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Semidiones in the bicyclo [3.1.0] hexane system

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SEMIDIONES IN THE BICYCLO[3.1.0]HEXANE SYSTEM

by

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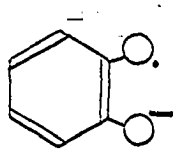
TABLE OF CONTENTS

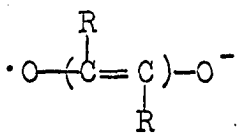
INTRODUCTION

Reviews of the contributions of electron spin resonance (ESR) spectroscopy to the solution of problems in organic chemistry are available (1,2,3). p-Semiquinones, o-semiquinones, and semidiones 1 can be viewed as derivatives of the paramagnetic superoxide anion, $:\ddot{O}—\ddot{O}\cdot^{-} \leftrightarrow \cdot\ddot{O}—\ddot{O}:^{-}$

p-Semiquinone



o-Semiquinone

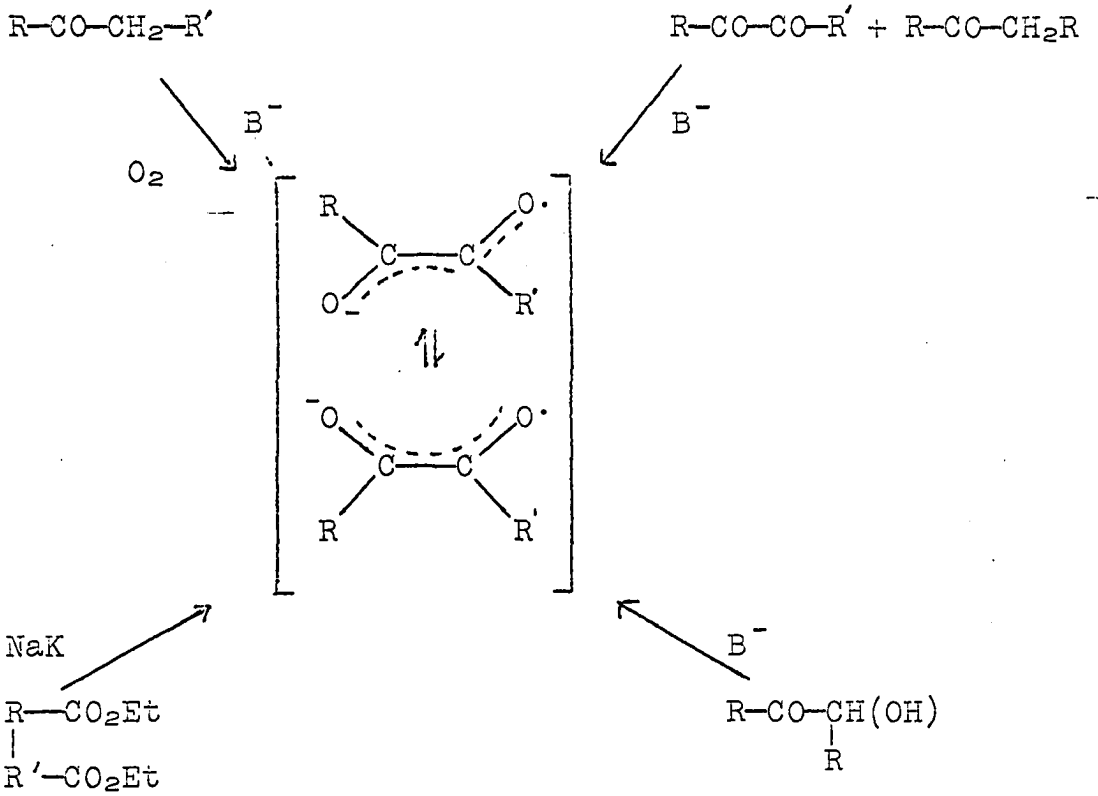


Semidione

1

Semidiones with aromatic -R- groups have been studied by Dehl and Fraenkel (4). Semidiones with one aromatic -R- and one aliphatic -R- were introduced by Russell and Strom (5) and in this same communication aliphatic semidiones were reported. Semidiones can be prepared by a variety of routes 2. All of the semidiones in this thesis were prepared by oxidation of α methylene ketones.

Hückel molecular orbital calculations indicate that the spin density is about equally divided between the 2 carbon atoms and 2 oxygen atoms of the semidione. ESR studies of carbon-13 and oxygen-17 labeled semidiones are in agreement with the molecular orbital calculations. The spin density



2

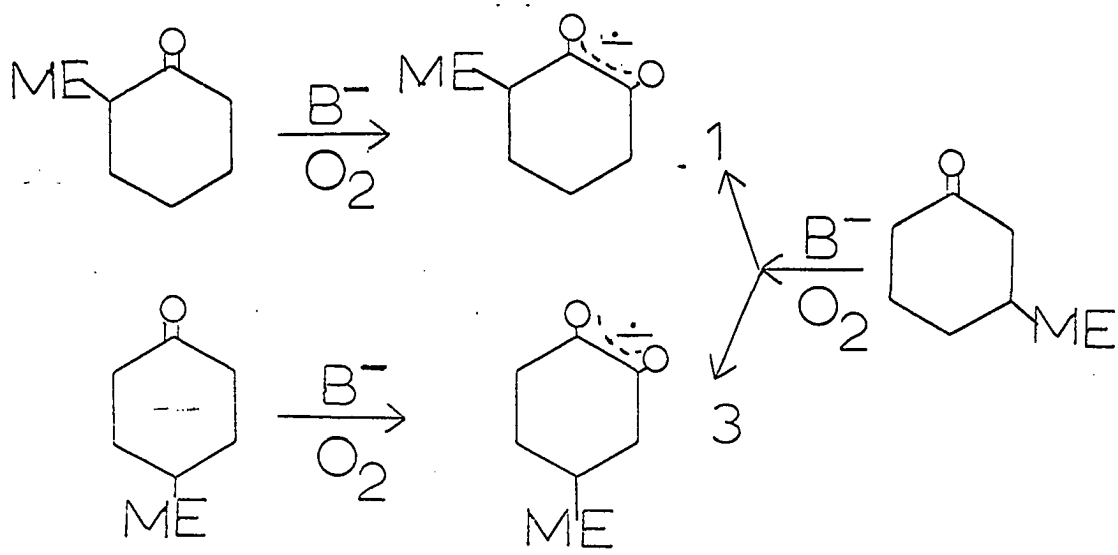
distribution is slightly dependent on the cis-trans stereochemistry of the oxygen atoms 3.

3

a^H = 6.9 gauss a^H = 5.70 gauss

The semidione is a conveniently introduced spin label and the study of semidiones by ESR spectroscopy has been applied to structural and conformational problems (5,6,7,8,9).

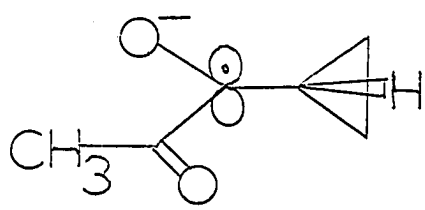
For example, the isomers of methylcyclohexanone can be easily distinguished, 4.



4

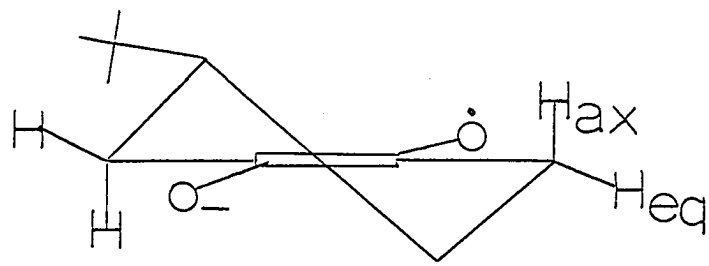
The differences in chemical reactivity of non-equivalent methylene groups which are -α- to a ketone can be ascertained by ESR spectroscopy as shown in the oxidation of 3-methyl-cyclohexanone 4. This technique has been especially useful in studying the chemical reactivity of α-keto-methylene positions and the type of ring fusion in steroidal ketones.

The most stable conformation of cyclopropyl semidiones (10) has been shown to have the α cyclopropyl hydrogen in the nodal plane of the semidione π system 5.



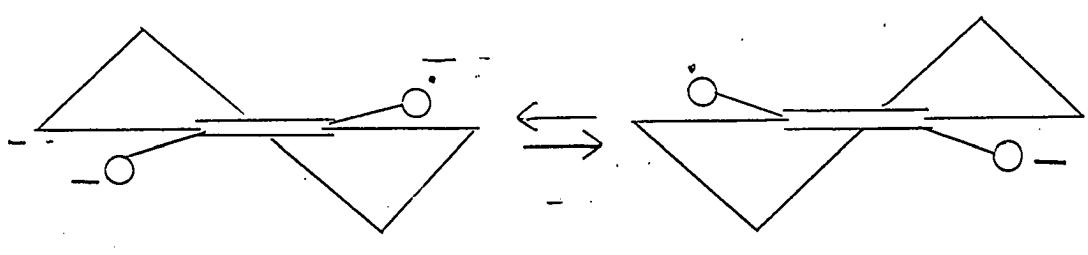
5

The ESR spectra of cyclohexane semidiones have been carefully examined in regard to equilibrium and dynamic geometries (11). The 4-t-butylcyclohexane semidione is rigid and the ESR spectrum does not change with temperature between -100° and +80°C. The α methylene hydrogens are rigidly held in quasi axial and quasi equatorial pairs and their hyperfine splitting constants are not the same, 6.



6

Cyclohexane semidione is conformationally changing rapidly, since 4 equivalent α hydrogens have been observed by ESR spectroscopy, 7. The enthalpy differences between conformations



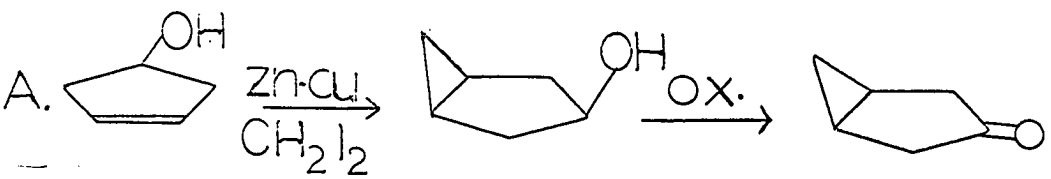
7

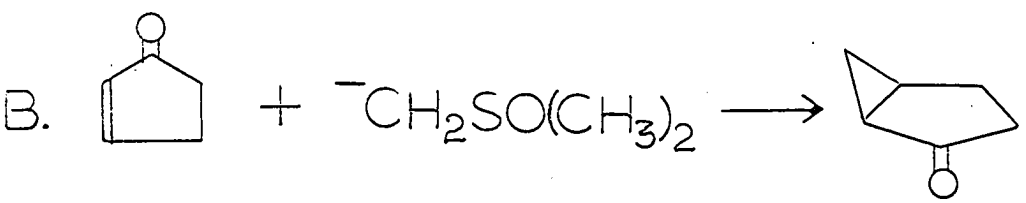
of various substituted methylcyclohexane semidiones have been determined by temperature variation studies.

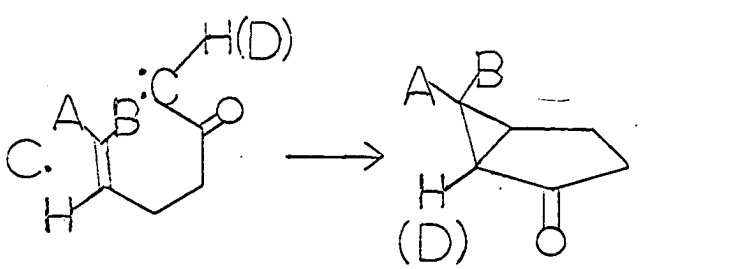
The methyl hyperfine splittings of semidiones derived from <u>para</u> substituted propiophenones correlate well with Hammet σ constants for a variety of substituents (12). Substituent effect can, therefore, be estimated quickly by this method.

Bicyclo[2.2.1] and bicyclo[2.2.2] semidiones have provided a wealth of information on long range interactions and these results have been integrated into the text of this thesis.

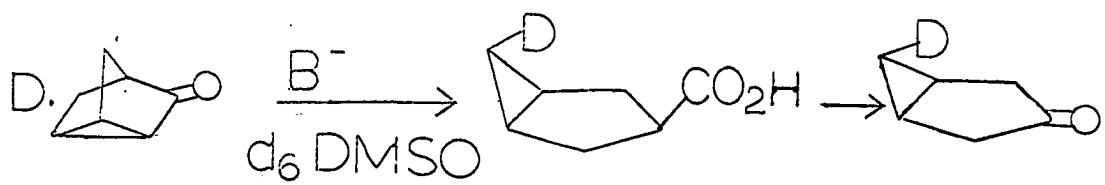
The ketonic precursors to the bicyclo[3.1.0]hexane semidiones were in general prepared as follows:







A	B
ET	H
H	ET
ME	H
H	ME

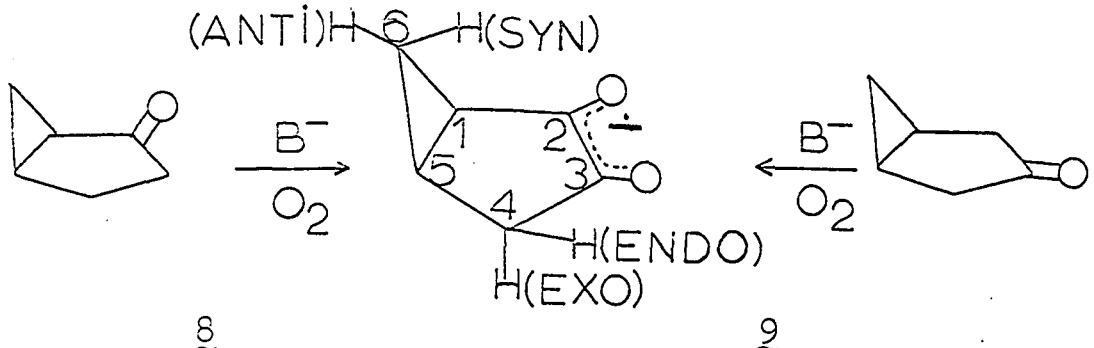


The details of the preparations are in the experimental section. Contributions contained herein in the areas of structure proof, long range interactions, stereoselective hydrogen-deuterium exchange, and molecular rearrangements are additional examples of the application of electron spin resonance spectroscopy to problems in organic chemistry.

RESULTS AND DISCUSSION

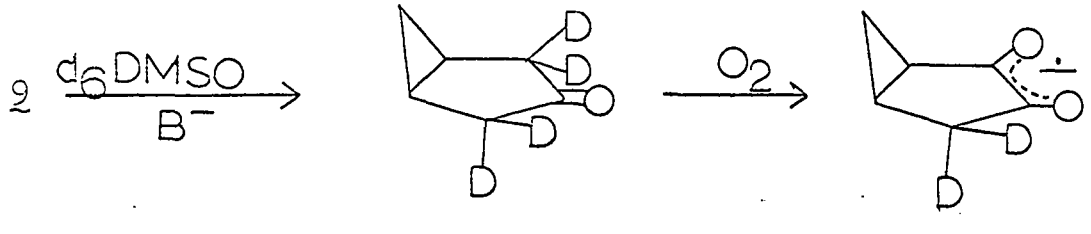
Assignment of Hyperfine Splitting Constants

The ESR spectrum (Figure 1) of the semidione resulting from the oxidation of bicyclo[3.1.0]hexan-2-one 8 or 3-one 9 in dimethyl sulfoxide (DMSO) solution containing an excess of potassium t-butoxide requires the hyperfine splitting by six hydrogen atoms (13,14). The assignment of the hyperfine splitting constants (hfsc) to the particular hydrogen atoms has been accomplished by deuterium and alkyl substitution.



8 9

When the oxidation of bicyclo[3.1.0]hexan-3-one is conducted in d_6-dimethyl sulfoxide (d_6-DMSO 10) the ESR spectrum from the resulting semidione (Figure 2) shows that 2 deuterium atoms have been incorporated into the molecule. The 14.9 gauss hydrogen splitting has been replaced by a deuterium splitting

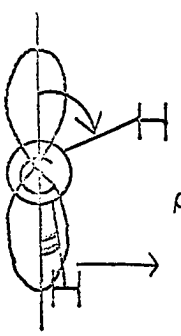


10

(spin = 1) of 2.3 gauss ($\underline{a}^D = \frac{a^H}{6.5} = \frac{14.9}{6.5}$ = 2.3 gauss calcd.) and the 7.9 gauss hydrogen splitting has been replaced with a deuterium splitting of 1.2 gauss ($\underline{a}^D = \frac{a^H}{6.5} = \frac{7.9}{6.5}$ = 1.2 gauss calcd). The ESR spectrum (Figure 3) of tricyclo[7.1.0.$0^{4,10}$]-decan-2,3 semidione shows in addition to smaller hyperfine splittings of 4.5, 1.5 and 0.7 gauss a larger hydrogen splitting of 14.8 gauss. The large splitting could be replaced by deuterium when the oxidation was performed in $\underline{d_6}$-DMSO. The 14.9 gauss hfsc in the unsubstituted bicyclo[3.1.0] semidione has been assigned to the <u>exo</u>-4-position hydrogen atom and the 7.9 gauss hfsc has been assigned to the <u>endo</u>-4-position hydrogen atom. The Heller-McConnell equation 15), $\underline{a}^H = \beta\rho\cos^2\theta$, would predict the C-H band of the former to be nearly coplanar with the ρ-orbitals of the semidione π system. The hydrogen atom with the 14.9 gauss hfsc is therefore predicted to be quasi-axial and the hydrogen atom with the 7.9 gauss hfsc is predicted to be quasi-equatorial to the semidione π system <u>11</u>.

$a^H = \beta\rho\cos^2\theta$

$a^H = 15$ for $\theta = 0°$

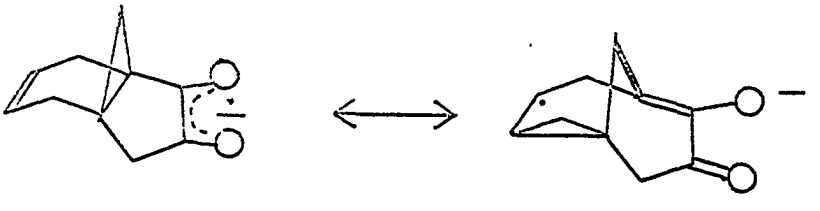


$\beta \cong 60$

ρ = spin density at C_2=0.25

$\theta = 0°$

Alkyl substitution at the 1-position removes a 4.0 gauss hydrogen splitting from the splitting pattern of the unsubstituted bicyclo[3.1.0]hexane semidione. This is clearly shown in the ESR spectrum of 1-methylbicyclo[3.1.0]hexane semidione (Figure 4). The ESR spectrum of 1-ethyl-5-methylbicyclo[3.1.0]-hexane semidione (Figure 5) requires that the 5-position hydrogen splitting in the unsubstituted semidione be small (0.8 gauss) since 5-position alkylation did not remove or replace any additional large hydrogen splittings. This result is verified by the ESR spectrum of tricyclo[4.3.1.0]decan-3-ene-7,8 semidione (Figure 6). Three large hydrogens are still observed at 14.7, 7.8 and 4.1 gauss. The smaller splittings are due to the syn-6-hydrogen and 3 hydrogens in the six-membered ring. The latter may result from 1,3 σ-π interaction 12.

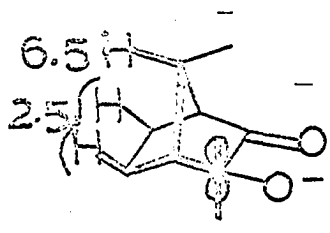


12

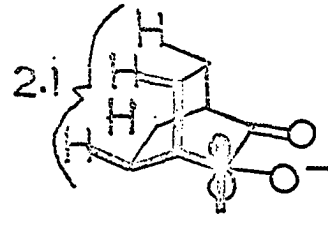
The ESR spectrum of syn-6-deuteriobicyclo[3.1.0]hexane semidione (Figure 7) clearly indicates the removal of a 0.8 gauss hydrogen splitting from the splitting pattern of the unsubstituted semidione. The deuterium hyperfine splitting

is very small and cannot be observed ($\underline{a}^D = \frac{a^H}{6.5} = \frac{0.8}{6.5} = 0.12$ gauss calcd.). The ESR spectrum of 6,6-dideuteriobicyclo[3.1.0]-hexane semidione (Figure 8) shows, in addition to the removal of a 0.8 gauss hydrogen splitting from the splitting pattern of the unsubstituted semidione, the replacement of a 4 gauss hydrogen splitting with ~0.7 gauss deuterium splitting ($\underline{a}^D = \frac{a^H}{6.5} = \frac{4.0}{6.5} = 0.7$ gauss calcd.). Although the isotopic purity and signal strength is not sufficiently high for accurate analysis the wing peak of this spectrum can be analysed as a four-line pattern with intensity ratios of 1:2:2:1. This is consistent with the presence of 1 deuterium atom and 1 hydrogen atom with about equal hfsc.

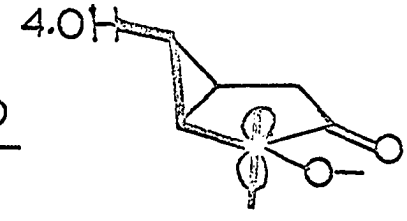
Strong hyperfine interactions of β hydrogens which are in a coplanar 2V arrangement with respect to a p-orbital in a paramagnetic center have previously been reported (16,17). Some examples of this type of interaction are 13, 14 and 15.



13

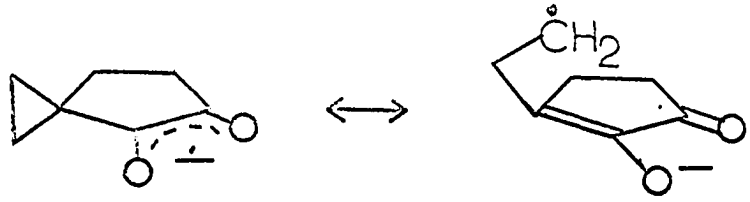


14



15

The 2V arrangement in 15 is apparently very efficient in transmitting spin density to properly aligned β hydrogens. The anti-7-hydrogen splitting in 14 is unusually large but it is opposite two paramagnetic centers. The necessity of a nearly coplanar arrangement of atoms in the 2V plan for long range interaction is illustrated in the ESR spectra of semidiones of bicyclo[4.1.0]heptane, bicyclo[5.1.0]octane, bicyclo[6.1.0]nonane, and spiro[2,4]heptane (Figures 9, 10, 11, and 12) respectively. The hyperfine splitting of the anti-7-hydrogen in the bicyclo[4.1.0] semidione is 1.3 gauss, but the long range interactions in the bicyclo[5.1.0] and [6.1.0] semidiones is small (>1 gauss). From molecular models, it does not appear that a good coplanar arrangement of atoms with the semidione p-orbital can be achieved in the latter cases. The semidione of 4 keto spiro[2.4]heptane shows an equivalent weak interaction of all 4 cyclopropyl hydrogens. Unlike the β interaction in the bicyclo[3.1.0] semidione, this interaction is non-directional. A carbon-carbon bond hyperconjugative coupling mechanism 16 would place an equal amount of spin density on the 4 β cyclopropyl hydrogens. This type of coupling seems to result from a steric driving force (17).

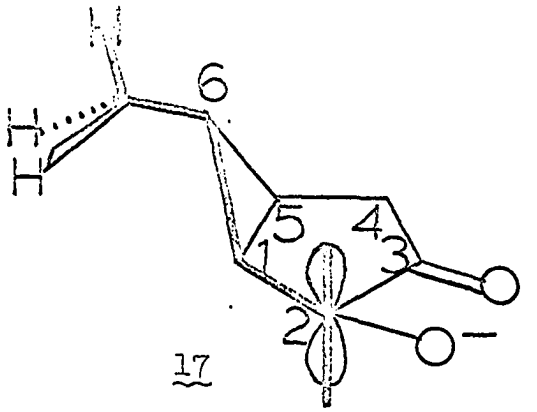


16

Alkyl substitution at the anti-6-position results in the replacement of the 4 gauss anti-6-position hydrogen splitting with smaller splittings from the α-alkyl hydrogens. Thus, the anti-6-methylbicyclo[3.1.0]hexane semidione has an ESR spectrum (Figure 13) which is consistent with hyperfine interaction of 8 hydrogen atoms. The three methyl hydrogens are equivalent, $a^{H}_{CH_3}$ = 0.4 gauss. In a similar manner the ESR spectrum of anti-6-ethylbicyclo[3.1.0]hexane semidione (Figure 14) is consistent with hyperfine splitting of the ethyl-CH_2-hydrogens, $a^{H}_{CH_2}$ = 0.75 gauss. The ESR spectrum of 6,6-dimethylbicyclo-[3.1.0]hexane semidione (Figure 15) is consistent with the long range hyperfine interaction of a single methyl group $a^{H}_{CH_3}$ = 0.4 gauss, and this methyl splitting has been assigned to the anti-6-methyl on the basis of the two previously studied anti-6-alkyl semidiones. This assignment is confirmed by the ESR spectrum of syn-6-methylbicyclo[3.1.0]hexane semidione (Figure 16) which indicates no spin density at the syn-6-methyl hydrogen.

It is apparent that anti-6-alkyl hydrogens interact with

unpaired spin on the semidione via a 2 1/2 V arrangement 17.



17

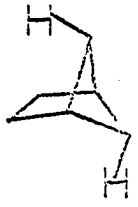
This long range interaction is very directional in nature. It is facilitated by a trans and coplanar arrangement of atoms with the nearest p-orbital of the paramagnetic center. The ESR spectrum of the semidione derived from dihydrolumisantoin (Figure 17) has in addition to the two large α-methylene hydrogen splittings a small hydrogen splitting of 1.1 gauss. Molecular models indicate that only one of the γ-methylene hydrogens at the anti-6-position is in a coplanar 2 1/2 V arrangement with the p-orbital of C-2 in the semidione. Phototestosterone has a methine hydrogen in the anti-6-position which is in a coplanar 2 1/2 V arrangement with the p-orbital of C-2. The ESR spectrum of the semidione derived from phototestosterone (Figure 18) is consistent with the long range interaction of 1γ-hydrogen, a^H = 1.5 gauss. The ESR spectrum derived from a deuterated isomer of phototestosterone (Figure 19) rules out the possibility of observation of

γ-methylene alkyl hydrogen at the 5-position.

Comparison of the PMR spectra of various methyl bicyclo-[3.1.0]hexan-2-ones (Figure 20) with the corresponding ESR spectra of the semidiones illustrates the usefulness of ESR spectroscopy in elucidating the structure of the ketonic precursor to the semidione. However, great care must be taken since subtle molecular rearrangements have been observed (see section on Molecular Rearrangements).

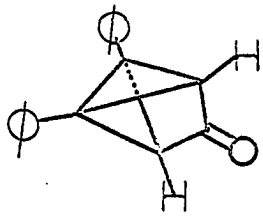
Discussion of Long Range Interaction

Long range interactions, spin-spin coupling of nuclei, has been observed by NMR spectroscopy (18, 19). Hydrogen atoms which are in a coplanar 2V or W plan 18a-d arrangement exhibit strong spin-spin coupling (20, 21, 22, 23).



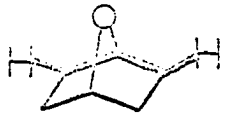
$^4J_{H-H}$ = 7.0 cps

18a



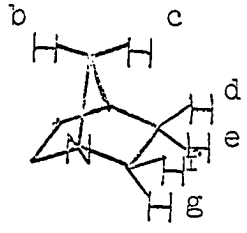
$^4J_{H-H}$ = 14 cps

18b



$^4J_{HH}$ = 3 cps

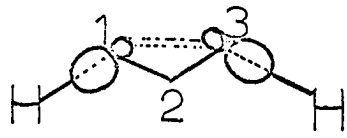
18c



$^4J_{H-N-C-H} = {}^4J_{H-C-C-H}$ = 2.5 cps

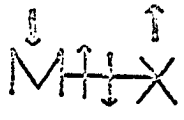
18d

The nature of this long range interaction has intrigued organic and theoretical chemists for the last five years. Meinwald and Lewis (20) suggested that the most efficient path for coupling is a direct route via overlap of the small backside orbitals of C-1 and C-3 19.



19

Fermi Contact (24) has been generally accepted as an important long range coupling mechanism. In general, electrons have some probability of being right at the nucleus. The portion of the electron density at the nucleus feels a different magnetic field and this intimate contact of electron and nucleus allows the spin of one to influence the spin of the other. It is therefore possible for a nuclear spin of a hydrogen atom to couple with the spin of an electron. The spin polarization between a nucleus and the electrons in an electron-pair bond attached to the nucleus is antiparallel 20.



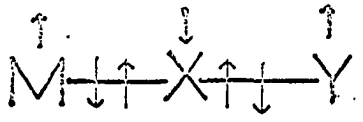
(↑ = nuclear spin)

(↑ = electron spin)

20

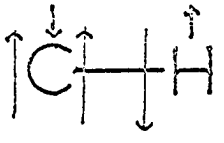
Usually the electrons on a given atom obey Hund's rule 4 (parallel alignment of electron spins). In this approach, it is assumed that perfect pairing of electrons in electron-pair bonds exists 21 (interatomic electron coupling is

antiparallel). The spin of an unpaired electron on a given atom can couple with the electrons in an electron pair bond



21

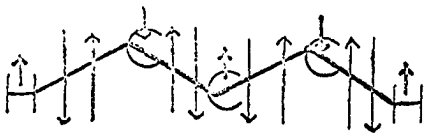
attached to that atom. In the case of carbon atoms and carbon-carbon or carbon-hydrogen bonds, this coupling is parallel (Q_{CC}^{C} or Q_{CH}^{H} is −) 22.



22

In 20 the nuclei of atoms M and X are in the lower energy antiparallel arrangement and this orientation is defined as positive coupling. In 21 the nuclei M and Y are parallel and a negative coupling occurs. In 22 the unpaired electron spin on carbon is opposite in sign to the unpaired spin on hydrogen and the coupling is negative.

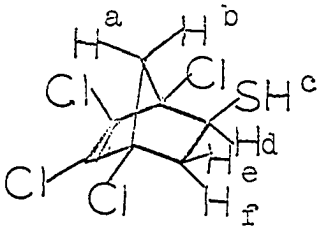
In general, Fermi Contact interactions predict hydrogen atoms separated by an odd number of bonds to exhibit positive coupling and hydrogen atoms separated an even number of bonds to exhibit negative coupling 23. A large body of data on the



23

relative sign of ^4JHH is not available but the pattern for the relative sign of ^1JHH, ^2JHH, and $^3JH\text{-}H$ is +, −, +. The type of intervening atom is sometimes important and may in fact change the expected sign (25). It is interesting to note that $^4JGB = {}^4JBE$ in 18d. This has been viewed as support for mechanism 19 (23). Presumably the nitrogen atom would alter the size of through bond coupling.

The sign of some $^4JH\text{-}H$ 24 and 25 has been shown to be positive by double resonance experiments (26, 27). These

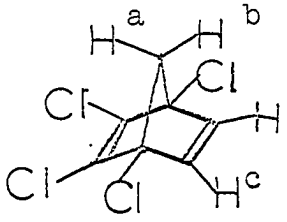


24

$^4JHaHd = +2.00$

$^4JHaHf = +2.5$

$^4JHfHc = +1.17$

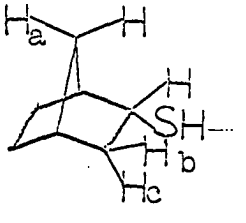


25

$Jac = 0.64$

$Jbc = -0.15$

experimental results are not predicted by the Fermi Contact mechanism. Recent calculations by the valence bond method (28, 29) are in agreement with long range spin-spin coupling, ^{4}JH-H, occurring by two mechanisms; namely indirectly 23 , through single bonds, and directly 19, through exchange interaction of atomic orbitals not formally connected by valence bonds. Mechanism 19 requires a stereospecific relationship between the atoms involved. Maximum interaction occurs when the atoms and bonds are in a zig-zag or W plan arrangement. Through-bond interactions 23 also are maximum in a zig-zag arrangement (29). However, conclusions based on such calculations disagree with each other even as to the sign with which each mechanism contributes to the value of ^{4}J. It is interesting to note that ^{4}JHaHb in 26 is negative in sign and ^{4}JHaHc is positive. The former is predicted



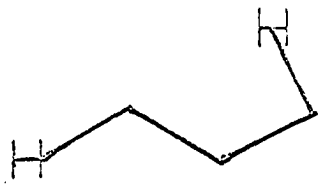
^{4}JHaHc = 1.81

^{4}JHaHb = -0.3

26

by through-bond Fermi Contact 23. Backside interaction 19 should be at a minimum for Ha and Hb and perhaps this negative coupling reflects only an indirect through-bond coupling

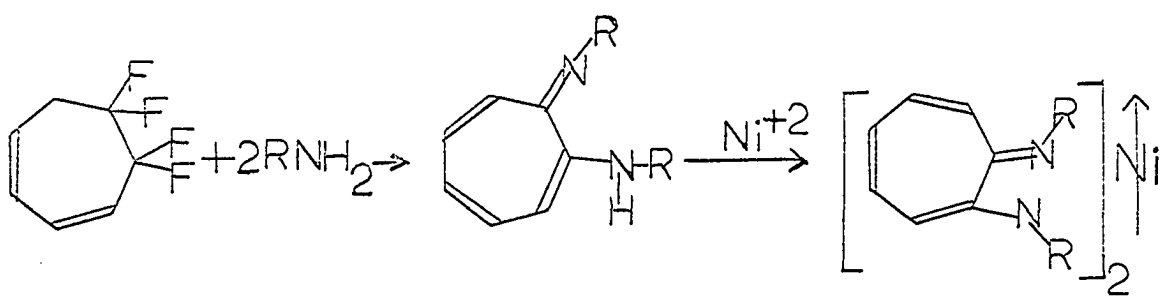
23. Mechanism 23 may have a moderate contribution in geometry 27 (29).



