ATTEMPTED ASYMMETRIC SYNTHESIS OF LACTOBACILLIC ACID

BY

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[redacted]

In the name of the Father,
and of the Son,
and of the Holy Spirit.

To my wonderful mother with love.

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F. F. Z. Georges

1973

ABSTRACT

This research work has been planned with the intention of proving the absolute configuration of lactobacillic acid. During the course of this work, attempts have been made to synthesize *cis*-2-carboxycyclopropane-1-acetic acid as a suitable resolvable material. As the results were not satisfactory, the synthesis of *cis*-2-carboxycyclopropane-1-propionic acid has been alternatively attempted by ring opening of bicyclo-[4.1.0]-heptan-2-one without much success.

Attempts to resolve or prepare bicyclo-[4.1.0]-heptan-2-one optically active are also reported.

On the other hand, a complete scheme is described for the possible synthesis of optically active lactobacillic acid.

If only bicyclo-[4.1.0]-heptan-2-one can be resolved or prepared optically active, this described scheme can be applied smoothly to the synthesis of enantiomeric lactobacillic acid.

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INTRODUCTION

Part I :-

Biotin, as a member of the vitamin B-complex, is known to be one of the essential nutrients in the growth of some bacterial species. It is normally provided with the other nutrients in the bacterial cultures. It was observed (1), however, that some unsaturated fatty acids exerted a marked sparing action on the biotin requirements of certain lactic acid organisms, a strange phenomenon which attracted some chemists and biologists to investigate the apparent possible resemblance between the biological functions of these fatty acids and biotin.

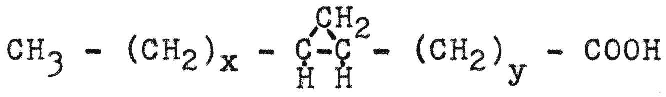
In 1950, Klaus Hofmann and Robert A. Lucas investigated (2) the chemical nature of the fatty acids of Lactobacillus arabinosus, a bacterial species in which this phenomenon was largely observed to be significant. It was possible to isolate an interesting "branched chain" fatty acid whose X-ray diffraction pattern indicated a chain length in the range of a C_{18} acid. The pattern was clearly distinguishable from those of known C_{18} fatty acids.

On hydrogenation, one mole of hydrogen was absorbed to give a solid fraction and a liquid one. X-ray studies on the solid fraction indicated a C_{19} saturated fatty acid, and mixed melting point determinations confirmed that fraction to be nonadecanoic acid. The liquid fraction was shown tobe a mixture of methyloctadecanoic acids.

On the other hand, a strange resistance of the newly discovered fatty acid towards potassium permanganate was noted. It also remained unchanged upon exposure to monoperphthalic acid. Treatment with hydrogen bromide solution in glacial acetic acid resulted in the formation of a new bromine-containing group of saturated acids (3).

The inconsistent behavior of the acid toward oxidation and addition reactions pointed to the presence of a cyclopropane ring somewhere in the molecule; this conclusion was further supported by the infrared absorption maximum at 9.8 microns, which is characteristic of cyclopropane rings (2).

Structure I was proposed for this newly discovered fatty acid, which was assigned the name "lactobacillic acid" in view of its first isolation from a Lactobacillus species.



$$CH_3 - (CH_2)_x - \overset{CH_2}{\underset{H}{C}-\underset{H}{C}} - (CH_2)_y - COOH$$

I

At this stage the ring position of lactobacillic acid was not yet established. Structures with the ring in the 9,10 and 11,12 positions were considered likely (4) because of their relation to the monoethenoid fatty acids (9-octadecenoic and 11-octadecenoic acids) which occur in bacterial lipids.

In order to elucidate this point, and to have a closer look at the stereochemistry of lactobacillic acid, four long-chain fatty acids containing the cyclopropane ring were synthesized : racemic *cis*- and *trans*-9,10-methyleneoctadecanoic acids and racemic *cis*- and *trans*-11,12-methyleneoctadecanoic acids.

On comparison of the racemic cis and trans acids with lactobacillic acid, it was found that *cis*-11,12-methyleneoctadecanoic acid is similar to, but not identical with, lactobacillic acid.

These findings shed some light on the

possible positions of the cyclopropane ring in lactobacillic acid, which was then confirmed by degradative studies (5) to be in the 11,12 position of octadecanoic acid.

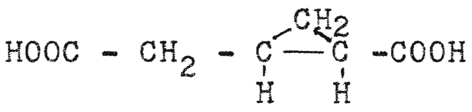
In addition to this, lactobacillic acid being the cis isomer rather than the trans one was confirmed by the fact that racemic *trans*-11,12-methylene-octadecanoic acid failed to support growth of *Lactobacillus delbrueckii* (6) whereas racemic *cis*-11,12-methyleneoctadecanoic acid exhibited approximately one-half the growth promoting activity of natural lactobacillic acid for the same organism (7).

This observation pointed also to either D- or L-*cis*-11,12-methyleneoctadecanoic acid as the configurational structure for lactobacillic acid. Since the latter has an unobservably small optical rotation, the absolute configuration of this acid remained unknown.

Since a knowledge of the absolute configuration of lactobacillic acid is important for the understanding of the mode of action of the enzyme responsible for the biosynthesis of this acid. We undertook studies to establish the absolute configuration of lactobacillic acid. These studies are presented on the following pages of this thesis.

Part II :-

For an asymmetric synthesis, it is logical to think of starting with a simple substance whose absolute configuration is known or which is easily established by relating it to a compound of known absolute configuration. Cis-2-carboxycyclopropane-1-acetic acid II seemed, at first, the most likely precursor. Hydrogenation of the resolved material would lead to D- or L-α-methyl glutaric acid (8), according to which we would thus establish the absolute configuration of our starting material.

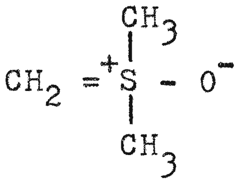


II

Synthesis of cis-2-carboxycyclopropane-1-acetic acid was attempted by treating an ethereal solution of diethyl glutaconate with diazomethane in ether in the presence of cuprous chloride as a catalyst; but the reaction was unsuccessful. The yield was so poor that it was not possible to isolate any product.

Since the original requirement was the cis-compound, our attention was then directed to starting with a ring system so that it would give us the cis-diacid by ring opening.

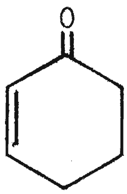
Reaction of an unsaturated ring with diazomethane seemed now less attractive, compared with Corey's method (9) of utilizing the reactivity of dimethyloxosulfonium methylide III toward α,β-unsaturated ketones in the syntheses of cyclopropane rings.



$$\mathrm{CH_2} = {}^{+}\mathrm{S}(\mathrm{CH_3})_2 - \mathrm{O}^{-}$$

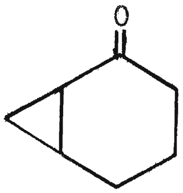
III

Starting with the readily available cyclohexanone, the conjugated monounsaturated ketone IV was made by a procedure described previously (10).



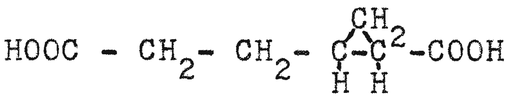
IV

Treatment of IV with dimethyloxosulfonium methylide in DMSO under nitrogen afforded bicyclo-[4.1.0]-heptan-2-one V in high yield. The absolute configuration of this compound was reported by Hill and Morgan (11) in a procedure devised to establish the absolute configuration of 2-cyclohexenol.



V

Exposure of this ketone to basic potassium permanganate should lead, in principle, to the diacid VI, with propionic acid moiety in position 2 instead of acetic acid, an alternative which should not make much difference since it can be related to D- or L-α-methyladipic acid (12) instead of D- or L-α-methylglutaric acid for the diacid II.

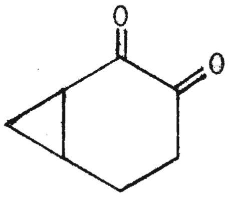


$$\mathrm{HOOC - CH_2 - CH_2 - \underset{H}{C}\overset{CH_2}{-}\underset{H}{C} - COOH}$$

VI

Unfortunately the yield was not high enough to serve for resolution and subsequent steps; besides, isolation of the product was attended by . a great deal of inconvenience due to the presence of a vast amount of manganese dioxide. Although it was suggested by Fieser and Fieser (13) that acidification of the reaction mixture and passing in sulfur dioxide to reduce MnO_2 to the soluble sulfate, which would seem a good way of getting rid of MnO_2, it was feared that a work-up with strong acid might open the cyclopropane ring.

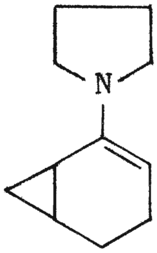
An alternative was to convert the bicyclic ketone V into the bicyclic diketone VII by a method (14) employing selenium dioxide as an oxidizing agent; ring opening would then be achieved by means of sodium periodate. Again the difficulty and inconvenience of isolating the reaction product posed the same problem as the potassium permanganate reaction.



VII

Our success in synthesizing the bicyclic ketone V in good yield has prompted us to use it directly rather than to develop alternate routes to the diacid II or VI. The knowledge of the absolute configuration of V would serve equally well to establish the configuration of product lactobacillic acid.

Resolution of V thus appeared to be a necessity as a point of start in the asymmetric synthesis of the optical enantiomers of lactobacillic acid; and since a delicate ketone such as V would require very mild resolution conditions, we therefore thought of resolving it through enamine VIII using D-camphorsulfonic acid as a resolving agent. Unfortunately the results were rather discouraging. Various reaction conditions have been tried between the optically active acid and enamine VIII, but in all cases we obtained a liquid diastereomeric mixture which could not be induced to crystallize by any means.



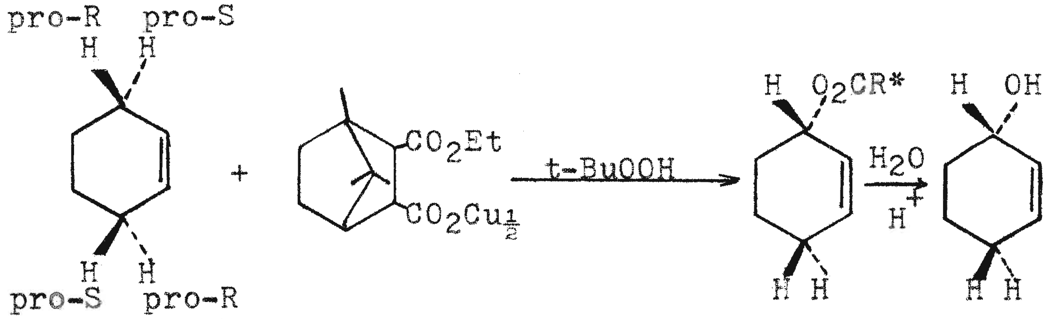
VIII

None of the resolving procedures seemed efficient for resolving this particular ketone without damaging the cyclopropane ring.

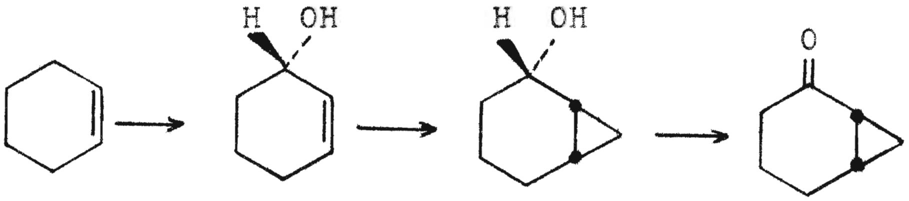
At this point it appeared desirable to explore other possible ways of preparing optically active compounds which could be applied to the preparation of optically active ketone V.

Since synthetic processes, carried out in the abscence of an asymmetric influence, normally lead to racemic products, the implication of an asymmetric reagent in a given synthetic process would be of considerable importance for an asymmetric synthesis to be achieved.

Based on the fact that an asymmetric synthesis is a process in which an achiral unit in the substrate molecule is converted by a reactant into a chiral unit in such a manner that the stereoisomeric products are produced in unequal amounts, Denney has been able to obtain some optically active allylic alcohols using the cupric salt of an optically active acid with the olefin and t-butylhydroperoxide in the following fashion: (15)



Tempted by Denney's success in this synthesis, we felt it was worth our while to try to synthesize ketone V optically active in the following sequence:



For this we had to perform two model experiments; in one of them we used cupric acetate, and in the other one we used the cupric salt of racemic O-methylmandelic acid. We were able to obtain this salt in 98% yield.

When cupric acetate was mixed with t-butylhydroperoxide in cyclohexene and stirred for four days at room temperature, 2-cyclohexenylacetate was obtained in almost a 60% yield based on the starting cupric salt.

On the other hand, when the racemic cupric O-methylmandelic acid was treated in the same manner, the major product was a mixture of 2-cyclohexenone and 2-cyclohexenol with the former being in excess. This was confirmed by comparison of the NMR spectrum of this mixture with the NMR spectra of authentic samples of both materials. The NMR of the crude mixture also showed a considerable amount of aromatic protons.

When this mixture was gas-chromatographed at 130° , a small amount of benzaldehyde was formed indicating the decomposition of either unreacted O-methylmandelic acid or the anticipated ester 2-cyclohexenyl-O-methylmandelate. The latter possibility appeared to be more likely since the cupric salt, when prepared, was washed carefully free of the acid. Yet the yield was not of the desired order to consider the reaction successful, presumably because of the insolubility of the salt in cyclohexene.

