Cyclisation Reactions, Photochemistry And 13-C NMR Of 9-Thiabicyclo [3,3,1] nonanes

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by

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To my loving wife Carol

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C O N T E N T S

SUMMARY

Both O— and C—acylated products have been isolated from the acid-catalysed acylations of 9-thiabicyclo [3,3,1] nonan-2,6-dione with acid anhydrides. In particular, high acid concentration favours C-acylation with intramolecular aldol condensation of the initially formed products producing derivatives of 2-thiaadamantane. Structural assignment of these products was achieved by examining their chemical reactivity and by the application of a new ^{13}C double resonance technique to elucidate their complex proton spectra. Acylations with acid halides were found to give inferior yields of both O— and C-acylated products.

Photolytic sulphur extrusion from diketones and bisenones of the 9-thiabicyclo [3,3,1] nonane series and the related 9-oxides and 9,9-dioxides has been investigated.

Selected derivatives of 9-thiabicyclo [3,3,1] nonane and 9-thiabicyclo [3,3,1] non-2-ene were synthesised and tested for fungicidal, insecticidal and pharmaceutical activity.

Chapter 1

1. A Review of ^{13}C NMR Spectroscopy relating to Off-Resonance and Gated Decoupling.

Since its discovery in the 1940's nuclear magnetic resonance (NMR) spectroscopy has become one of the principal analytical techniques used in structure identification. Although technological progress in instrumentation has consistently lagged behind theoretical advances in this field several branches of NMR spectroscopy have been developed to a highly sophisticated level e.g. nuclear magnetic double resonance (NMDR).

The method of double resonance was originally based on a proposal made by Bloch in 1954[1] and successfully carried out by Royden in the same year[2]. The basic requirement for any NMDR experiment is the presence of at least two magnetic nuclei (Table 1) in a polarizing static magnetic field H_0. These nuclei can either be of the same type (homonuclear double resonance) or different (heteronuclear double resonance). The transitions between the energy levels of one nucleus are measured by applying two oscillating magnetic fields H_1 and H_2, the former being used to observe this nucleus as the latter perturbs the second nucleus. In his experiment Royden determined the Larmor frequency of ^{13}C in methyl iodide ($^{13}CH_3I$) by observing the collapse of the proton doublet into the optimal singlet during the frequency sweep of the perturbing field H_2 over the ^{13}C frequency range.

Since 1954 advances in spectrometer technology have given rise to a large number of different experimental techniques in the field of double resonance which differ in the instrumentation used to record NMDR spectra with the corresponding information derived from these spectra more comprehensive than that obtained

in the initial work of Royden. Thus the chemist today can apply noise[3], off-resonance[3], gated[4], spin[2], selective spin[5] and Indor[6] decoupling techniques along with spin tickling[5], chemical exchange[7], Torrey oscillations[8], generalised[9] and nuclear[10] Overhauser studies to the nuclear spin system in question. The information derived from these double resonance experiments includes the location of hidden or weak resonances, assignment of chemical shifts, determination of the sign and magnitude of scalar coupling constants, structure elucidation with the solution to stereochemical problems, measurement of relaxation and correlation times, and the construction of energy level diagrams with assignment of observed transitions to definite energy levels. As the literature concerned with each of these methods and their applications is abundant it would be impossible to give a complete review of NMDR spectroscopy in the space available. The discussion has therefore been curtailed to recent advances which are of relevance to the NMR study described in the following section.

In 1966 Ernst and Anderson[11] gave the first demonstration of 'Fourier Transform (FT) NMR', a technique which has made a particularly significant impact on NMR spectroscopy over the last decade. Prior to the publication of this work all single and double resonance experiments had been carried out in the continuous wave (CW) mode with satisfactory spectra obtained for those nuclei of high magnetic sensitivity viz. ^{1}H, ^{19}F and ^{31}P (Table 1). As a direct consequence of the long periods required for each scan in the CW mode, usually ca.500 sec., the acquisition of an adequate signal-to-noise (S/N) ratio for nuclei of lower sensitivity e.g. ^{13}C, ^{15}N (Table 1) is a

lengthy process even when time-averaging (multiscanning) is carried out. Although this problem is improved by the application of 'broad band proton decoupling' in NMDR experiments Fourier transformation has effectively taken over the detection of low intensity signals.

