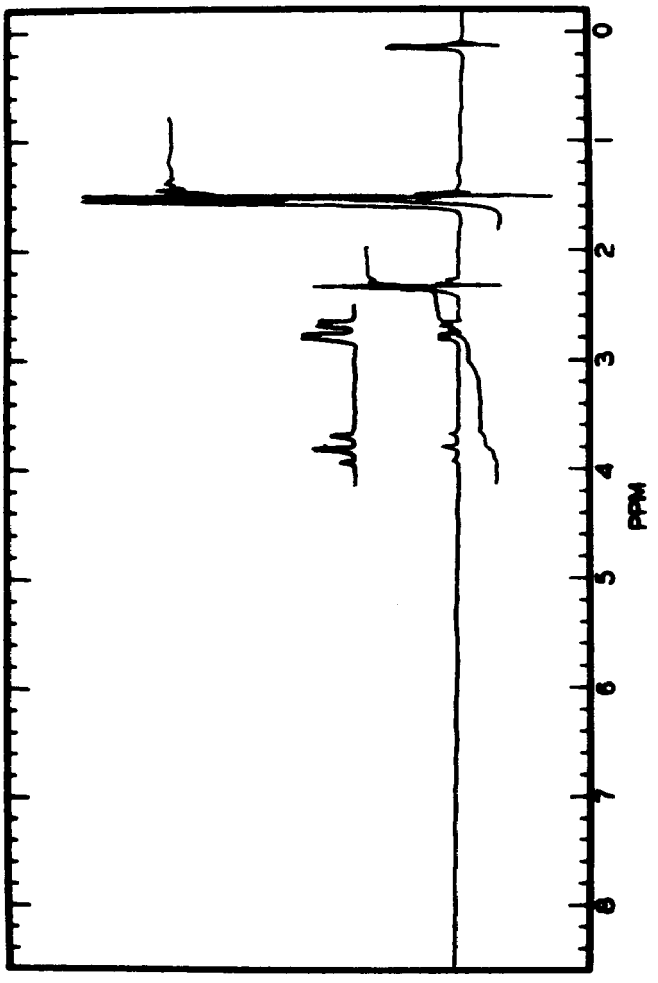
168

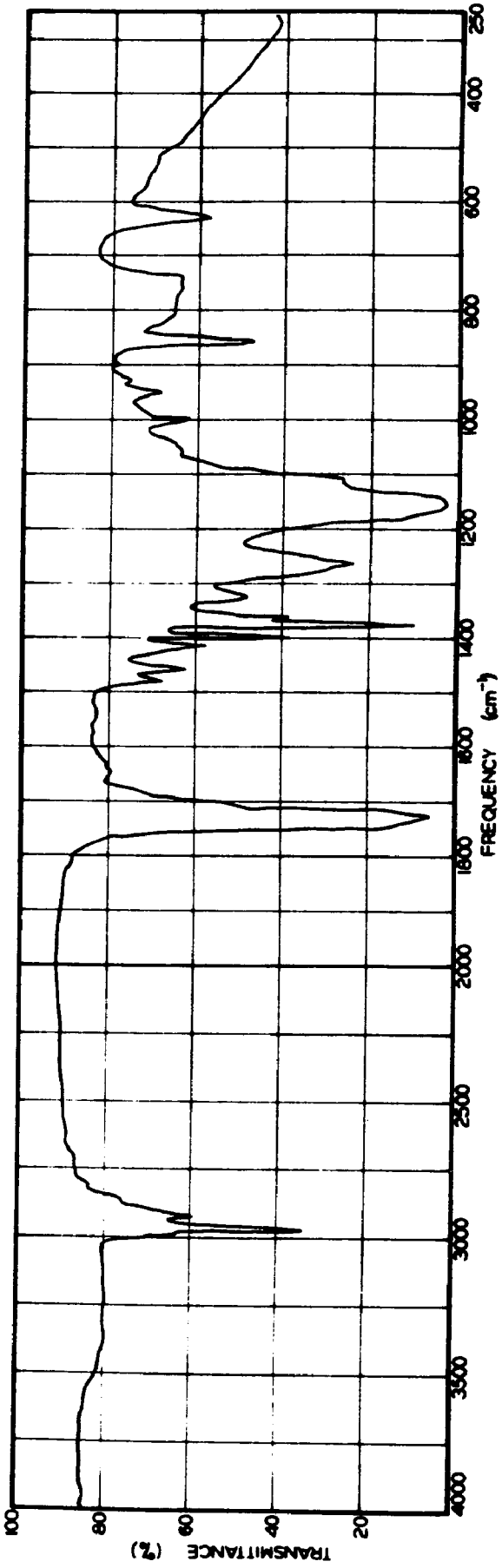

0
1
2
3
4
5
6
7
8
PPM

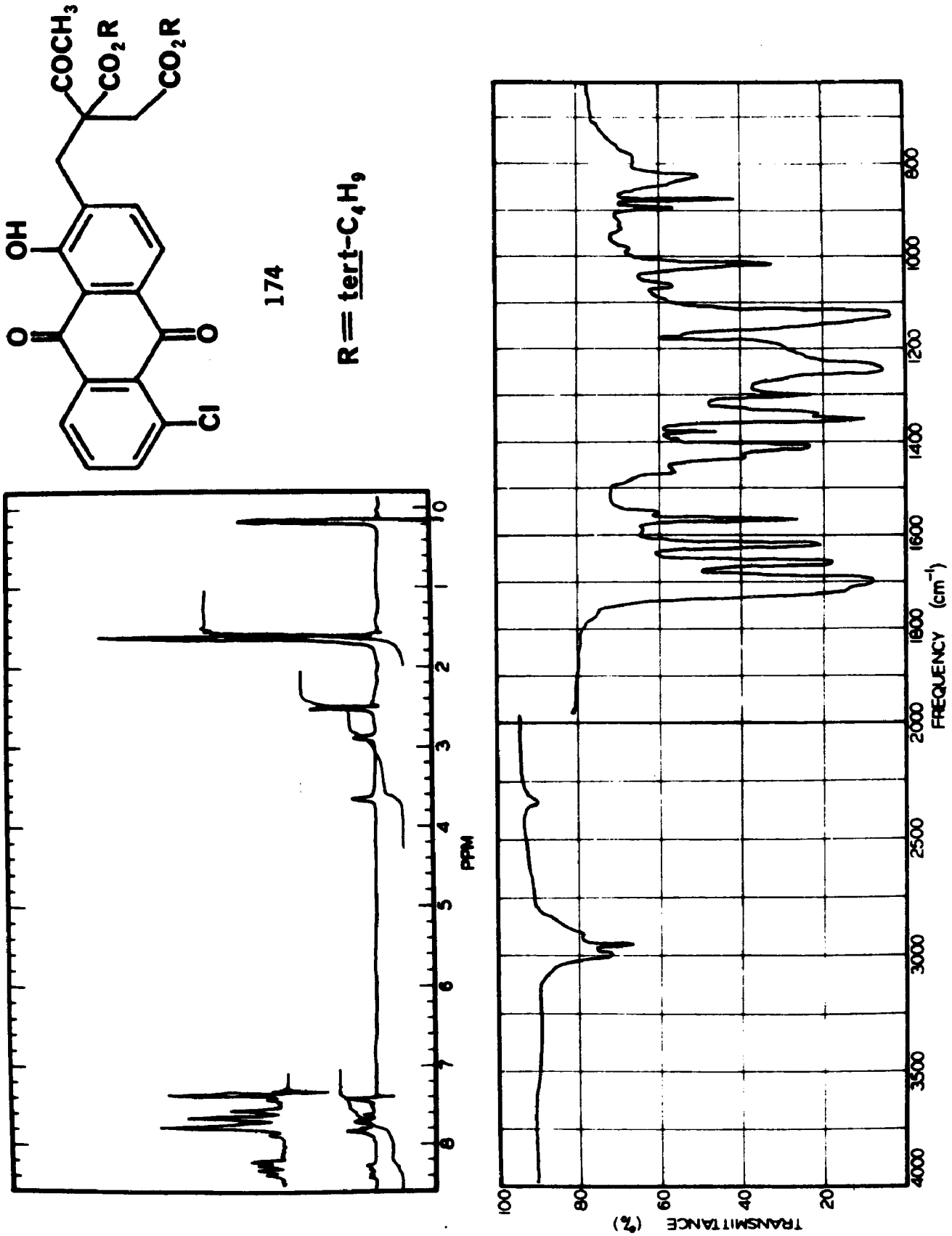

100
80
60
40
20
TRANSMITTANCE (%)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
FREQUENCY (cm-1)