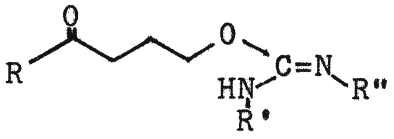
Our efforts in the preparation of optically active 2-cyclohexenol were also extended to biological asymmetric transformations. Enzymes are the chiral reagents in these processes. They are complex optically active proteinoid catalysts which are produced by living organisms. A fundamental property of enzymatic reactions is a high degree of steric specificity. Of particular importance are biochemical asymmetric syntheses which are brought about by enzymes. In many cases the product is nearly optically pure. The method is, however, of limited practical use since dilute solutions are essential and therefore the amounts obtained will be small. Moreover, one enantiomer is always destroyed and it is necessary to find organisms or enzymes which can selectively assimilate the substance without being poisoned.

In 1964, Mosher has reported some stereoselective ketone reductions by actively fermenting yeast (16). Although the method did not prove to be of high stereoselectivity in some cases, it seemed possible to use it to serve our purposes. Unfortunately we were not successful in obtaining the desired optically active alcohol by this method.

The fourth method in our attempts to obtain compound V in an optically active form relates to the kinetic resolution theory. This is interesting from a mechanistic point of view since diastereomeric transition states or intermediates (including complexes and solvates) are the controlling factors in the stereochemical course of the reaction. In these processes the ground state free energies of the reactants for the competing pathways must be identical ($\Delta G^o = 0$). Only the free energies of activation

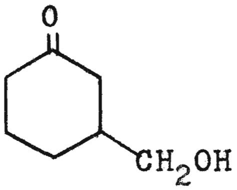
($\Delta G^{\ddagger}$) of the two pathways differ, hence the rates of reaction, k(-) and k(+), of the enantiomers of a racemic substrate, (-A) and (+A), with chiral reagent must differ. This difference becomes experimentally important from the standpoint of kinetic resolution when the reaction in question is incomplete with respect to the racemic substrate. Thus, if the racemic substrate reacts with insufficient chiral reagent for complete conversion to products, the remaining unconverted substrate is enriched in the less reactive isomer and no longer consists of a 50:50 racemic mixture. The same is true if there are equivalent amounts of substrate and reagent, but the reaction is interrupted before it has reached completion.

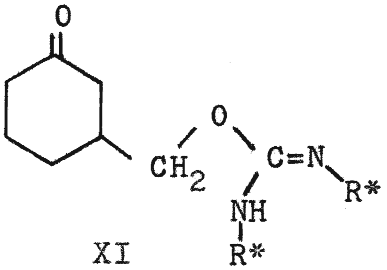
Our idea was based on the use of carbodiimides in the dehydration of γ-hydroxyketones under basic conditions to give cyclopropane-containing ketones and the corresponding urea (17). In such reactions, intermediates such as IX are formed followed by the displacement of the urea molecule. Thus, if an optically



IX

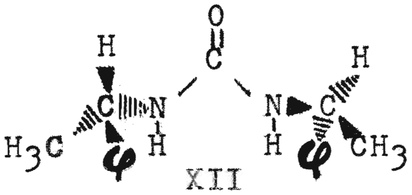
active carbodiimide is reacted with racemic γ-hydroxyketone X, and the reaction was interrupted at a certain time, it might be possible to isolate the intermediate XI as well as the unreacted starting material (if any) which would be enriched in the less reactive isomer, provided that the rates of reaction of both isomers are reasonably different.


X

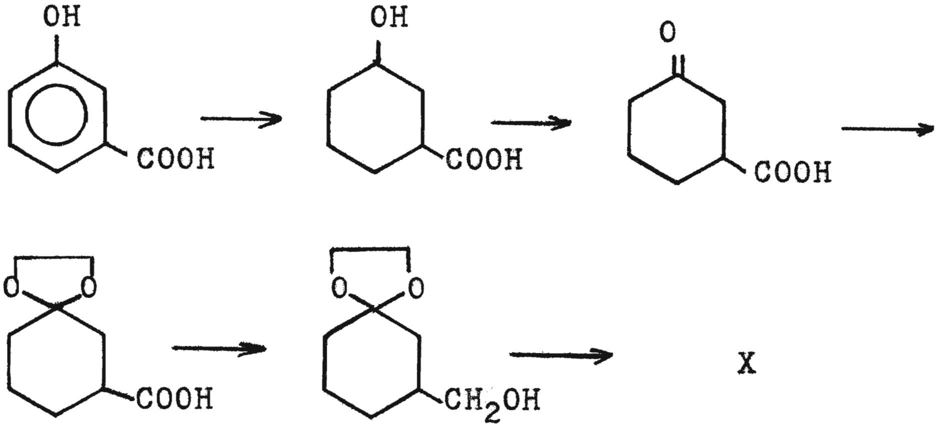

XI

If, on the other hand, both isomers were equally reactive so that no separation would be possible, and if the isolated intermediate was a solid material, we might still be able to separate the diastereomeric intermediate isomers by fractional crystallization.

One way of preparing carbodiimides is the dehydration of the corresponding ureas. For our purpose, we were able to obtain the optically active urea XII by reaction of D-(+)-α-methylbenzylamine with dimethyl


XII

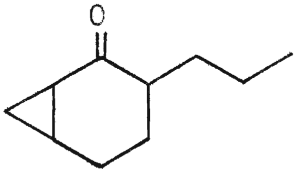
carbonate. Compound X may be obtained from hydrogenation of 3-hydroxybenzoic acid:



Unfortunately we could not continue with this experiment for the lack of time.

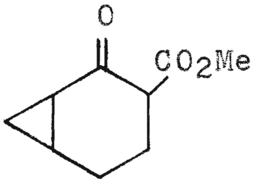
As the time started running out, we then decided to complete the synthesis with racemic ketone V, taking the necessary care as if we were dealing with optically active materials. Once we obtain the racemic lactobacillic acid, the validity of our scheme will be realized and it would then be applicable for future work on optically active compounds.

Two different kinds of transformations had to be performed on ketone V before ring opening can take place. The first thing was to mono-alkylate to ketone XIII, which we attempted by the action of potassium amide and iodopropane in liquid ammonia.

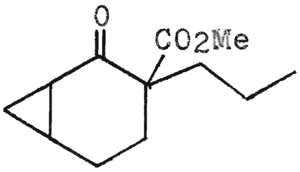


XIII

Although the major product was XIII, it was contaminated with a fair amount of a heavier molecular weight compound which was assumed to be the dialkylated ketone. A better yield of the mono-alkylated compound was obtained by converting V into the β-ketoester XIV, followed by alkylation to XV and then decarboxylation to XIII.

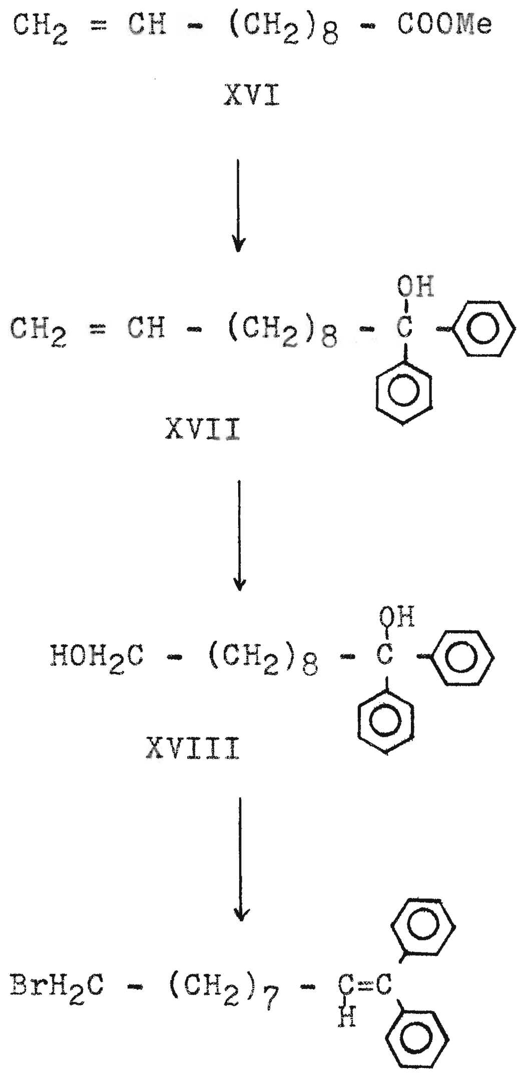


XIV



XV

To conclude our constructing process, we had to prepare a suitable Grignard reagent for the next reaction with ketone XIII. This Grignard reagent was prepared from the ester methyl-10-undecenoate XVI in the following sequence:



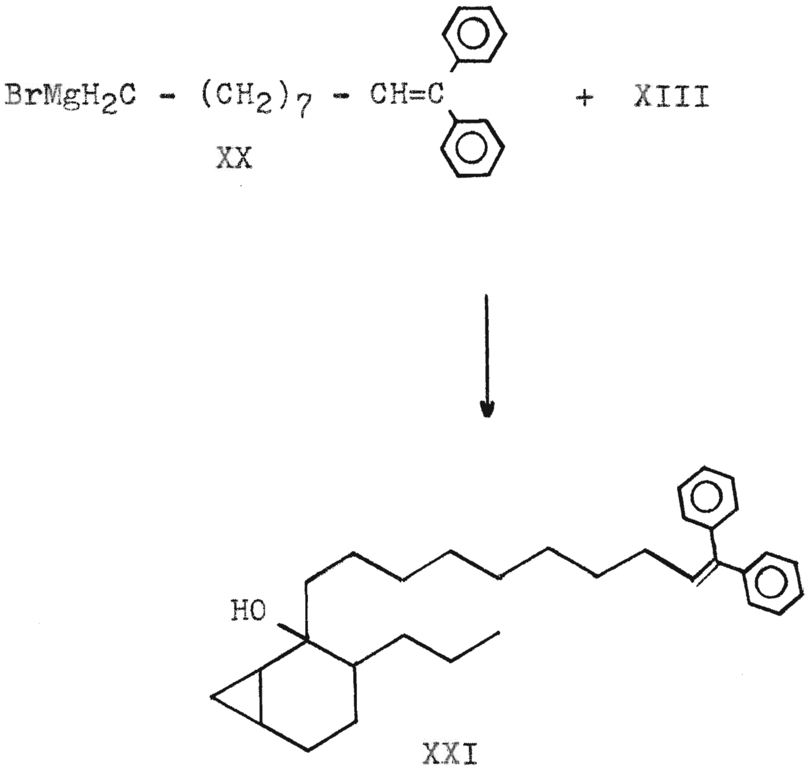
XVI

XVII

XVIII

XIX

Reaction of the bromo-compound XIX with magnesium would normally lead to the Grignard reagent XX. This would then be capable of reacting further with ketone XIII to form compound XXI, which can be reacted in two different ways as outlined in chart I.


$BrMgH_2C - (CH_2)_7 - CH=C$
$+$ XIII
XX
HO
XXI

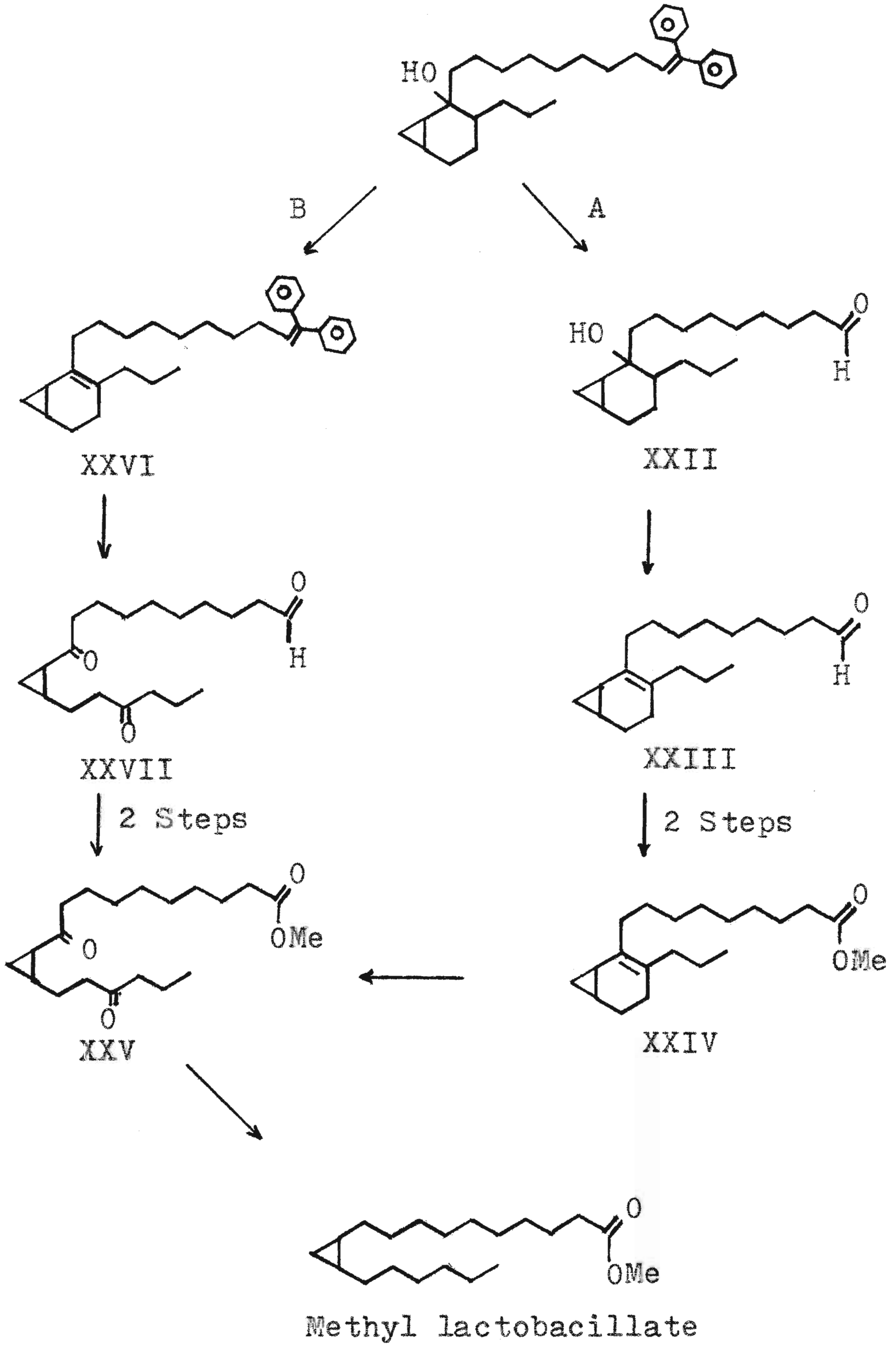

HO
B
A
XXVI
HO
XXII
XXVII
XXIII
2 Steps
2 Steps
XXV
XXIV
OMe
OMe
OMe
Methyl lactobacillate

Chart no. I

Sequence A was the one which we followed for reasons which will be mentioned later in the section of results and discussion.