Ernst and Anderson[11] had found that the response of an NMR sample to a high energy pulse of excitation could be converted by Fourier transformation into a 'normal' frequency - domain spectrum with an overall gain in sensitivity. Under normal practical conditions a steady-state [12,13] is set up owing to the initiation of a second pulse before the response to the first pulse has completely died away. Although the sensitivity enhancement obtained is greater than that proposed by Ernst and Anderson[11] because of the refocusing effects of the sequence, the steady-state gives rise to anomalies in phase and intensity. However, by altering the pulse interval e.g. after every 60 pulses, new steady-states are set up and the anomalies effectively removed by averaging the decays set up by these random steady-states.

The principal advantage of pulsed Fourier transform over CW NMR spectroscopy is associated with the much shorter time it requires for each scan i.e. of the order of 1 sec. As the S/N ratio is proportional to the square root of the number of scans recorded, the acquisition of an adequate NMR spectrum by FT is much faster than by CW with the application of FT to ^{13}C NMR spectroscopy being largely responsible for its emergence as a major analytical technique.

The related concepts of 'Overhauser enhancement' and 'relaxation times' play significant roles in the acquisition of

double resonance spectra irrespective of the particular NMDR technique employed. The term Overhauser enhancement covers two distinct effects each of which change the intensity of the observed spectral transitions by altering the populations of the corresponding nuclear energy levels. When the intensity changes observed in double resonance are for connected transitions in spin systems with exclusively scalar coupling they are known collectively as the 'generalised Overhauser effect (GOE)'[9]. The first effect of this kind was noted by Anderson and Freeman [14] when they perturbed (spin tickled) one line of the methyl doublet of acetaldehyde and observed the change in intensity of the aldehydic proton quartet. The resulting population changes in the energy level diagram of acetaldehyde enhanced those transitions which were progressively connected to the perturbed line with the intensity of regressive lines being decreased. By repeating this experiment using Fourier transform NMR (vide supra) Freeman[15] was able to observe the relative intensities of this quartet relax to their equilibrium 1:3:3:1 ratio. The magnitude of the changes involved in GOE are small and must be detected by comparison with the normal unperturbed spectral lines.

In contrast the 'nuclear Overhauser effect (NOE)'[10] gives rise to larger fluctuations in intensity and is therefore more important in double resonance spectroscopy. It can be distinguished from the generalised Overhauser effect in that (1) the relaxation mechanisms involved are inter-or intra-molecular in nature (scalar coupling not being essential), and (2) one type of nucleus is monitored as the total signal of the second type is irradiated by a high power rf field.

The close relationship between the NOE and relaxation mechanisms is best understood by considering these phenomena at the same time. By applying an rf field at the Larmor frequency corresponding to one particular type of nucleus the nuclei are promoted from the lower to the higher nuclear spin energy level. The relaxation times T_1 and T_2, which are two of the most important parameters in NMR spectroscopy, are dependent on the relaxation mechanisms by which the relative populations of these energy levels return to the ratio indicated by the Boltzman distribution for the spin system at thermal equilibrium. Of these two parameters, the spin-lattice relaxation time T_1 is of greater importance to the NOE and is normally defined as the time required for the nuclear spins to dissipate their excess energy to the lattice, a term which normally refers to the translational and rotational degrees of freedom of the molecules in which the nuclei are situated.

The relaxation mechanisms which usually contribute to T_1 are dipole-dipole interactions. Every nucleus which bears a magnetic spin also possesses a magnetic dipole moment which couples with the local magnetic field (H_I) experienced by it. Most NMR spectra are recorded in the fluid state in which H_I fluctuates with time and averages out as zero i.e. $\langle H_I(t) \rangle = 0$ due to the molecular motion taking place. Typically, however, the translational and rotational motion of molecules in the fluid state cause the fluctuations of H_I to have a component at the Larmor frequency of the nuclear spins which allows H_I to induce transitions between the nuclear energy levels and hence cause relaxation.

Every nuclear interaction that contributes to H_I is capable of causing this relaxation. For spin-$\frac{1}{2}$-nuclei e.g. ^1H, ^{13}C in the fluid state the most important mechanisms are intermolecular dipole-dipole, intramolecular dipole-dipole and spin-rotation, scalar coupling being unimportant unless chemical exchange takes place. In the intermolecular dipole-dipole relaxation mechanism interactions between nuclear spins on different molecules permits the excess nuclear spin energy to be dissipated to the translational motion of the molecules especially when high concentrations of nuclei with large magnetic moments (e.g. ^1H or ^{19}F) are present. Normally there are four possible sources for this type of mechanism viz. identical solute molecules, solvent, lock sample (if an internal lock is used) and paramagnetic impurities. Relaxation by solvent was the main mechanism involved in the first observation of an NOE[16]. In this work Kaiser monitored the increase in intensity of the chloroform proton signal in a mixture of chloroform and cyclohexane when the cyclohexane protons were saturated.