27

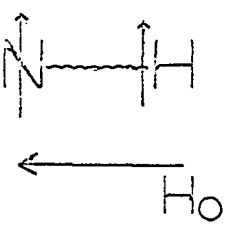
It appears that there are both direct and indirect contribution to ^4J and that perhaps they are opposite in sign, the former being − and the latter +. Accordingly in 7 the largest contribution to ^4JHaHc would be mechanism 19.

Unpaired electron distribution in σ systems has recently been studied by the NMR contact shift method (30, 31, 32). Acyclic and a few cyclic nickel II aminotroponiminates have been examined by this technique 28.

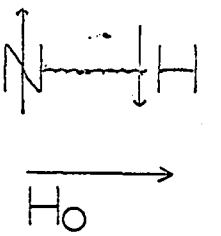


28

The differences in chemical shift of the alkyl hydrogens in the paramagnetic complex relative to the diamagnetic zinc complex provide data on the magnitude and relative sign of the unpaired electron density at the hydrogen nuclei. The paramagnetic molecule becomes aligned with the magnetic field of the spectrometer and if the unpaired spin density on a hydrogen atom is aligned in the same direction as the molecule as a whole the hydrogen resonance will be shifted to lower field 29. If the unpaired spin density is aligned in the opposite direction as the molecule as a whole the hydrogen resonance will be shifted to higher field 30.

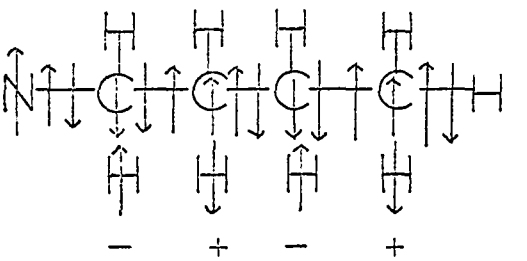


29



30

Fermi Contact would predict the signs of unpaired electron spin to alternate in an aliphatic chain 31.



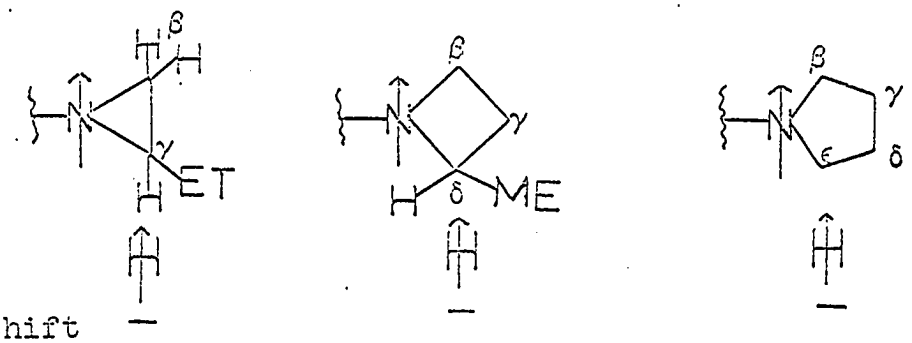
\- + - +

Shift predicted by Fermi Contact

-10,603 -697 -431 -212 Experimental in cps

31

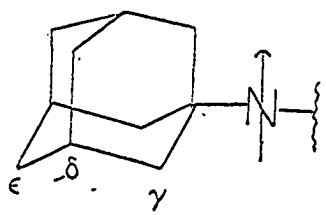
Experimentally the resonance shifts are all shown to be to lower field indicating the unpaired electron spin on all the hydrogens are the same as the molecule as a whole. A direct coupling mechanism 32 has been proposed (32) to accommodate this experimental observation.



32

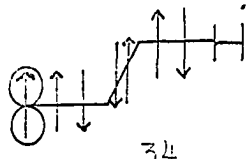
When the alkyl group attached to the nitrogen is adamantane the p-orbital on the nitrogen containing unpaired spin cannot directly interact with the γ, δ or ϵ hydrogens. Alternation of chemical shift is observed as predicted by Fermi Contact 33.

ϵ	δ	γ	
+	−	+	Predicted by Fermi Contact
+45	-109	+185	Observed shifts cps
6H	3H	6H	

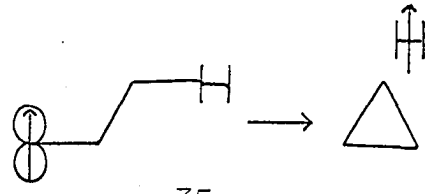


33

The assignments of chemical shifts to hydrogen atoms have been proven by substitution at the ϵ position. It is clear that direct placement of unpaired spin on the γ protons observed in 31 is opposite in sign to indirect placement of unpaired spin on the γ protons observed in 33. Thus indirect 34 and direct 35 spin contact interaction are opposite in sign.

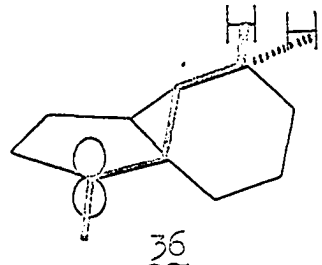


34

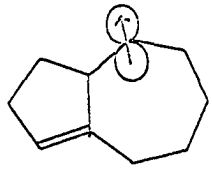


35

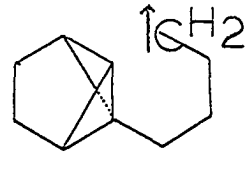
The 2 1/2V long range interaction 36 has been proven to be very directional in nature; therefore, non-directional carbon-carbon bond hyperconjugative coupling mechanisms 37 and 38 can be eliminated as a means of placing unpaired spin density on the ϵ hydrogens. A direct interaction between a



36

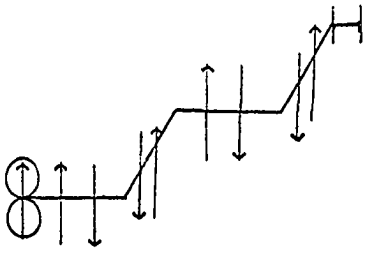


37



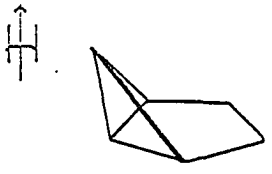
38

p-orbital of the semidione π system and the ϵ hydrogens is geometrically very unfavorable and it seems reasonable that the 2 1/2V coupling should be through bonds. Fermi Contact would predict the sign of the coupling to be positive 39.

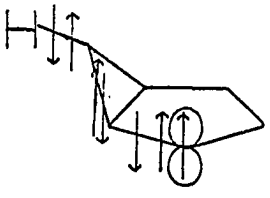


39

A direct 40 and an indirect 41 coupling mechanism can be envisioned as a means of stereospecifically placing unpaired spin density on the anti-6-hydrogen of the bicyclo-[3.1.0]hexane semidione.

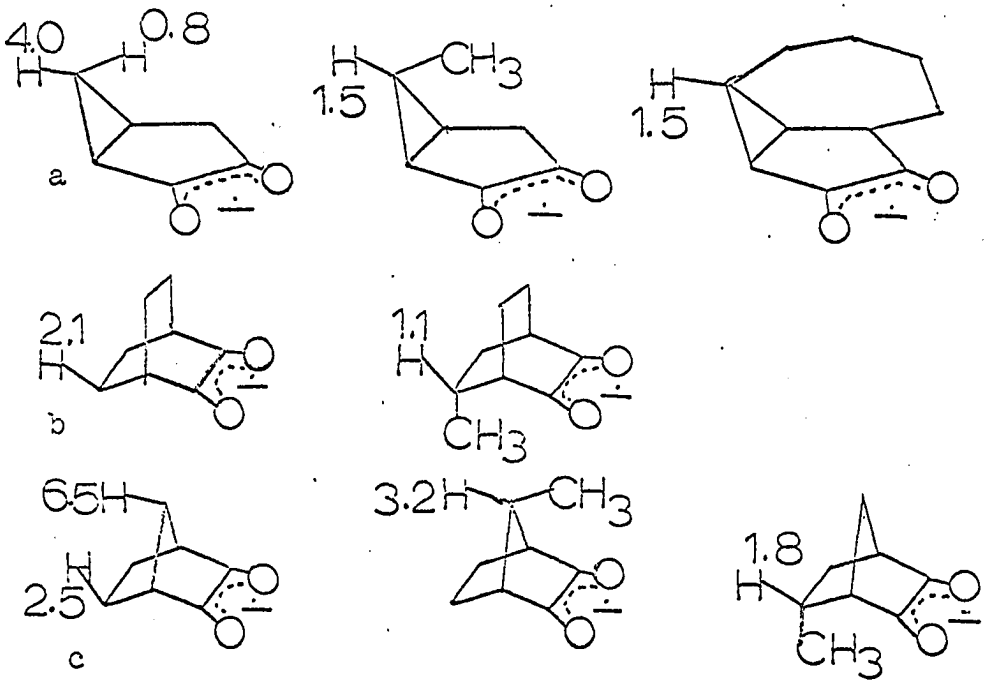


40



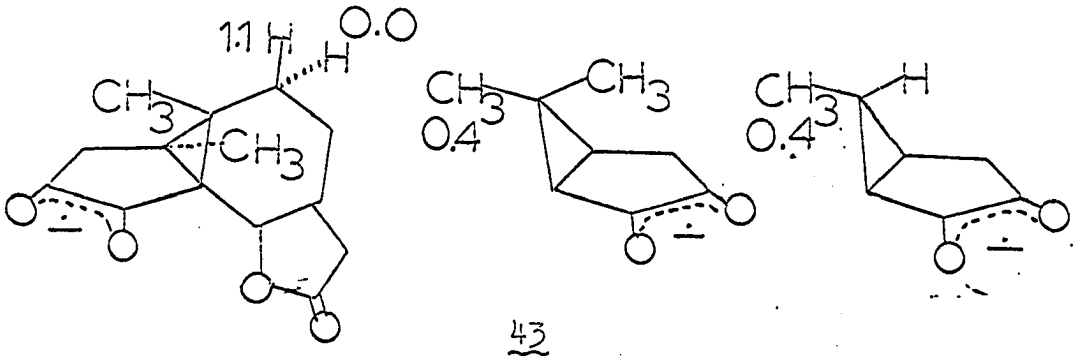
41

Frontside alkyl substitution seems to reduce the 2V hydrogen splitting about one half 42a,b,c and this is presumably due to a steric inhibition to mechanism 40.



42

Frontside substitution seems to have no effect on the 2 1/2V interaction 43



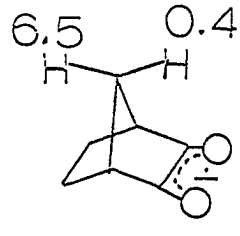
43

NMR studies indicate the spin contact dropoff between γ and δ hydrogens should be about 2 to 1. The hfsc in the δ (2 1/2V) is rather large and would seem to imply a substantial through-bond contribution. A situation in which

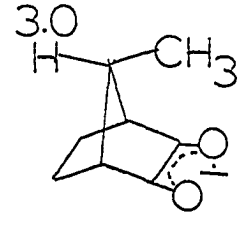
2 1/2 gauss of negative spin density was transmitted to the anti-6-hydrogen through mechanism 41 and 6.5 gauss of positive spin density was transmitted through mechanism 40 would provide a satisfactory explanation for the experimental observations in the bicyclo[3.1.0]hexane system.

Additional support for this theory is obtained from the ESR spectrum of 1-azabicyclo[2.2.2]octane semidione (Figure 20a). The assignment of the hfsc is based on bicyclo[2.2.2]-octane semidione (17). Perhaps the more electronegative nitrogen would be expected to facilitate the negative through bond mechanism and thereby reduce the observed 2V splitting by one half.

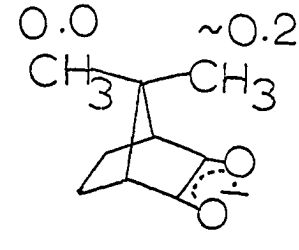
Semidiones 44, 45, and 46 can also be explained if the 6.5 gauss anti-7-hydrogen coupling is considered to arise almost entirely from mechanism 46. One would not expect to see the anti-7-methyl hydrogens in 46 via a carbon-carbon bond hyperconjugative mechanism 47.



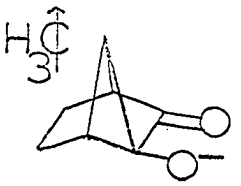
44



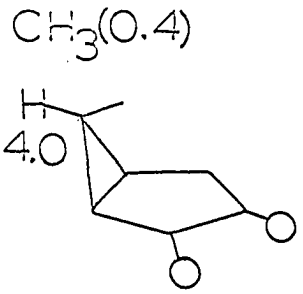
45

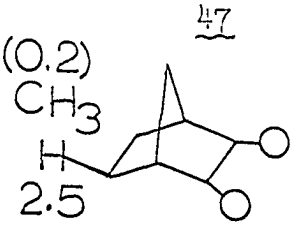


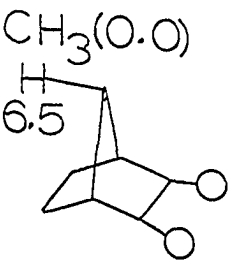
46



47



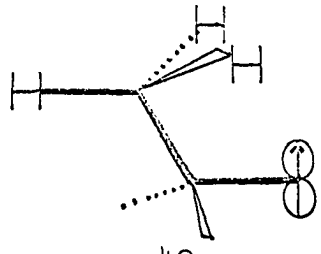




48

Reasonable values for the indirect 2V contributions are listed in 48a-c. These values are based on the size of the 2 1/2V methyl hydrogen splitting which is assumed to arise via the indirect mechanism (a_{CH_3} x 3 x 2). The x3 compensates for the averaging effect and x2 compensates for the 2V → 2 1/2V drop-off in the indirect mechanism. The geometry in 48a provides the most efficient direct and indirect coupling route.

Extended Hückel calculations (33) have been performed on neutral alkyl radicals and several bicyclic aliphatic semidiones. The calculations on the neutral alkyl radicals point to qualitative rules for maximum long range interaction. The most efficient long range interaction pathway is 49. In 50



49

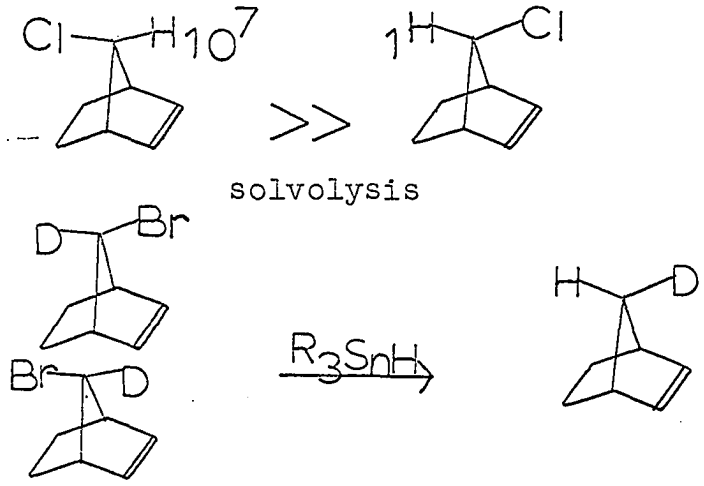
the calculated and experimental hfsc of bicyclo[3.1.0]hexane-2,3 semidione are given. The calculated results are exceedingly sensitive to changes in geometry and the exact geometry

Position	1	4 exo	4 endo	5	6 anti	6 syn
Hfsc, expt.	4.00	7.86	14.9	0.8	4.0	0.8
Hfsc, calcd..	7.6	9.4	16.3	5.0	1.0	0.1

50

of the bicyclo[3.1.0] semidione system is unknown. Since the hfsc was calculated by $a^H = C^2_{HOMO}$ 878, the relative sign of the coupling constants cannot be predicted by EHT. INDO (34) and CNDO/2 (35) calculations may perhaps provide better agreement between experimental and calculated results. However, great discrepancies have been observed between EHT, CNDO/2 and experimental results in regard to rotational barriers (36).

In the bicyclo[2.2.1] system a stereoselective direct interaction between the p orbitals of the 2 and 3 position and the anti-7-hydrogen is supported by solvolysis and radical reactivity studies (37, 38) 51. In the bicyclo[3.1.0]



51

system a strong interaction between the p orbital at the C-2 position and the anti-6-hydrogen is supported by studies in molecular rearrangement (see section on Molecular Rearrangements).

Figure 1. First derivative ESR spectrum of bicyclo[3.1.0]hexane semidione prepared by oxidation of bicyclo[3.1.0]hexan-2- or -3-one in DMSO containing a 3 to 1 molar ratio of potassium t-butoxide to ketone.

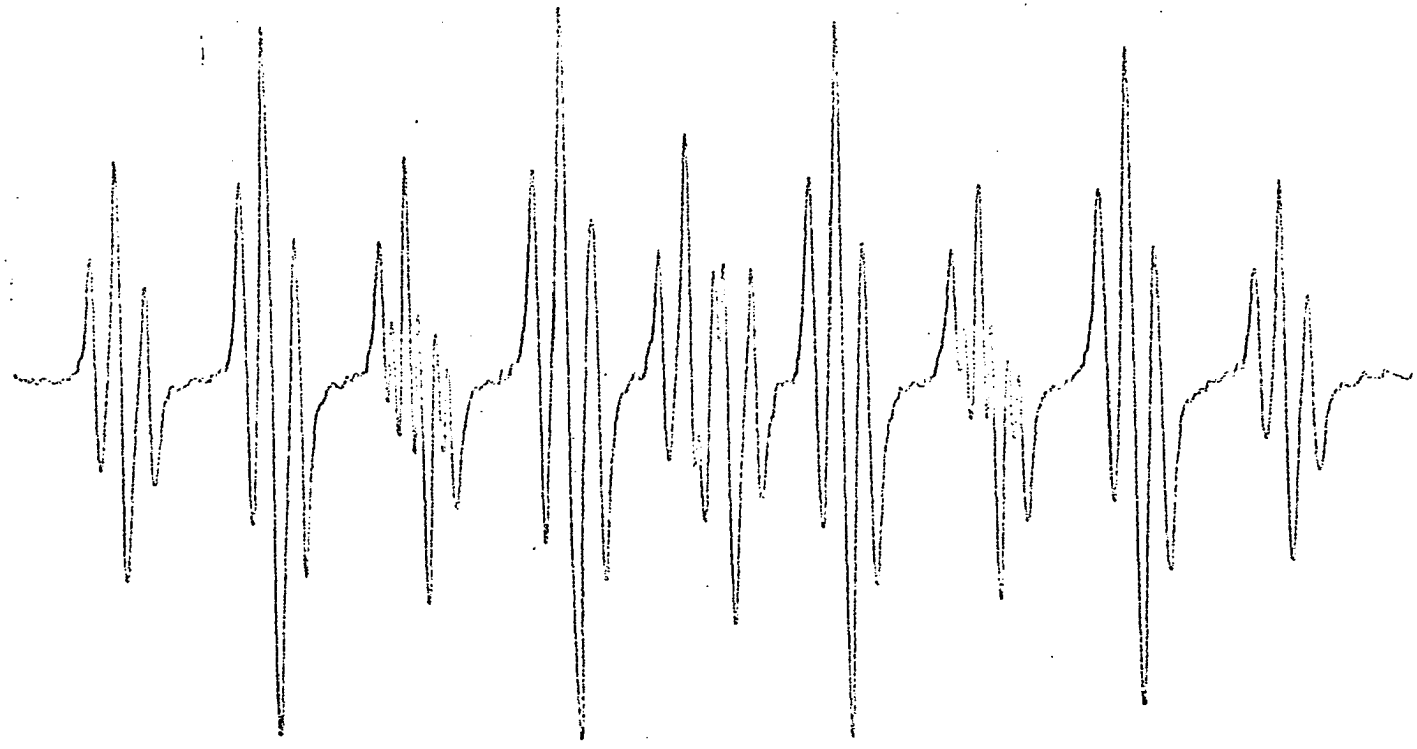

(4.0)H
H(0.8)
(4.0)H
(0.8)H
H(7.9)
H(14.9)
0
5
10
GAUSS

Figure 2. First derivative ESR spectrum of 4,4-dideuteriobicyclo[3.1.0]hexane semidione prepared by oxidation of bicyclo[3.1.0]hexan-3-one in $\underline{d}_6$-DMSO containing a 3 to 1 molar ratio of potassium $\underline{t}$-butoxide to ketone.

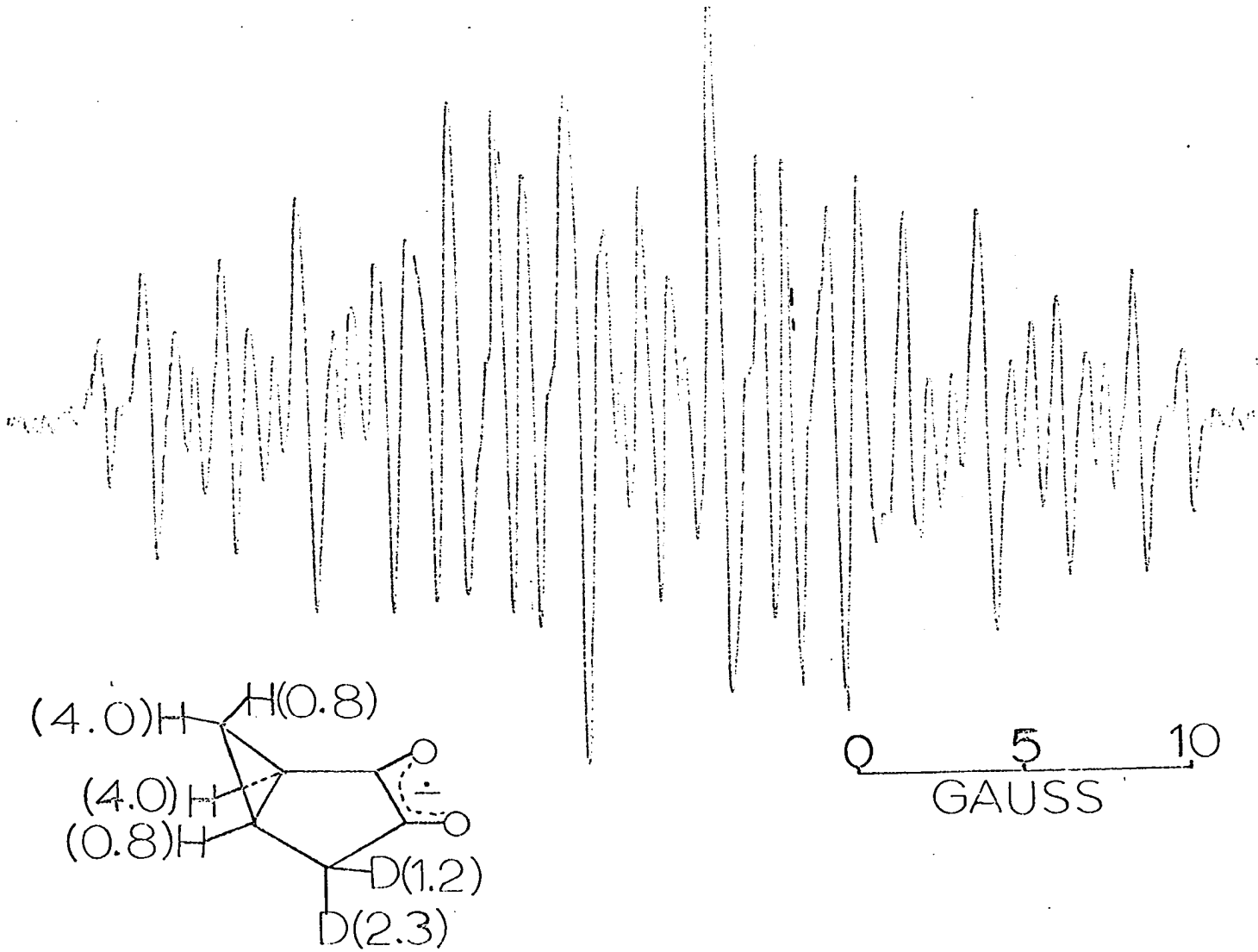
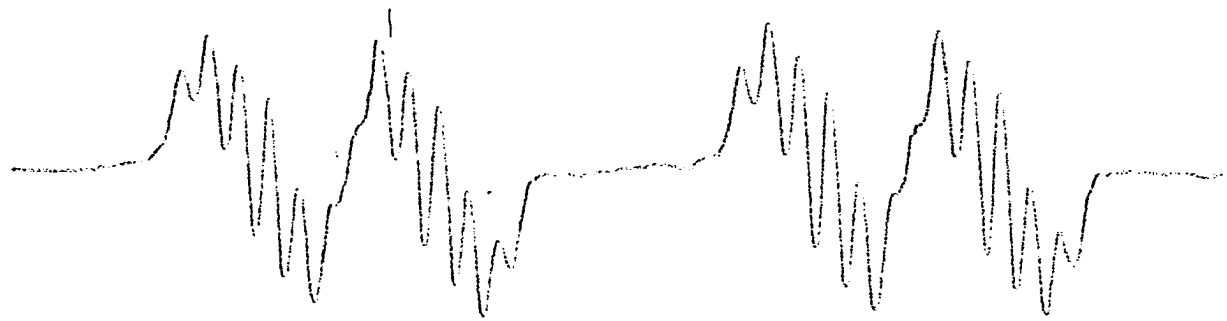
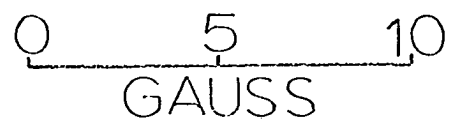

(4.0)H
H(0.8)
(4.0)H
(0.8)H
D(1.2)
D(2.3)
0
5
10
GAUSS

Figure 3. First derivative ESR spectrum of tricyclo[7.1.0.$0^{4,10}$]decan-2,3-semidione prepared by oxidation of tricyclo[7.1.0.$0^{4,20}$]decan-2-one in DMSO containing a 3 to 1 molar ratio of potassium t-butoxide to ketone.




0
5
10
GAUSS

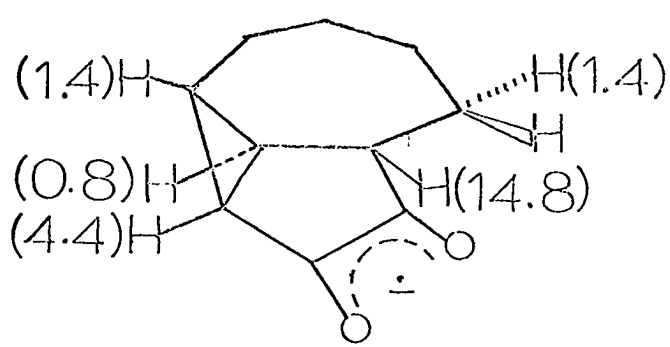

(1.4)H
H(1.4)
H
(0.8)H
H(14.8)
(4.4)H
O
O
·
−

Figure 4. First derivative ESR spectrum of 1-methylbicyclo[3.1.0]hexane semidione prepared by oxidation of 1-methylbicyclo[3.1.0]hexan-2-one in DMSO containing a 3 to 1 molar ratio of potassium t-butoxide to ketone.

0 5 10
GAUSS

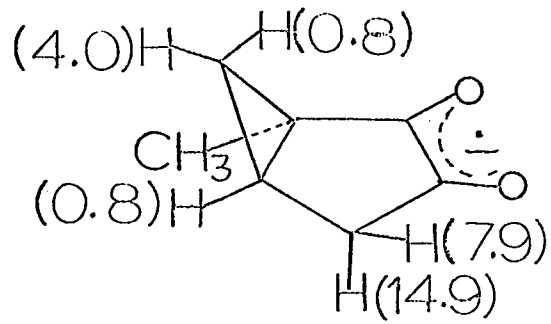
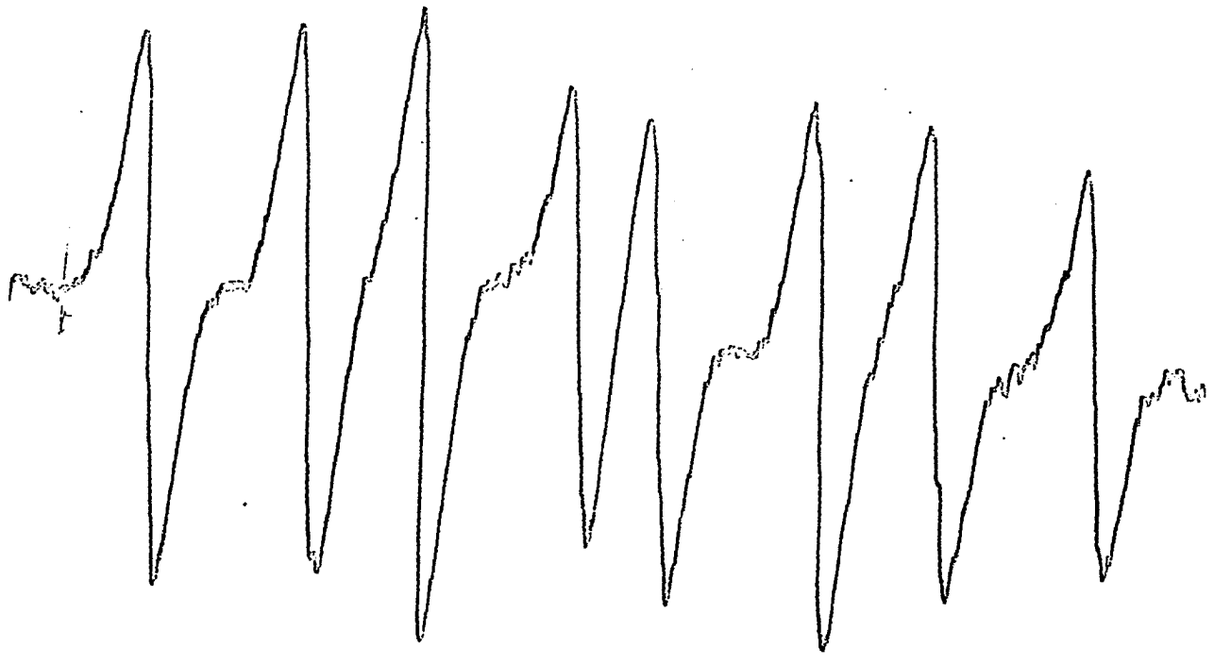
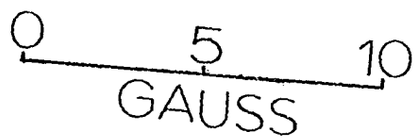


Figure 5. First derivative ESR spectrum of 1-ethyl-5-methylbicyclo[3.1.0]hexane semidione prepared by oxidation of 1-ethyl-5-methylbicyclo[3.1.0]hexan-2-one in DMSO containing a 3 to 1 molar ratio of potassium t-butoxide to ketone.




0
5
10
GAUSS

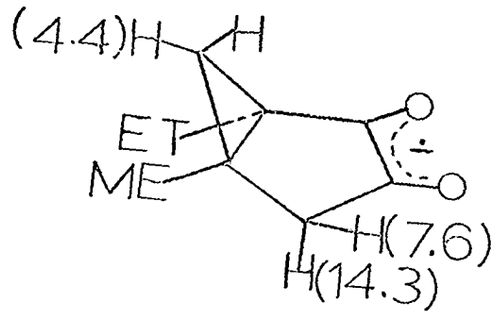
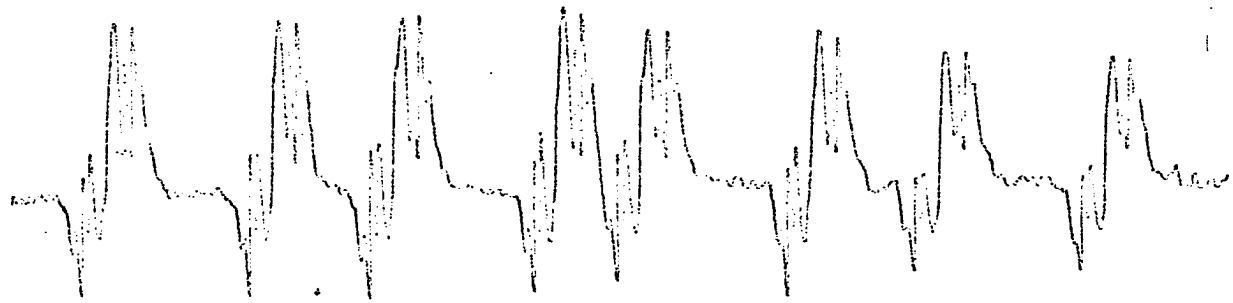
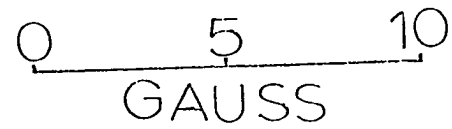

(4.4)H
H
ET
ME
O
O
H(7.6)
H(14.3)

Figure 6. First derivative ESR spectrum of tricyclo[4.3.1.0]decan-3-ene-7,8-semidione prepared by oxidation of tricyclo[4.3.1.0]decan-3-en-8-one in DMSO containing a 3 to 1 molar ratio of potassium t-butoxide to ketone.




