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RADICAL ANIONS DERIVED FROM BRIDGED BICYCLIC $\underline{\alpha}$-DIKETONES

by

Kuo-Yuan Chang

A Dissertation Submitted to the
Graduate Faculty in Partial Fulfillment of
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DOCTOR OF PHILOSOPHY

Major Subject: Organic Chemistry

Approved:

Signatures have been redacted for privacy.

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of Science and Technology
Ames, Iowa

1965

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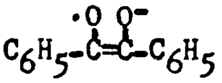
INTRODUCTION

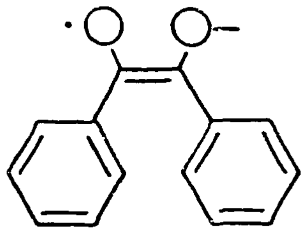
Various aromatic acyloins have been shown to display characteristic colors in an aerated basic solution; for example, furoin gives a blue color (1), benzoin a purple color (2), and 2,2'-thenoin a green color (3). These autoxidation reactions have been reported to produce the corresponding diketones. Later work showed that benzoic acid and benzilic acid are also formed in addition to benzil in the oxidation of benzoin (4, 5).

Michaelis and Fetcher (6) suggested that the colored species in the autoxidation of benzoin is  $C_6H_5-\overset{\cdot O}{C}=\overset{O^-}{C}-C_6H_5$ (I) radical anion, which is akin to the well-known semiquinone. The suggestion was based on their colorimetric dilution experiment on the anaerobic mixture of benzoin and benzil in basic solution. The presence of this radical anion (I) was first demonstrated by Venkataraman and Fraenkel (7) and further substantiated by Russell, Janzen, and Strom (8) using electron spin resonance (e.s.r.) techniques. The existence of this paramagnetic species was also proved by susceptibility experiments (9).

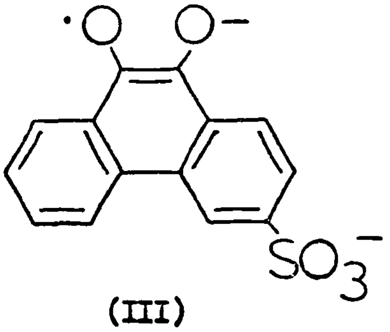
Doering and Haines (10) reported that autoxidation of propiophenone, butyrophenone, and acetophenone in t-butyl alcohol containing potassium t-butoxide gives benzoic acid as the main product. Under the same conditions cyclohexanone gives mainly a tar from which the expected cleavage product adipaldehydic acid was not isolated. However, under the same conditions carbon-carbon bond cleavage products have not been observed from a number of steroidal ketones. Thus, a diosphenol is obtained frOm a ketone present in the citrus bitter principle limonin (11) and diketones in their enolic forms have been isolated from several 3-ketosteroids by this autoxidation (12).

Evidently, autoxidation of ketones having α-methylene protons occurs widely. Since autoxidation of desoxybenzoin gives similar products as that of benzoin (10), it would be predicted that similar paramagnetic species can also be detected in the autoxidation of ketones; but, prior to the investigations of Russell and Strom, no work has been done concerning this problem.

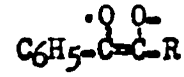
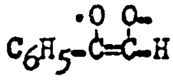
There is no doubt that the two phenyl rings of (I) stabilize the otherwise aliphatic radical anion by delocalization of the unpaired electron or the charge into the rings. The importance of this factor has been demonstrated by comparison of the equilibrium concentrations of the two radical anions, (II) and (III), generated from their diketone and α-ketol (9). (III) with a fixed coplanarity has an equilibrium concentration of 31-44% whereas (II) exists at an equilibrium concentration of only 3%.

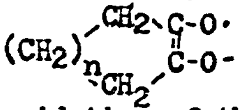


(II)



(III)

Although aromatic substituents are important in stablizing radical anions, the mixed type of aromatic and aliphatic,  $C_6H_5-\overset{\cdot O}{C}=\overset{O^-}{C}-R$ (IV), can be obtained without difficulty. Radical anions with R = methyl (IVa), ethyl (IVb), and t-butyl (IVc) are formed, respectively, when propiophenone, butyrophenone, and phenylpivalylcarbinol are oxidized in dimethyl sulfoxide (DMSO)-t-butyl alcohol (80-20) solution containing potassium t-butoxide with a trace of air (13). However, acetophenone can not be oxidized in the same fashion to give the radical anion,  $C_6H_5-\overset{\cdot O}{\overset{|}{C}}=\overset{O^-}{\overset{|}{C}}-H$ (IVd) or any other by-product that can be detected by e.s.r.. Since the hyperfine splitting constants (h.f.s.c.) of α-hydrogen atoms in the alkyl groups of (IVa) and (IVb) are always the largest, it was thought that the stabilization by hyperconjugation with alkyl groups is extremely important. Nevertheless, (IVd) can be obtained by a modified Kornblum reaction by treating phenacyl bromide with potassium t-butoxide in DMSO (14).

The greatest surprise came from the detection of the radical anion of cyclohexane-1,2-dione which was obtained from the oxidation of 2-hydroxycyclohexanone with oxygen in DMSO-t-butyl alcohol (80-20) solution containing potassium t-butoxide (13, 15). Cyclic radical anions  (V) with n = 1 to 8 and 10 to 12 have been generated by oxidation of the corresponding cycloalkanones under conditions just described.

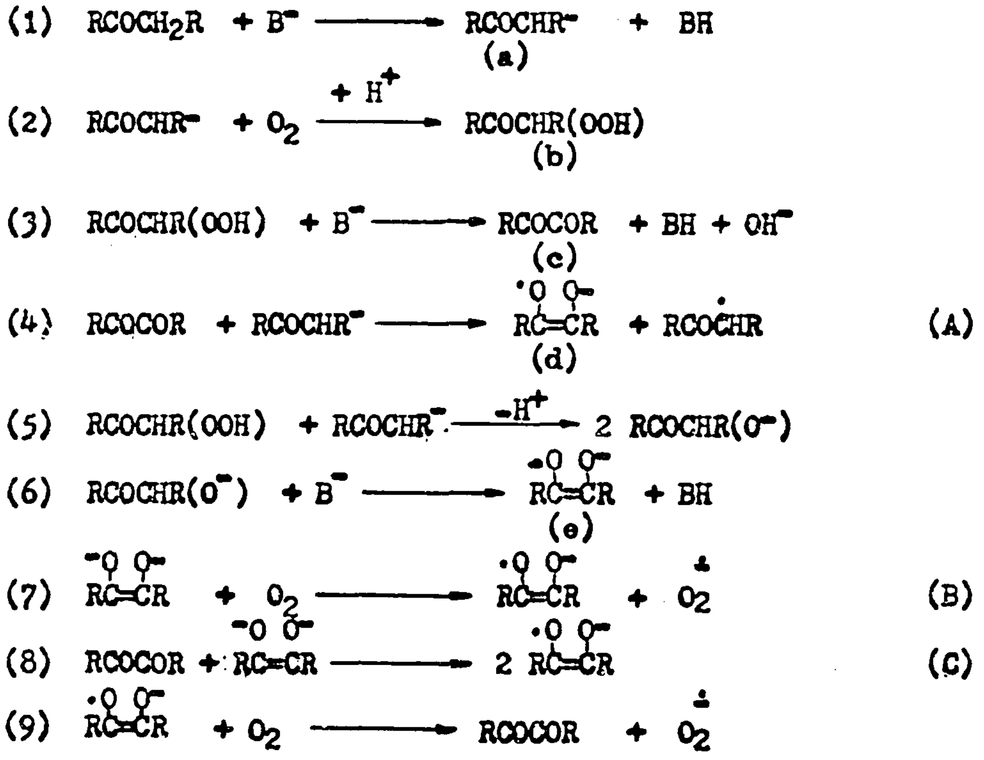
Cyclohexanesemidione, in contrast to 4-t-butylcyclohexanesemidione, does not possess conformational stability in terms of the spectrometer frequency (10^4 Mc./sec.). For example, the spectrum of the oxidation product of cyclohexanone has four equivalent α-hydrogens whereas the spectrum from oxidation of 4-*t*-butylcyclohexanone has two pairs of equivalent protons, indicating that the latter has a frozen conformation.

Acyclic semidiones, $CH_3(CH_2)_{n-1}-\overset{\cdot O}{C}=\overset{O^-}{C}-(CH_2)_n-CH_3$ with n = 2 can not be prepared readily by oxidation of the respective ketones in the usual manner, whereas, the semidione $(CH_3)_3C-\overset{\cdot O}{C}=\overset{O^-}{C}-C(CH_3)_3$ can be obtained without difficulty (16). The latter does not possess *α*-hydrogen atoms. One may infer from these contrasting results that acyclic ketones with *α*-hydrogen atoms which are less hindered are prone to undergo condensation and hence fail to give a semidione. A better method for formation of semidiones of simpler type involves the treatment of appropriate *α*-bromoketones with a basic DMSO solution (14). By employing this method with the aid of a flow system, a semidione of the simplest type $CH_3\overset{\cdot O}{C}=\overset{O^-}{C}H$, so far, has been detected from *α*-bromoacetone in basic DMSO solution (14).

Therefore, by proper choice of method of preparation a variety of semidiones can be produced and detected. Clearly, the delocalization of the unpaired electron or the charge in $-\overset{\cdot O}{C}=\overset{O^-}{C}-$ alone is sufficient to impart stability to the radical anion in aprotic solvents at room temperature (16). Resonance stabilization from substituents is important but is not required for the formation of this class of radical anions.

There are four general methods for preparation of semidiones. The four methods are classified according to four different ketones from which semidiones can be prepared. The four kinds of compounds are ketones with an adjacent *α*-methylene group, *α*-hydroxyketones, *α*-diketones, and *α*-bromoketones.

The most generally used method for obtaining a semidione is to oxidize a ketone having an <u>α</u>-methylene group in DMSO containing potassium <u>t</u>-butoxide with a trace of oxygen (Method I) (13, 15). The availability of ketones makes this method the first choice. Unfortunately, this method has its limitations. It can not be applied to generate simple aliphatic semidiones (16) or some steroidal semidiones whose parent compounds are oxygenated with difficulty (14). During the present investigation this method was also found inadequate to prepare semidiones from norcamphors lacking a <u>syn</u>-7-methyl group. This method often gives a mixture of semidiones when the starting ketone is unsymmetrical and has two different <u>α</u>-methylene groups. The mechanism of formation of semidiones from ketones is probably complicated and may involve three pathways, which are shown by the following equations:



(1) $RCOCH_2R + B^- \longrightarrow \underset{(a)}{RCOCHR^-} + BH$

(2) $RCOCHR^- + O_2 \xrightarrow{+H^+} \underset{(b)}{RCOCHR(OOH)}$

(3) $RCOCHR(OOH) + B^- \longrightarrow \underset{(c)}{RCOCOR} + BH + OH^-$

(4) $RCOCOR + RCOCHR^- \longrightarrow \underset{(d)}{R\overset{\cdot O}{C}{=}\overset{O^-}{C}R} + RCO\dot{C}HR$ (A)

(5) $RCOCHR(OOH) + RCOCHR^- \xrightarrow{-H^+} 2\ RCOCHR(O^-)$

(6) $RCOCHR(O^-) + B^- \longrightarrow \underset{(e)}{R\overset{^-O}{C}{=}\overset{O^-}{C}R} + BH$

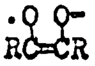
(7) $R\overset{^-O}{C}{=}\overset{O^-}{C}R + O_2 \longrightarrow R\overset{\cdot O}{C}{=}\overset{O^-}{C}R + O_2^{\overset{\cdot}{-}}$ (B)

(8) $RCOCOR + R\overset{^-O}{C}{=}\overset{O^-}{C}R \longrightarrow 2\ R\overset{\cdot O}{C}{=}\overset{O^-}{C}R$ (C)

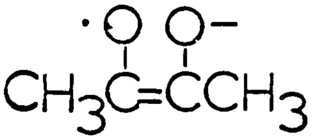
(9) $R\overset{\cdot O}{C}{=}\overset{O^-}{C}R + O_2 \longrightarrow RCOCOR + O_2^{\overset{\cdot}{-}}$

The pathway (B) illustrates the second method by which semidione can be obtained in rather high concentration. This method involves the oxidation of an *α*-hydroxyketone in DMSO containing potassium *t*-butoxide with a trace of air (Method II). This is a favorable method for obtaining a semidione whenever an *α*-hydroxyketone is available. In two cases it was reported that an irradiation with light of suitable wavelength is necessary to produce semidiones from *α*-hydroxyketones (17). By this variation Heller was able to obtain isobutyril and pivalil anion radical by irradiation (3130 Å) of basic solutions of butyroin and pivaloin, either without or with a sensitizer (benzophenone).

Pathways (A) and (C) illustrate another method of preparation of semidiones starting with *α*-diketones (Method III). In the absence of oxygen, a semidione can be obtained immediately when a mixture of *α*-diketone and its *α*-ketol is mixed in a basic medium. This method is definitely the best way to prepare a semidione when both the *α*-diketone and *α*-ketol are available at the same time because it gives a high concentration of semidione in the absence of oxygen which means that a higher resolution can be attained. *α*-Diketones can also be reduced with other electron donating carbanions such as enolate anion of propiophenone (8), with potassium metal (18), and electrolytically (7). However, reduction of biacetyl in a basic solution does not afford butane-2,3-semidione but forms 2,5-dimethylsemiquinone instead.

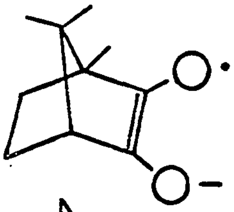
Treatment of an *α*-bromoketone in DMSO solution containing potassium *t*-butoxide presents the fourth method of preparation of a semidione (Method IV) (14). This method is noted for its ability to form semidiones which are not obtainable by other methods. For example, semidiones;  $R\overset{\cdot O}{C}=\overset{O^-}{C}R$ with R = R'= methyl; R = phenyl, R' = H; and R = methyl, R' = H; are obtained smoothly from corresponding bromoketones. α-Bromoketones may undergo a reaction of the Kornblum type and form α-diketones or α-ketoaldehydes which are reduced by some carbanion as described in the third method, to give semidiones. However, this mechanism is rather doubtful because it can not account for the failure to prepare butane-2,3-semidione and phenylglyoxal semidione from reduction of the preformed biacetyl and phenylglyoxal if they are indeed the precursors for the formation of these two semidiones. The alternative mechanism probably is that a portion of the α-bromoketone is hydrolyzed in basic DMSO solution to the α-hydroxyketone which then yields the semidione by electron transfer to the slower formed α-diketone as in the former mechanism. This is true only if one can assume that the electron transfer reaction is faster than the condensation reaction. Although the mechanism of this method is not clear, it provides a useful method for preparing semidiones from some steroidal ketones which are not readily oxygenated in basic solution (14). For example, 6-, 7-, 11-, or 12-keto-5α- or 5β-steroids fail to form stable semidiones by air oxidation in basic solution, whereas 6α-bromo-5α-cholestan-7-one in DMSO containing potassium t-butoxide is converted easily to the expected semidione. In most cases the isolation of an α-bromoketone is not necessary, since it can be generated *in situ* by treating a ketone with an equivalent amount of bromine in t-butyl alcohol containing potassium t-butoxide and subsequently mixing with a DMSO solution containing the same base to give a semidione. However, by this method α-bromocamphor fails to give the camphorquinone radical anion which will be discussed later.

Radical anions of the type, $R\overset{\cdot O}{C}=\overset{O^-}{C}R$, have been named as semiquinone (6-8), acylil (14, 17), and *semidione*. Among them, semidione is the most appropriate one because the radical itself is aliphatic in nature in contrast to a semiquinone. Acylil usually indicates a diketone and is inadequate to name an unsymmetrical radical anion. Throughout this thesis the name semidione will be used to indicate a molecule having the $-\overset{\cdot O}{C}=\overset{O^-}{C}-$ function. The molecule is then named after its parent hydrocarbon according to Geneva system. The position of the functional group is indecated by two consecutive numbers used in the same manner as in the naming of diketones. A few representative examples are given below.

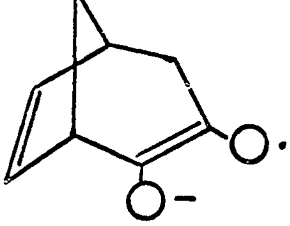


$CH_3\overset{\cdot O}{C}=\overset{O^-}{C}CH_3$

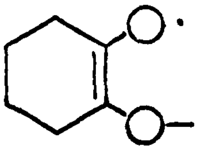
n-Butane-2,3-semidione



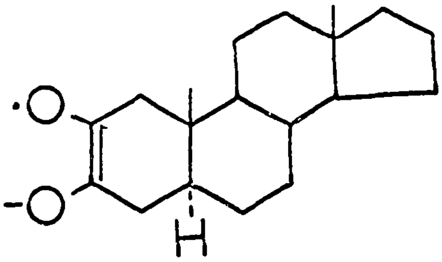
1,7,7-Trimethylbicyclo[2,2,1]-
heptane-2,3-semidione



Bicyclo[3,2,1]octene-6-semidione-
2,3

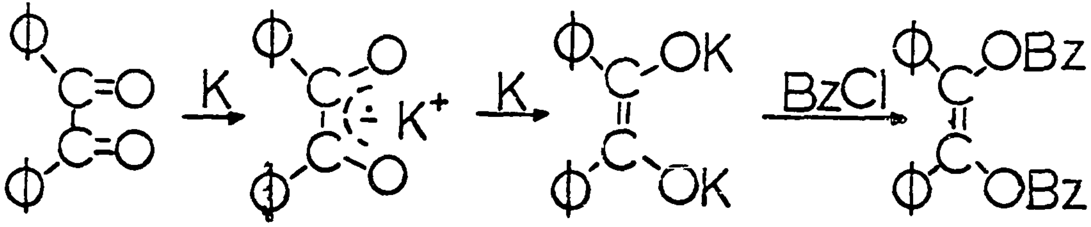


Cyclohexane-2,3-semidione



5$\underline{\alpha}$-Androstane-2,3-semidione

There is little information concerning the stereochemistry of semidiones which can exist in trans and cis forms. Cyclooctene has been found to exist in both forms but not cycloheptene and smaller cycloalkenones which can only have cis structures. By analogy cyclic semidiones with ring size larger than eight carbon atoms could have both forms just as acyclic semidiones. Bauld (18) found that addition of excess of benzoyl chloride to the dianion, prepared from two stage reduction of benzil with potassium metal in boiling benzene and tetrahydrofuran yielded predominantly the cis stilbenediol dibenzoate isomer. Therefore, diphenylsemidione must exist predominantly in cis form under these condi-

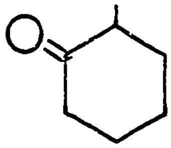


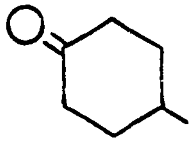
tions. However, he also found that by increasing the polarity of the solvent and by reducing a benzil homogeneously, the amount of trans form increased. Most of the semidiones discussed herein were prepared homogeneously in DMSO which is much more polar than benzene and tetrahydrofuran and is known to solvate the cation strongly. In this medium semidiones may well exist preferentially in trans forms as would be predicted on the basis of the nonbonding and the Coulombic repulsions. Unfortunately, experiments similar to those of Bauld (18) cannot be performed in DMSO to confirm this assumption because DMSO and an acyl halide react explosively.

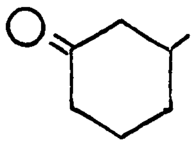
The existence of a wide variety of cyclic and acyclic semidiones not only provides opportunities for theoretical studies but also lends itself to many practical applications for conformational and structural studies.

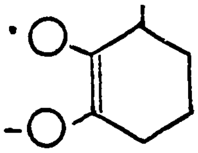
Cycloalkanesemidiones with rings larger than six carbon atoms possess considerable conformational stability with the exception of the cyclooctyl derivative. The four α-protons are no longer equivalent as in cyclohexanesemidione (13, 15). They generally show two pairs of equivalent protons. It has been proposed that the hyperfine splitting constants for protons attached to a carbon atom adjacent to another carbon atom carrying a free electron should satisfy the equation, $a^H = B\rho \mathrm{Cos}^2\theta$, where θ is the dihedral angle between the $H-C_\alpha-C_\pi$ and the $C_\alpha-C_\pi-\pi$ orbital planes and ρ the spin density on C_π (19). Since two splitting constants are known, $B\rho$ and θ can be calculated. From two equations there are obtained two sets of solutions. By discarding the unrealistic value of $B\rho > 58.5/2$ and by assuming that the same B that holds for alkyl radicals also holds for the cycloalkanesemidiones, both dihedral angles for axial and equatorial protons and the spin densities can thus be obtained for cycloalkanesemidiones. The value of θ_{axial} for the $\underline{\alpha}$-hydrogens of the 4-$\underline{t}$-butylcyclohexane-1,2-semidione is in good agreement with that found for cyclohexene by n.m.r. (20).

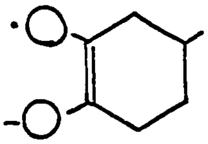
The splitting pattern of an e.s.r. spectrum of a semidione can often be used to prove structure of position isomers. The assignment of structure can be made from first principles on the basis of the number of semidiones formed and the number of magnetically different hydrogen atoms in each semidione without reference to model compounds. Application of e.s.r. techniques to the proof of structure of the three isomeric methylcyclohexanones is illustrated below (21). Oxidation of (A) and (B) by


(A)


(B)


(C)

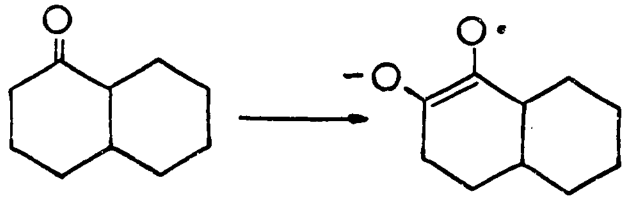

(VI)


(VII)

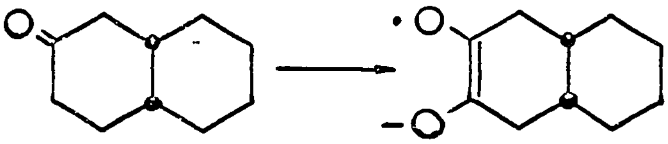
Method I give (VI) and (VII), respectively. Since an alkyl substituent imparts conformational stability to a cyclohexene ring in terms of e.s.r. frequencies, there are three magnetically nonequivalent $\underline{\alpha}$-hydrogen atoms in (VI) and it would be expected to give a spectrum which has 2^3 lines with equal intensities. In (VII) there are two pairs of almost equivalent protons, and it would be expected to possess 3^2 lines (triplet of triplets) in its spectrum. Oxidation of (C) gives a mixture of (VI) and (VII) (1:3), resulting from oxygenation at 2 and 4 positions. Therefore, these three isomers can be distinguished clearly by examination of the e.s.r. spectra of their oxidation products.

This same technique can be used to distinguish between 1-decalones, and *cis-* and *trans*-2-decalones (21, 22). These results have been extended to the related steroidal ketones (21, 22).

By Method I, 1-decalone (*cis* or *trans*) gives semidione (VIII). In

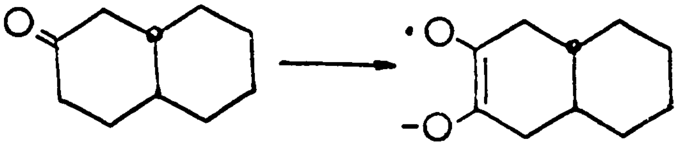


(*cis* or *trans*) (VIII)



+ (VIII)

(IX)



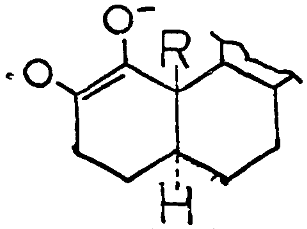
+ (VIII)

(X)

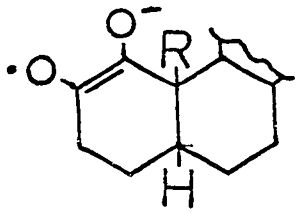
the case of the *cis* isomer a base catalyzed epimerization at C-10 occurs. Under low resolution, the e.s.r. spectrum of (VIII) shows a sextet, which indicates two equivalent axial protons and one equatorial proton. *cis-* and *trans*-2-Decalones form mixtures of (IX) and (VIII), and (X) and

(VIII), respectively, in which (VIII) decays faster and thus dies out first. Both semidiones (IX) and (X) have four α-protons, yet (IX) gives a 13 line spectrum, whereas (X) gives a 7 line pattern. In (IX), the two methylene carbons are different because C-5 and C-10 are differently substituted, One equatorially and one axially, while in (X) the two methylene carbons are equivalent because C-5 and C-10 are axially substituted. Of course, (IX) is necessarily in a frozen conformation. It is thus clear that these decalones can be distinguished readily by an analysis of their e.s.r. spectra without reference to a model compound.

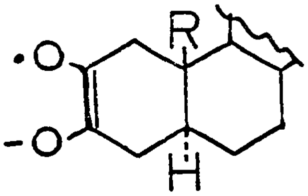
Although steroidal A- or D-ring ketones are numerous and complex in their structures, if one considers only their partial structures—the part containing the decalone-skeleton—most of them can form only one or a mixture of the following semidiones by Method I (14, 21, 22)*



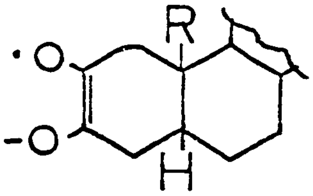
(XIa), R = CH_3
(XIb), R = H



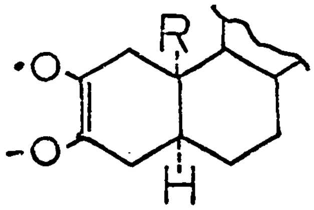
(XIIa), R = CH_3
(XIIb), R = H



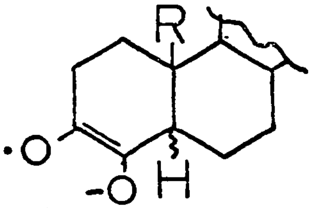
(XIIIa), R = CH_3
(XIIIb), R = H



(XIVa), R = CH_3
(XIVb), R = H



(XVa), R = CH_3
(XVb), R = H



(XVIa), R = CH_3
(XVIb), R = H

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*G. A. Russell and E. R. Talaty, Ames, Iowa. Structure-proof of steroidal ketones by e.s.r. Private communication. 1965.

Semidiones, (XIb), (XIIb), (XVIa), and (XVIb) are similar in structures and they should give similar spectra (6 lines) as found for the semidione derived from 1-decalones. Steroidal ketones, 17α-methyl-19-nor-5α-androstane-3β,17β-diol-4-one and 18-nor-D-homo-5β-androstane-3α-ol-17a-one which form semidiones (XVIb) and (XIa), respectively, give 6 line spectra. The same spectrum is the predominant one in the oxidation of 5β-androstan-17β-ol-3-one, 5β-androstan-3,17-dione, 5β-cholestan-3-one, 5β-pregnan-3-one, and 5β-pregnane-3,20-dione all of which have a *cis* A/B ring juncture and form predominantly (XVIa). However, 3-ketosteroids with a *trans* A/B ring juncture form (XIIIa) predominantly and give 14 line spectra as shown by the following steroids: 5α-androstane-17β-ol-3-one, 5α-androstane-3,17-dione, 5α-cholestan-3-one, and 5α-pregnan-3,20-dione. Thus, the nature of initial A/B ring juncture of 10β-methyl-3-ketosteroids can be easily defined by e.s.r. spectroscopy.

