THE SYNTHESIS AND CHEMISTRY OF vic-CYCLOPROPANEDIOLS

Thesis for the Degree of Ph. D.
MICHIGAN STATE UNIVERSITY
DUANE B. PRIDDY
1971

This is to certify that the

thesis entitled

The Synthesis and Chemistry
of vic-Cyclopropanediols

presented by

Duane B. Priddy

has been accepted towards fulfillment
of the requirements for

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William Reusch

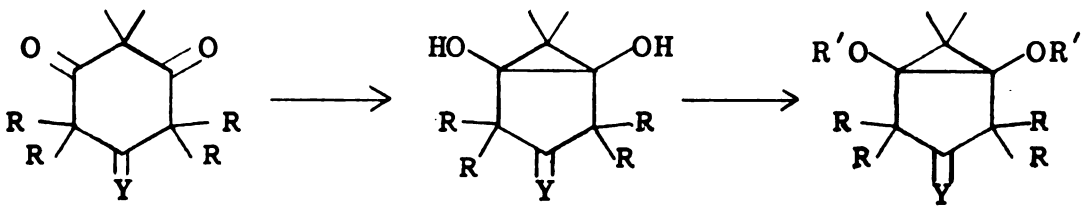
Major professor

Date May 19, 1971

ABSTRACT

THE SYNTHESIS AND CHEMISTRY
OF vic-CYCLOPROPANEDIOLS

vic-Cyclopropanediols IV, V and VI were prepared by lithium in ammonia reduction of 2,2-dimethylcyclohexane-1,3-dione derivatives I, II and III respectively. V was also prepared by Clemmensen reduction of II. All of the vic-cyclopropanediols were readily converted to their respective diacetate derivatives and V was also converted to the dimethyl derivative IX.



I - III IV - VI VII - X

I R=H; Y=$(CH_3)_2$

II R=CH_3; Y=O

III R=CH_3; Y=OH,H

IV R=H; Y=$(CH_3)_2$

V R=CH_3; Y=O

VI R=CH_3; Y=OH,H

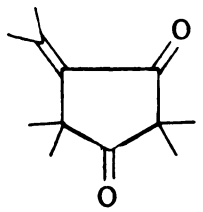
VII R=H, R'=AC; Y=$(CH_3)_2$

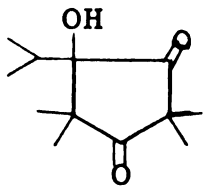
VIII R=CH_3; R'=AC; Y=O

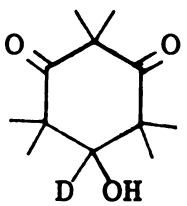
IX R=R'=CH_3; Y=O

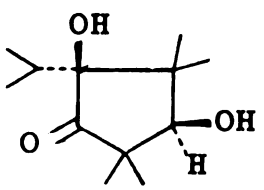
X R=CH_3; R'=AC; Y=OAC,H

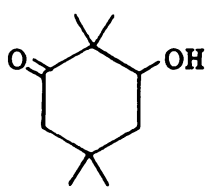
Acid and base catalyzed rearrangements of V and VI and the reaction of VII with base were studied and found to react as shown.

V $\xrightarrow{H_2SO_4}$ 

V $\xrightarrow[H_2O]{HCl}$ 

V $\xrightarrow[2)\ H^{\oplus}]{1)\ NaH,\ d_6DMSO}$ 

VI $\xrightarrow[\text{or base}]{\text{aqueous acid}}$ 

VII $\xrightarrow[KOH]{\text{methanolic}}$ 

Possible mechanisms for these reactions and the reaction of molecular oxygen with vic-cyclopropanediols are discussed.

THE SYNTHESIS AND CHEMISTRY OF *vic*-CYCLOPROPANEDIOLS

BY

Duane B. Priddy

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To Donna Mae

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The author wishes to express his appreciation to Professor William Reusch for his assistance and encouragement during the course of this investigation.

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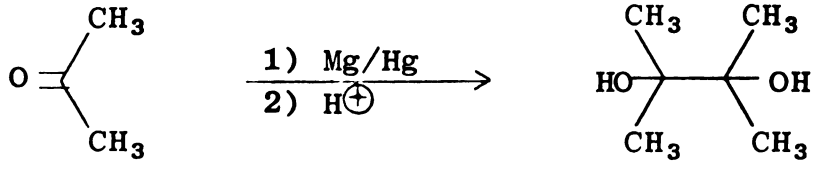
INTRODUCTION

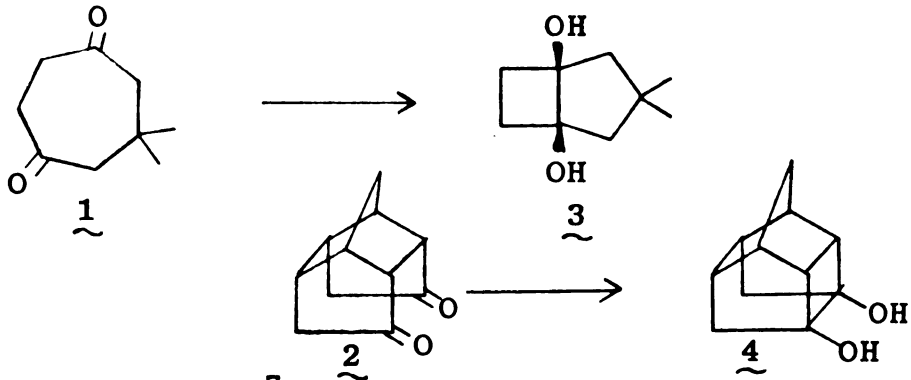
This thesis reports the synthesis of vic-cyclopropanediols via intramolecular pinacol reductions of β-diketones, and describes some of the characteristic chemical reactions of these compounds.

Pinacols have been prepared by many methods, the most common being the treatment of ketones with active metals in aprotic or weakly protonating solvents.[1]



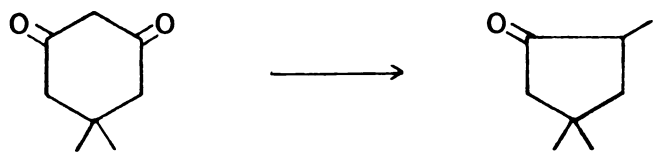
Pinacols have also been formed from ketones by electrochemical[2] and photochemical[3] reductions and may occur as by-products in Clemmensen[4] and metal-ammonia[5] reductions.

Intramolecular reductions of diketones to cyclic pinacols can occur, but have not been widely observed. The work of Wenkert and Yoder[6], involving Clemmensen reduction of the 1,4-diketones 2,2,6-trimethylcycloheptane-1,4-dione (1) and tetracyclo $\left[6.3.0^{1,8}.0^{5,9}.0^{4,11}\right]$ undecan-3,6-dione (2) to the vic-cyclobutanediols 3 and 4 respectively, illustrate these transformations.



1 3 2 4

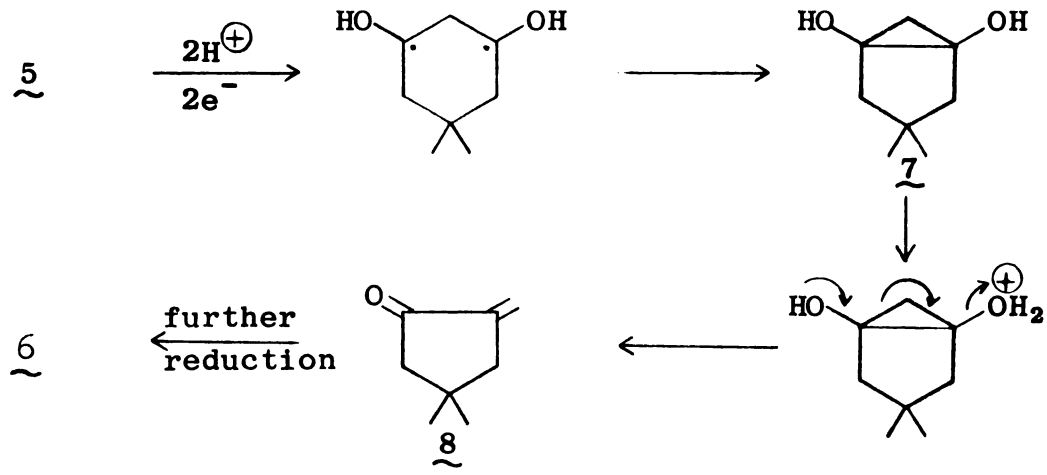
In 1933, Khuda[7] subjected 5,5-dimethyl-cyclohexane-1,3-dione (dimedone) (5) to Clemmensen reduction and obtained a saturated monoketone which proved not to be the expected 3,3-dimethylcyclohexanone. On repeating this work, Dey and Linstead[8] were able to identify the anomolous product as the ring contracted ketone 2,4,4-trimethylcyclohexanone (6).



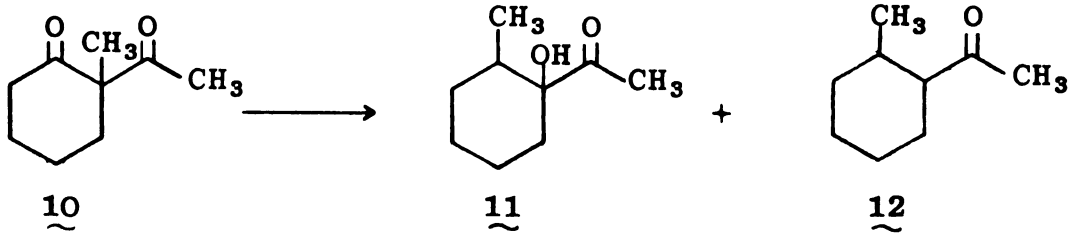
5 6

Staschewski[9] has proposed a mechanism for this rearrangement (equation 1), involving the formation of a vic-cyclopropanediol intermediate 7 which suffers acid catalyzed ring opening to 8 followed by subsequent reduction to 6.

(1)

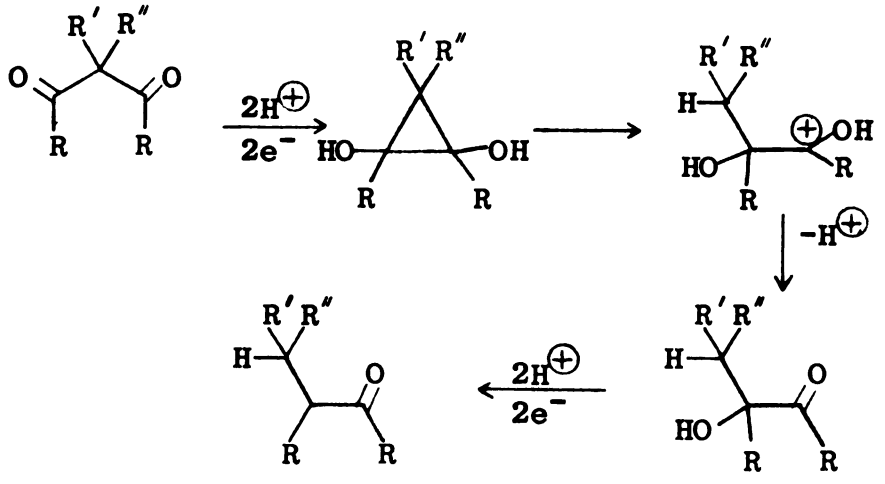


Having observed that brief Clemmensen reduction of 2-methyl-2-acetylcyclohexanone (10) gave a mixture of ketol 11 and ketone 12 (the former diminishing on more vigorous reduction), Karin and Wenkert[10] proposed an alternate mechanism (equation 2) in which the vic-cyclo-

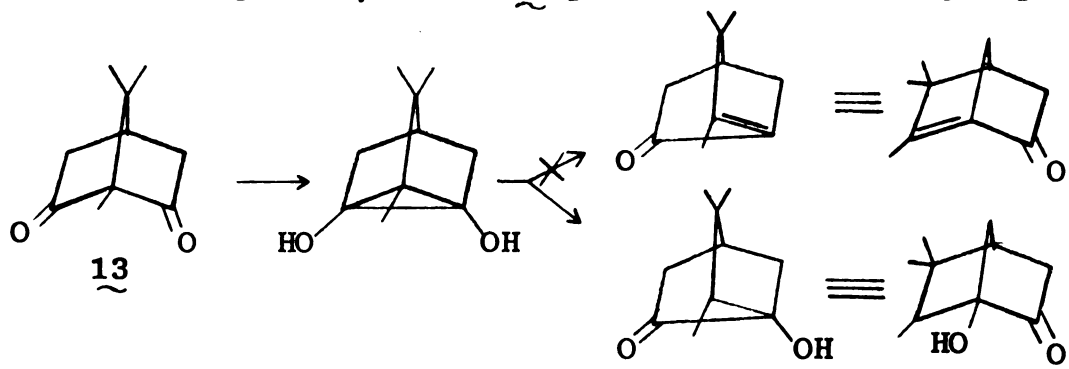


propanediol intermediate is opened to an α-ketol which is then further reduced to a ketone.

(2)

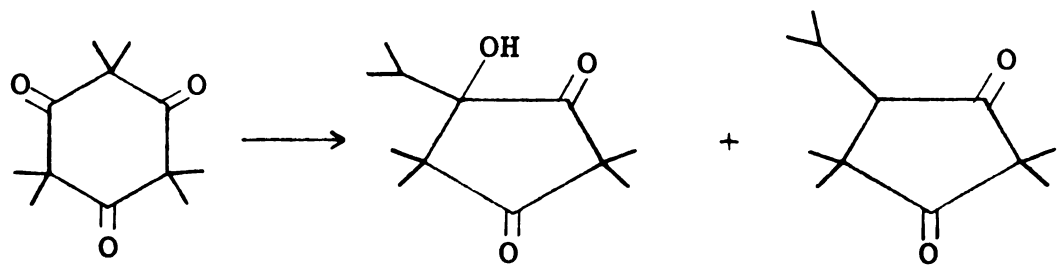


Chuang and Scott[11] have described the Clemmensen reduction of β-diketone 13, which can only proceed via the Wenkert mechanism, since formation of an α,β-unsaturated ketone is prohibited by the structural constraints of the [2.2.1] bicycloheptane ring system (i.e. Bredt's Rule). As expected, ketol 14 proved to be the major product.



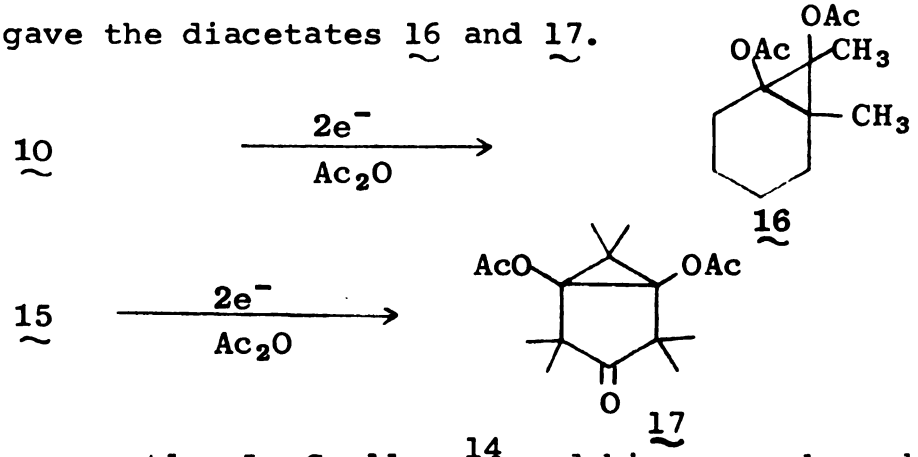
13 14

Recently, Curphey and McCartney[12] provided further support for the Wenkert mechanism by isolating the ketol 16 from a Clemmensen reduction of 2,2,4,4,6,6-hexamethyl-1,3,5-cyclohexanetrione (15).

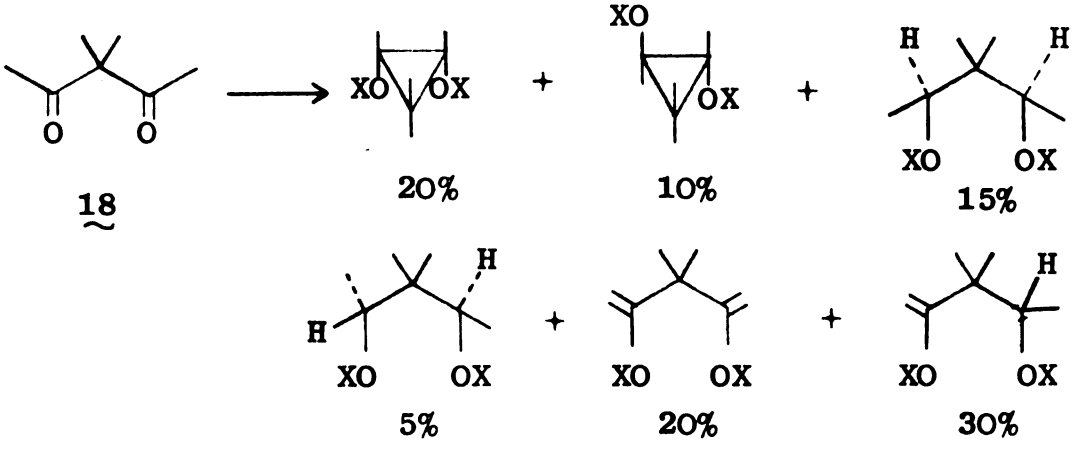


15 16

After the investigations described in this thesis were essentially finished, two other research groups reported the isolation of vic-cyclopropanediol derivatives from reduction of 1,3-diketones. Curphey and co-workers[13] found that electrochemical reduction of 10 and 15 in tetrohydrofuran, using acetic anhydride as a trapping agent, gave the diacetates 16 and 17.



More recently, Le Goaller [14] and his co-workers have investigated the reduction of 3,3-dimethyl-1,3-pentanedione (18) by a sodium dispersion in the presence of trimethylsilyl chloride. A mixture of products including trimethylsilyl ethers of cis and trans-cyclopropanediols, was obtained.

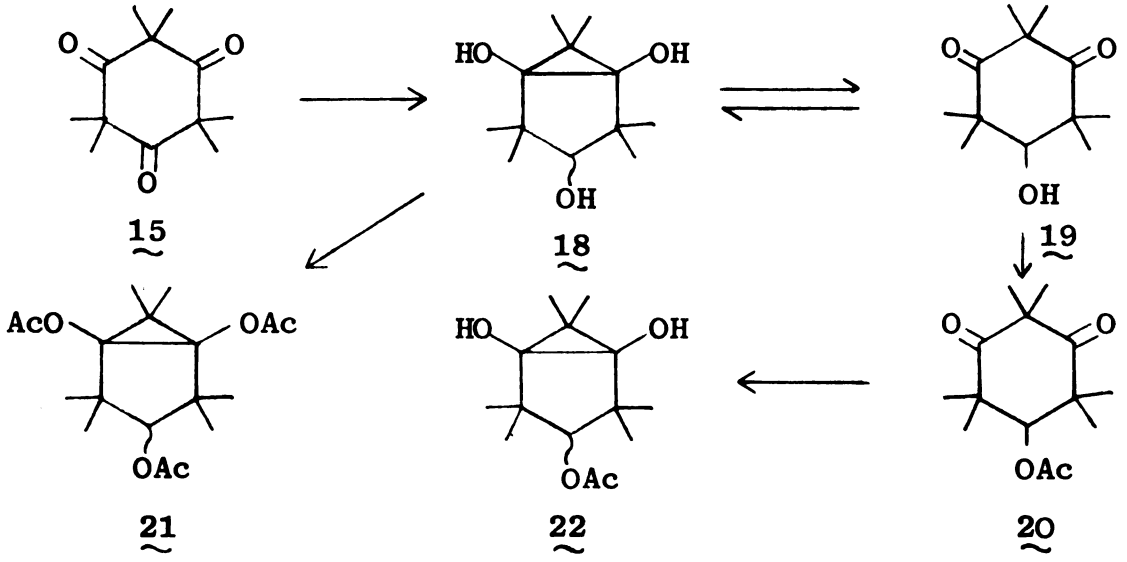


X = $(CH_3)_3Si$

RESULTS AND DISCUSSION

In this investigation, the preparation of vic-cyclopropanediols was first attempted by reduction of 2,2,4,4,6,6-hexamethyl-1,3,5-cyclohexanetrione with an excess of lithium metal dissolved in an ammonia-tetrahydrofuran solvent mixture. The relatively insoluble powder thus obtained in 65-95% yield was essentially transparent in the carbonyl stretching protion of the infrared, except for a slight impurity absorbing at 1710 cm^{-1}. Crystallization of the powder from acetic acid and pyridine followed by sublimation neither improved the melting point (melts with decomposition above 160°) nor removed the impurity. This material, however, gave a clearly defined nmr spectrum (p.54) which was consistent with its assignment as 2,2,4,4,6,6-hexamethyl-1,3,5-trihydroxybicyclo [3.1.0] hexane (18).