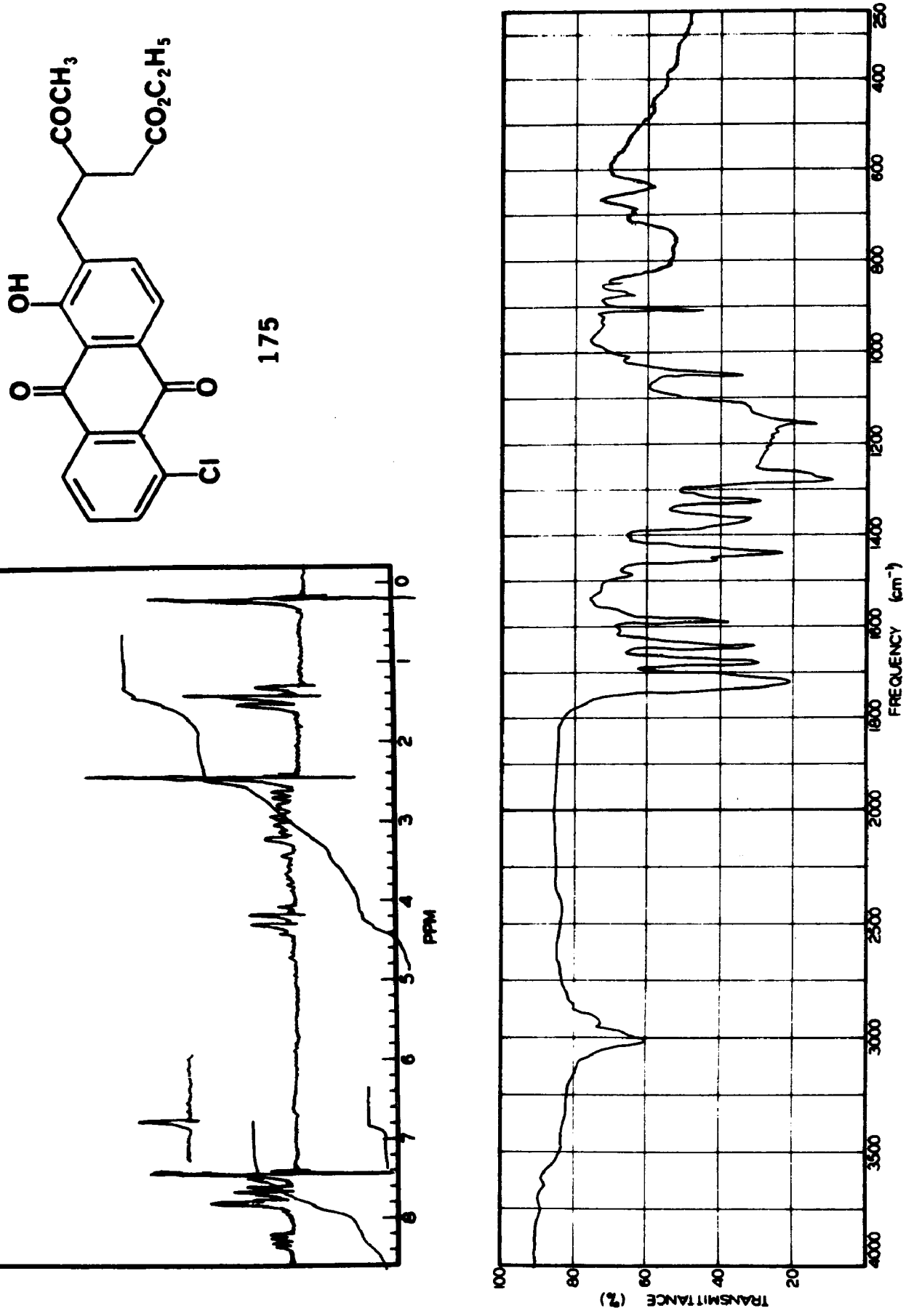

CO2
CO2
O

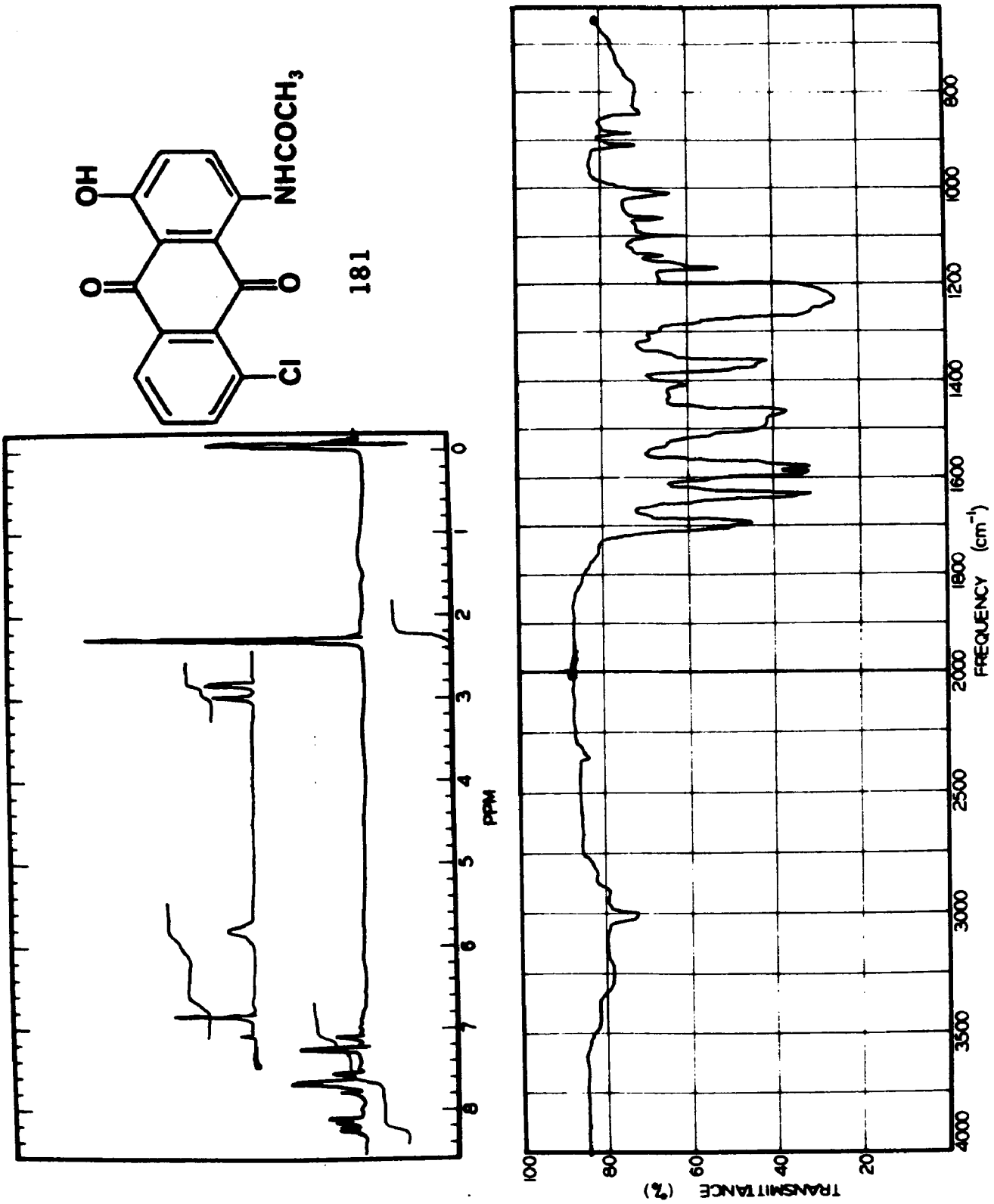
173

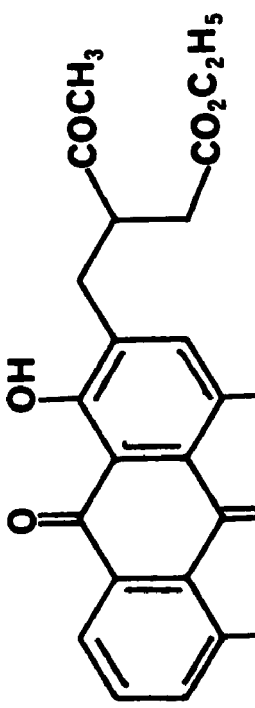

0
1
2
3
4
5
6
7
8
PPM


100
80
60
40
20
TRANSMITTANCE (%)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400
250
FREQUENCY (cm⁻¹)