19-Nor-3-ketosteroids and 18-nor-D-homo-17-ketosteroids whose partial structures have the same A/B and C/D ring juncture respectively, can be considered as enantiomers. They do not possess an angular methyl group and are similar to 2-decalones which do not form semidiones selectively but give a mixture of two semidiones. These two series of steroids with *trans* ring fusion form more (XIIIb) than XVIb) and with *cis* fusion form more (XVIb) than (XIVb). In both mixtures (XVIb) is less stable and decays more rapidly. Even when formed in minor quantity the e.s.r. spectrum of (XIVb) is sufficient to show that the initial steroidal ketone had a *cis* ring juncture. 19-Nor-5α,10β-androstan-17β-ol-3-one

17β-acetoxy-19-nor-5α-,10β-androstan-3-one, 3-methoxy-D-homo-18,19-bisnorandrosta-1,3,5(10)-trien-17-one, and 3α-,11α-diacetoxy-D-homo-18-nor-5β-androstan-17-one, and 3α-hydroxy-D-homo-18-nor-5β-androstane-11,17-dione all have *trans* ring fusion and form semidione (XIIIb) which shows a 7 line spectrum. On the other hand, 17β-acetoxy-19-nor-5β,10β-androstan-3-one, 17α-ethyl-19-nor-5β,10β-androstan-17β-ol-3-one, 3-methoxy-D-homo-18,19-bisnor-13α-androsta-1,3,5(10)-triene-17-one, D-homo-18-nor-5β,13α-androstane-3α,11β-diol-17-one, 3α-hydroxy-D-homo-18-nor-5β,13α-androstane-11,17-dione, 17β-acetoxy-19-nor-5α,10α-androstan-3-one, 17α-ethyl-19-nor-5α,10α-androstan-17β-ol-3-one, and 17β-hydroxy-5α,9β,10α-19-norandrostan-3-one all have a *cis* ring juncture and form semidione (XIVb) which shows 13-16 line spectrum. Once again, 19-nor-3-ketosteroids and 18-nor-D-homo-17-ketosteroids with *cis* and *trans* A/B or C/D ring junctures can be distinguished, without reference to a model compound.

This e.s.r. technique in connection with oxidation provides an elegant alternative method to optical rotatory dispersion in assigning *cis-trans* configurations to decalones and related steroids. This method does not require an optically active ketone and consumes only a few mg. of the ketone.

Purpose of the present study was to investigate semidiones derived from bridged bicyclic ketones and to extend the knowledge to the challenging problems that remain in the study of the semidione derived from camphor (13, 15). The spectrum of this semidione has been shown to be a quartet with some unresolved fine splittings. The quartet was thought to arise from one of the three methyl groups in the camphor molecule. It had been assumed to be the one at 7-*syn* position because of its proximity to the semidione system. It was also assumed that bridgehead protons, although α to the dicarbonyl system, would not couple with the unpaired spin density, since it has been reported that semiquinones prepared from 2,5-dihydroxytriptycene and 1-methyl-2,5-dihydroxytriptycene fail to show a coupling between the bridgehead proton and methyl protons and the unpaired spin density (23, 24). The results described herein show that both assumptions were erroneous.

RESULTS AND DISCUSSION

The e.s.r. spectra were obtained using a Varian V-4500 spectrometer equipped with 100 Kc./sec. field modulation and with 9-in. magnets. A flat fused silica cell (Varian V-4548 aqueous solution sample cell) in connection with an inverted U-tube (8) (Figure 1) was used for all experiments. Typically, 0.5 ml. of DMSO solutions containing 0.1 M of potassium t-butoxide and 0.05 M of a ketone (or an α-diketone and a donor, an α-hydroxyketone, or an α-bromoketone) were deoxygenated separately in the two legs of the U-tube by introducing prepurified nitrogen through two 5-in. hypodermic needles extending below the surface of each solution for 15-20 minutes. The exit was stopped before the hypodermic needles were withdrawn. The two solutions were mixed and shaken into the flat cell. In case oxygen was required, it was introduced by opening the stopper and one of the rubber septa for 10-15 seconds with a gentle swirling action.

Oxidation of bicyclo[2,2,2]octan-2-one with a trace of oxygen in d_6-DMSO containing potassium t-butoxide, reduction of bicyclo[2,2,2]-octane-2,3-dione by the propiophenone enolate anion in DMSO, or treatment of 3-bromobicyclo[2,2,2]octan-2-one (generated in situ) with potassium t-butoxide in DMSO produces a semidione which is stable for hours at room temperature and is shown in Figure 2. It consists of a simple quintet with peak height ratios, 1:4:6:4:1. It indicates that there are four equivalent hydrogen atoms (a^H = 2.09 G) interacting with the unpaired electron. In this semidione, there are two bridgehead, four syn

Figure 1. Apparatus for preparing semidiones prior to mixing and insertion into the cavity of the e.s.r. spectrometer.

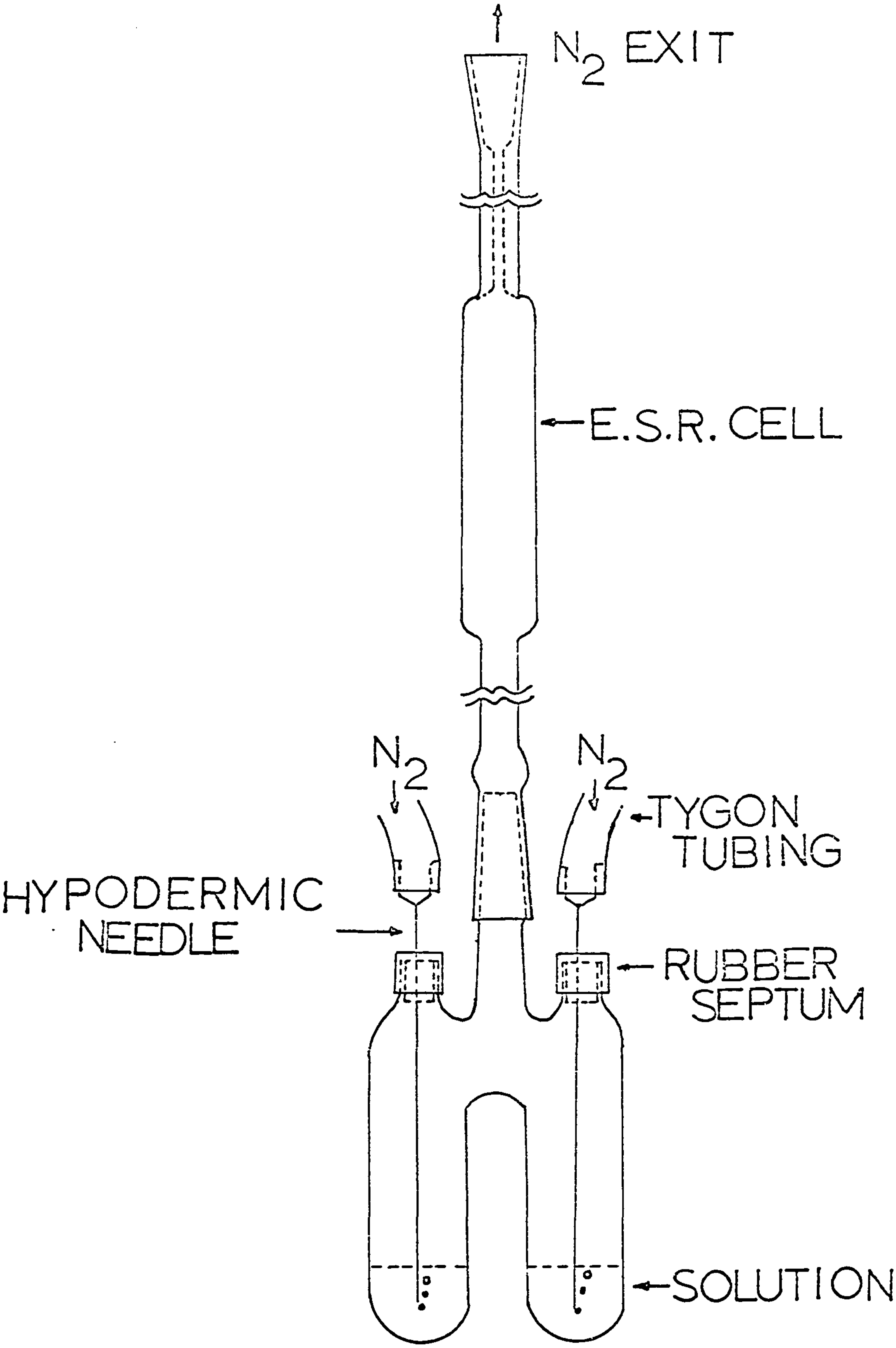
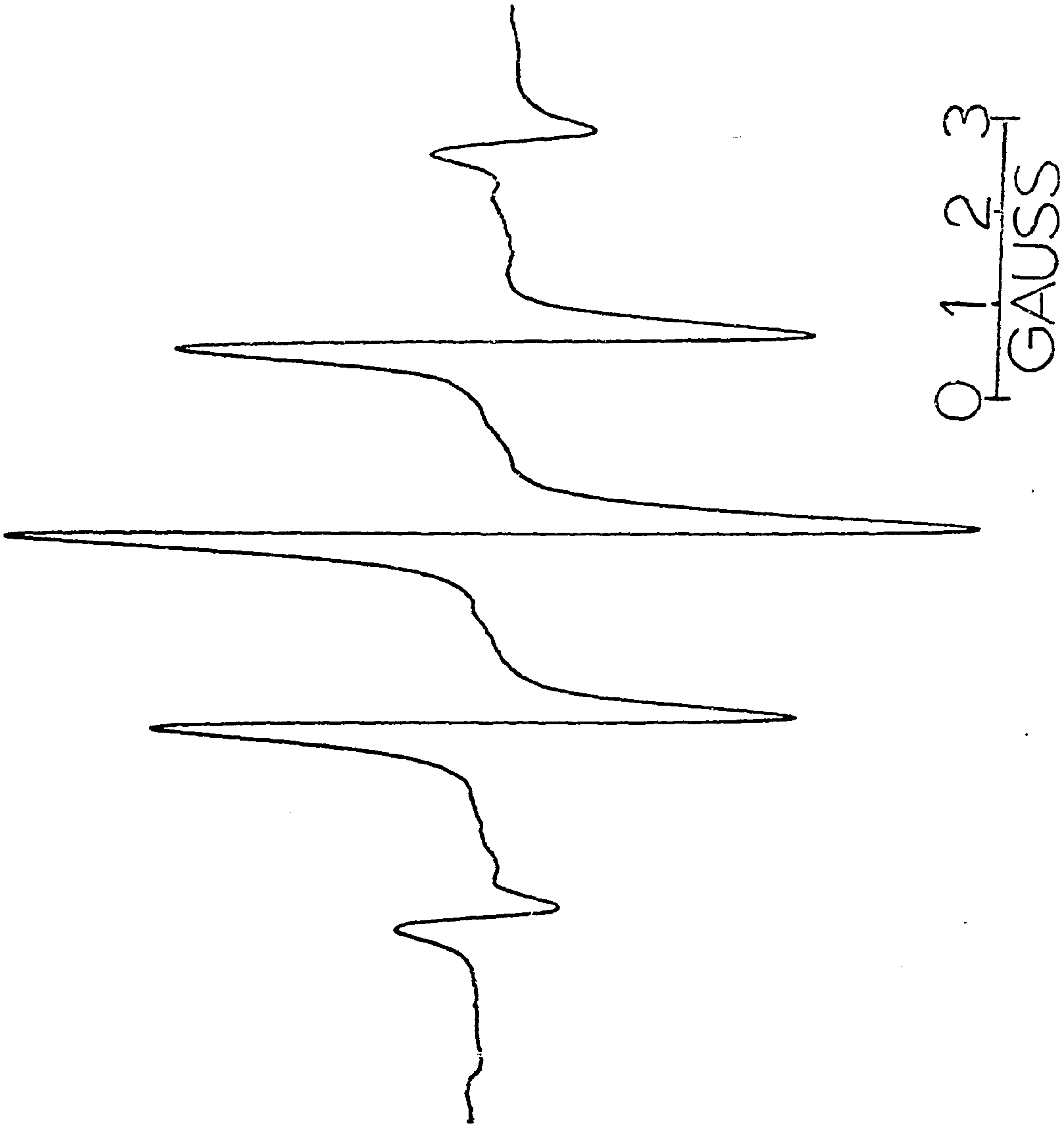

N_2 EXIT
E.S.R. CELL
N_2
N_2
TYGON TUBING
HYPODERMIC NEEDLE
RUBBER SEPTUM
SOLUTION

Figure 2. First derivative e.s.r. spectrum of bicyclo[2,2,2]octane-2,3-semidione prepared by reaction of a trace of oxygen with bicyclo[2,2,2]octan-2-one (0.05 M) in d_6-DMSO containing potassium t-butoxide (0.10 M) at 25° or by reduction of bicyclo[2,2,2]-octane-2,3-dione (0.05 M) by propiophenone (0.05 M) in the presence of potassium t-butoxide (0.10 M).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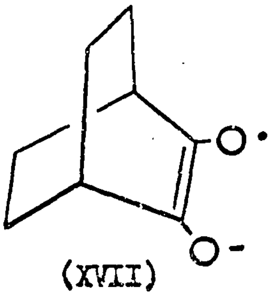
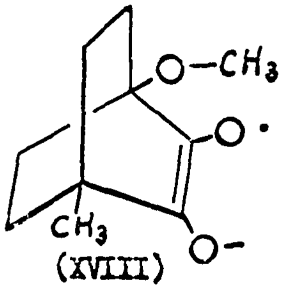
GAUSS

and four anti methylene protons. The two bridgehead protons not only are insufficient in number but also situated in the nodal plane of the carbonyl-carbon p_z-orbitals and thus can be ruled out. Furthermore, a five line spectrum (Figure 3) was obtained upon oxidation of 1-methyl-4-methoxybicyclo[2,2,2]octan-2-one (25), which does not possess any bridgehead protons, as indicated in (XVIII). The spectrum of (XVIII) shows some line broadening as expected for four hydrogen atoms (a^H = 2.14 G) that are nearly but not exactly equivalent.

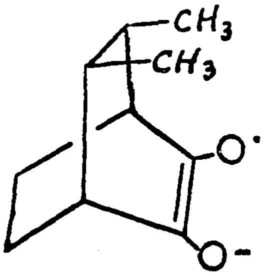


(XVII)



(XVIII)

The hyperfine splitting is believed to be due to the four hydrogen atoms anti to the dicarbonyl system in both (XVII) and (XVIII), because oxidation of endo, endo-5,6-dimethylbicyclo[2,2,2]octan-2-one in DMSO or d_6-DMSO yields a semidione with hyperfine splitting by two pairs of equivalent hydrogen atoms as shown in Figure 4. This spectrum is only consistent with anti hydrogen splitting in the semidione (XIX).



(XIX)

Figure 3. First derivative e.s.r. spectrum of 1-methyl-4-methoxybicyclo[2,2,2]octane-2,3-semidione prepared by reaction of a trace of oxygen with 1-methyl-4-methoxybicyclo[2,2,2]-octan-2-one (0.05 M) in DMSO containing potassium *t*-butoxide (0.10 M) at 25°.

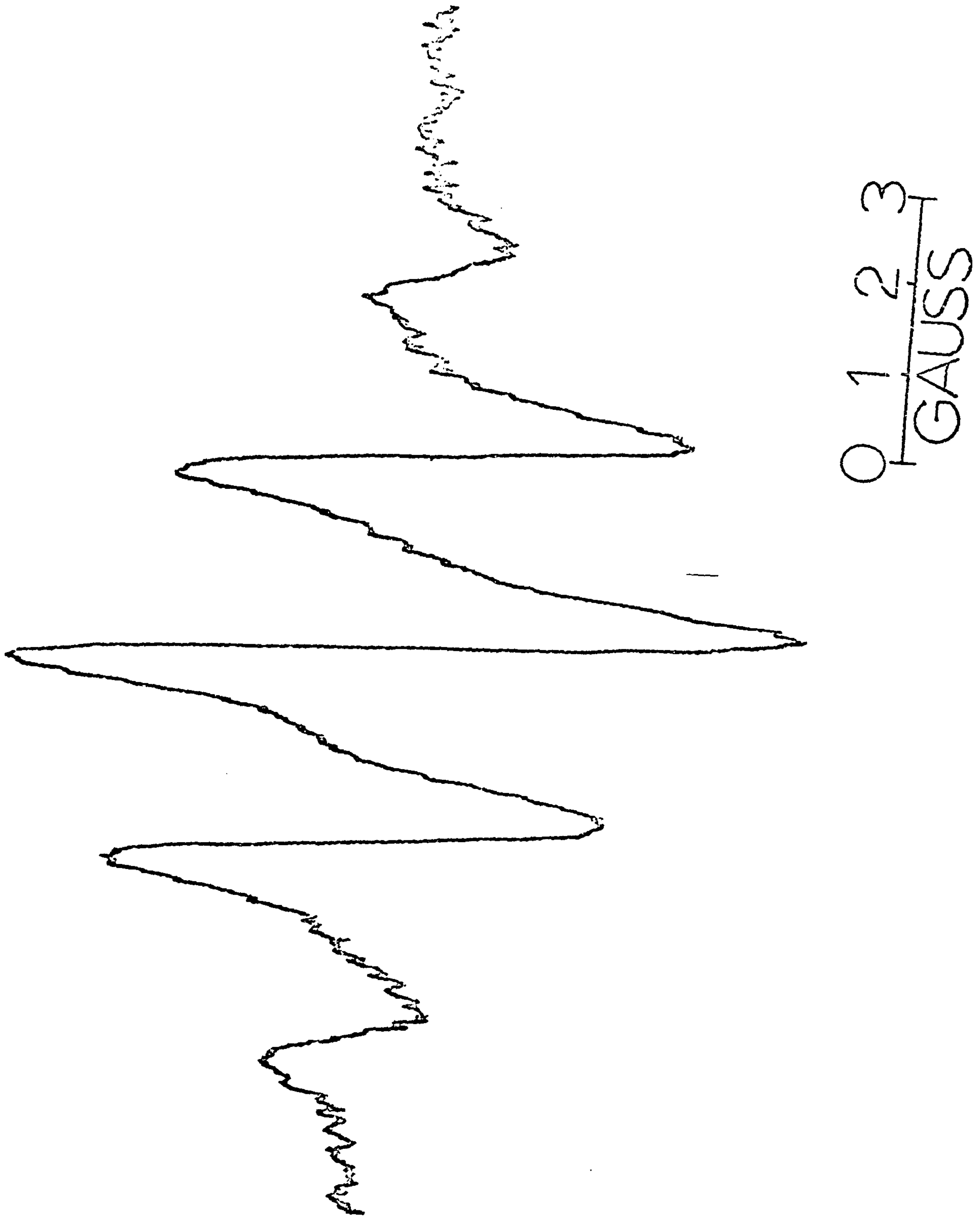

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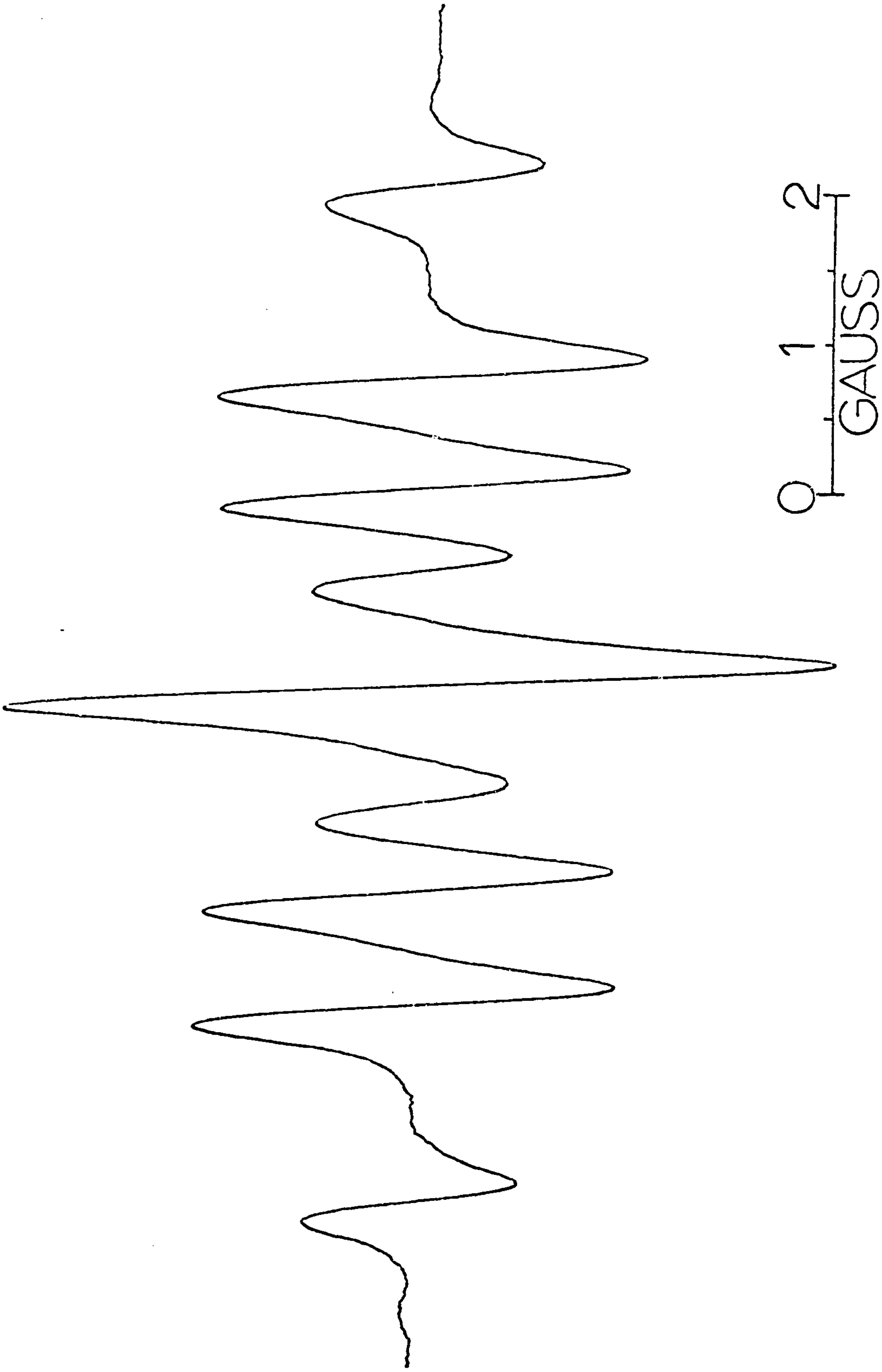
Figure 4. First derivative e.s.r. spectrum of *endo*, *endo*-5,6-dimethylbicyclo[2,2,2]octane-2,3-semidione prepared by reaction of a trace of oxygen with *endo*,*endo*-5,6-dimethylbicyclo[2,2,2]octan-2-one (0.05 M) in DMSO containing potassium *t*-butoxide (0.10 M) at 25°.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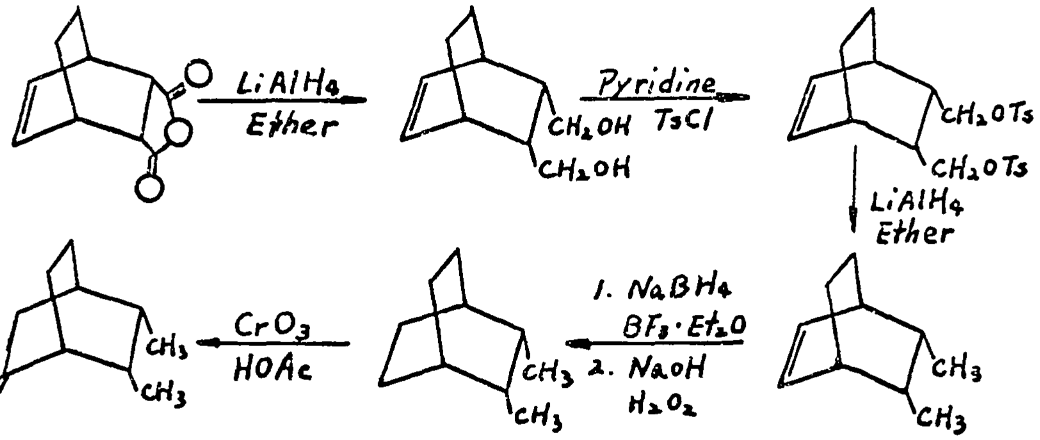
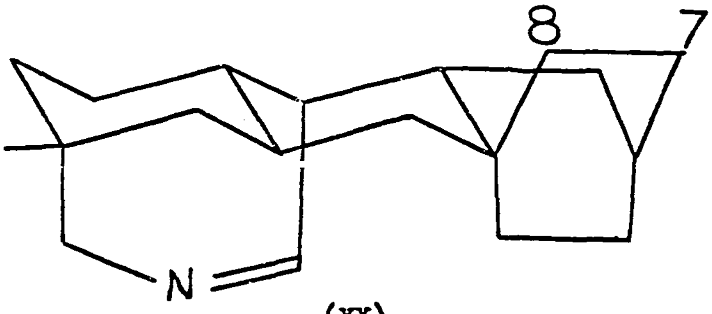
The above *endo,endo*-dimethylketone was prepared from bicyclo[2,2,2]-octene-5-*endo,endo*-2,3-dicarboxylic anhydride, a Diels-Alder adduct established to have *endo,endo* structure (26, 27), by the following transformations. The *endo,endo* configuration of the methyl groups was also



proved by n.m.r. which showed two different doublets centered at 0.97 p.p.m. and 0.75 p.p.m. from tetramethylsilane due to the anisotropic effect of the keto group. It will benefit later discussion to note here that no splitting is observed for methyl protons.

The *anti* or *exo* splitting by hydrogen atoms in respect to the carbonyl carbon p_z-orbital is consistent with the quartet splitting, a^H = 2.20 G, observed for the semidione prepared by oxidizing the atisine



(XX)

(XXa) 7 = H_2, 8 = O

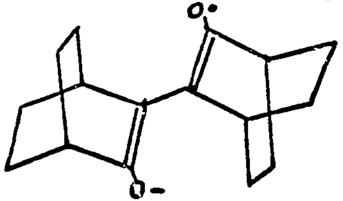
(XXb) 7 = O, 8 = H, OAc

(XXc) 7 and 8 = $\overset{\cdot O\quad O^-}{\backslash\_/}$

derivatives (28), (XXa) in $\underline{d}_6$-DMSO and (XXb) in DMSO. (XXb) may have been hydrolyzed to the α-hydroxyketone by a trace of moisture present in DMSO or on the surface of cells. This is a variation of Method II and shows that a semidione can be obtained from an α-acetoxyketone in addition to the four types of ketones discussed in the introduction. Under high resolution the spectrum (Figure 5) shows additional fine splitting probably due to two additional β-hydrogen atoms.

Since only anti or exo hydrogen atoms in bicyclo[2,2,2]octane-2,3-semidione are interacting with the unpaired electron, e.s.r. spectroscopy appears to be a convenient method for assigning structure to substituted bicyclo[2,2,2]octanones. For example, oxidation of 1,5-dimethyl-4-methoxybicyclo[2,2,2]octan-2-one (25) gives a semidione whose e.s.r. spectrum (Figure 6) indicates a quartet ($\underline{a}^H$ = 2.10 G) and a doublet ($\underline{a}^H$ = 0.93 G) splittings. Thus the 5-methyl group in this ketone is assigned the syn structure.

Among five bicyclo[2,2,2]octan-2-ones examined, only the parent bicyclo[2,2,2]octan-2-one and the 8-keto derivative (XXa) form different radical anion species in DMSO and $\underline{d}_6$-DMSO upon oxidation. The spectrum of the former in DMSO (Figure 7) clearly requires hyperfine splitting by two sets of four equivalent hydrogen atoms, $\underline{a}^H$ = 1.5 and 1.09 G. This radical anion is believed to be (XXI) having a dimeric structure. A



(XXI)

Figure 5. First derivative e.s.r. spectrum of semidione (XXc) prepared by reaction of a trace of oxygen with atisine derivative (IVa) (0.025 M) in *d*$_6$-DMSO containing potassium *t*-butoxide (0.05 M) or by mixing (IVb) (0.025 M) in DMSO conatining potassium *t*-butoxide (0.05 M) at 25°.