0
5
10
GAUSS

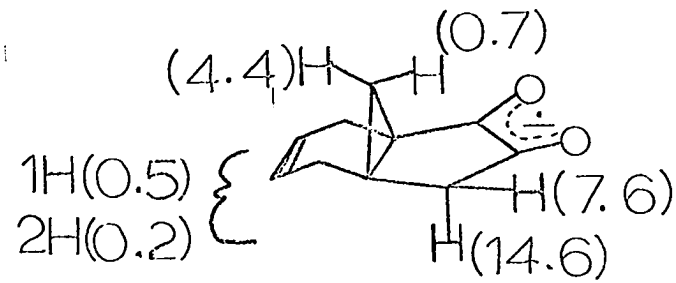
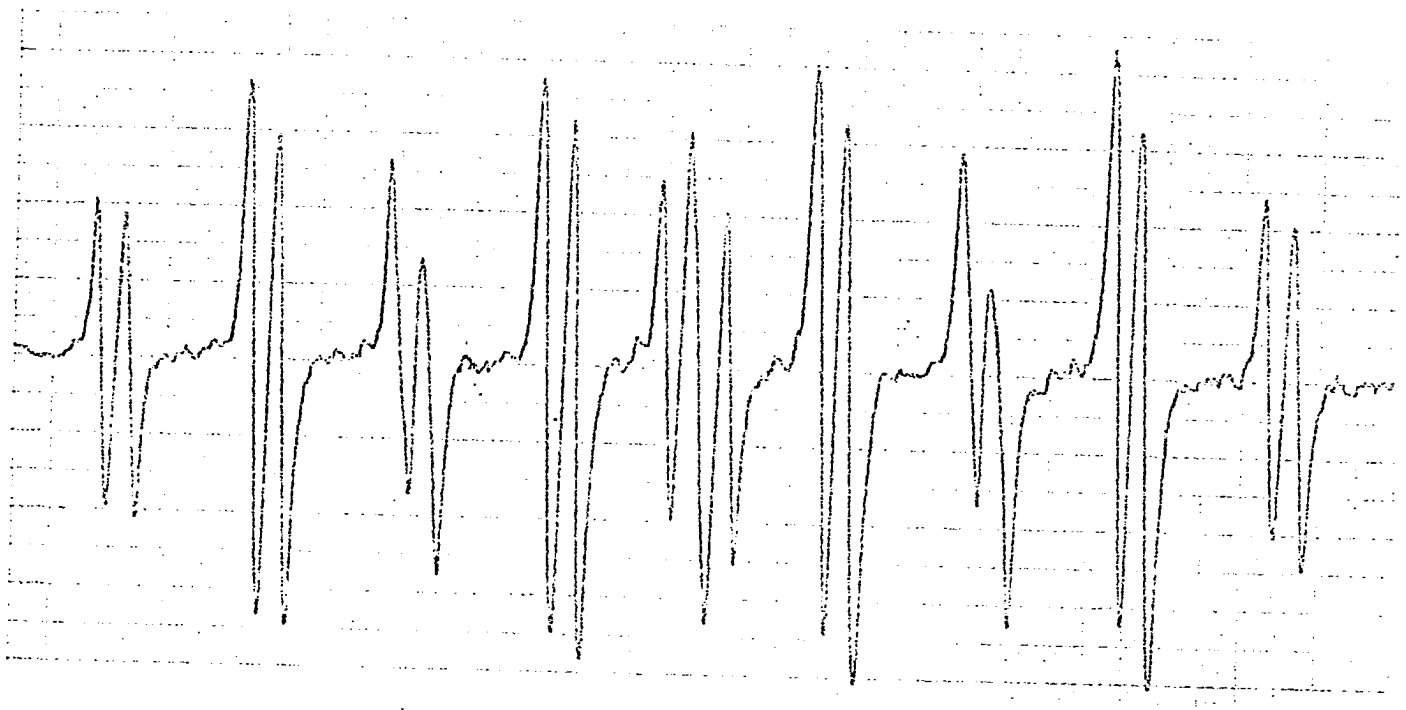

(0.7)
(4.4)H
H
O
O
1H(0.5)
2H(0.2)
H(7.6)
H(14.6)

Figure 7. First derivative ESR spectrum of syn-6-deuteriobicyclo[3.1.0]hexane semidione prepared by oxidation of syn-6-deuteriobicyclo[3.1.0]hexan-3-one in DMSO containing a 3 to 1 molar ratio of potassium t-butoxide to ketone.


0 5 10
GAUSS

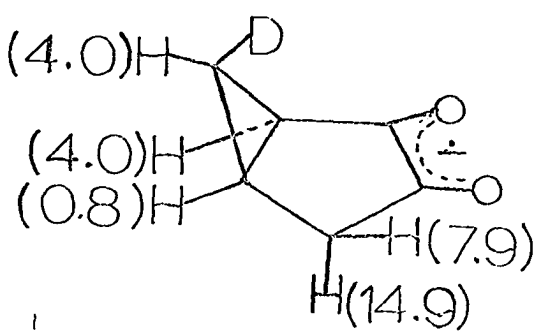
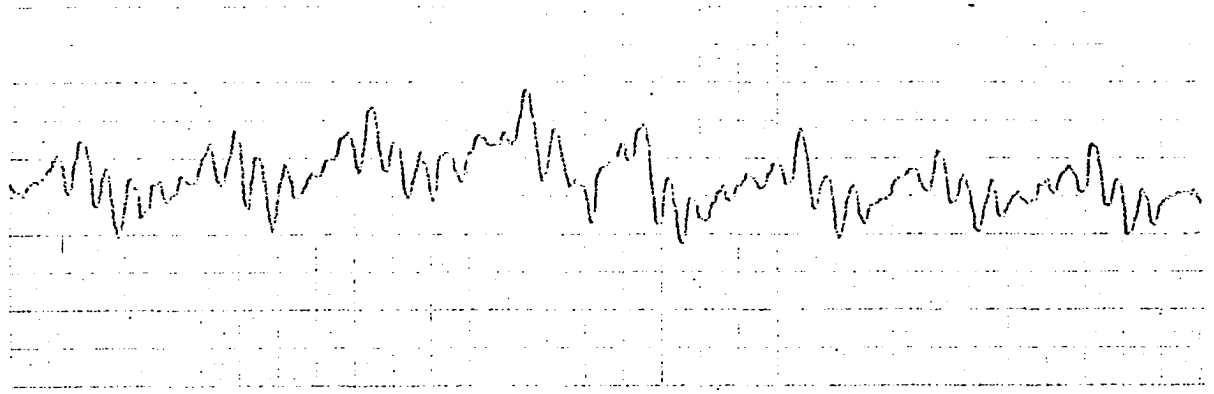
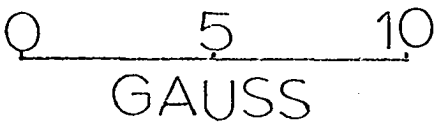

(4.0)H
D
(4.0)H
(0.8)H
O
O
H(7.9)
H(14.9)

Figure 8. First derivative ESR spectrum of 6,6-dideuteriobicyclo[3.1.0]hexane semidione prepared by oxidation of 6,6-dideuteriobicyclo[3.1.0]hexan-2-one in DMSO containing a 3 to 1 molar ratio of potassium t-butoxide to ketone.




0
5
10
GAUSS

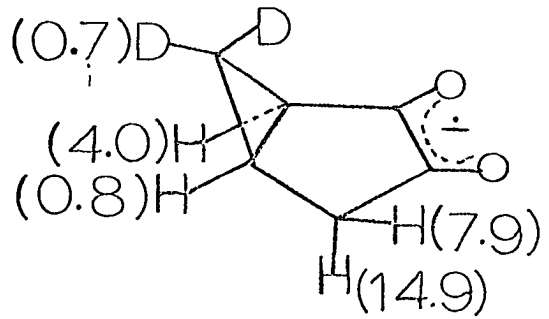

(0.7)D
D
O
(4.0)H
O
(0.8)H
H(7.9)
H(14.9)

Figure 9. First derivative ESR spectrum of bicyclo[4.1.0]heptane 2,3 semidione prepared by oxidation of the corresponding α-hydroxy ketone in DMSO containing a 3 to 1 molar ratio of potassium t-butoxide to ketone.

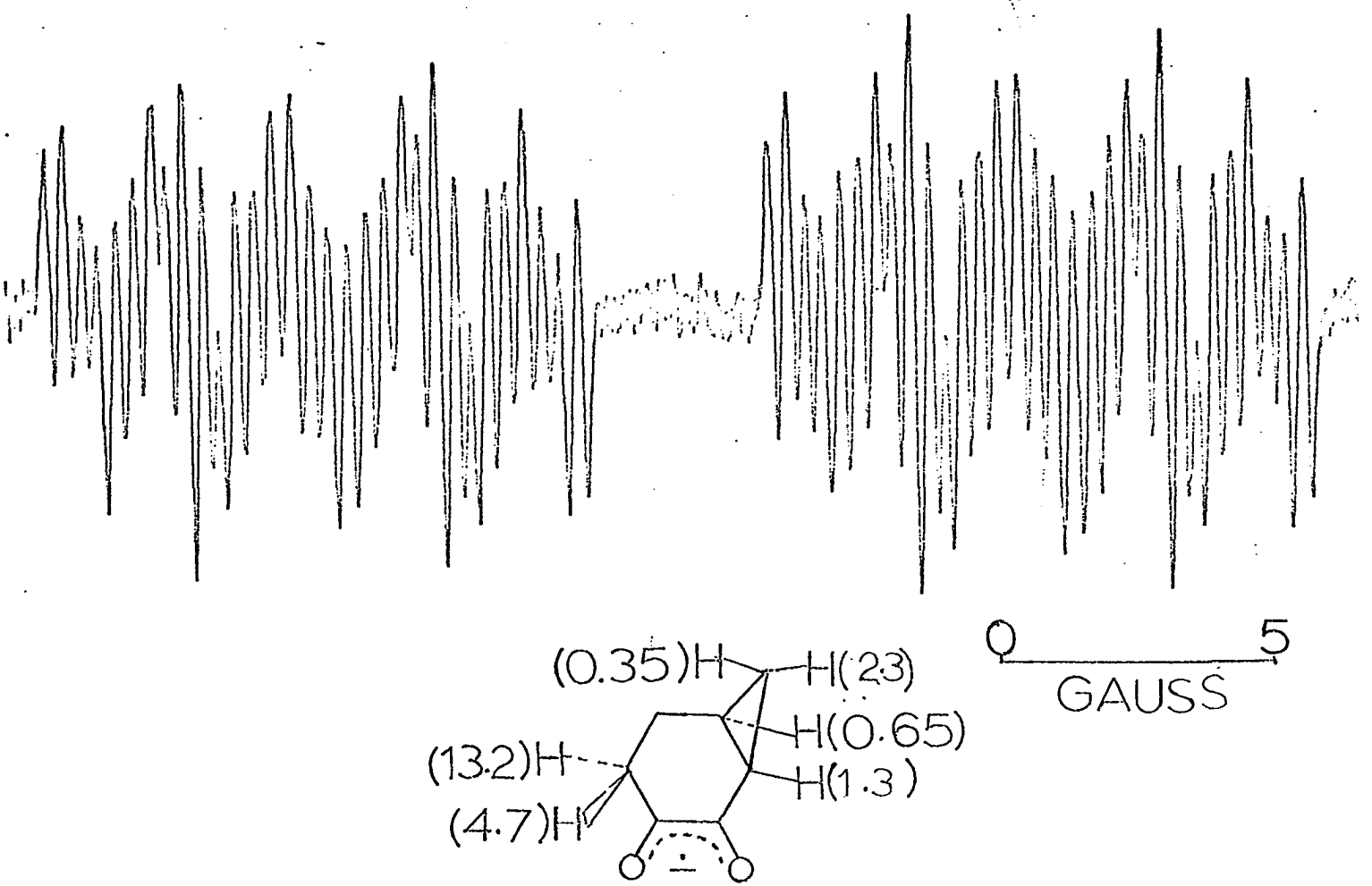
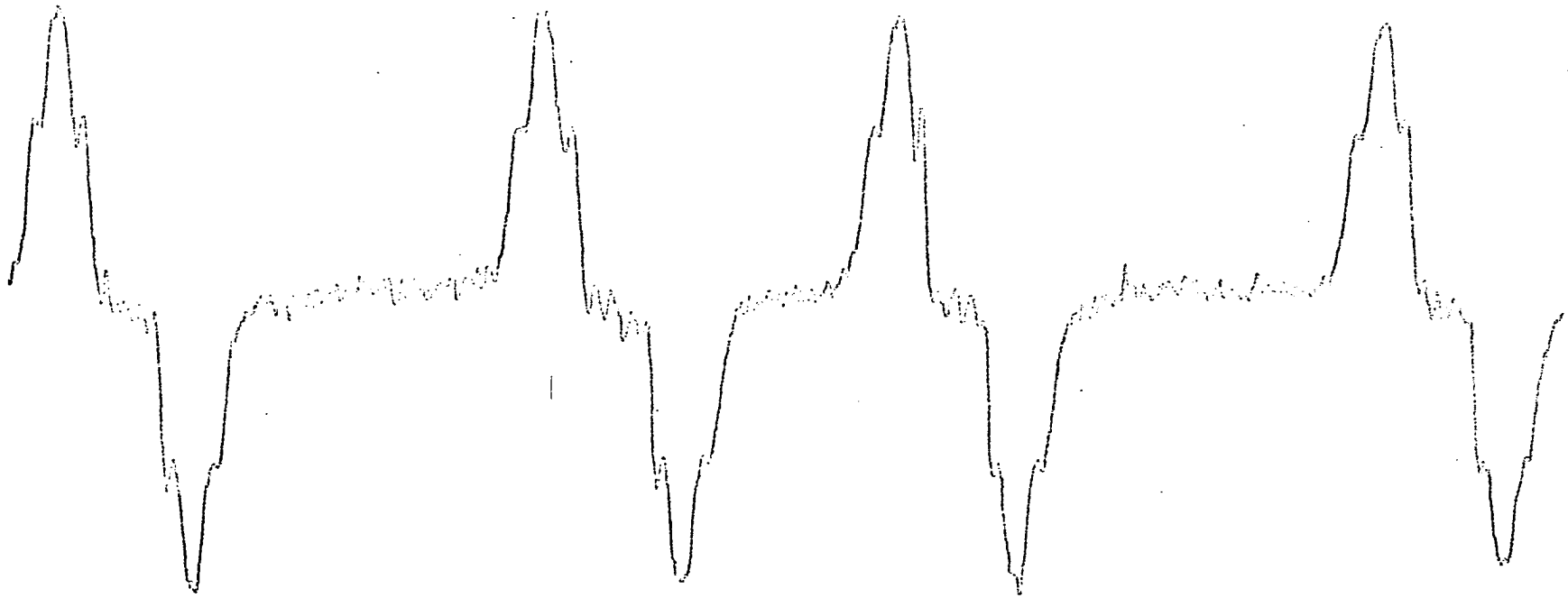

0
5
GAUSS
(0.35)H
H(2.3)
H(0.65)
H(1.3)
(13.2)H
(4.7)H

Figure 10. First derivative ESR spectrum of bicyclo[5.1.0]octane 2,3 semidione prepared by oxidation of bicyclo[5.1.0]octan-2-one in DMSO containing a 3 to 1 molar ratio of potassium t-butoxide to ketone.



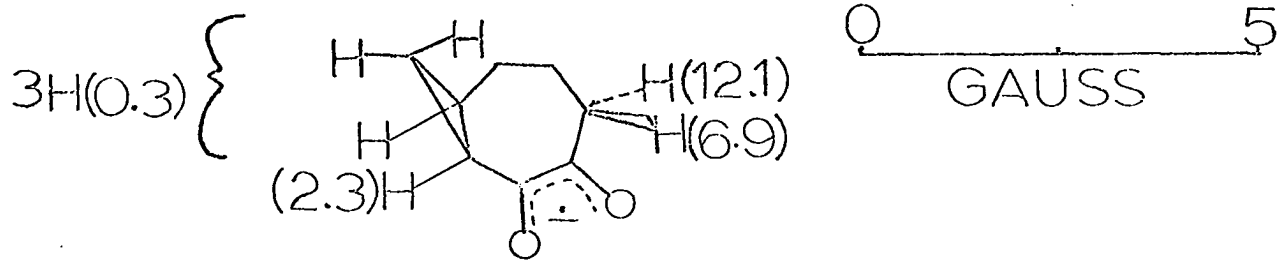

3H(0.3)
H
H
H
H(12.1)
H(6.9)
(2.3)H
O
O
0
5
GAUSS

Figure 11. First derivative ESR spectrum of bicyclo[6.1.0]nonane-2,3 semidione prepared by oxidation of bicyclo[6.1.0]nonan-2-one in DMSO containing a 3 to 1 molar ratio of potassium t-butoxide to ketone.

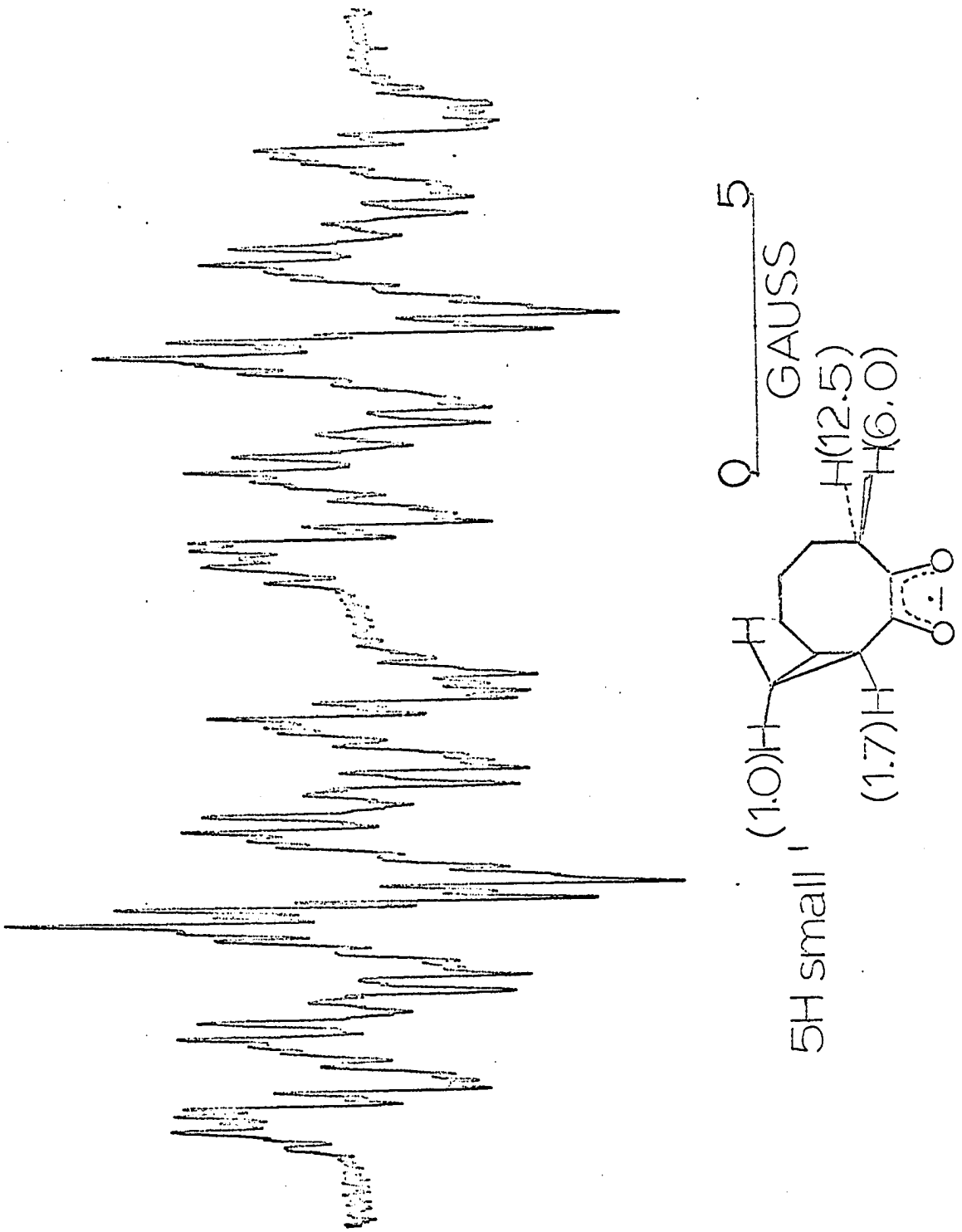
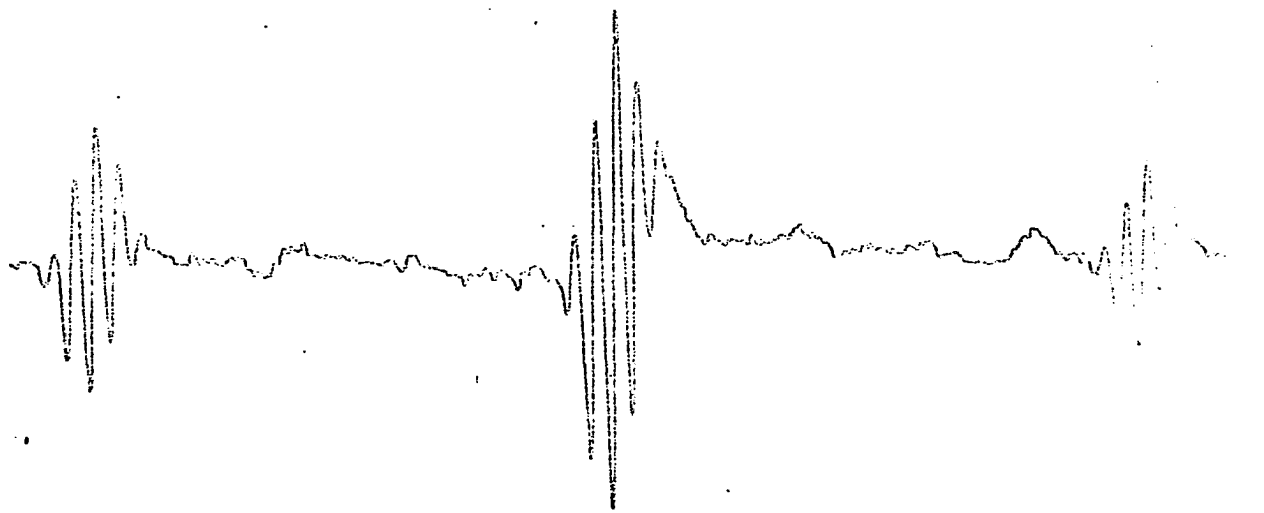
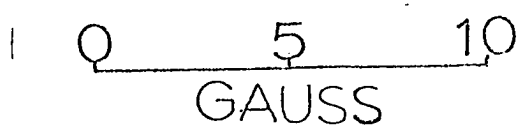

5
GAUSS
H(12.5)
H(6.0)
(1.0)H
(1.7)H
5H small I

Figure 12. First derivative ESR spectrum of spiro[2.4]heptane s idione prepared by oxidation of 4-keto spiro[2.4]heptane in DMS containing a 3 to 1 molar ratio of potassium t-butoxide to ketone




0
5
10
GAUSS

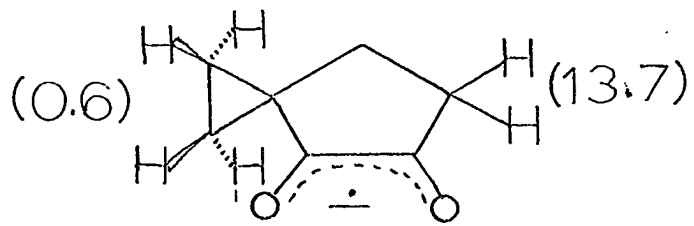
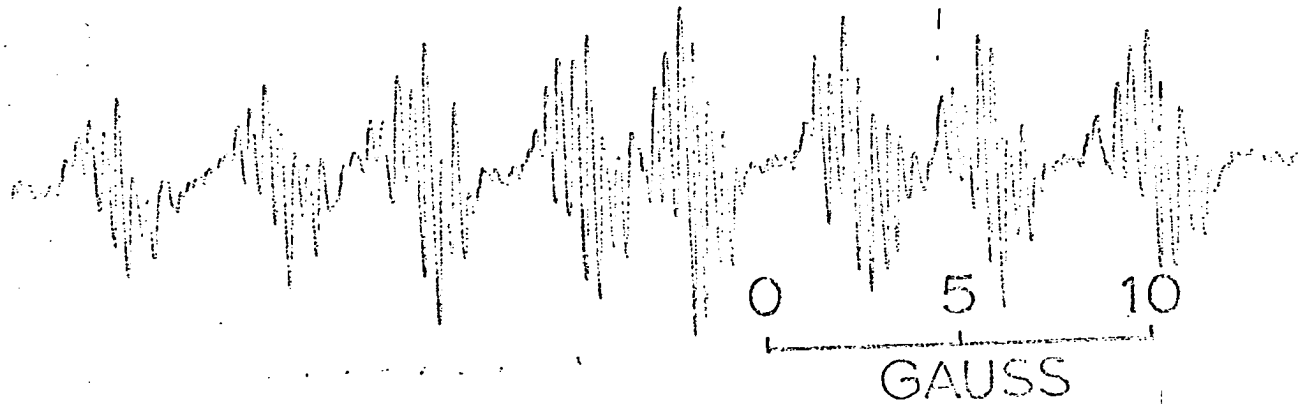

(0.6)
(13.7)

Figure 13. First derivative ESR spectrum of anti-6-methylbicyclo[3.1.0]hexane semidione prepared by oxidation of anti-6-methylbicyclo[3.1.0]hexan-2-one in DMSO containing a 3 to 1 molar ratio of potassium t-butoxide to ketone.


0
5
10
GAUSS

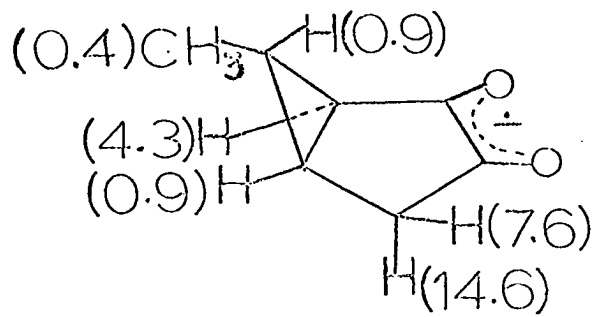
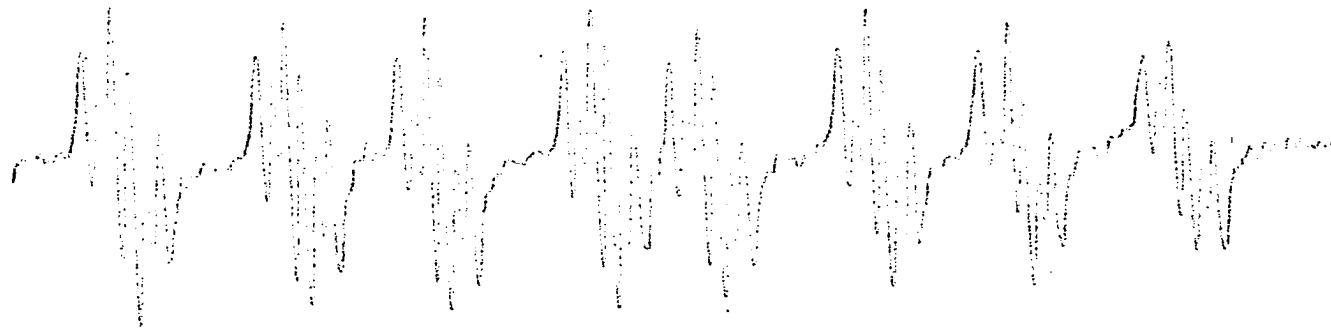
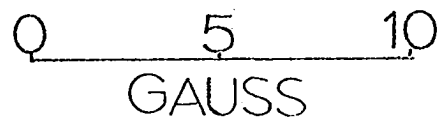

(0.4)CH3
H(0.9)
(4.3)H
(0.9)H
H(7.6)
H(14.6)

Figure 14. First derivative ESR spectrum of anti-6-ethylbicyclo[3.1.0]hexane semidione prepared by oxidation of syn or anti-6-ethylbicyclo[3.1.0]-hexan-2-on in DMSO containing a 3 to 1 molar ratio of potassium t-butoxide to ketone.




0
5
10
GAUSS

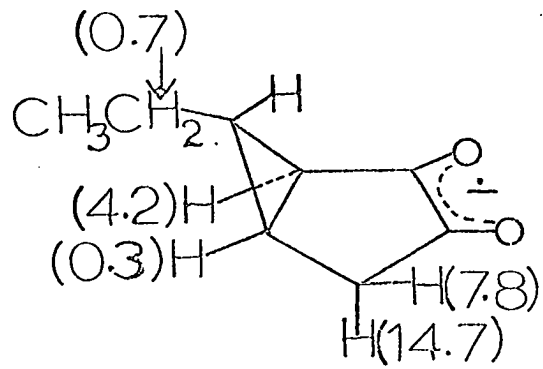
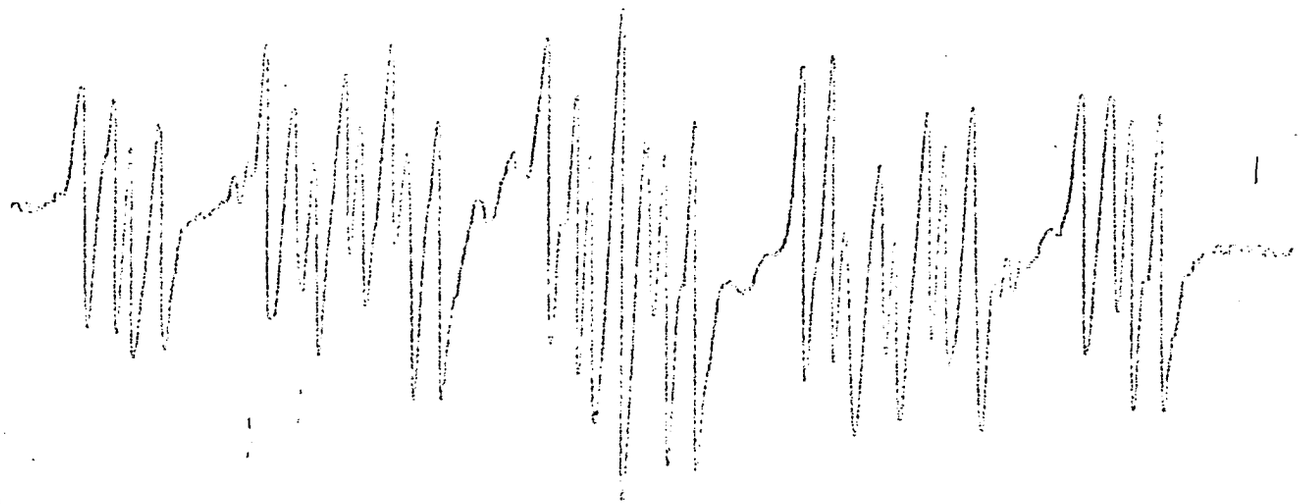
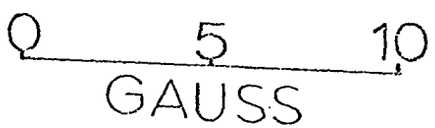

(0.7)
CH3CH2.
H
(4.2)H
(0.3)H
H(7.8)
H(14.7)

Figure 15. First derivative ESR spectrum of 6,6-dimethylbicyclo[3.1.0]hexane semidione prepared by oxidation of 6,6-dimethylbicyclo[3.1.0]hexan-2-one in DMSO containing a 3 to 1 molar ratio of potassium t-butoxide to ketone.


0
5
10
GAUSS
(0.4)CH3
CH3
(5.1)H
(0.9)H
H(7.6)
H(14.6)

Figure 16. First derivative ESR spectrum of syn-6-methylbicyclo[3.1.0]hexane semidione prepared by oxidation of syn-6-methylbicyclo[3.1.0]hexan-2-one in DMSO containing a 3 to 1 molar ratio of potassium t-butoxide to ketone.