Treatment of 18 with refluxing acetyl chloride in acetic acid gave the triacetate derivative 21, characterized by a strong infrared absorption at 1750 cm^{-1}. The nmr spectrum showed nine acetoxy protons at δ 2.12, one proton geminal to an acetoxy group at 4.95 and eighteen methyl protons arranged as singlets at 1.65, 1.15, 1.07 and 1.0 in a ratio of 3:6:6:3 respectively.

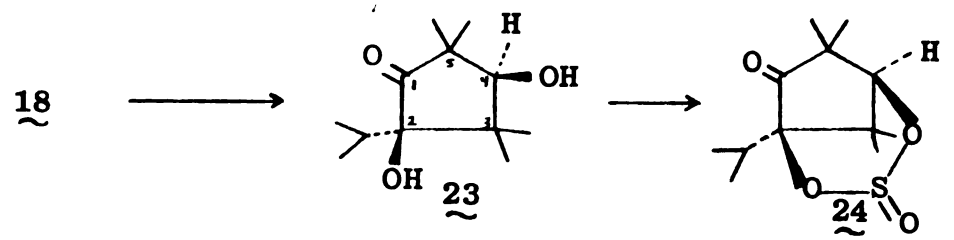


Crude 18 was readily oxidized to the hydroxydiketone 19 by mild oxidizing agents such as aqueous-methanolic ferric chloride, chromic oxide in pyridine (Sarett's reagent) or molecular oxygen. Compound 19 exhibited strong infrared absorption at 1690 and 1720 cm^{-1}, (typical of a non-enolizable β-diketone) and the nmr spectrum displayed methyl singlets at δ1.27, 1.21 and 1.19 in a ratio of 3:9:6, and two one proton doublets typical of a secondary hydroxy group at 3.69 and 3.51 ($J \approx 5$ cps). Treatment of 19 with a refluxing solution of acetyl chloride in acetic acid gave a monoacetate derivative 20, which was characterized by infrared absorption at 1690, 1720 and 1730 cm^{-1}. The nmr spectrum of 20 showed 3 acetoxy protons at δ2.04, one proton geminal to an acetoxy group at 5.0 and 18 methyl protons appearing as three singlets at 1.10, 1.23 and 1.28 in a ratio of 6:9:3 respectively. Reduction of 19 with

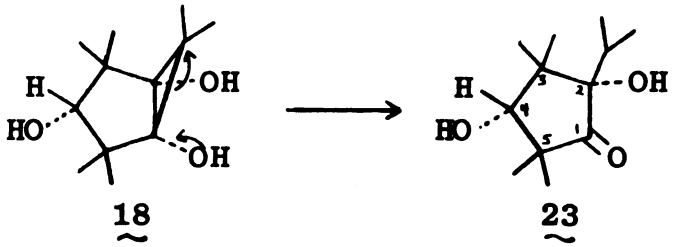
lithium in an ammonia-tetrahydrofuran solution produced a sample of 18 free from the carbonyl containing impurity mentioned previously. Furthermore, reduction of 20 by the slow addition of two equivalents of lithium to a refluxing ammonia-ether solution of the compound gave the monoacetate derivative 22. This result indicates that addition of two electrons to the β-diketone moiety occurs much faster than reduction of the ester.

The stereochemistry of compounds 18, 21 and 22 could not be established solely by spectroscopic analysis; however, chemical evidence points to a cis-orientation for all the hydroxyl groups. Treatment of 18 with refluxing hydrochloric acid, refluxing methanolic-potassium hydroxide or thermolysis in an evacuated sealed tube at 250° gave the cis-dihydroxy cyclopentanone 23, characterized by a strong absorption at 1735 cm^{-1} in the infrared. The nmr spectrum of 23 showed two one proton doublets at δ2.48 and 3.80 characteristic of a secondary hydroxyl group, a tertiary hydroxyl proton singlet at 2.88, a tertiary isopropyl group with restricted rotation displayed as a one proton multiplet at 1.90 and two doublets (3H each) at 0.72 and 1.07 (J≈6.5 cps), and four methyl singlets at 0.79, 1.07, 1.15 and 1.18. The cis relationship of the hydroxyl groups in 23 was established by its conversion to the cyclic sulfite ester 24, characterized

by strong infrared absorption at 960, 1210 and 1760 cm^{-1}. The nmr spectrum of 24 shows a one proton singlet at δ4.20, a one proton multiplet at 2.18, two three proton doublets at 1.10 and 1.20 (J≈6.5 cps) and twelve methyl protons appearing as three singlets at 1.51, 1.28 and 1.12 in a ratio of 6:3:3 respectively.

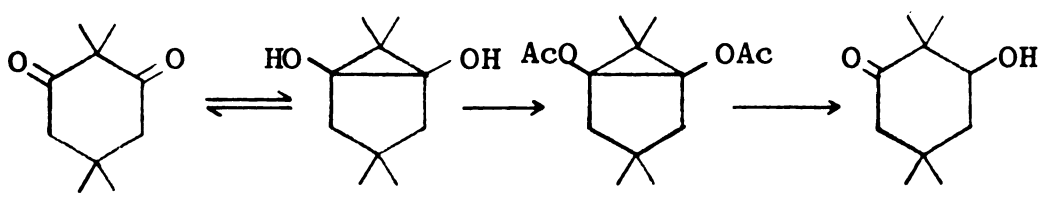


Since the configuration at carbon atoms 2 and 4 in 23 cannot have changed during the reaction with thionyl chloride, it is clear that the stereochemistry of the three hydroxyl groups in 18 must also be cis.



Reduction of 2,2,5,5-tetramethyl cyclohexane-1,3-dione (25) by lithium in an ammonia-tetrahydrofuran solvent mixture gave an unstable white crystalline solid. This material, which was assumed to be the corresponding vic-cyclopropanediol 26, was essentially transparent in the carbonyl stretching region of the infrared; but upon

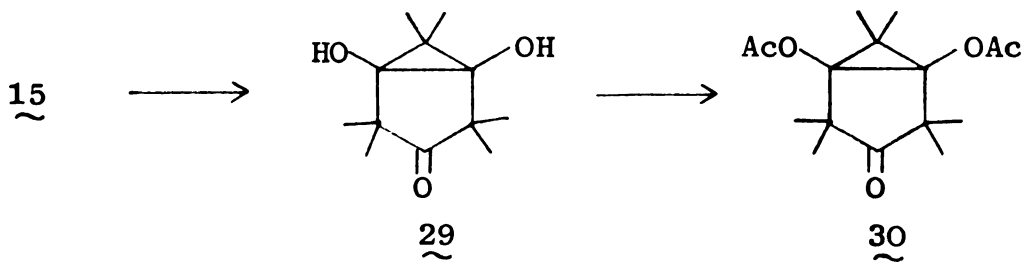
exposure to air it reverted to the diketone 25 in a few hours. Fortunately, this diol could be trapped as the stable diacetate derivative 27 by treatment with a refluxing solution of acetyl chloride in acetic acid. The structure of 27 was confirmed by a strong acetate absorption at 1735 cm^{-1} in the infrared and a nmr spectrum displaying a six proton acetoxy singlet at δ2.10, a four proton AB quartet for the methylene protons at 1.65 and 2.00 (J≈14 cps) and 12 methyl protons displayed as three singlets at 0.92, 0.96 and 1.16 in a ratio of 3:3:6 respectively. Saponification of this diacetate with refluxing methanolic-potassium hydroxide under nitrogen gave 2,2,5,5-tetramethyl-3-hydroxycyclohexanone (28), which proved to be identical to an authentic sample prepared by partial reduction of 25.[17]



25 26 27 28

The slow addition of two equivalents of lithium to a solution of 15 in a refluxing ammonia and ether solution produced 2,2,4,4,6,6-hexamethyl-1,5-dihydroxybicyclo [3.1.0] hexane-3-one (29). Crystallization of the

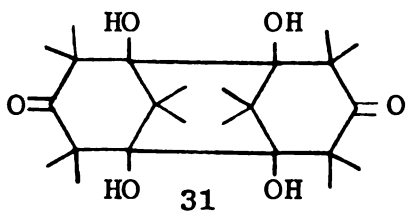
crude reduction product from ether gave 29 in the form of its monohydrate as indicated by a four proton hydroxy signal in the nmr. Sublimation of this hydrate gave pure 29, which was characterized by strong infrared absorption at 1735 cm^{-1} and a nmr spectra displaying a two proton tertiary hydroxyl signal at δ 4.68 and 18 methyl protons appearing as four singlets at 1.18, 1.12, 1.02 and 0.93 in a ratio of 6:3:6:3 respectively. Treatment with acetyl chloride in acetic acid gave a diacetate derivative 30, displaying infrared absorptions at 1750 and 1735 cm^{-1} and nmr singlets at δ 1.17, 1.27, 1.43 and 2.14 in a ratio of 3:9:6:6.



29 30

Some of these cyclopropanediol derivatives were examined by mass spectrometry, but the results were not very informative. Since the molecular ions could not be detected and since complex fragmentation patterns were observed, the molecular weights of 21 and 30 were confirmed by vapor pressure osmometry (due to the rapid air oxidation of dilute solutions of 29, its molecular weight could

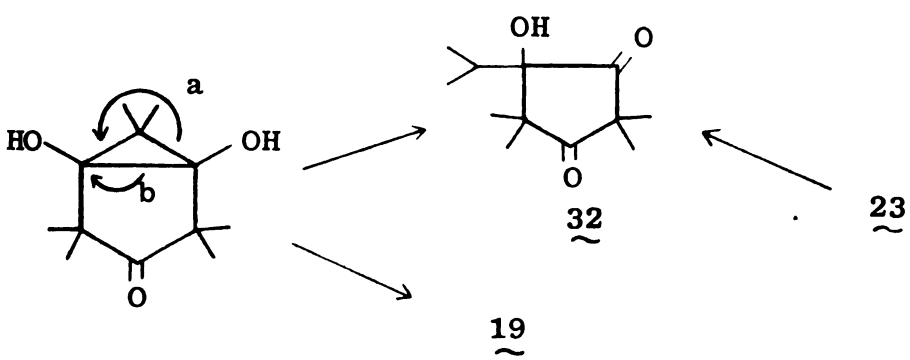
not be determined by this method). This was done to eliminate any possibility of these compounds being dimeric pinacols such as 31 which might conceivably possess similar chemical and spectroscopic properties. The observed molecular weights agreed well with the expected values: 21, 347 ± 10 (calc 340); 30, 297 ± 6 (calc 296).



31

Investigations of the chemistry of 29 yielded many interesting results. Treatment of 29 with a refluxing solution of methanolic-potassium hydroxide in the absence of oxygen gave the hydroxycyclohexadione 19. However, refluxing concentrated hydrochloric acid transformed 29 into the hydroxycyclopentadione 32[12], which was identical with the product obtained from Jones oxidation of 23.

Two modes of cyclopropyl ring opening have been observed (i.e. path a and path b). Cyclopropanediol 18 opens exclusively by path a with either acid or base

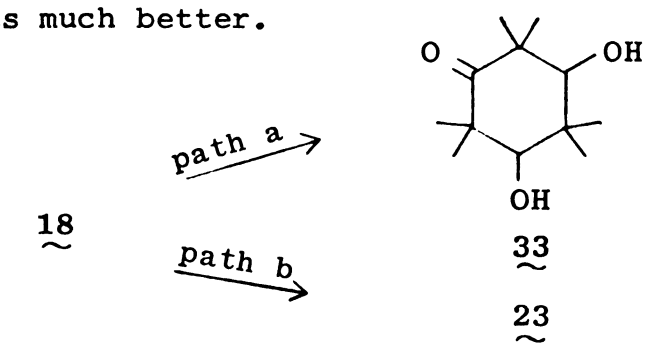


32 23

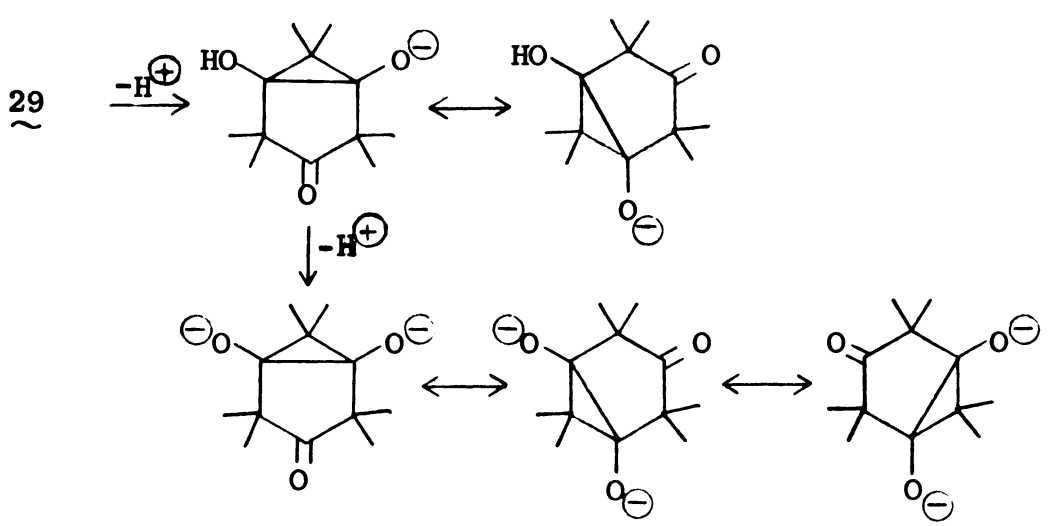
19

catslysis, cyclopropanediol diacetate 27 is opened by path b on treatment with base and cyclopropanediol 29 opens by path a with acid and path b with base.

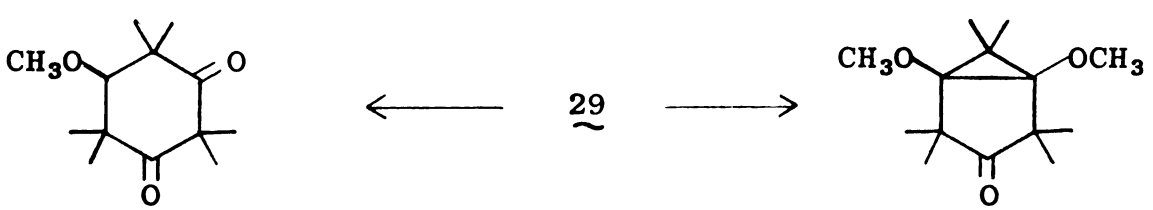
Compound 18 only reacts via path b since reaction by path a would produce a sterically unfavored six membered ring 33 due to crowding of the substituents on the ring. The planarity of the five membered ring in 23 is able to accomadate the bulk of all the substituents much better.



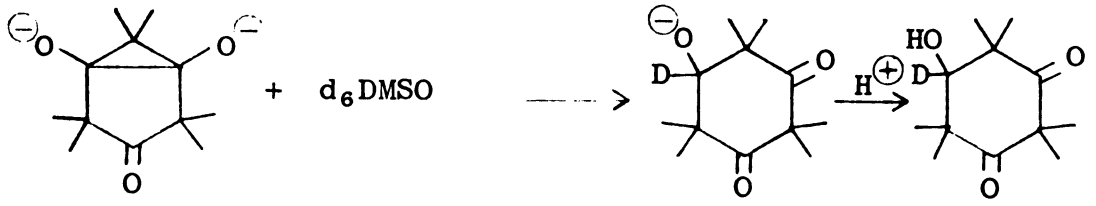
Since both modes of cyclopropyl ring opening were observed with 29 while only path a was observed for 18, the base catalyzed reaction of 29 is apparently modified by participation of the carbonyl group (possibly as shown in the following equation).



Attempts to prepare the dimethyl derivative (35) of cyclopropanediol 29 revealed an unexpected reaction of the bis conjugate base. When 29 was treated with two equivalents of sodium hydride in a 1:1 dimethylformamide-benzene solution followed by the addition of excess methyl iodide the major product was the methoxycyclohexanedione 34 characterized by infrared absorption at 1720 and 1690 cm^{-1} and a parent ion at m/e 226 in the mass spectrum. In contrast, similar treatment of a hexamethylphosphoramide (HMPA) solution of 29 gave the diether 35, characterized by infrared absorption at 1735 cm^{-1}. The nmr spectrum of 35 shows the six methoxy protons as a singlet at δ3.49, and 18 methyl protons as signlets at 1.34, 1.28, 1.23 and 1.11 in a ratio of 3:6:6:3.



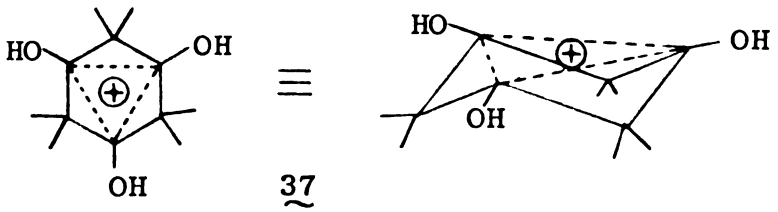
Apparently the conjugate base of 29 is sufficiently reactive to abstract a proton from dimethylformamide. Indeed, a similar proton transfer from dimethyl sulfoxide was disclosed by the isolation of 36 from the reaction of 29 with an excess of sodium hydride in perdeuterated dimethylsulfoxide followed by an aqueous work-up.



36

The surprisingly slow conversion of 29 to 32 in acid (8 hours in refluxing concentrated hydrochloric acid) prompted a study of the Clemmensen reduction of 15 under mild conditions. This led to the remarkable discovery that reduction of 15 with amalgamated zinc dust in a refluxing ethanol-concentrated hydrochloric acid mixture for two and a half hours gave 29 in nearly quantitative yield. Although cyclopropanediol derivatives were recently isolated from Clemmensen type reductions of β-diketones, this work represents the first case in which a cyclopropanediol itself has actually been isolated from a Clemmensen reduction. Thus the intermediacy of cyclopropanediols in the abnormal Clemmensen reduction of 1,3-diketones has been established beyond question.

The unusual stability of 29 in acidic media suggested that its conjugate acid might have the trishomocyclopropenyl cation structure 37. Evidence supporting less highly substituted cations of this kind as intermediates



37

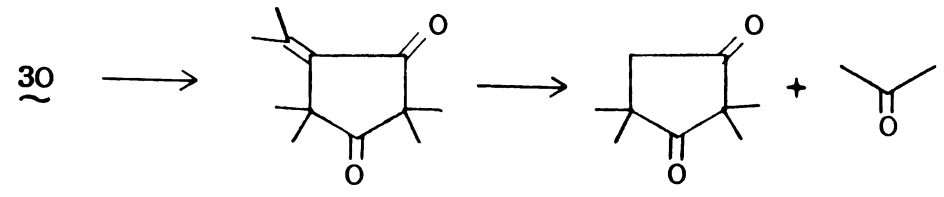
in solvolsis reactions of 3-substituted bicyclo [3.1.0] hexane derivates has been reviewed by Winstein and co-workers.[15] The importance of steric hinderance by the gem. dimethyl groupings in 37 is difficult to estimate; however, the chair-like conformation required by 37 must suffer serious non-bonded methyl compressions. Furthermore, Olah and co-workers[16] have noted that the positive charge in protonated ketones resides mainly on the oxygen atom; consequently the effect of homoaromatic stabilization may be obscured by charge localization by the hydroxyl substituents.

Additional information concerning the question of homoaromatic stabilization of the conjugate acid of 29 was obtained from its nmr spectrum in strong acids. If 37 were formed, one would expect the methyl resonance signals in this ion to appear either as a single peak or a pair of equally intense peaks depending upon the rate of ring inversion. In any event, a significant simplification of the original nmr spectrum was anticipated.