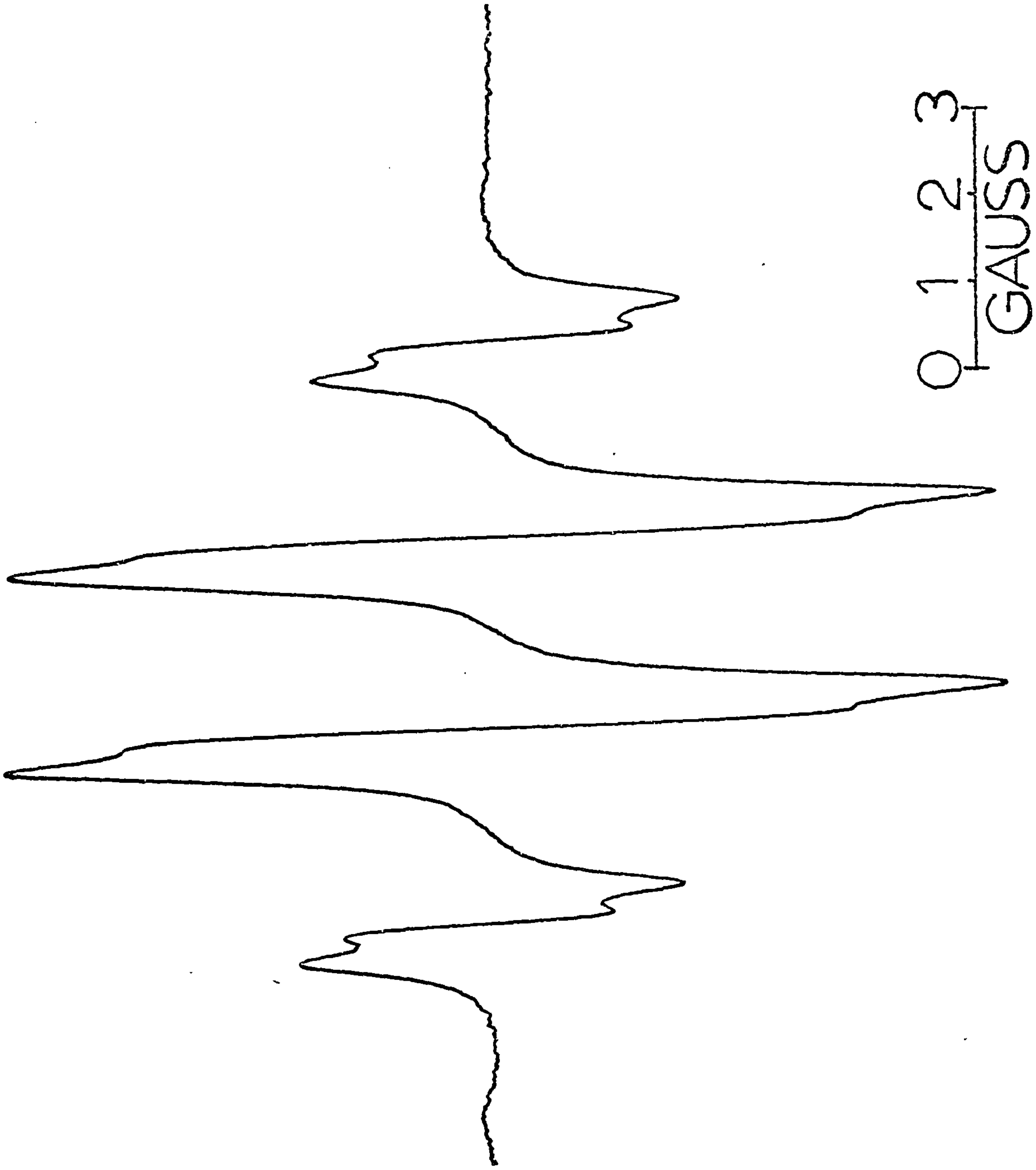

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Figure 6. First derivative e.s.r. spectrum of 1,5-dimethyl-4-methoxybicyclo[2,2,2]octane-2,3-semidione prepared by reaction of a trace of oxygen with 1,5-dimethyl-4-methoxybicyclo[2,2,2]octan-2-one (0.05 M) in DMSO containing potassium _t_-butoxide (0.10 M) at 25°.

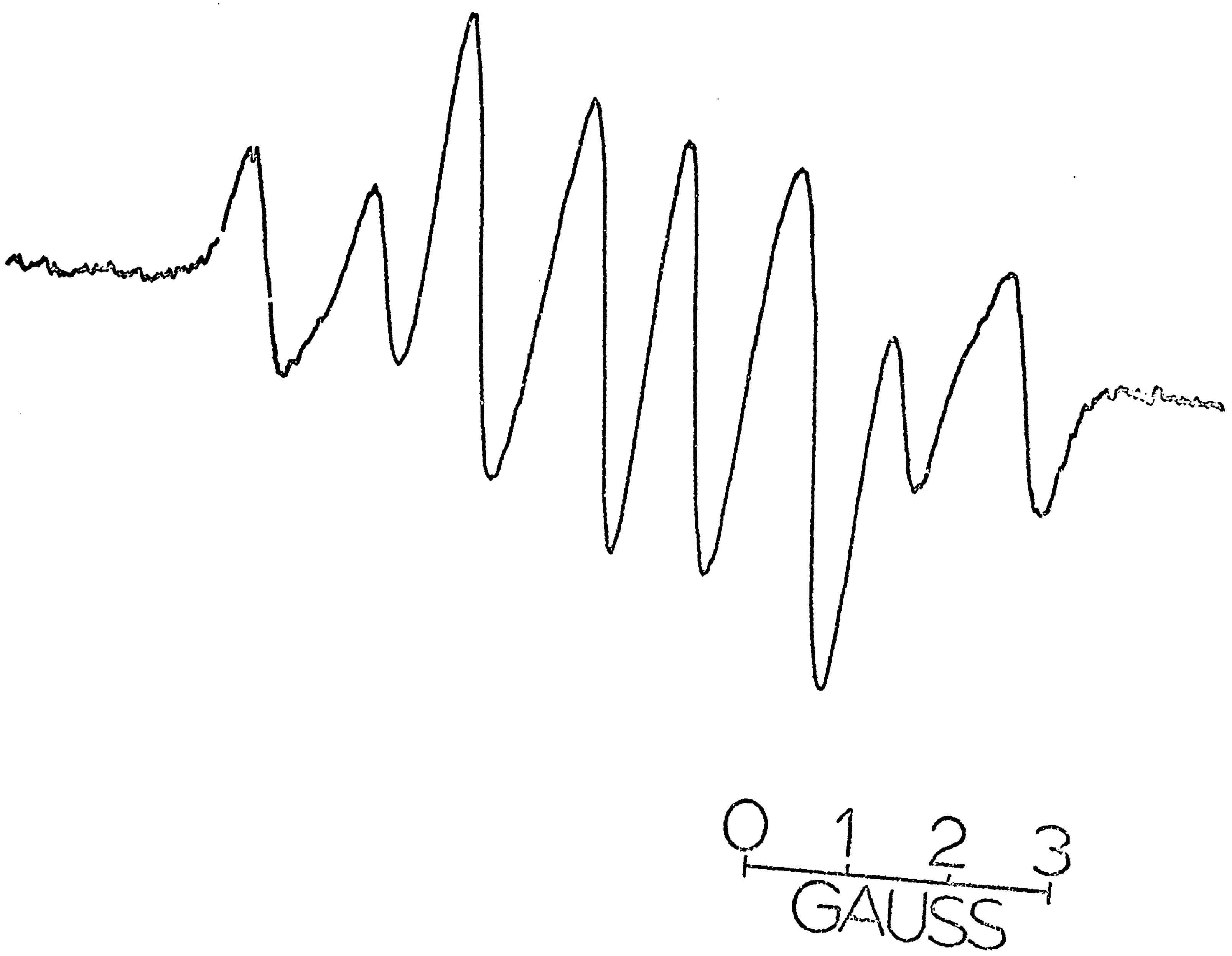
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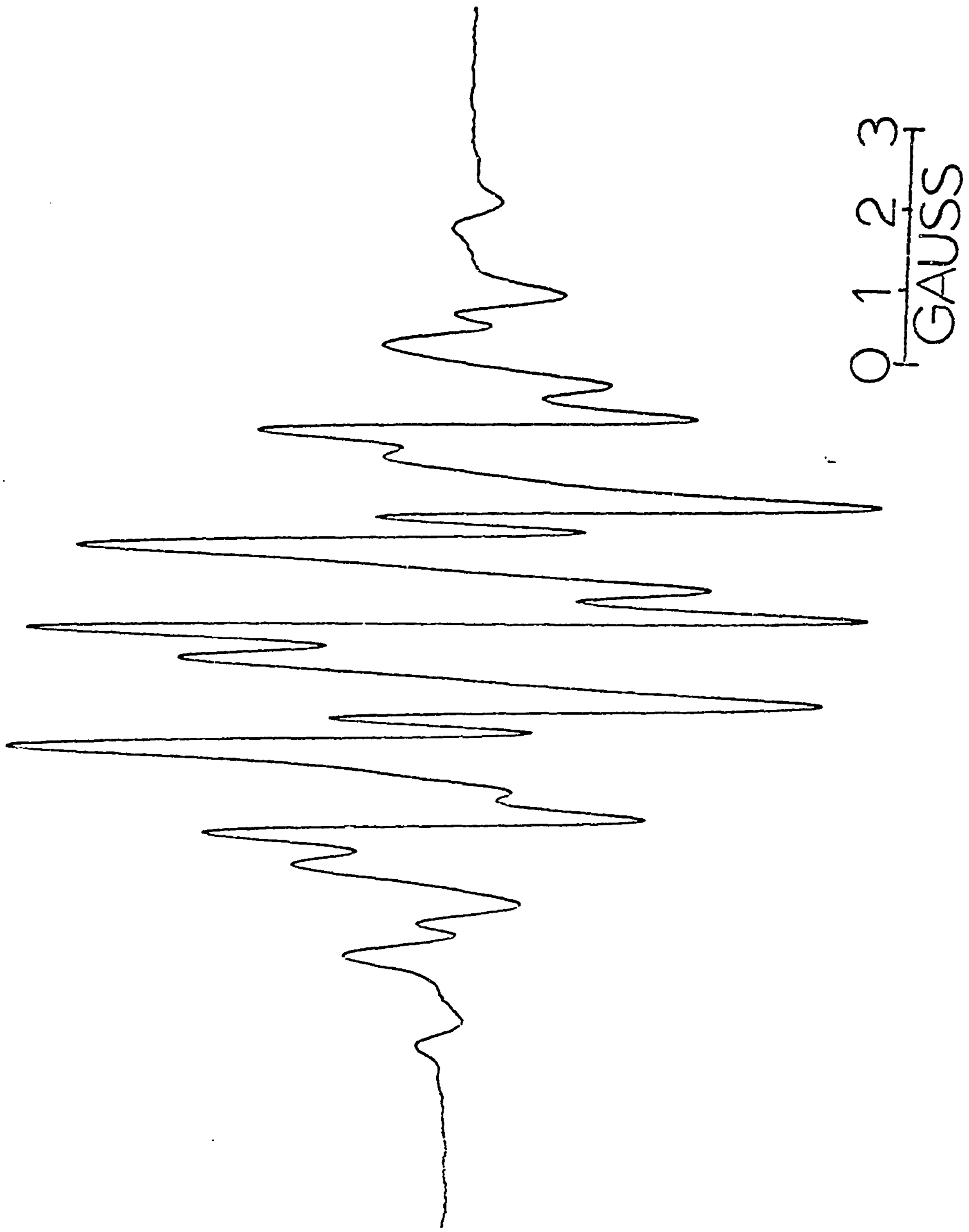
Figure 7. First derivative e.s.r. spectrum of semidione (XXI) prepared by reaction of a trace of oxygen with bicyclo[2,2,2]octan-2-one (0.05 M) in DMSO containing potassium _t_-butoxide (0.10 M) or by mixing bicyclo[2,2,2]octan-2-one (0.05 M) with bicyclo[2,2,2]octan-2,3-dione (0.05 M) in DMSO containing potassium _t_-butoxide (0.10 M) at 25°.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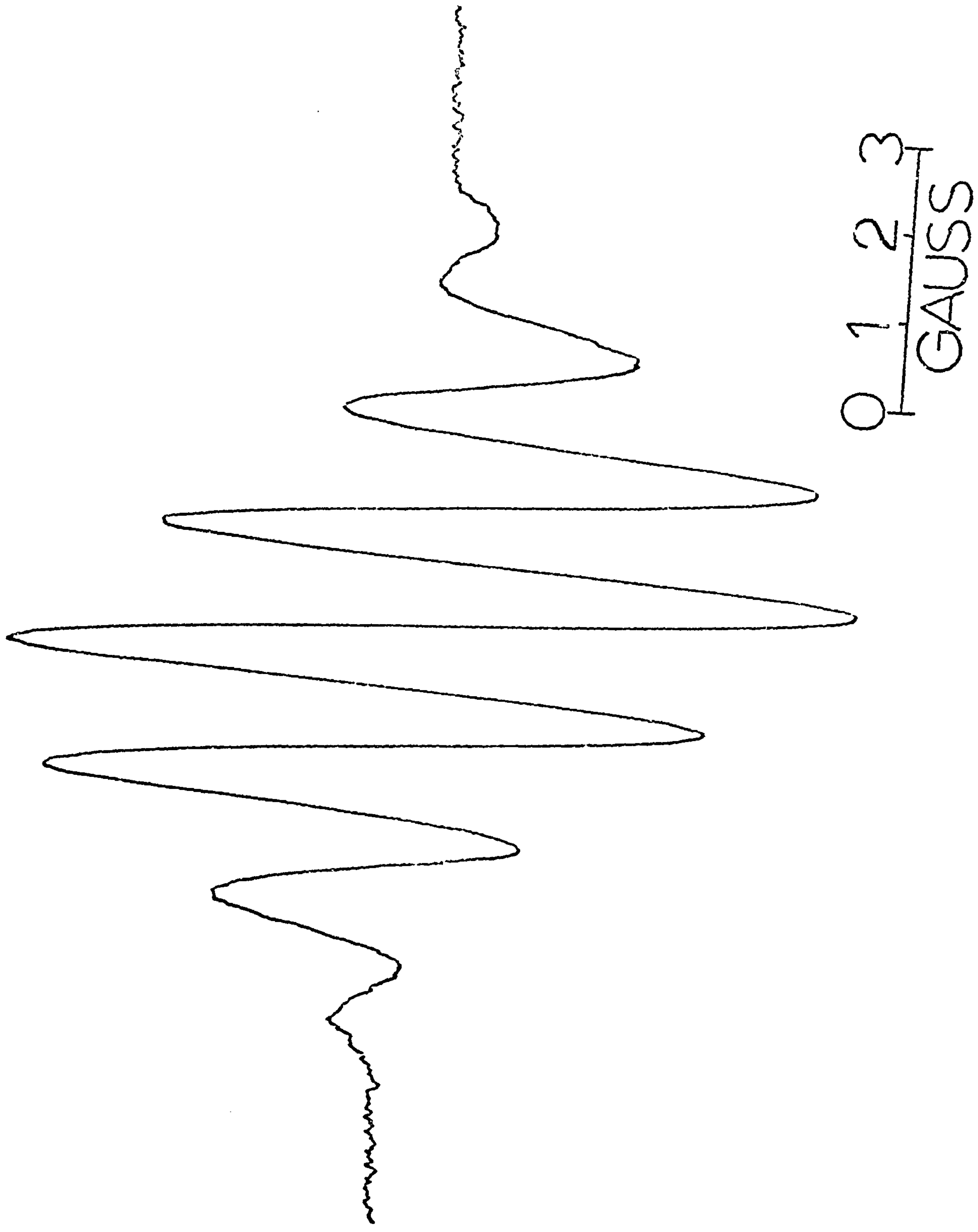
conjugated diketone probably results from the condensation of the carbanion of the monoketone with the diketone formed in the oxidation reaction which then accepts an electron to give semidione (XXI). This is confirmed by the fact that an identical spectrum was obtained from a mixture of bicyclo[2,2,2]octan-2-one and bicyclo[2,2,2]octane-2,3-dione in DMSO containing potassium t-butoxide in the absence of oxygen. Oxidation of (XXb) in DMSO gives a seven line spectrum as shown in Figure 8 which is consistent with 6 fortuitously equivalent protons, a^H =1.45 G. Therefore, this radical anion probably exists in a dimeric form analogous to (XXI). This kind of dimerization was not observed in any of the other bicyclic systems studied. It provokes three interesting questions. Why does the dimerization only occur in the bicyclo[2,2,2]octane system? Why do two out of five bicyclo[2,2,2]octan-2-ones form dimers butnot all of them? Why does the dimerization not take place in d_6-DMSO?

To answer these questions requires a better understanding of the mechanism through which a semidione can be formed by oxidation of the monoketone. It has been shown in the introductory section that there are possibly three pathways for the formation of a semidione from a monoketone. If reaction (5) is faster than reaction (3), it is impossible to have dimer formation because any diketone (c) formed will disproportionate immediately with the dianion (e) to give semidiones (pathway C). This represents all the bridged bicyclic systems except the bicyclo[2,2,2]octane where reaction (3) is faster than (5). For example, the maximum concentration of semidione obtained by mixing equivalent amounts

Figure 8. First derivative e.s.r. spectrum of the dimeric semidione prepared by reaction of a trace of oxygen with atisine derivative (XXa) (0.025 M) in DMSO containing potassium t-butoxide (0.05 M) at 25°.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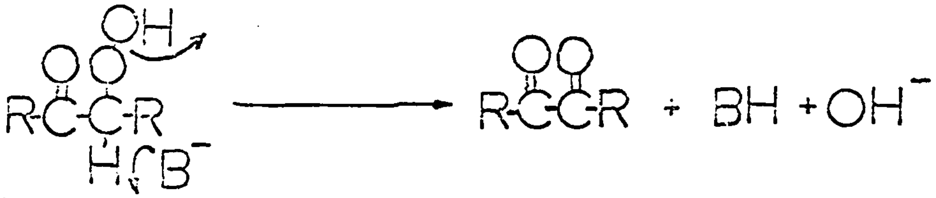
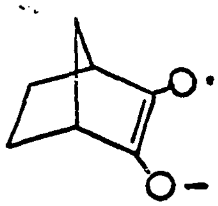
of camphorquinone and camphor in DMSO containing potassium *t*-butoxide in the absence of oxygen is only *one tenth* of that obtained by oxidation of the same amount of camphor with oxygen. Considering the amount of diketone that will be formed actually by oxidation and the amount of oxygen introduced, the ratio could have a value well under 1/1000. This answers the first question. Furthermore, no dimeric semidione was observed when camphor and camphorquinone were mixed together. This indicates that a condensation reaction is slow in sterically hindered detones since those three bicyclo[2,2,2]octan-2ones which do not form dimer are all highly substituted. The third question can be answered by isotope effect since the formation of a diketone involves the abstraction of proton with sub-

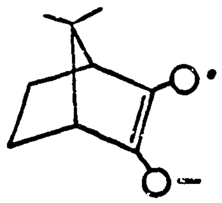


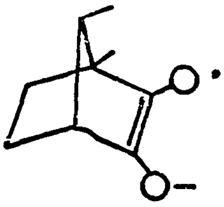
sequent loss of a hydroxy group to give the diketone. In d_6-DMSO the reaction involves the abstraction of a deuterium and hence favors the reaction (5). Therefore, dimerization is not observed in d_6-DMSO.

Bicyclo[2,2,1]heptane-2,3-semidione can not be prepared by oxidation of bicyclo[2,2,1]heptan-2-one in the usual manner. This is also true for the 1-methyl, 1,7 *anti*-dimethyl- and 5,6-dimethylbicyclo[2,2,1]heptan-2-ones which all lack a C-7 *syn* methyl group. Camphor, apocamphor, and *β*-santenone which have a C-7 *syn* methyl group form semidiones readily upon oxidation. Thus a *syn* methyl group at C-7 in bicyclo[2,2,1]heptan-2-one is required to form the semidione by Method I. Apparently, the methyl group blocks the upper-front side of C-2,3 and prevents side reactions, which may lead to the destruction of the intermediates in the processes forming the semidiones. This view seems reasonable since bicyclo[2,2,1]heptanesemidione once formed is quite stable. Beckmann and Mezger (29) reduced a large number of bicyclo[2,2,1]heptan-2-ones with lithium aluminum hydride and found that those ketones without a C-7 *syn* methyl group gave almost exclusively the *endo* alcohols, whereas those with a C-7 *syn* methyl group gave the *exo* alcohols. They also found that a methy group at the bridgehead does not alter the reduction product. Thus 1-methylnorcamphor gave the corresponding *endo* alcohol. This observation supports the reasoning given above.

Bicyclo[2,2,1]heptane-2,3-semidione can be prepared from bicyclo-[2,2,1]heptane-2,3-dione by reduction with propiophenone enolate anion and also from α-bromonorcamphor by treatment with a basic DMSO solution, and its spectrum is shown in Figure 9. It consists of a large doublet (a^H = 6.54 G), a quintet (a^H = 2.43 G), and another doublet (a^H = 0.41 G). These splittings are assigned to the *anti* C-7; the C-1, C-4, *exo* C-5, and *exo* C-6; and to the C-7 *syn* proton(s) respectively. These assignments undoubtedly seem ambiguous to the reader at the present time. However, by keeping in mind the splitting of *anti* hydrogen atoms in semidione (XIX) and by comparison of (XXII) with 7,7-dimethylbicyclo-


(XXII)


(XXIII)


(XXIV)

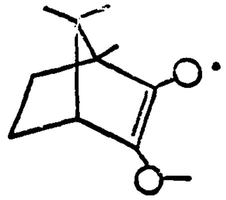
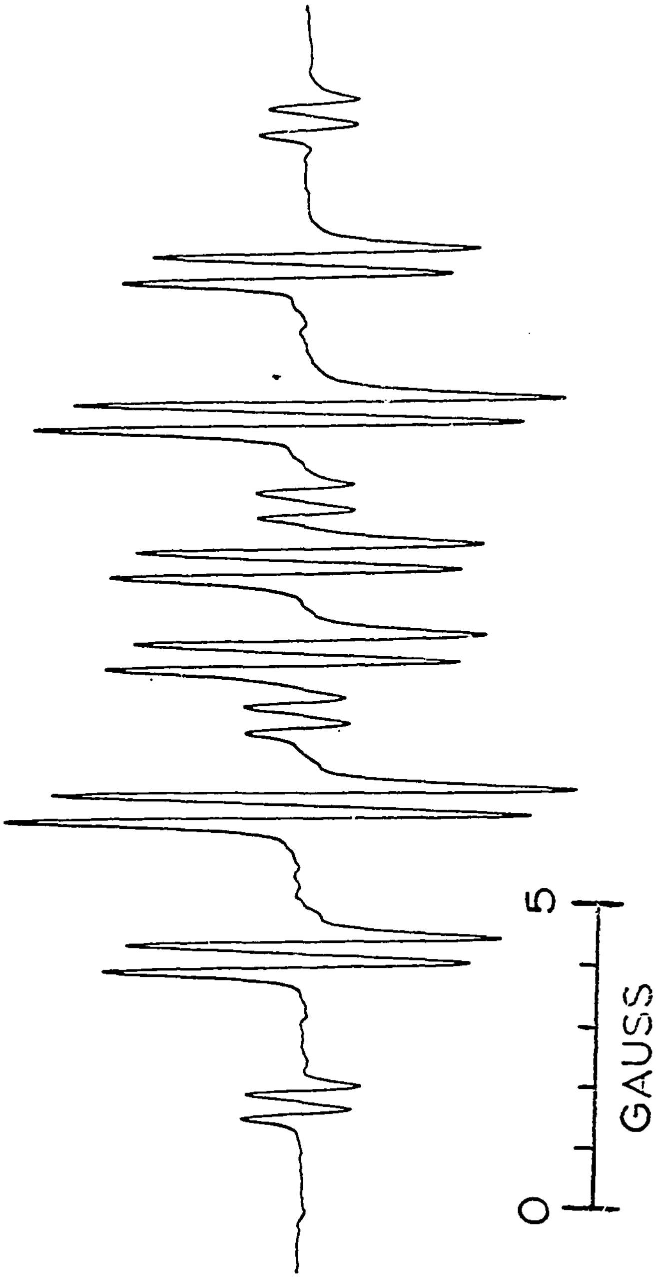

(XXV)

Figure 9. First derivative e.s.r. spectrum of bicyclo[2,2,1]heptane-2,3-semidione in DMSO solution prepared by reduction of bicyclo[2,2,1]heptane-2,3-dione (0.05 M) by propiophenone (0.05 M) in the presence of potassium _t_-butoxide (0.10 M) or by dissolving _α_-bromonorcamphor in DMSO containing potassium _t_-butoxide at 25°.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[2,2,1]heptane-2,3-semidione (XXIII), 1,<u>syn</u>-7-dimethylbicyclo[2,2,1]-heptane-2,3-semidione (XXIV), and 1,7,7-trimethylbicyclo[2,2,1]heptane-2,3-semidione (XXV), the reasons for the particular assignments will become clear.

Semidione (XXIII) is obtained by oxidation of apocamphor and its spectrum is shown in Figure 10. The spectrum of (XXIII) is interpreted to be due to three pairs of equivalent protons and one methyl group interacting with the unpaired spin density. The two pairs of protons are assigned to have hyperfine splitting constants of $\underline{a}^H = 2.90$ and 2.07 G, respectively. Then, each of these 9 overlapping lines are further split into quartets by the three methyl protons, $\underline{a}^H = 0.53$ G, and to triplets, $\underline{a}^H = 0.26$ G, by the two <u>endo</u> hydrogen atoms. The methyl group is assigned to be the one at the <u>anti</u> C-7 position on the basis that the smae splitting is observed in (XXV) but not in (XXIV). These assignments are tentative, therefore, the h.f.s.f. for the two large doublets can well be exchanged.

Under low resolution, a quintet is shown in the spectrum of semidione (XXIV) prepared by oxidation of $\underline{\beta}$-santenone. With higher resolution, the two wing peaks are further split into heptets and the three center peaks into decets as shown in Figure 11. This is interpreted as follows: there are two overlapping quartets each of which is split into a heptet by the two methyl groups. Moreover four lines of one heptet overlap with four lines of another heptet giving the 10 line pattern in the three center peaks. A synthetic spectrum using $\underline{a}^H = 3.05$ G (doublet), 2.55 G

Figure 10. First derivative e.s.r. spectrum of 7,7-dimethylbicyclo[2,2,1]heptane-2,3-semione prepared by reaction of a trace of oxygen with apocamphor (0.05 M) in DMSO containing potassium t-butoxide (0.10 M) at 25°.