0
5
10
GAUSS

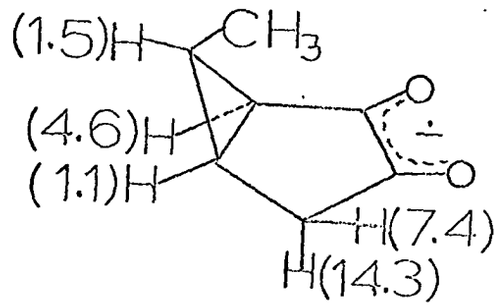
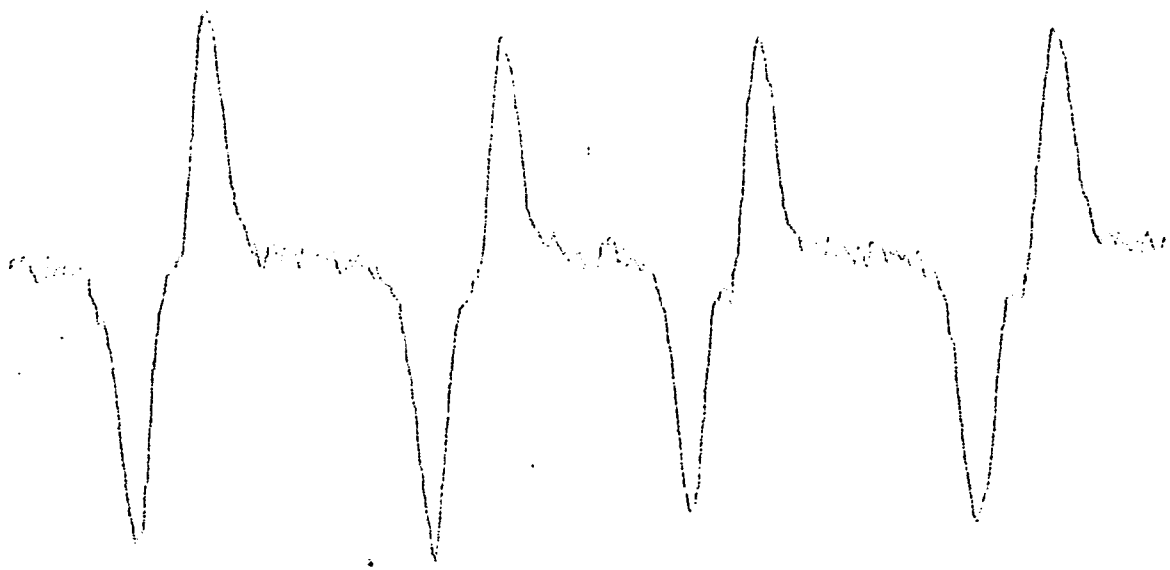
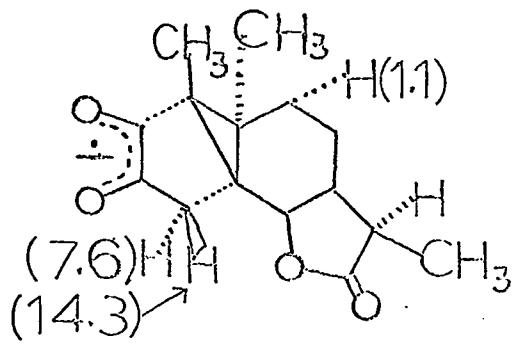

(1.5)H
CH3
(4.6)H
(1.1)H
O
O
H(7.4)
H(14.3)

Figure 17. First derivative ESR spectrum of the semidione derived from dihydrolumisantoin. The oxidation was performed in DMSO containing a 3 to 1 molar ratio of potassium t-butoxide to ketone.




CH3
CH3
H(1.1)
H
(7.6)H
H
(14.3)
CH3
O
O
O
O

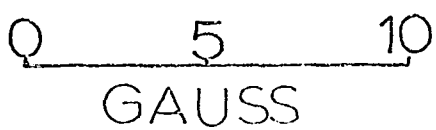
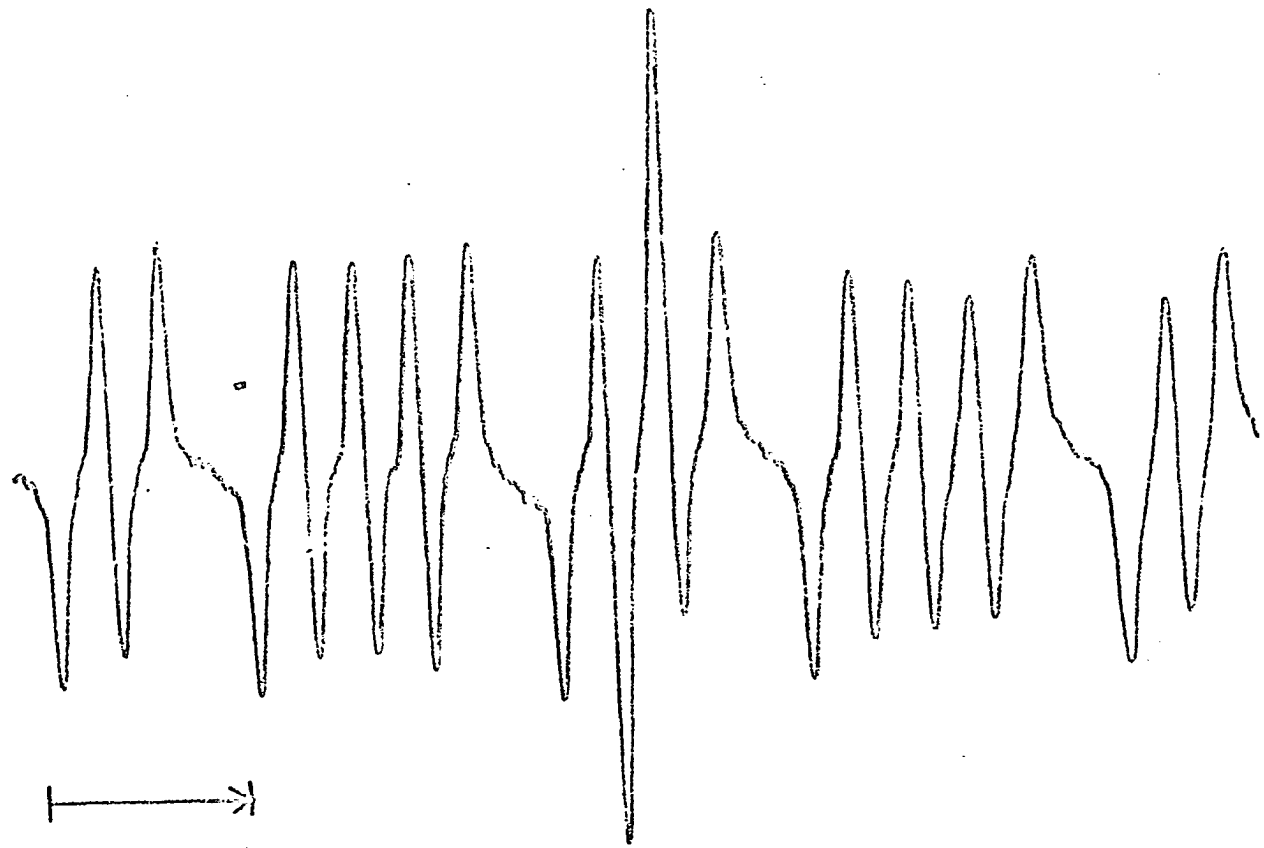

0
5
10
GAUSS

Figure 18. First derivative ESR spectrum of the semidione derived from photo-testosterone. The oxidation was performed in DMSO containing a 3 to 1 molar ratio of potassium t-butoxide to ketone.



5 GAUSS

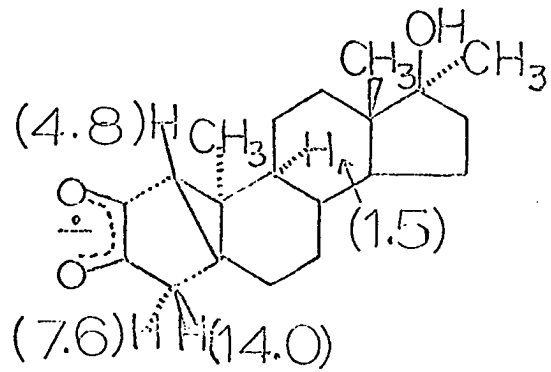
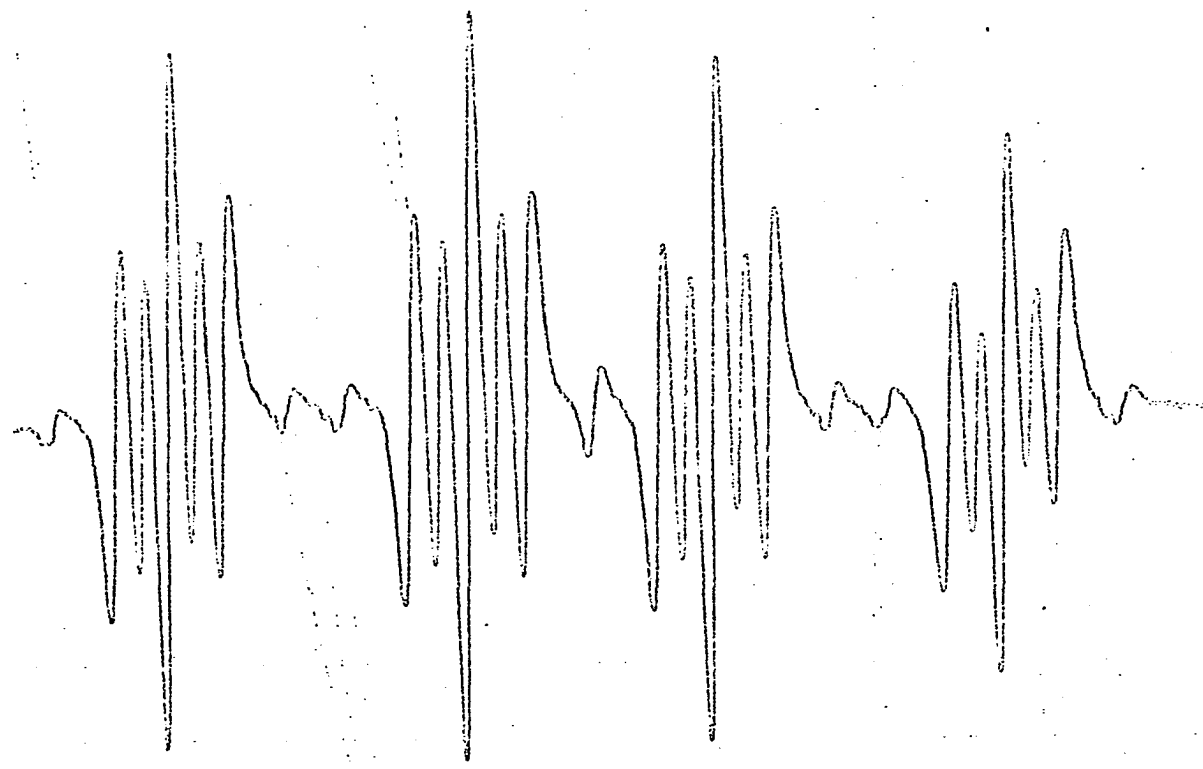
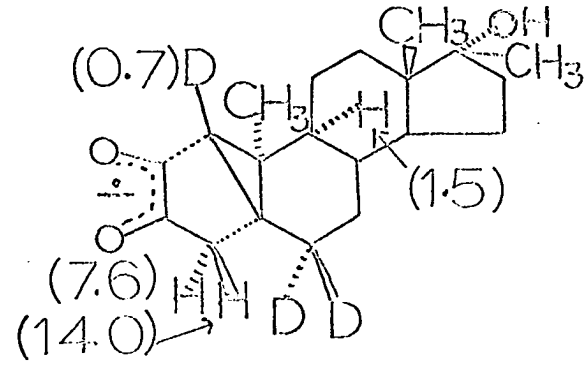


Figure 19. First derivative ESR spectrum of the semidione derived from photo-testosterone which has been deuterated as shown in the drawing. The oxidation was performed in DMSO containing a 3 to 1 molar ratio of potassium t-butoxide to ketone.




(0.7)D
CH3
OH
CH3
H
(1.5)
(7.6)
H
H
D
D
(14.0)

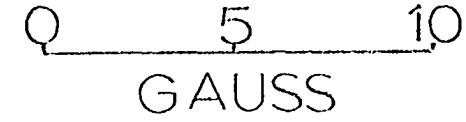

0
5
10
GAUSS

Figure 20. NMR spectra of 1-methylbicyclo[3.1.0]hexan-2-one, anti 6-methylbicyclo[3.1.0]hexan-2-one and syn 6-methylbicyclo[3.1.0]hexan-2-one in carbon tetrachloride.

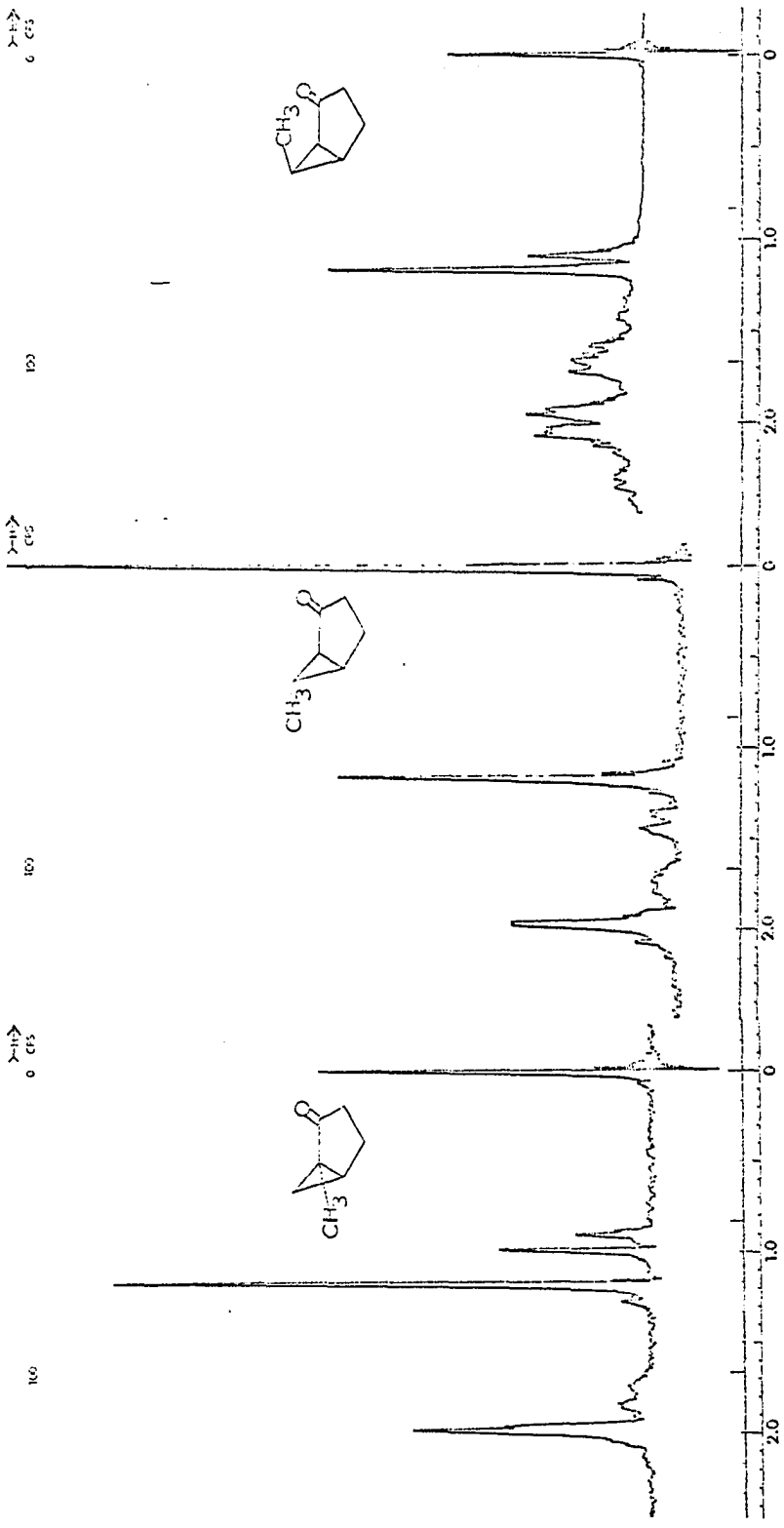
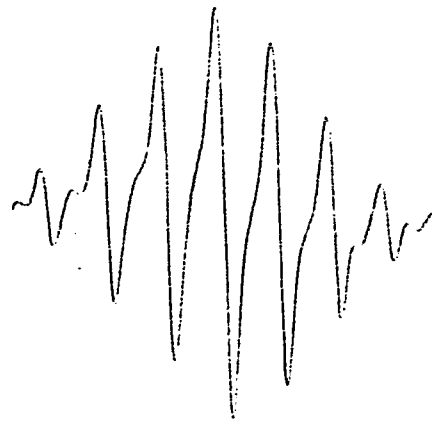
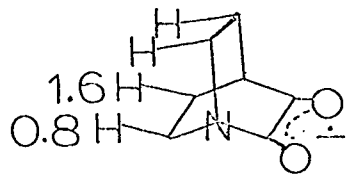

CH3
CH3
CH3
1.0
2.0
1.0
2.0
1.0
2.0

Figure 20a. First derivative ESR spectrum of 1-azabicyclo[2.2.2] semidione prepared by oxidation of quinuclidinone hydrochloride in DMSO containing a 4 to 1 molar ratio of potassium t-butoxide to ketone.

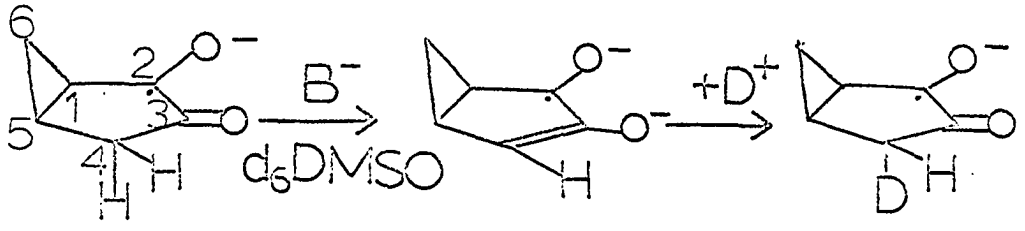


0 2.5
GAUSS



Hydrogen Deuterium Exchange

When bicyclo[3.1.0]hexan-2-ones are oxidized in basic d_6-DMSO solution, the three position must be oxidized before the four position hydrogens can be replaced by deuterium 52.



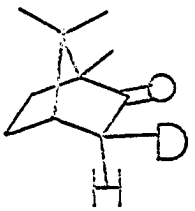
52

The hydrogen-deuterium exchange is remarkably stereoselective; the exo-4-methylene hydrogen is exchanged at a far greater rate than the endo-4-hydrogen. In most cases the exo-4-methylene hydrogen is exchanged exclusively. The ESR spectra (Figures 21, 22,23,24,25) of semidiones originating from 2-ketones indicate that only the exo-4-methylene hydrogen of about 14 gauss hfsc has been replaced by deuterium. This behavior is clearly unusual since the α methylene protons of cyclopentane and cyclohexane semidione exchange rapidly and quantitatively in basic d_6-DMSO solution.

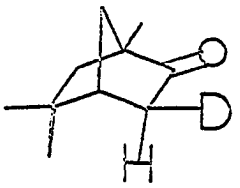
It is necessary to recall that all of the methylene protons of bicyclo[3.1.0]hex-3-one exchanged rapidly in basic d_6-DMSO solution. Steric accessibility of the α-methylene protons to the base does not appear to be a factor in governing

the stereoselectivity of the hydrogen-deuterium exchange.

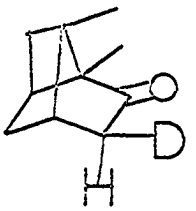
Stereoselective hydrogen-deuterium exchange in bicyclo-[2.2.1]α methylene ketones has previously been observed (39,40 41, 42). Camphor 53 exchanges the exo hydrogen four times



53

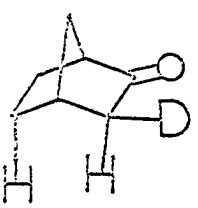


54

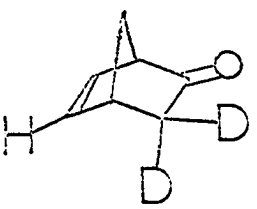


55

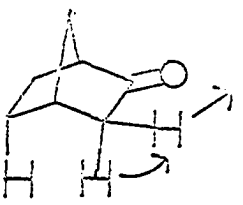
more rapidly than the endo hydrogen. Isofenchone 54 and carvonecamphor 55 exchange the exo hydrogen exclusively. Sunko (40) has attributed the stereoselectivity in 56 to the relief of non-bonded interactions between the 3 and 5 endo hydrogens in the transition state leading to the formation of the exo carbanion 58. Both α methylene hydrogens exchange in dehydrononcamphor 57.



56

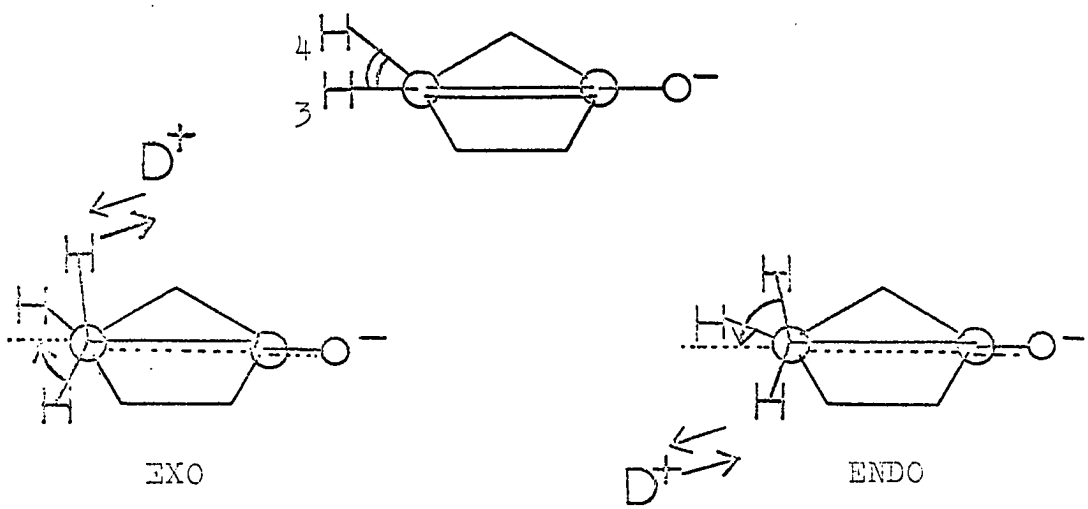


57



58

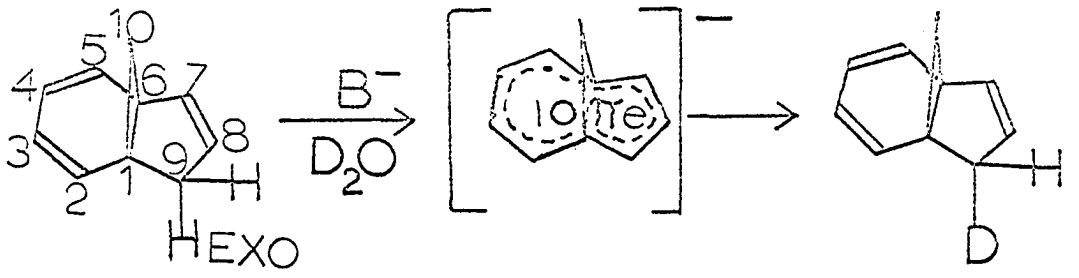
presumably because the same type of non-bonded interaction present in 56 is not available to promote selectivity in 57. Schleyer (42) has attributed the stereoselectivity of hydrogen-deuterium exchange in bicyclo[2.2.1] ketones to a torsional effect. Exo attack, 59, of D^+ on the enolate anion provides



59

a larger angle between hydrogens 3 and 4 in the transition state than does endo D^+ attack. The stereoselectivity of hydrogen-deuterium exchange of the α methylene hydrogens in the bicyclo[2.2.1] ketone appears to be critically dependent on very small changes in geometry.

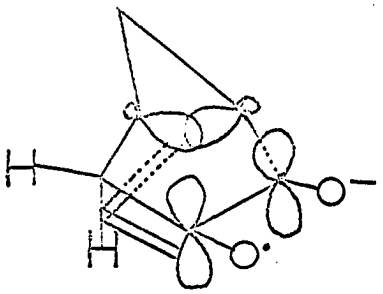
Radlick and Rosen (43) discuss a stereoselective hydrogen deuterium exchange more closely related to the one observed in bicyclo[3.1.0]hexane semidione. Tricyclo[4.3.1.0]-deca-2,4,7-triene 60 incorporates deuterium exclusively in the exo-9-position under a variety of basic conditions.



60

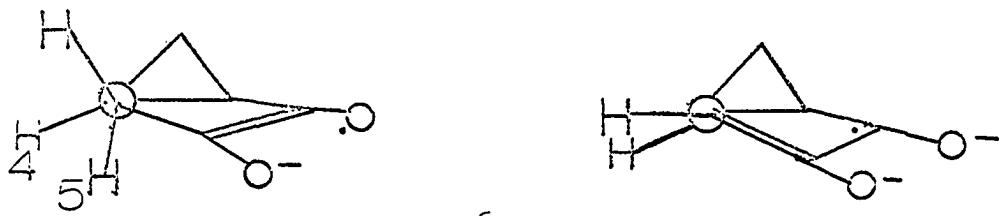
Radlick and Rosen contend that the stereospecificity of the exchange of hydrogen for deuterium is due to the rigid stereo electronic requirement that the cyclopropane ring places upon the molecule. In their opinion, the exo hydrogen is more readily abstracted by base than the endo hydrogen because the electron pair in the orbital between C-9 and the exo hydrogen can overlap much more efficiently in the transition state with the electron pair of the cyclopropane C_1-C_6 bond than can the C-9-endo hydrogen bond.

As mentioned earlier in the semidione the Heller-McConnell equation predicts the 14.9 gauss α-methylene hydrogen to be quasi-axial and the 7.9 gauss hydrogen to be quasi-equatorial. Stabilization of the transition state leading to the formation of the exo carbanion by more efficient overlap with the semidione π system as well as the internal cyclopropyl bond can 61 readily be envisioned. Application of tortional effects described by Schleyer also predict the exo hydrogen to be more easily removed and then replaced according to the principle of



61

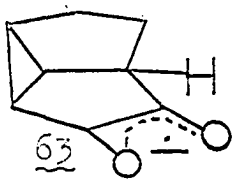
microscopic reversibility 62 . Removal of the exo hydrogen



62

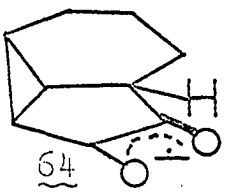
requires only a slight readjustment of the position of the endo hydrogen to achieve the enolate dianion structure. Removal of the endo hydrogen requires an eclipsing interaction between hydrogen 4 and 5 to achieve the enolate dianion structure.

The ESR spectra of tricyclo semidiones (Figures 26, 27, 28) indicate a relationship between structure, acidity and hfsc of bridgehead α-methine hydrogens. The acidity of the α-methine hydrogens increases in the series 63<64<65 as indicated by the time for hydrogen deuterium exchange in d_6-DMSO. The Heller-McConnell relationship predicts the hfsc of the α-methine hydrogen to increase as the methine C-H bond becomes more



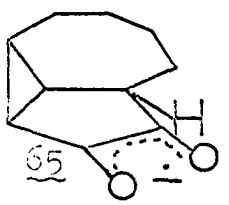
63

hfsc gauss	time for H→D
9.4	> 24 hrs.



64

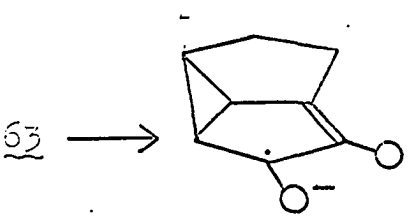
12.1	3 hrs.



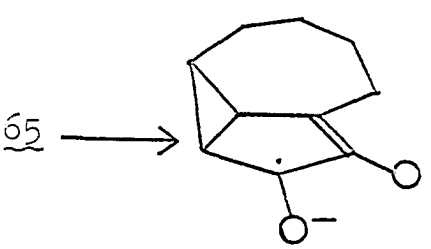
65

14.8	< 1 min.

perfectly coplanar with the semidione π system. In semidione 63 the α-methine hydrogen is rigidly held in less than an axial configuration, a^H = 9.6 gauss. Bredt's rule considerations predict enolate structure 66 to be very forbidden and it is not surprising that the α-methine hydrogen in 63 is not acidic.



63 → 66



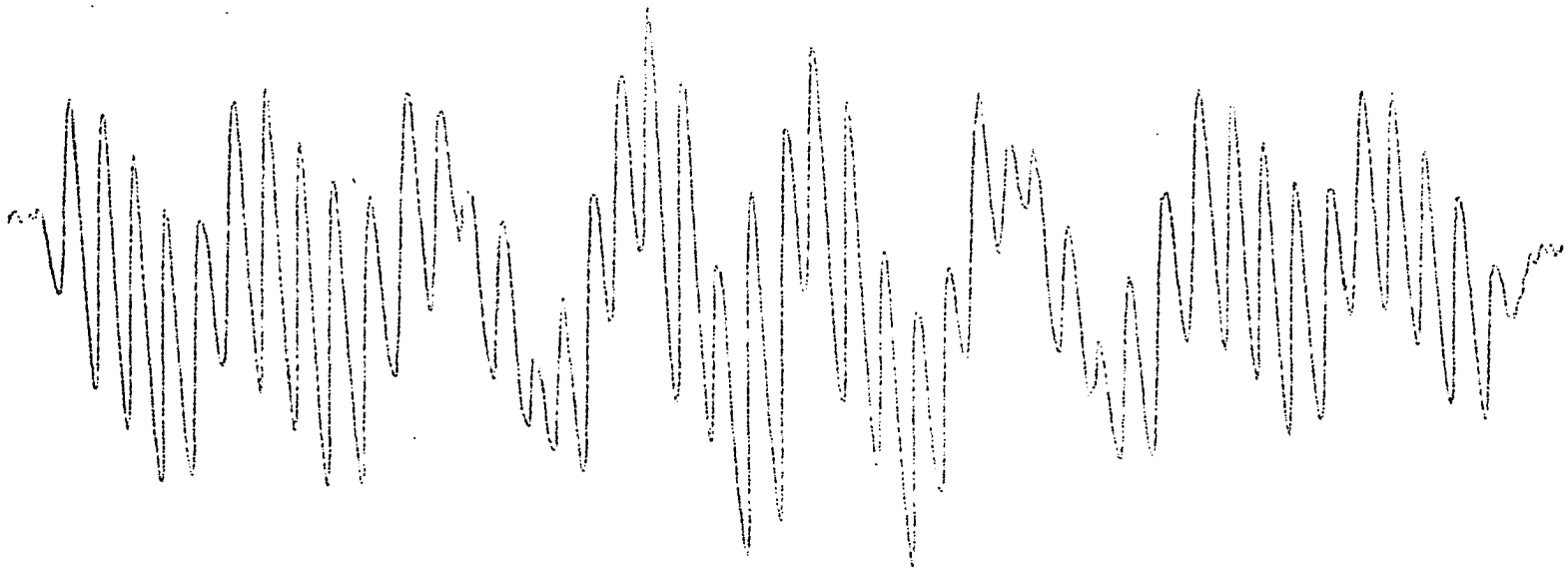
65 → 67

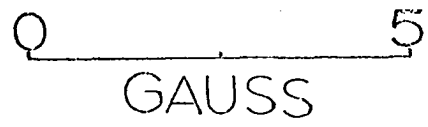
The α-methine hydrogen of semidione 65 apparently achieves a quasi-axial conformation a^H = 14.8 gauss. The rapid rate of hydrogen-deuterium exchange would indicate that enolate structure 67 is not forbidden.

The torsional effects described by Schleyer cannot be

ruled out as a contributing factor to the stereoselectivity of hydrogen-deuterium exchange in bicyclo[3.1.0]hexane semidiones. However, the ESR studies indicate that the conformation of the molecule is such that one of the α-methylene protons is quasi-axial and the other is quasi equatorial. The stabilization of the transition state leading to the formation of the exo-carbanion by overlap with the semidione, π system, as well as the cyclopropyl C_1-C_6 bond appears to be the major cause of stereoselective hydrogen deuterium exchange in the bicyclo[3.1.0]hexane semidiones.

Figure 21. First derivative ESR spectrum of 6,6-dimethyl exo 4 deuterio-bicyclo[3.1.0]hexane semidione prepared by oxidation of 6,6-dimethyl-bicyclo[3.1.0]hexan-2-one in d_6-DMSO containing a 3 to 1 molar ratio of potassium t-butoxide to ketone.