The four methyl singlets displayed in the nmr spectrum of 29 in perdeuterated dimethyl sulfoxide solution were

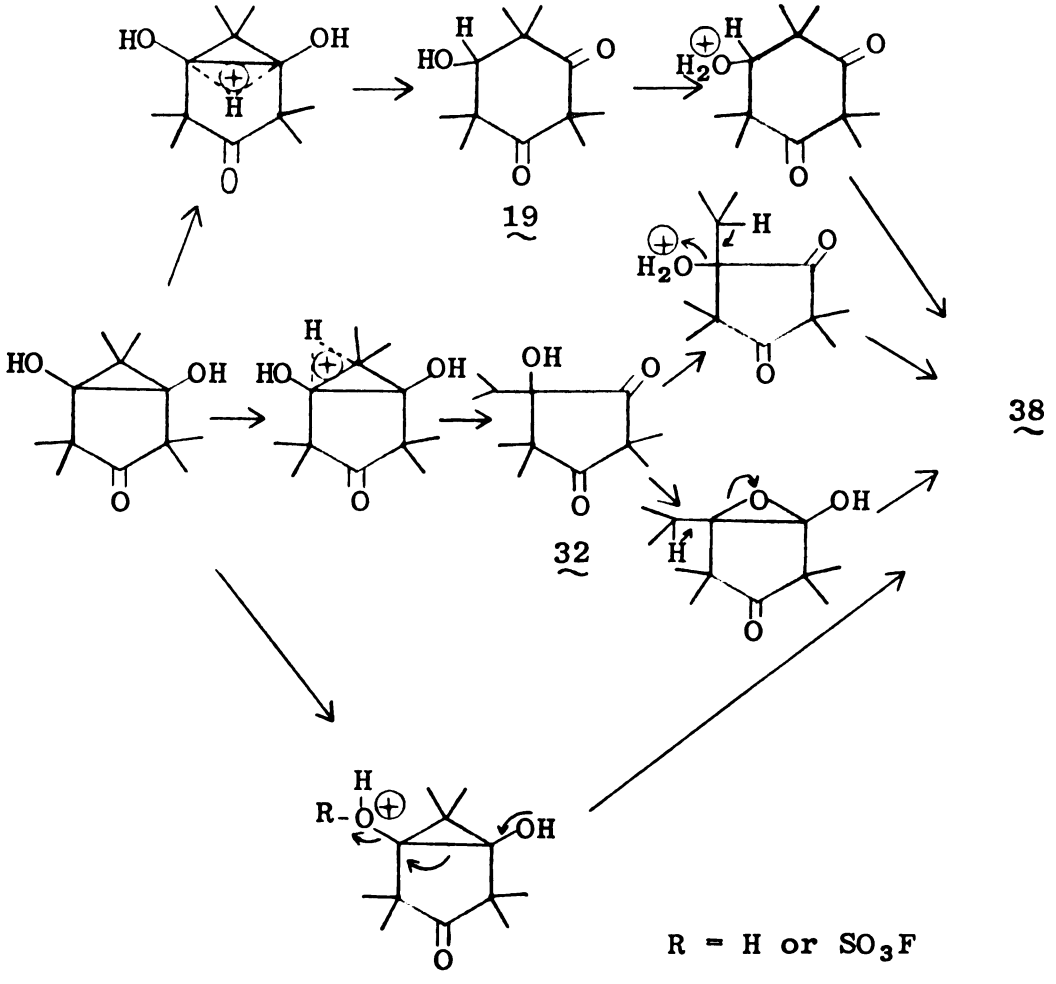
essentially unchanged in mixed fluorosulfonic acid and sulfur dioxide solution at -40° . However, when the temperature of this solution was increased to -10° , several new peaks appeared, and on recooling this solution to -40° the complex spectrum suffered only a slight signal broadening. The absence of any structural rearrangement was demonstrated by recovery of unchanged 29 upon quenching the sample in ice water. Thus homoaromatic stabilization does not seem to be significant in this system.

When 29 was dissolved in fluorosulfonic acid at room temperature and allowed to stand for forty-five minutes (or in concentrated sulfuric acid for twenty-four hours), it was transformed to the isopropylidenecyclopentanedione 38. This volatile crystalline solid was characterized by infrared absorptions at 1750, 1690 and 1606 cm^{-1}, and an nmr spectrum displaying four methyl singlets at δ2.30, 2.16, 1.38 and 1.09 in a ratio of 3:3:6:6. Further confirmation of this structure (38) was obtained by retro-aldol cleavage in refluxing methanolic-potassium hydroxide, which gave acetone (dinitrophenylhydrazone derivative mp 125-126°) and tetramethylcyclopentanedione 39 (a volatile oil having infrared absorption at 1760 and 1725 cm^{-1}, nmr signals at δ1.16 (6H), 1.26 (6H) and 2.68 (2H), and a parent ion at m/e 154 in the mass spectrum.



38 39

The nature of the species obtained from solutions of 29 in strong acids and the mechanism for the rearrangement of 38 are not immediately obvious. Three possible rearrangement pathways can in fact be conceived:



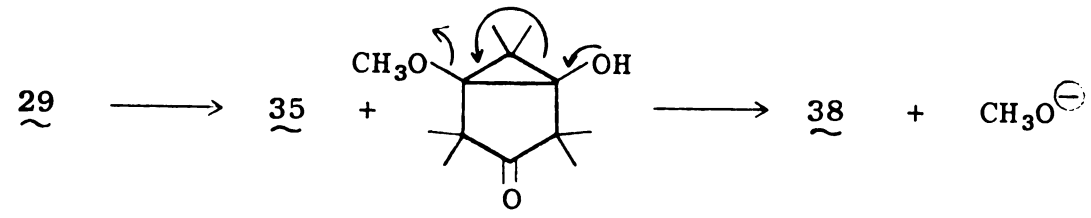
R = H or SO_3F

Path 1 involves the formation of 19 as an intermediate, and the subsequent 1,2-acyl shift is analogous to the acid catalyzed transformation of 2,2,5,5-tetramethyl-3-hydroxycyclohexanone to 2-isopropylidene-4,4-dimethylcyclopentanone reported by Eschenmoser et al.[17] Although a solution of 19 in fluorosulfonic acid does in fact rearrange to 38 at a slightly faster rate than 29, 19 has never been detected in any acid catalyzed reactions of 29.

Path 2 is considered primarily because the intermediate was actually isolated from the reaction of 29 in aqueous acid, as described previously. Indeed, a solution of 32 in fluorosulfonic acid rearranged to 38 within a few seconds at room temperature. This unexpectedly facile dehydration of an α-ketol may proceed as a concerted elimination or via an epoxide.

Path 3, in which a conjugate acid or a fluorosulfonate ester (40) serves as a leaving group in the ring opening step, does not proceed via an isolable intermediate. Nevertheless, this mechanism deserves serious consideration, since formation of the unsymmetrical intermediate 40 provides a rationale for the nmr observations described previously and would easily give 29 back again upon aqueous treatment. In this respect it should be noted that several attempts to obtain the unsymmetrical methyl ether 41 failed

(a mixture of 35 and 38 were always obtained from treatment of 29 with sodium hydride and one equivalent of methyl iodide in HMPT solution); presumably due to a similar elimination-rearrangement reaction.



It was mentioned previously that vic-cyclopropanediols are readily oxidized to diketones by the action of oxygen. vic-Cyclopropanediols appear to be much more reactive toward oxygen than are cyclopropanols. Thus, an ethyl acetate solution of 29 absorbed one molar equivalent of oxygen in 30-60 minutes, giving 15 as the sole product (ca. 95% yield): and 26 was readily oxidized to 2,2,5,5-tetramethylcyclohexane-1,3-dione even in the solid state. This should be compared with 24-48 hr. time reported for the oxidation of methyl substituted cyclopropanols in hexane[18].

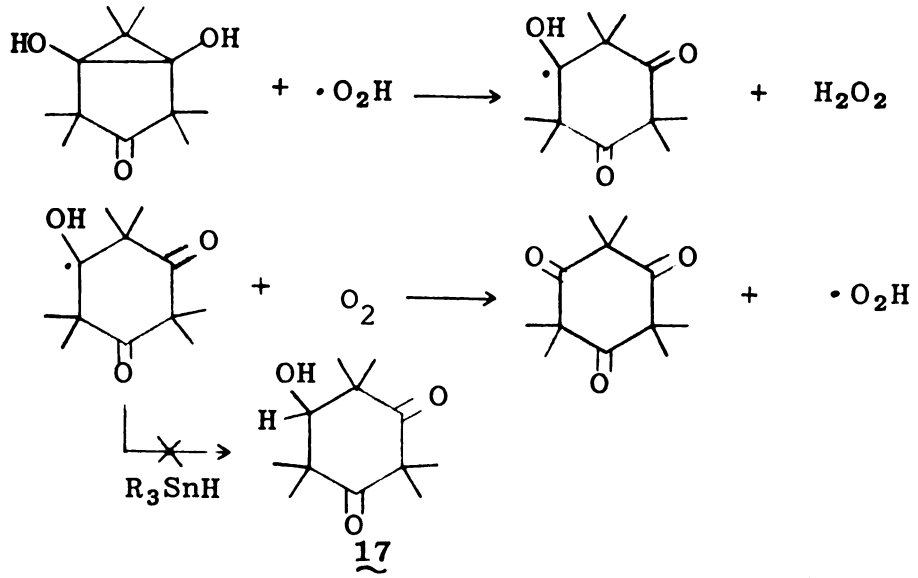
The absorption of oxygen by solutions of 29 was easily followed with the aid of a small gas buret, and the formation of a peroxide containing product was determined by iodometry. The results from several dozen experiments showed considerable variation: oxygen uptake was 70-95% of theoretical (assuming a 1:1 stoichiometry) and the

peroxide concentration always ran a bit lower. Since the gasometric and iodometric measurements corresponded more closely during the early stages of the oxidation, it appears that the peroxide suffered a slow decomposition.

Other facts germane to this reaction are:

1) A short induction period (ca. 5 min.) was normally observed.
2) The oxidation of 29 to 15 could also be effected by nitric oxide; however, the stoichimetry was complex (ca. 1:3.5 respectively). A transient blue color was noted in these reactions, but no intermediates could be isolated.
3) The dimethyl ether 35 and diacetate 30 derivatives of 29 were not affected by prolonged exposure to oxygen or nitric oxide.

These facts suggest that the reaction of vic-cyclopropanediols with oxygen proceeds by a radical mechanism (equation 3) similar to that proposed by Gibson and DePuy[18]. The opening of the three membered ring is shown to be concerted with hydrogen abstraction in order to rationalize the reactivity order: vic-cyclopropanediol>cyclopropanol > other cyclic> 3° -alcohols.



17

Numerous attempts to trap the intermediate carbinol radical by conducting the oxidation of 29 in solvent mixtures having large mole excesses of tri-n-butylstannane or triphenylstannane were all unsuccessful. The conversion of 29 to 15 proceeded at the customary rate and gave no detectable 19 (as little as 0.5% VI could have been detected by our infrared and nmr analysis). These results suggest that carbinol radicals are oxidized by molecular oxygen with extraordinary ease; indeed, a similar oxygen effect was reported by Pitts et. al.[19] in their study of the photoreduction of benzophenone.

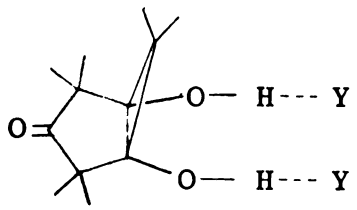
When three molar equivalents of p-chlorothiophenol was added to a solution of 29 in ethyl acetate, the oxidation to 15 was completely stopped (ie. no change in the

concentration of 29 and no uptake of oxygen was detected over a 24 hr. period). The reasons for this behavior are not clear. It may be that the thiophenol scavanges hydroperoxy radicals so effectively that the chain reaction cannot function (this explanation implies that molecular oxygen does not itself significantly attack cyclopropanols). Alternatively, thiophenol inhibition may be due to the hydrogen bonding effect discussed in the following paragraph.

In the course of these studies a curious solvent effect on the rate of oxidation of 29 was noted:

$CH_3CO_2C_2H_5 > CH_3COCH_3 > C_2H_5OH >>$ Pyridine, DMSO.

The time required for a test solution to absorb greater than 90% of the stoichiometric amount of oxygen ranged from 30-60 minutes for ethyl acetate and acetone to 24-48 hr. for pyridine and DMSO. A similar reactivity order was observed for nitric oxide oxidations. In addition, small amounts of DMSO were observed to inhibit oxidations in ethyl acetate solution. These facts can be explained by hydrogen bonding of the cyclopropanol hydrogen atoms. Since intramolecular hydrogen bonding is precluded by the molecular geometry of the vic-cyclopropanediols, intermolecular bonding, as in 42 can occur when strong hydrogen bond acceptors (eg Y = DMSO, pyridine) are present in the reaction mixture. These interactions apparently render radical attack at O-H more difficult.



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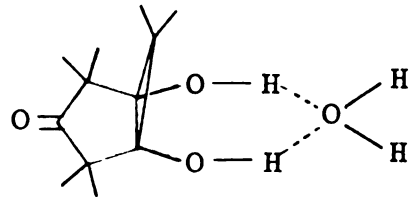

43

Compound 29 also forms a hydrate, which may have a cyclic hydrogen bonded structure similar to 43. It was found that solutions of this hydrate in ethyl acetate are oxidized much more slowly than pure 29.

EXPERIMENTAL

EXPERIMENTAL

General

Melting points were taken in capillary tubes on a Hoover-Thomas apparatus. Infrared spectra were recorded on a Perkin-Elmer 327B spectrophotometer in potassium bromide pellets or as neat liquid smears. Nuclear magnetic resonance spectra were obtained with a Varian A-60 spectrometer. Tetramethylsilane was used as an internal standard with the exception of figure 29 in which tetramethylammonium tetrafluoroborate was used. Elemental analyses were obtained from Spang Microanalytical Laboratory.

2,2,4,4,6,6-hexamethyl-1,3,5-trihydroxybicyclo [3.1.0] hexane (18). To a 250 ml, three necked flask equipped with a magnetic stirrer, dry ice-acetone condenser, soda lime drying tube and addition funnel was added 100 ml of anhydrous ammonia and 270 mg of lithium metal. Two grams of 2,2,4,4,6,6-hexamethylcyclohexane-1,3,5-trione[20] (15) was dissolved in 25 ml of tetrahydrofuran and added dropwise over 10 minutes to the refluxing ammonia solution. After a five minute reflux period, 5 g of ammonium chloride was added to the reaction mixture. The ammonia was allowed to evaporate under a stream of air and the residue was slurried with water and filtered to yield 1.9 g (94.5%) of a white powder, melting with decomposition above 150°.

Anal. Calc for $C_{12}H_{22}O_3$: C, 67.29; H, 10.28. Found: C, 67.31; H, 10.25.

The infrared spectrum of 18 is shown in figure 1 on page 39. The nmr spectrum is shown in figure 16 on page 54.

2,2,4,4,6,6-hexamethyl-5-hydroxycyclohexane-1,3-dione (19).

a) A 100 mg sample of 18 was dissolved in a mixture of 100 ml of methanol and 1 ml of concentrated hydrochloric acid. This mixture was kept at 40-50° for 3 days (exposed to the air) and the solution was allowed to evaporate under a stream of air until a thick slurry was obtained. Filtration gave 60 mg (60%) of long needles, mp 66-67° .

b) To a mixture of 100 mg of chromic anhydride in 2 ml of pyridine was added a solution of 10 mg of 18 in 2 ml of pyridine. After stirring at room temperature for 20 minutes, 20 ml of ether was added and the resulting solution was filtered. The filtrate was washed with water, 5% hydrochloric acid and allowed to evaporate under a stream of air, yielding 5 mg (50%) of white solid, mp 65-67° .

c) A slurry of 4.28 g of 18 in 150 ml of water and 100 ml of methanol was treated with a solution of 16 g of ferric chloride hexahydrate in 150 ml of water. After stirring at room temperature for one hour, the solution was extracted twice with 100 ml portions of ether. The

combined ether extracts were dried over anhydrous sodium sulfate and evaporated on a rotary evaporator to yield 4 g of a pink oil. This oil was crystallized from hexane to give 3.5 g (82%) of long white needles, mp 66-67° .

Anal. Calc for $C_{12}H_{20}O_3$: C, 67.92; H, 9.43. Found: C, 67.92; H, 9.39.

The infrared spectrum of 19 is shown in figure 2 on page 40. The nmr spectrum is shown in figure 17 on page 55.

2,2,4,4,6,6-hexamethyl-5-acetoxycyclohexane-1,3-dione (20). A solution of 500 mg of 19 in a mixture of 10 ml of acetic acid and 10 ml of acetyl chloride was heated at gentle reflux in an open beaker until only an oil remained. This oil was crystallized from hexane to give 350 mg (58%) of large white crystals, mp 76-79° .

Anal. Calc for $C_{14}H_{22}O_4$: C, 66.14; H, 8.66. Found: C, 66.10; H, 8.70.

The infrared spectrum of 20 is shown in figure 3 on page 41. The nmr spectrum is shown in figure 18 on page 56 .

2,2,4,4,6,6-hexamethyl-1,3,5-triacetoxybicyclo [3.1.0] hexane (21). A 1 g sample of 18 was dissolved in a mixture of 50 ml of acetic acid and 10 ml of acetyl chloride and heated at a gently boil in an open beaker until only an oil remained. The oil was crystallized twice from 50%

methanol giving 0.9 g (56%) of white needles, mp 158-160° .

Anal. Calc for $C_{18}H_{28}O_6$: C, 63.52; H, 8.24. Found: C, 63.52; H, 8.22.

The infrared spectrum of 21 is shown in figure 4 on page 42 .

2,2,4,4,6,6-hexamethyl-1,3-dihydroxy-5-acetoxybicyclo [3.1.0] hexane (22). To a 250 ml, three necked flask equipped with a magnetic stirrer and soda lime drying tube, was added 500 mg of 20, 100 ml of anhydrous ether and 50 ml of ammonia. The flask was placed in a dry ice-acetone bath for 5 minutes, 30 mg of lithium metal was then added and the cooling bath was removed. After 15 minutes, the reaction mixture was decomposed with excess ammonium chloride and the ammonia was evaporated under a stream of air. The ether which remained was washed with water, dried over anhydrous sodium sulfate and evaporated to give 100 mg (20%) of large prisms.

Anal. Calc for $C_{14}H_{24}O_4$: C, 65.62; H, 9.40. Found: C, 65.54; H, 9.56.

The infrared spectrum of 22 is shown in figure 5 on page 43 .

2,2,4,4-tetramethyl-cis-3,5-dihydroxy-5-isopropyl-cyclopentanone (23).

a) To a 250 ml three necked flask equipped with a magnetic stirrer and a nitrogen flushing valve was added 1.08 g of 18, 75 ml of deoxygenated ethanol, and 50 ml of 6N hydrochloric acid. The reaction mixture was

refluxed under nitrogen for 15 hours, concentrated to about half volume under a stream of nitrogen and the resulting solution extracted with ether. The ether extracts were dried over anhydrous sodium sulfate and evaporated to an oil which was crystallized from hexane to give 600 mg (55.5%) of large white crystals, mp 89-91° .

b) To a 250 ml, three necked flask equipped with a magnetic stirrer and nitrogen flushing valve was added 1.08 g of 18, 2 g of potassium hydroxide and 100 ml of deoxygenated methanol. This solution was refluxed for 4 hours under nitrogen, concentrated to about half its volume under a stream of nitrogen and the resulting solution extracted with ether. The ether extracts were dried over anhydrous sodium sulfate and evaporated to an oil, which was crystallized 15 times from hexane to give 150 mg (13.9%) of large prisms, mp 89-90.5° .

c) A 1.08 g sample of sublimed 18 was placed in an evacuated pyrex tube (11 mm x 15 cm) and heated to 250° for 1 hour. The oil thus obtained was recrystallized 15 times from hexane to give 200 mg (18.5%) of large prisms, mp 89-90.5° .

Anal. Calc for $C_{12}H_{22}O_3$: C, 67.30; H, 10.28. Found: C, 67.29; H, 10.58.

The infrared spectrum of 23 is shown in figure 6 on page 44 . The nmr spectrum is shown in figure 20 on page 58 .

1-isopropyl-2,2,4,4-tetramethyl-5-oxo-cis-1,3-cyclopentylene cyclic sulfite (24). A solution of 100 mg of 23 in 15 ml of pyridine was cooled to -5° and 2 ml of thionyl chloride was added dropwise over 10 minutes. The reaction mixture was maintained at -5° for seven hours and then poured onto ice and extracted with ether. The ether solution was dried over anhydrous sodium sulfate and evaporated. The brown solid which remained was recrystallized from hexane to give 70 mg (59.5%) of white needles, mp 68-70°.

Anal. Calc for $C_{12}H_{20}O_4S$: C, 55.38; H, 7.68. Found: C, 55.51; H, 7.78.

The infrared spectrum of 24 is shown in figure 7 on page 45.

2,2,5,5-tetramethyl-1,3-acetoxy bicyclo[3.1.0]hexane (27). To a 250 ml, three necked flask equipped with a magnetic stirrer and a nitrogen flushing valve was added 150 ml of ammonia, 180 mg of lithium metal and 2 g of 2,2,5,5-tetramethylcyclohexane-1,3-dione[17]. After being stirred at reflux for one hour, the reaction mixture was decomposed with an excess of ammonium chloride and the ammonia was completely evaporated under a stream of nitrogen. The residue was dissolved in a mixture of 50 ml of acetic acid and 50 ml of acetyl chloride; and this solution was heated to reflux under nitrogen for 30 minutes, and then poured into a beaker and evaporated at a gentle boil until

only a thick slurry remained. The slurry was added to cold water and extracted with hexane. The hexane extracts were washed with 10% sodium bicarbonate solution and concentrated to ca. 50 ml. This solution was cooled and the solid that appeared was removed by filtration to give 1.2 g (40%) white needles, mp 87-89° .

Anal. Calc for $C_{12}H_{20}O_3$: C, 67.92; H, 9.43. Found: C, 67.83; H, 9.53.

The infrared spectrum of 27 is shown in figure 8 on page 46. The nmr spectrum is shown in figure 22 on page 60 .