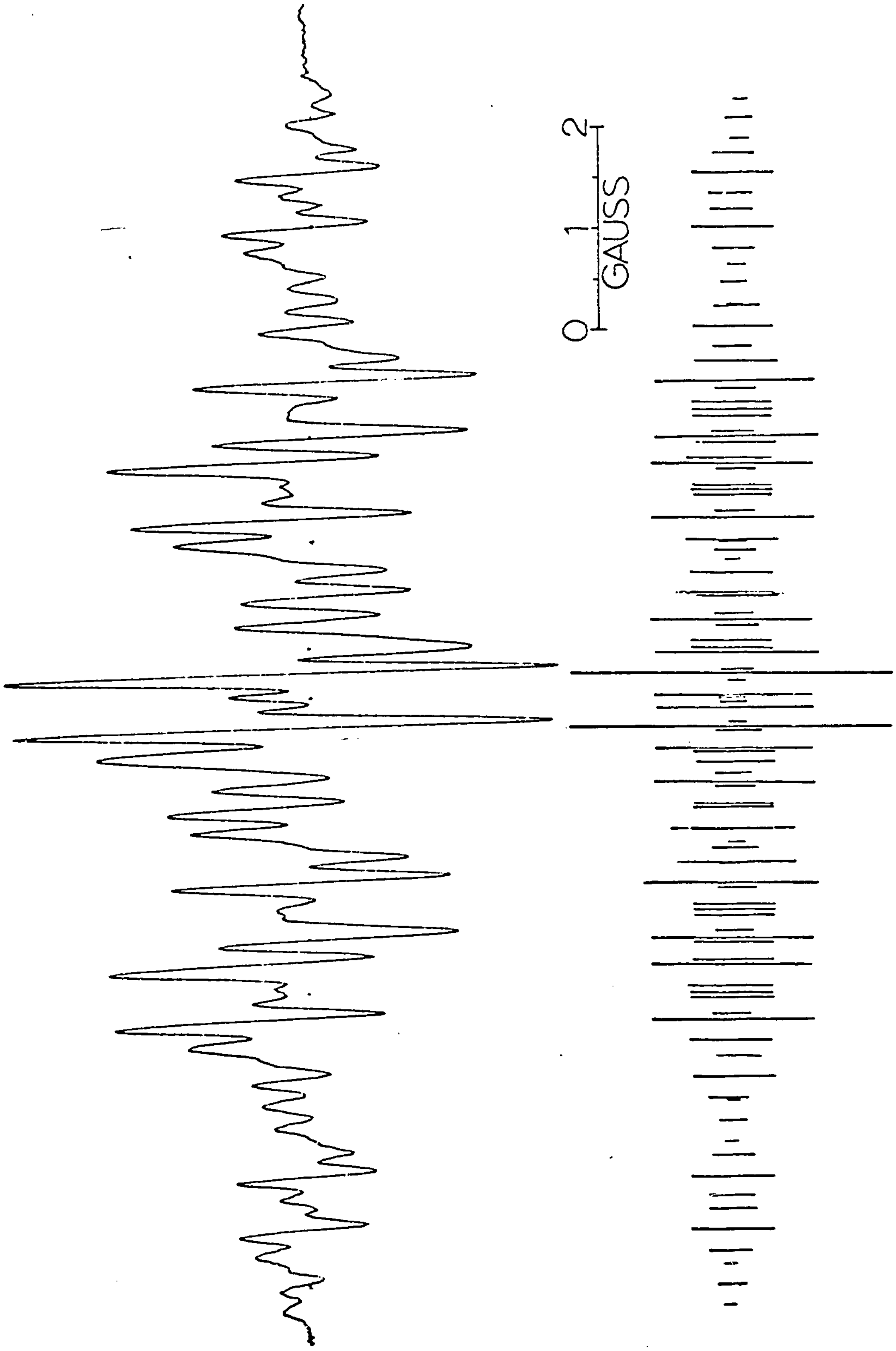
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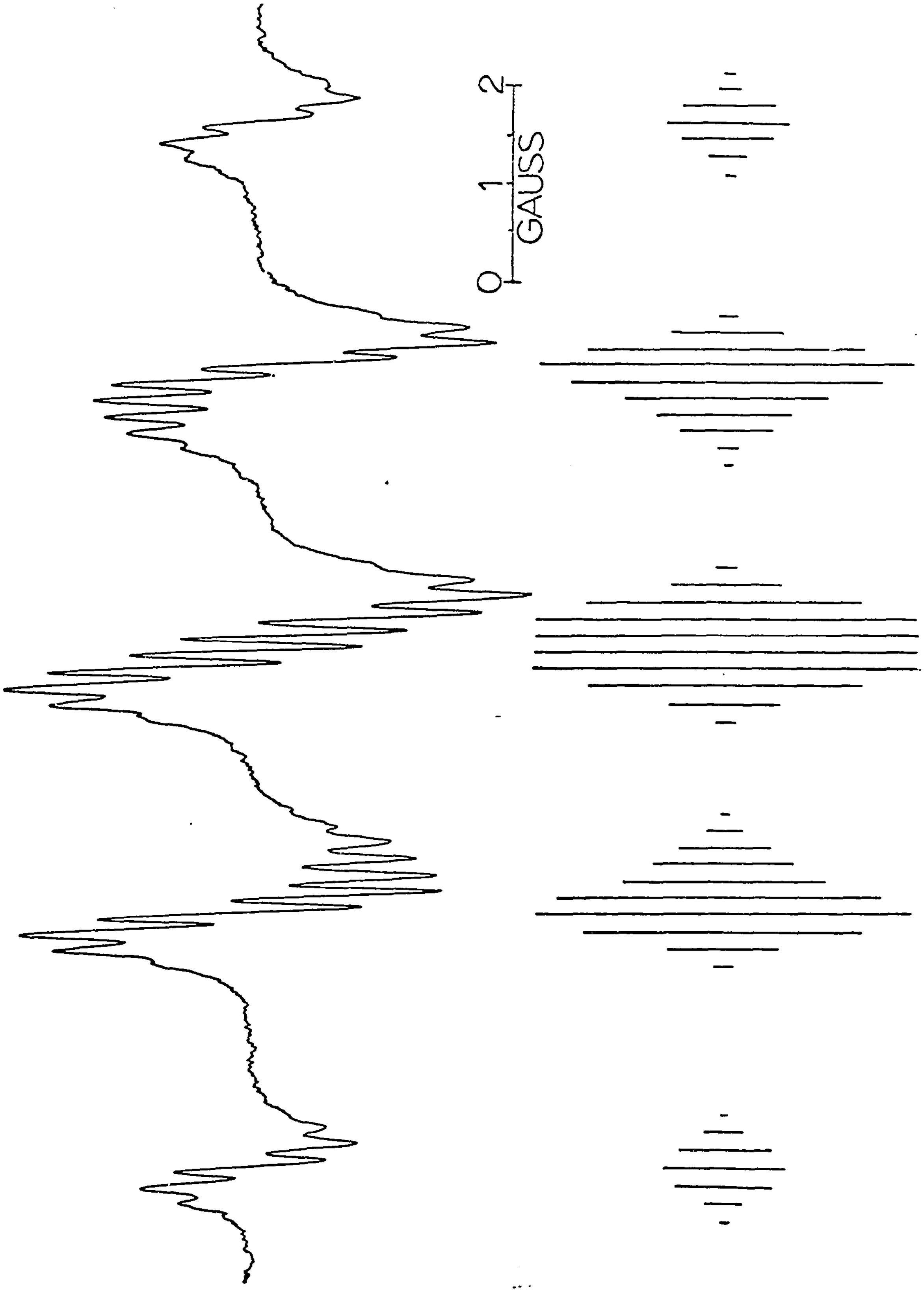
Figure 11. First derivative e.s.r. spectrum of 1,*syn*-7-dimethylbicyclo[2,2,1]heptane-2,3-semidione prepared by reaction of a trace of oxygen with *β*-santenone (0.05 M) in DMSO containing potassium *t*-butoxide (0.10 M) at 25°.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(quartet), and 0.18 G (heptet) is also shown in Figure 11.

The semidione derived from camphor by oxidation, or from camphorquinone by reduction with propiophenone, has been reported to give a four line spectrum with $a^H = 2.66$ G and the splitting was suggested to be due to the *syn* 7-methyl protons (13, 15). At higher resolutions, each of the four peaks further splits to at least 12 lines as shown in Figure 12. The interpretation is that it involves doublet ($a^H = 2.08$ G), triplet ($a^H = 3.01$ G), quartet ($a^H = 0.55$ G), doublet ($a^H = 0.22$ G), and quartet ($a^H = 0.15$ G) hyperfine splittings. These splittings are assigned to the proton or protons at C-4; *exo* C-5 and C-6; *anti* C-7 methyl; *endo* C-5; and C-1 methyl. A "blown-up" wing peak and a composed spectrum of (XXV) based on the last three splitting constants is shown in Figure 13. Apparently, *endo* splitting is no longer negligible in the presence of the *anti* C-7 methyl group as shown in semidiones (XXIII) and (XXV).

The assignment of the major hyperfine splitting in (XXII) to hydrogen atoms at C-1, C-4, *anti* C-7, and *exo* C-5 and *exo* C-6 is thus based on (a) the analogous *anti* splitting by hydrongen atoms at C-5 and C-6 in (XIX), and (b) the fact that the major splittings (as shown by low resolution spectra) of (XXIII), (XXIV, and (XXV) are by four (quintet), four (quintet) and three (quartet) hydrogens, respectively.

Oxidation of bicyclo[3,2,1]octan-2-one or 3-one in DMSO forms the same semidione (XXVI), the spectrum of which is shown in Figure 14. It consists of five major doublets, $a^H = 13.5$; 8.69; 3.45; 2.13; and 1.42 G, and small triplets, $a^H = 0.28$ G. The triplets coalesce into singlets

Figure 12. First derivative e.s.f. spectrum of 1,7,7-trimethylbicyclo[2,2,1]heptane-2,3-semidione prepared by reaction of a trace of oxygen with camphor (0.05 M) in DMSO containing potassium *t*-butoxide (0.10 M) at 25°.

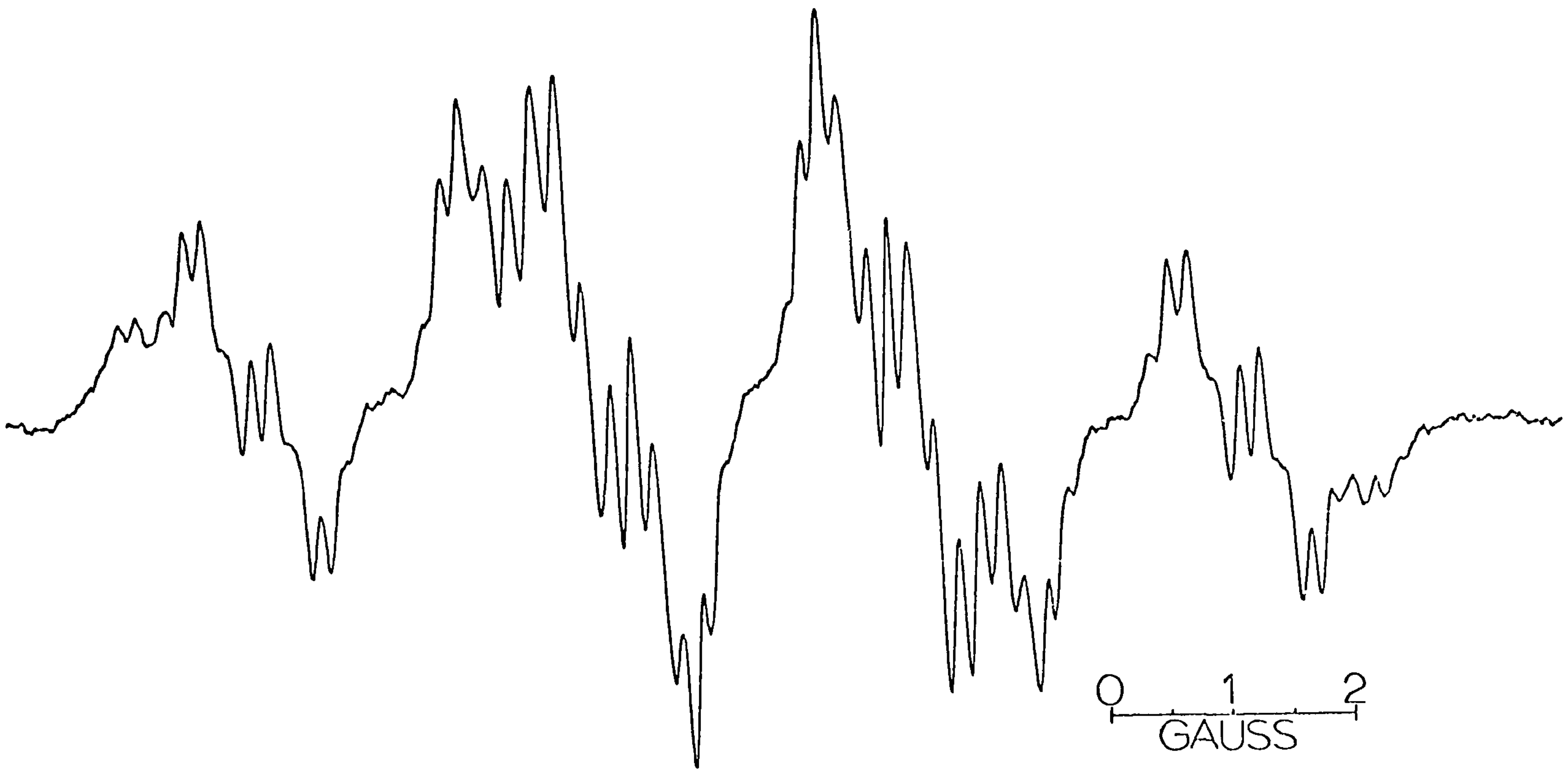
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Figure 13. A "blown up" wing peak of semidione (XXV) and its synthetic spectrum.

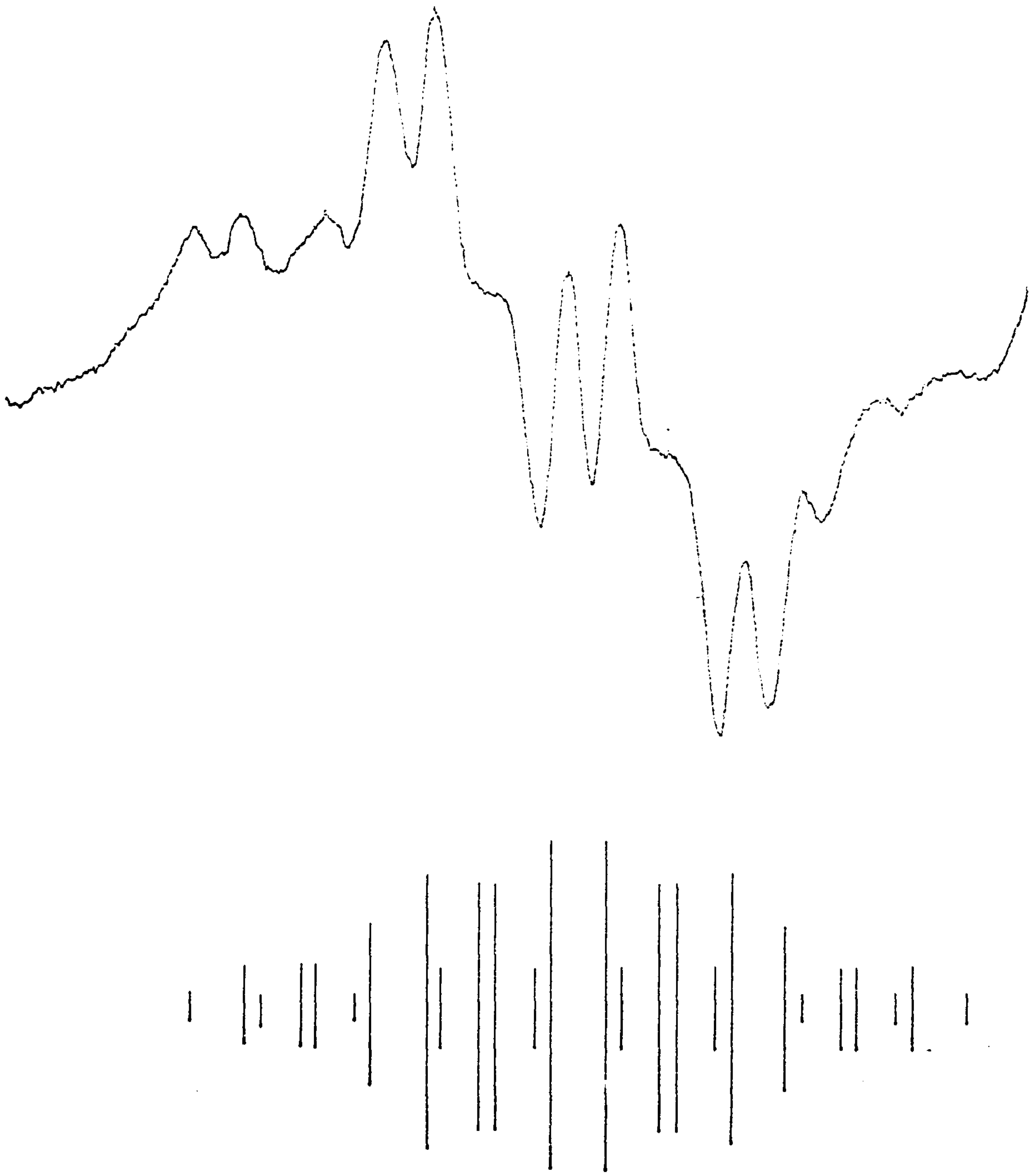
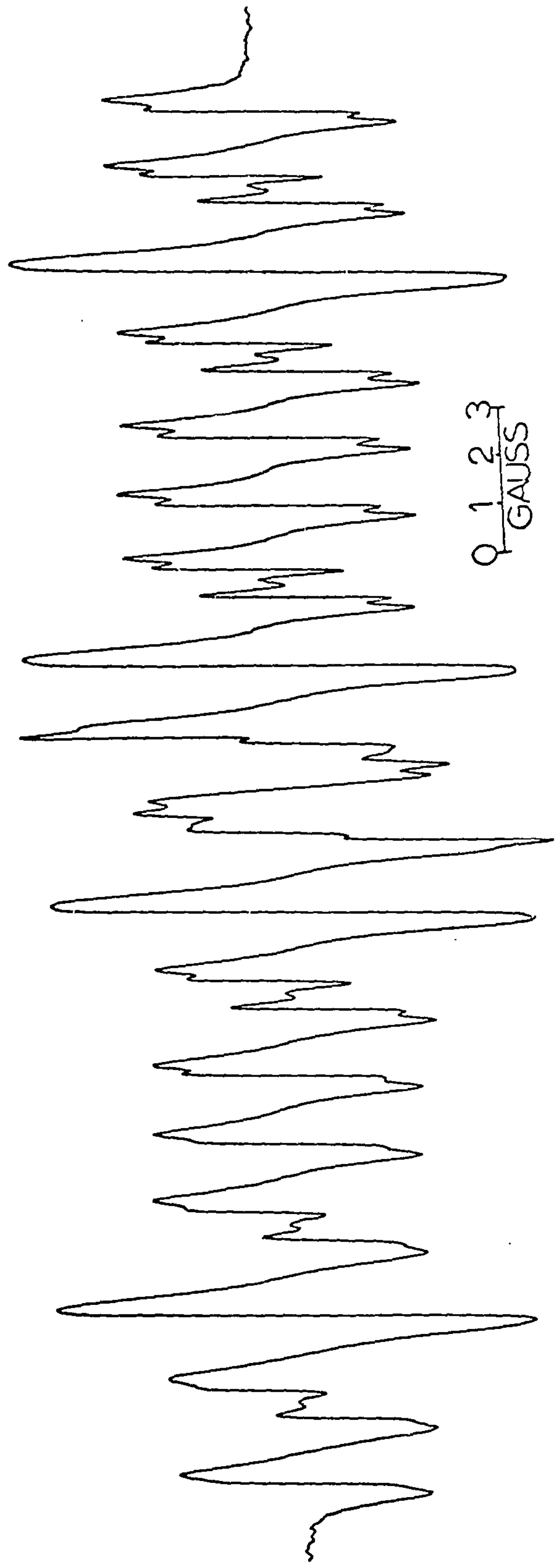


Figure 14. First derivative e.s.r. spectrum of bicyclo[3,2,1]octane-2,3-semidione prepared by reaction of a trace of oxygen with bicyclo[3,2,1]octan-3-one (0.05 M) in DMSO containing potassium *t*-butoxide (0.10 M) at 25°.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under moderate resolutions as shown in Figure 15 which includes a synthetic spectrum based on the five doublet splittings. The doublets are assigned to C-4 axial, C-4 equatorial, C-1, exo C-7, and anti C-8 hydrogen atoms; the last three assignments are by analogy with the assignments already made for the bicyol[2,2,1]heptane and bicyol[2,2,2]octane semidiones. The triplet splittings probably arise from the small interactions of endo C-7 and Anti C-8 protons. The two largest splittings are assigned to α-hydrogens at C-4 based on the fact that they are replaced by deuterium atoms in d_6-DMSO with a resultant change in spectrum width (Figure 16). The spectrum widths calculated (using $a^D = 1/6.4\ a^H$) (30) and found are 14.49 and 15.6 G, respectively. Attempts to analyze this spectrum have not been successful because of the extensive overlapping in lines caused by the near equivalence of values of a^H and a^D.

Semidione (XXVII) is obtained by oxidation of homocamphor and gives a smiple spectrum (Figure 17). The interpretation is simple. There are three different hydrogen atoms interacting with two lines overlapping in the center. These splittings are assigned to C-4 axial, $a^H = 12.5$ G; C-4 equatorial, $a^H = 8.4$ G; and exo C-7 protons; respectively. The width of spectrum obtained in d_6-DMSO is 11.9 G (calcd. 10.63 G). The spectrum obtained from d_6-DMSO is shown in Figure 18. Replacement of three of the hydrogen atoms in (XXVI) by methyl groups to give (XXVII) reduced the number of interacting protons from seven to three rather than four. This indicates that the 1-methyl group can retard the neighboring endo proton from interacting with the unpaired spin. The same effect

Figure 15. A less resolved e.s.r. spectrum of (XXVI) and its synthetic spectrum.

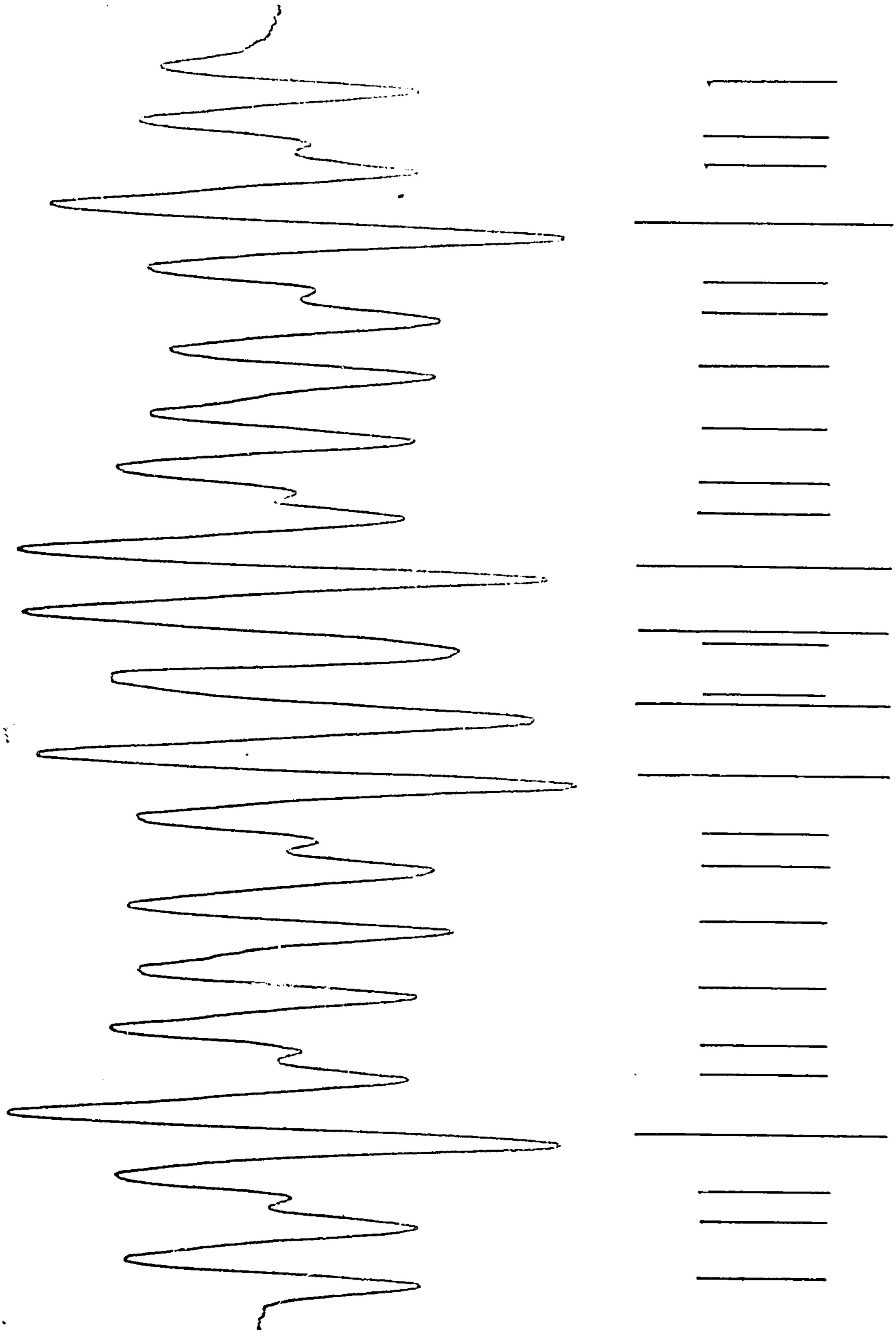

Figure 16. First Derivative e.s.r. spectrum of bicyclo[3,2,1]octane-2,3-semidione prepared by reaction of a trace of oxygen with bicyclo[3,2,1]octan-3- or 2-one (0.05 M) in $\underline{d}_6$-DMSO containing potassium $\underline{t}$-butoxide at 25°.

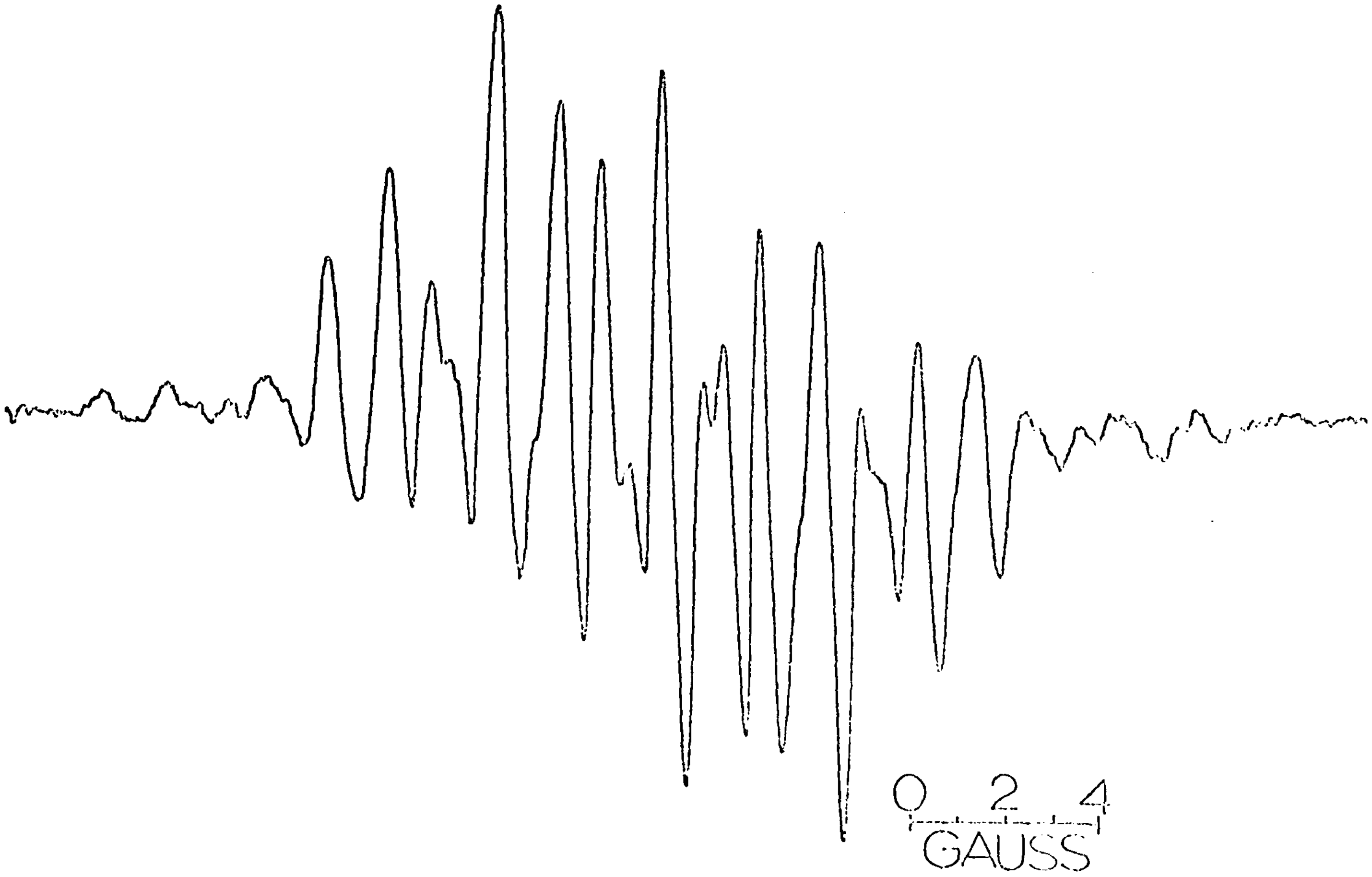
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Figure 17. First derivative e.s.r. spectrum of 1,8,8-trimethylbicyclo[3,2,1]octane-2,3-semidione prepared by reaction of a trace of oxygen with homocamphor (0.05 M) in DMSO containing potassium *t*-butoxide (0.10 M) at 25°.