In the intramolecular dipole-dipole relaxation mechanism interaction takes place between nuclear spins that belong to the same molecule and are close together in space. The significance of the NOE in structure elucidation, which was recognised by Anet and Bourn[17], is dependent on the contribution made by this type of mechanism to T_1. As a result double resonance spectra are usually recorded on samples of low concentration and in the absence of paramagnetic impurities to diminish the relative contribution made by the intermolecular dipole-dipole mechanisms to T_1, as compared to that of the

intramolecular interactions. The importance of intramolecular relaxation in the assignment of molecular structure arises from the magnitude of this type of mechanism's contribution to T_1 being dependent on the correlation time for molecular rotation and the internuclear separation (r) of the nuclear spins in question. Bell and Saunders[18] have shown that the magnitude of the NOE is inversely proportional to the sixth power of the internuclear separation by measuring a large number of NOE values in cases where r is known. Nouls[19] has used the NOE to identify the major component in a mixture of two isomeric ethylideneazabicyclo[2,2,2] octanes $\underline{1}_a$ and $\underline{1}_b$. Only structure $\underline{1}_a$ will give an enhanced signal for the bridgehead proton when the methyl resonance is saturated.

The contribution of spin-rotation to T_1 involves the interaction of the nuclear magnetic moment and the rotational magnetic moment of the molecule in which the nucleus is situated. It is of lesser importance than dipole-dipole relaxation only making a significant contribution to T_1 when the NMR spectrum is recorded at high temperatures.

In the preceding paragraphs the NOE has been expressed in terms of the population changes occurring in the nuclear energy levels of an observed nucleus as a result of the spin-lattice relaxation of a second perturbed nucleus. When nuclear spins are placed in a static magnetic field H_0 directed along the Z-axis (Fig.1) there is a small magnetization M_z induced due to the partial alignment of the spins with H_0. The system eventually reaches a position of thermal equilibrium with an equilibrium value for M_z i.e. M_0. Perturbation of the second nucleus can be

obtained when an rf field H_1, rotating in the XY plane at the spin's Larmor frequency, is applied at 90° to H_o e.g. along the X-azis. The effect of H_1 is to tilt the nuclear magnetic dipole towards the Y-axis resulting in the fluctuation of M_z and the formation of a transverse magnetization M_y. The spin-lattice or longitudinal relaxation time T_1 is the time constant for the decay of the nuclear M_z component of magnetization to its equilibrium value M_o. The spin-spin or transverse relaxation time T_2 is the time constant for the decay of the transverse magnetization M_y to zero. The disappearance of M_y is due to the dephasing of the spins as they precess round the Z-axis and may or may not involve the transfer of energy between the spins and the lattice e.g. an adiabatic exchange of energy between the spins (spin-spin relaxation) does not dissipate the excess spin energy to the lattice and hence T_2 makes at most a small contribution to the NOE.

The fact that ^{13}C NMR spectroscopy involves the direct observation of the molecular backbone in organic molecules accounts for its emergence as a major analytical technique in structure analysis. Nowadays the complete assignment of ^{13}C NMR spectra is commonly achieved by the combination of noise, off-resonance and gated decoupling experiments in a FT NMR spectrometer.

The technique of noise decoupling was first demonstrated by Ernst[3] in 1966 when he recorded the ^{19}F spectrum of a cis-trans isomeric mixture of 1,1,2-trifluoro-2-chloro-3-vinylcyclobutane ($\underline{2}_a$ and $\underline{2}_b$) while noise decoupling the protons; however, the most important use nowadays of proton noise decoupling is in the measurement of the ^{13}C resonance in organic molecules. In this method perturbation of the protons can be achieved either by the

application of random noise or by applying the perturbating field pseudo-randomly over the entire proton frequency range with the aid of a shift pulse generator so that all the proton nuclei are covered in a very short time. Both of these instrumental techniques give complete decoupling of the protons with the resulting collapse of the carbon resonances into singlets which show an increase in line intensity due to Overhauser enhancement (vide supra). For spin-spin decoupling as depicted in a three coordinate axis (Fig.1) application of the perturbating field H_1 directed along the X-axis tilts the proton magnetic dipole previously aligned with the static magnetic field H_o, through 90^o into the XY plane directed along the Y-axis. The spin-spin coupling constant, which is defined by equation [1] ,

$$J_{obs} = J_{hc} (I_h \cdot I_c) \qquad [1]$$

is therefore dependent on the scalar product of the proton and carbon spin vector operators, I_h and I_c, with the observed coupling constant (J_{obs}) varying with the cosine of the angle between them i.e. θ. In noise decoupling $\theta = 90^o$ as I_h and I_c are directed along the Y and Z — axis respectively accounting for the absence of spin-spin coupling in the recorded spectra.