2,2,5,5-tetramethyl-3-hydroxycyclohexanone (28). To a 100 ml, three necked flask equipped with a magnetic stirrer, a reflux condenser and a nitrogen flushing valve was added 100 mg of 27, 1 g of potassium hydroxide and 35 ml of methanol. This mixture was heated at reflux under nitrogen for 1 hour and then concentrated to about half volume under a stream of nitrogen. 30 ml of water was then added and the resulting solution was extracted with ether. The ether extracts were dried over anhydrous sodium sulfate and evaporated to give a white solid which was recrystallized from methanol to give 20 mg of white crystals, mp 55-56.6° (lit[17] mp 54-55°).

2,2,4,4,6,6-hexamethyl-1,3-dihydroxybicyclo [3.1.0] hexane-5-one (29).

a) A 2.1 g sample of 15 was dissolved in 100 ml of anhydrous ether placed in a 250 ml, three necked flask equipped with a magnetic stirrer and soda lime drying tube. Anhydrous ammonia (75 ml) was added followed by 140 mg of lithium metal (in seven portions). After the blue color dissipated, the reaction mixture was decomposed with excess ammonium chloride and the reaction mixture was evaporated under a clean air stream. The residue was slurried in ether and water and filtered to give a white solid, which on sublimation gave 800 mg (38%) of white crystalline solid melting with decomposition above 160°.

b) A solution of 6.3 g of 15 dissolved in 60 ml of ethanol was added to a 500 ml, three necked flask containing 40 g of amalgamated zinc dust in 100 ml of water. 50 ml of concentrated hydrochloric acid was added and the reaction mixture was refluxed two and one-half hours. The reaction mixture was cooled, filtered and allowed to stand. The crystals which formed were separated by filtration; resulting in 5.5 g (87%) of a white crystalline solid.

Anal. Calc for $C_{12}H_{20}O_3$: C, 67.92; H, 9.43: Found: C, 67.87; H, 9.45.

The infrared spectrum of 29 is shown in figure 9 on page 47. The nmr spectrum is shown in figure 23 on page 61.

2,2,4,4,6,6-hexamethyl-1,5-diacetoxybicyclo [3.1.0] hexane-3-one (30). A 500 mg sample of 29 was added to a mixture

of 10 ml of acetic acid and 10 ml of acetyl chloride in a beaker and refluxed gently until only an oil remained. This syrup was crystallized from hexane to give 500 mg (71.7%) of white crystals, mp 128-130° .

Anal. Calc for $C_{16}H_{24}O_5$: C, 64.87; H, 8.11: Found: C, 64.71; H, 8.07.

The infrared spectrum of 30 is shown in figure 10 on page 48 . The nmr spectrum is shown in figure 24 on page 62 .

2,2,4,4-tetramethyl-5-isopropyl-5-hydroxycyclopentane-1,3-dione (32). To a 100 ml, three necked flask equipped with a magnetic stirrer a reflux condenser and a nitrogen flushing valve was added 50 ml of concentrated hydrochloric acid and 1 g of 28. This mixture was heated at reflux under nitrogen for three hours, and then extracted with ether. The ether extracts were dried over anhydrous sodium sulfate and evaporated to give 1 g (100%) of a solid. Sublimation of this material gave a white crystalline solid, mp 37-38.5° (Lit[12] 37-38°).

The infrared spectrum of 32 is shown in figure 11 on page 49 .

2,2,4,4,6,6-hexamethyl-5-methoxycyclohexane-1,3-dione (34). To a 100 ml, three necked flask equipped with a magnetic stirrer, a nitrogen flushing valve and an addition funnel was added 107 mg of 23, 25 ml of dry benzene, 25 ml of dry dimethylformamide and 50 mg of sodium hydride. This mixture was stirred under nitrogen until hydrogen evolution ceased, and 1 ml of methyl iodide was then added

followed by another 2 hours of stirring. Water and ether were added, the immiscable layers were separated, and the organic layer was dried over anhydrous sodium sulfate and evaporated to give 87 mg (77%) of an oil. Glpc analysis of this oil showed that it was ca. 98% pure.

The mass spectrum of 34 showed a parent ion at m/e 226 (calc P + 1 and P + 2 for $C_{13}H_{22}O_3$; 13.44 and 1.43 respectively; Found: 13.1 and 1.2.

The infrared spectrum of 34 is shown in figure 12 on page 50 .

2,2,4,4,6,6-hexamethyl-1,3-dimethoxybicyclo[3.1.0] hexane-5-one (35). To a 100 ml, three necked flask equipped with a magnetic stirrer, nitrogen flushing valve and addition funnel was added 214 mg of 29, 10 ml of dry hexamethylphosphoramide and 100 mg of sodium hydride. After nitrogen evolution ceased, 1 ml of methyl iodide was added and the stirring was continued for one hour. The reaction mixture was quenched by 20 ml of water and the resulting solution was extracted with pentane. Evaporation of the pentane extracts gave a solid which was sublimed to give 100 mg (45.5%) of a white crystalline solid, mp 113-121° .

Anal. Calc for $C_{14}H_{24}O_3$: C, 70.00; H, 10.00 Found: C, 70.11; H, 10.04.

The infrared spectrum of 35 is shown in figure 13 on page 51 . The nmr spectrum is shown in figure 25 on page 63 .

2,2,4,4-tetramethyl-5-isopropylidenecyclopentane-1,3-dione (38). A 400 mg sample of 23 was dissolved in 1.8 ml of concentrated sulfuric acid, and after standing at room temperature for 24 hours, the mixture was poured into ice water and extracted with ether. The ether solution was dried over anhydrous sodium sulfate and evaporated to leave an oil, which on sublimation gave 270 mg (74.5%) of white crystals, mp 34.5-36°C .

The mass spectrum of 38 showed a parent ion at m/e 194 (calc P + 1 and P + 2 for $C_{12}H_{18}O_2$; 13.33 and 1.22 respectively; Found: 13.8 and 1.4). The infrared spectrum is shown in figure 14 on page 52 . The nmr spectrum is shown in figure 26 on page 64.

2,2,4,4-tetramethylcyclopentane-1,3-dione (39). A mixture of 582 mg of 30, 174 mg of potassium hydroxide, 40 ml of 95% ethanol and 10 ml of water was heated at reflux for four hours, cooled and then diluted with water and extracted with ether. The ether extracts were washed with water, dried over anhydrous sodium sulfate and evaporated to give 300 mg (65%) of a volatile brown oil.

The mass spectrum of 39 showed a parent ion at m/e 154 (calc P + 1 and P + 2 for $C_9H_{14}O_2$; 10.03 and 0.85 respectively; Found: 10.9 and 1.1. The infrared spectrum is shown in figure 15 on page 53 .

Attempt to prepare 2,2,4,4,6,6-hexamethyl-1-hydroxy-3-

methoxybicyclo [3.1.0] hexane-5-one (41). A 200 mg sample of 29 was placed in a 100 ml, three necked flask equipped with a nitrogen flushing valve and magnetic stirrer. 10 ml of dry hexamethylphosphoramide was added followed by 100 mg of sodium hydride. The reaction mixture was then stirred at room temperature for 10 minutes followed by the addition of 145 mg of methyl iodide. After stirring for another hour, 20 ml of water was added and the resulting solution then extracted with pentane. Evaporation of the pentane gave an oil. Glpc analysis of the oil showed that it contained about 45% each of 35 and 38. The nmr spectrum of the oil is shown in figure 28 on page 66.

Iodometric titration of mixture obtained during the oxidation of 2,2,4,4,6,6-hexamethyl-1,3-dihydroxybicyclo [3.1.0] hexane-5-one. After a mixture of 29 in the desired solvent had been subjected to molecular oxygen, it was added to 10 times its volume of glacial acetic acid. An excess of saturated potassium iodide solution was added and the resulting mixture allowed to stand for 5 min. The liberated iodine was then determined by titration with 0.1 normal sodium thiosulfate solution.

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BIBLIOGRAPHY

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APPENDIX

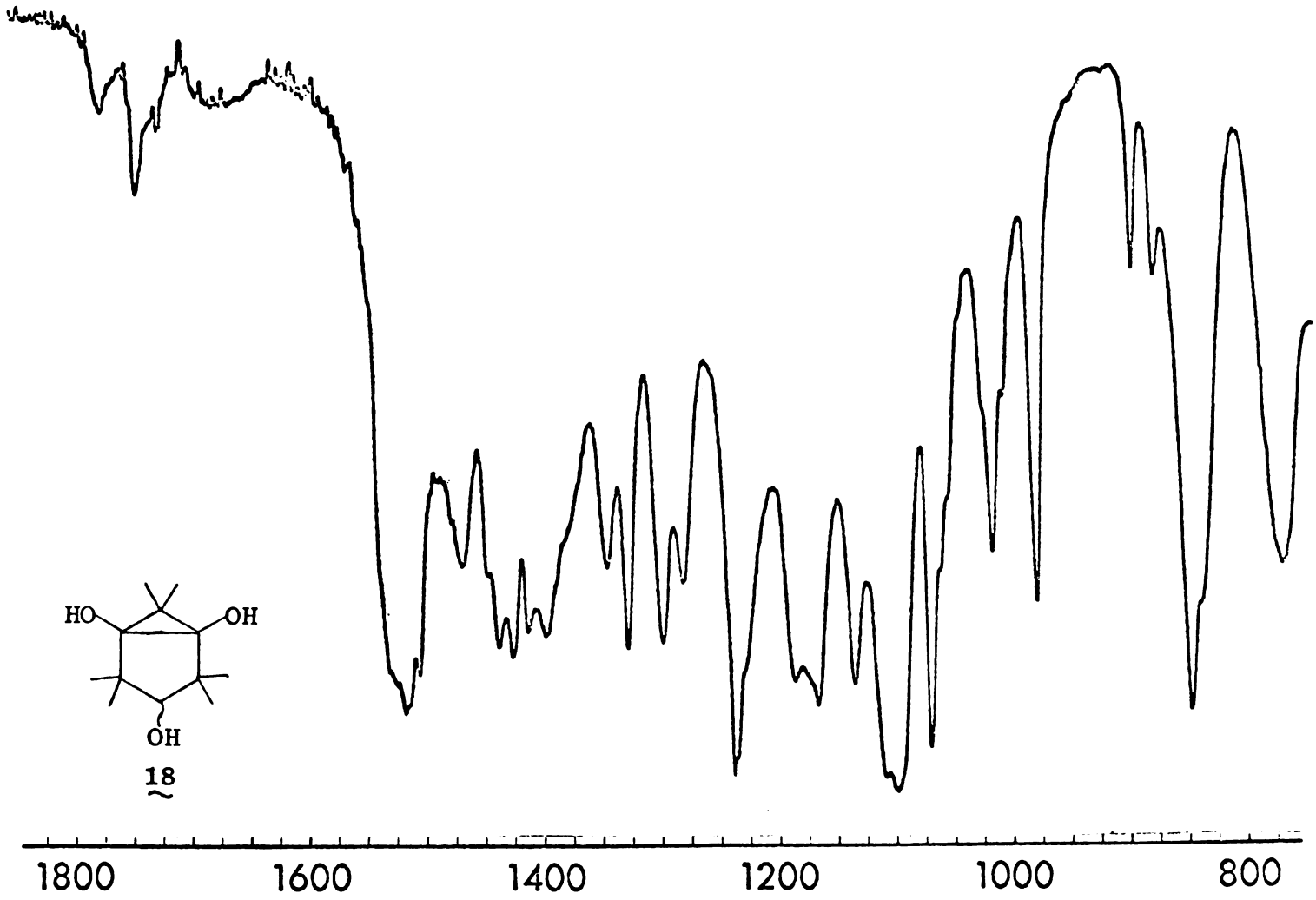

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Figure 1. Infrared spectrum of 2,2,4,4,6,6-hexamethyl-1,3,5-trihydroxybicyclo [3.1.0] hexane

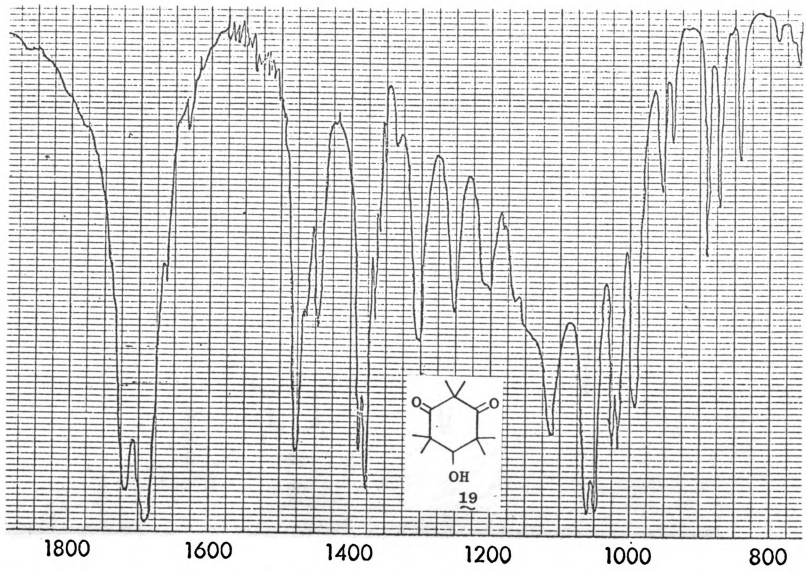

Figure 2. Infrared spectrum of 2,2,4,4,6,6-hexamethyl-5-hydroxycyclohexane-1,3-dione

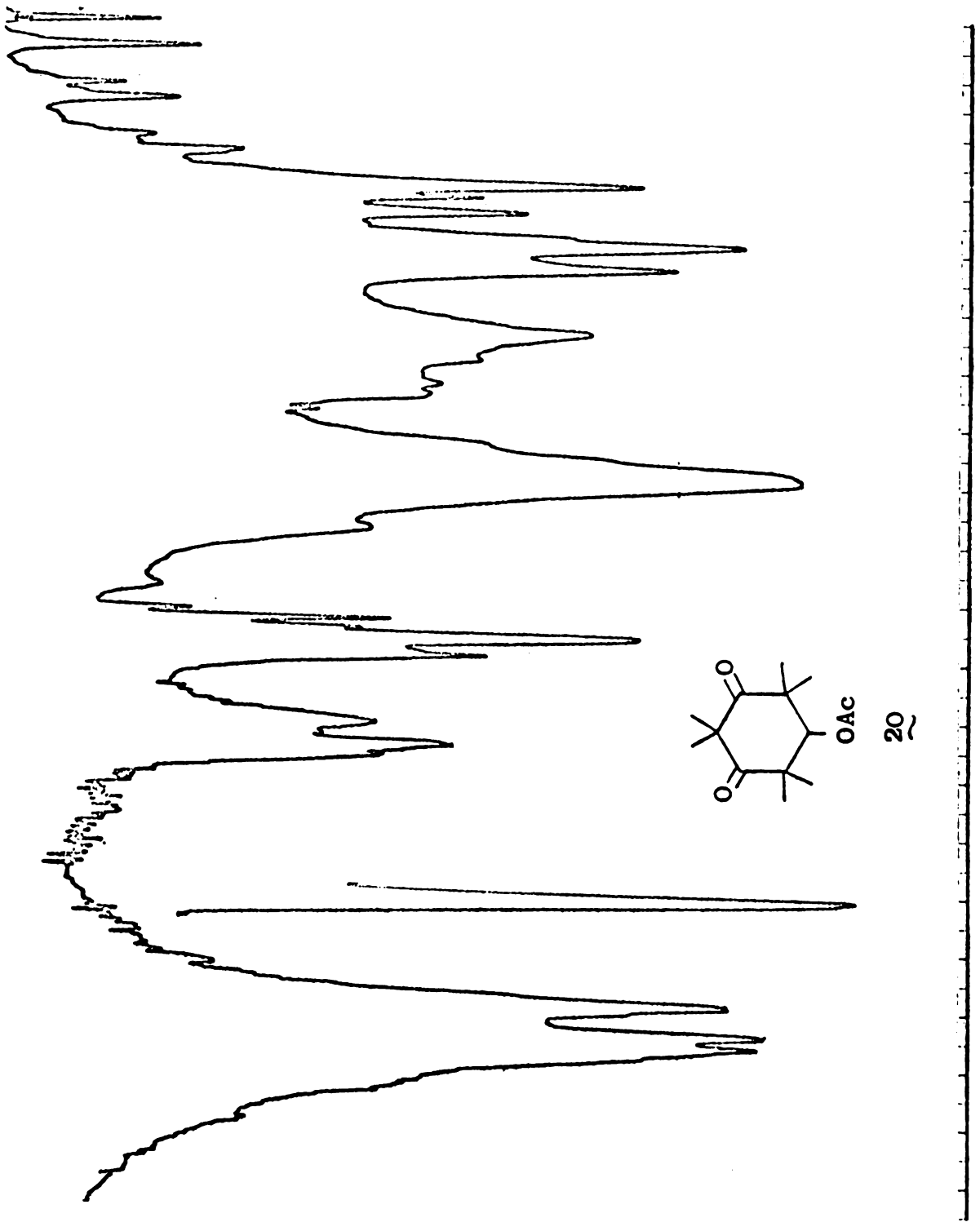

Figure 3. Infrared spectrum of 2,2,4,4,6,6-hexamethyl-5-acetoxycyclohexane-1,3-dione

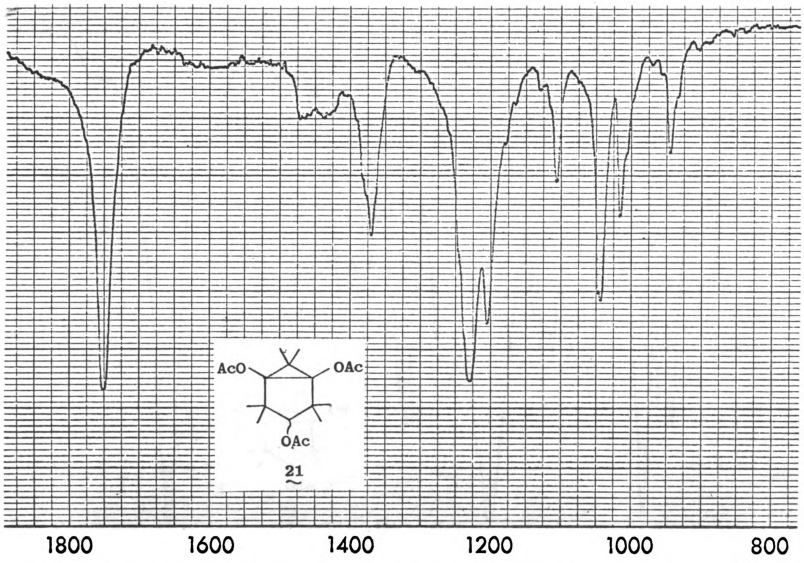

Figure 4. Infrared spectrum of 2,2,4,4,6,6-hexamethyl-1,3,5-triacetoxybicyclo [3.1.0] hexane