0
5
GAUSS

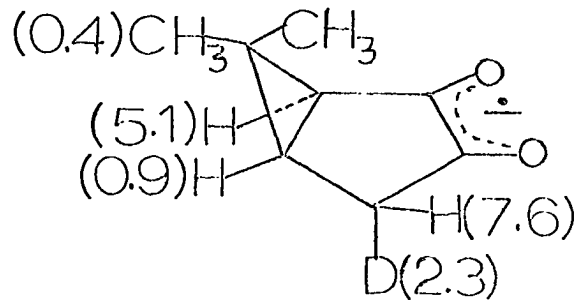
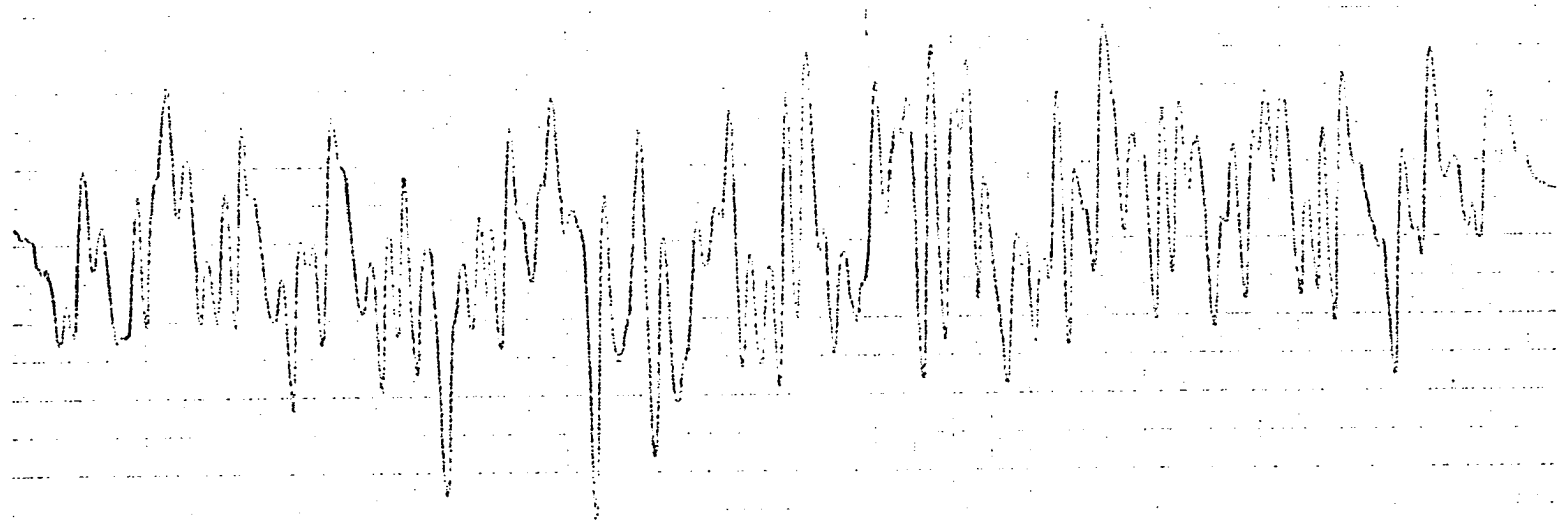
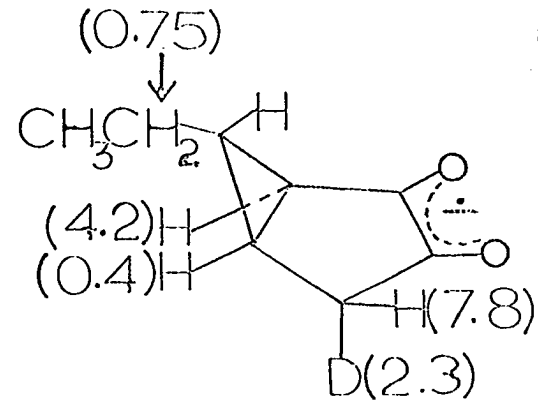

(0.4)CH3
CH3
(5.1)H
(0.9)H
H(7.6)
D(2.3)

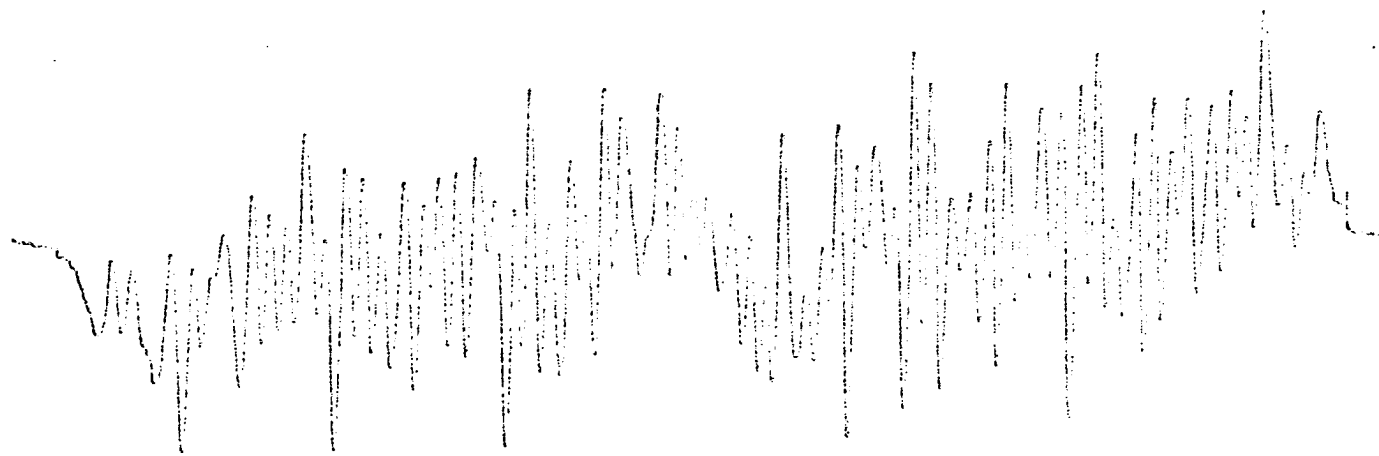
Figure 22. First derivative ESR spectrum of anti-6-ethyl-exo-4-deuteriobicyclo[3.1.0]hexane semidione prepared by oxidation of anti-6-ethylbicyclo[3.1.0]hexan-2-one in d_6-DMSO containing a 3 to 1 molar ratio of potassium t-butoxide to ketone.




(0.75)
CH3CH2
H
(4.2)H
(0.4)H
H(7.8)
D(2.3)


0
5
GAUSS

Figure 23. First derivative ESR spectrum of anti-6-ethyl-1, exo-4-dideuteriobicyclo[3.1.0]hexane semidione prepared by oxidation of 1-deuteriosyn-6-ethylbicyclo[3.1.0]hexan-2-one in d_6-DMSO containing a 3 to 1 molar ratio of potassium t-butoxide to ketone.




0
5
GAUSS

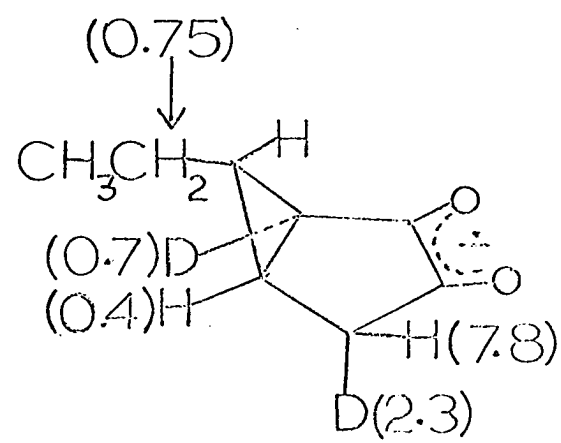

(0.75)
CH3CH2
H
O
(0.7)D
O
(0.4)H
H(7.8)
D(2.3)

Figure 24. First derivative ESR spectrum of 1-ethyl-*exo*-4-deuterio-5-methylbicyclo[3.1.0]hexane semidione prepared by oxidation of 1-ethyl-5-methylbicyclo[3.1.0]hexan-2-one in d_6-DMSO containing a 3 to 1 molar ratio of potassium *t*-butoxide to ketone.

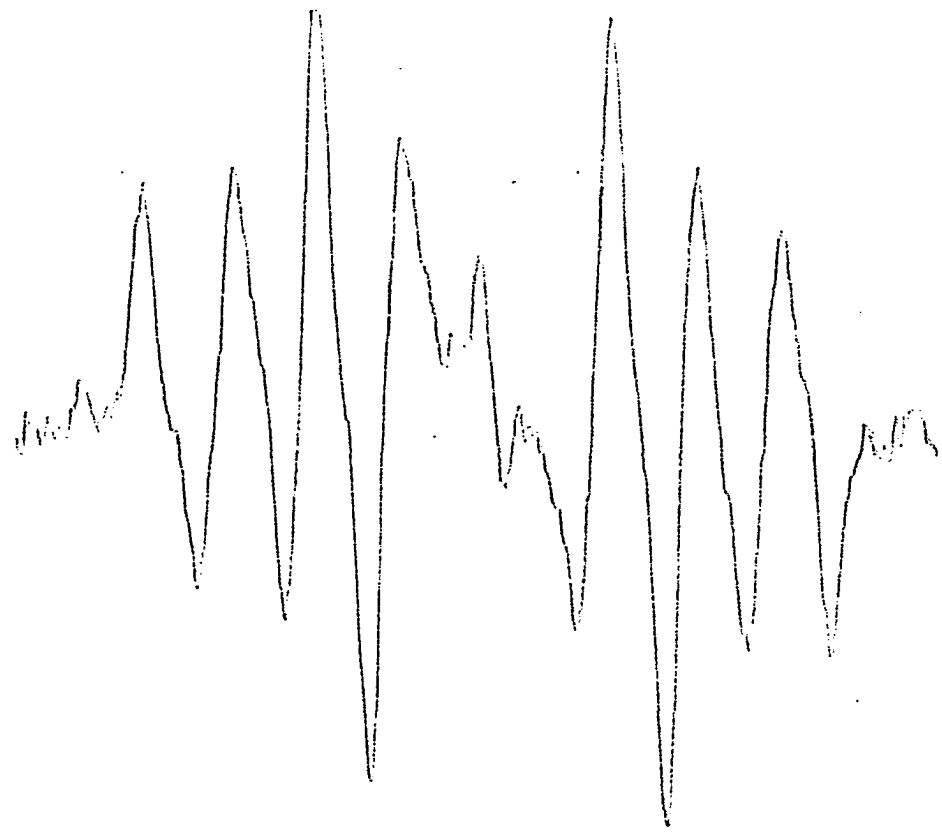
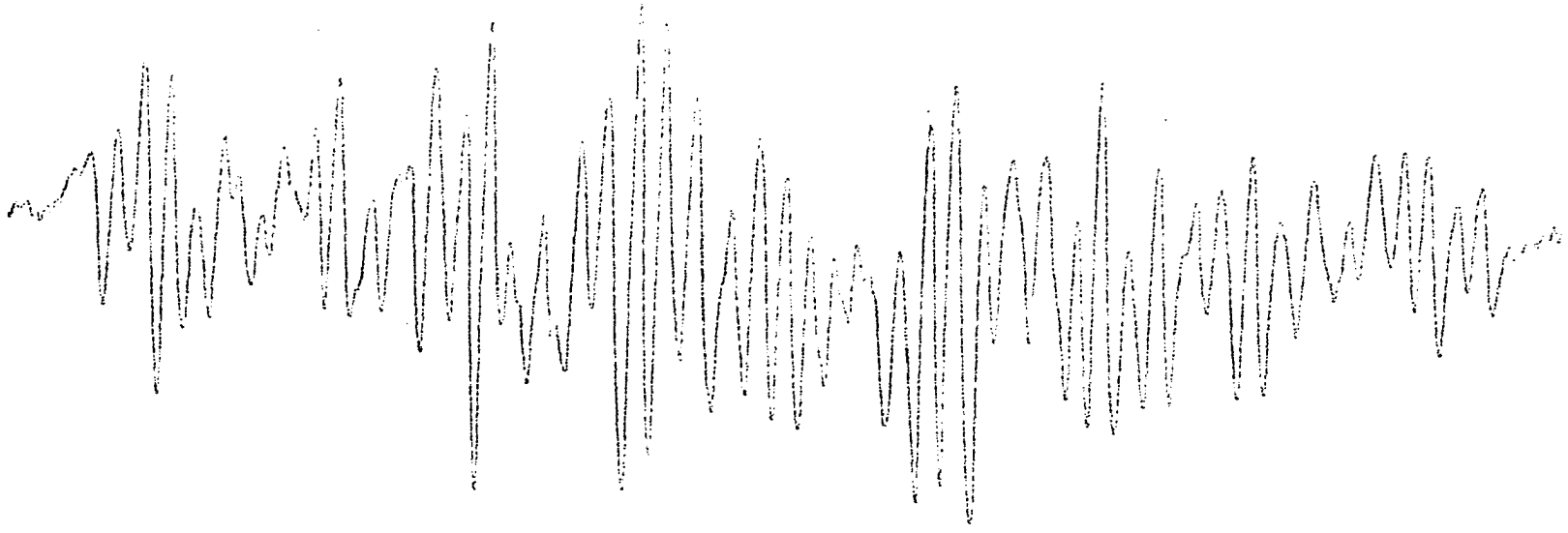
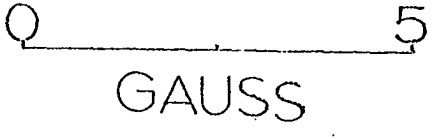

(4.4)H
H
ET
ME
H(7.6)
D(2.3)
O
O
0
5
10
GAUSS

Figure 25. First derivative ESR spectrum of syn-6-methyl-exo-4-deuteriobicyclo[3.1.0]hexane semidione prepared by oxidation of syn-6-methylbicyclo[3.1.0]hexan-2-one in d_6-DMSO containing a 3 to 1 molar ratio of potassium t-butoxide to ketone.




0
5
GAUSS

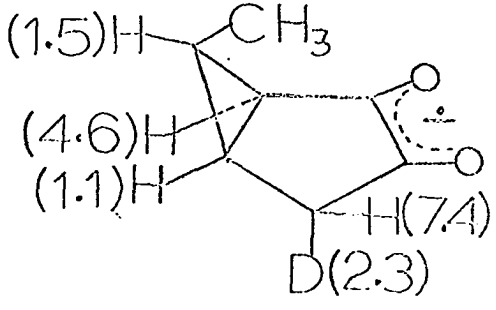
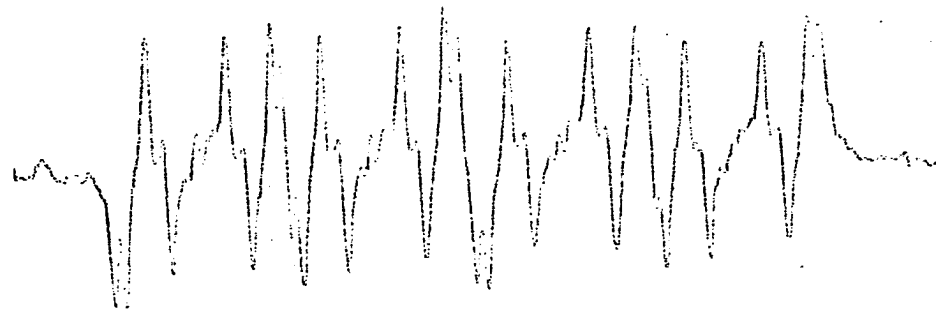
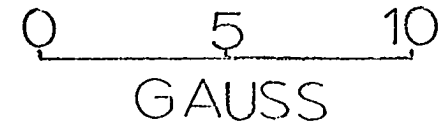

(1.5)H
CH3
(4.6)H
(1.1)H
H(7.4)
D(2.3)

Figure 26. First derivative ESR spectrum of tricyclo[5.1.0.$0^{4,8}$]octane semidione prepared by oxidation of tricyclo[5.1.0.$0^{4,8}$]octan-2-one in $\underline{d}_6$-DMSO containing a 3 to 1 molar ratio of potassium $\underline{t}$-butoxide to ketone. The identical spectrum was observed when the oxidation was conducted in DMSO.




0
5
10
GAUSS

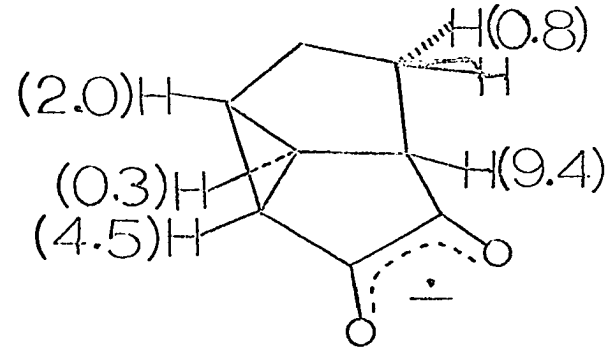
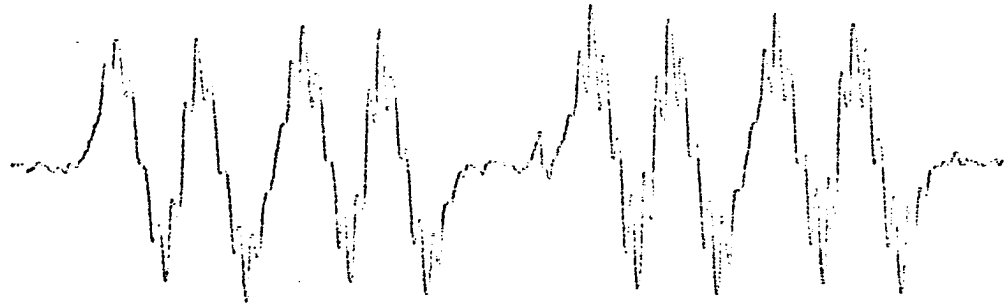

H(0.8)
H
(2.0)H
H(9.4)
(0.3)H
(4.5)H
O
O
•
−

Figure 27. First derivative ESR spectrum of tricyclo[6.1.0.$0^{4,9}$]nonane-2,3-semidione prepared by oxidation of tricyclo[6.1.0.$0^{4,9}$]nonan-2-one in DMSO containing a 3 to 1 molar ratio of potassium t-butoxide to ketone. The 12.6 gauss hydrogen splitting was completely replaced by deuterium splitting in 3 hours when the oxidation was conducted in d_6-DMSO.



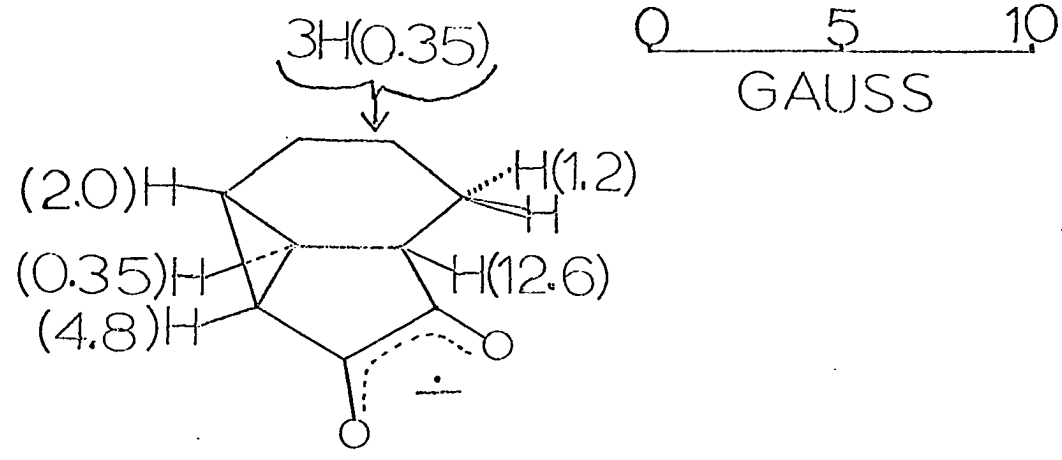
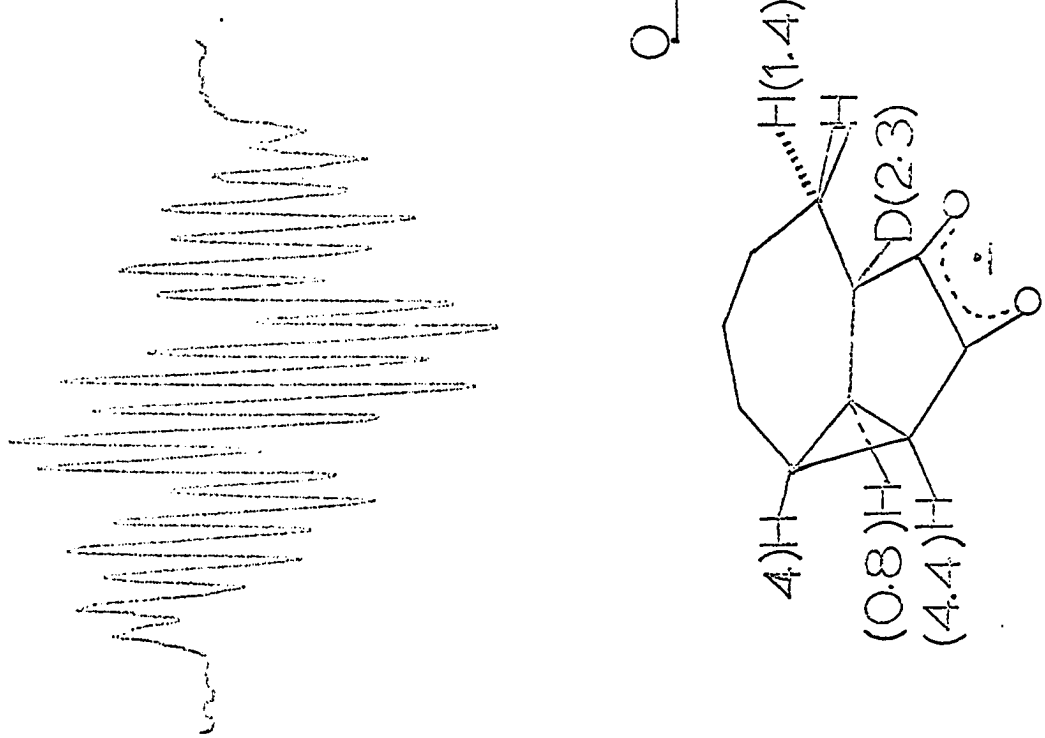
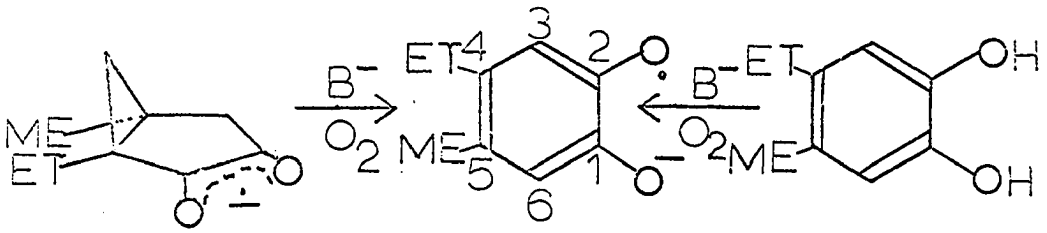

3H(0.35)
0
5
10
GAUSS
(2.0)H
H(1.2)
H
(0.35)H
H(12.6)
(4.8)H
O
O
·

Figure 28. First derivative ESR spectrum of 4-deuteriotricyclo[7.1.0.$0^{4,10}$]-decane-2,3-semidione prepared by oxidation of tricyclo[7.1.0.$0^{4,10}$]-decan-2-one in $\underline{d}_6$-DMSO containing a 3 to 1 molar ratio of potassium $\underline{t}$-butoxide.


0
5
10
GAUSS
H(1.4)
H
D(2.3)
O
O
4)H
(0.8)H
(4.4)H

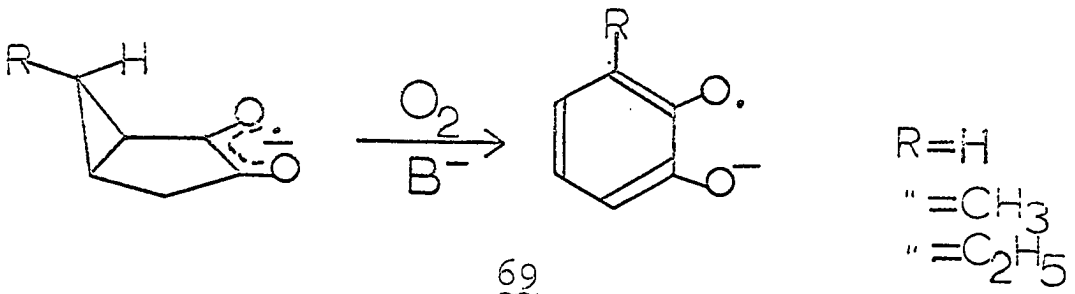
Molecular Rearrangements

Exposure of 1-ethyl-5-methylbicyclo[3.1.0]hexane semidione to excess oxygen results in the disappearance of the semidione and the appearance of a new paramagnetic species. The structure of the new paramagnetic species was identified as 4-ethyl-5-methyl-o-semiquinone (Figure 29) by independent oxidation of the corresponding 4-ethyl-5-methylcatechol 68.



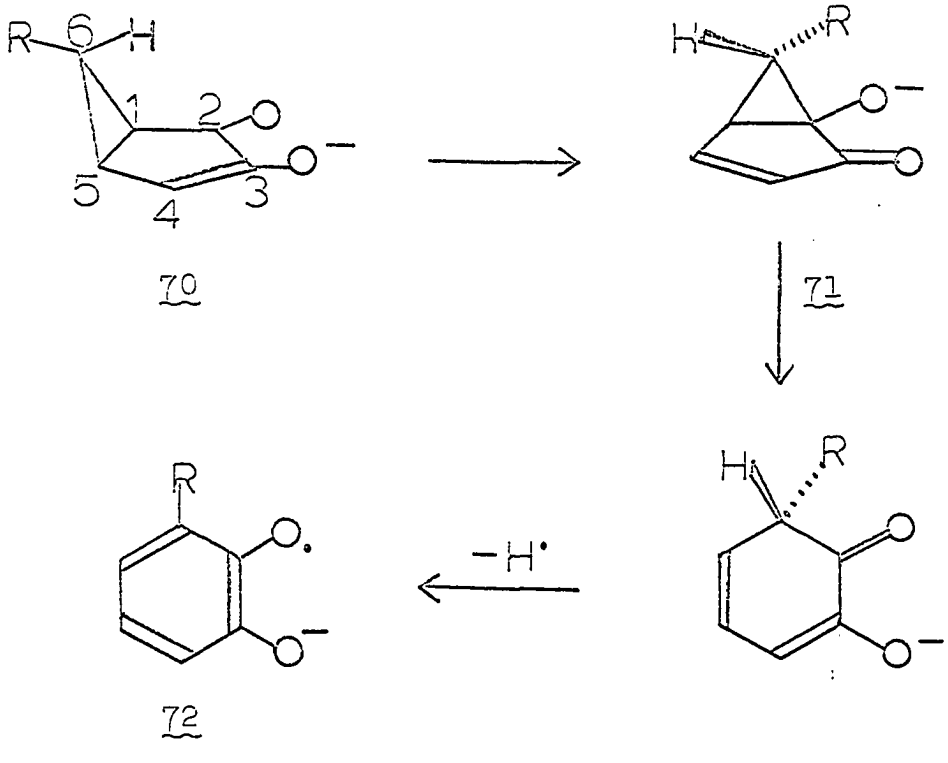
68

Semidiones with alkyl substituents at C-6 over oxidize to o-quinones with alkyl substituents in the 3-position 69 (Figures 30, 31, 32).



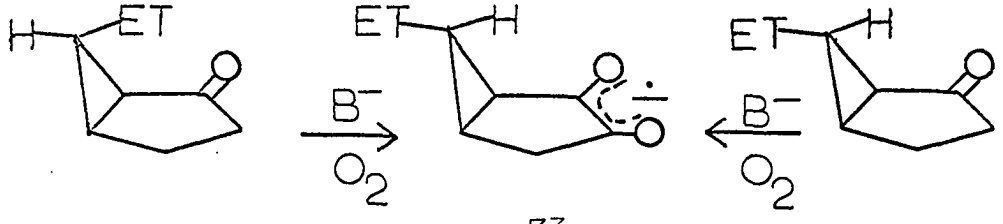
69

The structure of the hydrogen and methyl isomers were proven by independent oxidation of the respective catechols. The proposed structure of the ethyl isomer is in good agreement with the other members of the series as well as with the work of Stone and Waters (44). A mechanism involving a 1,4 sigma-tropic rearrangement from C-5 to C-2 of the enolate anion 70 is consistent with the observed product and molecular orbital symmetry rules (45). The cyclopropanol anion 71 can open internally to provide the proper topology of the carbon atoms in the o-quinone 72 .



70 71 72

Oxidation of syn- or anti-6-ethylbicyclo[3.1.0]hexan-2-one in DMSO containing potassium t-butoxide yields the same semidione 73 (Figure 14) whose hyperfine splitting constants are consistent with the more stable anti structure. If the syn-6-ethylbicyclo[3.1.0]hexan-2-one is oxidized in a weaker

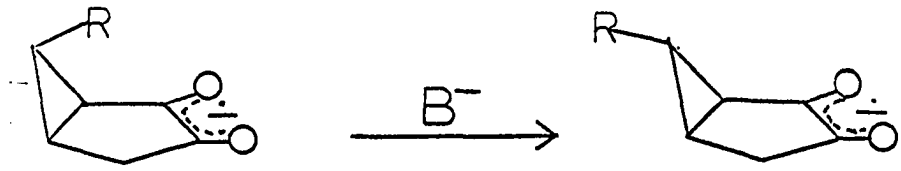


73

base, DMSO containing potassium t-butoxide and 2% tertiary butyl alcohol, a mixture of syn and anti-6-ethyl semidiones is observed (Figure 33) initially. The complex ESR signal in Figure 33 rapidly simplifies to the signal observed in Figure 14.

The syn-6-methyl semidione is much more stable and isomerization to the anti isomer can be followed by ESR spectroscopy (Figure 34). The rearrangement 74 with R = methyl proceeds to completion in dimethyl sulfoxide in the presence of potassium t-butoxide in 3 hours, whereas the rearrangement of the syn-6-ethyl compound occurs in 1 minute under similar conditions. The steric driving force is emphasized by the observation that the syn-6-deuterium compound does not show the

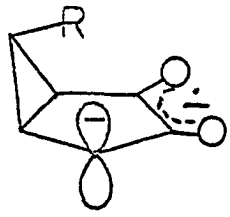
rearrangement. The syn-6-methyl semidione undergoes rearrangement 74 very rapidly in cesium t-butoxide. The effect of strong



74

R = Et >> Me >> D

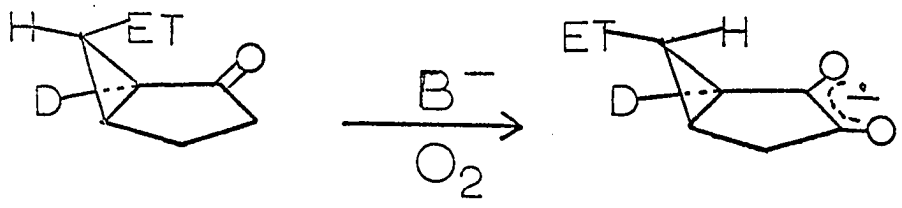
base on the rate of epimerization seems to implicate a radical dianion 75 as an intermediate.



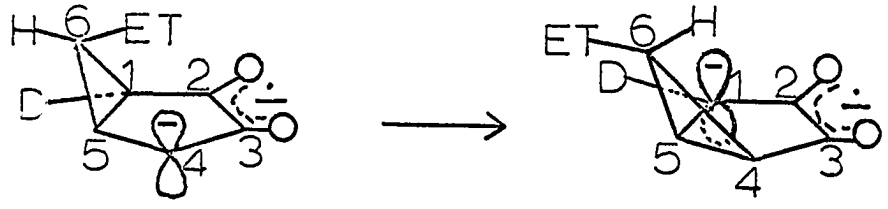
75

Mechanisms involving ionization of a cyclopropyl hydrogen can be eliminated since only the exo-4-position is deuterated when the oxidation is conducted in d_6-DMSO.

1-Deuterio-syn-6-ethylbicyclo[3.1.0]hexan-2-one oxidizes to 1-deuterio-anti-6-ethylbicyclo[3.1.0]hexane semidione 76 (Figure 35). This experimental observation demands that the same cyclopropyl bond broken in the epimerization is reformed. Therefore, a 1,4-sigmatropic rearrangement from C-1 to C-4 can be eliminated as an epimerization mechanism 77.