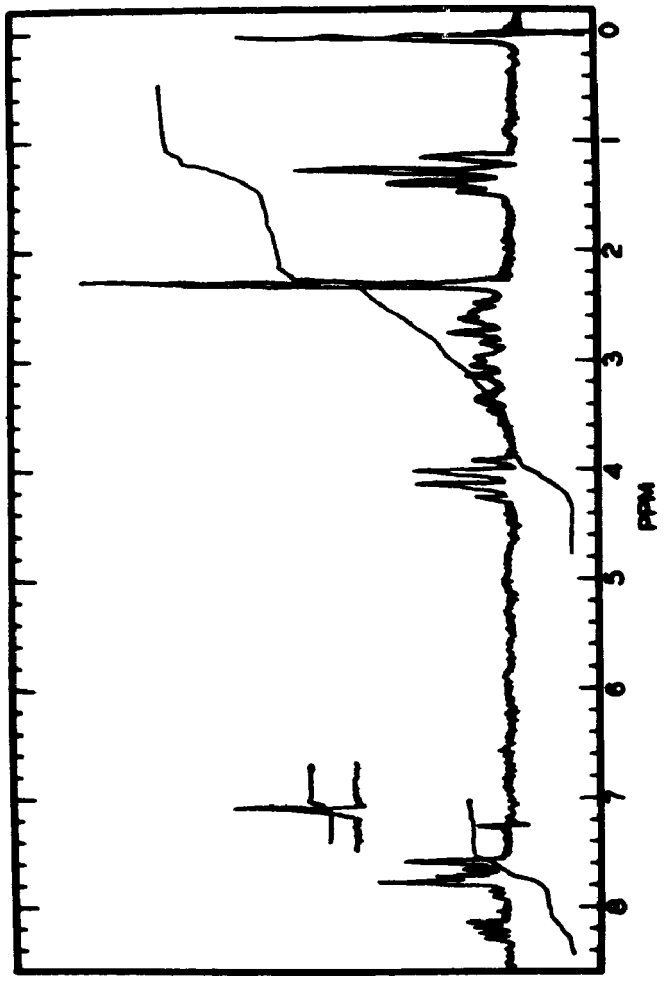

COCH3
CO2R
CO2R
OH
O
O
Cl
174
R = tert-C4H9
PPM
TRANSMITTANCE (%)
FREQUENCY (cm-1)

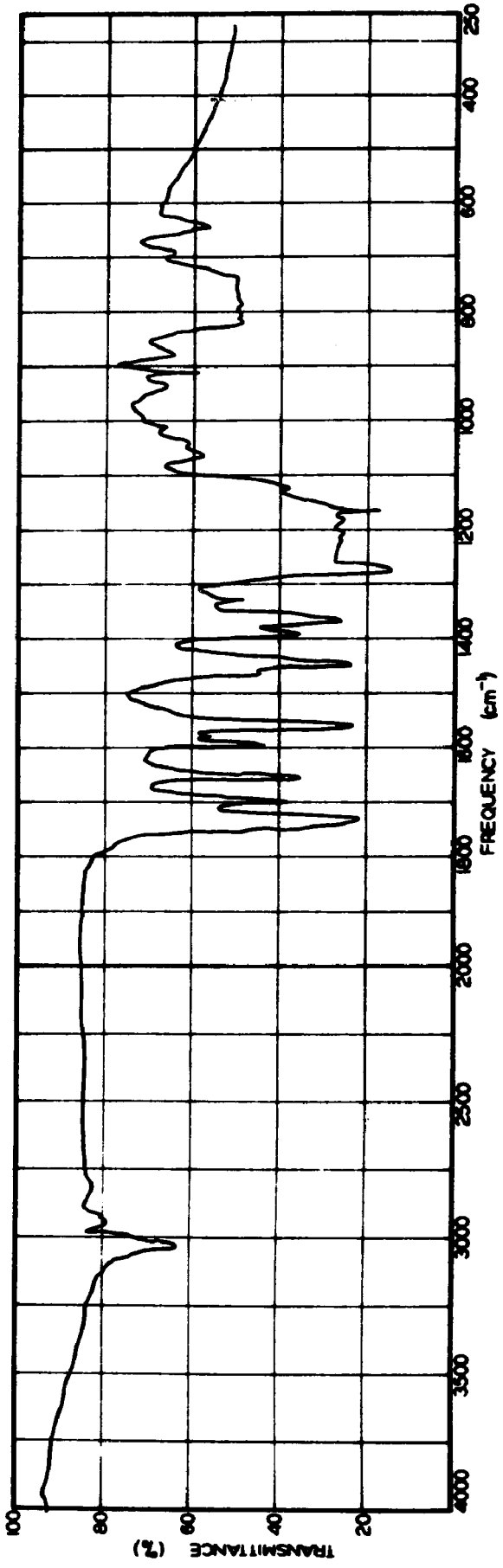

COCH3
CO2C2H5
OH
O
O
Cl
175
PPM
TRANSMITTANCE (%)
FREQUENCY (cm-1)

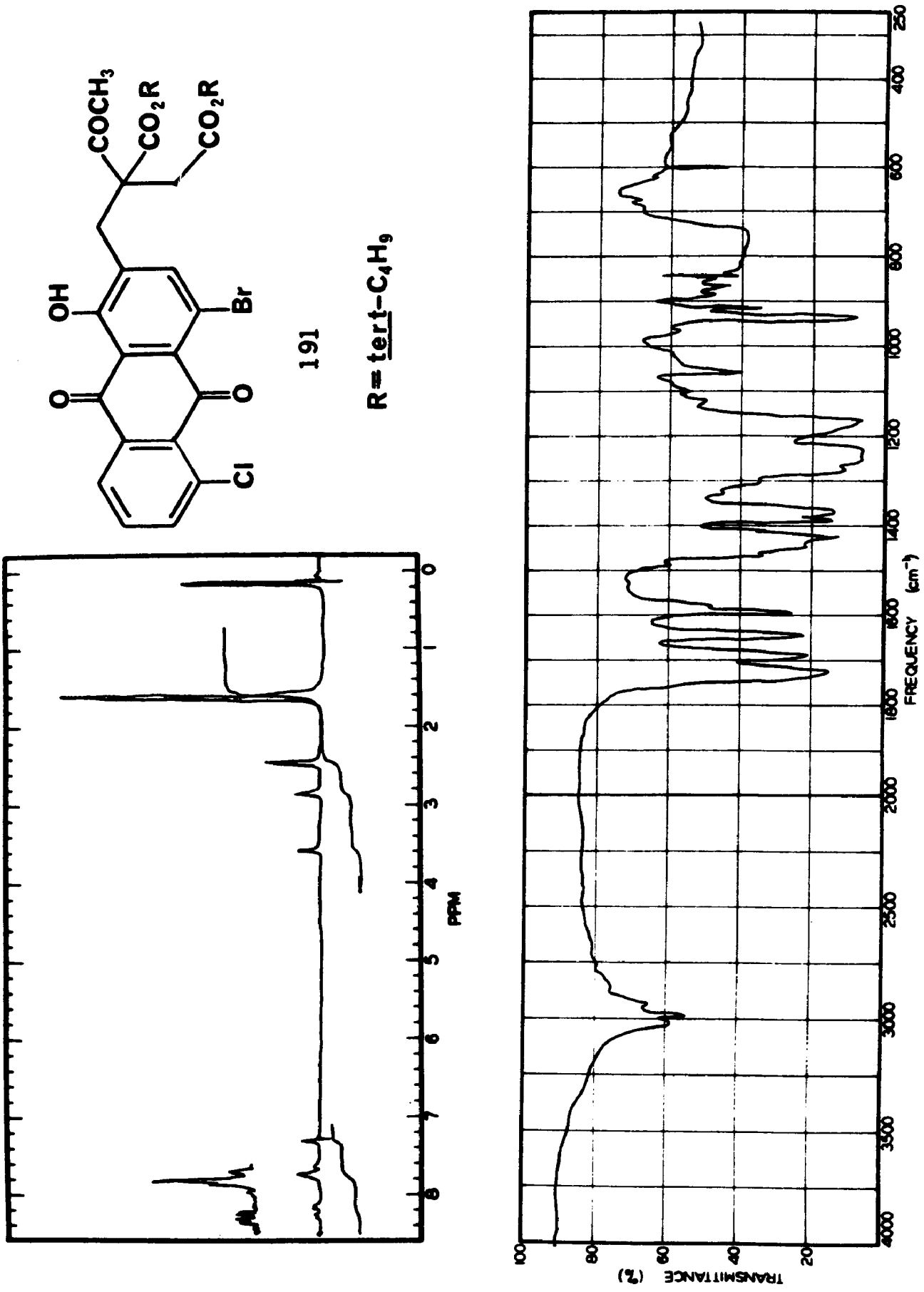

OH
NHCOCH3
O
O
Cl
181
PPM
0
1
2
3
4
5
6
7
8
TRANSMITTANCE (%)
100
80
60
40
20
FREQUENCY (cm-1)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800