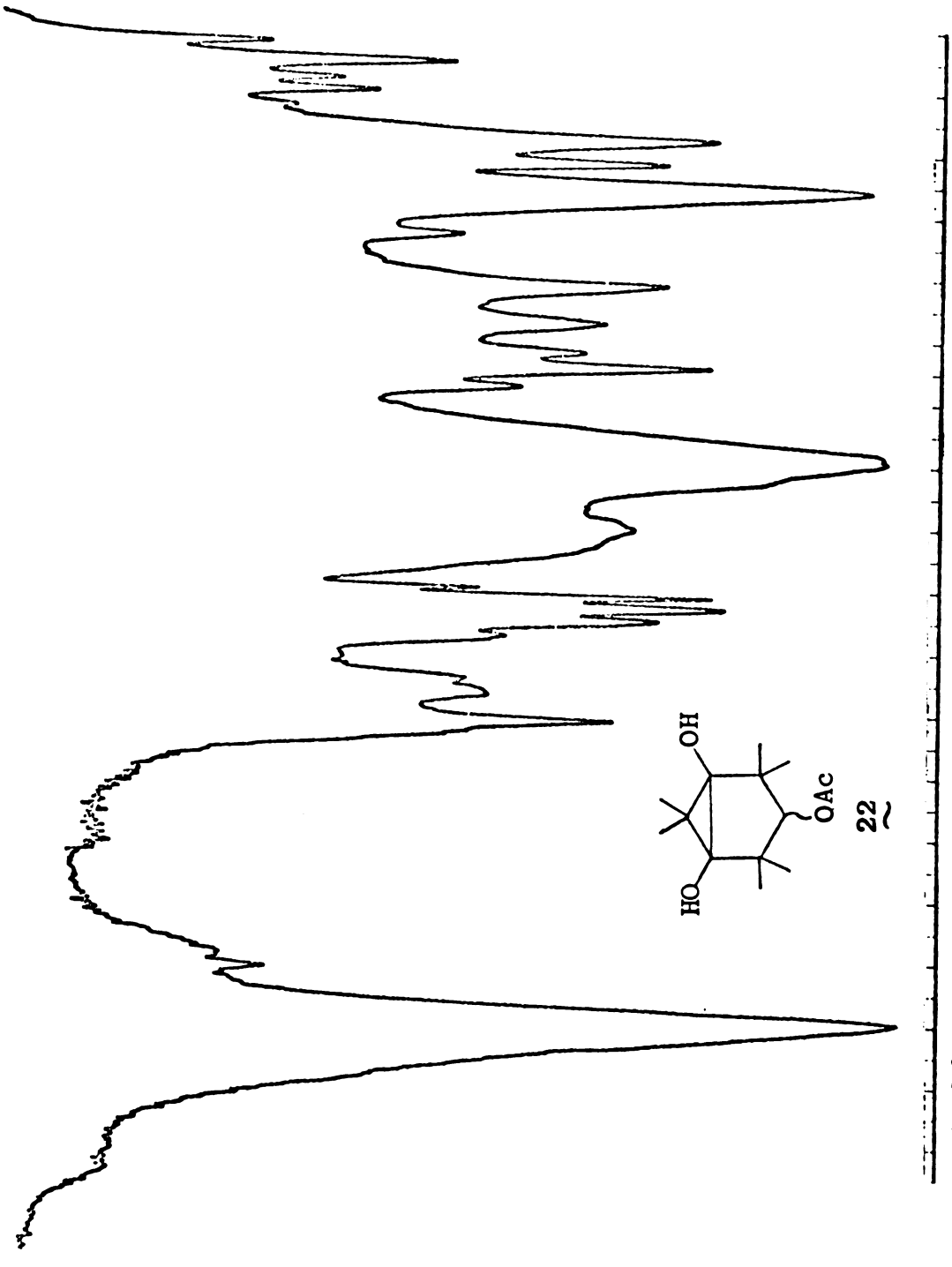

Figure 5. Infrared spectrum of 2,2,4,4,6,6-hexamethyl-1,3-dihydroxy-5-acetoxybicyclo [3.1.0] hexane

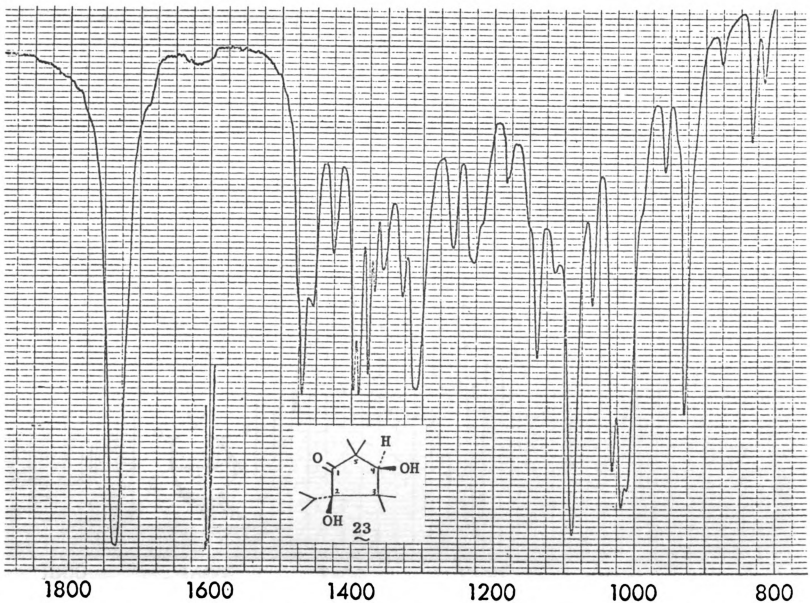

Figure 6. Infrared spectrum of 2,2,4,4-tetramethyl-cis-3,5-dihydroxy-5-isopropylcyclopentanone

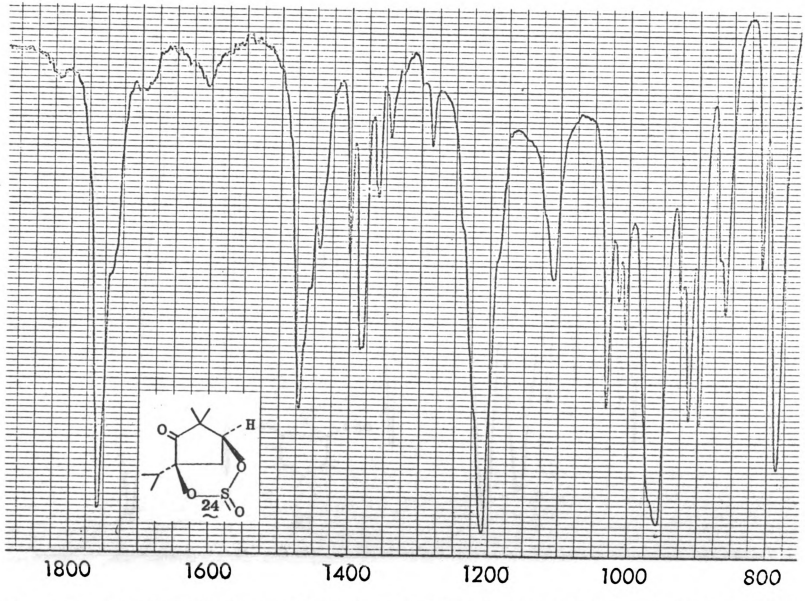

Figure 7. Infrared spectrum of 1-isopropyl-2,2,4,4-tetramethyl-5-oxo-cis-1,3-cyclopentylene cyclic sulfite

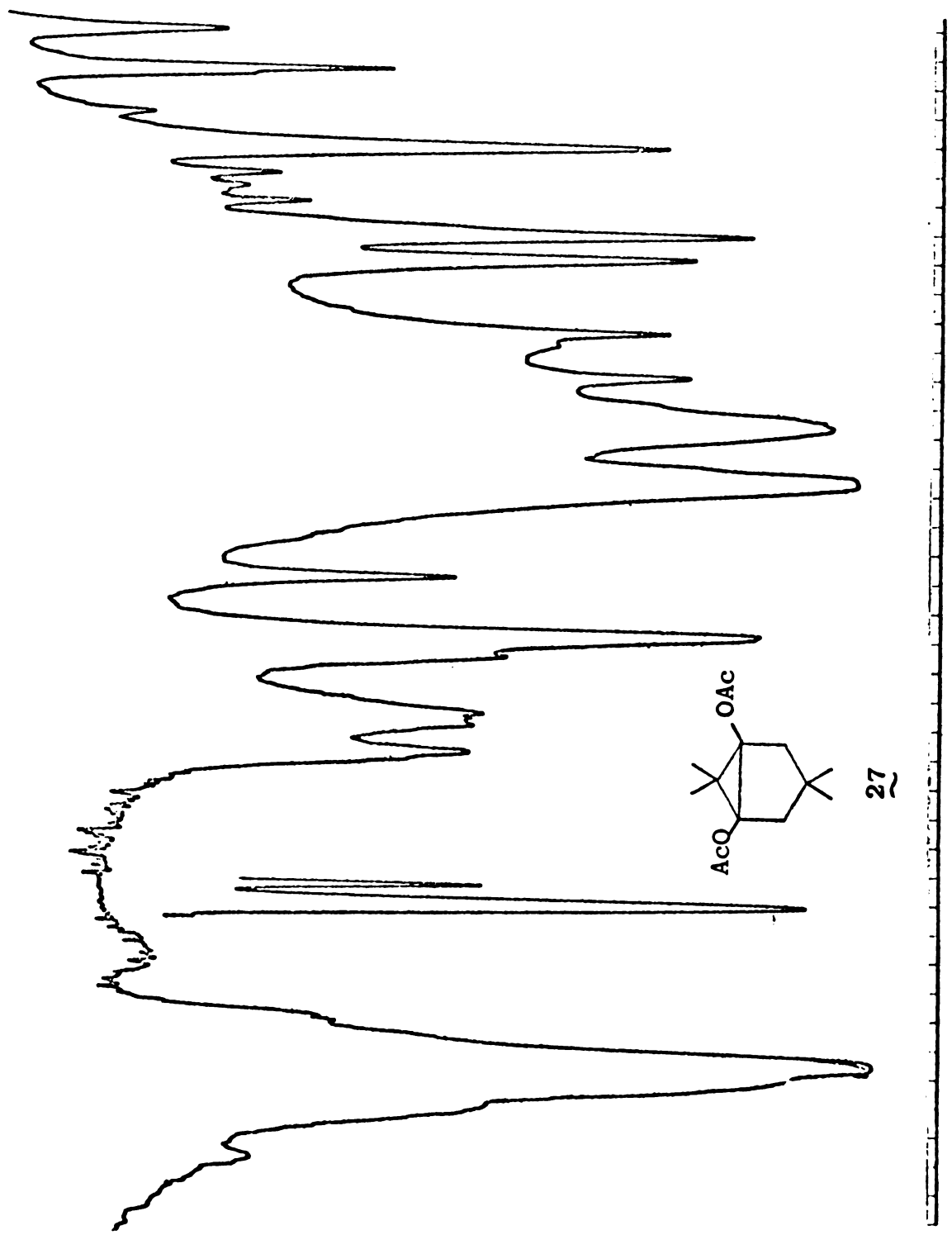

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Figure 8. Infrared spectrum of 2,2,5,5-tetramethyl-1,3-acetoxybicyclo [3.1.0] hexane

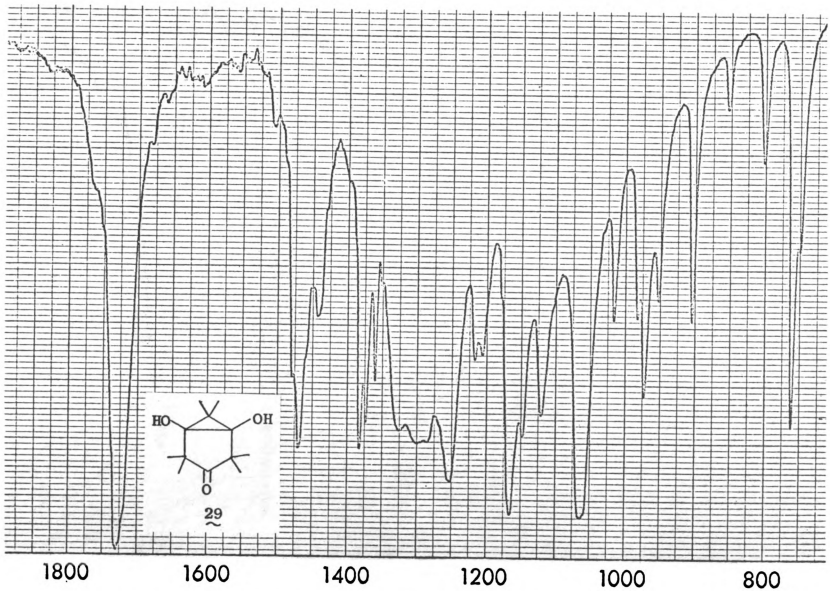

Figure 9. Infrared spectrum of 2,2,4,4,6,6-hexamethyl-1,3-dihydroxybicyclo [3.1.0] hexane-5-one

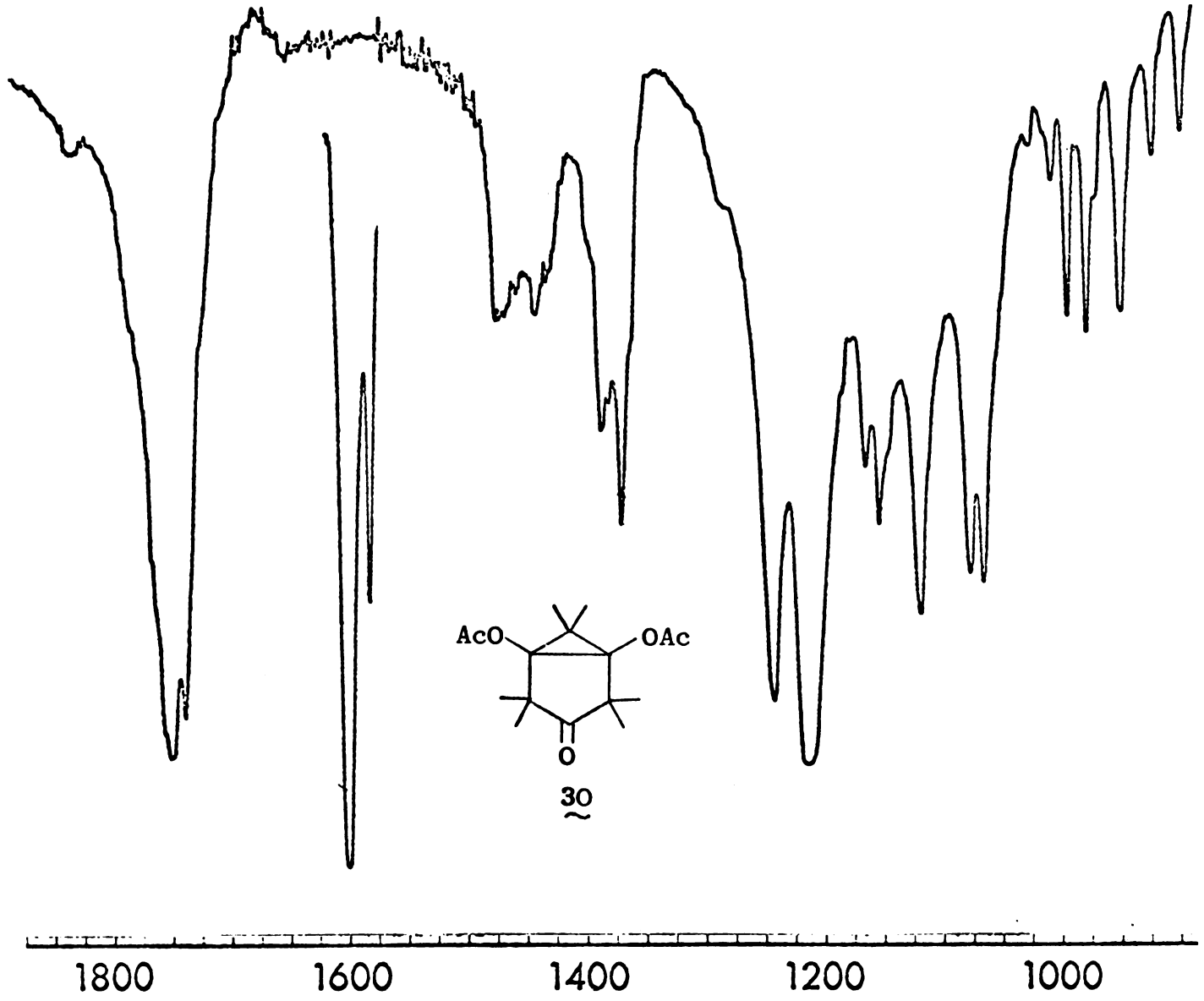

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Figure 10. Infrared spectrum of 2,2,4,4,6,6-hexamethyl-1,3-diacetoxybicyclo [3.1.0] hexane-5-one

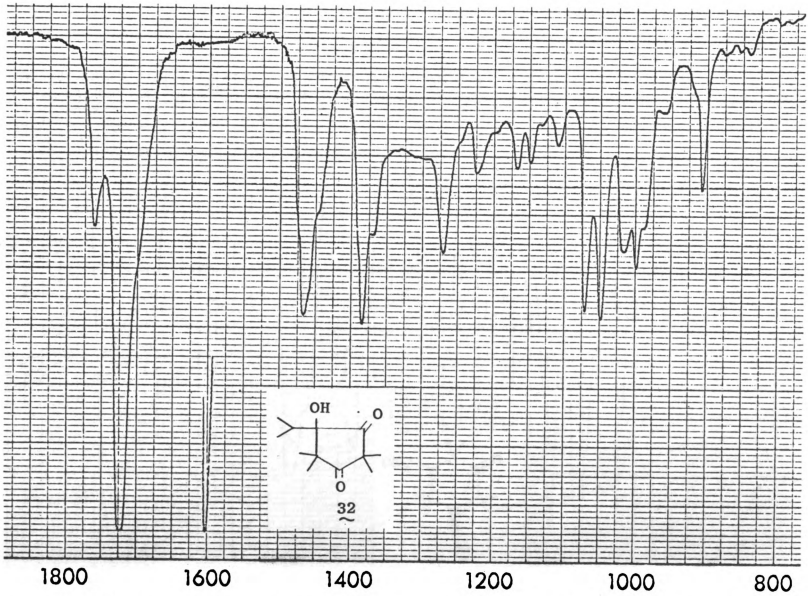

Figure 11. Infrared spectrum of 2,2,4,4-tetramethyl-5-isopropyl-5-hydroxycyclopentane-1,3-dione

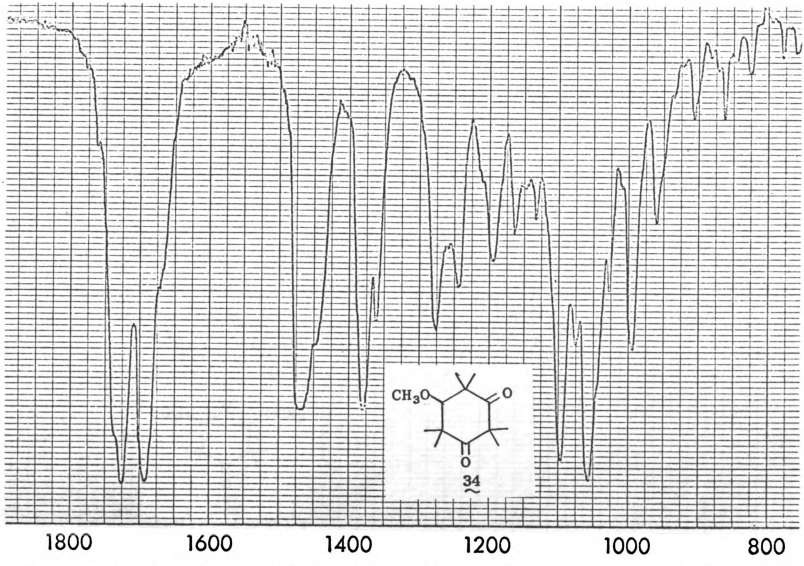

Figure 12. Infrared spectrum of 2,2,4,4,6,6-hexamethyl-5-methoxycyclohexane-1,3-dione

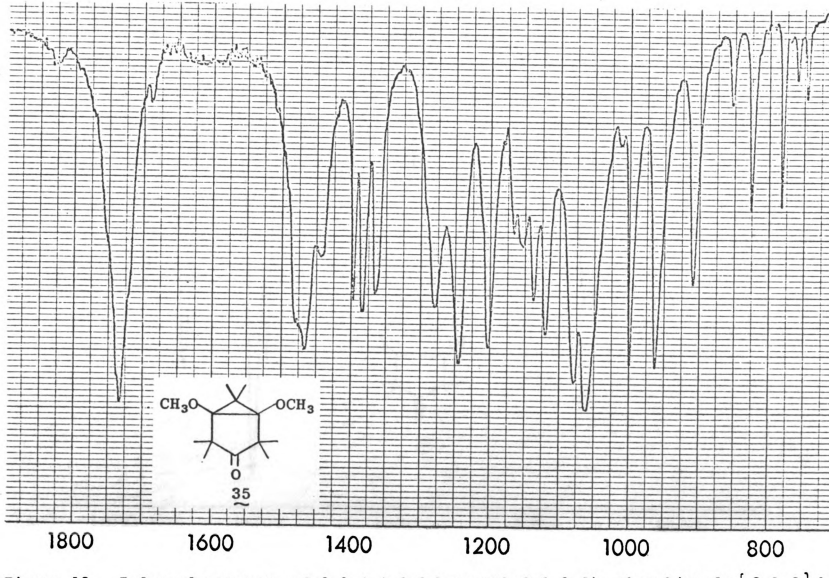

Figure 13. Infrared spectrum of 2,2,4,4,6,6-hexamethyl-1,3-dimethoxybicyclo [3.1.0] hexane-5-one