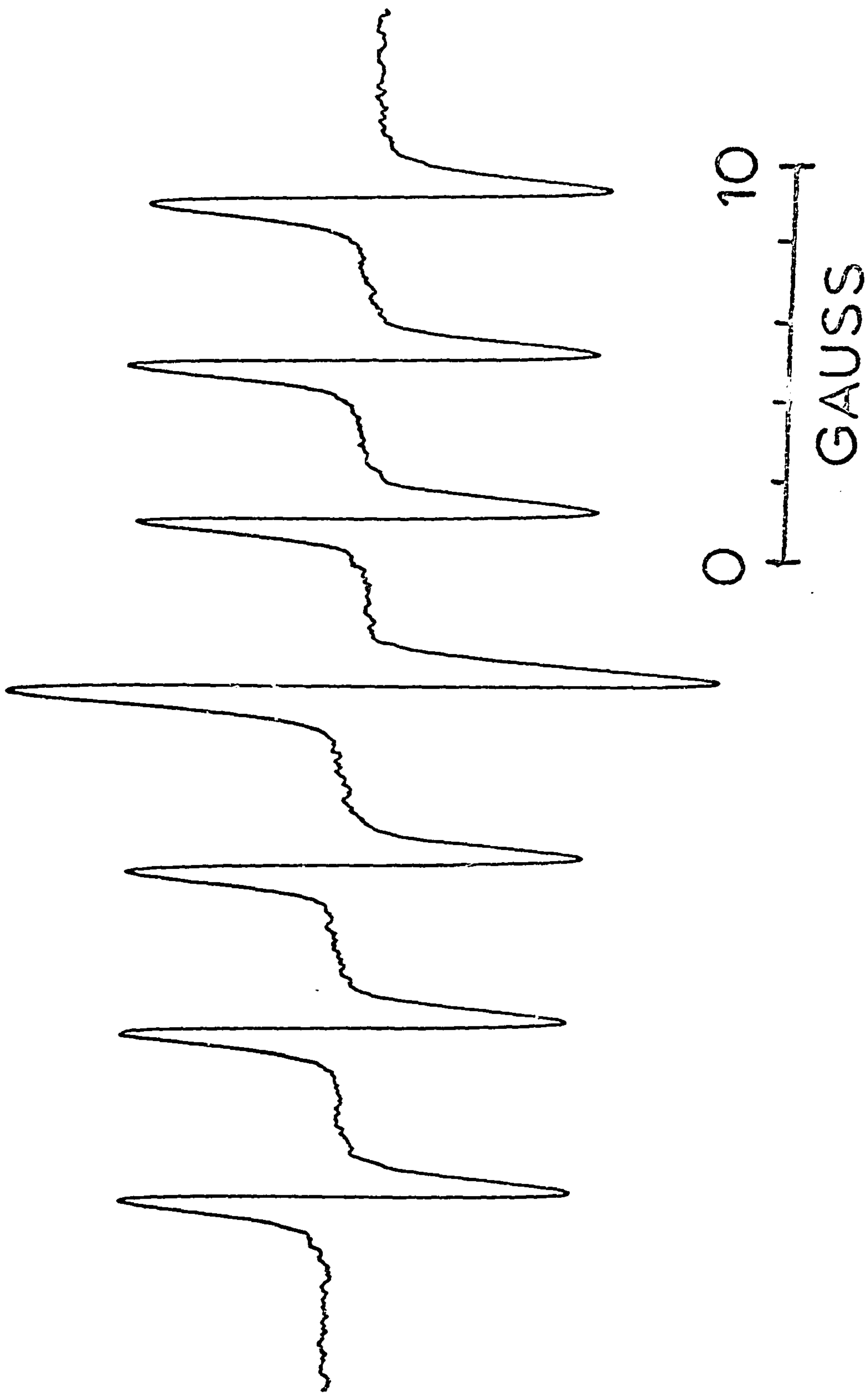
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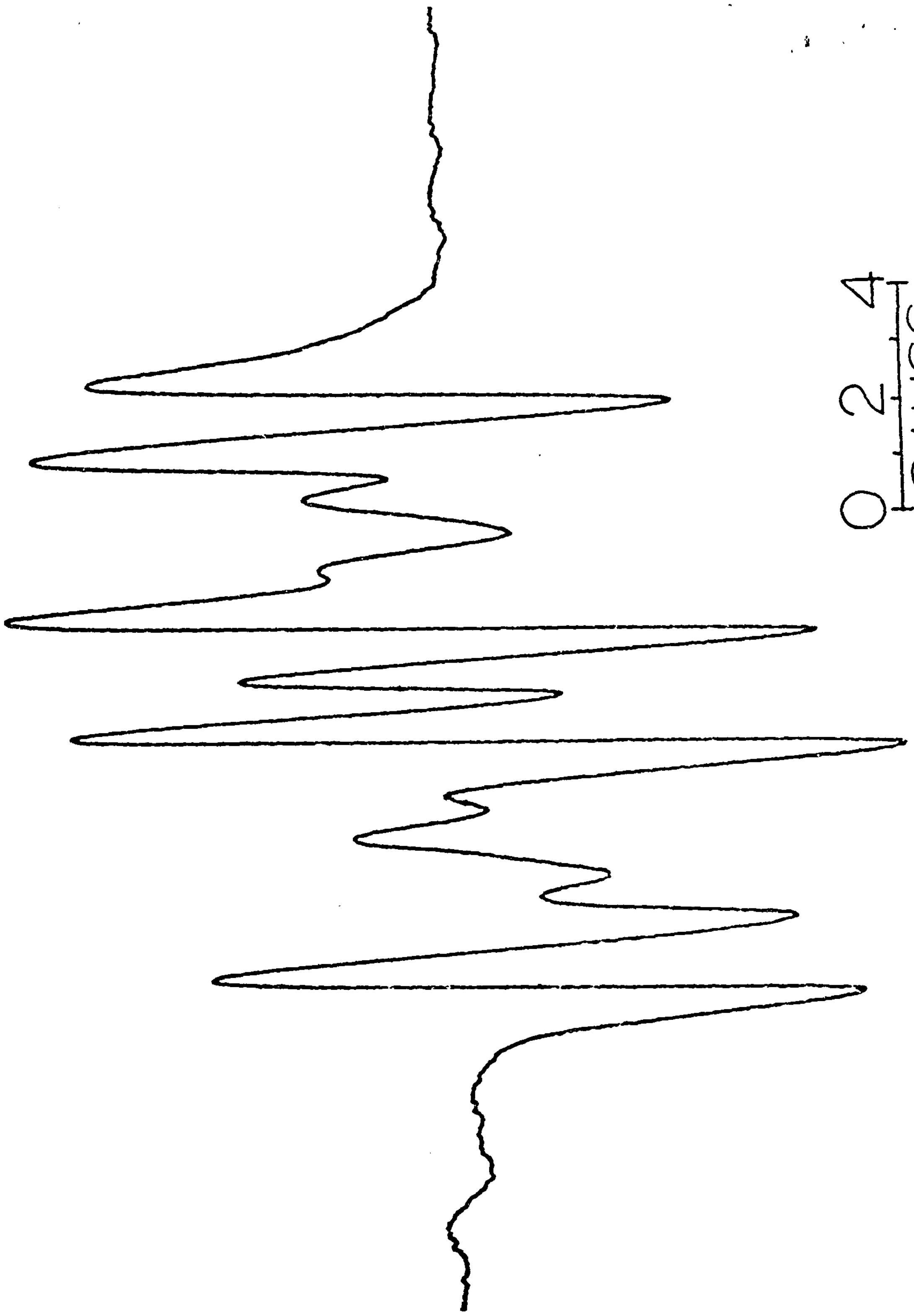
Figure 18. First derivative e.s.r. spectrum of 1,8,8-trimethylbicyclo[3.2.1]octane-2,3-semidione prepared by reaction of a trace of oxygen with homocamphor (0.05 M) in $\underline{d}_6$-DMSO containing potassium $\underline{t}$-butoxide (0.10 M) at 25°.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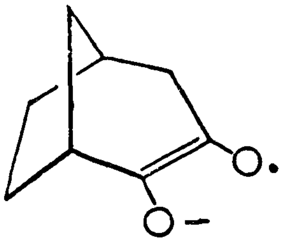
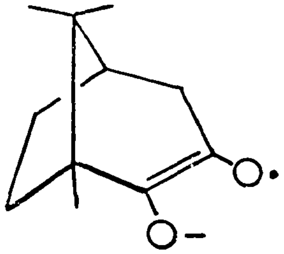
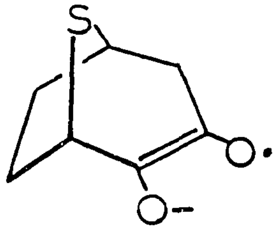
is found when (XXIII) and(XXV) are compared.



(XXVI)

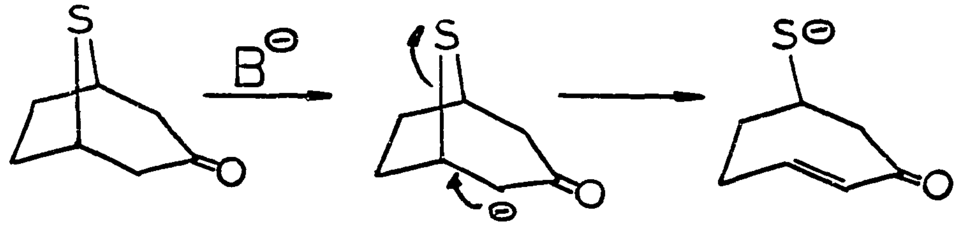


(XXVII)

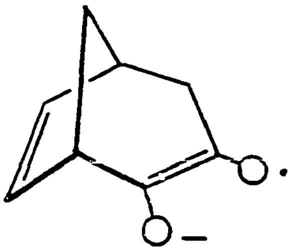


(XXVIII)

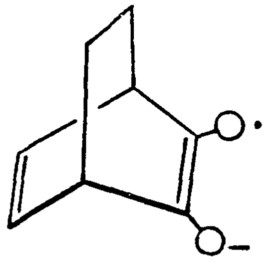
Oxidation of 8-thiabicyclo[3,2,1]octan-3-one fails to yield (XXVIII). The following reaction probably takes place under the influence of base. Otherwise, (XXVIII) would serve as a model compound for (XXVI).



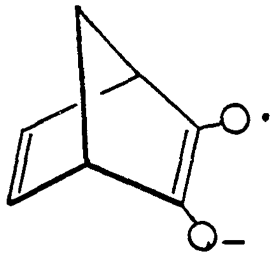
Semidione (XXIX) (Figure 19) was formed readily when bicyclo-[3,2,1]-6-octene-3-one was oxidized in the usual manner. It shows extensive long range couplings involving all eight hydrogen atoms with h.f.s.c., a^H = 8.74, 7.70, 2.66, 1.20, 0.71, 0.49, 0.14, and 0.14 G. Apparently unpared spin density can be transmitted from C-2 to C-6 and C-7 by interaction of the *p*-orbitals on C-2 and C-7. Unfortunately,



(XXIX)

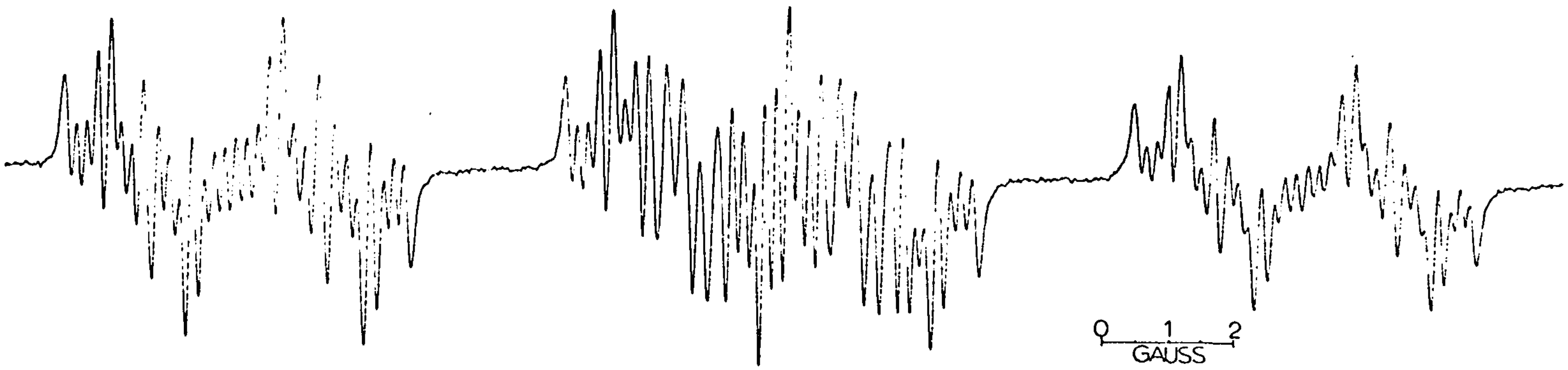


(XXX)



(XXXI)

Figure 19. First derivative e.s.r. spectrum of bicyclo[3,2,1]octene-6-semidione-2,3 prepared by reaction of a trace of oxygen with bicyclo[3,2,1]-6-octene-3-one (0.05 M) in DMSO containing potassium _t_-butoxide (0.10 M) at 25°.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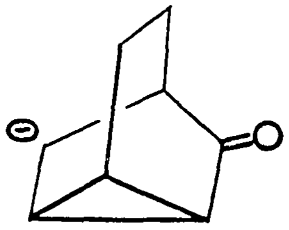
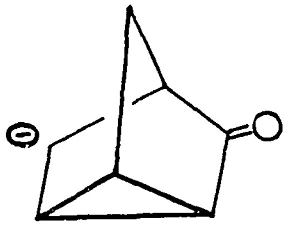
related semidiones of bicyclo[2,2,1]heptene (XXX) and bicyclo[2,2,2]octene (XXXI) cannot be prepared from the corresponding ketones by oxidation. Apparently formation of tricyclenes (XXXII) and (XXXIII) took place before oxidation leading to (XXX) and (XXXI) could occur. However,

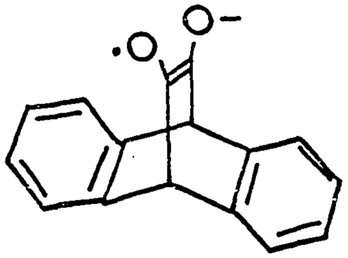


(XXXII)

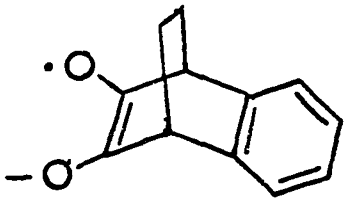


(XXXIII)

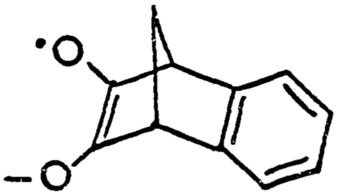
it may be possible to prepare (XXX) and (XXXI) by reduction of the corresponding diketones. In fact (XXXIV) is readily prepared by reduction



(XXXIV)



(XXXV)

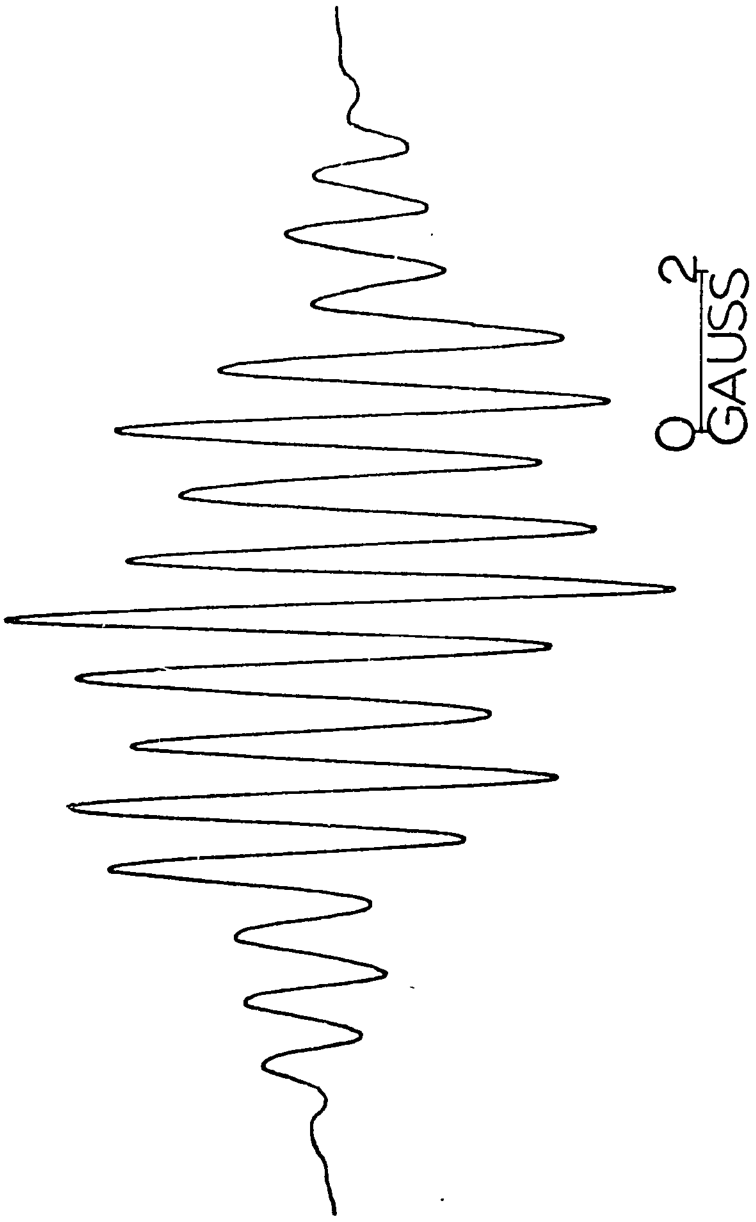


(XXXVI)

of the corresponding diketone by the enolate anion of propiophenone. Figure 20 gives the spectrum of (XXXIV) which is composed of an overlapping quintet of quintets, $\underline{a}^H = 0.96$ and 0.31 G. Again spin density has been transmitted from the carbonyl carbon $\underline{p}_z$ -orbital to the $\underline{p}$-orbitals of the benzene rings. It is likely that (XXXV) and (XXXVI) will show interesting long range couplings.

Bicyclo[3,2,1]octan-5-one, which has one more methylene carbon than

Figure 20. First derivative e.s.r. spectrum of dibenzobicyclo[2,2,2]octadiene-2,3-semidione prepared by reduction of dibenzobicyclo[2,2,2]octadiene-2,3-dione (1 mg.) by propiophenone (2 mg.) in 2 ml. of DMSO containing 4 mg. of potassium *t*-butoxide at 25° in the absence of oxygen.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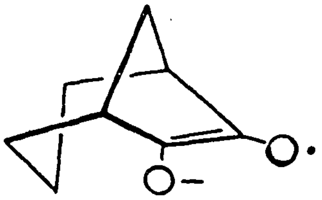
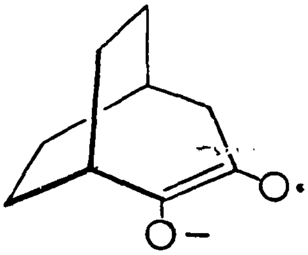
norcamphor, readily forms semidione (XXXVII) upon oxidation. Because there is a plane of symmetry (XXXVII) shows a much simpler spectrum (Figure 21) than that of its isomer (XXVI). It consists of triplet ($\underline{a}^H$ = 5.51 G), doublet ($\underline{a}^H$ = 4.03 G), and sextet ($\underline{a}^H$ = 0.53 G) hyperfine splittings. They are assigned to hydrogen atoms at exo C-2 and C-4; exo C-8; and the five fortuitously equivalent hydrogen atoms at C-1, C-4, endo C-2 and C-4, and syn C-8; respectively.



(XXXVII)



(XXXVIII)

The effect of symmetry in simplifying a spectrum is clearly demonstrated in semidione (XXXVIII) (Figure 22) which was obtained by oxidation of bicyclo[3,2,2]nonan-3-one. It indicates that there are two pairs of equivalent hydrogen atoms in (XXXVIII), $\underline{a}^H$ = 10.57 and 2.21 G, which are assigned to hydrogens at C-4 and anti hydrogens at C-7 and C-8. The equivalence of these two pairs of protons can be explained by rapidly interconverting asymmetric twist conformations in view of the reasonable flexibility of the molecule. However, the absence of bridgehead proton splitting suggests that (XXXVIII) has a static conformation since time averaging cannot make the dihedral angle between bridgehead carbon-hydrogen bond and the carbonyl carbon $\underline{p_z}$-orbital equal to 90 degrees. However, this dihedral angle is very close to 90 degrees in these two twist

Figure 21. First derivative e.s.r. spectrum of bicyclo[3,2,1]octane-6,7-semidione prepared by reaction of a trace of oxygen with bicyclo[3,2,1]octan-6-one (0.05 M) in DMSO containing potassium *t*-butoxide (0.10 M) at 25°.

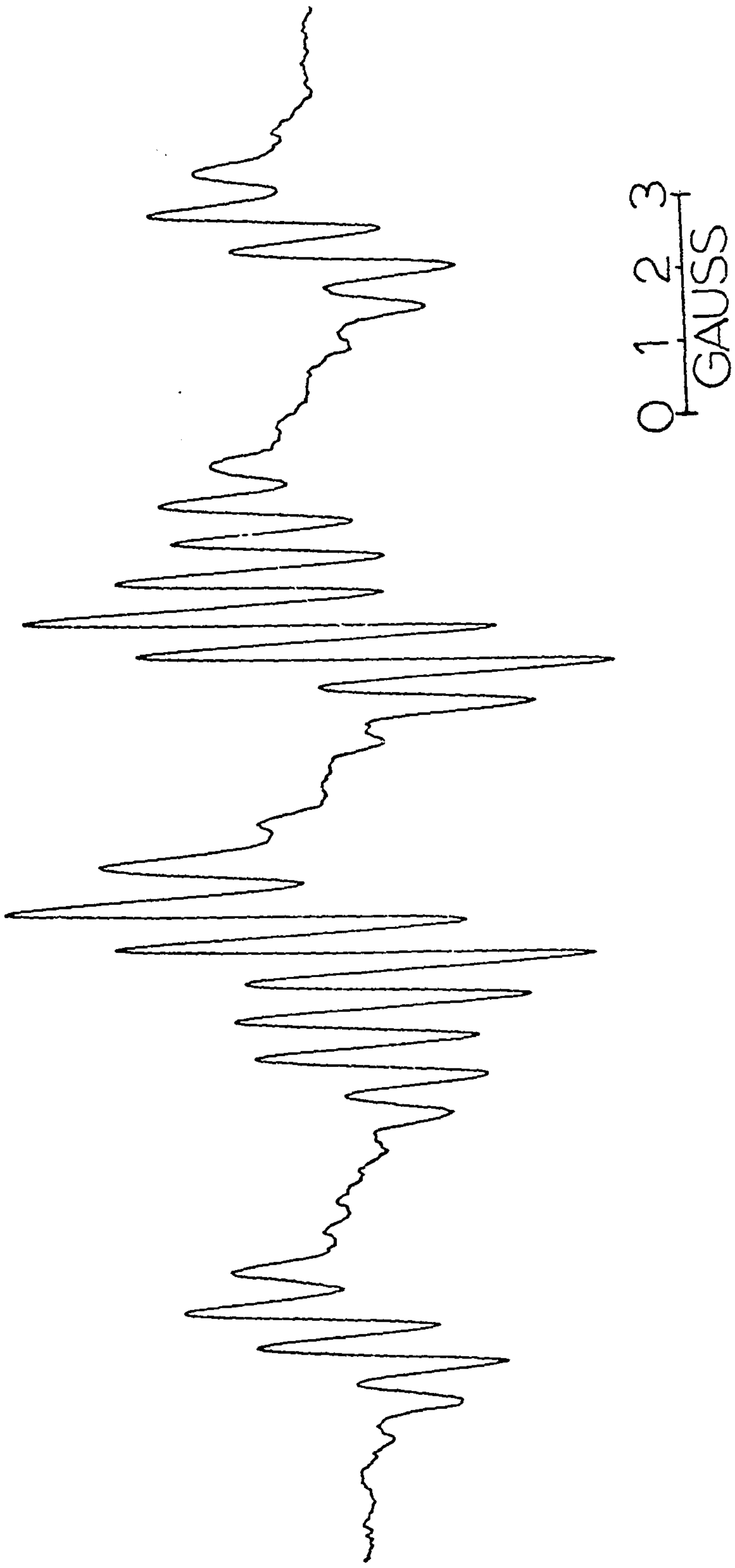

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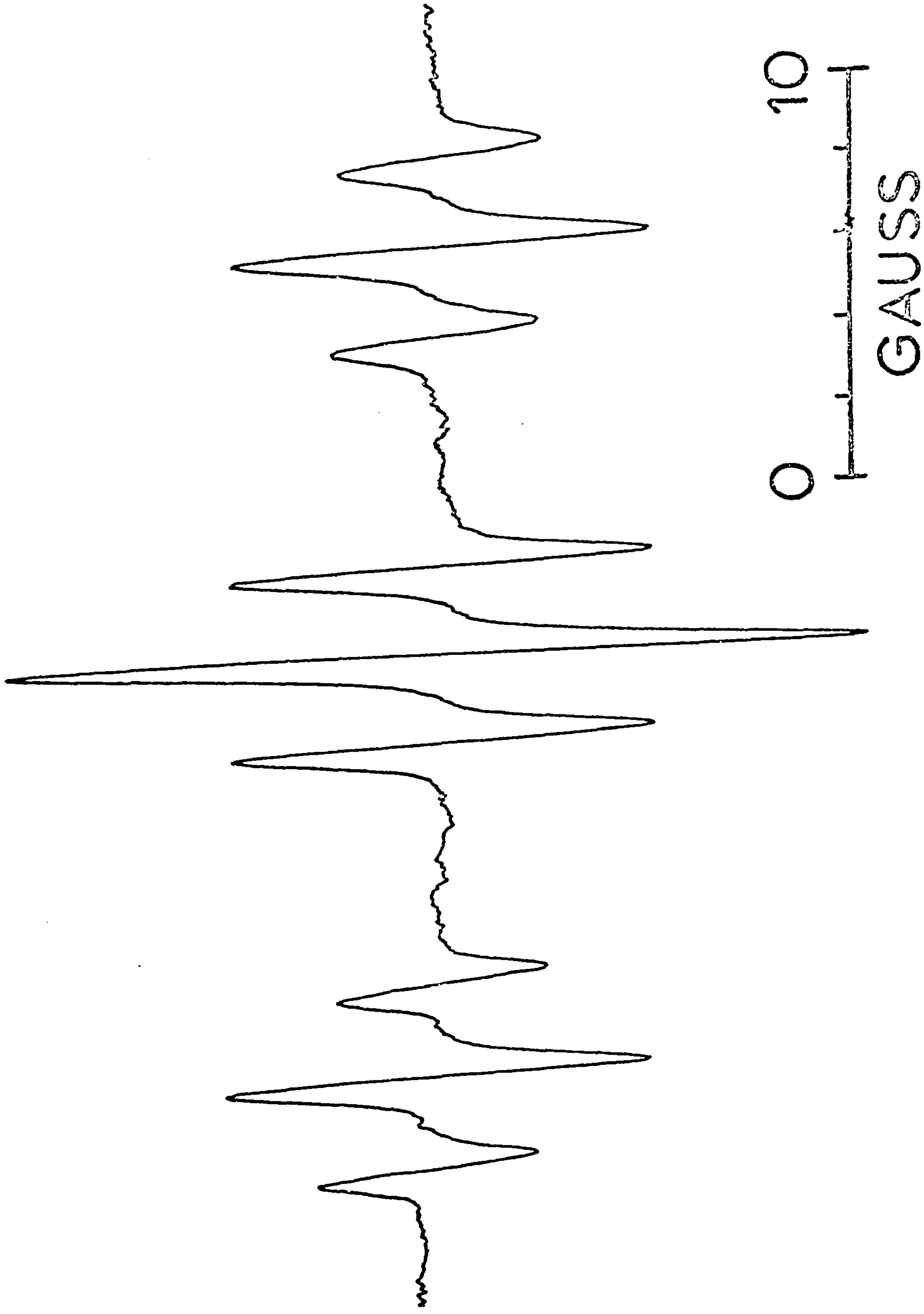
Figure 22. First derivative e.s.r. spectrum of bicyclo[3,2,2]nonane-2,3-semidione prepared by reaction of a trace of oxygen with bicyclo[3,2,2]nonan-3-one (0.05 M) in DMSO containing potassium _t_-butoxide (0.10 M) at 25°.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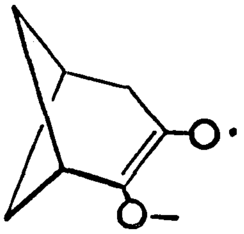
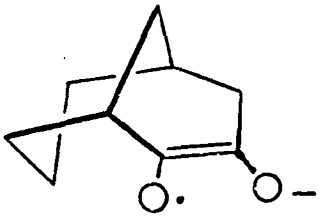
conformations and hyperfine splitting by the C-1 hydrogen atom may not have experimentally detected. The spectrum obtained by oxidation of bicyclo[3,2,2]nonan-3-one in $\underline{d}_6$-DMSO is shown in Figure 23. The spectrum widths calculated and found are 10.96 and 10.6 G, respectively.