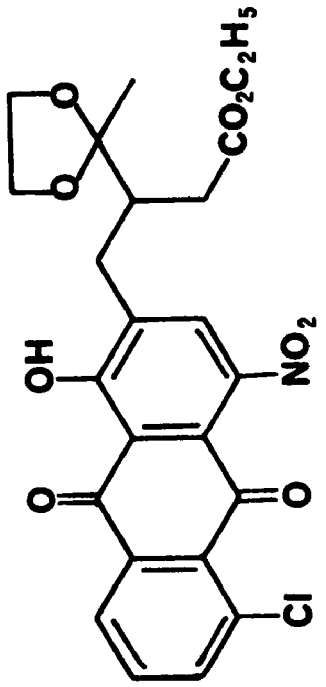

COCH3
CO2C2H5
OH
NO2
O
O
Cl

189

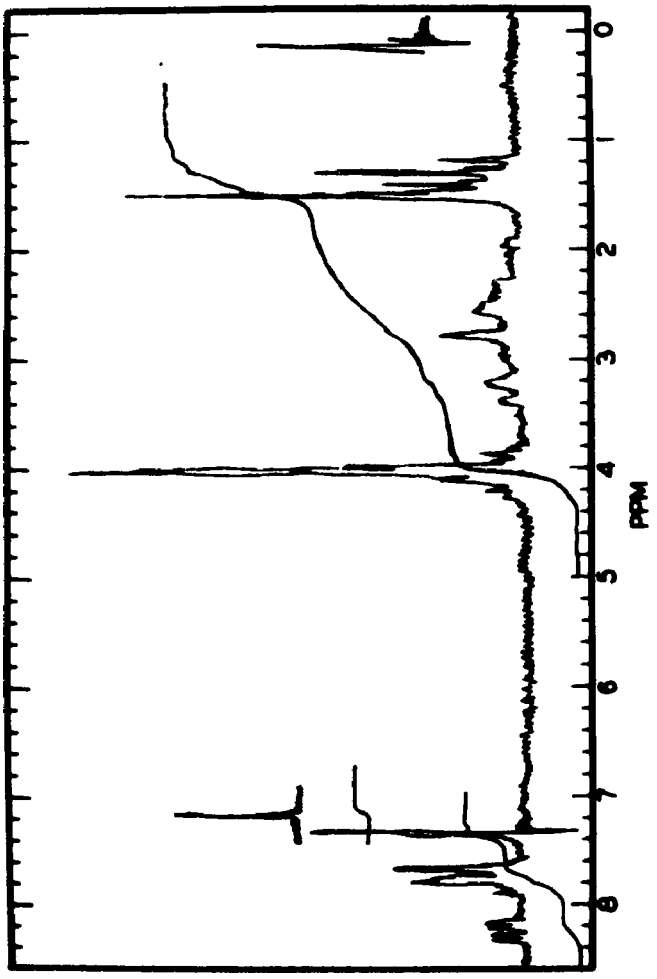

PPM
0
1
2
3
4
5
6
7
8

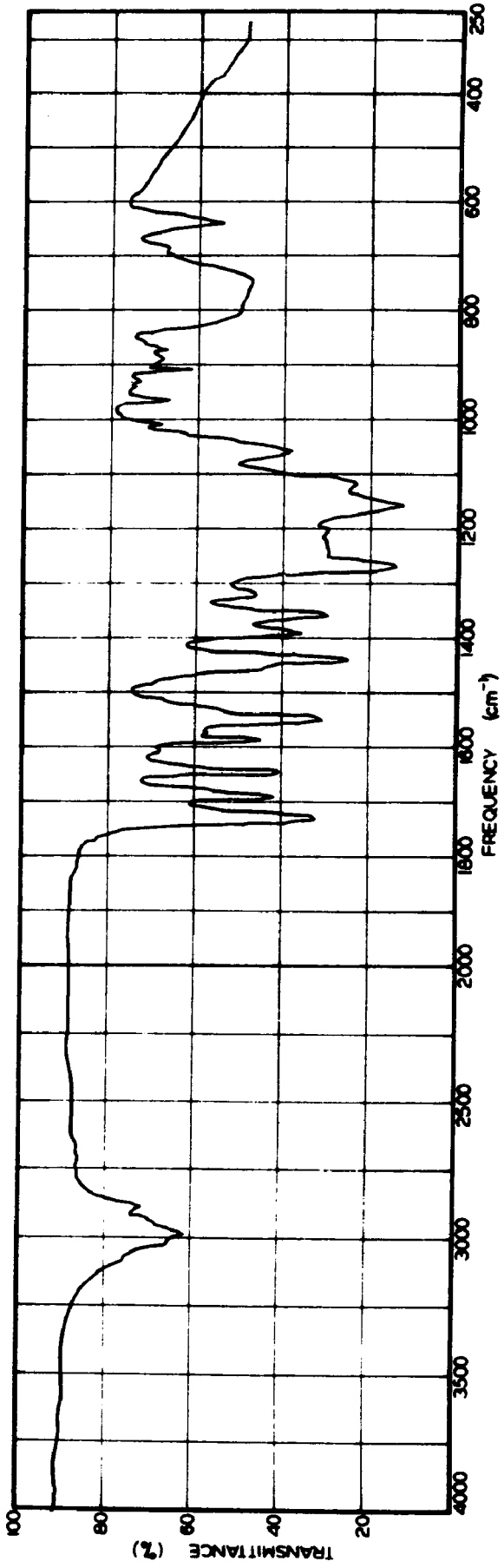

TRANSMITTANCE (%)
100
80
60
40
20
FREQUENCY (cm-1)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400
250

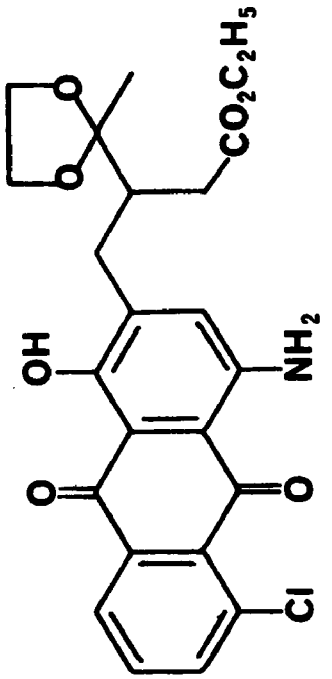

COCH3
CO2R
CO2R
OH
Br
O
O
Cl
191
R = tert-C4H9
PPM
TRANSMITTANCE (%)
FREQUENCY (cm-1)