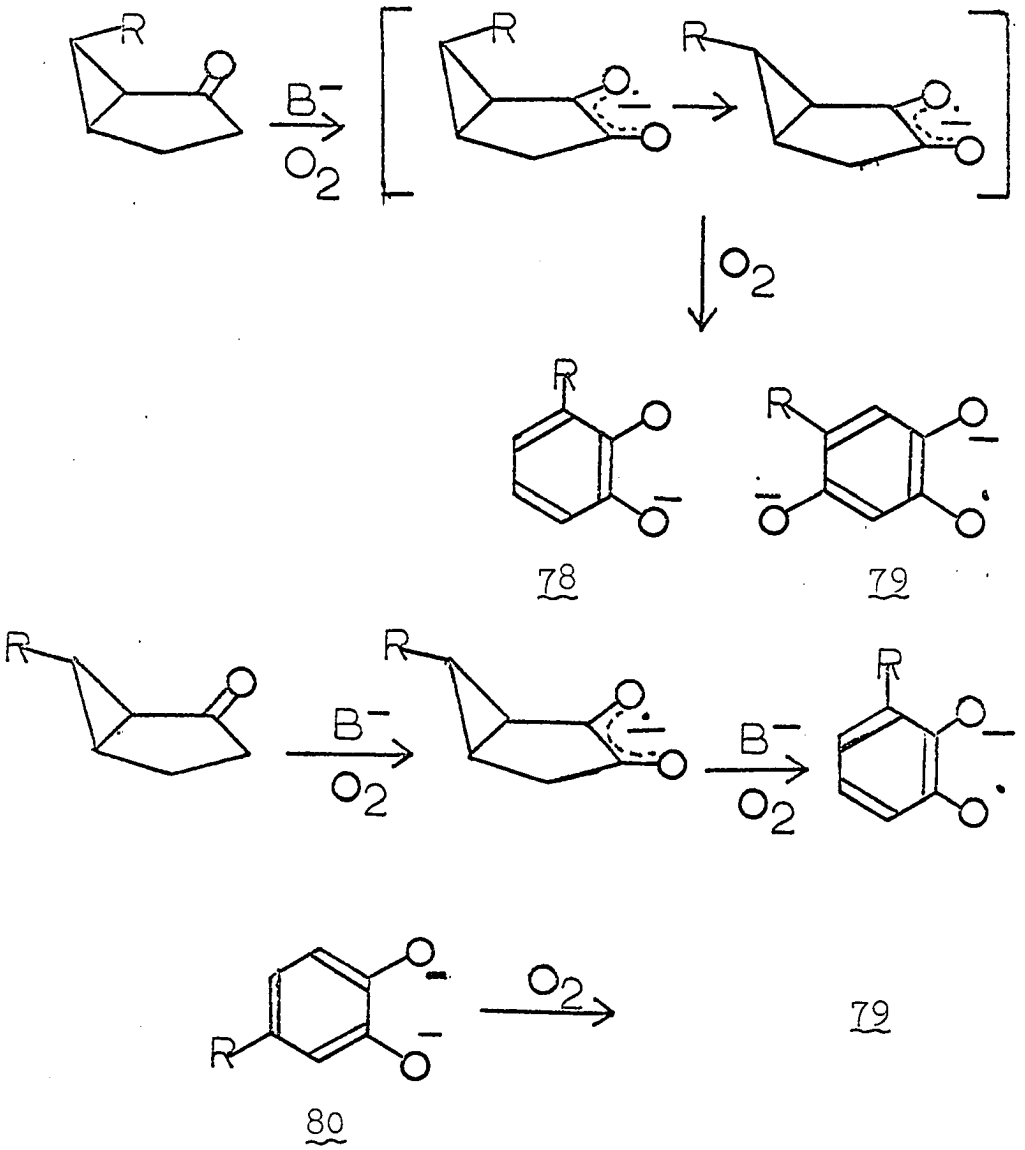


76



77

The overoxidation products 78 and 79 originating from the syn-6-alkyl ketones are distinctly different from those originating from the anti-6-alkyl ketones 78. The initial overoxidation product originating with a syn-6-alkyl ketone is semiquinone 79 which presumably arises from oxidation of 80. The oxidative behavior of 80 in basic solution has been reported by Stone and Waters (44) for R = Me, and the hyperfine splitting constants observed by Stone and Waters for 79 are identical to those observed in the overoxidation of syn-6-methylbicyclo[3.1.0]hexan-2-one (Figure 36). The syn-6-ethylbicyclo[3.1.0]hexan-2-one produces a similar orthoquinone (Figure 37). In addition to 79 the syn-6-alkyl ketones oxidize to the 3-alkyl-o-semiquinones 78 (Figures 31 and 32) presumably by the mechanism previously described. The



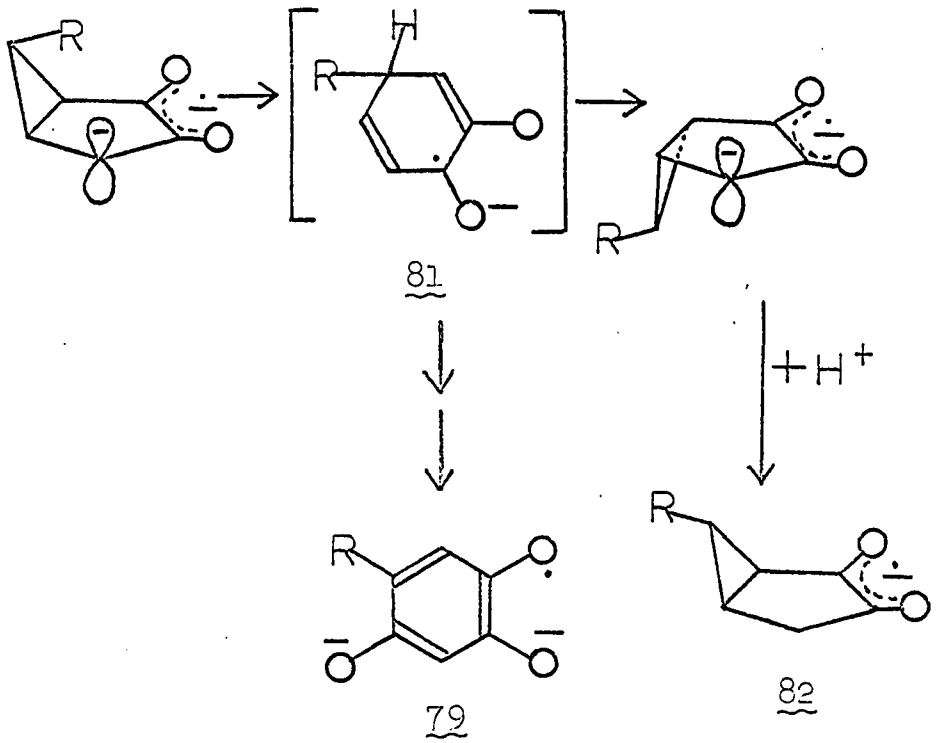
78 79

80 79

3-alkyl-o-semiquinones are the sole overoxidation products originating from the anti-6-alkyl ketones.

Isomerization 74 apparently involves ring inversion by rupture and reformation of the C-1—C-5 bond in the radical dianion stage. It is believed that 79 and 82 arise from a common intermediate 81 ; for this reason 79 appears only when

oxidation originates with the syn-6-alkyl ketone.



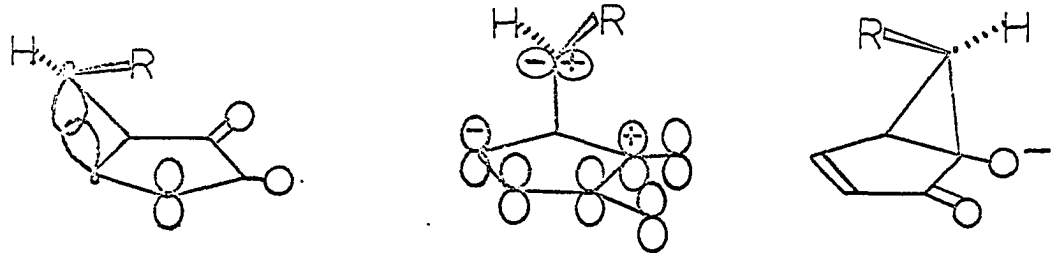
81

79

82

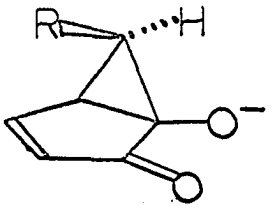
Molecular orbital symmetry rules can be used to predict the mode of a 1,4 sigmatropic rearrangement of a carbon atom (46). Since the p-orbital of an SP_3 carbon atom is anti-symmetrized, it can migrate between termini of opposite symmetry with inversion of configuration 83 . Alternately only one lobe of the p-orbital of the migrating carbon atom need be involved. This would allow migration between termini of the same sign and the configuration about the carbon atom would remain the same 84.

A 1,4 sigmatropic rearrangement 86 involving the syn-6-alkyl isomer is also permitted from symmetry considerations. However, this 1,4 sigmatropic rearrangement has unfavorable steric interactions throughout the course of the rearrangement. Process 86 is apparently not competitive with internal ring opening 81 which relieves strain. 1,4 sigmatropic rearrangements originating from the anti-6-alkyl ketones follow symmetry allowed path 85 to the exclusion of 81 because of the lack of



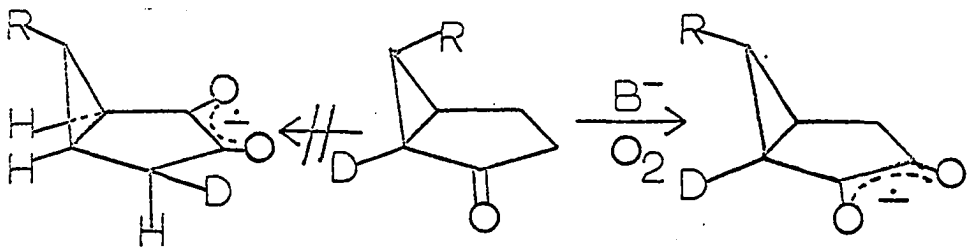
86

steric interference, i.e., the driving force for process 81 is steric relief of strain. It is concluded that the sigmatropic 1,4-rearrangement of a carbon atom can occur with inversion at the carbon atom. If inversion had not occurred, the product would have possessed a syn-6-alkyl group which would be sterically unfavorable 87 . These results do not exclude migration with retention of configuration if the termini of the MO have the same symmetry and if steric strain is not prohibitive.



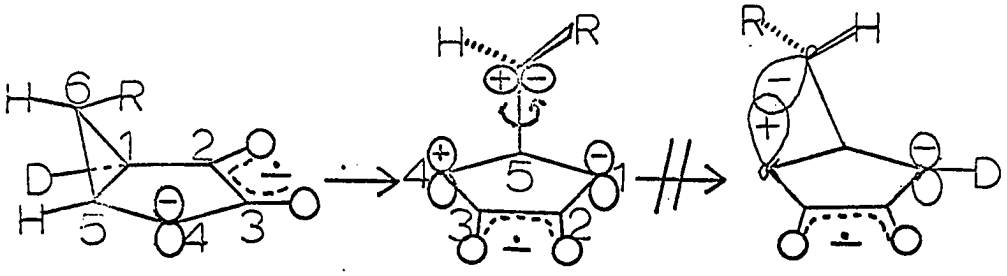
87

An epimerization mechanism involving a 1,4 sigmatropic rearrangement between C-1 and C-4 superficially seems very reasonable. However, this epimerization mechanism has been clearly eliminated by direct experimental observation[88] .



88

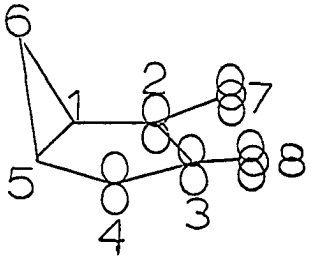
Molecular orbital symmetry considerations indicate this epimerization to be forbidden since the required migration process involving non-inversion about the carbon atom results in coupling of antisymmetric orbitals[89] .



89

	ψ_3	ψ_4
C-1	0.4082	-0.6163
C-2	0.4081	-0.2901
C-3	0.4082	0.2901
C-4	0.4082	+0.6163
O-7	-0.4081	-0.1897
O-8	-0.4082	0.1897

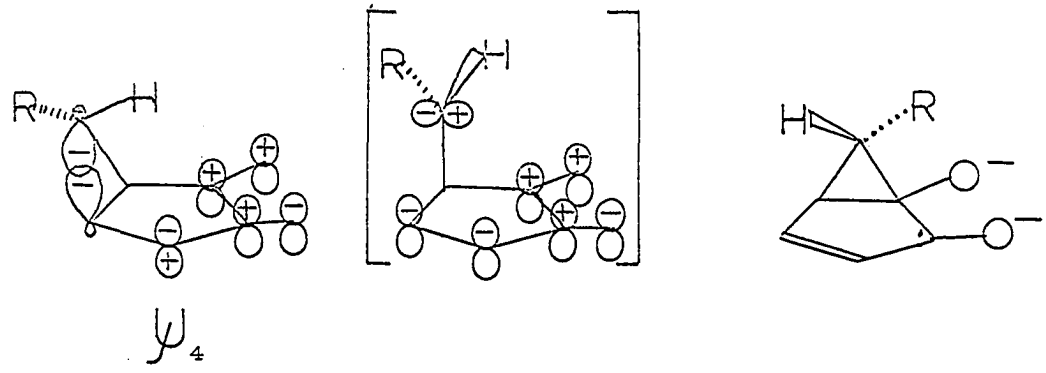
Calculations based on π system 90 predict an inversion



	ψ_3	ψ_4
C_2	-0.2236	0.6641
C_3	-0.4351	0.1786
C_4	-0.6231	-0.6161
O_7	0.5428	0.0998
O_8	+0.2790	-0.3710

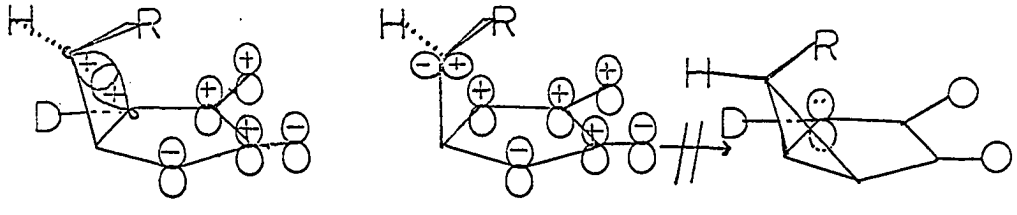
90

about C-6 in the radical dianion stage of the molecular rearrangement. In this approach the p orbital at C-4 is required to have the same sign as the SP_3 orbital on C-5, which forms the C-5 - C-6 cyclopropyl bond. The p orbital at C-2 is required to have opposite symmetry to the p orbital at C-4 to accommodate inversion at C-6 91. Molecular orbital calculations indicate that inversion can occur in ψ_4 the radical dianion stage (7π e) and not in ψ_3 the anion or radical stage (5 or 6π e).



ψ_4

91



91a

The orbital symmetry argument previously presented for 85 and 89 rationalized the experimental results. The calculations for 85 involving 7 electrons (ψ_4) in the p-orbitals at atoms 2, 3, 4, 5, 7 and 8 predicted the rearrangement of the C-5 — C-6 bond to C-6 — C-2 would occur with inversion at C-6, i.e., an anti-6-alkyl substituent would stay on the "outside" of the bicyclic ring system. An orbital symmetry "prediction" can be made ignoring the coefficient at C-5 in the LCAO treatment. Calculation 90 summarizes the results of considering 6 electrons (ψ_3) in the p-orbitals 2, 3, 4, 7 and 8. The coefficients at C-2 and C-4 have the same sign. Bonding between C-4 and C-5 would leave an orbital on C-6 with symmetry such that symmetry allowed formation of the C-4 — C-6 bond would require retention of configuration, i.e., R-outside group would isomerize to R-inside in the formation of the cyclopropanol anion. This is extremely unlikely from steric considerations. If ψ_4 is used the orbital symmetries predict rearrangement with inversion 91. However, the chemical evidence is not consistent with the formation of the rearranged semiquinone from 7π electron intermediate, such as a radical dianion. The rearrangement to the cyclopropanol is believed to involve the diketone enolate anion. Calculation 85 involving 6π electrons from the enolate anion and one electron from the C-6 — C-5 bond predicts the favorable stereochemical course for the rearrangement.

The epimerization at C-6 can also be considered in view of calculation 90. Here the chemical evidence points strongly to a radical dianion intermediate, 7π electron. If the orbital at C-5 is ignored in the LCAO the prediction is that the sigmatropic rearrangement would lend to inversion of configuration at C-6 91a. Calculation 90 predicts that the sigmatropic rearrangement would not lend to relief of steric strain and is consistent with the fact that this sigmatropic rearrangement was excluded by deuterium labeling. If the p-orbital on C-5 is included in the calculation 89, the same prediction is made, i.e., the sigmatropic rearrangement of a bond from C-6 — C-1 to C-6 — C-4 would occur in a concerted manner only if inversion of configuration at C-6 occurred. This inversion at C-6 causes an inside alkyl group to remain inside of the bicyclic ring system, and no steric relief of strain can occur.

Figure 29. First derivative ESR spectrum of 4-ethyl-5-methyl-o-semiquinone prepared by overoxidation of 1-ethyl-5-methylbicyclo[3.1.0]-hexan-2-one in DMSO containing a 3 to 1 molar ratio of potassium t-butoxide to ketone. This spectrum was also obtained by oxidation of 4-ethyl-5-methylcatechol in basic DMSO solution.

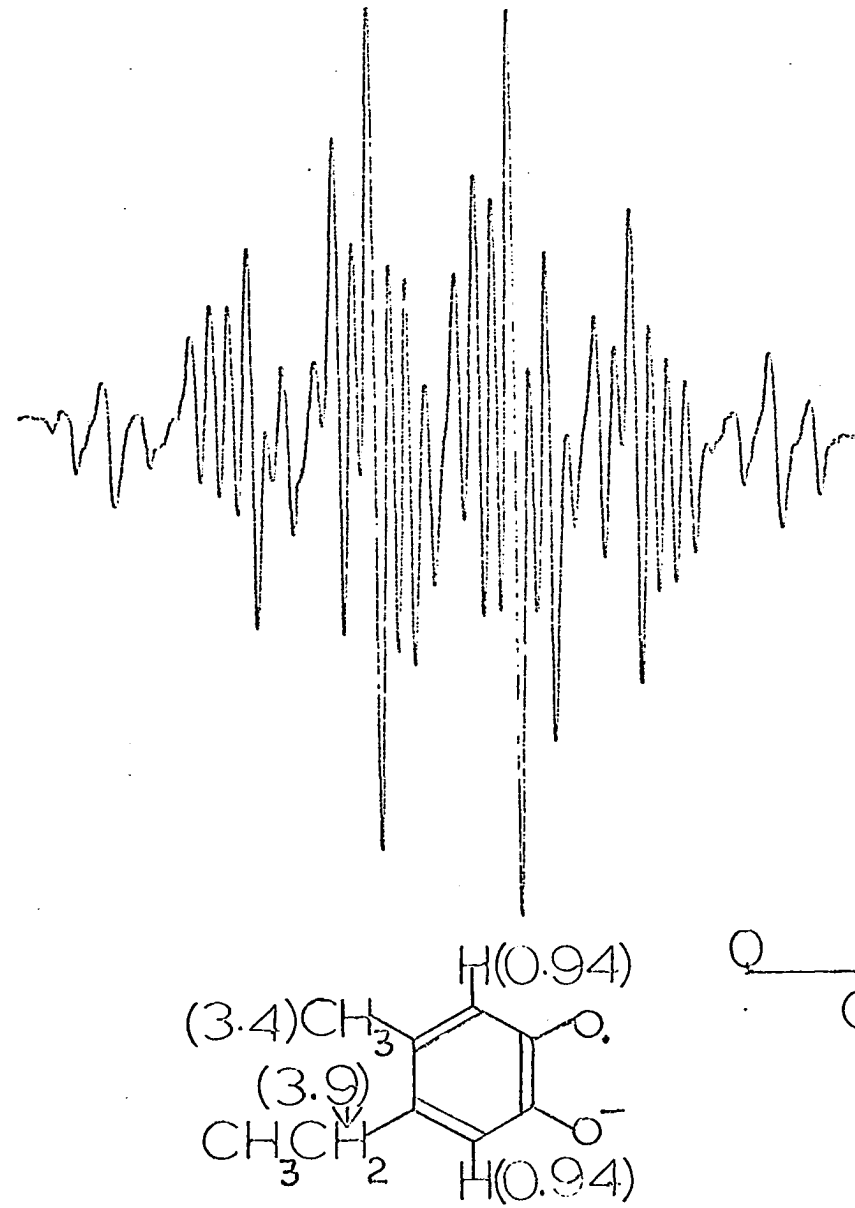
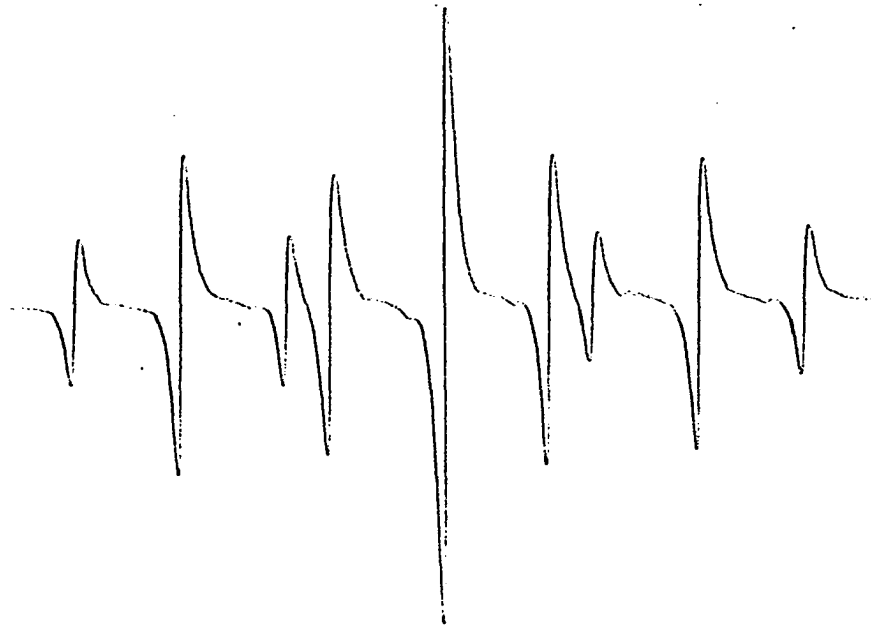

H(0.94)
(3.4)CH3
O.
(3.9)
O−
CH3CH2
H(0.94)
0
5
10
GAUSS

Figure 30. First derivative esr spectrum of o-semiquinone prepared by over-oxidation of bicyclo[3.1.0]hexan-3-one in DMSO containing a 3 to 1 molar ratio of potassium t-butoxide to ketone.



0 5 10
GAUSS

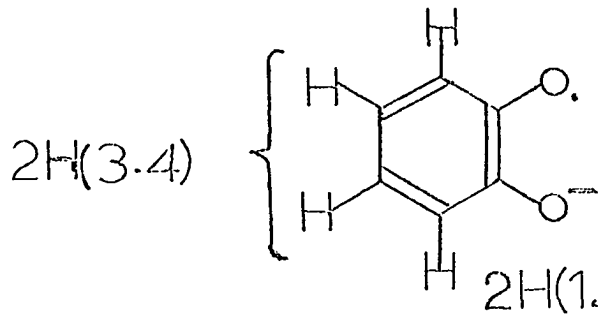
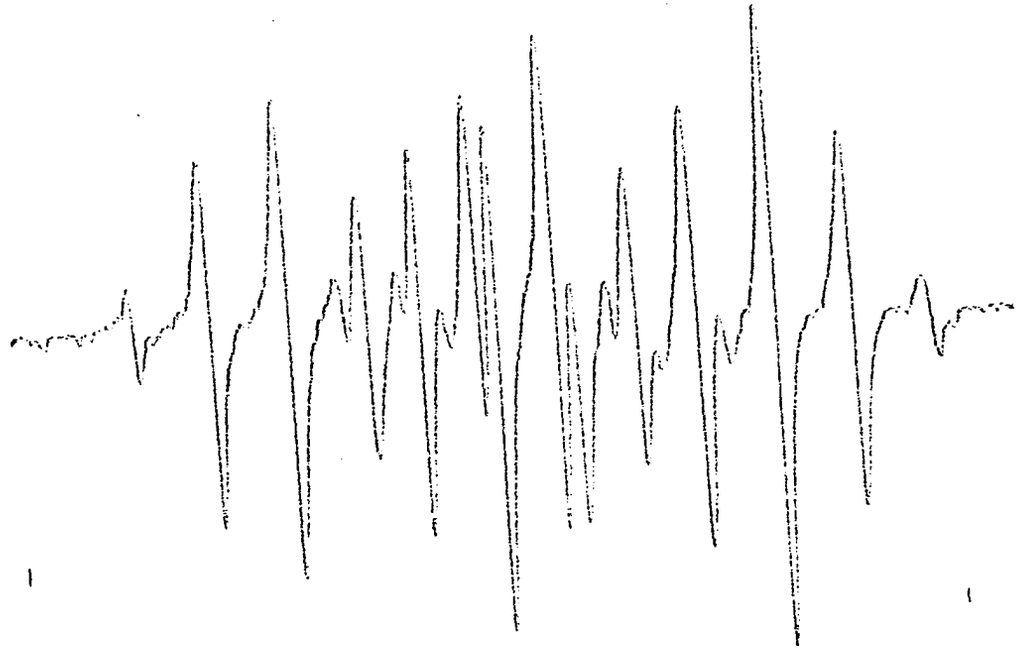
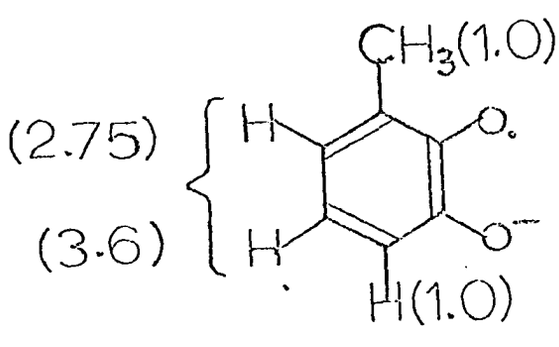


Figure 31. First derivative ESR spectrum of 3-methyl-o-semiquinone prepared by overoxidation of syn or anti-6-methylbicyclo[3.1.0]hexan-2-one in DMSO containing a 3 to 1 molar ratio potassium t-butoxide to ketone.




CH3(1.0)
(2.75)
H
O.
(3.6)
H
O−
H(1.0)

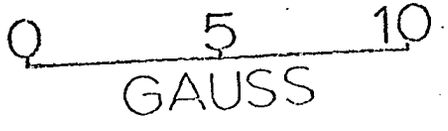
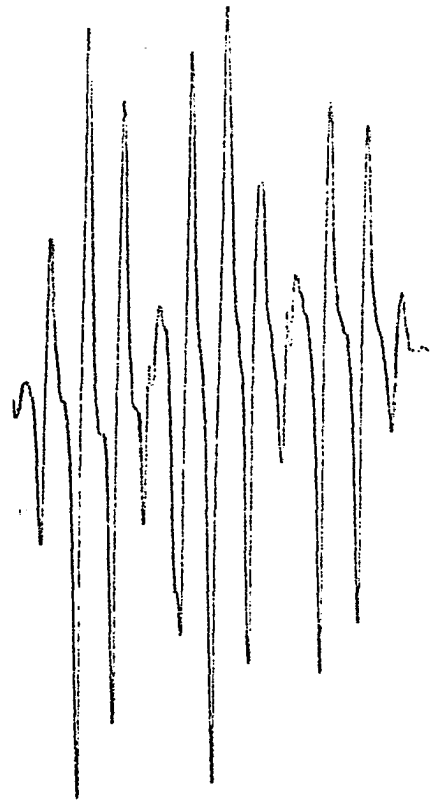
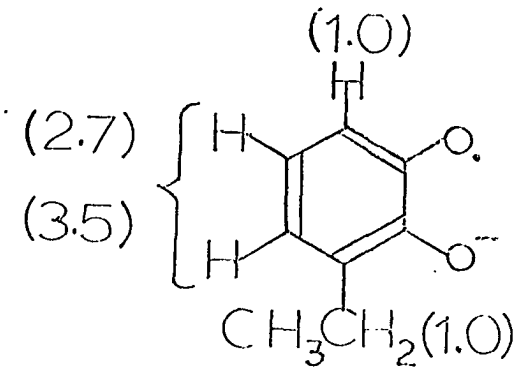

0
5
10
GAUSS

Figure 32. First derivative ESR spectrum of 3-ethylo-semiquinone prepared by overoxidation of syn or anti-6-ethylbicyclo[3.1.0]hexan-2-one in DMSO containing a 3 to 1 molar ratio of potassium t-butoxide to ketone.




(1.0)
H
(2.7)
(3.5)
H
H
O·
O⁻
CH3CH2(1.0)

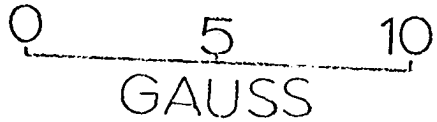

0
5
10
GAUSS

Figure 33. First derivative ESR spectrum of a mixture of *syn* and *anti*-6-ethylbicyclo[3.1.0]hexane semidiones prepared by oxidation of *syn*-6-ethylbicyclo[3.1.0]hexan-2-one in DMSO containing 2% *t*-butanol and a 3 to 1 molar ratio of potassium *t*-butoxide to ketone.

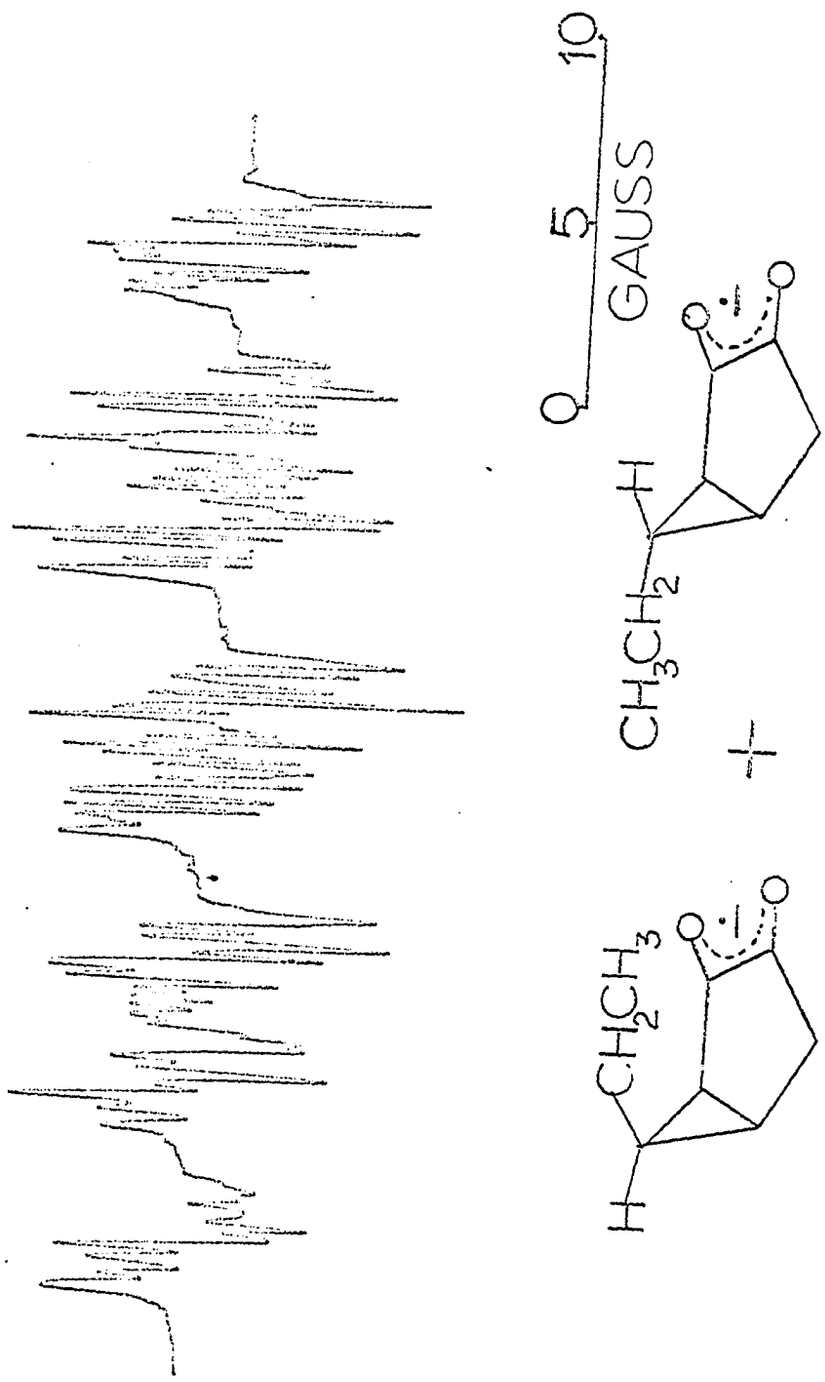

0
5
10
GAUSS
CH_3CH_2
H
+
CH_2CH_3
H

Figure 34. First derivative ESR spectrum of a mixture of syn and anti-6-methyl-bicyclo[3.1.0]hexane semidiones prepared by oxidation of syn-6-methyl-bicyclo[3.1.0]hexan-2-one in DMSO containing a 3 to 1 molar ratio of potassium t-butoxide to ketone. This spectrum was recorded 1.5 hours after the initial oxidation.