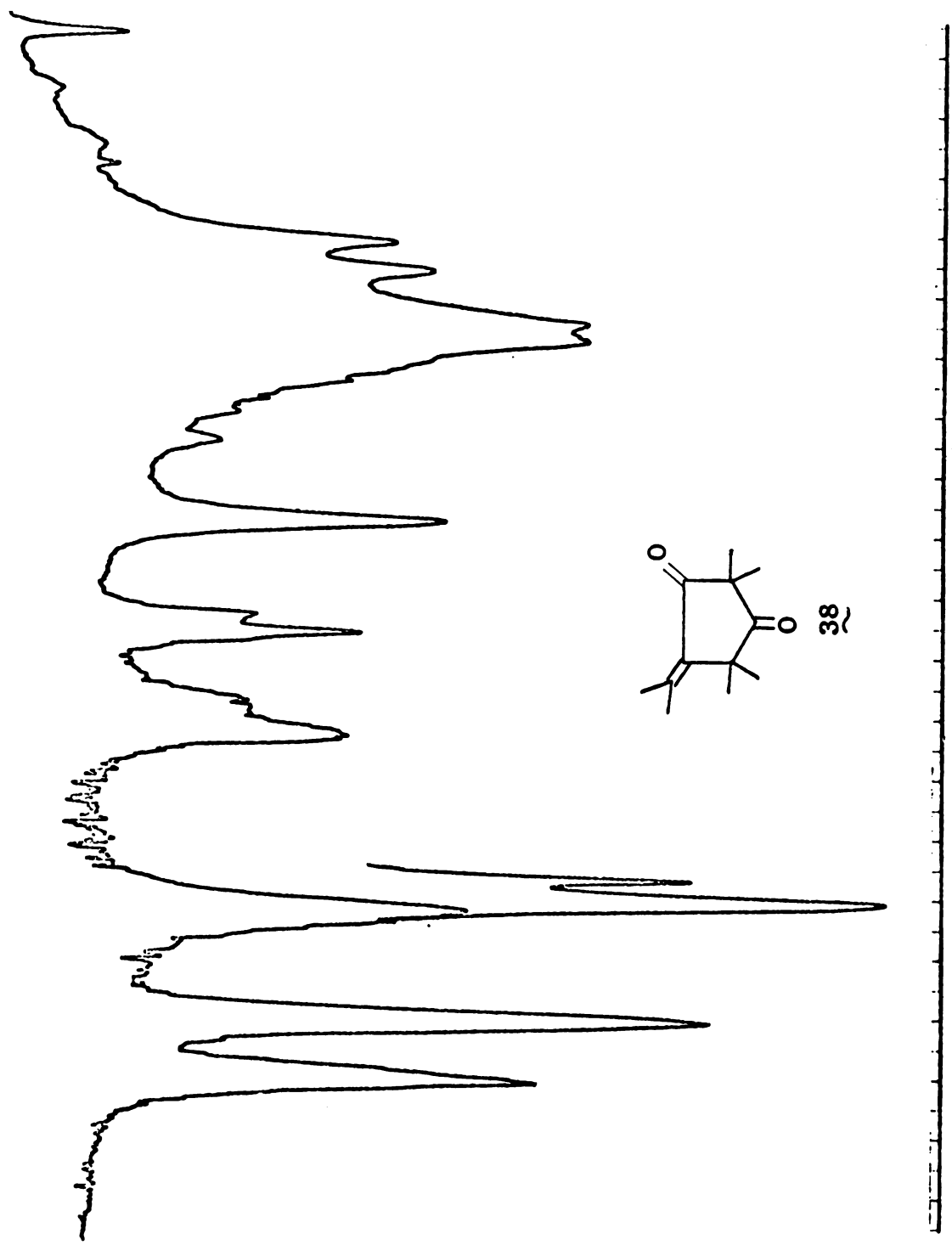

Figure 14. Infrared spectrum of 2,2,4,4-tetramethyl-5-isopropylidenecyclopentane-1,3-dione

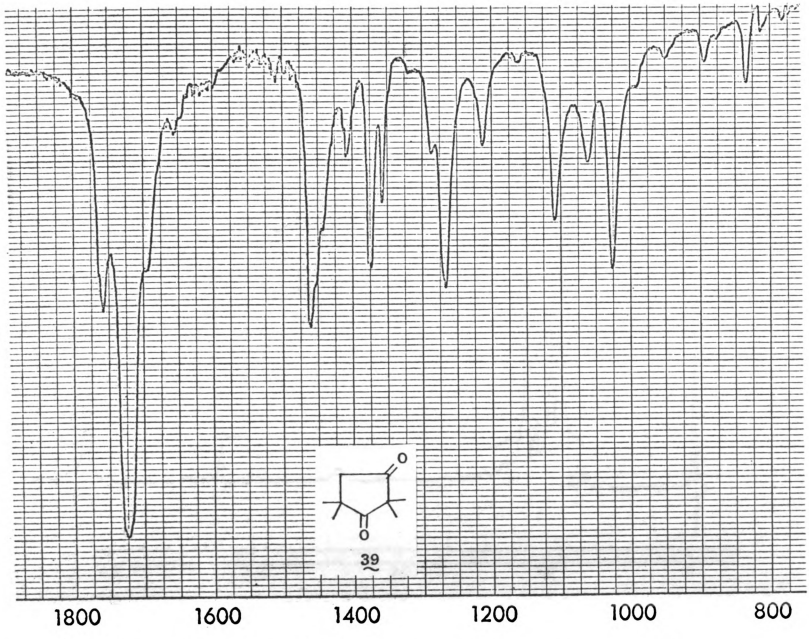

Figure 15. Infrared spectrum of 2,2,4,4-tetramethylcyclopentane-1,3-dione

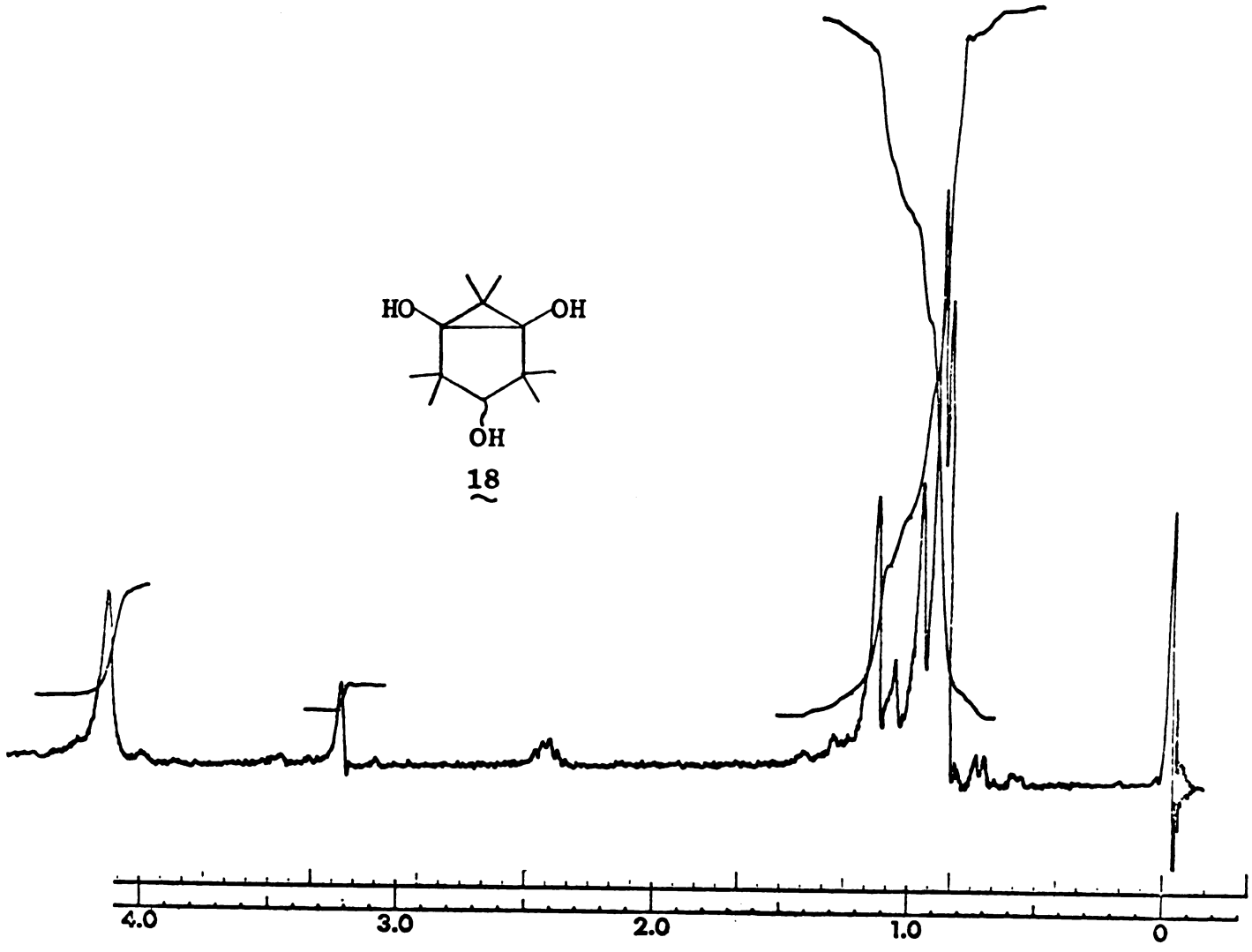

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Figure 16. The nmr spectrum of 2,2,4,4,6,6-hexamethyl-1,3,5-trihydroxybicyclo [3.1.0] hexane

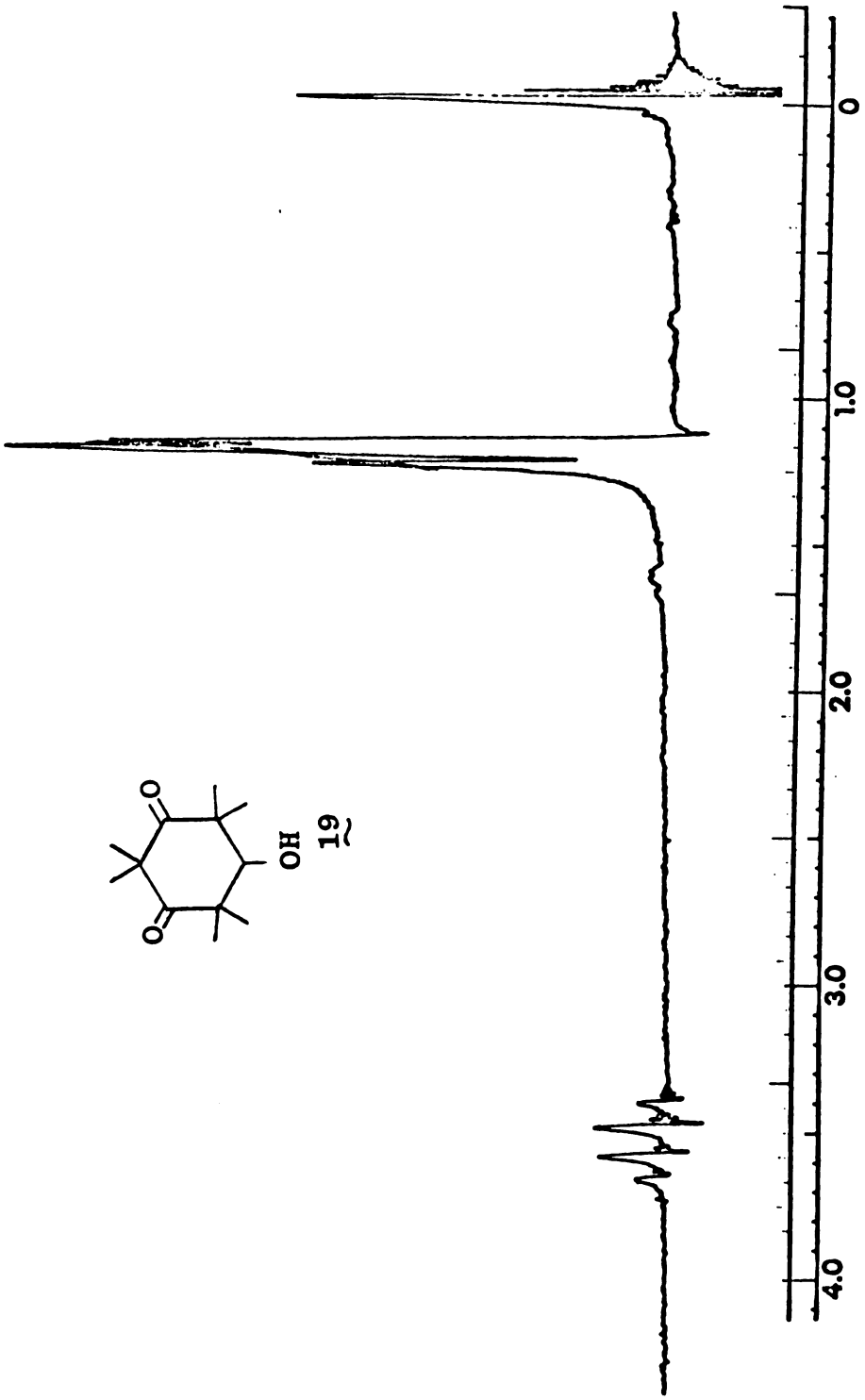

Figure 17. The nmr spectrum of 2,2,4,4,6,6-hexamethyl-5-hydroxycyclohexane-1,3-dione

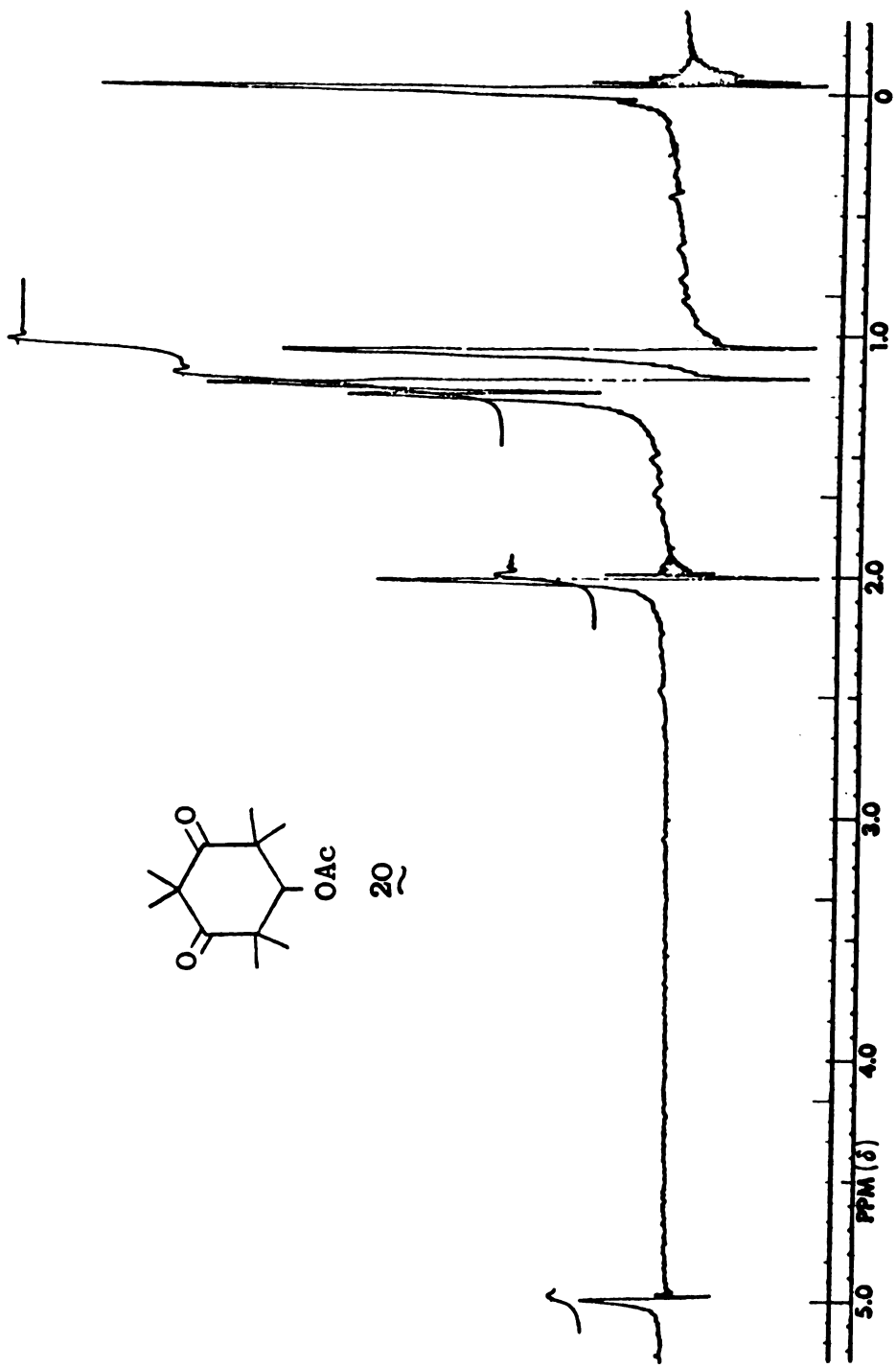

Figure 18. The nmr spectrum of 2,2,4,4,6,6-hexamethyl-5-acetoxycyclohexane-1,3-dione

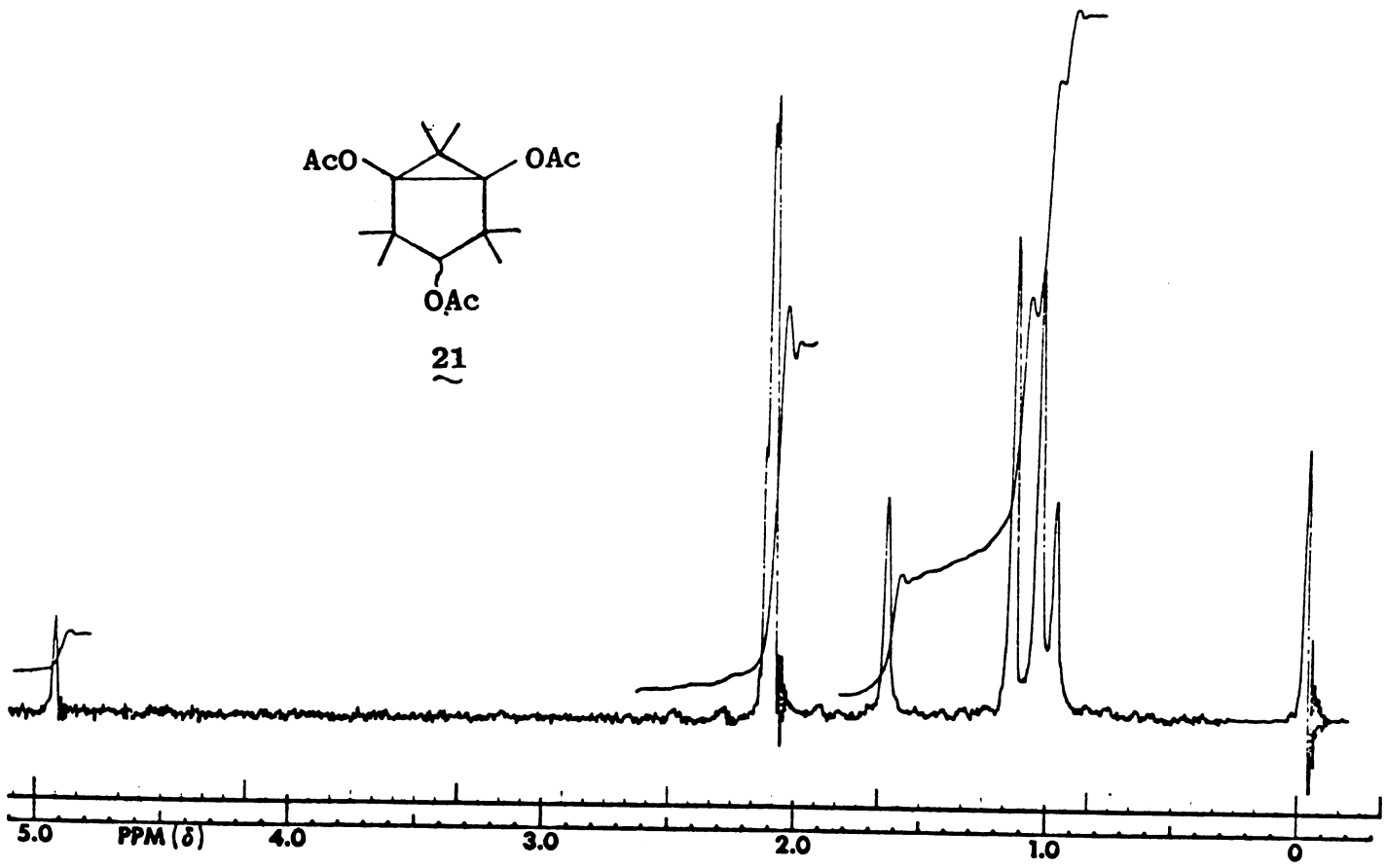

Figure 19. The nmr spectrum of 2,2,4,4,6,6-hexamethyl-1,3,5-triacetoxybicyclo [3.1.0] hexane