$CO_2C_2H_5$
OH
NO_2
O
O
Cl

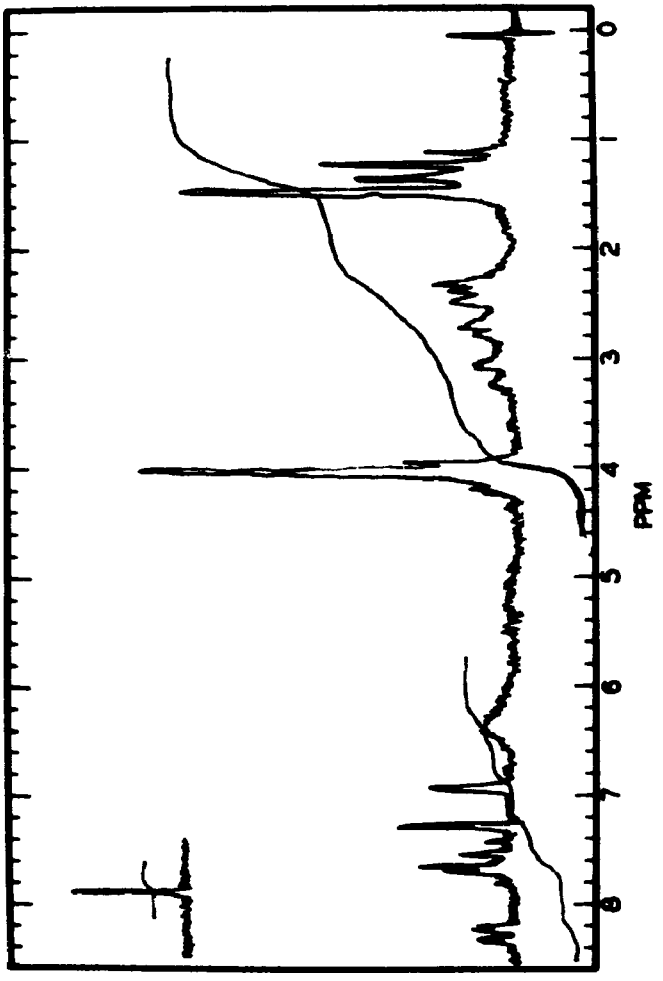
194

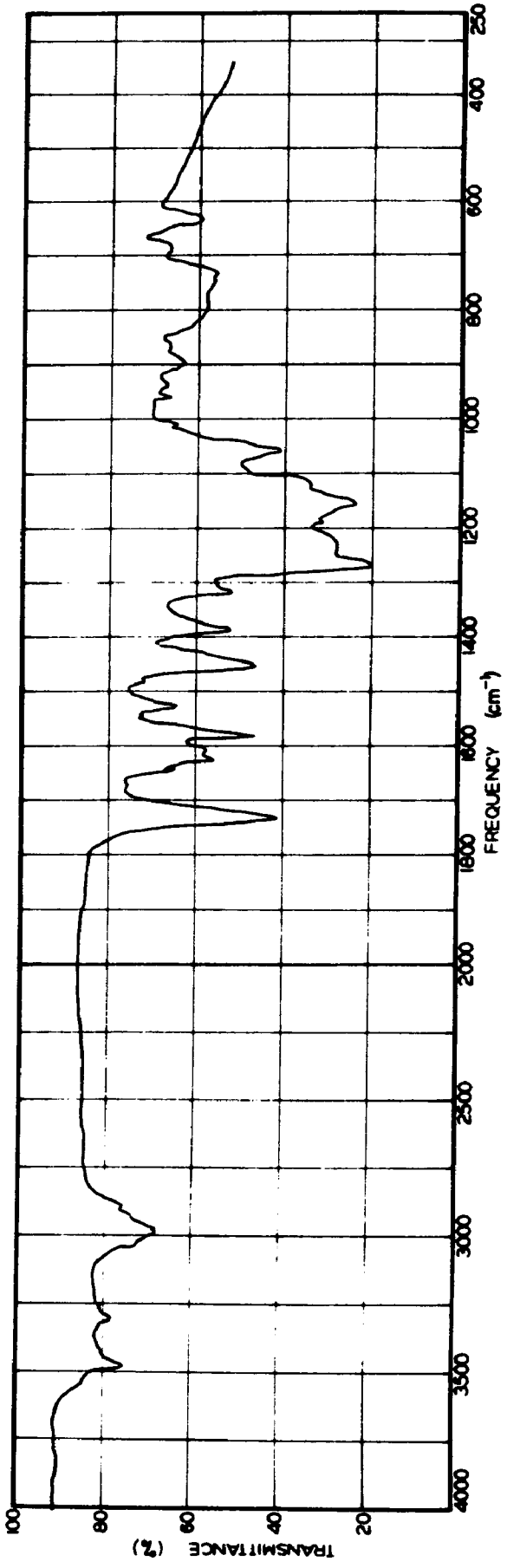

PPM
0
1
2
3
4
5
6
7
8

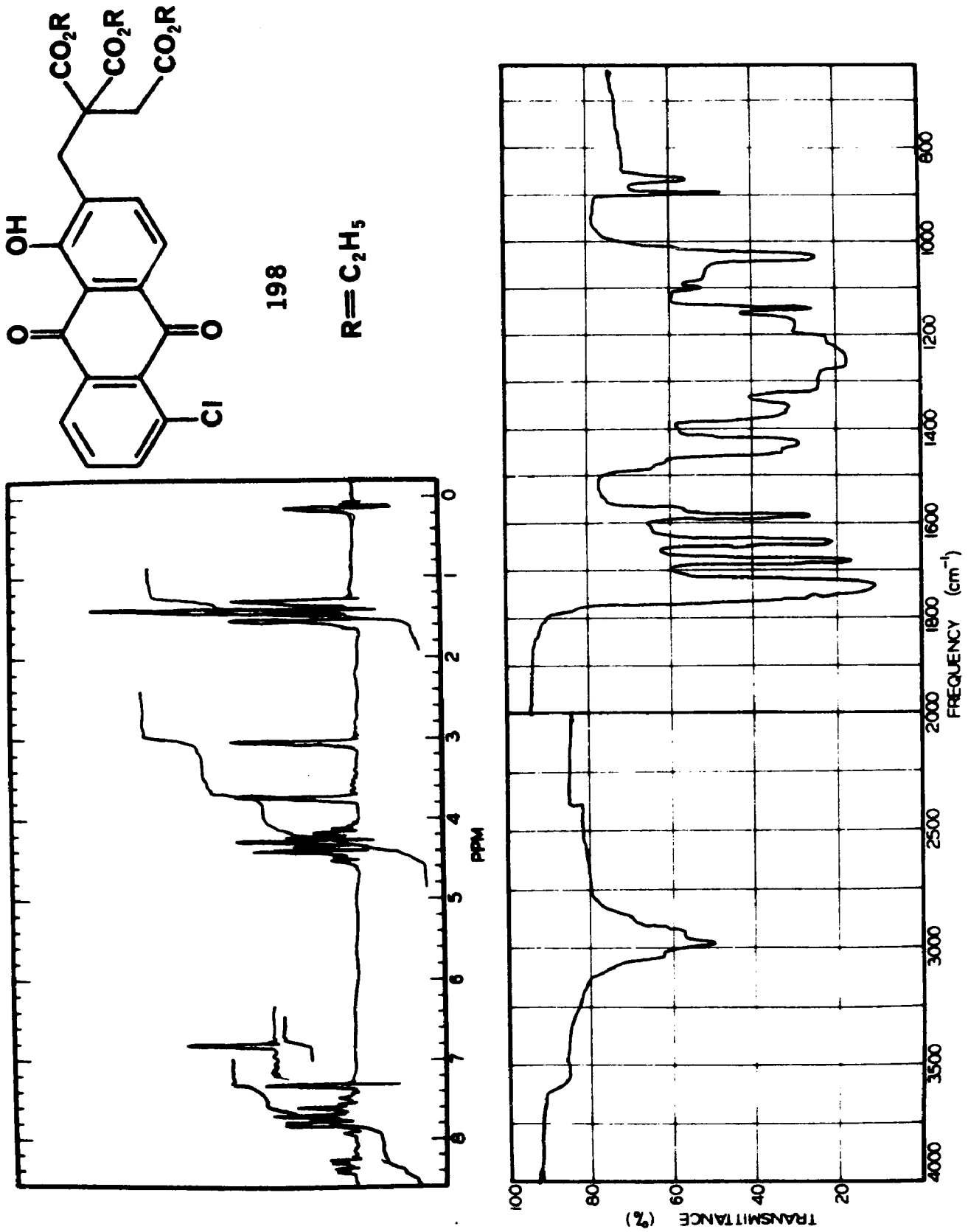

TRANSMITTANCE (%)
100
80
60
40
20
FREQUENCY (cm^{-1})
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400
250