EXPERIMENTAL

Attempted reaction of diethyl glutaconate with diazomethane:

Method (1):

To a magnetically stirred solution of 2 grams (0.01 mole) of diethyl glutaconate and 1.0 gram (0.02 mole) of cuprous chloride in 25ml of ether, a solution of 0.02 mole of diazomethane in ether (18) was added dropwise. The addition was accompanied by the formation of a black precipitate. When all the diazomethane solution was added, stirring was continued for 5 hours at room temperature. Filtration and removal of ether under vacuum afforded 1.4 grams of a yellow oil whose NMR spectrum was identical with that of the starting material. Thin layer chromatography showed the major component of this oil to be unreacted diethyl glutaconate.

Method (2):

A solution of 0.02 mole of diazomethane in ether was added in one portion to a stirring mixture of 2 grams of diethyl glutaconate and 1.0 gram of cuprous chloride in ether. Stirring was continued for one hour, at room temperature, after which the mixture was brought to a gentle reflux for additional 5 hours. Filtration and removal of ether at atmospheric pressure gave 1.2 grams of the same yellow oil obtained from method (1). Thin layer chromatography showed one major spot, corresponding to starting material, in addition to a second spot of lower R_f value and much lower concentration. It was not possible to detect any reaction product by NMR.

Reaction of dimethyloxosulfonium methylide with 2-cyclohexenone:

Following Corey's procedure (9), the ylide was generated *in situ* using the salt trimethyloxosulfonium iodide with sodium hydride in DMSO (dried over molecular sieves type 5-A) under dry nitrogen atmosphere. 2-Cyclohexenone (10) in dry DMSO was added from a dropping funnel and the mixture was stirred under nitrogen for 3 hours at room temperature and one hour at 50-60°c. Work-up as described by Corey afforded bicyclo-[4.1.0]-heptan-2-one in 77% yield; b.p. 40-41°c at 2 mm (lit. b.p. 85-85.5°c at 10 mm (19)).

The 2,4-dinitrophenylhydrazone melted at 163-164°c (lit. m.p. 162-163°c (20)).

Attempted oxidation of bicyclo-[4.1.0] -heptan-2-one with potassium permanganate:

Potassium permanganate (12.6 grams; 0.08 mole) was completely dissolved in 120ml of distilled water in a 500-ml conical flask. Bicyclo-[4.1.0] -heptan-2-one (5 grams; 0.045 mole) was added, followed by 2ml of a 10% sodium hydroxide solution. The mixture was stirred and the temperature was kept at 50-55° by cooling in an ice-water bath. After the exothermic reaction had subsided, the mixture was heated to maintain the temperature at 50-55° until no more permanganate was present (one hour). The reaction mixture was then boiled and filtered while hot and the dark brown manganese dioxide was collected and boiled again with 200ml of distilled water for 30 minutes. After filtration, the combined aqueous solution was concentrated to 100ml and acidified to pH 5-4 with very dilute HCl. The mixture was then transferred to an ether continuous-extraction apparatus and was extracted for 48 hours. When ether was dried (anhydrous calcium chloride) and evaporated under vacuum at 35° , a very few milligrams of crude unidentifiable material were left. Attempts to extract more material were unsuccessful.

Attempted oxidation of bicyclo-[4.1.0]-heptan-2-one with selenium dioxide:

A solution of selenium dioxide (1.11 grams, 0.011 mole) in 30ml of dioxane and 6ml of water was added dropwise over a period of 2 hours with stirring and cooling to 6 grams (0.054 mole) of bicyclo-[4.1.0]-heptan-2-one in 25ml of dioxane. After the addition was complete, the mixture was heated to 80°c for 5 hrs. in a water bath. At the end of the reaction the mixture was red and full of selenium lumps. Suction filtration of this was not possible. Precipitation of selenium metal out of the mixture was attempted by boiling it under reflux for 3 hours. Some (but not all) metallic selenium precipitated. Water and ether were added to the reaction flask and heated to a gentle reflux. After one hour ether was decanted into a separatory funnel and separated from the accompanying aqueous layer and washed with sodium chloride solution and dried over anhydrous sodium carbonate. Concentration of this ethereal solution under vacuum afforded 0.9 grams of a red, viscous substance (mostly selenium) which was very hard to be taken to any stage further.

Enamine VIII:

Bicyclo-[4.1.0]-heptan-2-one (5 grams, 0.045 mole) was added to a solution of 6.39 grams (0.09 mole) of pyrrolidine in 23ml of dry benzene. The mixture was refluxed over night. Water was removed continuously by means of a Dean-Stark trap. Distillation of the mixture afforded 4.7 grams (64.4%) of enamine VIII, b.p. 130-132°c (12 mm). NMR spectrum showed a complex signal at 0.1-0.9δ for the two methylene protons of the cyclopropane ring. It also showed the presence of a double bond. This was taken in $CDCl_3$.

Attempted resolution of enamine VIII with D-camphorsulfonic acid:

Following a procedure described by W.R. Adams et al (21), no crystalline product could be obtained. Variation in solvents and occasional scratching were unsuccessful in trying to induce crystallization of the viscous oily product.

3-Carbomethoxybicyclo- [4.1.0] -heptan-2-one XIV :

A procedure described by Corey (22) for a similar reaction was followed with slight changes.

In a 1000-ml three-necked round-bottomed flask, fitted with a mechanical stirrer, a dropping funnel and a thermometer, there were placed 58.5 grams (0.65 mole) of dimethyl carbonate and 6.2 grams (0.26 mole) of sodium hydride in 100 ml of dry dioxane. The mixture was heated under nitrogen to 80-85°c by means of a water bath. Bicyclo- [4.1.0] -heptan-2-one, 14 grams (0.13 mole) in 30 ml of dry dioxane, was added dropwise with stirring over a period of 3 hours. After the addition was complete, the mixture was stirred for further 2 hours at the same temperature.

As the reaction proceeded, the mixture became thick and the rate of stirring had to be increased. At the end of the reaction, the mixture was worked up as described by Corey. The yield of XIV was 15 grams (71.4%), b.p. 129-131°c (15 mm). The NMR spectrum was similar in type to the reported one for ketone V (19) with a methyl ester singlet at 3.74 ; Fig. (1).

Analysis; calcd. for $C_9H_{12}O_3$: C, 64.28%; H, 7.14%. Found; C, 64.47%; H, 7.12%.

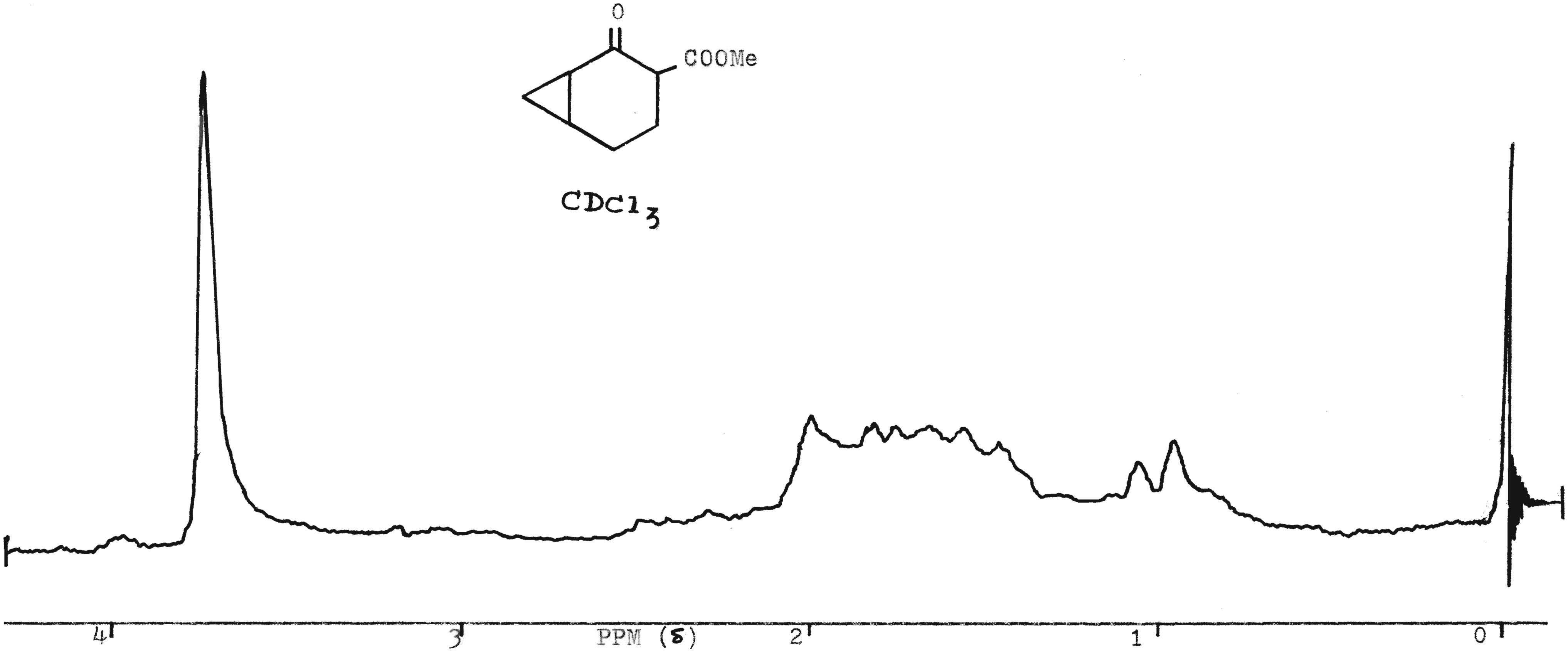


FIG. (1)

3-Carbomethoxy-3-n-propylbicyclo-[4.1.0]-heptan-2-one XV :

A procedure described by Conley (23) for a similar reaction was followed with some changes.

Sodium metal (1.36 grams, 0.059 g-atom) was introduced in small pieces into 80 ml of absolute ethanol contained in a 300-ml three-necked round-bottomed flask fitted with a dropping funnel and a reflux condenser. When sodium had completely reacted, the solution was magnetically stirred and the ketoester XIV (10 grams, 0.059 mole) was added. The mixture was heated to reflux and iodopropane (10 grams, 0.059 moles) was added dropwise. Stirring and refluxing were continued over night, and the mixture was concentratedby distilling out most (but not all) of the solvent. The mixture was then cooled and the solid sodium iodide was filtered off. The latter was washed twice with 25-ml portions of anhydrous ether and the washings were added to the alcoholic solution. The solvents were removed under vacuum. Distillation of the residual oil afforded 9 grams (75%) of XV; b.p. 159-161°c (16 mm). The NMR spectrum was almost the same as that of ketone XIII with the presence of a methyl singlet at 3.65δ, (Fig. 2). Analysis; calcd. for $C_{12}H_{18}O_3$: C, 68.57%; H, 8.57%. Found; C, 68.79%; H, 8.78%.