The semidione (XXXIX) represents the only example of bicyclo[3,1,1]heptane-2,3-semidione now known. (XXXIX) can be obtained by oxidation


(XXXIX)


(XL)

of nopinone. The spectrum (Figure 24) involves three doublets (two of them are nearly identical) and a sextet splittings. They are attributed to the C-4 "axial" ($\underline{a}^H = 9.46$ G); C-4 "equatorial" ($\underline{a}^H = 9.04$ G); C-7 anti ($\underline{a}^H = 3.88$ G); and fortuitously equivalent C-6 anti methyl, syn C-7, and C-1 hydrogen atoms, respectively. A spectrum of (XXXIX) is also recorded in $\underline{d}_6$-DMSO (Figure 25) which has a width of 11.6 G (calcd., 11.75 G). The semidione of the parent bicyclo[3,1,1]heptan-2-one would be predicted to give a beautiful 27 line spectrum involving three pairs of equivalent protons with quite different splitting constants since the nonequivalency caused by the methyl groups is removed and the bridgehead protons will be in the nodal plane as in the case of (XXXVIII).

Semidione (XL) can be obtained readily by oxidation of bicyclo-[3,3,1]nonan-3-one. Its spectrum (Figure 26) shows 31 lines which indi-

Figure 23. First derivative e.s.r. spectrum of bicyclo[3,2,2]nonane-2,3-semidione prepared by reaction of a trace of oxygen with bicyclo[3,2,2]nonan-3-one (0.05 M) in d_6-DMSO containing potassium *t*-butoxide (0.10 M) at 25°.

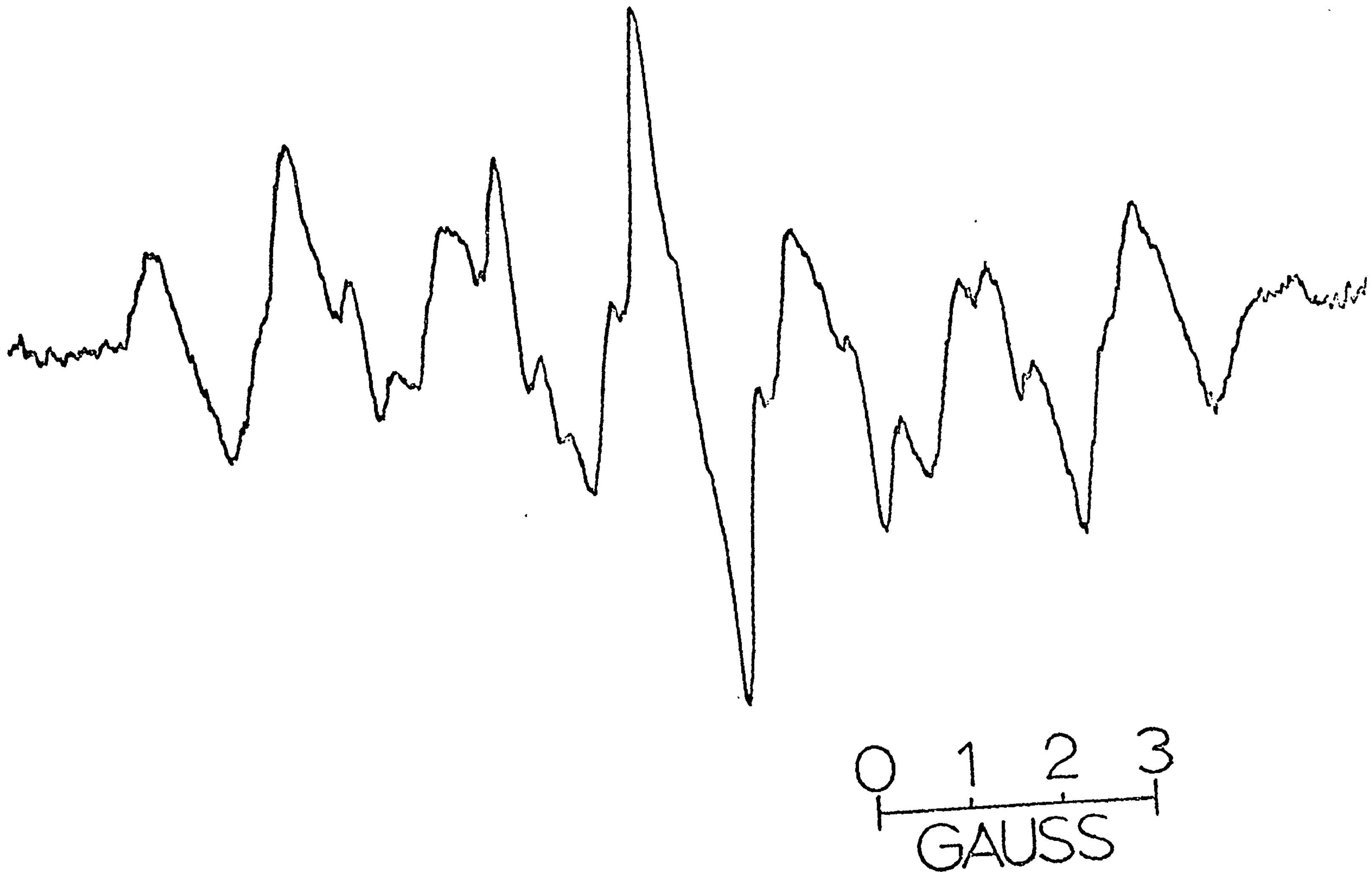

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Figure 24. First derivative e.s.r. spectrum of 6,6-dimethylbicyclo-[3,1,1]heptane-2,3-semidione prepared by reaction of a trace of oxygen with nopinone (0.05 M) in DMSO containing potassium t-butoxide (0.10 M) at 25°.

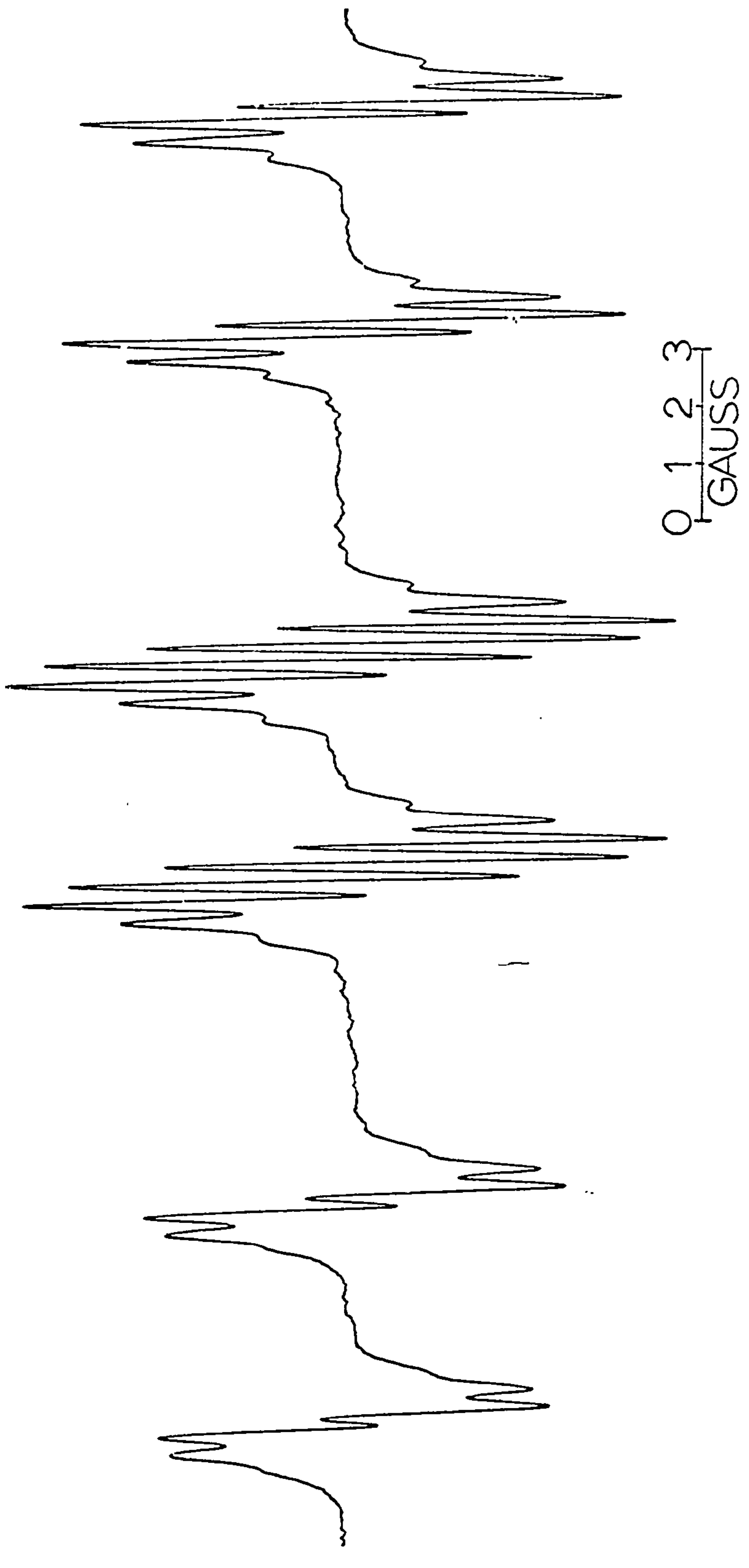
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Figure 25. First derivative e.s.r. spectrum of 6,6-dimethylbicyclo[3,1,1]heptane-2,3-semidione prepared by reaction of a trace of oxygen with nopinone (0.05 M) in $\underline{d}_6$-DMSO containing potassium $\underline{t}$-butoxide (0.10 M) at 25°.

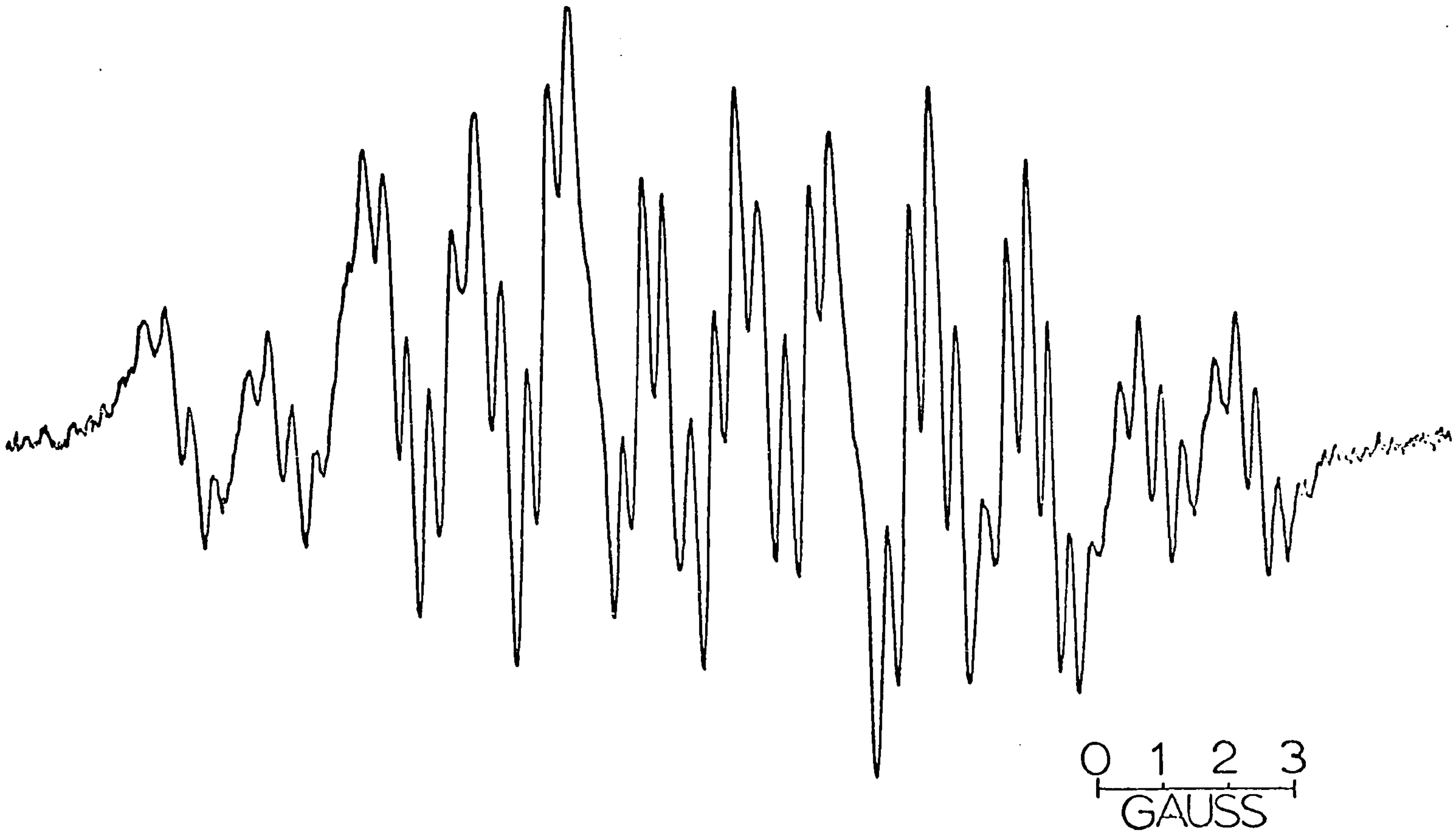
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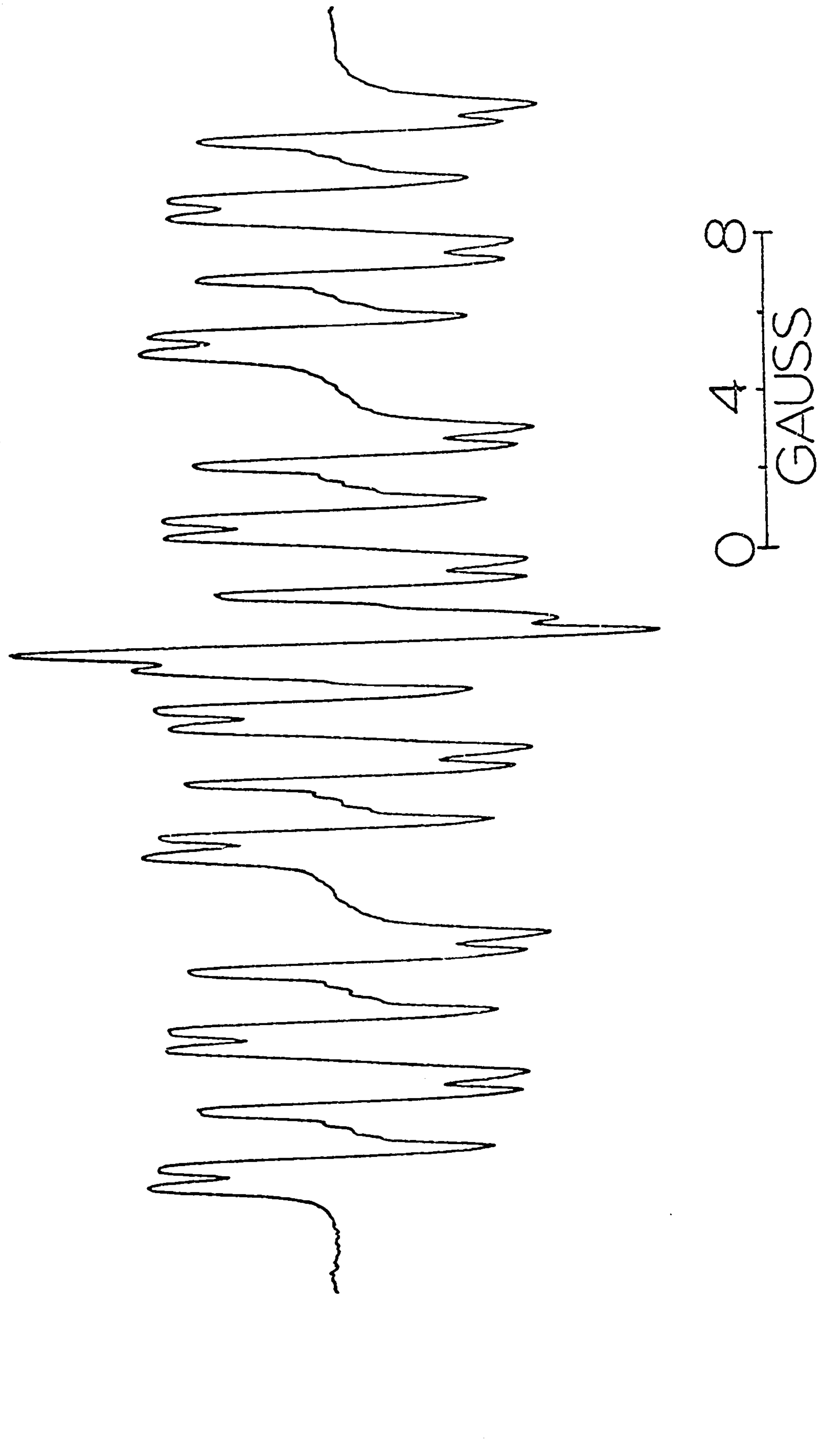
Figure 26. First derivative e.s.r. spectrum of bicyclo[3,3,1]nonane-2,3-semidione prepared by reaction of a trace of oxygen with bicyclo[3,3,1]nonan-3-one (0.05 M) in DMSO containing potassium t-butoxide (0.10 M) at 25°.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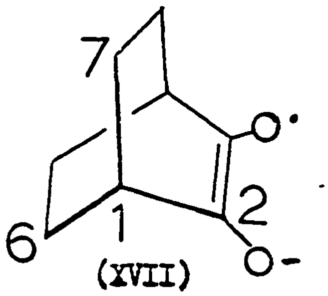
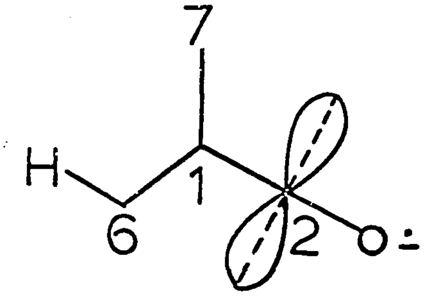
cates that there are five different hydrogen atoms interacting with the unpaired spin with hyperfine splitting constants of 12.74, 6.93, 3.35, 1.96, and 0.56 G. They are assigned to C-4 axial, C-4 equatorial, *exo* C-8 or *anti* C-9, *anti* C-9 or *exo* C-8, and C-1 hydrogen atom, respectively. The spectrum of (XL) obtained in d_6-DMSO is shown in Figure 27, and has a width of 12.3 G (calcd., 12.01 G).

In the previous paragraphes, some of the assignments of hyperfine splitting constants are tentative. A considerable amount of work such as replacing the specific proton with a methyl group, a deuterium atom, or other suitable groups is required before rigorous assignments can be made to all hyperfine splitting constants.

However, all bridged bicyclic semidiones show strong interactions of β-hydrogens which are *exo* or *anti* to the carbonyl carbon p_z-orbital in a W-plan or zigzag arrangement as shown in the following diagram.

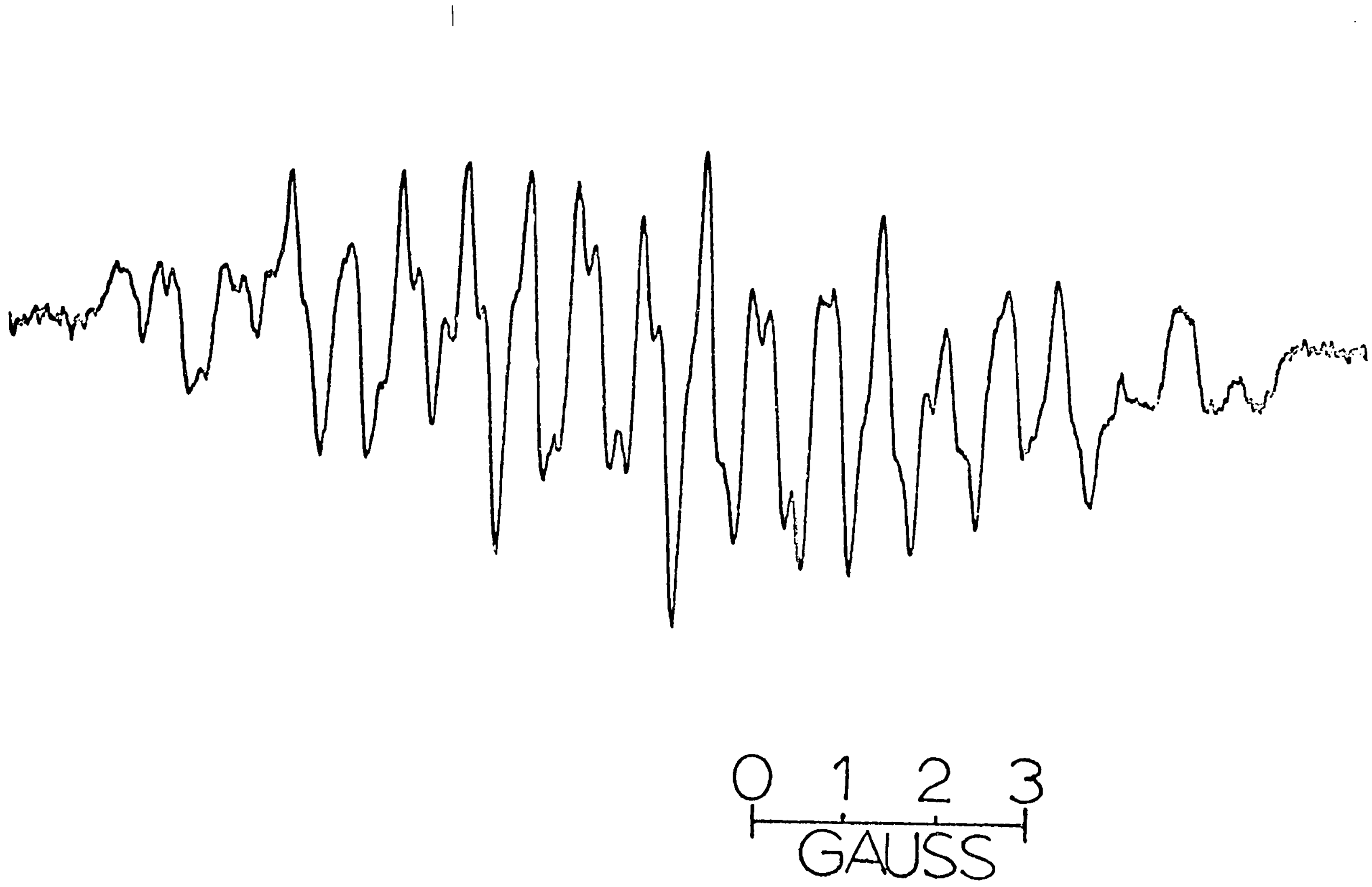


(XVII)



This W-plan interaction has been rigorously established in (XVII) and has been used satisfactorily to interpret splittings of other bridged bicyclic semidiones. This consistent observation of strong interactions in bridged bicyclic semidiones is indeed surprising since in acyclic, monocyclic, and other bicyclic (with 1,2 ring fusion) semidiones, only

Figure 27. First derivative e.s.r. spectrum of bicyclo[3,3,1]nonane-2,3-semidione prepared by reaction of a trace of oxygen with bicyclo[3,3,1]nonan-3-one (0.05 M) in d_6-DMSO containing potassium *t*-butoxide (0.10 M) at 25°.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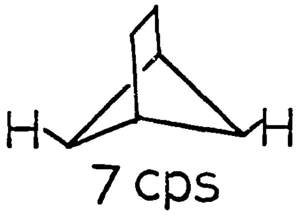
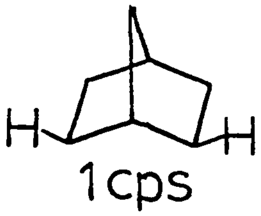
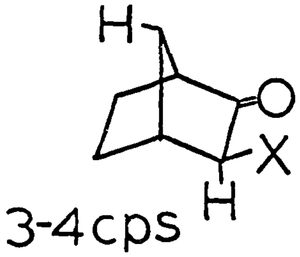
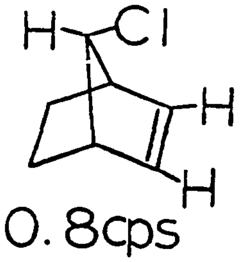
those hydrogen atoms α to the dicarbonyl system show strong hyperfine splittings and in no cases do β hydrogen atoms display unusually large h.f.s.c. (that is no larger than 0.5 G).

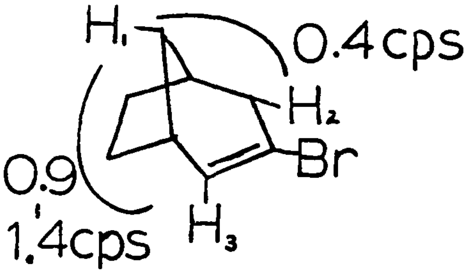
This type of interaction may be not unusual at all considering the inherently rigid structures of bridged bicyclic molecules, since analogous long range spin-spin couplings between protons similarly situated in a large number of bicyclic compounds have been widely observed in n.m.r. A few examples are given below with their coupling constants (31-36).