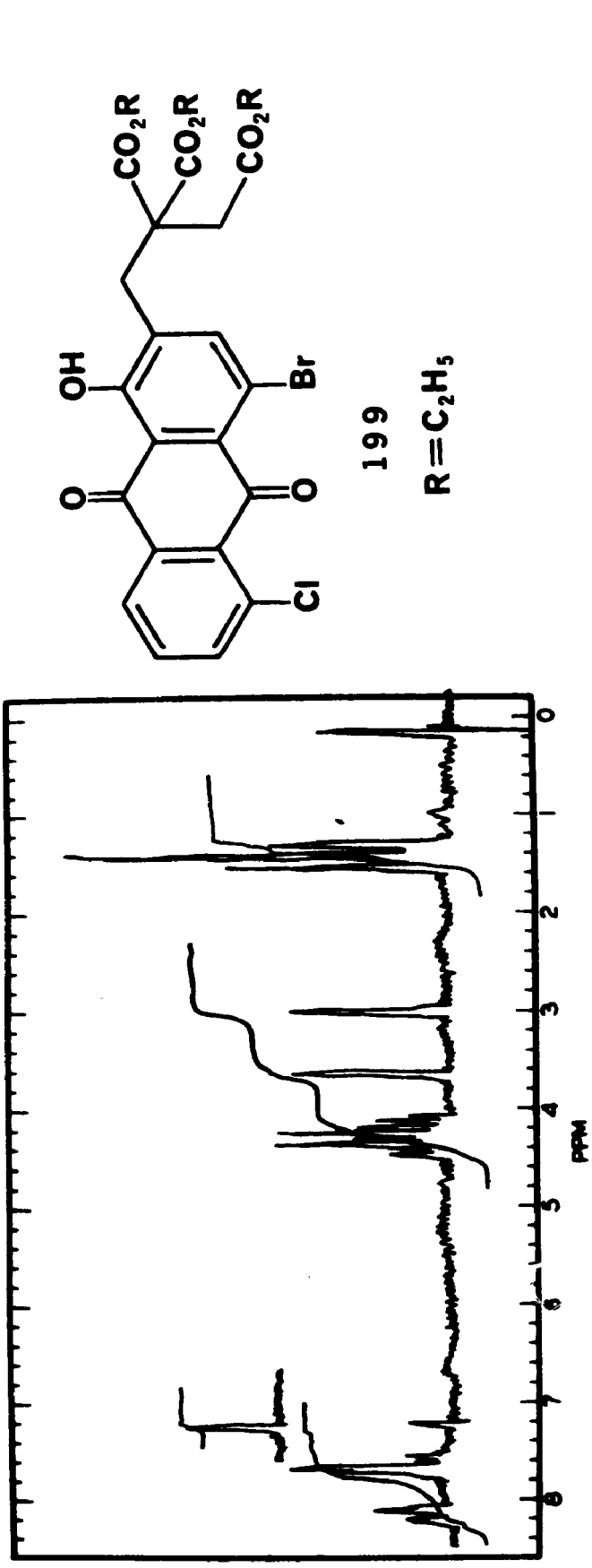

$CO_2C_2H_5$
O
O
OH
NH_2
O
O
Cl

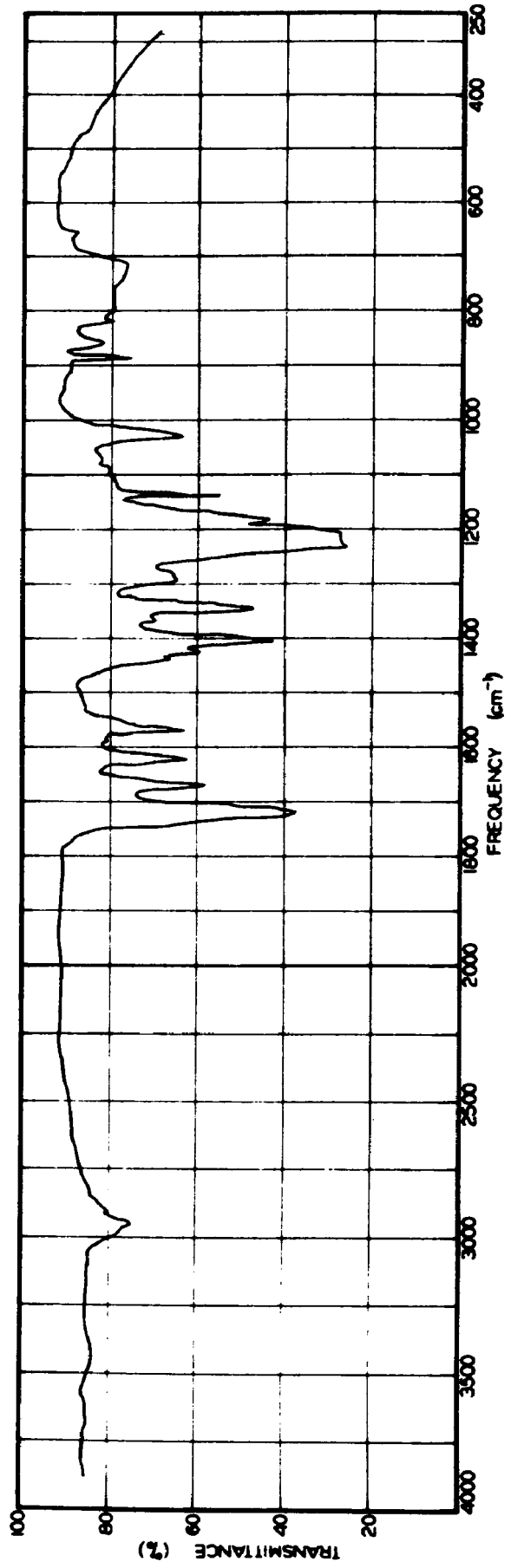
195

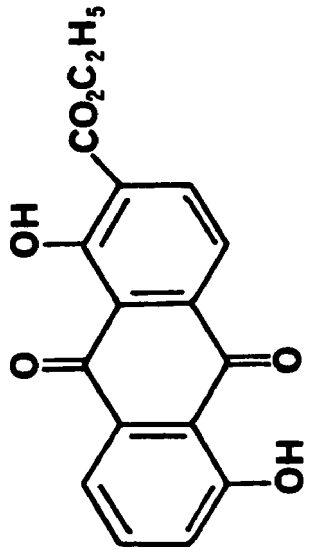

PPM
0
1
2
3
4
5
6
7
8


TRANSMITTANCE (%)
100
80
60
40
20
FREQUENCY (cm⁻¹)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400
250

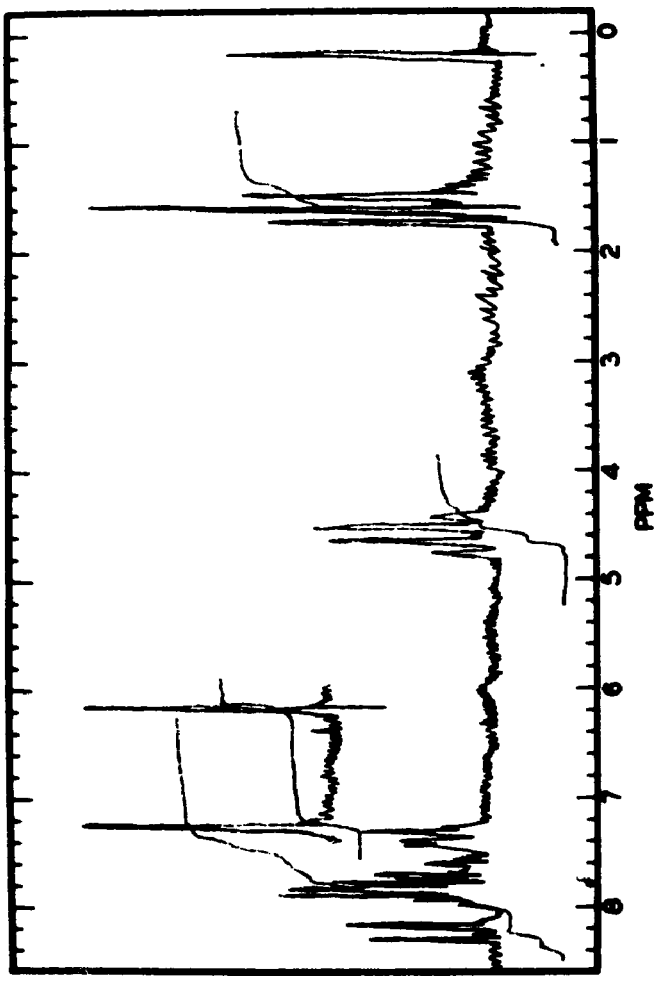

CO2R
CO2R
CO2R
OH
O
O
Cl
198
R=C2H5
PPM
TRANSMITTANCE (%)
FREQUENCY (cm-1)