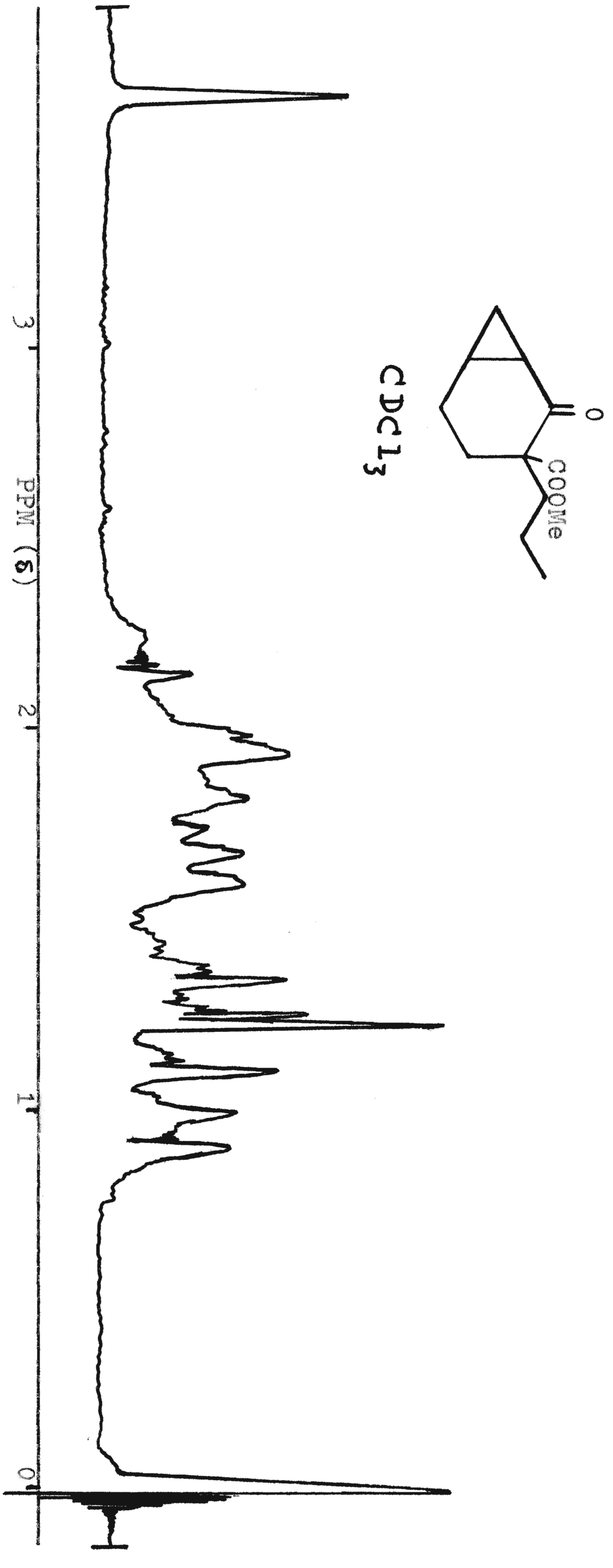


FIG. (2)

3-n-Propylbicyclo-[4.1.0]-heptan-2-one XIII :

Method (1) :

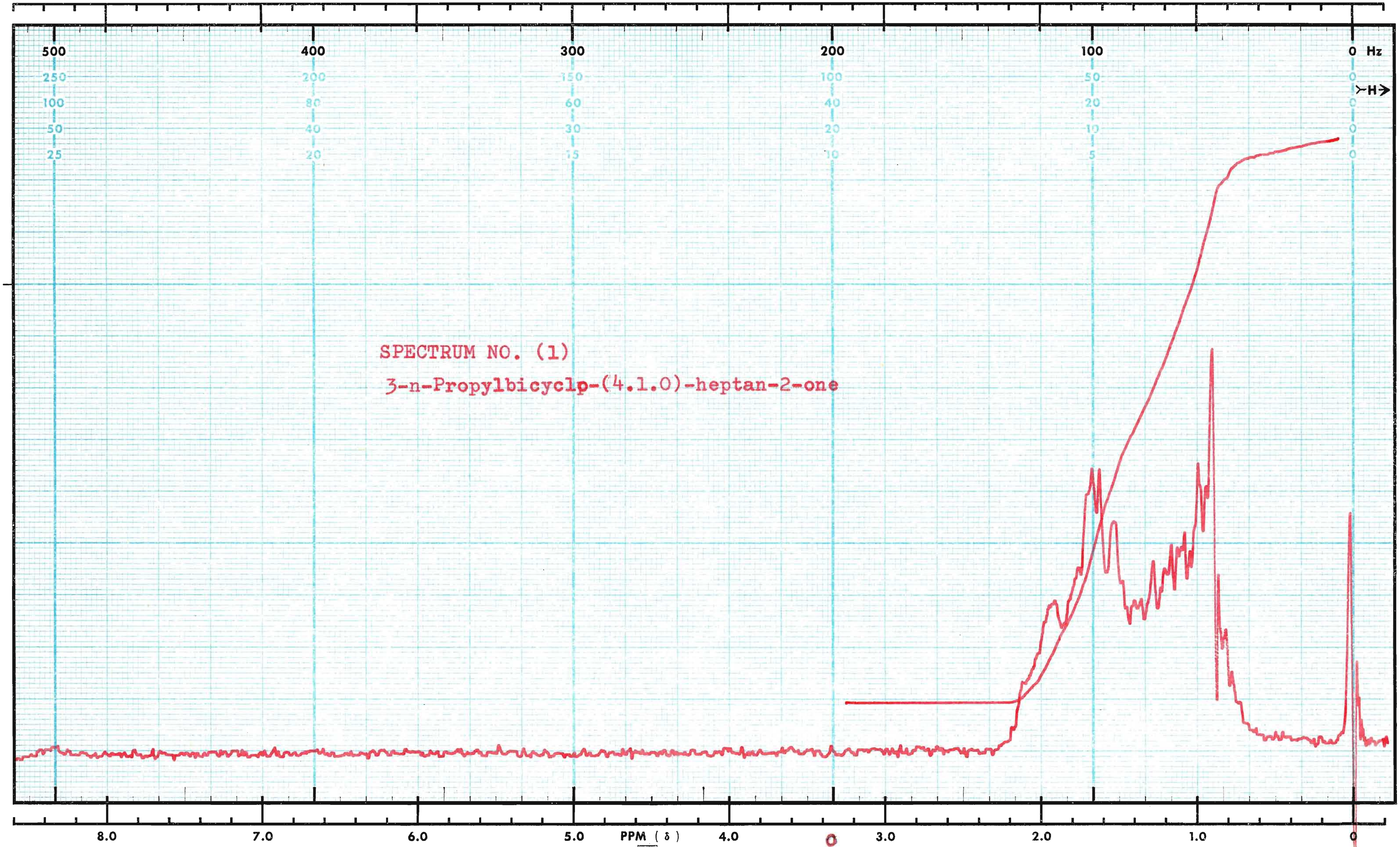
A 1000-ml three-necked round-bottomed flsk was fitted with a stoppered dropping funnel, an all glass mechanical stirrer and a dry ice condenser with a drying tube of silica gel attached to the side arm. The flask was kept in a dry ice/acetone mixture while about 200 ml of dry liquid ammonia was being distilled into it from another flask containing about 300-400 ml of commercial liquid ammonia with a few pieces of sodium metal.

Stirring was started and potassium metal (1.7 grams, 0.045 g-atom) was introduced in small pieces. A few crystals of ferric nitrate were added. After about 15 minutes the color changed from deep blue to yellowish gray. Bicyclo-[4.1.0]-heptan-2-one (5 grams, 0.045 mole) was then added followed by the dropwise addition of 7.6 grams (0.045 mole) of iodopropane in 50 ml of anhydrous ether. Stirring was continued for 4 hours. At the end of the reaction, ammonium chloride was added carefully to destroy unreacted potassium amide. Liquid ammonia was allowed to evaporate at room temperature over night. The product was taken up in ether and washed twice with water and twice with a saturated solution of sodium chloride and dried over sodium carbonate. Removal of the solvent under vacuum afforded 4 grams of crude product, G.L.C. analysis of which showed the presence of at least three components with ketone XIII being the major one. This was collected by G.L.C. on silicon QF/fluoro 10% on gas-chrom at 165°c with retention time of 4.30 minutes.

Method (2) :

In a 500-ml round-bottomed flask fitted with a reflux condenser, there was placed a mixture of 8 grams (0.038 mole) of XV and 4.6 grams (0.114 mole) of sodium hydroxide in 150 ml of methanol. The mixture was refluxed for 15 hours. Aqueous acetic acid was added followed by ether extraction. The ethereal solution was washed two times with a saturated solution of sodium chloride and dried over sodium carbonate. Removal of the solvent and distillation of the product afforded 4.6 grams (80%) of XIII; b.p. 40-41°c (2 mm). NMR: Spec. (1). Analysis of this compound was done twice: calcd. for $C_{10}H_{16}O$; C, 78.94%; H, 10.52%. Found: (1) C, 77.78%; H, 10.58%; (2) C, 77.02%; H, 10.46%, (see discussion). The IR shows the presence of a keto group and the cyclopropane ring (9.87 microns)

CHART S-60T
MADE IN U.S.A.



SPECTRUM NO. (1)

3-n-Propylbicyclp-(4.1.0)-heptan-2-one

MANUAL

SWEEP OFFSET (Hz): -

SPECTRUM AMPLITUDE: 1X5.0

INTEGRAL AMPLITUDE: 10 X 1.25

SPINNING RATE (RPS):

SWEEP TIME (SEC): 50 | ~~250~~ 250

SWEEP WIDTH (Hz): 25 | 50 | 100 | 250 | 500 1000

FILTER: 4 1 | 2 | 3 | ~~4~~ | 5 | 6 | 7 | 8

RF POWER LEVEL: 0.04

AUTO ☐

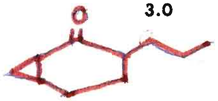
(250)

(500)

(2)

(.05)

SAMPLE:



SOLVENT: CCl_4

REMARKS: Separated by G.L.C.
100 % pure

varian
analytical instrument division

DATE: 28/5/1972

OPERATOR: F. G.

60 MHz NMR
SPECTRUM NO. (1)

Methyl 10-undecenoate XVI :

To a stirred solution of 64.4 grams (0.35 mole) of 10-undecenoic acid in 150 ml of benzene in 1000-ml round-bottomed flask, thionyl chloride (83.3 grams, 0.70 mole) was added dropwise from a pressure equalized dropping funnel over a period of 2 hours at room temperature. Stirring was continued for further 6 hours after the addition was complete. The reaction flask was then placed in a slightly-cold water bath and 128 grams of absolute methanol were added dropwise with stirring and continuous cooling. After all the alcohol was added, the water bath was removed and stirring was continued at room temperature for 6 more hours. Distillation of the solvents under reduced pressure afforded the crude ester. Water was added and the ester was extracted twice with 100-ml portions of ether. The combined ether extracts were washed several times with 30-ml portions of saturated solution of sodium bicarbonate, followed by 3 times with 30-ml portions of a saturated solution of sodium chloride. After drying over sodium carbonate, ether was evaporated and the product was distilled to give 60 grams (82.1%) of XVI, b.p. 130°c at 15 mm; lit. b.p. 124°c at 10 mm (24).

11,11-Diphenylundec-1-en-11-ol XVII :

In a dry 1000-ml three-necked round-bottomed flask, fitted with 2 dropping funnels and a reflux condenser, were placed 18 grams (0.75 g-atom) of magnesium turnings and covered with 150 ml of anhydrous ether. One of the dropping funnels contained 117.7 grams (0.75 mole) of bromobenzene in 100 ml of anhydrous ether, while the other contained 50 grams (0.25 mole) of methyl 10-undecenoate in 100 ml of anhydrous ether. All openings were protected with drying tubes of silica gel.

The reaction was initiated by adding about 10 ml of the bromobenzene solution to the reaction flask followed by the addition of a small crystal of iodine. The rest of the bromobenzene solution was then added dropwise while cooling occasionally on an ice-water bath. After the addition was complete (about 2 hours), an additional half hour was required before the self-refluxing reaction subsided. Methyl 10-undecenoate was then added dropwise with cooling as described above.

As the addition of the ester went on, a white precipitate formed. After all the ester was added the mixture was allowed to stand overnight. Saturated ammonium chloride solution was then added with stirring to free the product alcohol from its salt (no excess of ammonium chloride solution was required). A white thick precipitate formed. The ether layer was transferred to a separatory funnel and the thick precipitate was washed a few times with ether. The combined ether washings were shaken twice with saturated sodium chloride solution and dried over anhydrous sodium carbonate. Evaporation of ether at reduced pressure gave 60.5 grams (75%) of crude viscous oil which was used without further purification. The infrared spectrum shows a split band at 2.8-3.0 microns (OH); four small bands at 5.23-5.78 microns (aromatic); and one band at 6.26 microns (double bond). NMR spectrum shows a complex signal (Fig. 3) at 4.75-5.17δ for the two protons of C_1 and another multiplet at 5.45-6.10δ for the one proton on C_2. It also indicates the presence of 10 aromatic protons at 7.1-7.7δ as well as the disappearance of the methyl ester signal. The mass spectrum indicated a molecular weight of 304 (loss of a water molecule).