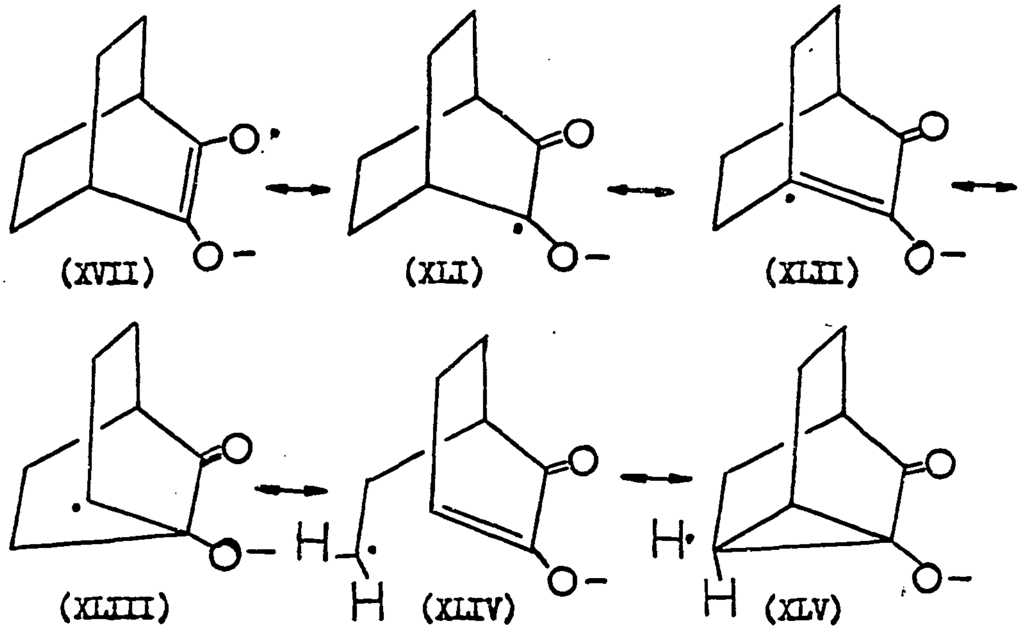




Meinwald and Lewis (31) have suggested that the two hydrogens couple by a direct interaction involving appreciable overlap of the "rear lobes" of the hybrid orbitals. Alternatively, Barfield (37) has proposed that the long range coupling is due to non-perfect pairing of bonding electrons and showed taht the maximum long-range coupling constants require the two interacting protons in a planar zigzag arrangement.

Although the mechanisms of long-range coupling of e.s.r. and n.m.r. may differ, the analogy is interesting for two reasons. It not only supports our assignment that strong interactions are due to *exo* or *anti* β-hydrogen atoms, but it also implies that our results can be used to facilitate the analysis of n.m.r. spectra of bicyclic compounds having similar structure. Therefore, it would be predicted that *exo* C-5 and C-6 hydrogen atoms will couple with C-2 and C-3 hydrogens in 7,7-dimethylbicyclo[2,2,1]heptene-2.

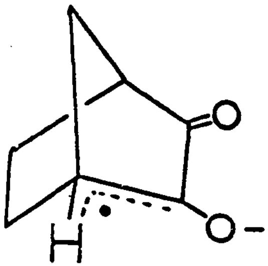
The classical resonance structures indicating the splittings of hydrogen atoms α to the carbon carrying the free electron by hyperconjugation are no longer applicable to the bridged bicyclic systems. Structures (XLII) and (XLIII) are excluded because they would predict a hyperfine splitting by bridgehead protons in (XVII). In addition, (XLII) also violates Bredt's rule. Structure (XLIV) is also excluded since it predicts eight nearly equivalent hydrogen atoms in the spectrum of (XVII). Even in semidione (XXIII) where both the *exo* and *endo* protons interact with the unpaired spin their interactions are different in mag-



nitude that structures of type (XLIV) can be excluded. Only the homoconjugation-type structure (XLV) accounts for the stereospecific long range interaction of four equivalent protons.

The lack of bridgehead splittings in the semidione (XVII) where the dihedral angle is exactly 90 degrees is in agreement with Heller and McConnell (19) equation and indicates that α splitting is indeed through hyperconjugation and which shows a stereoelectronic restriction.

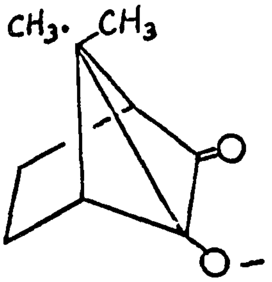
To explain the splittings caused by bridgehead protons, one is compelled to draw partial double bonds for semidiones in which the dihedral angle of the proton is not 90 degrees as exemplified by (XLVI).



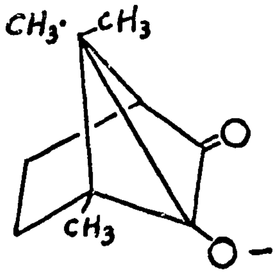
(XLVI)

The splitting of C-7 syn hydrogen in semidione (XXII) is the most difficult to explain. The strong splitting of C-7 anti hydrogen atoms (6.54 G) probably "induces" a spin density at C-7 which then interacts with C-7 syn hydrogen by spin polarization. The observation of C-7 syn methyl protons of semidione (XXIV) can be similarly explained.

The r splittings of methyl protons of semidiones (XXIII) and (XXV) can be accounted for by structures (XLVII) and (XLVIII). The choice of the anti over the syn methyl group as the cause of the splittings is based on the facts that the anti methyl splitting is consistent with

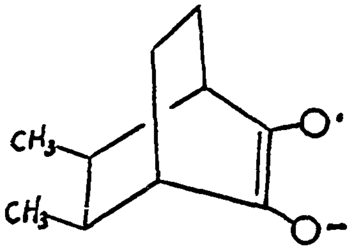


(XLVII)

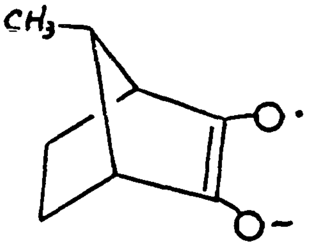


(XLVIII)

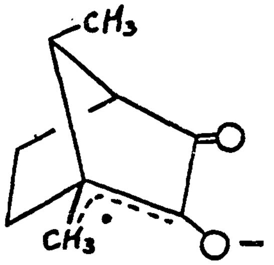
W-plan zigzag arrangement. In semidione (XIX) the two endo methyl groups do not interact with the p_z-orbital of the free electron irrespective of their close proximity. Quartet splitting of about 0.5 G is not observed in semidione (XXIV) but are observed in (XXIII) and (XXV). To substantiate this choice, semidiones (XLIX) and (L) should be prepared. The latter can also be used to verify the assumption made above



(XLIX)



(L)

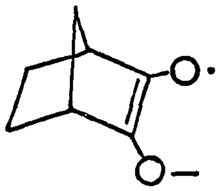


(LI)

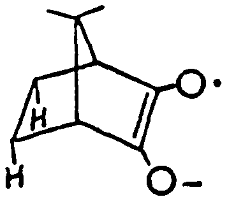
that the C-7 anti hydrogen atom is responsible for the splittings of the C-7 syn hydrogen atom and the C-7 syn methyl protons.

Structures similar to (XLVI) e.g. (LI) can be used to account for the bridgehead methyl hydrogen atom splittings in (XXIV) and (XXV). However, the observation that none of the three methyl groups of (XXVII) interacts with the unpaired spin remains as a perplexing problem.

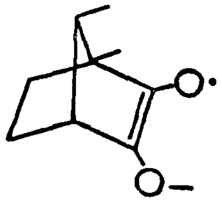
The inconsistency of the splitting of endo hydrogen atoms in semidiones of the bicyclo[2,2,1]heptane system is rather difficult to account for. By comparison of the following formulas it appears that



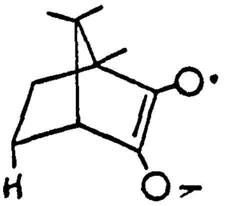
(XXII) none



(XXIII) two



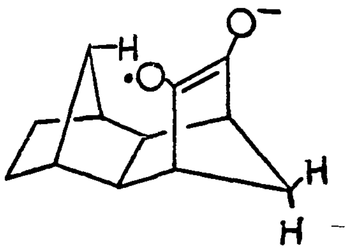
(XXIV) none



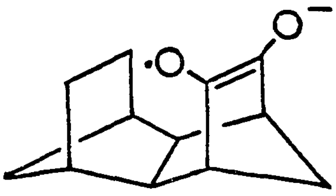
(XXV) one

the two methyl groups at C-7 alter the geometry of the semidiones to such an extent as to force the two endo protons into positions that will cause an interaction with the p_z-orbital of the unpaired electron. A methyl group in the bridgehead seems to insulate this kind of interaction which is why only one of the endo protons interacts in semidione (XXV). This also explains why the C-7 endo proton in (XXVI) interacts but does not in (XXVII).

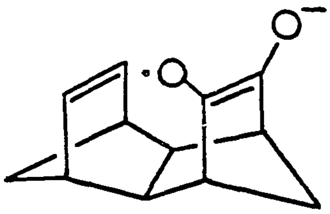
A similar type of direct interaction probably operates in the semidione(LII) which was prepared by the oxidation of the ketone derived



(LII)



(LIII)



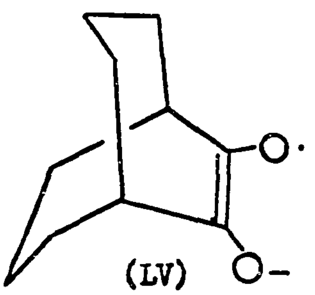
(LIV)

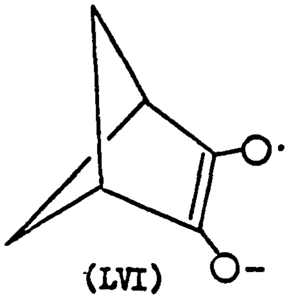
from decahydro-1,2,5,8-exo,endo-dimethano-exo-2-naphthol. Its spectrum (Figure 28) consists of eight lines of equal intensity with a^H = 8.22,

Figure 28. First derivative e.s.r. spectrum of semidione (LII) prepared by reaction of a trace oxygen with 1,4,5,8-endo,exo-dimethano-2-decalone (0.05 M) in DMSO containing potassium *t*-butoxide (0.10 M) at 25°.

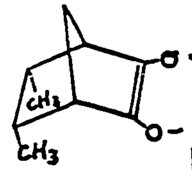
5.29, and 1.42 G which could be attributed to the three hydrogen atoms indicated in (LII). However, the lack of triplet splitting from the hydrogen atoms at 4a and 8a carbons as would be expected for (LII) together with the failure to prepare the analogous semidiones (LIII) and (LIV) points out that the interpretation is rather doubtful. These three interesting semidiones probably can be prepared from their respective diketones by reduction. However, the diketones are presently unknown.

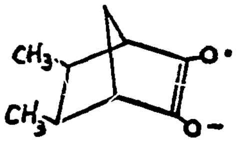
In future studies should be extended to larger and smaller bicyclic systems, for example, semidiones (LV) and (LVI), to see the effects of ring size on the splitting of bridgehead hydrogen atoms and the strong interaction of β hydrogen atoms in the W-plan arrangement.

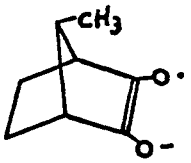

(LV)

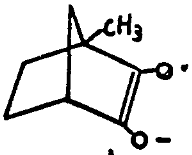

(LVI)

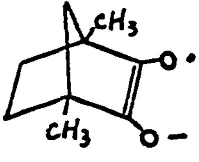
Besides preparing those additional semidiones previously suggested, the following semidiones should be prepared to gain more information so

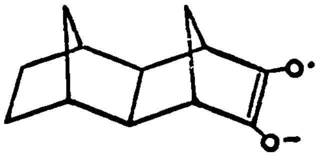


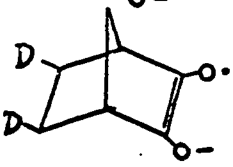






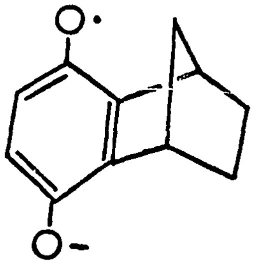


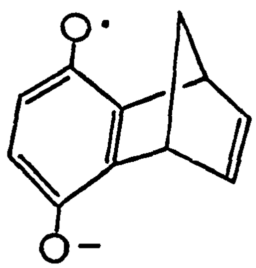




as to obtain a concrete assignment of splitting constants to the right protons.

Another group of radical anions that display long range W-plan couplings are the semiquinones with bicyclic substituents. In the course of this work semiquinones (LVII) and (LVIII) were prepared. These


(LVII)


(LVIII)

semiquinones, whose e.s.r. spectra are shown in Figure 29 and 30, are readily formed by dissolving the corresponding hydroquinone acetates in DMSO containing potassium *t*-butoxide. The spectrum of (LVII) shows triplet and quartet splittings; $\underline{a}^H$ = 2.50 and 0.70 G respectively. These h.f.s.c are assigned to aromatic hydrogens, *exo* hydrogens at C-5 and C-6, and to the *anti* hydrogen at C-7. The spectrum of (LVIII) shows triplet, doublet and quartet splittings; $\underline{a}^H$ = 2.34, 0.80, and 0.40 G; respectively. They are assigned to aromatic hydrogens; *syn* hydrogen at C-7; and two olefinic hydrogens and *anti* hydrogen at C-7; respectively.

Regardless of the fact that long range interactions are influenced strongly by subtle changes in geometry of the bicyclic semidiones, the extension of this work to the assignment of structure of derivatives of bicyclic ketones of synthetic or natural origin is obvious and in certain

Figure 29. First derivative e.s.r. spectrum of semiquinone (LVII) prepared by dissolving 5,8-diacetoxy-1,2,3,4-tetrahydro-1,4-methanonaphthalene (0.05 M) in DMSO containing potassium t-butoxide (0.10 M) at 25°.

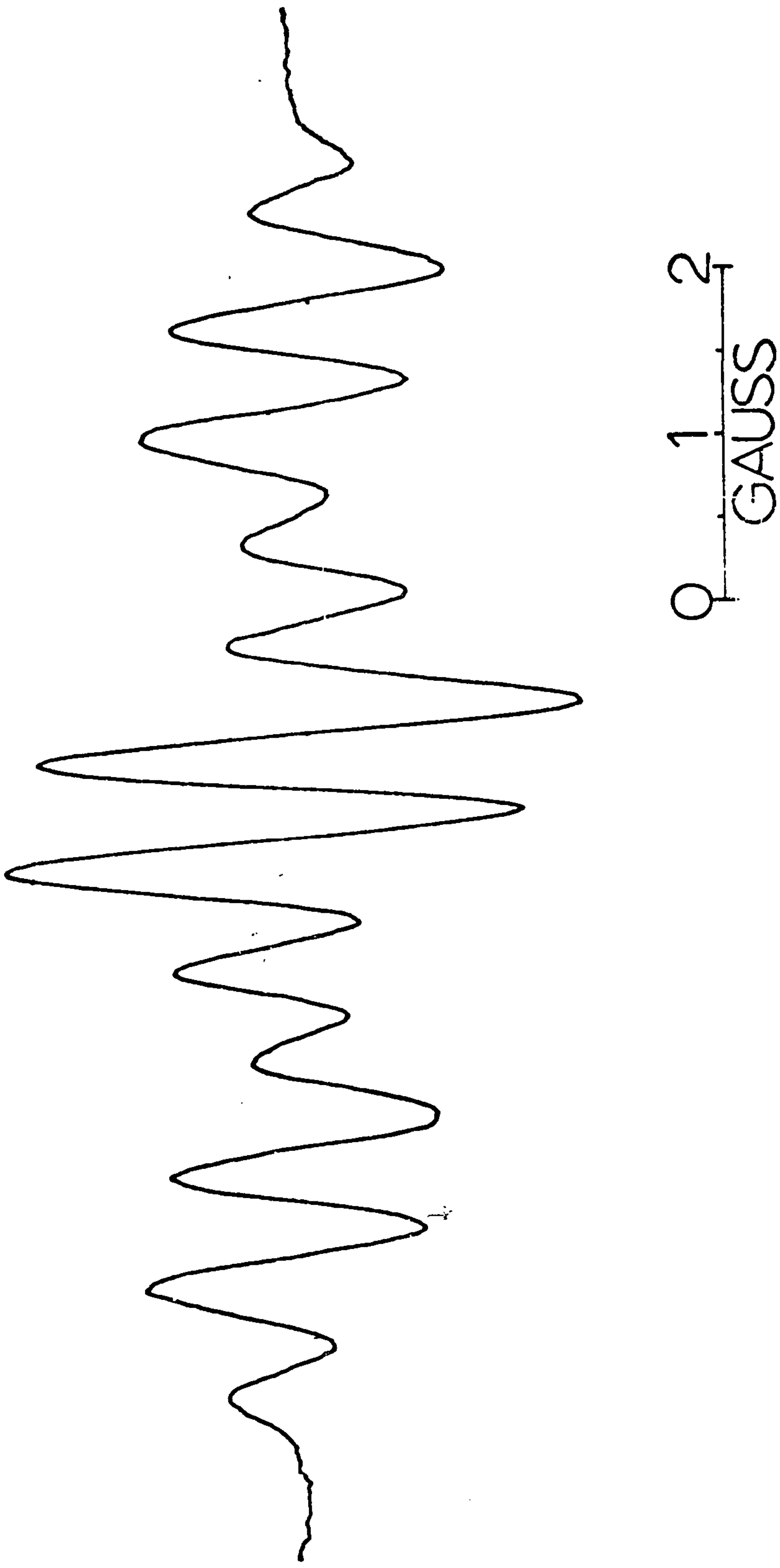
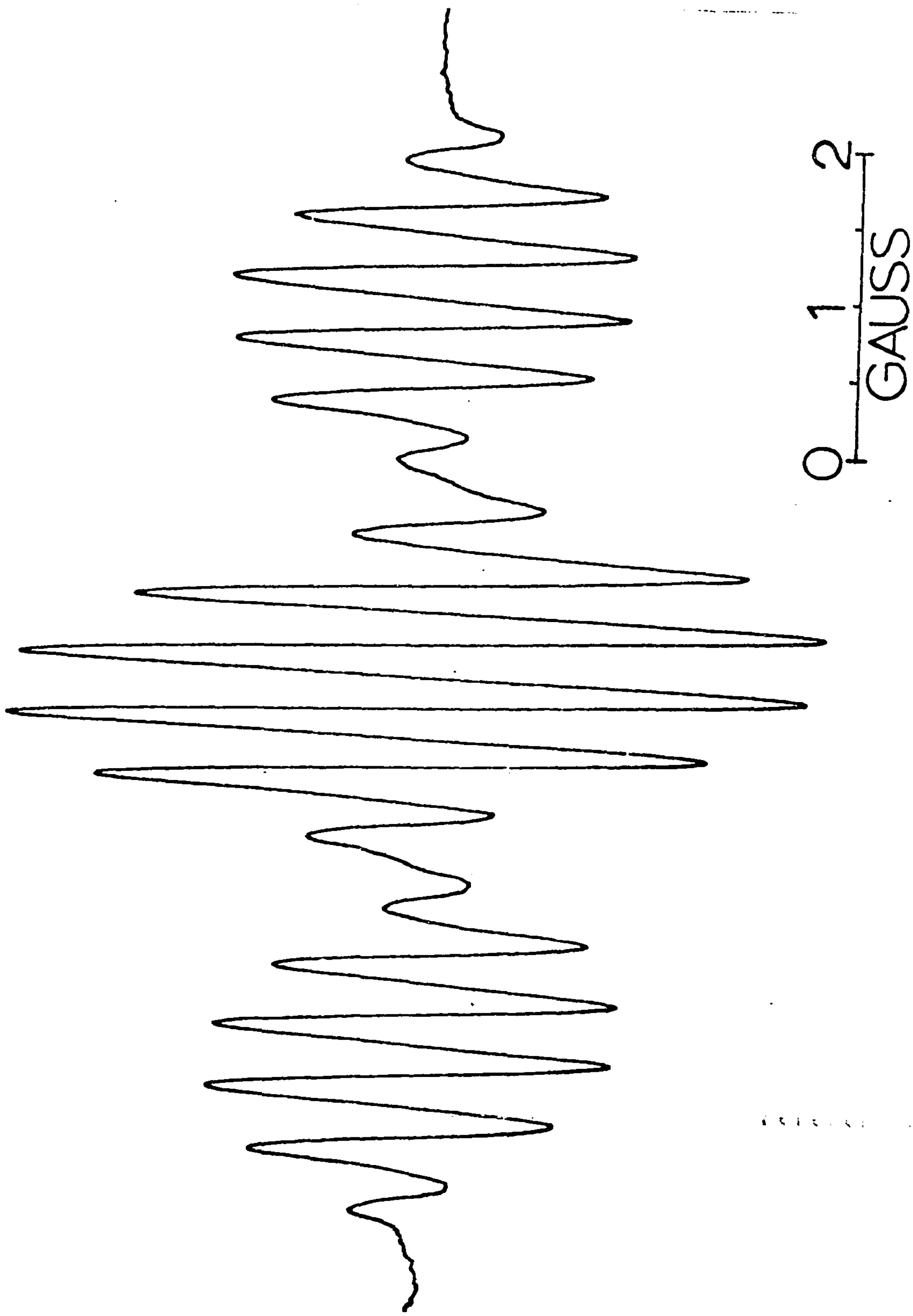

0
1
2
GAUSS

Figure 30. First derivative e.s.r. spectrum of semiquinone (LVIII) prepared by dissolving 5,8-diacetoxy-1,4-dihydro-1,4-methanonaphthalene (0.05 M) in DMSO containing potassium _t_-butoxide (0.10 M) at 25°.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cases an assignment can be made without a full assignment of all hyperfine splitting constants.

EXPERIMENTAL

endo, endo-Bicyclo[2,2,2]-2-octene-5,6-dicarboxylic anhydride (26). To a solution of 51 g. (0.52 mole) of maleic anhydride in 150 ml. of benzene chilled in an ice bath was added with stirring 41.7 g. (0.52 mole) of 1,3-cyclohexadiene. A yellow-green color developed immediately and dissappeared after 8 hours at room temperature. At the end of this period there was obtained 59.2 g. of a needle, mp. 140-144°. After two recrystallizations from benzene, the melting point was raised to 146-147°. The mother liquor gave 23.2 g. of a second crop. The reaction gave the anhydride in 88.7% yield.

endo,endo-5,6-Dimethylolbicyclo[2,2,2]octene-2 (38). In a 1 l. three necked round bottom flask equipped with a mechanical stirrer, a stopper, and a Soxhlet extractor with an efficient condenser was placed 10 g. of lithium aluminum hydride and 500 ml. of anhydrous ether. In the thimble was placed 34.3 g. of *endo,endo*-bicyclo[2,2,2]-2-octene-5,6-dicarboxylic anhydride. The solution was heated to reflux till all the anhydride was added to the flask. Water was added dropwise to the cold mixture to decompose the excess lithium aluminum hydride. The mixture was poured into an ice-hydrochloric acid mixture and extracted three times with ether. The combined ether extracts were washed with water, dried over anhydrous sodium sulfate, and concentrated to give 12.6 g. of *endo,endo*-5,6-dimethylolbicyclo[2,2,2]octene-2, m.p. 92-94°, which was recrystallized from ether at -5° to give 10.4 g. of pure diol, m.p. 93-94°. From the mother liquor, there was obtained 2.6 g. of a second crop of the diol (total yield: 48.2%).

Ditosylate of endo,endo-5,6-dimethylolbicyclo/2,2,2/octene-2 endo,endo-5,6-Dimethylolbicyclo/2,2,2/octene-2, 10.4 g. (0.062 mole), was dissolved in 120 ml. of freshly distilled pyridine (over barium oxide) and chilled in a salt-ice mixture to -5°. To the cold solution was added 30 g. of p-toluenesulfonyl chloride (recrystallized from pentane prior to use) in small portions over a 30 minutes period. The solution was kept in a refrigerator for two and one half days. Whence the contents were poured into 1.5 l. of ice water. A white solid appeared after scraping the wall of the flask. It was collected in a funnel by filtration and washed with cold dilute hydrochloric acid solution to remove pyridine. The solid was dried over anhydrous calcium chloride in a vacuum desiccator overnight, then recrystallized from benzene and pentane to give 20 g. (69%) of the ditosylate, m.p.99-101°. Further recrystallization from cyclohexane-benzene mixture raised the melting point to 102-104°.

endo, endo-5,6-Dimethylbicyclo/2,2,2/octene-2 (39). In a 500 ml. round bottom flask equipped with a Soxhlet extraction apparatus was placed 8 g. of lithium aluminum hydride and 300 ml. of ether. In the thimble was added 18 g. of the ditosylate which was added to the reaction flask by solution in refluxing ether. The mixture was heated for 20 hours with magnetic stirring. At the end of this period, water was added cautiously to destroy the excess hydride. The mixture was filtered with difficulty. The solid was dissolved in 6 N hydrochloric acid solution which was extracted with ether. The ether extracts and the filtrate were combined, washed with dilute potassium hydroxide solution and water, and dried over anhydrous sodium sulfate. The ether was removed by distillation to give 4.2 g. of a liquid which was distilled to give 3.14 g. of *endo,endo*-5,6-dimethylbicyclo[2,2,2]octene-5, (57.5%), b.p. 145-148°/749 mm., λ_{max} 2.79 μ (*cis* -CH=CH-), n.m.r. vinyl to methyl protons = 2 to 6.

endo,endo-5,6-Dimethylbicyclo[2,2,2]octan-2-ol (40). To a mixture of 2.87 g. of *endo,endo*-5,6-dimethylbicyclo[2,2,2]octene-2 and 0.5 g. of sodium boronhydride in 15 ml. of diglyme was added dropwise 2 g. of boron trifluoride etherate in 5 ml. of diglyme with stirring over an hour period. The mixture was allowed to stand for an hour before 2 ml. of water was added to destroy the excess hydride. Then, 5 ml. of 3 N sodium hydroxide solution was added. Finally to the mixture was added 5 ml. of 30% hydrogen peroxide solution at such a rate as to keep the mixture refluxing. The mixture was extracted with ether, washed with water, dried over anhydrous sodium sulfate. Removal of ether gave 3.64 g. of a semisolid which was filtered to remove some oily material. sublimation of the solid yielded 1.96 g. of pure alcohol, m.p. 94-96°, (60.5%).

endo,endo-5,6-Dimethylbicyclo[2,2,2]octan-2-one. To 1.52 g. of *endo,endo*-5,6-dimethylbicyclo[2,2,2]octan-2-ol in 2 ml. of glacial acetic acid was added dropwise 0.65 g. of chromium trioxide in 3.5 ml. of glacial acetic acid and 0.9 ml. of water. The mixture was stirred at room temperature for 8 hours. The mixture was poured into water and extracted with ether. The ethereal solution was washed with saturated sodium bicarbonate solution followed by water and dried over anhydrous sodium sulfate. Removal of ether gave 1.5 g. of a solid, which was sublimed under vacuum to yield 1.14 g. of <u>endo,endo</u>-5,6-dimethylbicyclo-[2,2,2]octan-2-one (75%), m.p. 67.5-68.5°, λ_{max} 5.81 μ(CCl_4). The n.m.r. spectrum showed two different methyl protons centered at 0.75 and 0.93 p.p.m. from tetramethylsilane.

<u>Anal</u>. Cacld. for $C_{10}H_{16}O$: C, 78.90; H, 10.66

Found: C, 78.78; H, 10.82

<u>Norcamphorquinone</u>. A mixture of 5 g. of norcamphor and 5 g. of selenium doxide in 15 ml. of xylene was refluxed and stirred for four hours. The selenium was filtered off. The filtrate was distilled to remove xylene. The red residue was distilled under vacuum to give a semisolid, which was sublimed under vaccum to give a yellow solid with some oily material. It was resublimed but failed to give a well defined melting point as reported, 112-113° (41).