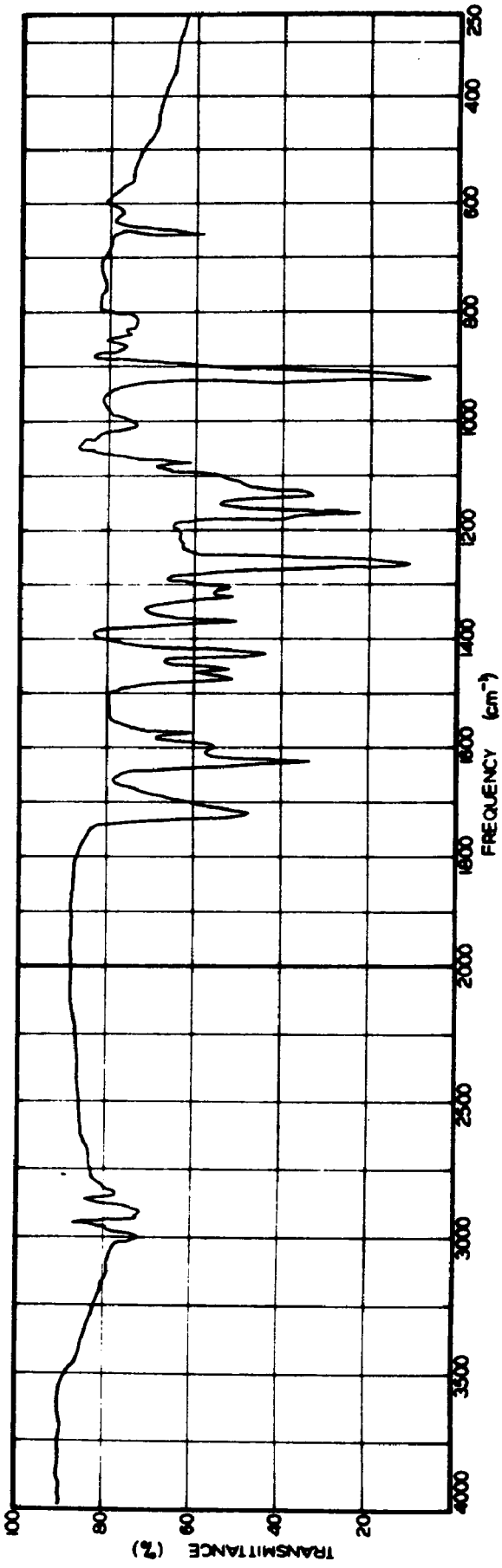

CO2R
CO2R
CO2R
OH
Br
O
O
Cl
199
R=C2H5
PPM
0
1
2
3
4
5
6
7
8

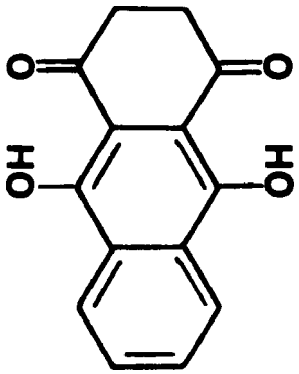

TRANSMITTANCE (%)
100
80
60
40
20
FREQUENCY (cm-1)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400
250


CO2C2H5
OH
O
O
OH

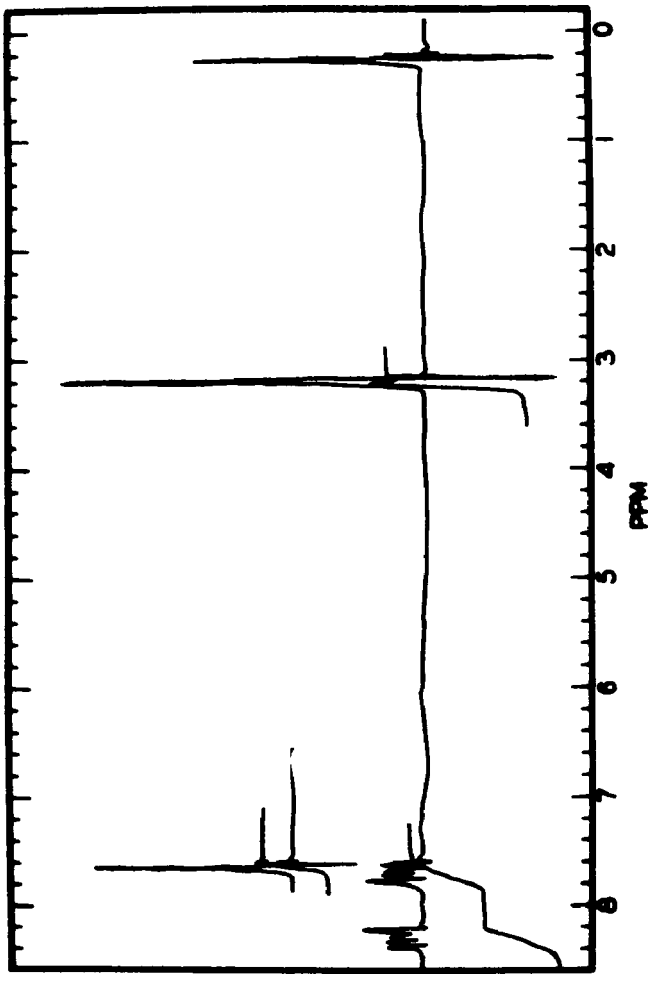
203


PPM
0
1
2
3
4
5
6
7
8


TRANSMITTANCE (%)
100
80
60
40
20
FREQUENCY (cm⁻¹)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400
250


O
O
OH
OH

229


0
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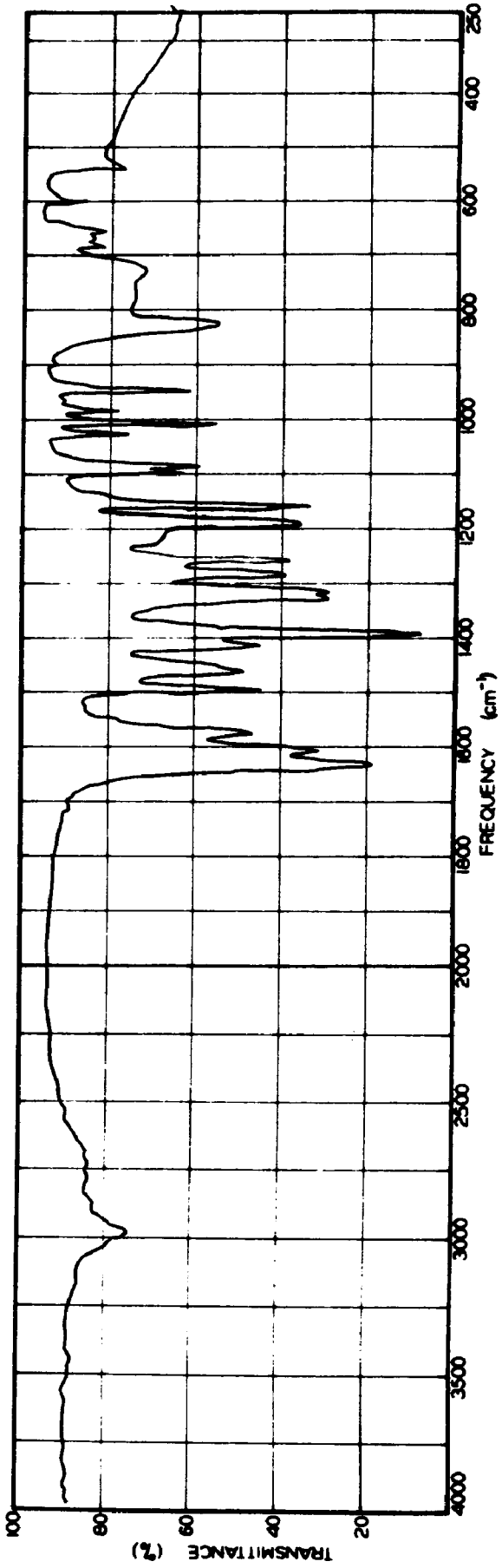
8
PPM


100
80
60
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TRANSMITTANCE (%)
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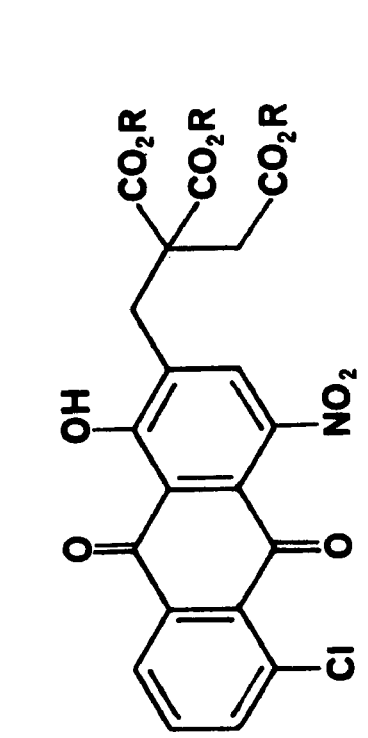
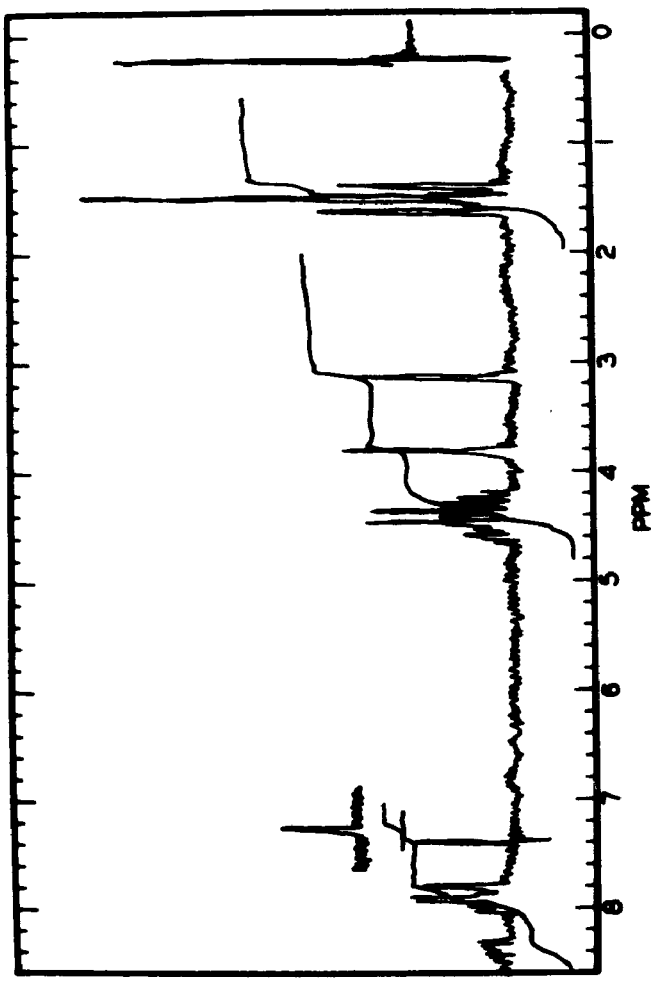
FREQUENCY (cm⁻¹)