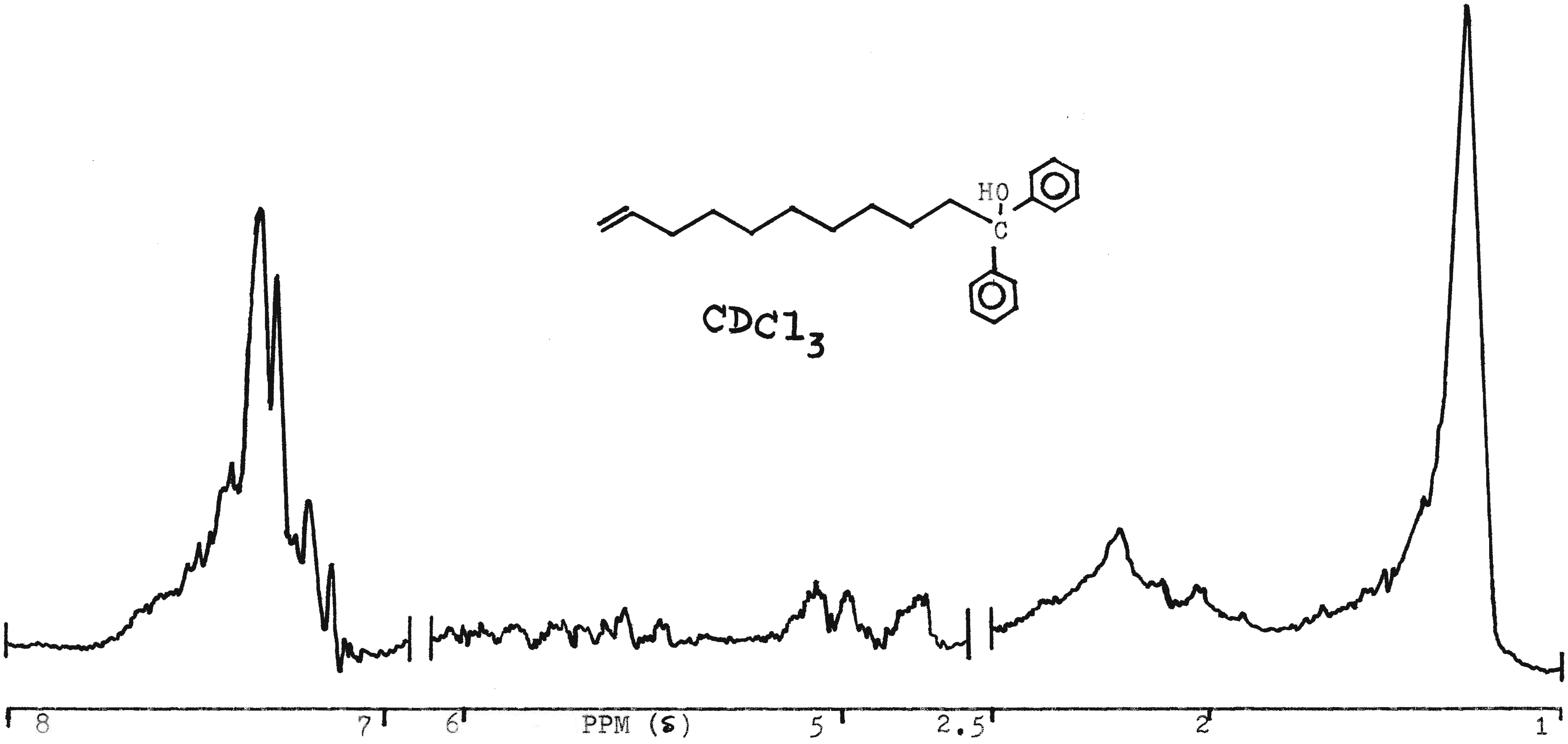


FIG. (3)

10,10-Diphenyldecan-1,10-diol XVIII :

The crude unsaturated t-alcohol XVII (50 grams) was dissolved in 100 ml of methanol and placed in a standard ozonolysis apparatus cooled in an ice-salt bath. Ozone was passed through the solution at a rate of 2.0 grams per hour for four hours. The ozonide solution was then transferred into a dropping funnel and was added dropwise to a cooled solution of 18 grams of sodium borohydride in 100 ml of 50% aqueous ethanol. The mixture was then stirred overnight at room temp. Methanol and ethanol were distilled out of the mixture at atmospheric pressure followed by ether extraction of the aqueous solution. Ether extracts were combined and washed several times with saturated solution of sodium chloride and dried over sodium carbonate. Evaporation of ether under vacuum afforded 45 grams of crude diol XVIII, (about 90%). The infrared spectrum showed an OH band at 2.9-3.0 microns. The NMR spectrum showed a triplet at 3.42-3.70δ for the two protons on C_1. It (Fig. 4) also showed the disappearance of the olefinic protons of the starting material. The mass spectrum indicated a molecular weight of 308 (loss of H_2O molecule).

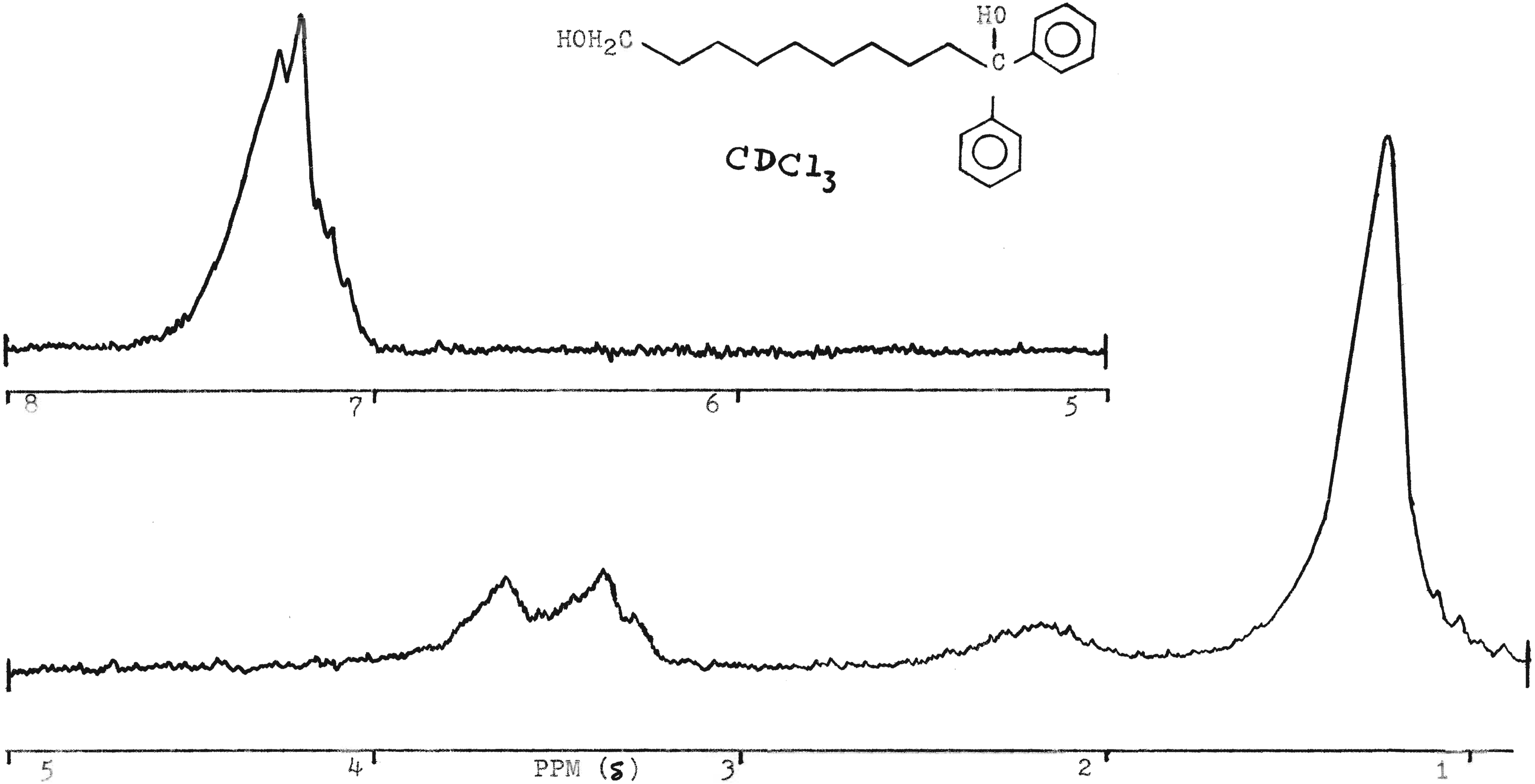


FIG. (4)

1,1-Diphenyl-10-bromodecene XIX :

Method (1) :

The crude XVIII (15 grams) was boiled with 25 ml of 48% hydrobromic acid for 2 hours, after which time water was added and the organic material was extracted into ether and washed with saturated solutions of sodium bicarbonate and sodium chloride respectively. Drying over anhydrous sodium carbonate and evaporation of the solvent under vacuum afforded 14 grams of crude 1,1-diphenyl-10-hydroxydec-1-ene which solidified upon standing overnight. This can be recrystallized with some loss of the product from a minimal amount of methanol over a period of 2 days. Identification of this alcohol was established by the presence of a hydroxyl band at 2.8-3.0 microns and a distorted signal at 3.40-3.70δ for the two protons on the terminal carbon which carries the hydroxyl group, spec.(2). The mass spectrum showed a molecular weight of 308. The melting point of this compound is 39-40° .

Refluxing with a slight excess of phosphorus tribromide for 6 hours in benzene converted this alcohol into the bromo-compound XIX. This was washed with sodium bicarbonate and sodium chloride solutions and dried over

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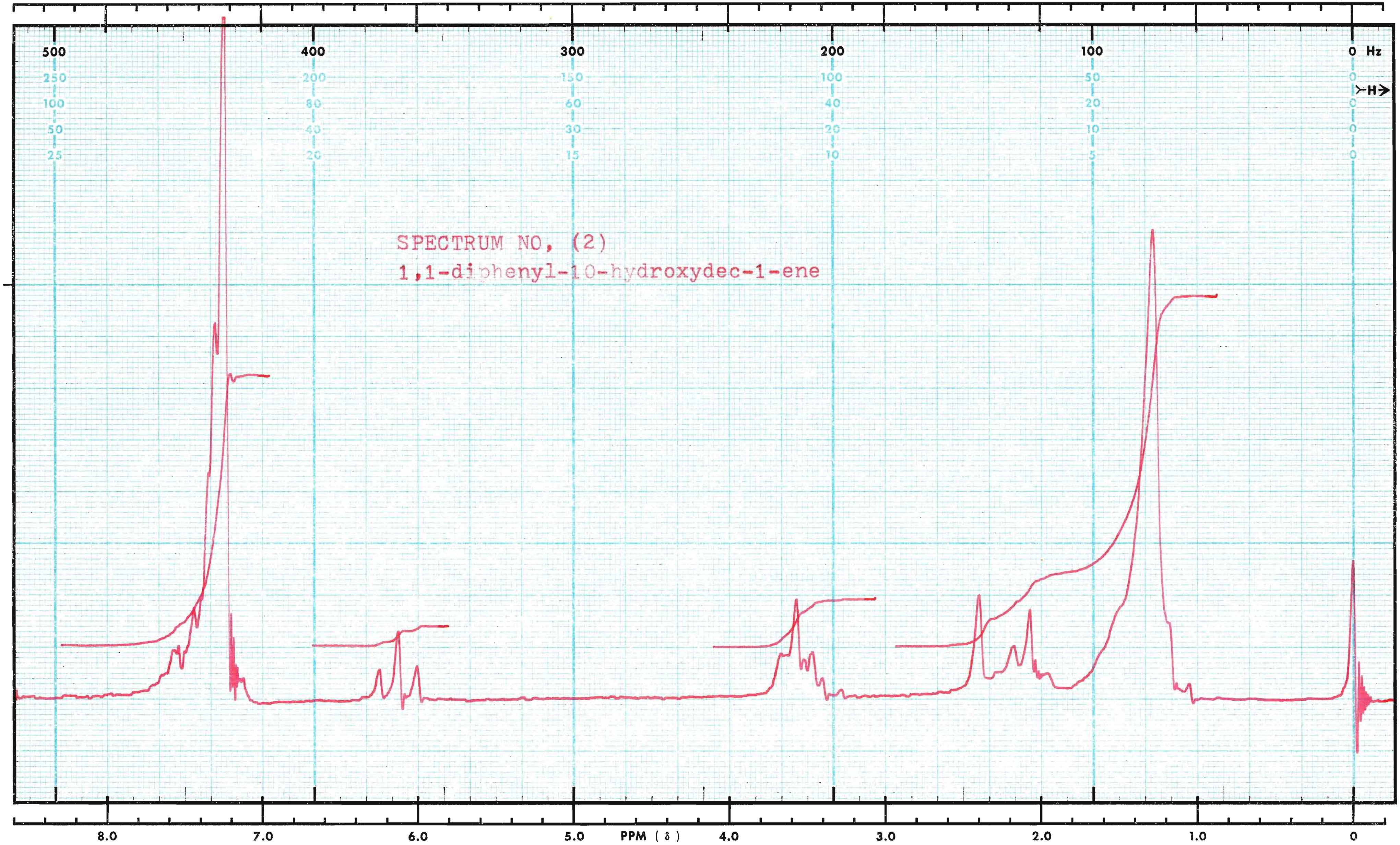


SPECTRUM NO, (2)
1,1-diphenyl-10-hydroxydec-1-ene

MANUAL

AUTO ☐

SWEEP OFFSET (Hz): ______

SPECTRUM AMPLITUDE: 1 x 2.5

INTEGRAL AMPLITUDE: 10 x 2.5

SPINNING RATE (RPS): ______

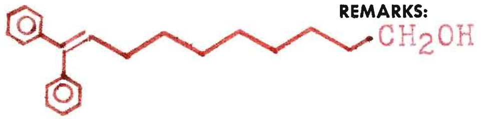
SWEEP TIME (SEC): 50 [✓ 250] (250)

SWEEP WIDTH (Hz): 1000 25 50 100 250 500 (500)

FILTER: 1 2 3 [✓ 4] 5 6 7 8 (2)

RF POWER LEVEL: 0.02 (.05)

SAMPLE:



REMARKS:

SOLVENT: $CDCl_3$

varian
analytical instrument division

DATE: ______

OPERATOR: F.G.