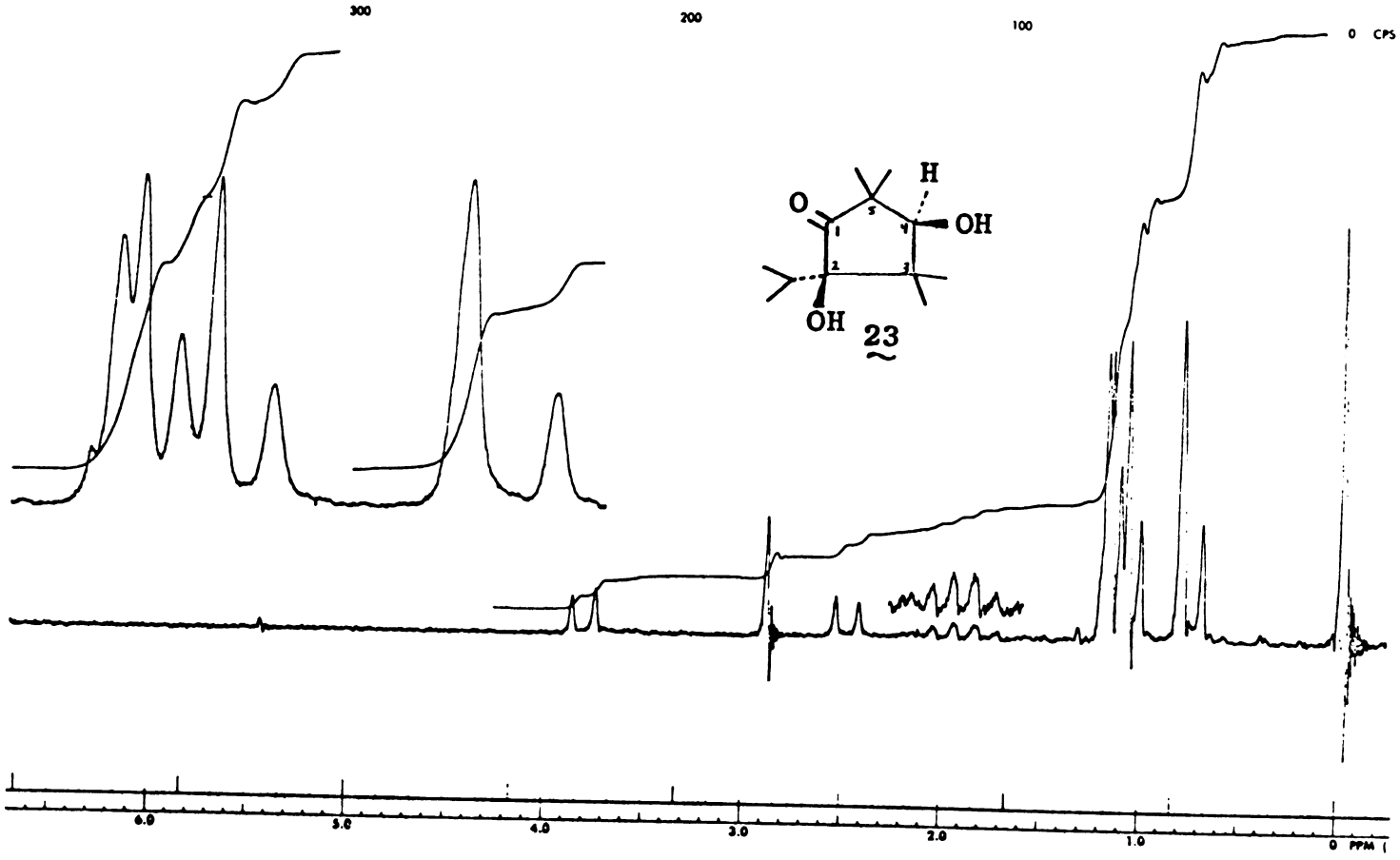

Figure 20. The nmr spectrum of 2,2,4,4-tetramethyl-cis-3,5-dihydroxy-5-isopropylcyclopentanone

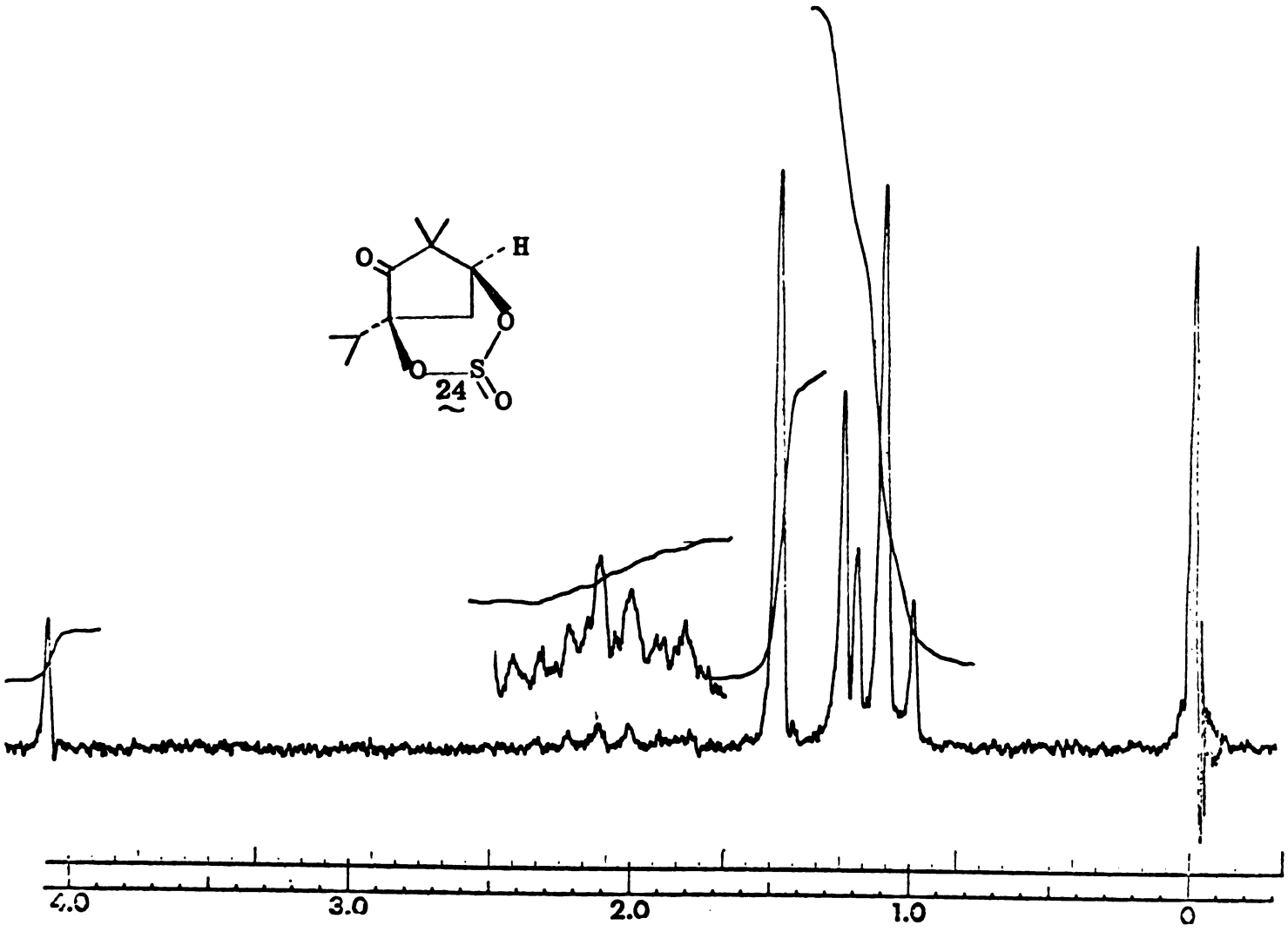

Figure 21. The nmr spectrum of 1-isopropyl-2,2,4,4-tetramethyl-5-oxo-cis-1,3-cyclopentylene cyclic sulfite

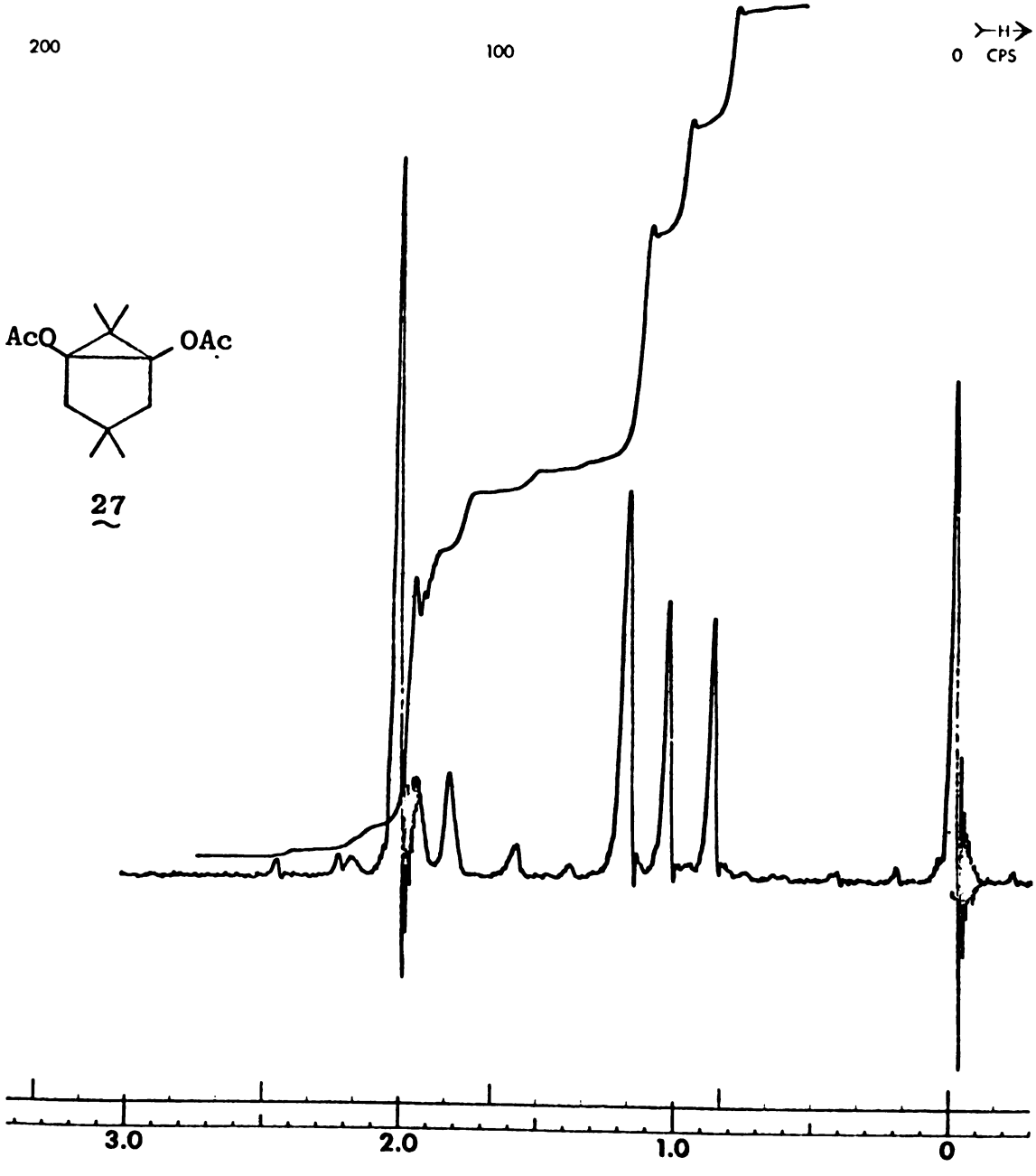

Figure 22. The nmr spectrum of 2,2,5,5-tetramethyl-1,3-acetoxy-bicyclo [3.1.0] hexane

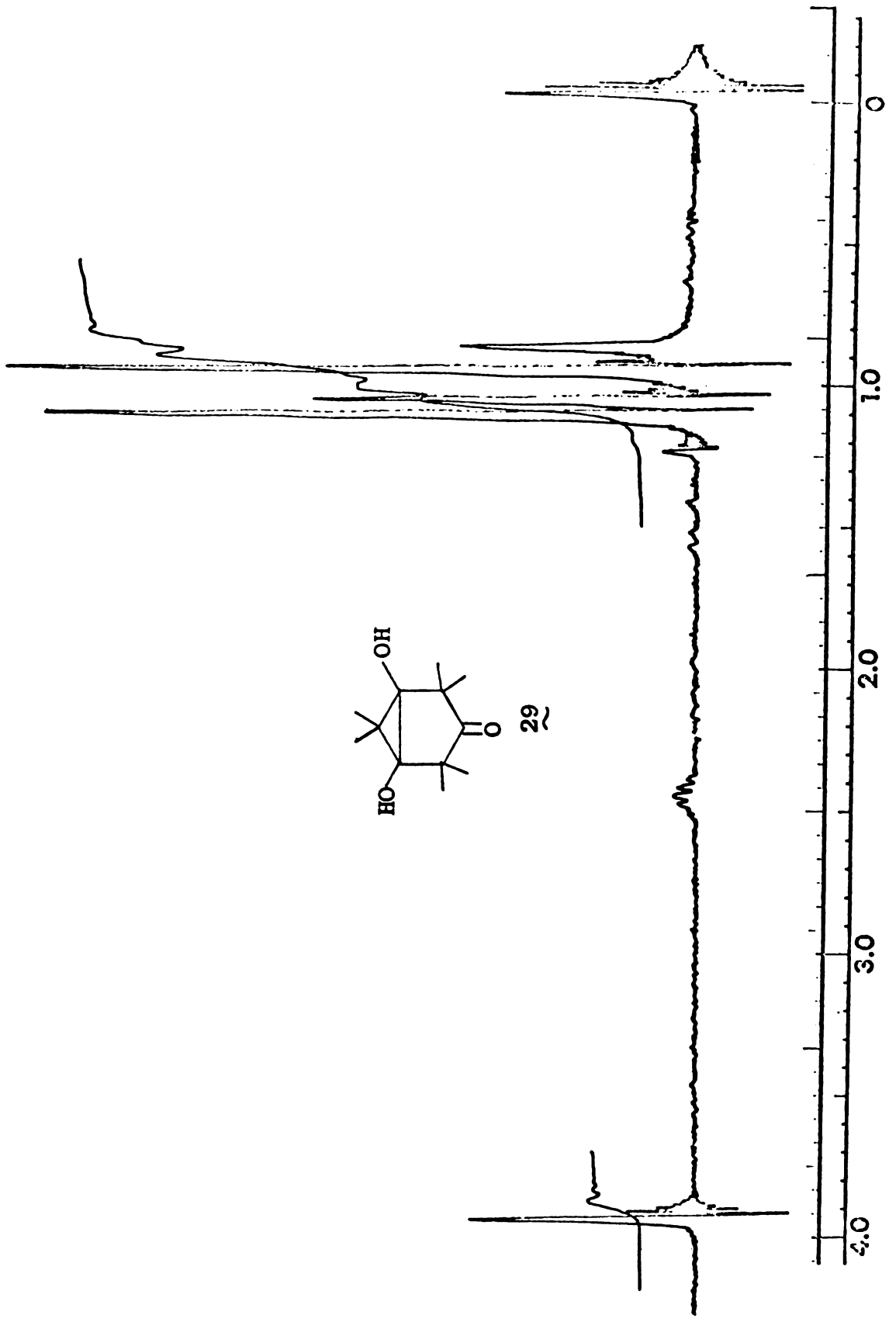

Figure 23. The nmr spectrum of 2,2,4,4,6,6-hexamethyl-1,3-dihydroxybicyclo[3.1.0]hexane-5-one

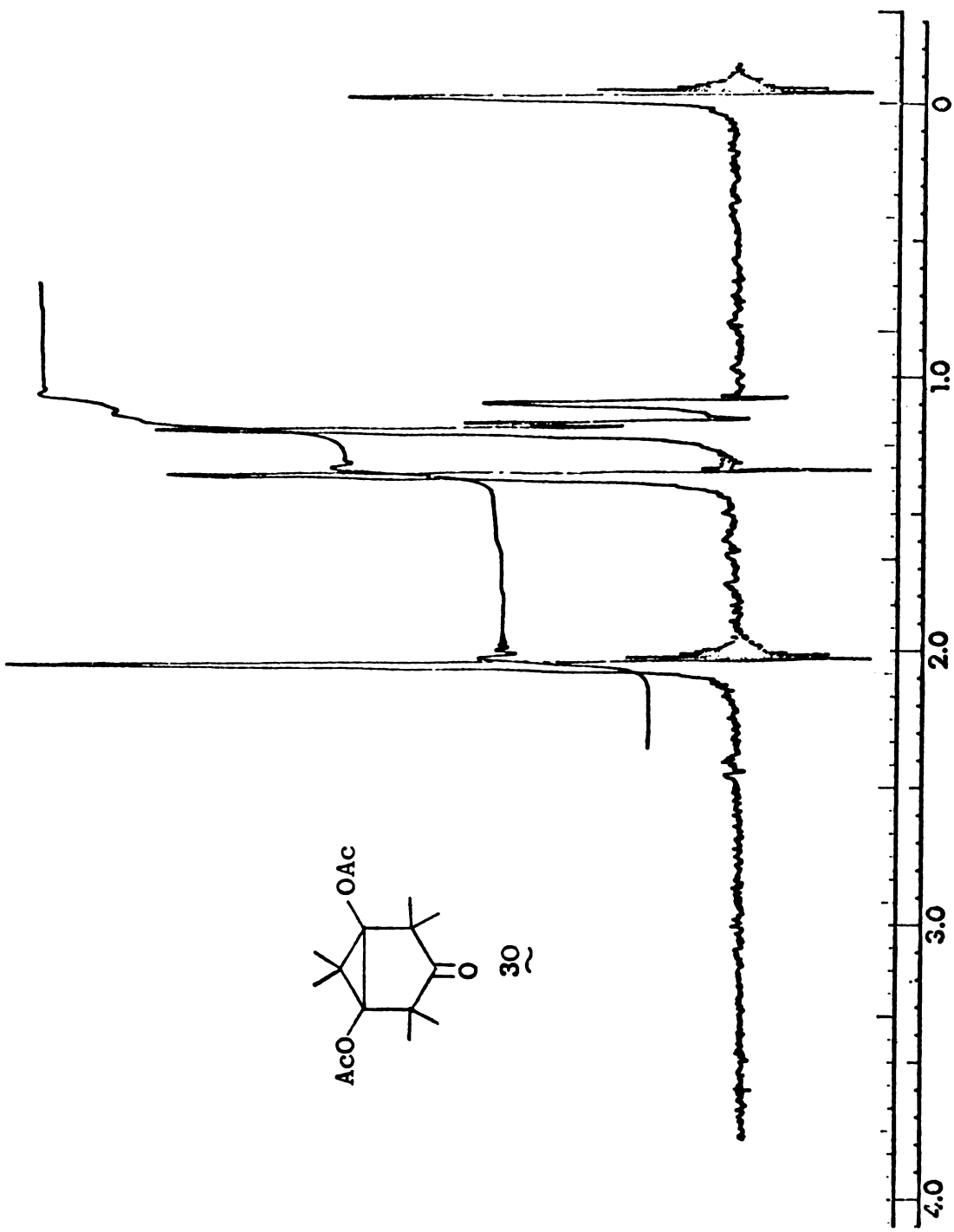

Figure 24. The nmr spectrum of 2,2,4,4,6,6-hexamethyl-1,3-diacetoxybicyclo [3.1.0] hexane-5-one