CO2R
CO2R
CO2R
OH
NO2
O
O
Cl

232

R = C_2H_5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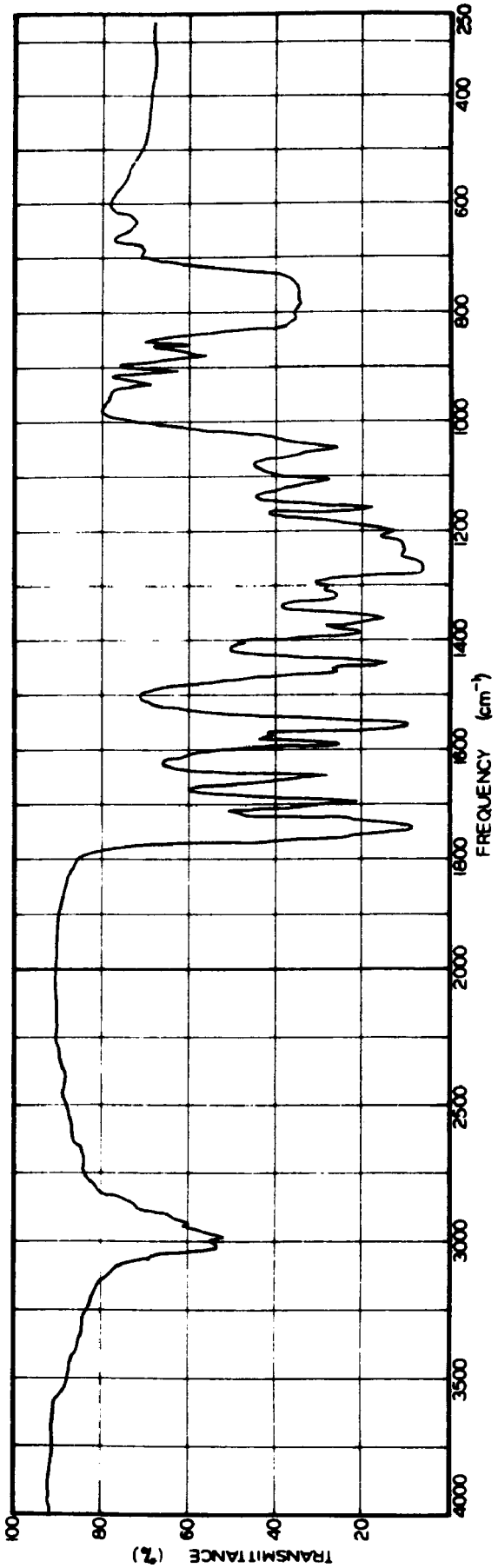
PPM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TRANSMITTANCE (%)
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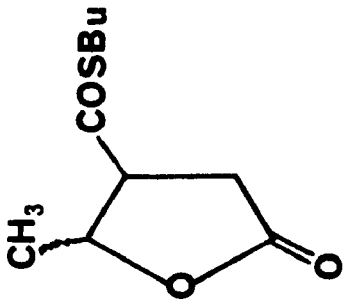
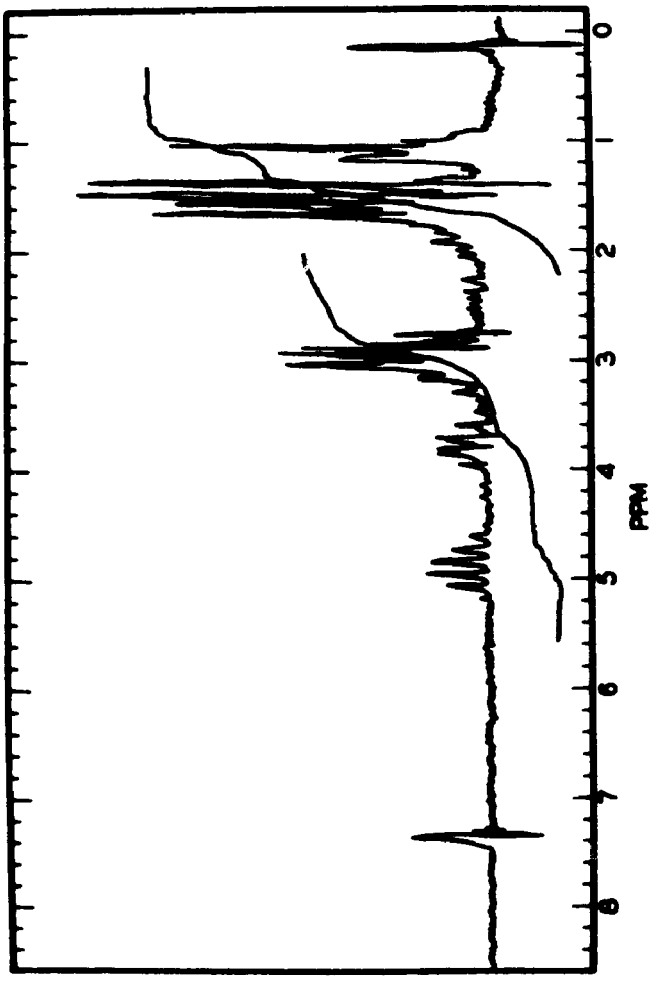
FREQUENCY (cm⁻¹)


COSBu
CH3
O
O

243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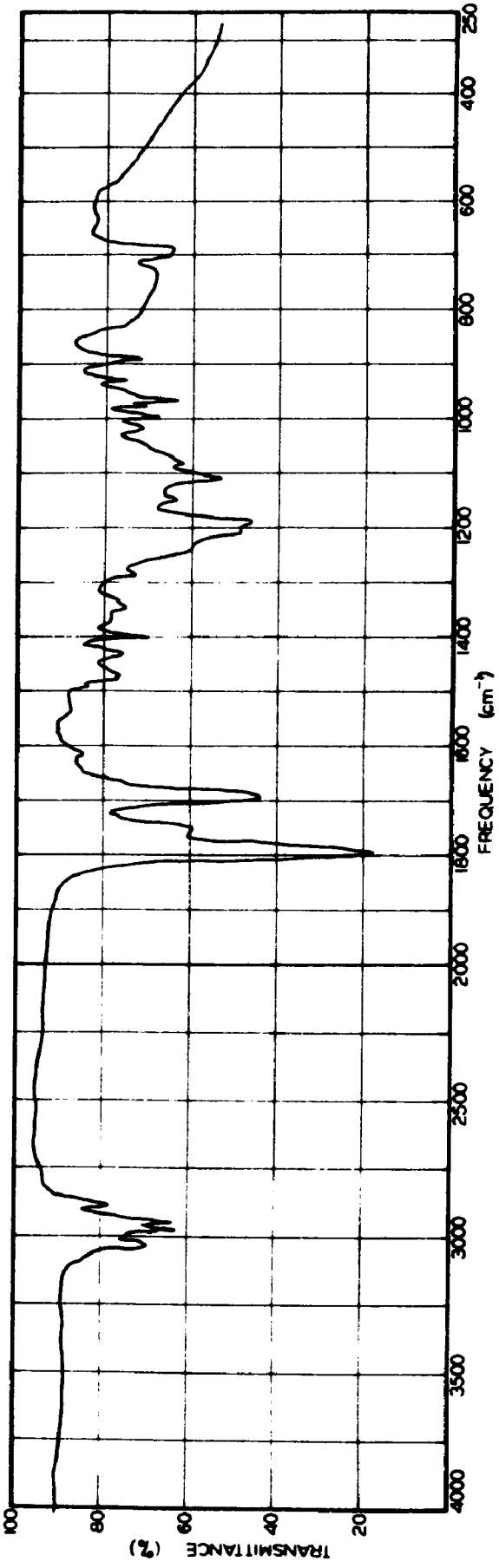
PPM


TRANSMITTANCE (%)
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FREQUENCY (cm⁻¹)

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