60 MHz NMR
SPECTRUM NO. (2)

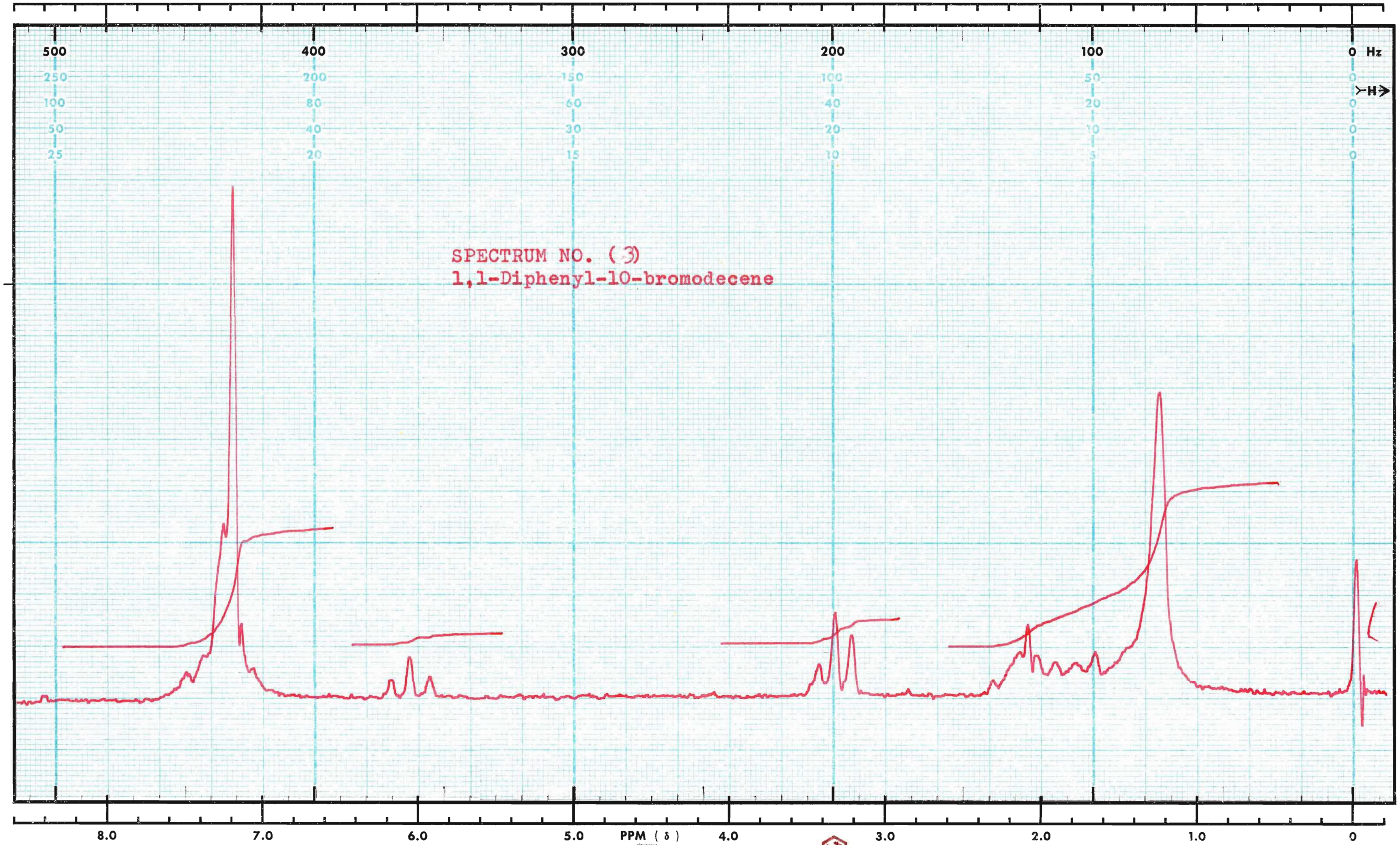
anhydrous magnesium sulfate. Distillation afforded 11 grams of the product XIX; b.p. 249°c (15 mm). The mass spectrum indicated a molecular weight of 370.

NMR: Spec. (3).

Method (2) :

The crude XVIII (15 grams) was refluxed with 18.4 grams (0.069 mole) of phosphorus tribromide overnight in benzene. Work-up as described in method (1) afforded 9 grams of crude XIX. Distillation of this gave 8 grams of product.

CHART S-60T
MADE IN U.S.A.



SPECTRUM NO. (3)
1,1-Diphenyl-10-bromodecene

MANUAL

SWEEP OFFSET (Hz):

SPECTRUM AMPLITUDE: 1 x 1.25

INTEGRAL AMPLITUDE: 10 x 1.25

SPINNING RATE (RPS):

SWEEP TIME (SEC): 50 [✓ 250]

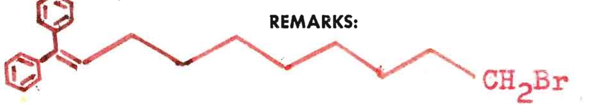
SWEEP WIDTH (Hz): 1000 25 50 100 250 500

FILTER: 1 2 3 [✓ 4] 5 6 7 8

RF POWER LEVEL: 0.02

AUTO ☐
(250)
(500)
(2)
(.05)

SAMPLE:



REMARKS:

SOLVENT: $CDCl_3$

varian
analytical instrument division

DATE: NOVEMBER 24,1972

OPERATOR: F. GEORGES

60 MHz NMR
SPECTRUM NO. (3)

Synthesis of alcohol XXI :

In a dry 300-ml three-necked round-bottomed flask, fitted with two dropping funnels, a reflux condenser, and a magnetic stirrer, 1.15 grams (0.048 g-atom) of magnesium turnings were placed. Anhydrous ether (50 ml) was added followed by a small crystal of iodine. One of the dropping funnels contained a solution of 18 grams (0.048 mole) of 1,1-diphenyl-10-bromodecene in anhydrous ether. In the other dropping funnel a soln. of 5 grams (0.032 mole) of 3-n-propylbicyclo-[4.1.0]-heptan-2-one in anhydrous ether was placed. The system was flushed with dry nitrogen and a continuous nitrogen pressure was maintained throughout the reaction period. The bromo-compound was added dropwise over a period of 2 hours during which, ether was observed to reflux very slowly. After the addition was complete, the mixture was stirred for additional 30 minutes or until no more bubbling was observed. The ketone was then added dropwise with stirring over a period of 30 minutes after which time the mixture was refluxed with continuous stirring for one hour. A minimum amount of a saturated solution of ammonium chloride (enough just to free the product alcohol from its magnesium complex (25) was added dropwise with stirring. The ethereal supernatant was decanted into a conical flask and dried over anhydrous sodium carbonate. Evaporation of ether under vacuum afforded 21 grams of crude material used directly without further purification. The infrared spectrum showed the presence of a hydroxyl group and no carbonyl group was present. The presence of the cyclopropane ring was demonstrated by an absorption band at 9.9 microns. The mass spectrum indicated a molecular weight of 426, corresponding to the dehydration product XXVI (dehydration takes place at the probe of the mass spectrometer). The NMR spectrum (Fig. 5), is not superimposable on any of the starting materials.

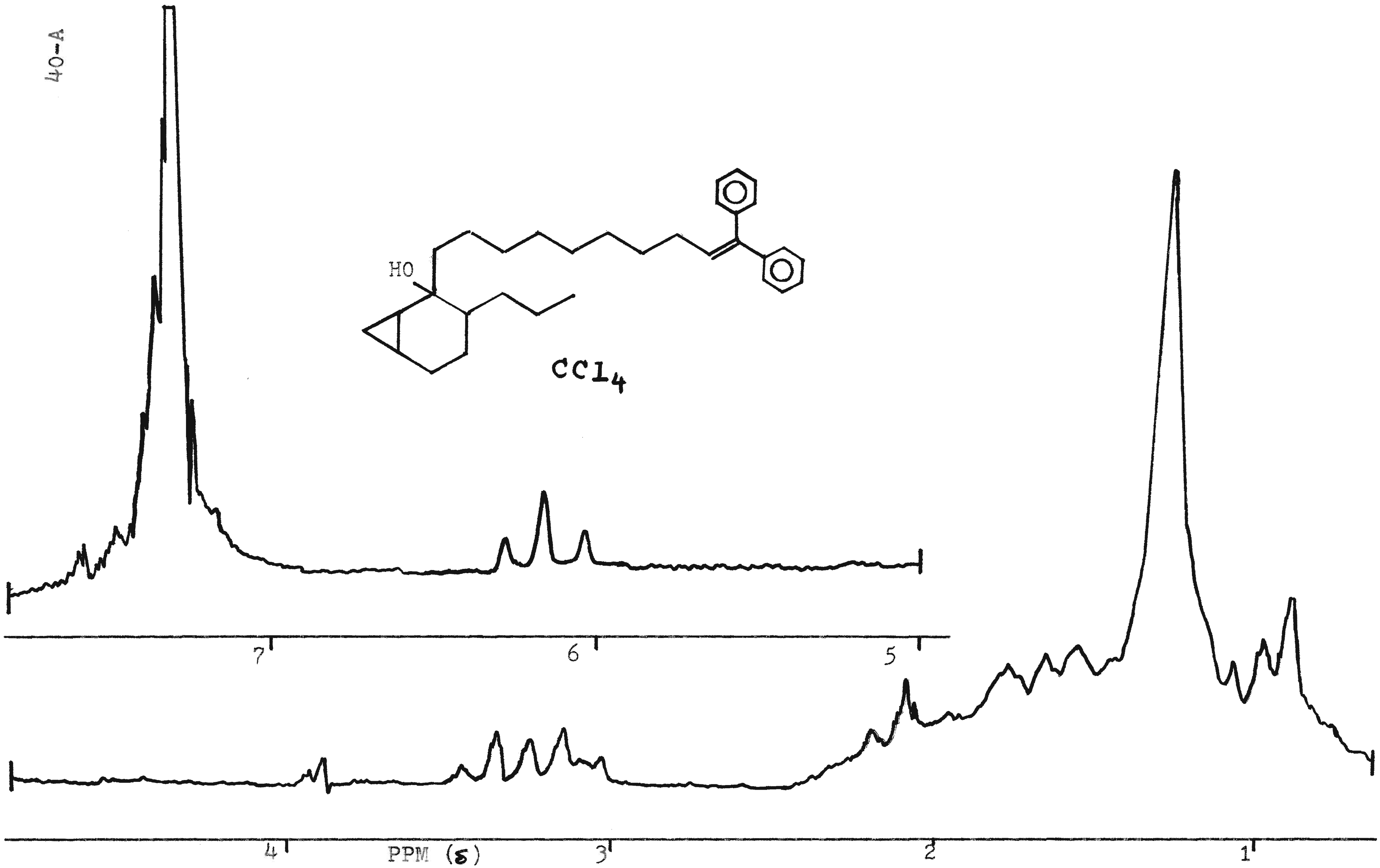
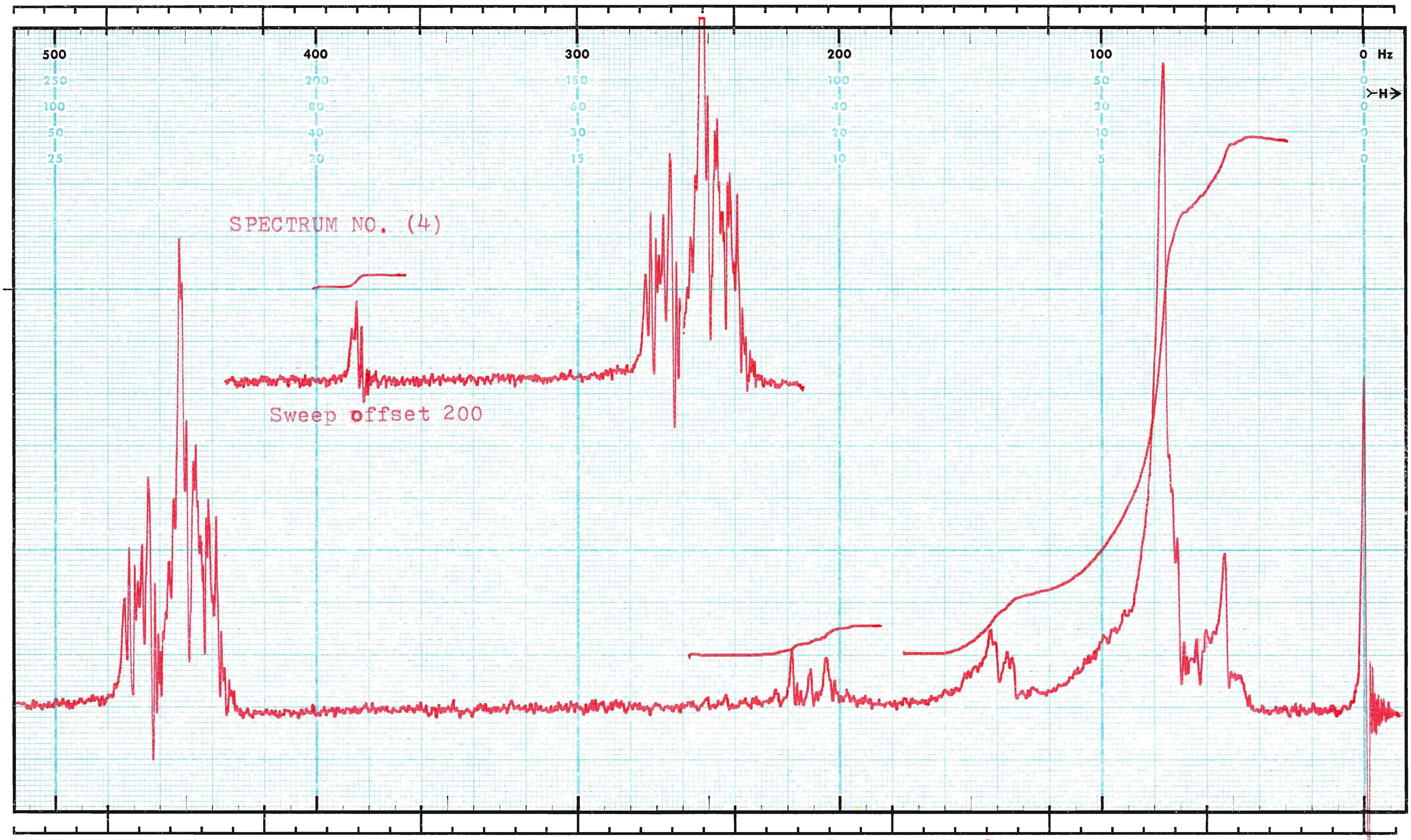


FIG. (5)

Ozonolysis of alcohol XXI :

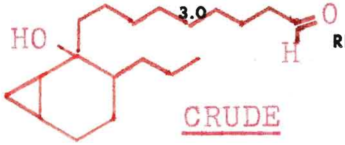
The procedure was exactly the same as for the ozonolysis of XVII with the exception of using n-hexane as solvent instead of methanol. 18 Grams of the crude alcohol were used. At the end of the reaction (2 hours at the rate of 2 grams of ozone/hr.), 10 ml of absolute ethanol was added to clear up the cloudy solution and the mixture was added dropwise to a mixture of 200 ml of 80% solution of potassium iodide in water and 50 ml of absolute ethanol. Stirring was continued overnight and the free iodine was reduced by the addition of solid sodium thiosulfate to the stirring mixture which was then transferred into a separatory funnel where the hexane layer was separated from the aqueous alcoholic one. Hexane solution was dried over sodium carbonate followed by removal of the solvent under vacuum. A residue of 12 grams of crude product was obtained. Ethanol was distilled under vacuum from the aqueous solution and the mixture was extracted twice with 50 ml portions of n-hexane. The combined hexane extracts were dried over anhydrous sodium carbonate and the solvent was removed under reduced pressure to give 1.7 grams more of crude product. Column chromatography of this product (eluted with pentane on alumina neutral) afforded 5.6 grams of impure yellowish solid whose mass spectrum showed a relatively small parent peak at 276. The pattern was very similar to that of XXI. The infrared spectrum showed the presence of the hydroxyl group as well as a strong carbonyl band at 5.9 microns. Cyclopropane absorption band was also obtained at 9.9 microns. A positive silver mirror test confirmed the presence of the aldehydic group. NMR: Spec. (4) shows the impure sample of this aldehyde before chromatography. It also shows the formation of benzophenone.