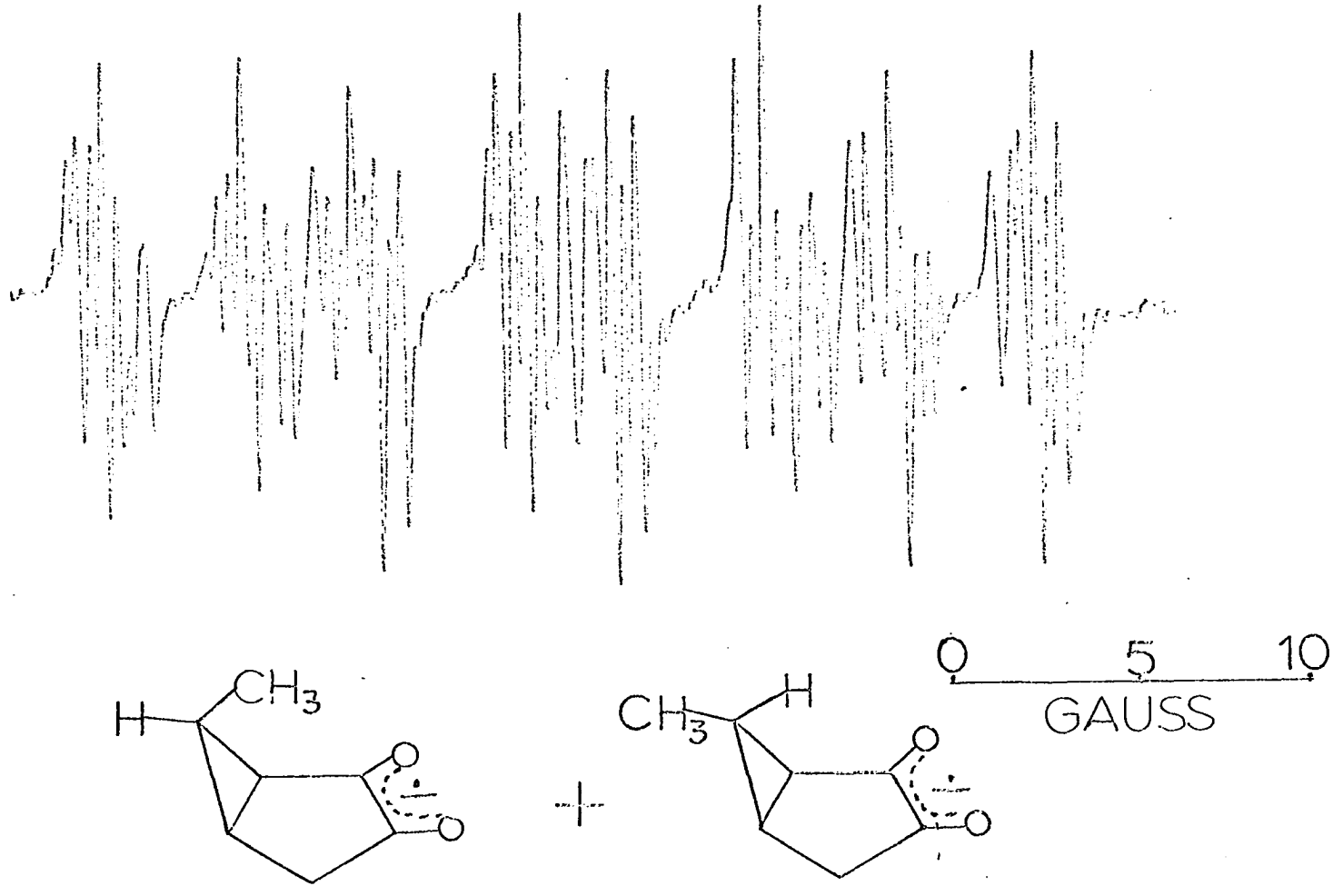
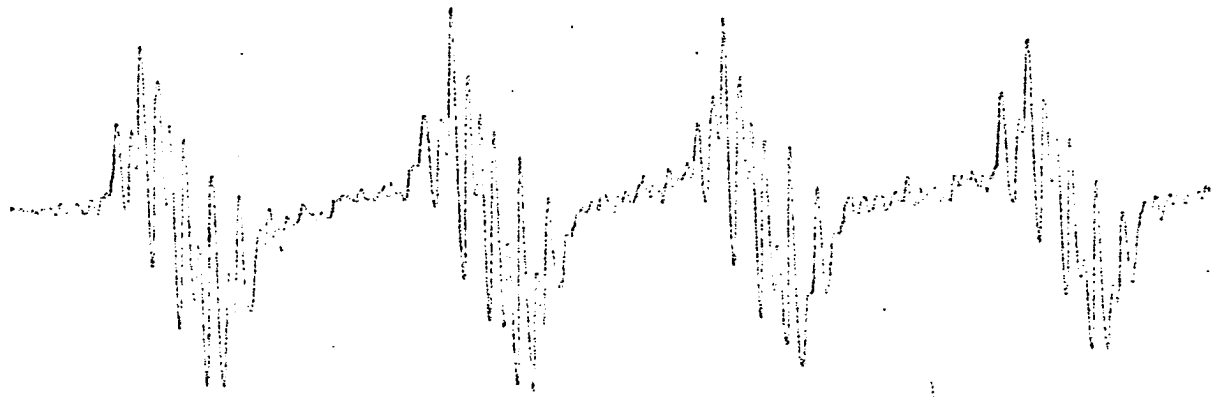
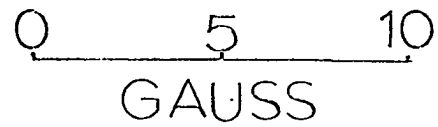

0
5
10
GAUSS
H
CH3
CH3
H
O
O
O
O

Figure 35. First derivative ESR spectrum of 1-deuterio anti-6-ethylbicyclo-[3.1.0]hexane semidione prepared by oxidation of 1-deuterio-syn-6-ethylbicyclo[3.1.0]hexan-2-one in DMSO containing a 3 to 1 molar ratio of potassium t-butoxide to ketone.




0
5
10
GAUSS

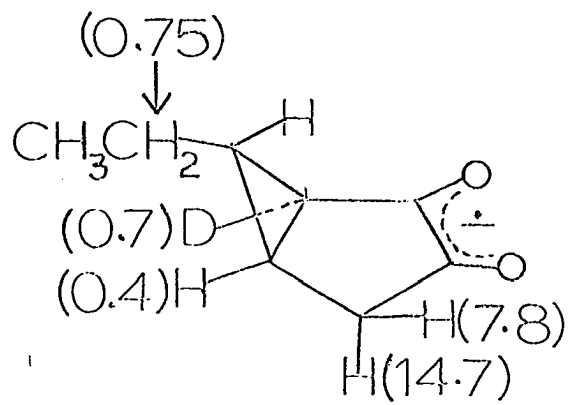
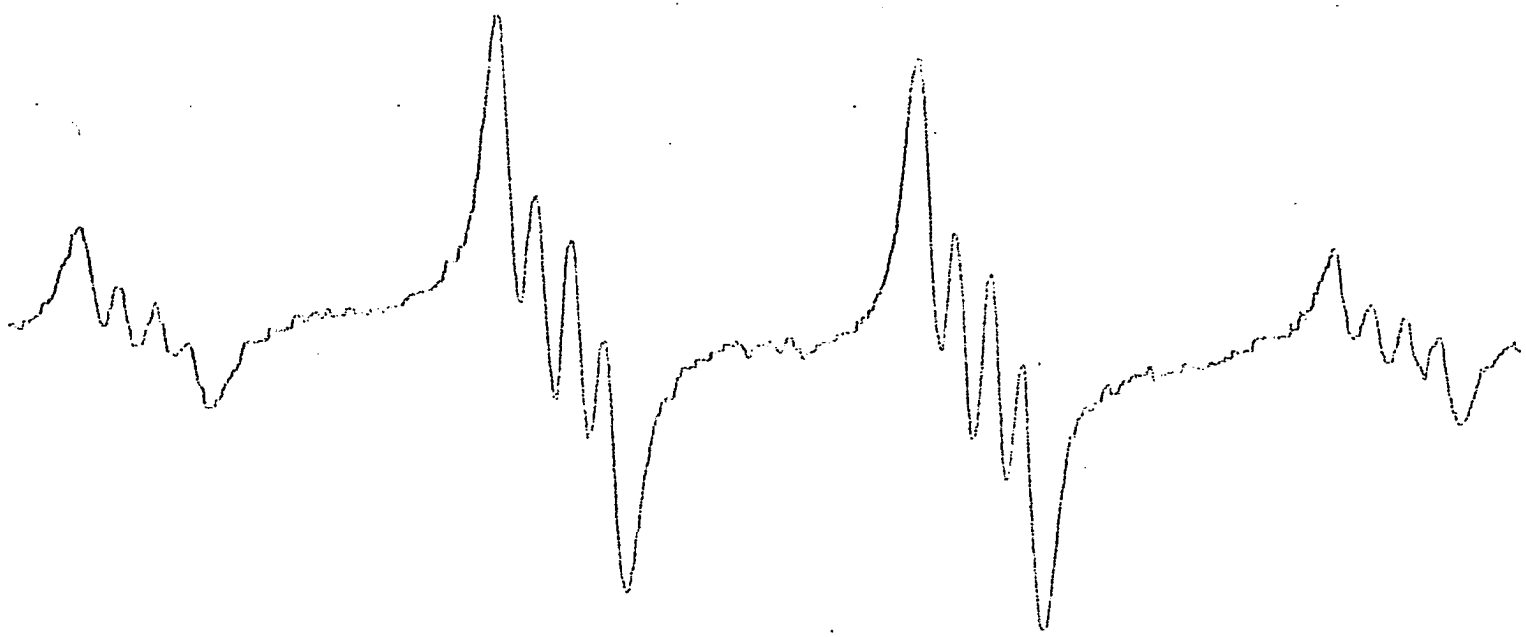
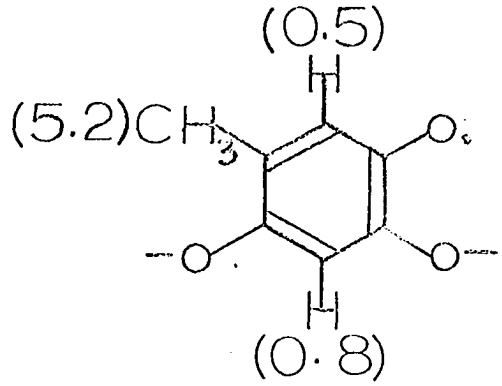

(0.75)
CH3CH2
H
(0.7)D
(0.4)H
H(7.8)
H(14.7)

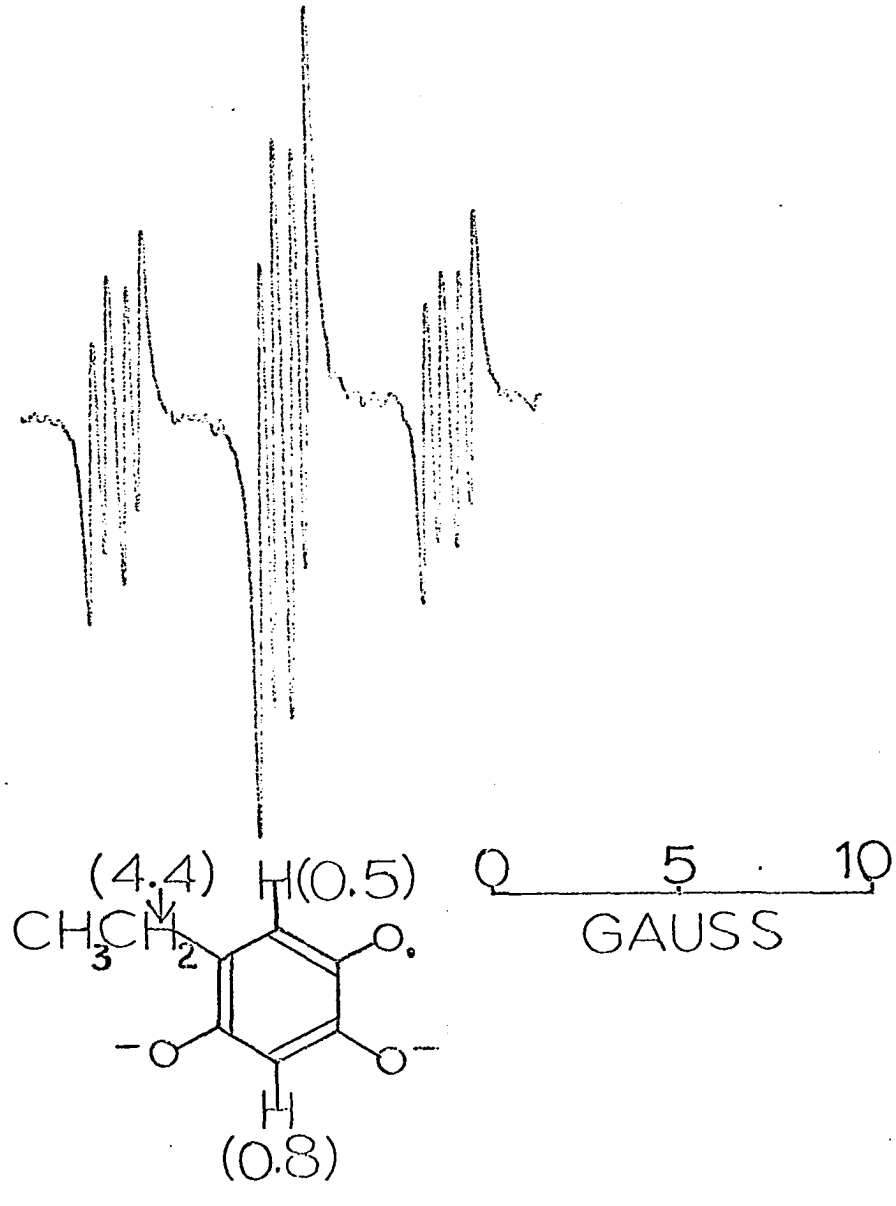
Figure 36. First derivative ESR spectrum of 4-methyl-5-oxy-o-semiquinone prepared by overoxidation of syn-6-methylbicyclo[3.1.0]hexan-2-one in DMSO containing a 3 to 1 molar ratio of potassium t-butoxide to ketone.




(0.5)
(5.2)CH3
O
O
O
(0.8)


0
5
GAUSS

Figure 37. First derivative ESR spectrum of 4-ethyl-5-oxy-o-semiquinone prepared by overoxidation of syn-6-ethylbicyclo[3.1.0]hexan-2-one in DMSO containing a 3 to 1 molar ratio of potassium t-butoxide to ketone.


(4.4)
H(0.5)
CH3CH2
O.
-O
O-
H
(0.8)
0
5
10
GAUSS

EXPERIMENTAL

Synthesis of Ketones

Bicyclo[3.1.0]hexan-3-one

Δ^3-Cyclopentenol. Diborane (47,48,49) was produced by adding a solution of 38 g. (1.0 mole) of sodium borohydride in 500 ml. of dry diglyme to an ice cold solution of 210 g. (1.5 mole) of boron trifluoride etherate in 350 ml. of dry diglyme. The resulting diborane, entrained in nitrogen, was bubbled through an ice cold solution of 450 g. (6.8 mole) of cyclopentadiene in 1500 ml. of diglyme. The reaction was conducted slowly so that a very gentle evolution of diborane occurred. After the addition of the sodium borohydride solution to the boron trifluoride solution was completed nitrogen was allowed to sweep the system for 1 hour. The reaction vessel was allowed to warm to room temperature and the excess cyclopentadiene was removed by means of a rotatory evaporator. The diglyme was distilled under reduced pressure and the alkyl borane remained as a viscous oil. The alkyl borane was dissolved in ethyl ether and oxidized with 100 ml. of 3 molar sodium hydroxide and 50 ml. of 30% hydrogen peroxide. The ether layer was dried over magnesium sulfate and distilled to provide 20.6 g. of Δ^3-cyclopentenol, b.p. 67-68°C (33mm).

Zn-Cu couple. To a hot solution of 2 g. of cupric acetate in 50 ml. of acetic acid was added 32 g. (0.5 mole of zinc dust (50). The mixture was allowed to stir for 3 minutes and was filtered while hot. The couple was washed with several

hundred ml. of ether by suction filtration and immediately placed in the reaction flask.

(cis-Bicyclo[3.1.0]hexan-3-ol). To 28 g. (0.428 mole) of Zn-Cu couple in 150 ml. of dry ether in a 500 ml. three-neck flask equipped with a mechanical stirrer, condenser, and nitrogen inlet was added slowly a mixture of 9 g. (0.107 mole) of Δ^3-cyclopentenol and 54 g. (0.214 mole) of methylene iodide. After a short initiation period a vigorous reaction occurred. The rate of addition was adjusted so that reflux of the ether was maintained. After the addition was completed the reaction was refluxed for 1 hour by heating on a water bath. The reaction vessel was then immersed in an ice bath and 50 ml. of water was added to the reaction mixture. The reaction mixture was filtered and the collected salts were thoroughly washed with ether. The clear filtrate separated into aqueous and ethereal layers. The aqueous layer was saturated with sodium chloride and sodium carbonate. The latter was found to be effective in removing zinc iodide dissolved in the ethereal layer. The ethereal layer was separated and dried over magnesium sulfate. The ether was removed by evaporation and the alcohol was obtained in pure form by column chromatography on neutral alumina. Methylene iodide, the main impurity, was eluted with pentane and the cis-bicyclo[3.1.0]hexan-3-ol was eluted with ether. The yield was 6.0 (65%). The compound was identified by IR and NMR spectroscopy.

Bicyclo[3.1.0]hexan-3-one. To a solution of 9 g. (0.09 mole) of chromium trioxide in 20 ml. of pyridine was added 2 g. of cis bicyclo[3.1.0]hexan-3-ol (51). The reaction mixture was stirred at room temperature for 20 hours. One hundred ml. of water was added to the reaction mixture and the aqueous solution was extracted five times with 50 ml. of ether. The combined ether extracts were washed with 10% hydrochloric acid until the aqueous layer was acid to litmus. The ether was then washed with 10% sodium bicarbonate and dried over magnesium sulfate. The ether was removed by distillation and 0.8 g. of the crude ketone remained. A pure fraction was obtained by preparative glpc (SF 96, 20% on firebrick).

M^+/e: Parent peak at 96.

IR: (Neat) Cyclopropyl hydrogens at 3.26μ and a carbonyl band at 5.75μ.

NMR: (CCl_4) One cyclopropyl proton at 0.8 ppm and one at -0.1 ppm. Six additional protons between 1 and 3 ppm were present.

Derivative: 2,4-Dinitrophenylhydrazone, m.p. 149-150°C; Lit. (49) m.p. 149.2-149.8°C.

Bicyclo[3.1.0]hexan-2-one

A solution of dimethyl sulfoxonium methylide was prepared (52) under nitrogen by slowly adding 25 ml. of dimethyl sulfoxide to a mixture of 0.5 g. (0.21 mole) of sodium hydride and 4.62 g. (0.021 mole) of trimethyl sulfoxonium iodide. The ylid solution

was stirred for 15 minutes and 1.62 g. (0.02 mole) of cyclopentenone in 5 ml. of dimethyl sulfoxide was added slowly with vigorous stirring. The reaction was stirred at room temperature for 2 hours and at 50°C for 1 hour. The reaction mixture was treated with 80 ml. of water and extracted three times with 50 ml. of ether. The ether extracts were washed with saline solution and dried over anhydrous sodium sulfate. The ether was removed by distillation and the remaining oil was distilled at reduced pressure to provide 1.1 g. (65% yield) of bicyclo-[3.1.0]hexan-2-one, b.p. 55°C (10 mm); Lit.(53) b.p. 58°C (13 mm).

M^+/e: Parent peak at 96.

IR: (Neat) cyclopropyl hydrogens at 3.29μ and a carbonyl band at 5.82μ. The latter is characteristic for carbonyl conjugated with a cyclopropyl ring.

NMR: (CCl_4) Complex pattern between 2.2 and 0.8 ppm.

Derivative: 2,4-Dinitrophenylhydrazone m.p. 169-171°C; Lit.(53) m.p. 170-172°C.

syn-6-Deuteriobicyclo[3.1.0]hexan-3-one

Nortricyclyl acetate. A mixture of 156 g. (1.7 mole) of bicyclo[2.2.1]hepta-2,5-diene, 105 g. (1.75 mole) of glacial acetic acid, and 3 ml. of boron trifluoride etherate was placed in a 500 ml. flask. The flask was equipped with a condenser and drying tube. The mixture was heated on a steam bath for 6 hours, cooled to room temperature, and diluted with 250 ml. of

ether. The ethereal solution was washed successively with two 50 ml. of 3V ammonia and 50 ml of water. The ethereal solution was dried over magnesium sulfate and the ether was removed by distillation. The dark residue was distilled under reduced pressure to give about 200 g. of a mixture of nortricyclyl acetate and bicyclo[2.2.1]hepta-5-en-2-yl acetate. The acetate mixture was dissolved in 500 ml. of chloroform, cooled to -10°C, and treated with nitrosyl chloride gas until the solution turned brownish-green. The olefin formed a white precipitate (the dimer of the nitrosyl chloride adduct) which was removed by filtration. The filtrate was washed with sodium carbonate and sodium chloride solutions respectively and dried over magnesium sulfate. The solvent was removed by distillation and the residue was fractionated under reduced pressure to provide 138 g. (56% yield) of nortricyclyl acetate (8), b.p. 83-85°C (13 mm).

Nortricyclanol. Nortricyclyl acetate (138 g.) was added to a solution of 0.5 g. of sodium in 500 ml. of anhydrous methanol. The solution was heated on a steam bath, and the methanol was slowly removed by distillation. The residue was cooled and diluted with 250 ml. of ether. The ethereal solution was washed with saline solution and dried over magnesium sulfate. The solvent was removed by means of a rotatory evaporator and the nortricyclanol (82 g., 43% overall yield) was collected as a solid, m.p. 108-110°C.

Tricyclo[2.2.1.$0^{2,6}$]heptan-3-one (nortricyclanone). The oxidation reagent was prepared by dissolving 70 g. (0.70 mole) of chromium trioxide in 100 ml. of water in a 500 ml. beaker. The beaker was immersed in an ice bath and 112 g. of concentrated sulfuric acid was added. Water (200 ml.) was added slowly with stirring. A solution of 82 g. of nortricyclanol in 500 ml. of acetone was cooled to -5°C in a 2 liter three-necked flask. The flask was equipped with a mechanical stirrer, a thermometer, and a pressure compensated dropping funnel. The oxidation reagent was added with vigorous stirring and the reaction temperature was not allowed to exceed 20°C. Stirring was continued for 3 hours after the addition was completed. Sodium bisulfate was added in small portions until the brown color of chromic acid disappeared. The reaction mixture was extracted with three 200 ml. portions of ether. The ethereal extracts were washed with sodium bicarbonate and saline solutions, and dried over magnesium sulfate. The solvent was removed by distillation, and the residue was distilled under reduced pressure to provide 60 g. (77%) yield of nortricyclanone (54), b.p. 103-105°C (77 mm).

syn-6-Deuterio-cis-bicyclo[3.1.0]hexane-3-carboxylic acid.

A 250 ml. three-necked flask equipped with a mechanical stirrer and nitrogen inlet was placed 100 g. of d_6-dimethyl sulfoxide, 40 g. (0.37 mole) of potassium t-butoxide, and 2.3 g. (0.055 mole) of deuterium oxide. Nortricyclanone, 6 g. (0.055 mole was added and the reaction mixture was stirred for 2 hours. The reaction was quenched with 75 ml. of deuterium oxide and

acidified with deuterium chloride. The acidified reaction mixture was extracted four times with 50 ml. of ether. The ether extracts were washed with saline and dried over calcium chloride. The ether was removed by means of a rotatory evaporator and the residual oil was distilled under reduced pressure to provide 4.2 g. (59% yield) of syn-6-deuterio-cis-bicyclo-[3.1.0]hexane-3-carboxylic acid (55), b.p. 69-70°C (0.25 mm). Mass spectral analysis showed very high >98% deuterium isotopic purity of the acid. NMR analysis indicated that the high field syn-6-hydrogen was absent.

syn-6-Deuterio-cis-3-acetylbicyclo[3.1.0]hexane. An ethereal solution of methyl lithium, prepared by adding 27.2 g. (0.192 mole) of methyl iodide in 75 ml. of ether to 2.8 g. (0.4 g-atom) of lithium pieces in 70 ml. of ether, was added dropwise to a stirred solution of 4.2 g. (0.032 mole) of syn-6-deuterio-cis-bicyclo[3.1.0]hexane-3-carboxylic acid. The addition required 1 hour and the solution was stirred for an additional hour. The reaction mixture was poured over crushed ice and the ethereal layer was separated and dried. The solvent was evaporated and the residual oil was distilled to provide 3.2 g. (80% yield) of the methyl ketone (9), b.p. 71-72°C (10 mm). Mass spectral and NMR analysis indicated that the isotopic and stereochemical integrity of the syn-6-position was retained.

syn-6-Deuterio-cis-3-isopropanol bicyclo[3.1.0]hexane. A Grignard reagent, prepared from 0.85 g. (0.035 mole) of

magnesium turnings and 5.0 g. (0.035 mole) of methyl iodide, was added to a solution of 3.2 g. (0.26 mole) of syn-6-deuterio-cis-3-acetylbicyclo[3.1.0]hexane in 25 ml. of ether. The reaction was allowed to stir for 1 hour after the addition was completed; then ice and hydrochloric acid were added to quench the reaction. The ethereal layer was separated, washed with 5% sodium bicarbonate, and dried over sodium sulfate. The ether was removed by means of a rotatory evaporator and the residual oil was distilled to provide 3.2 g. (90% yield) of syn-6-deuterio-cis-3-isopropanol-bicyclo[3.1.0]hexane, b.p. 76°C (9 mm). Mass spectral and NMR analysis indicated that the isotopic and stereochemical integraty of the syn-6-position was retained.

syn-6-Deuteriobicyclo[3.1.0]hexan-3-one.

Dehydration. To an ice cold nitrogen covered solution of 3.2 g. of syn-6-deuterio-cis-3-isopropanol bicyclo[3.1.0]-hexane in 100 ml. of dry pyridine was added 10 ml. of phosphorous oxychloride. The reaction mixture was heated at 100° C for 2 hours, cooled to room temperature, and quenched by adding small pieces of ice. The pyridine solution was added to 200 ml. of water and exhaustively extracted ether. The ether extracts were washed with 10% hydrochloric acid until the odor of pyridine could no longer be detected. The ether extracts were dried over sodium sulfate and the ether was evaporated to provide syn-6-deuterio-cis-3-isopropenebicyclo[3.1.0]hexane. The IR showed

the complete absence of hydroxyl stretching at 2.95μ. The NMR of the crude material was consistent with dehydration, as well as the retention of the isotopic and stereochemical integraty of the syn-6-position. This product was used without purification.

Ozonalysis. The crude bicyclo[3.1.0] olefin was dissolved in 50 ml. of carbon tetrachloride and azonized at 0°C. The ozonide was allowed to stand in solution overnight before the addition of 20 ml. of 30% hydrogen peroxide and 20 ml. of 10% sodium carbonate solution. The mixture was stirred for 30 minutes and then heated for 30 minutes at 70°C. The reaction mixture was washed with water, dried over sodium sulfate, and concentrated to give a light brown oil. The syn-6-deuteriobicyclo[3.1.0]hexan-3-one was collected by preparative glpc (SF 96, 20%, on firebrick). The fraction collected had the identical retention time of the authentic undeuterated bicyclo-[3.1.0]hexan-3-one.

M^+/e: Parent peak at 97.

IR: (Neat) Cyclopropyl hydrogens at 3.26μ, deuterium at 4.5μ, and a carbonyl band at 5.75μ.

NMR: (CCl_4) The -0.1 ppm cyclopropyl proton multiplet which was present in the undeuterated isomer was absent. This multiplet has been assigned to the syn-6-hydrogen (56). A clean triplet integrating to 1 proton at 0.825 ppm, J = 8 cps indicated that the 6 position cyclopropyl hydrogen was cis to two

equivalent protons--*cis* cyclopropyl proton coupling constants are larger than *trans* cyclopropyl proton coupling constants.

Derivative: 2,4-Dinitrophenylhydrazone, m.p. 145-148°C.

6,6-Dideuterio bicyclo[3.1.0]hexan-2-one

Δ^2-Cyclopentenol. Freshly distilled cyclopentadiene, 66 g. (1 mole) was placed in a 250 ml. three-necked flask and cooled to -70°C. Hydrochloric acid gas was passed through the solution until the volume increased 20% (57). The resulting 3-chlorocyclopentenol was crudely distilled at 30°C (20 mm). The crude distillate was stirred with 500 ml. of 30% sodium bicarbonate solution for 5 hours. The sodium bicarbonate solution was saturated with sodium chloride and extracted with three 200 ml. portions of ether. The ether extracts were combined and dried over sodium sulfate. The ether was removed by distillation and the residual oil was fractionated at reduced pressure to provide 30 g. (49% of Δ^2-cyclopentenol, b.p. 52°C (12 mm).

Dideuteriomethylene iodide. To a solution of sodium iodide, 45 g. (0.3 mole) in 210 ml. of deuterioethanol and 64 g. (3.2 mole) of deuterium oxide was added 7 g. (0.3 g-atom) of sodium in small pieces. Methylene iodide (80 g., 0.3 mole) was added (58). The two phase system was stirred for two weeks. The partially deuterated methylene iodide was separated and the above process was repeated. After the second exchange was completed the methylene iodide was separated, dried and

distilled. This method provided 18 g. (25% yield) of deuterated methylene iodide. The isotopic distribution by mass spectroscopy was CD_2I_2 (85%), $CDHI_2$ (13%), and CH_2I_2 (2%).

cis-6,6-Dideuteriobicyclo[3.1.0]hexan-2-ol. The dideuterio methylene insertion was performed in the manner described for the preparation of cis-bicyclo[3.1.0]hexan-3-ol. The dideuterio methylene insertion was conducted on 1/4 the scale of the previously described procedure. One gram of the crude oil which was contaminated with methylene iodide was obtained.

6,6-Dideuteriobicyclo[3.1.0]hexan-2-one. The crude alcohol was oxidized in the manner previously described for the oxidation of cis-bicyclo[3.1.0]hexan-3-ol to cis-bicyclo-[3.1.0]hex-3-one. About 0.3 g. of the crude ketone was obtained. Unfortunately this compound was not obtained in pure form since methylene iodide had the same glpc retention time under the conditions used. This compound had the identical glpc retention time as the undeuterate bicyclo[3.1.0]hexan-2-one.

M^+/e: Parent peak at 97 and 98 and an impurity at 270.

IR: (Neat) Cyclopropyl hydrogens 3.29μ, deuterium at 4.5μ and carbonyl at 5.82μ.

NMR: (CCl_4) Complex pattern between 2.2 and 1.4 ppm. A very slight absorption between 0.8 and 1.3 ppm due to residual 6 position protons was observed.

1-Methylbicyclo[3.1.0]hexan-2-one

2-Methylcyclopenten-2-one. 1-Methylcyclopentene, 25 g. (0.31 mole) was dissolved in ether and the ethereal solution was cooled to -30°C. Nitrosyl chloride gas was bubbled through the cold solution until the solution became brown (59). A white precipitate, the nitrosyl chloride adduct dimer, soon formed. The precipitate was collected by filtration and hydrolysed in 1 liter of 2% sulfuric acid for four hours. The aqueous solution was steam distilled and the distillate was extracted with three 100 ml. portions of ether. The combined ether extracts were dried over sodium sulfate. The ether was removed by distillation and the residual oil was fractionated at reduced pressure to provide 3.0 g. (10% yield) of 2-methylcyclopenten-3-one, b.p. 48°C (14 mm).

1-Methylbicyclo[3.1.0]hexan-2-one. The methylene insertion was performed exactly as described in the preparation of bicyclo[3.1.0]hexan-2-one from cyclopentenone. A pure sample was obtained by preparative VPC (SF 96, 20%, on firebrick).

M^+/e: Parent peak at 110.

IR: (Neat) Cyclopropyl hydrogen at 3.29μ and a carbonyl band at 5.85μ.

NMR: (CCl_4) There are 5 protons between 1.7 and 2.0 ppm, a methyl absorption, 3 protons, at 1.2 ppm, and 2 protons above 1 ppm.

Derivative: 2,4-Dinitrophenylhydrazone, m.p. 135-136°C.

Anal. Calcd. for $C_{13}H_{14}N_4O_4$: C, 53.79; H, 4.83.

Found: C, 53.68; H, 4.81.

M^+/e: Parent peak 290.

1-Ethyl-3-methylbicyclo[3.1.0]hexan-2-one

Heptanoic acid-3-hydroxymethyl, γ, lactone. A Grignard reagent was prepared in ether and under nitrogen from 30 g. (0.25 mole) of n-propylbromide and 6 g. (0.25 g-atom) of magnesium. One hundred ml. of benzene was added to the Grignard reagent and the ether was evaporated in a stream of nitrogen. An additional 50 ml. of benzene was added to the Grignard reagent. Ethyl levulinate, 36 g. (0.25 mole) was dissolved in 300 ml. of benzene and placed in an ice cooled flask equipped with a mechanical stirrer and nitrogen inlet. The benzene solution of Grignard reagent was slowly added from a pressure compensated addition funnel. The reaction was stirred for 2 hours and then hydrolysed with ice and dilute sulfuric acid. The benzene layer was washed with a saline solution and dried over sodium sulfate. The benzene was removed by distillation and the residual oil was fractionated at reduced pressure to provide 16 g. (51% yield) of the lactone of 3-(hydroxymethyl)-heptanoic acid (60), b.p. 126-7°C (20 mm).

2-Ethyl-3-methylcyclopentenone. The lactone was placed in 100 ml. of commercial polyphosphoric acid and heated at 100°C for 2 hours. The flask was equipped with a condenser which was fitted with a calcium chloride drying tube. The reaction

solution was poured on cracked ice and extracted with ether. The ether extracts were washed with a saline solution and dried over sodium sulfate. The ether was removed by distillation and the residual oil was fractionated at reduced pressure to provide 13 g. (87% yield) of 2-ethyl-3-methylcyclopentenone, b. p. 95-96°C (18 mm).

2-Methyl-3-ethyl-Δ^2-cyclopentene-1-ol. To a well-stirred mixture of 3.8 g. (0.1 mole) of lithium aluminum hydride in 200 ml. of anhydrous ether, there was added a solution of 13 g. (0.095 mole) of 2-ethyl-3-methylcyclopentenone over a 30-minute period. The mixture was stirred at room temperature for 1 hour and then under reflux for 2 hours. The mixture was cooled and a solution of 20 g. of methanol in 20 ml. of ether was added over a 15-minute period. The ether layer was separated and the aqueous layer was extracted with two 100 ml. portions of ether. The combined ether extracts were dried over sodium sulfate. The ether was evaporated and the product was distilled to provide 10 g. (80% yield) of 2-methyl-3-ethyl-Δ^2-cyclopentene-1-ol, b.p. 76°C (6 mm).

1-Ethyl-5-methylbicyclo[3.1.0]hexan-2-ol. The methylene insertion was performed exactly as described in the preparation of bicyclo[3.1.0]hexan-3-ol from Δ^3-cyclopentenol. This procedure provided a 4.5 g. (55% yield) of 1-ethyl-5-methylbicyclo[3.1.0]hexan-2-ol, b.p. 83-84°C (10 mm). The alcohol was identified by IR and NMR spectroscopy.

1-Ethyl-5-methylbicyclo[3.1.0]hexan-2-one. The alcohol was oxidized in the manner previously described for the oxidation of bicyclo[3.1.0]hexan-3-ol to bicyclo[3.1.0]hexan-3-one. A pure sample was obtained by preparative glpc (SF 96, 20%, on firebrick).

M^+/e: Parent peak at 138.

IR: Cyclopropyl hydrogens at 3.28μ and a carbonyl band at 5.85μ.

NMR: A complex pattern between 0.6 and 2.0 ppm. A sharp methyl singlet occurs at 1.3 ppm.