<u>Isosantene (exo and endo)</u> (42). A mixture of 3-methylnorcamphane-2-methanol (50 g.) and 8 g. of sodium in 60 ml. of toluene was refluxed for 23 hours. The excess sodium was removed from the cold solution and then was diluted with 120 ml. of ether before 30 g. of carbon disulfide was added dropwise to it. Thirty minutes after the addition of carbon disulfide, 50 g. of methyl iodida was added. The mixture was refluxed for four hours. The cold mixture was poured into water. The organic

layer was washed with water, dried over anhydrous sodium sulfate, and distilled under vacuum. The higher boiling fraction, b.p. 129-130°/2.1 mm., was pyrolyzed between 260-280° to give a liquid which was distilled over sodium twice to yield 27.2 g. (62%) of isosantene isomers, b.p. 137-140°.

Santenol (α and β) (43). Isosantene (23.81 g.) was heated with 48 ml. of glacial acetic acid in the presence of 24 drops of concentrated sulfuric acid over a steam bath for four hours. The mixture was poured into water, extracted with ether. The ether extracts were washed with a 10% sodium hydroxide solution and then with water, and dried over anhydrous sodium sulfate. Removal of ether and distillation under vacuum yielded 27.8 g. (73.3%) of the acetate; with predominant I.R. peaks at 5.75μ, 8.04μ. The acetate was hydrolyzed with excess potassium hydroxide in 40 ml. of 95% ethanol. The santenol isomers was distilled under vacuum through a short and wide coulumn into a receiving flask chilled in ice. The reaction gave 19.37 g. of santenol isomers, m.p. 84-87°.

α- and β- Santenone. To 3 g. of santenol isomers in 1.6 ml. of glacial acetic acid was added dropwise a chromium trioxide (1.5 g.) solution in 0.9 ml. of water and 1.5 ml. of glacial acetic acid. The mixture was stirred magnetically for 9 hours. The mixture was diluted with water and extracted with ether three times. The ether extracts were combined, washed with a saturated sodium bicarbonate solution and then with water, and dried over anhydrous sodium sulfate. Removal of ether gave an oil which was shown to have two major components by g.p.c. The two components were separated by preparative g.p.c. by discarding the overlapping fraction. The first peak consisted of β-santenone. Its n.m.r. spectrum showed two different methyl groups, a singlet at 1.66 p.p.m. and a doublet centered at 1.46 p.p.m. Its semicarbazone melted at 224-226° (lit. (44) 223-224°). The second peak consisted of α-santenone. Its n.m.r. spectrum also showed two different methyl groups, a singlet at 1.66 p.p.m. and a doublet centered at lower field 1.8 p.p.m. Its semicarbazone melted at 205-210° (lit. 235-236°).

2-Mthyl-2-norborneol. A solution of 33 g. (0.3 mole) of norcamphor in 100 ml. of anhydrous ether was added dropwise to excess methylmagnesium iodide, prepared from 71.5 g. of methyl iodide and 25 g. of magnesium in 260 ml. of ether. When the addition was completed, the mixture was hydrolyzed in a saturated ammonium chloride solution and extracted with ether three times. The ether extracts were combined, washed, and dried over anhydrous sodium sulfate. Removal of ether yielded 38.32 g. of a liquid which was distilled under vacuum to give 31.7 g. (85%) of 2-methyl-2-norborneol, b.p. 72-74°/14 mm.

1-Methyl-2-norborneol (45). In 60 ml. of glacial acetic acid was dissolved 31.6 g. of 2-methyl-2-norborneol. The mixture was heated at 50-60° in the presence of 40 drops of concentrated sulfuric acid for 5 hours. The light yellow liquid was added to water and extracted with ether. The ether extract was washed with sodium bicarbonate solution and water, dried over anhydrous sodium sulfate, and concentrated to give a liquid, which was distilled under vacuum. The last fraction was distilled through a spinning band column to give 16.8 g. of pure 1-methyl-2-norbornyl acetate. The acetate was hydrolyzed in 95% ethanol containing excess potassium potassium hydroxide to give 11.3 g. of 1-methyl-2-norborneol, m.p. 72-75°, after distilled under vacuum (b.p. 84°/20 mm.).

1-Methylnorcamphor. In 10 ml. of glacial acetic acid was dissolved 11 g. of 1-methyl-2-norborneol. To the solution was added dropwise a chromium trioxide (6.5 g.) solution in 6.5 ml. of glacial acetic acid and 4 ml. of water. The mixture was stirred for five hours before it was diluted with water and extracted with ether. The ether extracts were combined, washed with a saturated sodium bicarbonate solution and water, dried over anhydrous sodium sulfate, and concentrated to give a liquid. The liquid was distilled under vacuum to give 7.5 g. of 1-methylnorcamphor, b.p. 63-65°/15 mm, λ_{max} 5.74 μ.

8-Thiabicyclo/3.2.1/octan-3-one. A mixture of 6.63 g. of tropinone methiodide and 6.63 g. of $Na_2S{:}9H_2O$ in 35 ml. of water was heated under nitrogen atmosphere at 80-90° for three hours. The cooled mixture was extracted three times with ether and the extracts was concentrated. The crude product was steam distilled to give 50% of the ketone, m.p. 153-155° (lit. m.p. 155°) (46).

5-Norborenen-2-one. To a solution of 5 g. of 5-norborenen-2-ol in 50 ml. of acetone chilled in ice was added dropwise under nitrogen 20 ml. of chromium trioxide reagent (47) (prepared from 26.7 g. of chromium trioxide in 23 ml. of concentrated sulfuric acid diluted with water to a volume of 100 ml.). The addition was finished in 30 minutes to give a green mixture which was diluted with 200 ml. of water and extracted three times with ether. The ethereal solution was washed with saturated sodium bicarbonate solution and then with water, and dried over anhydrous sodium sulfate. Removal of ether gave 3 g. of an oil; λ_{max} 5.74μ, semicarbazone, m.p. 205-206°(decomp.) (48) A pure sample was obtained by preparative g.p.c. which was used for n.m.r. analysis and e.s.r. experiment.

cis-Dimethyl hexahydroisophthalic acid. In a Parr high pressure reactor was charged 5 g. of platinum oxide, 300 ml. of glacial acetic acid, and 102 g. of dimethyl isophthalate, which was prepared by esterfication of isophthalic acid with methanol in the presence of catalytic amount of sulfuric acid. The reactor was evacuated, pressurized with hydrogen, and kept at 50 psi until no more hydrogen was absorbed. After the pressure was released, the contents were filtered. The filtrate was distilled to remove the acetic acid to give a fragrant liquid which was distilled under vacuum through a spining band column to separate the cis and trans isomers. The higher boiling cis-dimethyl hexahydroisophthalate, b.p. 148/20 mm., was obtained in 50% yield. The diester was hydrolyzed to give 42.7 g. of the diacid; which after one recrystallization from water melted at 156-158°.

cis-Hexahydroisophthalic anhydride. Under a hood, a mixture of 20 g. of cis-hexahydroisophthalic acid and 26 g. of acetyl chloride was heated over a steam bath for three hours. Excess acetyl chloride was

was removed by distillation. The residue was allowed to cool and then filtered to give 15.2 g. of the anhydride, which was recrystallized from benzene to give 13.8 g. of pure anhydride, m.p. 186-188°.

Half methyl ester of cis-hexahydroisophthalic acid. A mixture of 13.8 g. of *cis*-hexahydroisophthalic anhydride and 2.87 g. of anhydrous methanol was heated over a steam bath for an hour. The reaction mixture was chilled in an ice bath, then filtered. The solid was washed with a small amount of pentane to give 15.5 g. of the half ester, m.p. 57-59°.

cis-Hexahydrohomoisophthalic acid (49). The half methyl ester of *cis*-hexahydroisophthalic acid (15.5 g.) was added to a chilled solution of 12.5 ml. of thionyl chloride in 50 ml. of benzene containing a few drops of pyridine. The mixture was protected against moisture by a drying tube and let stand for 90 minutes at room temperature. The solvent was removed by distillation, more benzene added and the distillation repeated. The solution was filtered to remove some pyridine hydrochloride and added dropwise to 300 ml. of an ethereal solution of diazomethane, (which was prepared from 30 g. of N-nitrosomethylurea), at 0-5°. Thirty minutes later, the ether was removed under a reduced pressure to give a yellow oil which was taken up into 30 ml. of anhydrous methanol. To the methanol solution was added dropwise 10 ml. of triethylamine containing 1 g. of silver benzoate (50). After nitrogen evolution stopped, a small amount of Norit A was added to the mixture before it was heated to reflux. The cold mixture was filtered and the filtrate was distilled to give an oil. The oil was distilled under vacuum to give 13.1 g. of *cis*-dimethyl hexahydrohomoisophthalate, b.p. 118-121°/3 mm. The ester was hydrolyzed to the diacid, m.p. 155-157° (from water).

Bicyclo[3.2.1]octan-6-one. A mixture of 4.2 g. of *cis*-hexahydrohomoisophthalic acid, 3.5 g. of barium oxide, and 4 ml. of water was stirred and heated over a steam bath for three hours. The white barium salt was dry distilled between 360-370° to give a waxy solid, which melted at 148-150° [lit. 157-158° (51) and 150-152° (52)] after sublimation under vacuum; λ_{max} 5.75 μ.

cis-Bishomohexahydroisophthalic acid. Protected from moisture by a drying tube, a mixture of 10 g. (0.0526 mole) of *cis*-1,3-hexahydroisophthalic acid and 22.3 g. (0.1032 mole) of phosphorous pentachloride in 50 ml. of benzene was refluxed over night. Removal of solvent under reduced pressure gave an oil which did not contain any acid or anhydride as indicated by its infrared spectrum. The oil (the diacid chloride) was added to an ethereal solution of diazomethane (prepared from 30 g. of N-nitrosomethylurea) to give a yellow solid which was taken up into 150 ml. of anhydrous methanol. To this solution was added dropwise 20 ml. of triethylamine containing 2 g. of silver benzoate. After the evolution of nitrogen ceased, a small amount of Norit A was added before the mixture was heated for 30 minutes. The mixture was filtered after the solvent was removed to give 0.5 g. of an unidentified solid. The filtrate was dissolved in ether and washed with sodium bicarbonate solution, dried over anhydrous sodium sulfate, and evaporated to give an oil which was distilled under vacuum to give 6.94 g. of the diester, b.p.

102-104°/0.65 mm. The diester, 3.1 g. was hydrolyzed to give 2.1 g. of the diacid, m.p. 136-138°. This diacid had a neutral equivalent of 207 (calcd.,200).

Bicyclo/3.3.1/nonan-3-one. A mixture of 1.36 g. of cis-hexahydrobishomoisophthalic acid and 1.53 g. of barium oxide and 2 ml. of water was heated in a mortar over a steam bath to dryness. The salt was ground to a fine powder and transfered to a tube which was then sealed under vacuum. The salt was then heated between 360-380° for 2 hours. There was obtained 400 mg. of the ketone in the cold end of the tube. The solid melted at 175-177° (lit. 180-182°)(53) after sublimed under vacumm; λ_{max} 5.85μ, 2,4-dinitrophenylhydrazone, m.p. 206-208° (lit. 208-209°).

Nopinone (54). β-Pinene, 20 g. in 250 ml. of carbon tetrachloride was ozonized at 0°. The ozonide was allowed to stand in the solution overnight before addition to a mixture of 100 ml. of 30% hydrogen peroxide and 100 ml. of 10% sodium carbonate solution. The mixture was stirred for 30 minutes and then heated for 30 minutes at 70°. The solution was then washed with water, dried over anhydrous sodium sulfate, and concentrated to give an oil. The oil was distilled under reduced pressure to give 8.44 g. of nopinone (90% pure by g.p.c.). A pure sample was obtained by preparative g.p.c. and was used for n.m.r. analysis and for e.s.r. experiments.

1,2,3,4,10,10-Hexachloro-5,6,7,8,4a,8a-hexahydro-1,4,5,8-endo,endo-dimethano-6-exo-naphthol (40). To 52.7 g. (0.144 mole) of Isodrin and

1.5 g. of sodium borohydride dissolved in 140 ml. of diglyme was added 8.5 g. of boron trifluoride etherate in 10 ml. of diglyme over an hour period. The mixture was stirred for an additional hour before 20 ml. of water was added to decompose the excess hydride. To the mixture was added 20 ml. of 3 N sodium hydroxide solution followed by 20 ml. of 30% hydrogen peroxide solution at such a rate as to maintain a gentle reflux. The reaction mixture was poured into 700 g. of ice and extracted four times with ether. The ethercal solution was washed with water and dried over anhydrous sodium sulfate. The ether was removed by a rotarary evaporator to give 62.4 g. of an oil, which show alcoholic (2.75μ, 2.87μ) and olefinic (6.24μ) absorptions in its infrared spectrum. This alcohol was used directly in the following reaction without purification.

6,7-Dehydro-1,4,5,8-endo,endo-dimethano-2-decalone (55, 56). In 300 ml. of tetrahydrofuran containing 140 ml. of t-butyl alcohol was dissolved 15 g. of the crude alcohol prepared above. The mixture was chilled in an ice bath before 18 g. of finely cut lithium wire was added under nitrogen. The ice bath was removed and the mixture stirred. After a while the mixture started to reflux. When the refluxing stopped the excess lithium was removed by pouring the mixture through a glass wool plug. The solution was poured into one liter of water and extracted with ether. The ether extracts were combined, washed with water, and dried over anhydrous sodium sulfate. Removal of ether gave 8.2 g. of an oil. The oil was chromatographed over 200 g. Woelm alumina containing 8 ml. of water and eluted with Skelly A containing 10% of ether to give 2.3 g. of the dechlorinated alcohol, m.p. 97.5-98.5°, 1 g. of which was oxidized with excess chromium trioxide-pyridine mixture (57) to give the decalone in 81% yield; m.p. 127-129 (lit. 128-130°) (58), λ_{max} 5.74μ.

1,4,5,8-endo,endo-Dimethano-2-decalone. Hydrogenation of 1,2,3,4,4a,5,8,8a-octahydro-1,4,5,8-endo,endo-dimethano-2-exo-naphthol with 10% palladium on charcoal as the catalyst in ethanol gave a quantitative yield of decahydro-1,4,5,8-dimethano-2-exo-naphthol, m.p. 106-107°; which was oxidized with chromium trioxide in acetic acid and water mixture to the ketone, m.p. 89-91°, λ_{max} 5.73μ.

1,4,5,8-endo,exo-Dimethano-2-decalone. To 200 mg. of decahydro-1,4,5,8-endo,exo-dimethano-exo-2-naphthol in 1 ml. of glacial acetic acid was added slowly 100 mg. of chromium trioxide in 0.5 ml. of glacial acetic acid and a few drops of water. The mixture was stirred for two hours and then poured into water, and extracted with ether. The ether extracts were washed with saturated sodium carbonate solution and then with water, dried over anhydrous sodium sulfate. Removal of ether gave an oil which was sublimed under vacuum to give 121 mg. of the ketone, m.p. 36-37°, λ_{max} 5.74μ.

Bicyclo/2,2,2/octan-2-one. Bicyclo[2,2,2]octanyl acid phthalate was hydrolyzed to the alcohol, m.p. 218-220°, in 95% ethanol containing excess of potassium hydroxide. The alcohol was oxidized with chromium trioxide in acetic acid and water mixture to the ketone, m.p. 175-177°, λ_{max} 5.80μ.

SOURCES OF CHEMICAL

The DMSO used in these studies was obtained from Crown Zellerbach. The solvent was dried and distilled from calcium hydride at reduced pressure between 60-80°. $\underline{d}_6$-DMSO was purchased from Columbia Southern and distilled in the above manner prior to use.

Potassium t-butoxide was either made by the reaction of potassium with t-butyl alcohol or purchased from MSA Research, and was sublimed under reduced pressure at 170° prior to use.

Many compounds used in this study were kindly supplied by other workers and were used directly without further purification. They are listed in the following table with commercially available compounds.

Chemical	Source
Bicyclo[3,2,1]octan-3-one	Prof. C. W. Jefford (59)
Bicyclo[3,2,1]octan-2-one	Prof. H. M. Walborsky
Bicyclo[3,2,2]nonan-3-one	Prof. C. W. Jefford
Bicyclo[2,2,2]oct acid phthalate	Prof. H. M. Walborsky
Bicyclo[2,2,2]octane-2,3-dione	Prof. P. Yates
1,3-cyclohexadiene	Aldrich
Atisine derivatives	Prof. O. E. Edwards (28)
1-Methyl-4-methoxybicyclo[2,2,2]octan-2-one	Dr. K. Morita (25)
1,5-Dimethyl-4-methoxybicyclo[2,2,2]-octan-2-one	Dr. K. Morita (25)
Norcamphor	Aldrich
α-Bromonorcamphor	Dr. L. G. Schnack (60, 61, 62)
α-Bromobicyclo[2,2,1]-5-heptene-2-one	Dr. L. G. Schnack (60, 61, 62)
Apocamphor	Prof. H. C. Brown
Camphor	Geo. T. Walker & company
3-Methylnorcamphane-2-methanol	Aldrich
Camphorquinone	Aldrich
α-Bromocamphor	Aldrich

(continued)

Chemical	Source
Isophthalic acid	Aldrich
Tropinone	Aldrich
5-Norbornen-2-ol	Aldrich
Isodrin	Velsicol
Decahydro-1,4,5,8-*endo*-*exo*-dimethano-*exo*-2-naphthol	Prof. J. K. Stille (63)
Homocamphor	Prof. G. Büchi (64) and Prof. G. Quinkert
4,5-Ethanobicyclo[2,1,1]hexan-2-one	Prof. J. Meinwald
Selenium dioxide	Alfa Inorganics
Bicyclo[2,2,2]-5-octene-2-one	Dr. L. G. Schnack (65, 66)
5,8-Diacetoxy-1,4-dihydro-1,4-methanonaphthalene	Dr. L. G. Schnack (67)
5,8-Diacetoxy-1,2,3,4-tetrahydro-1,4-methanonaphthalene	Dr. L. G. Schnack (68)
5,8-Dihydroxy-1,2,3,4-tetrahydro-1,4-methanonaphthalene	Dr. L. G. Schnack (69)
endo-7-Isopropylidene-bicyclo[2,2,1]-heptan-2-one	Dr. L. G. Schnack (70)
endo-7-Isopropylidene-bicyclo[2,2,1]-5-heptene-2-one	Dr. L. G. Schnack (70)
Dibenzobicyclo[2,2,2]octadiene-2,3-dione	Prof. S. J. Cristol
5,5-Dimethylbicyclo[2,2,1]heptyl-2-acetate	Dr. W. Trahanovsky
Bicyclo[3,2,1]-6-octene-3-one	Prof. N. LeBel

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APPENDIX

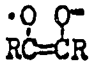
Ketones that failed to yield semidiones upon oxidation and have not been mentioned in the text are 4,5-ethanobicyclo[2,1,1]hexan-2-one, endo-7-isopropylidene-bicyclo[2,2,1]heptan-2-one, and endo-7-isopropylidene-bicyclo[2,2,1]-5-heptene-2-one.

Attempts to reporduce the result reported for tropinone (15) were unsuccessful. Oxidation of tropinone in the usual manner gave apparently a mixture of radical anions since the resulting e.s.r. spectrum was an unsymmetrical one. Furthermore, this spectrum does not, in anyway, resemble the one reported (doublets of a quartet).

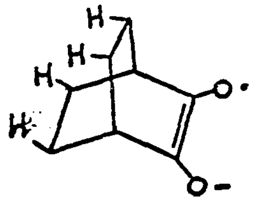
α-Santenone appeared to be pure by g.p.c. but it slowly formed a mixture of radical anions in low yield upon oxidation as the e.s.r. spectrum was not well resolved.

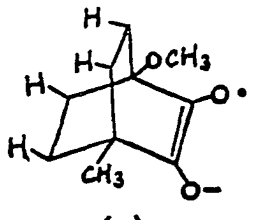
Treatment of α-bromocamphor with a basic DMSO solution failed to give camphorsemidione. In this case Wagner-Meerwein rearrangement leading to a ketone which could not give a semidione might have occurred.

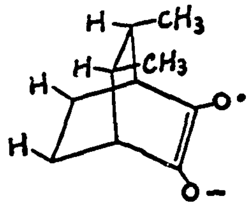
SUMMARY

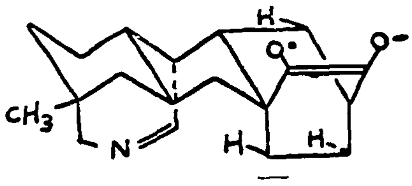
The e.s.r. spectra of acyclic or monocyclic semidiones  $R\overset{\cdot O}{C}=\overset{O^-}{C}R$ involve predominant hyperfine splitting by hydrogen atoms *α* to the dicarbonyl system. This splitting is a function of the dihedral angle ($\underline{a}^H \approx$ Cos$^2\theta$) between the carbon-hydrogen bond and the carbonyl carbon $\underline{p}_z$-orbital. Hydrogen atoms *β* to the dicarbonyl system interact only weakly with hyperfine splitting constants (h.f.s.c) considerably less than 0.5 gauss. Bicyclic semidiones derived from decalones and other ketones with 1,2-ring fusion do not display any unusually strong h.f.s. by *β*-hydrogen atoms. However, extremely strong splittings by certain *β*-hydrogen atoms were observed in many bridged bicyclic semidiones.

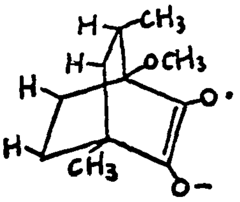
Bicyclo[2,2,2]octane-2,3-semidione (1) showed a quintet e.s.r. spectrum. The hyperfine splitting is believed to be due to the four hydrogens *exo* to the dicarbonyl system since a similar quintet is observed for 1-methyl-4-methoxybicyclo[2,2,2]octane-2,3-semidione (2),


(1)

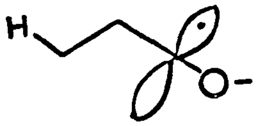

(2)


(3)


(4)

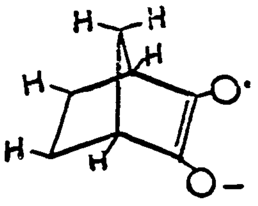

(5)

while *endo*,*endo*-5,6-dimethylbicyclo[2,2,2]octane-2,3-semidione (3) gives a nine line (triplet of triplets) e.s.r. spectrum which demands the interaction of two pairs of equivalent hydrogen atoms which are necessarily in the *anti* positions. The *exo* or *anti* splitting by hydrogen atoms in a W-plan or zigzag arrangement with the carbonyl carbon $\underline{p}_z$-orbital is

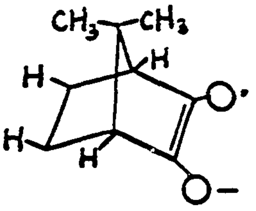


consistent with the quartet splitting observed for the semidione prepared from the atisine derivtives (4). E.s.r. spectroscopy thus provides a convenient method for assigning structure to substituted bicyclo[2,2,2]-octanones. The 5-methyl group in 1,5-dimethyl-4-methoxybicyclo[2,2,2]-octan-2-one is assigned the *syn* structure on the basis of the semidione (5) whose e.s.r. spectrum shows a quartet and a doublet splitting.

In bicyclo[2,2,2]octane-2,3-semidione the dihedral angle (θ) of the bridgehead hydrogen atom is exactly 90 degrees and this hydrogen does not interact with the unpaired electron. However, hyperconjugation is not completely restricted for bridgehead hydrogens in other bicyclic systems where θ<90 degrees. Thus, bicyclo[2,2,1]heptane-2,3-semidione



(6)



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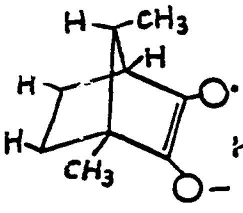
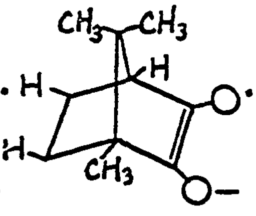


(8)

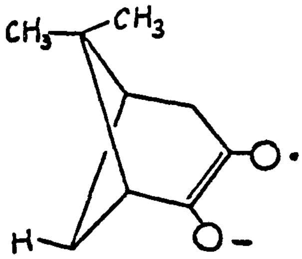


(9)

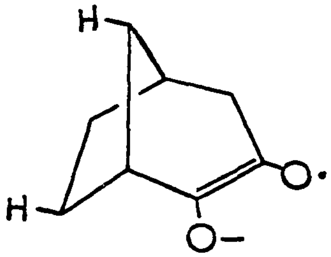
(6) showed a more complex e.s.r. spectrum involving doublet, quintet,

doublet h.f.s. These splittings are assigned to the anti-7-H, the C-1, C-4, exo C-5, exo C-6, and to the syn 7-H, respectively. These assignments are based on the e.s.r. spectra observed for semidiones derived from apocamphor (7), β-santenone (8), and camphor (9). Under low resolution (7), (8), and (9) give quintet, quintet, and quartet splittings, respectively. The only combination of hydrogen atoms that would predict such major splitting and also be consistent with the spectra of (6) and (3), would be nearly magnetically equivalent hydrogen atoms at C-1, C-4, exo C-5, exo C-6 and anti C-7. Under higher resolution differences in these hydrogen atoms can be observed in addition to smaller splittings by methyl groups. [one in (7), two in (8) and (9)] and by the endo hydrogen atoms in (7) and (8) with smaller h.f.s.c.

The W-plan long range interaction and splitting due to bridgehead hydrogen atom are also observed in bicyclic semidiones (10-15) with addi-



(10)



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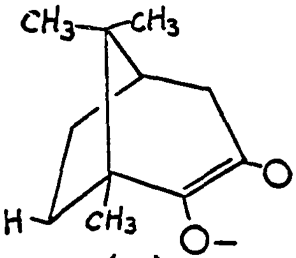

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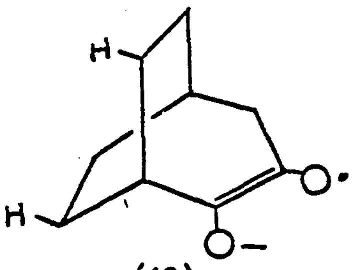
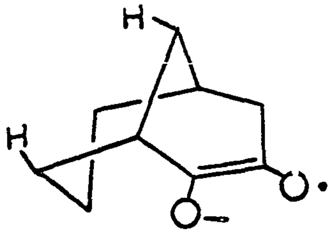
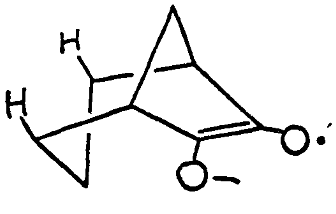


(13)



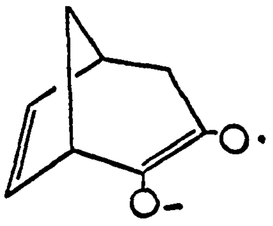
(14)



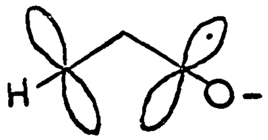
(15)

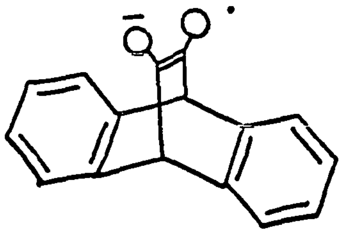
tional smaller splittings by some endo and syn hydrogen atoms, and by methyl groups. Analysis of the hyperfine splitting in semidiones (10-14) is simplified by the fact that in d_6-DMSO the α-hydrogen atoms, with the exception of those at a bridgehead, are replaced by deuterium atoms with a resultant change in the e.s.r. spectrum ($a^D = 1/6.4\ a^H$).

It was also observed that an unpaired spin can be transmitted to p-orbitals which is in the W-plan arrangement with the p_z-orbitals of the dicarbonyl system since all hydrogen atoms in semidiones (16) and (17) interact with the unpaired electron.



(16)





(17)