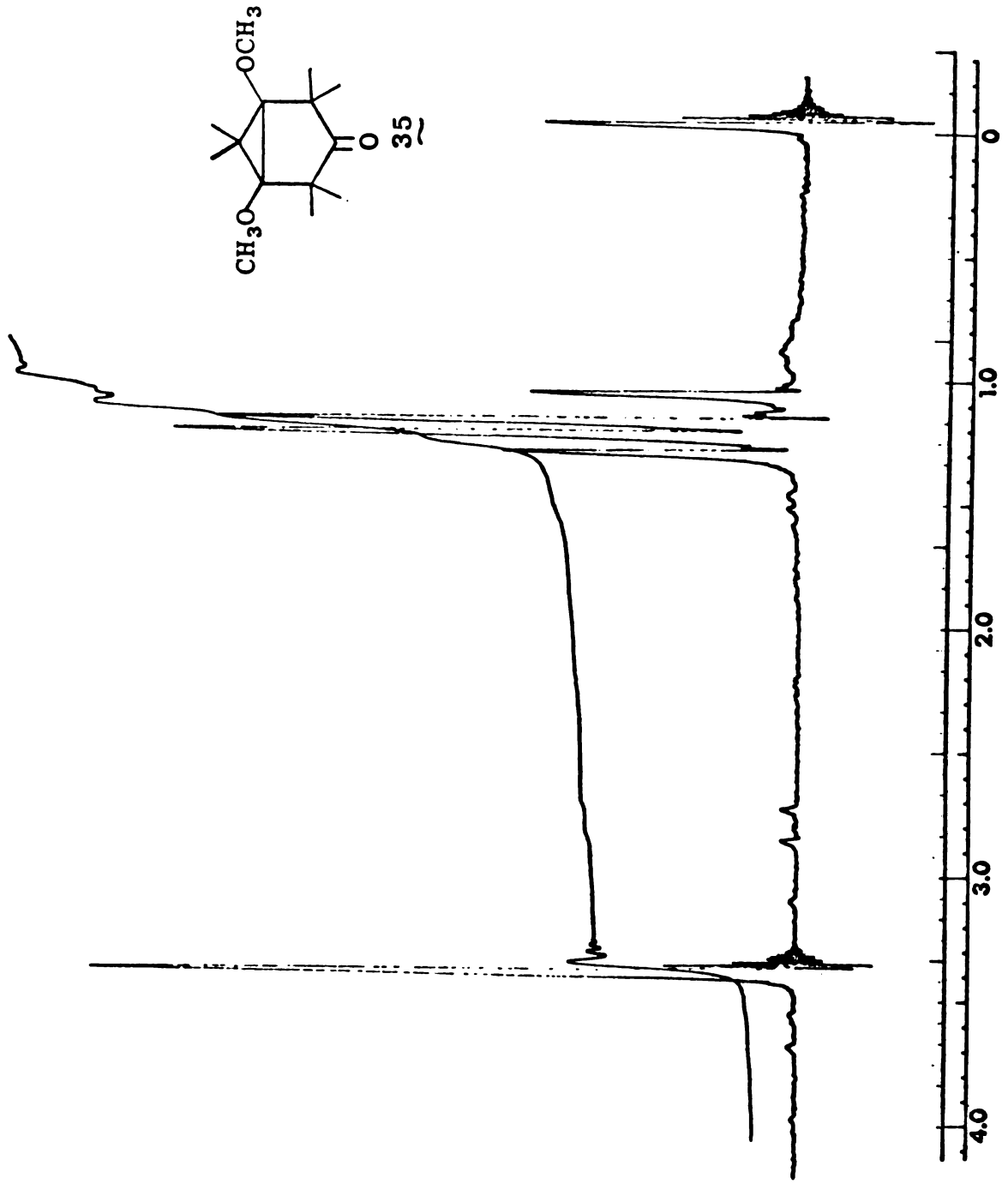

Figure 25. The nmr spectrum of 2,2,4,4,6,6-hexamethyl-1,3-dimethoxybicyclo[3.1.0]hexane-5-one

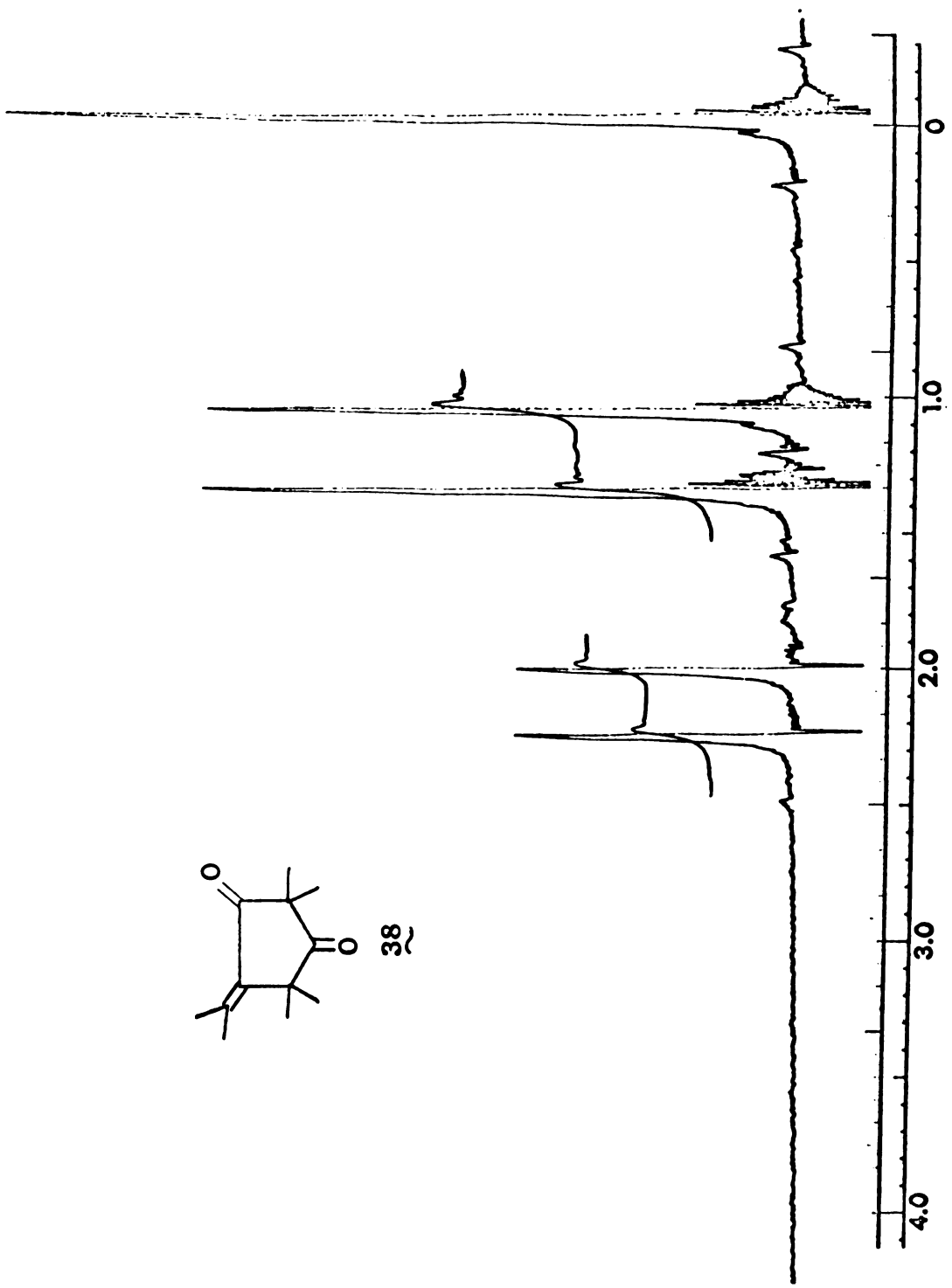

Figure 26. The nmr spectrum of 2,2,4,4-tetramethyl-5-isopropylidenecyclopentane-1,3-dione

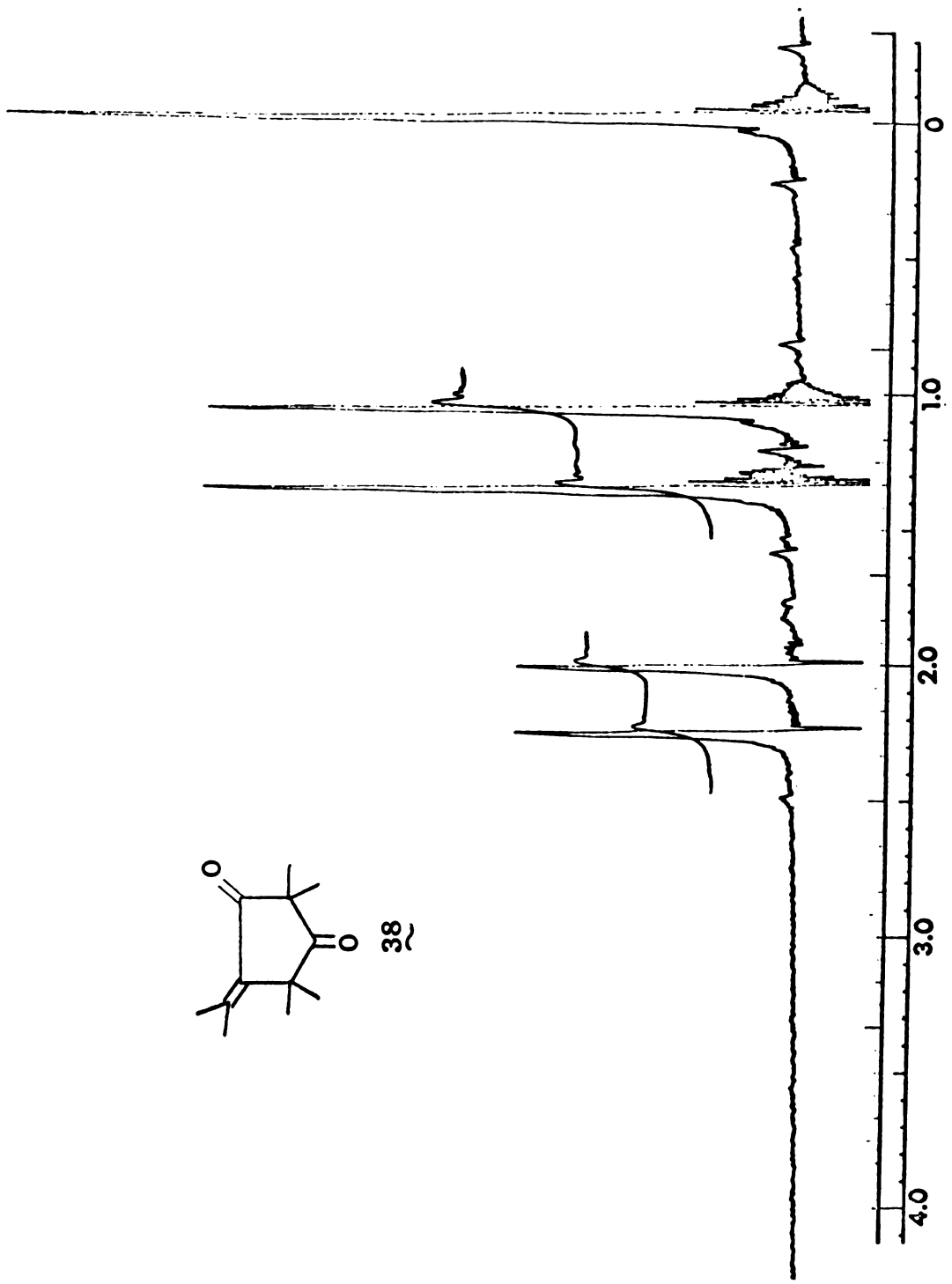

Figure 26. The nmr spectrum of 2,2,4,4-tetramethyl-5-isopropylidenecyclopentane-1,3-dione

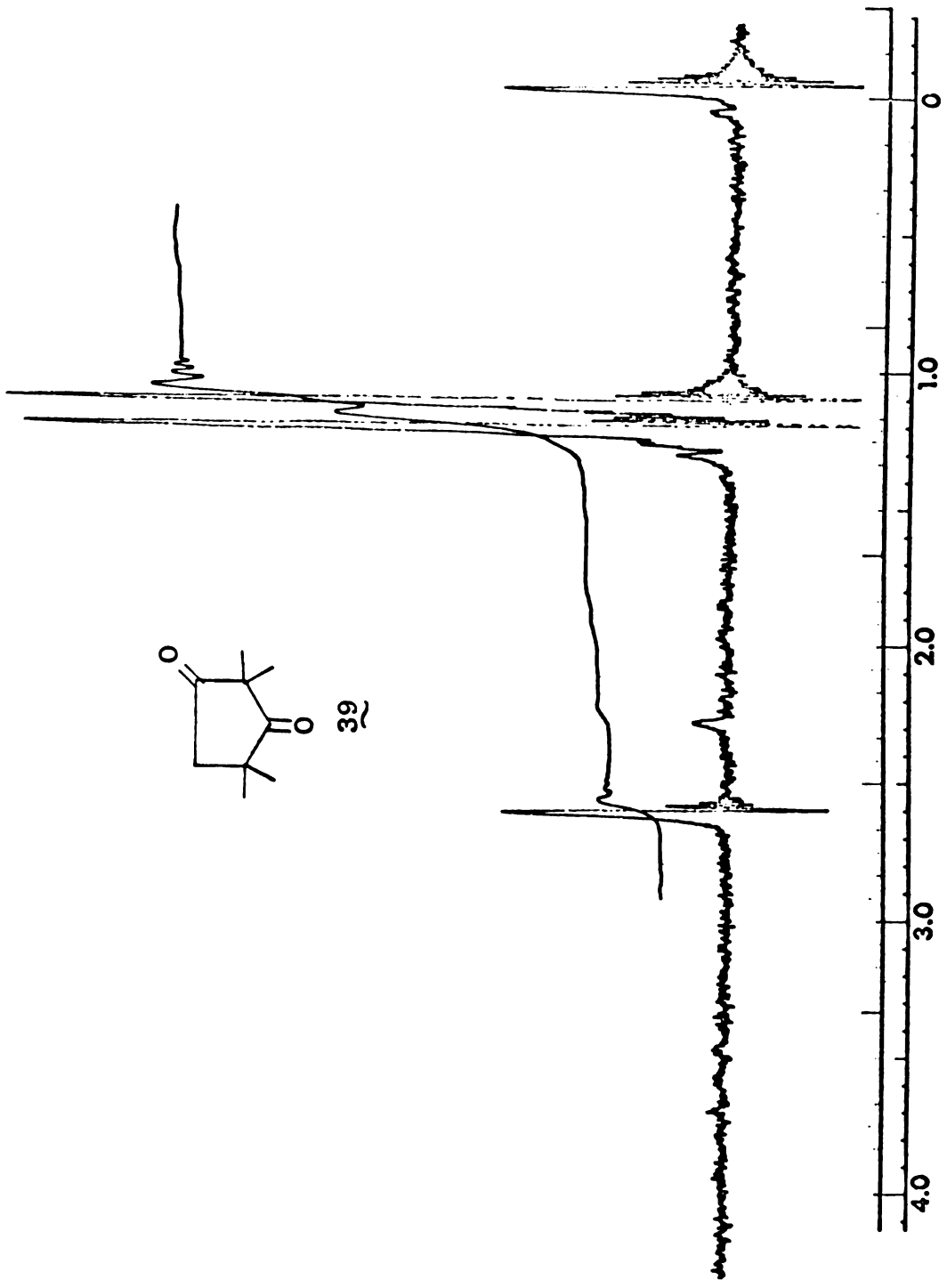

Figure 27. The nmr spectrum of 2,2,4,4-tetramethylcyclopentane-1,3-dione

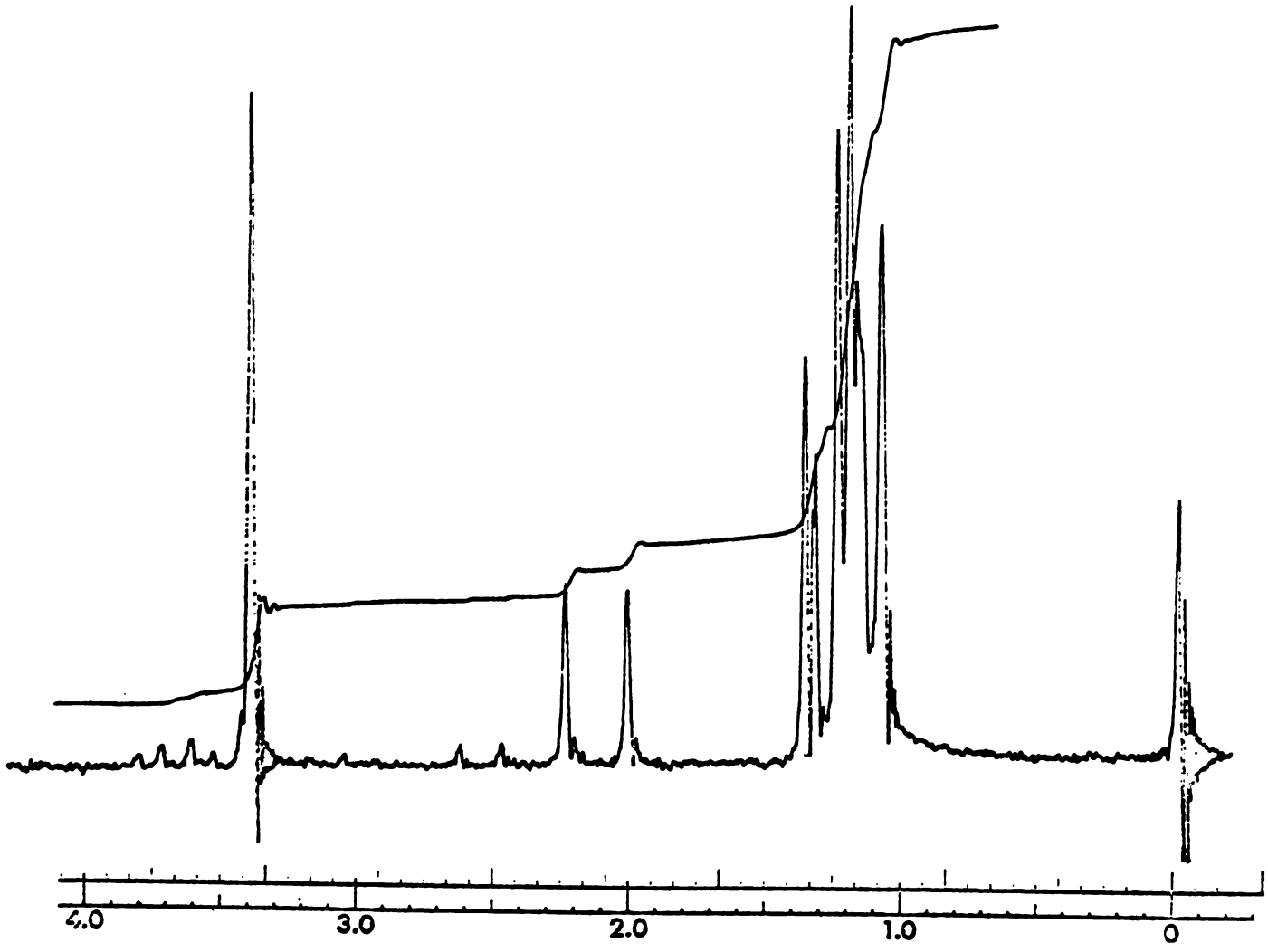

Figure 28. The nmr spectrum of the product mixture from the attempt to prepare 2,2,4,4,6,6-hexamethyl-1-hydroxy-3-methoxybicyclo [3.1.0] hexane-5-one

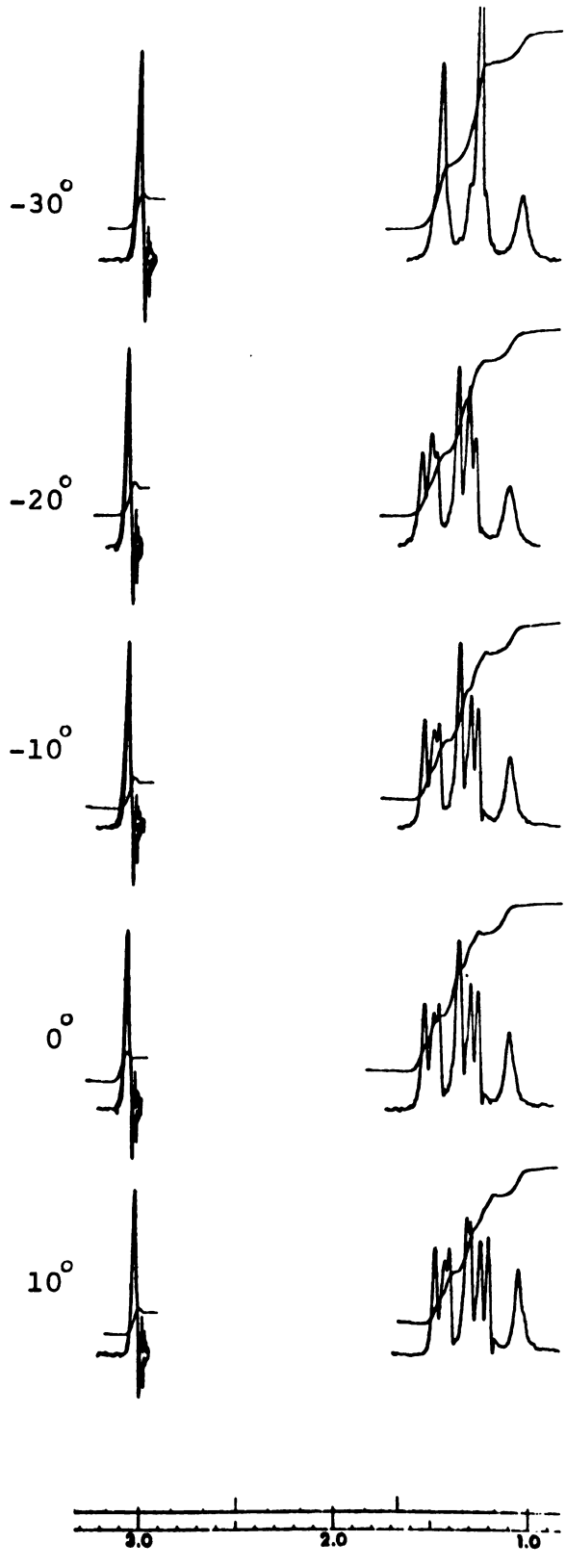

Figure 29. The nmr spectrum of 2,2,4,4,6,6-hexamethyl-1,3-dihydroxybicyclo [3.1.0] hexane in fluorosulfonic acid at various temperatures