CHART S-60T
MADE IN U.S.A.



	MANUAL	AUTO ☐	
SWEEP OFFSET (Hz):	SWEEP TIME (SEC): 50 [✓ 250]	(250)	
SPECTRUM AMPLITUDE: 1 x 2.0	SWEEP WIDTH (Hz): 1000 [✓ 25] 50 100 250 500	(500)	
INTEGRAL AMPLITUDE: 10 x 2.0	FILTER: 1 2 3 [✓ 4] 5 6 7 8	(2)	
SPINNING RATE (RPS):	RF POWER LEVEL: 0.02	(.05)	

SAMPLE:



CRUDE

REMARKS: BEFORE CHROMATOGRAPHY

SOLVENT: $CDCl_3$

varian
analytical instrument division

DATE: DEC. 29, 1972

OPERATOR: F.G.

60 MHz NMR
SPECTRUM NO. 4

Dehydration of XXII :

The impure aldehyde XXII (5 grams) was refluxed with a few milligrams of p-toluenesulfonic acid in dry benzene under a Dean-Stark trap for 12 hours. The mixture was washed with sodium bicarbonate and sodium chloride solutions respectively and dried over sodium carbonate. Benzene was removed under reduced pressure to give 3.8 grams of crude product which was used immediately for the next step. The infrared spectrum was identical with that of XXII with the disappearance of the hydroxyl band, and the new absorption at 6.23 microns (double bond).

The NMR of this crude material did not show any olefinic protons.

Synthesis of ester XXIV :

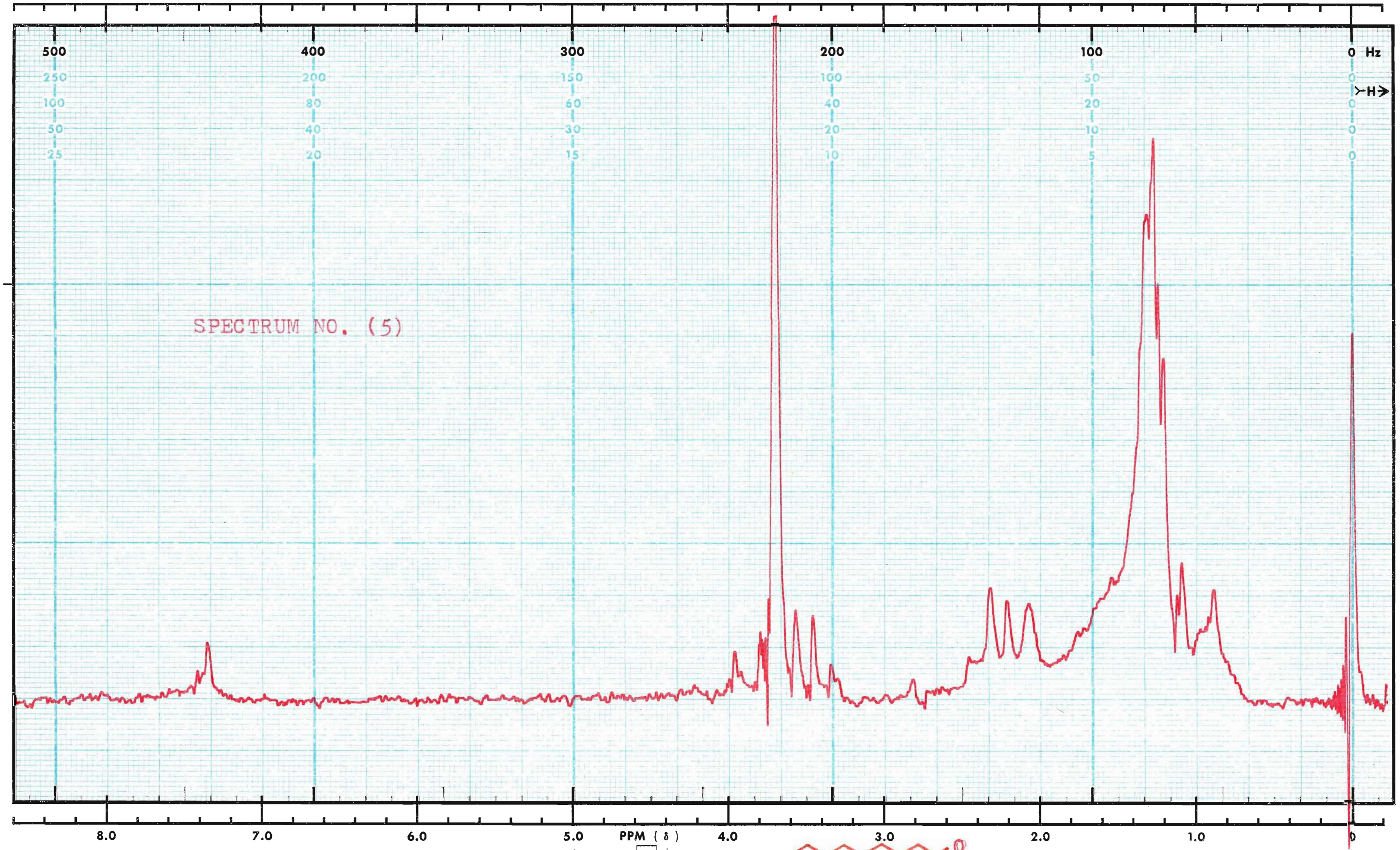
Silver nitrate (11.15 grams, 0.066 mole) was dissolved in 50 ml of distilled water. While magnetically stirring, a solution of 2.64 grams (0.066 mole) of sodium hydroxide in 15 ml of distilled water was added. After stirring for several minutes the precipitated silver oxide was collected by suction filtration and washed with about 20 ml of distilled water to remove excess silver nitrate. The wet freshly prepared silver oxide was added to a stirring solution of 3.5 grams of crude dehydration product XXIII in 50 ml of distilled water. Sodium hydroxide (1 gram) in 10 ml of distilled water was added and the mixture was stirred at 80° for half hour after which it was boiled for 2 minutes and filtered while hot. The aqueous solution was concentrated to about 20 ml by boiling and the cooled mixture was acidified to pH 5 with 3% HCl while surrounded with an ice-water bath. The organic acid was extracted immediately into ether and washed with distilled water and dried over calcium chloride.

Into this ethereal solution, an excess of diazomethane was distilled and the mixture was magnetically stirred for 3 hours at room temperature. The mixture was dried again over calcium chloride and ether was evaporated under vacuum to give 2.4 grams of crude ester XXIV whose infrared spectrum indicated the preservation of the cyclopropane ring (9.85 microns) as well as the presence of a carboxylic ester at 5.75 microns. The NMR spectrum (Spec. 5), indicated a methyl singlet at 3.64 δ for the ester group and no aromatic protons.

Ozonolysis of ester XXIV :

Ozone was passed through a solution of the crude ester (2 grams) in methanol for 1.5 hours and the ozonide solution was treated in exactly the same way as in the ozonolysis of alcohol XXI. Methanol was distilled off under reduced pressure and the product was extracted into ether and dried over sodium carbonate. Evaporation of the solvent gave 0.5 grams of crude product whose NMR spectrum indicated an impure mixture. The IR spectrum indicated the disappearance of a band at 11.5 microns and the diminishing of a band at 6.23 microns. (see discussion).

CHART S-60T
MADE IN U.S.A.



SPECTRUM NO. (5)

MANUAL

SWEEP OFFSET (Hz): ________

SPECTRUM AMPLITUDE: 1 x 5.0

INTEGRAL AMPLITUDE: ________

SPINNING RATE (RPS): ________

SWEEP TIME (SEC): 50 [✓ 250]

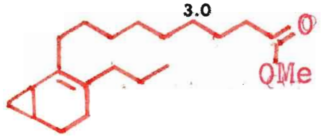
SWEEP WIDTH (Hz): 1000 25 | 50 | 100 | 250 | 500

FILTER: 1 [✓ 2] 3 4 5 6 7 8

RF POWER LEVEL: 0.1

AUTO ☐
(250)
(500)
(2)
(.05)

SAMPLE:



SOLVENT: $CDCl_3$

REMARKS:

varian
analytical instrument division

DATE: DEC. 31, 1972

OPERATOR: F.G.

60 MHz NMR
SPECTRUM NO. (5)

ATTEMPTS TO PREPARE OPTICALLY ACTIVE V :-

2-Cyclohexenylacetate :

Following exactly the same procedure described by Denney (15), we obtained this crude ester in about 60% yield. This was a model experiment.

Cupric-dl-0-methylmandelate :

Potassium acetate (2.94 grams, 0.03 mole) in 55 ml of water was added to a solution of 5 grams (0.03 mole) of 0-methylmandelic acid in 55 ml of methanol. To this mixture, a solution of 7 grams (0.03 mole) of cupric sulfate pentahydrate in 60 ml of water was added in portions with stirring over one hour at room temperature. After an additional hour of stirring the mixture was filtered off by suction and the solid material was pressed dry on the filter paper. It was then transferred into a beaker and stirred for 15 minutes with a 10% solution of sodium bicarbonate. The mixture was filtered again with pressing it as dry as possible, and was washed twice with ether and dried under vacuum. The product melted at 183° and the yield was 11 grams (98%).

Attempted synthesis of 2-cyclohexenyl-O-methylmandelate :

The same procedure of Denney was followed, and the solvent (cyclohexene) was removed under vacuum at 35-40°c. The crude product showed to consist mainly of 2-cyclohexenone and some 2-cyclohexenol by comparing its NMR spectrum with the NMR spectrum of authentic samples of both materials. The spectrum of the crude mixture also indicated the presence of a considerable amount of aromatic protons. Benzaldehyde was produced when the crude material was run into GLC for analysis at a column temperature of 130° . However, it was not possible to isolate any pure ester.

Attempted asymmetric reduction of 2-cyclohexenone by fermenting yeast :

The procedure described by Mosher (16) was exactly followed and the product collected by steam distillation was analyzed by GLC after extraction. The analysis indicated the presence of at least three components which were separated by the same technique (GLC). These fractions were examined by NMR and none of them proved to be the desired reduction product.

Reaction of D-(+)-α-methylbenzylamine with dimethyl carbonate :

D-(+)-α-Methylbenzylamine was refluxed in dimethyl carbonate for three hours with a few crystals of p-toluenesulfonic acid as a catalyst. The cooled reaction mixture was then allowed to stand overnight during which time the urea XII separated as fine white needles. The liquid layer was decanted into another flask (for another crop) and the crystals were washed (with suction) with anhydrous ether. The crystals were then collected and allowed to dry at 80° for 30 minutes. The mass spectrum indicated a molecular weight of 268. The melting point is 196-197° ; $[\alpha]_D^{25}$ =+83 (1% EtOH).

Attempted catalytic hydrogenation of m-hydroxybenzoic acid :

Following the procedure of Noyce (26), the starting material was completely recovered. No absorption of hydrogen was observed.

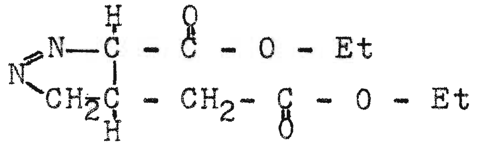
Research Equipment Used

1) Varian A60 Nuclear Magnetic Resonance Spectrometer.
2) Perkin-Elmer 225 High Resolution I.R. Spectrophotometer.
3) Aerograph analytical gas chromatograph.
4) Parr Low-Pressure Hydrogenator.
5) T408 Welsbach Ozonator.

RESULTS AND DISCUSSION

Diacids II and VI :

Because of its reactivity toward the α,β-unsaturated carbonyl compounds, diazomethane seemed to be a suitable reagent for our purposes in the synthesis of compound II. It is usually known that a reaction of this kind would first lead to the pyrazoline intermediate XXVIII followed by the loss of a nitrogen molecule to give the product. When we tried this reaction, however, we were not able to obtain any useful product. It was even noticed that no pyrazoline intermediate was formed during this experiment. This was indicated by the fact that the olefinic protons of the starting material remained unchanged.



XXVIII

We, once more, repeated the experiment, but in a slightly different way, and again no product could be obtained. These rather discouraging results suggested that an alternate approach was necessary in the synthesis of our desired diacid.