Derivative: 2,4-Dinitrophenylhydrazone, m.p. 164-166°C.

Anal. Calcd. for $C_{15}H_{18}N_4O_4$: C, 56.60; H, 5.66.

Found: C, 56.51; H, 5.56.

anti-6-Methylbicyclo[3.1.0]hexan-2-one

Diethylcrotyl-1-malonate. Sodium 17.2 g. (0.75 g-atom) was dissolved in 400 ml. of dry ethanol. To the chilled sodium alkoxide solution was added 120 g. (0.75 mole) of diethyl malonate followed by the dropwise addition of 100 g. (0.74 mole) of crotyl bromide. The solution was heated on a steam bath for 1 hour under reflux. The ethanol was then removed by distillation. Water was added to the remaining material and the resulting solution was extracted with ether. The ether extracts were dried over calcium chloride and fractionated to yield 70 g. (45% yield) of diethylcrotyl malonate (61), b.p. 130-132° C (20 mm).

Crotylmalonic acid. Into a boiling hot solution of 40 g. of potassium hydroxide in 40 ml. of water and 120 ml. of methanol was slowly added 70 g. of diethyl crotyl malonate. The solution was refluxed for 1 hour and the ethanol and methanol were removed by distillation. The remaining thick solution was diluted with 200 ml. of water, brought to a pH of 2, and extracted with ether. The ether was removed by means of a rotatory evaporator and the solid acid was recrystallized from benzene. The yield was 45 g. (95% yield), m.p. 115-116°C; Lit. (61) m.p. 115°C.

trans-n-Hex-3-enoic acid. Crotylmalonic acid was heated at 140°C for 1 hour and the resulting oil was fractionally distilled under reduced pressure. A 25 g. fraction of pure trans-n-hex-3-enoic acid (62), b.p. 110°C (16 mm) was obtained. The acid gave a bromophenacyl ester, m.p. 82-83°C; Lit. (62) m. p. 82°C. This acid had a strong IR absorption at 10.35μ which is characteristic for our of plan CH bending of trans disubsti-tuted double bonds.

trans-n-Hex-3-enoic acid chloride. Into a nitrogen filled flask equipped with a condenser and magnetic stirring bar was placed 13.6 g. (0.1 mole) of the trans acid. Thionyl chloride 15 g. (0.125 mole) was added dropwise and the solution was allowed to stir overnight. The reaction mixture was distilled directly to provide 12.5 g. (90% yield) of trans-n-hex-3-enoic acid chloride, b.p. 50°C (25 mm).

anti-6-Methylbicyclo[3.1.0]hexan-2-one. A 6.0 g. sample (0.045 mole) of trans-n-hex-3-enoic acid chloride was added dropwise to a freshly prepared ethereal solution of diazomethane (0.3 mole). The diazomethane was prepared from diazold, aqueous potassium hydroxide, and carbitol (63). This procedure conveniently provided a dry ethereal solution of diazomethane. The reaction mixture was allowed to sit for 6 hours; then the ether was removed by distillation. No attempt was made to purify the diazoketone. The crude oil was dissolved in 1000 ml. of cyclohexane. The cyclohexane solution was treated with 1 g. of anhydrous copper(II) sulfate and refluxed for 18 hours (64). The solution was filtered and the solvent was removed by distillation. The residual oil was fractionated at reduced pressure to provide 1.7 g. (40% yield) of anti-6-methylbicyclo[3.1.0]hexan-2-one, b.p. 74-76°C (8 mm).

M^+/e: Parent peak at 110.

IR: (Neat) Cyclopropyl hydrogens at 3.28μ and a carbonyl band at 5.85μ.

NMR: (CCl_4) A 3 proton singlet at 1.1 ppm, a 1 proton singlet 1.0 ppm, and a complex pattern of 6 protons between 1.15 and 2.2 ppm.

Derivative: 2,4-Dinitrophenylhydrazone, m.p. 118-120°C.

Anal. Calcd. for $C_{13}H_{14}N_4O_4$: C, 53.79; H, 4.83.

Found: C, 53.71; H, 4.80. M^+/e: Parent peak 290.

syn-6-Methylbicyclo[3.1.0]hexan-2-one

cis-n-Pent-3-ene-1-ol. One half mole of 3 pentyine-1-ol was dissolved in 150 ml. of ethyl acetate and 1 g. of 5% palladium on barium sulfate catalyst was added to the solution. The alkyne solution was hydrogenated in a Parr apparatus until 1/2 mole of hydrogen was taken-up. The solution was filtered and distilled to provide 38 g. (86% yield) of cis-n-pent-3-en-1-ol, b.p. 51°C (15 mm). IR indicated absence of the trans double bond.

cis-n-Pent-3-enyl-1-bromide. cis-n-Pent-3-en-1-ol, 38 g. (0.43 mole) was dissolved in 10 ml. of dry pyridine. The flask was equipped with a magnetic stirrer and a nitrogen inlet. The flask was immersed in a Dry Ice acetone bath and 47 g. (0.17 mole) of phosphorous tribromide was added over a period of 2 hours. The flask was allowed to come to room temperature and the reaction mixture was crudely distilled under reduced pressure. Ether (75 ml.) was added to the distillate and the ethereal solution was washed with 10% sodium hydroxide, 10% sulfuric acid, and dried over sodium sulfate. The ether was removed and the residual oil distilled to provide 37 g. (63% yield) of cis-n-pent-3-enyl-1-bromide, b.p. 70°C (75 mm).

cis-n-Pent-3-enoic acid. A Grignard reagent was prepared from 37 g. (0.25 mole) of cis-n-pent-3-enyl-1-bromide and 8 g. (0.33 g-atom) of magnesium in 100 ml. of anhydrous ether. The reagent was cooled with an ice-salt bath and carboxylated by passing dry carbon dioxide gas over the surface

of the stirred solution. Finally a large excess of crushed Dry Ice was added to the reaction flask. Fifty ml. of 10% sulfuric acid was added to the reaction flask. The ether layer was separated and extracted with 10% sodium hydroxide solution. The basic aqueous extracts were acidified and extracted with ether. The ethereal solution was dried and distilled to provide 20.2 g. (62% yield) of cis-n-pent-3-enoic acid (62), b.p. 80°C (1.5 mm); p-bromophenylacyl ester, m.p. 55°C; Lit. (62) m.p. 55°C. The IR and NMR spectra of this compound are characteristically different from those of the trans isomer.

syn-6-Methylbicyclo[3.1.0]hexan-2-one. The cis acid was converted to the acid chloride, diazoketone, and syn-6-methylbicyclo[3.1.0]hexan-2-one in the same manner in which the trans acid was converted to the anti-6-methylbicyclo[3.1.0]-hexan-2-one. This procedure provided 2.5 g. (60% yield) of syn-6-methylbicyclo[3.1.0]hexan-2-one, b.p. 60-62°C (4 mm). The syn and anti-6-methyl ketones were shown to be independent of one another by glpc (13 ft. SF 96, 20%, on firebrick).

M^+/e: Parent peak at 110.

IR: (Neat) Cyclopropylhydrogens at 3.28μ and a carbonyl band at 5.85μ.

NMR: (CCl_4) A single proton at 1.05 ppm, a three proton singlet at 1.15 ppm, and 6 additional protons in a complex pattern between 1.2 and 2.3 ppm.

Derivative: 2,4-Dinitrophenylhydrazone, m.p. 124-127°C.

Anal. Calcd. for $C_{13}H_{14}N_4O_4$: C, 53.79; H, 4.83.

Found: C, 53.64; H, 4.77.

M^+/e: Parent peak 290.

anti-6-Ethylbicyclo[3.1.0]hexan-2-one

Δ^2-n-Hexenoic acid. To a cold mixture of n-butyraldehyde (1.5 mole) and triethanolamine (1.5 mole) dry malonic acid (1.5 mole) was added. The mixture was stirred mechanically for 6 hours and heated on a steam bath overnight. The liquid was cooled and acidified with 50% sulfuric acid. The organic layer was separated and the aqueous layer was extracted with three 150 ml. portions of ether. The combined ether extracts and original organic layer were extracted with 10% sodium hydroxide solution and the basic extracts were thoroughly washed with ether. The acid was liberated from the basic solution by acidification with concentrated hydrochloric acid, followed by ether extraction. The ether extracts were washed with saline solution and dried over calcium chloride. The ether was removed by means of a rotatory evaporator and the residual oil was fractionated under reduced pressure to provide 92 g. (52% yield) of Δ^3-n-hexenoic acid (65), b.p. 110°C (15 mm).

trans-n-Hex-3-en-1-ol. Into a 3 liter three-necked flask equipped with a mechanical stirrer, condenser, pressure compensated addition funnel, and nitrogen inlet was placed 1500 ml. of dry ether and 30 g. (0.8 mole) of lithium aluminum hydride. The Δ^3-n-hexenoic acid (90 g., 0.8 mole) was dissolved in 300 ml. of ether and the ethereal solution was added dropwise to

the lithium aluminum hydride solution. The reaction was completed by refluxing for 1 hour. The reaction flask was cooled and small pieces of ice were added to destroy the residual lithium aluminum hydride. Water (100 ml.) was added and the ether layer was separated and washed with dilute alkali and acid. The ether layer was dried over sodium sulfate and the ether was removed by distillation. Fractionation of the residual oil under reduced pressure provided 52 g. (63% yield) of trans-n-hex-3-en-1-ol (66), b.p. 51-53°C (9 mm). The IR showed a strong absorption at 10.35μ which is characteristic of trans-disubstituted olefins.

trans-n-Hep-3-enoic acid. trans-n-Hex-3-en-1-ol was converted to trans-n-hep-3-enoic acid, b.p. 81°C (0.85 mm) in the same manner by which cis-n-pent-3-en-1-ol was converted to cis-n-pent-3-enoic acid. The p-bromophenacyl ester was prepared, m.p. 78.5-79.5°C.

anti-6-Ethylbicyclo[3.1.0]hexan-2-one. trans-n-Hep-3-enoic acid was converted to anti-6-ethylbicyclo[3.1.0]hexan-2-one in the same manner in which the cis and trans-n-hex-3-enoic acids were converted to the respective syn and anti-6-methylbicyclo[3.1.0]hexan-2-one derivatives. This procedure provided 4.0 g. (49% yield) of anti-6-ethylbicyclo[3.1.0]hexane-2-one, b.p. 60°C (3.6 mm).

M^+/e: Parent peak at 124.

IR: (Neat) Cyclopropyl hydrogen at 3.28μ and a carbonyl band at 5.84μ.

NMR: (CCl_4) A complex pattern between 0.8 and 2.1 ppm.

Derivative: 2,4-Dinitrophenylhydrazone, m.p. 136-138°C.

Anal. Calcd. for $C_{14}H_{16}N_4O_4$: C, 55.29; H, 5.26.

Found: C, 55.21; H, 5.22.

M^+/e: Parent peak at 304.

syn-6-Ethylbicyclo[3.1.0]hexan-2-one

cis-n-Hep-3-enoic acid. cis-n-Hex-3-en-1-ol (Aldrich Chemical Co.) was converted to cis-n-hep-3-enoic acid in the same manner in which cis-n-pent-3-en-1-ol was converted into cis-n-hex-3-enoic acid. This procedure provided 20.2 g. (60% yield) of cis-n-hep-3-enoic acid, b.p. 85°C (1.5 mm). The p-bromophenylacyl ester was prepared, m.p. 50.5-51.5°C. The IR band at 10.35μ is characteristic of trans-substituted double bonds was absent.

syn-6-Ethylbicyclo[3.1.0]hexan-2-one. cis-n-Hep-3-enoic acid was converted to syn-6-ethylbicyclo[3.1.0]hexan-3-one in the same manner in which cis and trans-n-hex-3-enoic acids were converted to the respective syn and anti-6-methylbicyclo[3.1.0]-hexan-2-one derivatives. This procedure provided 3.3 g. (39.3% yield) of syn-6-ethylbicyclo[3.1.0]hexan-2-one, b.p. 65°C (4 mm). The syn and anti-6-ethyl ketone were shown to be independent of one another by glpc (13 ft. SF 96, 20%, on firebrick).

M^+/e: Parent peak at 124.

IR: (Neat) Cyclopropyl hydrogens at 3.28μ and a carbonyl band at 5.83μ.

NMR: (CCl_4) A complex pattern between 0.8 and 2.0 ppm.

Derivative: 2,4-Dinitrophenylhydrazone, m.p. 113-114°C.

Anal. Calcd. for $C_{14}H_{16}N_4O_4$: C, 55.29; H, 5.26.

Found: C, 55.23; H, 5.24.

M^+/e: Parent peak at 304.

1-Deuterium-syn-6-ethylbicyclo[3.1.0]hexan-2-one

Diazomethane-d_2. Partially deuterated diazomethane was generated from diazold, deuterium oxide, carbitol, and potassium hydroxide (63). To an ice cold ethereal solution of partially deuterated diazomethane was added 50 ml. of deuterium oxide containing 1 g. of potassium carbonate. The two-phase solution was stirred for 45 minutes by means of a Teflon coated stirring bar and magnetic stirrer. The aqueous layer was removed by inserting a fire polished bent glass tube to the bottom of the flask and then exerting a positive nitrogen pressure on the liquid surface. The exchange procedure was repeated and the aqueous layer was removed. The ethereal diazomethane-d_2 solution was redistilled directly from the exchange vessel. The usual precautions were taken (63). This procedure provided large quantities (0.4 mole) of dry ethereal solution of diazomethane-d_2 (>97% deuterium incorporation).

1-Deuterio-syn-6-ethylbicyclo[3.1.0]hexan-2-one. cis-n-Hep-3-enoic acid was converted to the 1-deuterio-syn-6-ethylbicyclo[3.1.0]hexan-2-one in the same manner in which this acid was converted to the undeuterated ketone. Diazomethane-d_2 was used to convert the acid chloride to the diazoketone. This

procedure provided 3.1 g. (35% yield) of 1-deuterio-*syn*-6-ethylbicyclo[3.1.0]hexan-2-one, b.p. 65°C (4 mm). The glpc retention time was identical to that of the undeuterated *cis* isomer. The *trans* ketone was shown not to be present by glpc analysis.

M^+/e: Parent peak at 125. Parent peak at 124 could not be detected.

IR: (Neat) Cyclopropyl hydrogen at 3.28μ, deuterium at 4.4μ, and a carbonyl band at 5.83μ.

NMR: (CCl_4) A complex pattern between 0.8 and 2.0 ppm.

Tricyclo[5.1.C.$0^{4,8}$]octan-2-one

Cyclopentene-3-acetic acid (Aldrich Chemical Co.) was converted to the acid chloride, diazoketone, and tricycloketone in the same manner in which the acyclic acids were converted to the bicycloketones. This procedure provided 3.9 g. (67% yield) of tricyclo[5.1.0.$0^{4,8}$]octan-2-one, b.p. 62-63°C (1.3 mm).

M^+/e: Parent peak at 122.

IR: (Neat) Cyclopropyl hydrogens 3.28μ and a carbonyl band at 5.82μ.

NMR: (CCl_4)

Derivative: 2,4-Dinitrophenylhydrazone, m.p. 173.5-175°C.

Anal. Calcd. for $C_{14}H_{14}N_4O_4$: C, 55.62; H, 4.63.

Found: C, 55.45; H, 4.59.

M^+/e: Parent peak at 302.

Tricyclo[6.1.0.$0^{4,9}$]nonan-2-one

3-Bromocyclohexene. In a 2 liter three-necked flask equipped with a mechanical stirrer and nitrogen inlet was placed 125 g. (1.5 mole) of cyclohexene and 275 g. (1.5 mole) of N-bromosuccinimide in 800 ml. of carbon tetrachloride. One gram of benzoyl peroxide was added to the above mixture which was refluxed on a steam bath until the gentle ensuing reaction subsided. The reaction mixture was stirred for an additional 15 minutes and allowed to cool. The succinimide was removed by filtration and the carbon tetrachloride was removed by distillation. Fractional distillation of the residual oil provided 100 g. (40% yield) of 3-bromocyclohexene, b.p. 65°C (20 mm).

Cyclohexene-3-acetic acid. 3-Bromocyclohexene was converted to cyclohexene-3-acetic acid in the same manner in which crotyl bromide was converted to trans-n-hex-3-enoic acid. The malonic ester chain extention procedure provided 40 g. of cyclohexene-3-acetic acid, b.p. 97-99°C (0.44 mm). The amide derivative was prepared, m.p. 147-148°C. Lit. (67) m.p. 149-150°C.

Tricyclo[6.1.0.$0^{4,9}$]nonan-2-one. Cyclohexene-3-acetic acid was converted to the tricycloketone in the same manner in which the acyclic acids were converted to bicyclic ketones. This procedure provided 3.5 g. (37% yield) of tricyclo-[6.1.0.$0^{4,9}$]nonan-2-one, b.p. 74° (1.5 mm).

M^+/e: Parent peak at 136.

IR: (Neat) Cyclopropyl hydrogens at 3.28μ and a carbonyl band at 5.83μ.

NMR: (CCl_4) Complex pattern between 1 and 3 ppm.

Derivative: Oxime, m.p. 89-90°C; Lit. (67) m.p. 90-91°C.

Tricyclo[7.1.0.$0^{4,10}$]deca-2-one

3-Bromocycloheptene. 3-Bromocycloheptene, b.p. 60° (5.4 mm) was prepared in the manner described in the preparation of 3-bromocyclohexene. 3-Cycloheptene-3-acetic acid, b.p. 104° (0.3 mm) was prepared by the malonic ester synthesis as previously described. The amide derivative was prepared, m.p. 130°C; Lit. (21) m.p. 128-129°C. Cycloheptene-3-acetic acid was converted to the tricycloketone in the same manner in which the acyclic acids were converted to bicycloketones. This procedure provided 2.1 g. (26% yield) of tricyclo[7.1.0.$0^{4,10}$]-deca-2-one, b.p. 80°C (0.9 mm).

M^+/e: Parent peak at 150.

IR: (Neat) Cyclopropyl hydrogens at 2.27μ and a carbonyl band at 5.85μ.

NMR: (CCl_4) A complex pattern between 1 and 3 ppm.

Derivative: Oxime, m.p. 105-108°C; Lit. (67) 106-108°C.

6,6-Dimethylbicyclo[3.1.0]hexan-2-one

Three grams of 4,4-dimethyl-2-cyclohexenone (a gift from Mr. Loren Barber at Iowa State University) was placed in 600 ml. of dry t-butyl alcohol and irradiated with a mercury arc lamp in a water cooled immersion apparatus for 48 hours. The

t-butyl alcohol was distilled and the remaining oil was separated by glpc (6 ft. LAC-446, 5%, on 80-100 mesh Chromosorb P). The fraction with a retention time of 5.5 minutes was shown to be 6,6-dimethylbicyclo[3.1.0]hexan-2-one (68).

M^+/e: Parent peak at 124.

IR: (Neat) Cyclopropyl hydrogens at 3.32μ and a carbonyl band at 5.81μ (68).

NMR: (CCl_4) A six proton singlet at 1.1 ppm and a complex pattern of 6 protons between 1.42 and 2.5 ppm (68).

Dihydro-lumesantoin

Lumisantoin. Five g. of santoin (Aldrich Chemical Co.) was dissolved in 300 ml. of dioxane. This solution was irradiated for 2.5 hours with a Hanovia lamp in a Pyrex, water-cooled, immersion well apparatus. The dioxane was removed by means of a rotatory evaporator and the remaining material was separated by column chromatography (300 g. silica-gel). The crude lumisantoin, 2.5 g., was eluted with 10% ether in pentane. Recrystallization from acetone-pentane provided pure lumisantoin (69), m.p. 156-159°C; lit. (69) m.p. 156-157°C.

Dihydro lumisantoin. Lumisantoin, 500 mg., was dissolved in 40 ml. of ethyl acetate containing 10 mg. of 10% palladium-on-charcoal catalyst. The hydrogen up-take was carefully measured in a semi-micro apparatus. The hydrogenation was stopped when an equimolar amount of hydrogen

had been incorporated. The hydrogenation mixture was filtered, the solvent was removed, and the product was recrystallized from hexane. This procedure provided 350 mg. of dihydro-lumisantoin, m.p. 162-166°C; lit (69) 164-165°C.

M^+/e: Parent peak at 248.

IR: ($CHCl_3$) Lactone carbonyl band at 5.62μ, and another carbonyl at 5.84μ.

Tricyclo[4.3.1.0]deca-3-en-8-one

β-Indanol. Indene oxide (Columbia Chemical Co.), 30 g. (0.25 mole) was dissolved in 150 ml. of dioxane. Three g. of a relatively inactive Raney-Nickel catalyst was added and the oxide was hydrogenated in a Parr apparatus until 0.25 mole of hydrogen was absorbed. The solution was filtered and the solvent was removed. This procedure provided 31 g. (97%) of β-indanol, m.p. 67-70°C; lit. (70) m.p. 68-69.5°C.

4,7-Dihydroindan-2-ol. β-Indanol, 3 g. (0.24 mole) was dissolved in 50 ml. of anhydrous ethanol. The ethanolic solution was added to 1.5 l. of liquid ammonia and sodium metal, 16 g. (0.7 g-atom) was added in small pieces. The ammonia was evaporated and the residue was diluted with water. The aqueous solution was acidified, saturated with sodium chloride, and extracted with ether. The ether extracts were dried and the ether was removed. The residual oil was distilled to provide 24.1 g. (70% yield) of 4,7-dihydroindan-2-ol (71), b.p. 100°C (1.5 mm).

Tricyclo[4.3.1.0]deca-3-en-8-ol. The methylene insertion was performed as described in the preparation of bicyclo[3.1.0]hexan-3-ol from Δ^3-cyclopentenol. The yield was very high (85%). The crude product was recrystallized from hexane to produce a white crystalline solid, m.p. 68-70°C; lit. (71) m.p. 69-70°C. The spectral properties were in good accord with those reported in the literature (71).

Tricyclo[4.3.1.0]deca-3-en-8-one. The oxidation was performed as described in the preparation of bicyclo[3.1.0]-hexan-3-one from bicyclo[3.1.0]hexan-3-ol. The crude product was distilled to provide 1.0 g. of tricyclo[4.3.1.0]deca-3-en-8-one (72), b.p. 73°C (1.5 mm).

M^+/e: Parent peak at 148.

IR: (Neat) Cyclopropyl hydrogens at 3.28μ and a carbonyl band at 5.75μ.

NMR: (CCl_4) A 1 proton multiplet at 0.17 ppm, a 1 proton multiplet at 0.9 ppm, an 8 proton multiplet at 2.31 ppm, and 2 vinyl protons at 5.55 ppm.

Bicyclo[5.1.0]octan-2-one

3-Acetoxycycloheptene. Cycloheptene, 129 g. (1.34 mole), mercuric acetate 480 g. (1.5 mole) and 700 ml. of acetic acid were placed in a 3 liter three-necked flask fitted with a mechanical stirrer and reflux condenser. The mixture was stirred for 45 minutes at room temperature while a yellow precipitate formed and then refluxed for 10 hours. The dark solution was cooled to room temperature in an ice bath and filtered

to remove the metallic mercury. The solution was concentrated by removing acetic acid on a rotatory evaporator. The residue was poured into 1500 ml. of cold water and extracted with four 300 ml. portions of ether. The combined ether extracts were washed with 5% sodium bicarbonate solution and dried over magnesium sulfate. The ether was removed and the crude product was distilled to provide 38.9 g. of pure monoacetate, b.p. 63-65°C (15 mm).

3-Cycloheptenol. 3-Acetoxycycloheptene, 38.9 g. (0.25 mole) was added dropwise to a solution of 28 g. of potassium hydroxide in 25 ml. of water and 75 ml. of ethanol. The saponified ester was poured into 500 ml. of saturated sodium chloride solution and the aqueous solution was extracted with ether. The ethereal extracts were dried and distilled to provide 30.1 g. (94% yield) of 3-cycloheptenol, b.p. 61-63°C (10 mm).

Bicyclo[5.1.0]octan-2-ol. 3-Cycloheptenol was converted to bicyclo[5.1.0]octan-2-ol in the same manner in which Δ^3-cyclopentenol was converted to bicyclo[3.1.0]hexan-3-ol. This procedure provided 5.3 g. (60% yield) of bicyclo[5.1.0]octan-2-ol, b.p. 90°C (10 mm), m.p. 39-42°C; lit. (73) 39-40°C.

Bicyclo[5.1.0]octan-2-one. Bicyclo[5.1.0]octan-2-ol was oxidized to the ketone in the same manner in which nortricyclanol was oxidized to nortricyclanone. This procedure provided 2.0 g. (52% yield) of bicyclo[5.1.0]octan-2-one, b.p. 70°C (3.5 mm).

M^+/e: Parent peak at 124.

IR: (Neat) Cyclopropyl hydrogens 3.3μ and a carbonyl band of 5.90μ.

NMR: (CCl_4) Complex pattern between 0.8 and 2.5 ppm.

Derivative: 2,4-Dinitrophenylhydrazone, m.p. 192-195°C; lit. (74) 195-196°C.

Bicyclo[6.1.0]nonan-2-one

Cyclooctene was converted to bicyclo[6.1.0]nonan-2-one in the same manner in which cycloheptene was converted to bicyclo-[5.1.0]octan-2-one. This procedure provided 2 g. of bicyclo-[6.1.0]nonan-2-one, b.p. 55-57°C (0.8 mm).

M^+/e: Parent peak at 138.

IR: (Neat) Cyclopropyl hydrogens at 3.34μ and a carbonyl band at 5.9μ.

NMR: (CCl_4) Complex pattern between 0.4 and 2.5 ppm.

4-Methyl-5-ethylpyrocatechol

2-Methyl-4,5-dimethoxyacetophenone. 4-Methylveratrole, (50 g. (0.33 mole) was dissolved in 200 ml. of carbon disulfide containing 30 g. of acetyl chloride. Aluminum chloride catalyst, 43 g. (0.33 mole) was added slowly and the mixture was stirred overnight by means of a mechanical stirrer. The reaction was heated on a steam bath for 2 hours, cooled and diluted cautiously with 100 ml. of water. The carbon disulfide was removed by distillation and the residual aqueous layer was extracted with ether. The ether extracts were washed with 5% potassium hydroxide and dried over sodium sulfate. The ether

was removed and the residual oil distilled to provide 30 g. of a product (50% yield), b.p. 204°C (70 mm). The product was identified by IR and NMR spectroscopy.

4-Methyl-5-ethyl-1,2-dimethoxybenzene. 2-Methyl-4,5-dimethoxyacetophenone, 20 g. (0.11 mole) was added to 100 g. of 5% Zn(Hg) amalgam in 200 ml. of concentrated hydrochloric acid. The mixture was heated for 15 hours, cooled, and extracted with chloroform. The chloroform extracts were washed with dilute potassium hydroxide and dried over sodium sulfate. To solvent was removed and the residual oil was distilled to yield 14 g. (78% yield) of 4-methyl-5-ethyl-1,2-dimethoxybenzene, b.p. 105°C (5 mm).

4-Methyl-5-ethylpyrocatechol. 4-Methyl-5-ethyl-1,2-dimethoxybenzene, 5 g., was dissolved in 75 ml. of hydroiodic acid (sp. g. 1.5). The mixture was refluxed under nitrogen for 1 hour, cooled and diluted with water. The aqueous solution was extracted with chloroform and dried over calcium chloride. The crude product was almost entirely 4-methyl-5-ethylpyrocatechol.

M^+/e: Parent peak at 152.

IR: (Neat) Hydroxyl absorption at 2.9μ.

NMR: Three proton triplet, 1.0 ppm coupled with a 2 proton quartet at 2.25 ppm. A methyl singlet at 2.0 ppm and 2 aromatic protons at 6.5 ppm. Two exchangeable hydroxyl protons at 6.05 protons.

Derivative: Diacetate, m.p. 70-74°C; lit. (75) m.p. 72-73°C.

Purification of Reagents

Dimethyl sulfoxide

Dimethyl sulfoxide (J. T. Baker Chemical Co.), 750 ml. was placed in a 1 liter flask which was fitted with a 30 cm. distillation column. Forty mesh calcium hydride (Ventron Corp.), 40 g., was added and the dimethyl sulfoxide was distilled under reduced pressure. The pot temperature was not allowed to exceed 90°C and distillation was discontinued when 400 ml. of distillate had been collected. The distillate was stored over Molecular Sieves (J. T. Baker Chemical Co., Type 4A).

Dimethyl sulfoxide-d_6

Dimethyl sulfoxide-d_6 (Fluka) was stored over Molecular Sieves (J. T. Baker Chemical Co., Type 4A) and used without further purification.

t-Butoxide bases

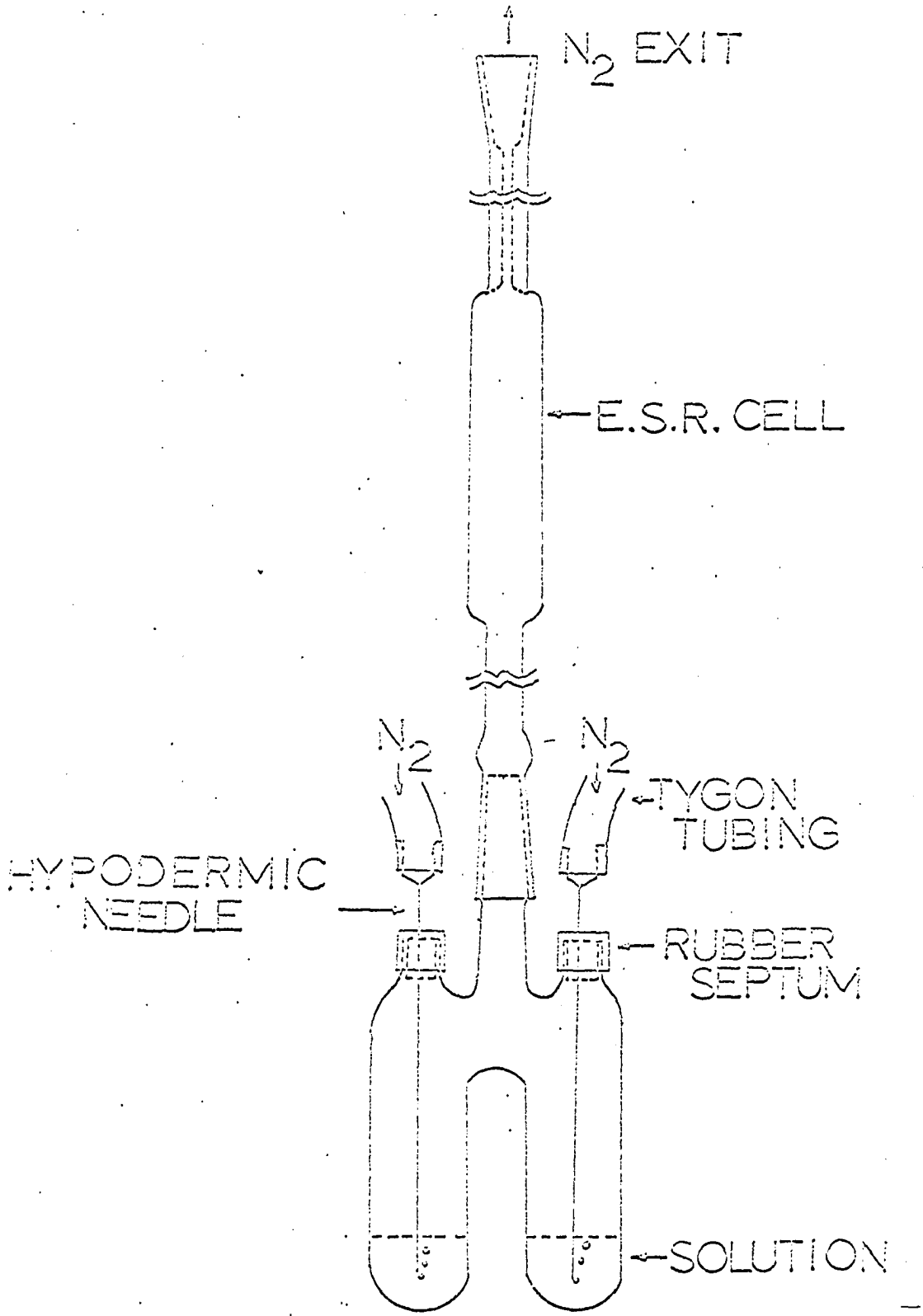
Sodium and cesium t-butoxide (Research Corp.) were sublimed in a cold finger apparatus at 110°C (0.5 mm). The bases were stored in ground glass stoppered bottles in a desiccator.

Oxidation Procedure

A Varian V-4548 aqueous solution cell was equipped with a H-cell (Figure 38). The openings in the H-cell would easily be closed with rubber septa.

A typical oxidation procedure involved placing 0.1 millimole of ketone in one side of the H-cell and 0.3 millimole of base in the other side. One half ml. of dimethyl sulfoxide

Figure 38. Apparatus for degassing and mixing ketone and base solutions.


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

was added to each chamber of the H-cell and the solutions were degassed by passing prepurified nitrogen for 20 minutes through hypodermic needles immersed in the solutions. The nitrogen flow was stopped and the exit part at the top of the ESR cell was immediately closed with a ground glass stopper. The hypodermic needles were removed and the solutions were mixed thoroughly. A trace of oxygen was admitted by removing a septum for 3 seconds. The solution was shaken for three minutes and the apparatus was inverted so that liquid filled the flat portion of the ESR cell.

Recording of ESR Spectra

The ESR spectra were recorded on a Varian V-4500 high resolution spectrometer equipped with a 9-inch magnet with Fieldial control and operating at 100 kcps field modulation.

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