The synthesis of bicyclo-[4.1.0]-heptan-2-one is reported in the literature in several different ways (17,19,20); and although it was not previously prepared by Corey's method (dimethyloxosulfonium methylide with α,β-unsaturated ketones), we were able to obtain it in good yield by this method. However, basic potassium permanganate when used for the ring opening of this compound to the diacid VI presented the problem of product isolation. This presumably is due to the strong adherence of the product acid salt to the surface of the manganese dioxide particles, even after boiling.

That a few milligrams of crude material were obtained from this reaction, was not of much use to us, since it was not even sufficient to take a conclusive NMR spectrum on it. On the other hand, even if this turned out to be the expected product, the method did not prove to be a high-yield one.

Oxidation of ketone V with selenium dioxide was the next approach in our attempts of ring opening of this compound. However, the same problem of product isolation was presented again by the appearance of selenium among the reaction products which turned the solution into a thick colloidal mixture whose work up was a difficult and tedious task.

The difficulties encountered with the attempted oxidative ring opening of this bicyclic system made it necessary for us to abandon the idea of dealing with diacid II or VI as a resolvable starting material in this synthesis, and to explore other possible ways.

The attempted resolution of bicyclo-[4.1.0]-heptan-2-one V :

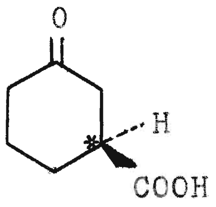
Enamines of asymmetric ketones are known to be resolvable, if the formation of a solid iminium salt with an optically active acid is possible (21). On this basis we prepared enamine VIII with the intention of resolving it using D-camphorsulfonic acid.

Unfortunately the results were not as expected. We obtained a liquid product instead of a solid one. This presumably is due to the fact that each diastereomeric salt was contaminated with the other so that the formation of solid crystals is inhibited. We were not able to induce this liquid product to crystallize. Variation in solvents as well as the use of different combinations of polar and nonpolar solvents at various concentrations were unsuccessful; in all cases the product was liquid.

Although other procedures were also described for the resolution of asymmetric ketones (27), the conditions used are not mild enough to assure the integrity of the cyclopropane ring from being damaged by strong acids.

The lack of mild resolution conditions and the failure of resolving the ketone via the iminium salt suggest that an asymmetric synthesis of this ketone might be more convenient than attempting to resolve it in the usual ways.

Apart from our attempts, discussed in the introduction, it should also be noticed that if 3-carboxycyclohexanone is resolved, it should be possible to reduce it to the optically active alcohol X which can then be reacted according to Alexandre's method to obtain the desired optically active ketone (17).



In speaking about 3-carboxycyclohexanone, one would normally think of catalytic hydrogenation of m-hydroxybenzoic acid followed by oxidation to the ketone (as outlined in the introduction) as the simplest way of preparing it.

In the literature (26), a similar reaction was employed successfully to convert p-hydroxybenzoic acid into 4-carboxycyclohexanol in acetic acid under hydrogen pressure.

As we carried out our experiment under exactly the same conditions, using the same catalyst (rhodium on alumina) and the same apparatus as described in the literature procedure, we expected to obtain a similar satisfactory result. However, no hydrogen was absorbed. This could be due to the fact that m-hydroxybenzoic acid is not as soluble as the para-compound in acetic acid. However, because of the lack of time we did not try another solvent for this particular reaction. We preferred to continue with racemic compounds rather than spending more time trying to resolve ketone V or prepare it optically active.

Further reactions on ketone V :

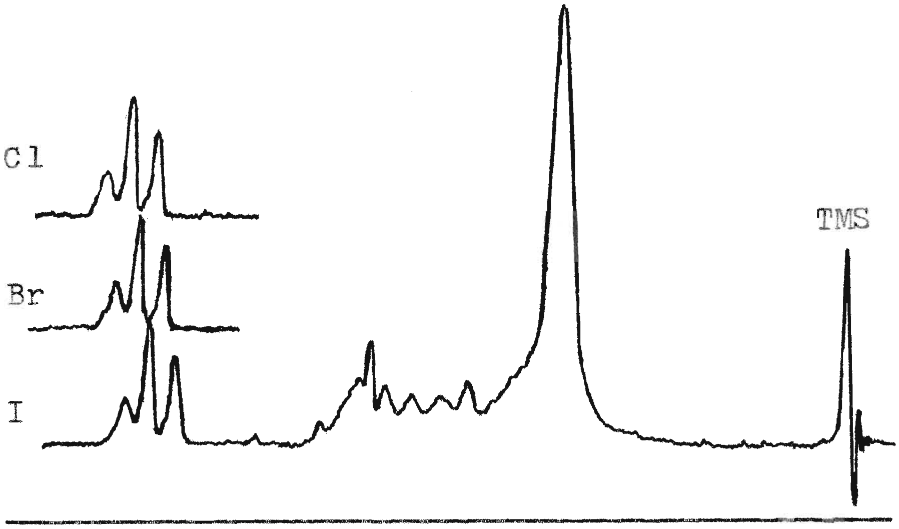
The specially built structure of ketone V provides a very convenient sequence of reactions in the course of this synthesis. The presence of a keto group flanked by two carbon atoms that differ in reactivity toward strong bases makes it possible to introduce the right groups into the right positions. On this basis we successfully introduced a propyl group into the relatively acidic carbon of this system, and the product was ketone XIII. In so doing, we made up the six-carbon skeleton of the smallest of the two side chains of lactobacillic acid. However, the fact that the microanalysis results were not as expected may be explained by a possible contamination of the samples with traces of some impurities that may have the same retention time on GLC as that of the ketone (microanalysis samples were collected by GLC). However, since this compound is the decarboxylation product of a carboxylic precursor with correct analysis and well established structure (XV), and according to the IR data and its NMR spectrum (Spec. 1), it is logical to accept structure XIII as the correct one for this compound.

As for the other side chain, a nine-carbon straight-chain carboxylic acid has to be attached to the carbonyl carbon. This in turn is going to make up the ten-carbon skeleton of the longer chain of lactobacillic acid. For this purpose we carried out the synthesis of the straight bifunctional chain XIX outlined on page 19. Ozonolysis of this long chain moiety at a later stage followed by an oxidation reaction would normally lead to a terminal carboxylic group as part of the ten-carbon side chain of the final product.

In the synthesis of XIX, it was interesting to note the difference in the yield of this compound in response to two different treatments on diol XVIII. When dehydration and bromination steps were carried out separately by first treating compound XVIII with hydrobromic acid and then with phosphorus tribromide, the yield was higher than when both steps were done at the same time by treating the same compound XVIII with phosphorus tribromide in a single step. This exemplifies the differrence in rates of E_1 (HBr vs PBr_3) and S_N2 (PBr_3) reactions happening together in the same molecule.

Under exactly the same experimental conditions, we prepared the corresponding chloro-compound, in one step, using thionyl chloride instead of phosphorus tribromide in approximately 71% yield, but it was completely inert to Grignard reaction of the next step. The chloro-compound was readily converted, almost quantitatively, into the iodo-compound by simply refluxing it with an excess of sodium iodide in acetone. Again this was not satisfactorily suitable for the next step since it was insufficiently pure; because of its high viscosity, it would be expected to distil at a very high temperature, even under vacuum, in which case it might undergo elimination of the iodide.

The bromo-compound, therefore, appeared to be the most reasonable halide to deal with. This gave us a chance to compare the NMR spectra of the three halides. These were identical in everything except for the chemical shift of the signal of the two protons on the terminal carbon atom that bears the halide group. This triplet was shifted up field in the order : Cl, Br, and I which is consistent with the relative electronegativity of each individual halide (Fig. 6).



(Fig. 6)

Grignard reaction on ketone XIII and subsequent steps :

A very important factor for the success of this experiment is maintaining a dry nitrogen atmosphere throughout the reaction period.

When we carried out this experiment for the first time under the usual anhydrous conditions (no nitrogen was used), we did not obtain any product whatsoever inspite of the disappearance of some, but not all, of the magnesium used. This indicates the extreme sensitivity of this particular reaction to the surrounding atmosphere.

When nitrogen was used, the reaction went on successfully and the isolated product was shown to be the tertiary alcohol XXI by the presence of a hydroxyl group in the infrared spectrum. In addition to this, the mass spectrum indicated a molecular weight of 426 which is correct for the corresponding dehydration product XXVI as it loses a molecule of water at the probe of the mass spectrometer.

On the way to the final product, it is possible to treat this tertiary alcohol in two different ways (chart no. I, page 21). Although route B is one step less than route A, we have chosen the latter for two reasons. In route B there will be the danger of epimerization at C_{11} when oxidation to the acid takes place in basic medium. On the other hand, following route A assures us that the ring opening will only be one step away from the end product which provides more certainty of the product being in the cis configuration.

On these bases we treated alcohol XXI according to sequence A; the steps went on very smoothly until we reached ester XXIV. Fig. (7) demonstrates the difference in the NMR spectra of the three compounds XIX, XXI, and XXIV to show that the starting compound XIX is not present among the reaction products at various atages. Ozonolysis of ester XXIV to XXV did not give a sufficient yield for a reasonable analysis. The IR, however, indicated an increased intensity in the carbonyl groups area, and a diminished band at 6.23 microns. This was a critical limiting stage at which we had to stop as the time had already run out completely.

The remaining reduction step however is not to be considered very critical since a very mild reduction

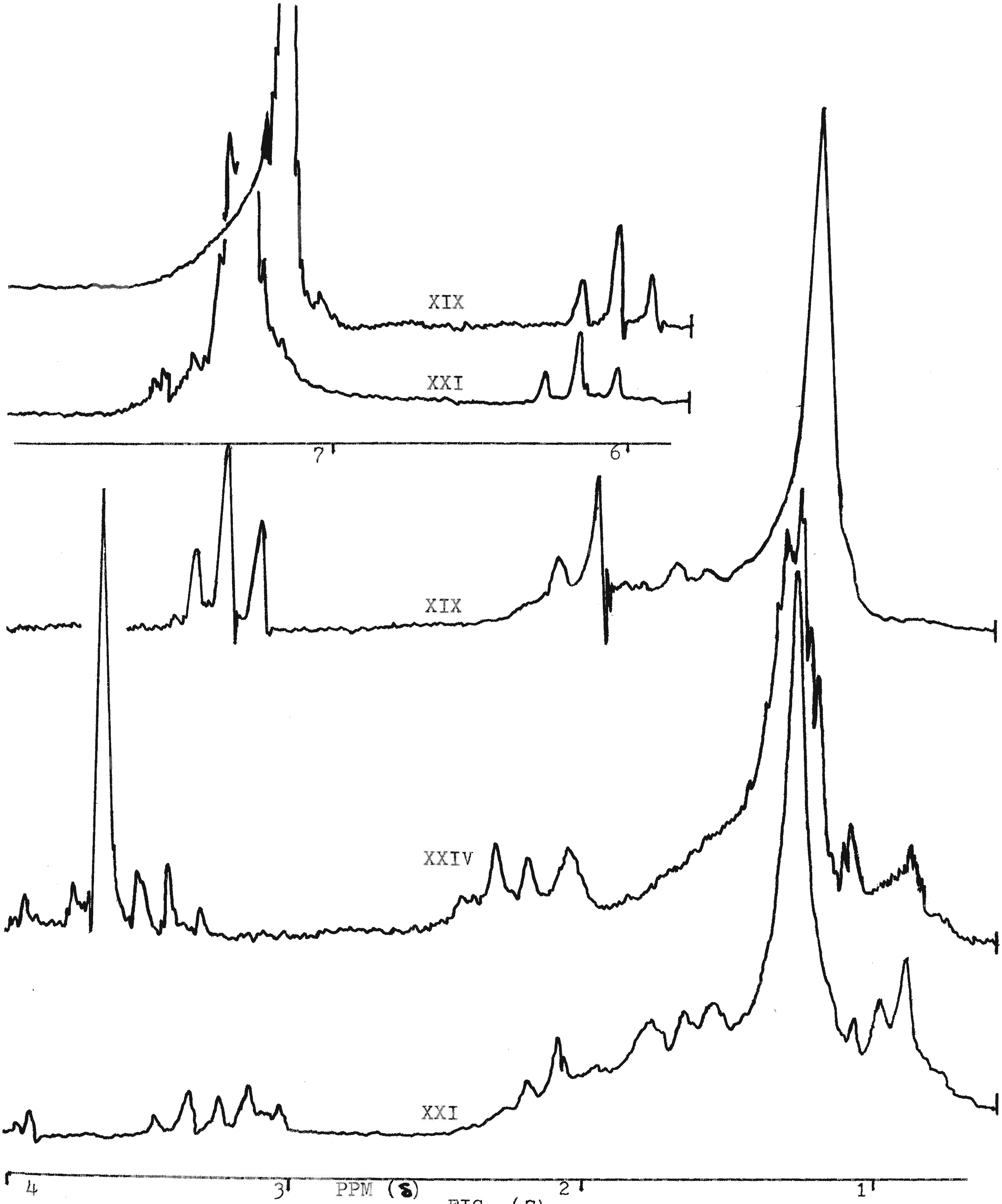


FIG. (7)

procedure has been described by Caglioti (28) in which various ketones were reported to have been successfully reduced to hydrocarbons in a very smooth way. In fact this can be a doubly advantageous method for work on optically active compounds since it is a two-step method which includes the formation of tosylhydrazone derivatives of ketones as a first step, followed by reduction of these derivatives by the use of sodium borohydride to the corresponding hydrocarbons. In this particular case, the first step can also be regarded, to a large extent, as a purification step on the basis that almost all of the tosylhydrazone derivatives are crystallizable solids.

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