The major drawback associated with noise decoupling is that by collapsing all ^{13}C resonances into singlets the information gained from the multiplicity of the carbon lines is lost i.e. the number of protons directly bonded to each carbon atom. In contrast, off-resonance decoupling [3] retains the carbon multiplicity with Overhauser enhancement but the observed splittings are less than those obtained from the undecoupled ^{13}C spectrum. In this technique the proton decoupler

is run in a coherent mode at a frequency which does not correspond to the resonant frequency of any of the protons in the molecule under investigation. In a three coordinate axis (Fig.1) the effective magnetic field experienced by the protons is between the Z and Y-axis and hence the proton magnetic dipole contains a component along the Z-axis. As the angle between I_h and I_c is in the range $0^\circ < \theta > 90^\circ$ the observed coupling constant takes on the residual value measured. Ernst[3] has shown that this residual splitting (J_r) is given by equation [2]

$$J_r = \left[(\Delta\nu - \tfrac{1}{2}J_o)^2 + (\gamma B_2)^2\right]^{\frac{1}{2}} - \left[(\Delta\nu + \tfrac{1}{2}J_o)^2 + (\gamma B_2)^2\right]^{\frac{1}{2}} \quad [2]$$

where $\Delta\nu$ is the offset of the decoupler from the proton resonance frequency in question, J_o is the true ^{13}C-^{1}H coupling constant and γB_2 is the power of the decoupling field. Under the strict limiting conditions that $\gamma B_2 >> |\Delta\nu|$ this equation can be simplified to [3], the first term of a binomial expansion of [2] .

$$\Delta\nu = J_r \gamma B_2 / J_o \quad [3]$$

Pachler[20] has reformulated equation [2] to give [4]

$$\Delta\nu = J_r \left[(\gamma B_2)^2 + \tfrac{1}{4}(J_o - J_r)^2\right]^{\frac{1}{2}} / (J_o^2 - J_r^2)^{\frac{1}{2}} \quad [4]$$

from which equation [5] is obtained under the far less stringent condition $\gamma B_2 >> \frac{1}{2}\left|J_o - J_r\right|$.

$$\Delta\nu = J_r \gamma B_2 / (J_o^2 - J_r^2)^{\frac{1}{2}} \quad [5]$$

Although the linearity of equation [3] is only held over a narrow frequency range it has been used by Freeman and Hill[13] as the basis for a graphical assignment of the ^{13}C resonances in 3,5-dimethylcyclohex-2-ene-1-one. The proton decoupler is incremented at a fixed power through the proton spectrum and the resultant ^{13}C spectra recorded. The data so obtained are plotted with ^{13}C resonance frequencies on one axis and the proton frequency of the

decoupler on the other axis. A series of parallel lines, the slope of which is proportional to the decoupling power, are drawn and the intersection of these lines relate a proton with its corresponding directly bonded ^{13}C atom. Although tedious, this technique, which requires the complete assignment of the proton spectrum, lends itself to the assignment of complex ^{13}C spectra. Birdsall and co-workers[21] have reported its use in the assignment of the ^{13}C resonances of nicotinamide adenine dinucleotide (Fig.2).

Günther et al.[22] have shown that the observed resonances for the C_α and C_β carbon atoms of indane (2) have a characteristic splitting pattern which can be used as a 'fingerprint' for molecules containing the $\overset{\alpha}{-CH}-\overset{\beta}{CH}-\overset{\beta}{CH}-\overset{\alpha}{CH}-$fragment. He later showed[23] that this splitting pattern was retained in the observed off-resonance decoupled spectra and that it was almost identical to that predicted by equation [3] .

In a separate approach Emsley et al.[24] have used equation [3] to assign the ^{13}C resonances of 1-nitronaphthalene by matching the $\Delta\nu$ values calculated for each ^{13}C resonance with those calculated for each signal in the assigned proton spectrum. Pachler[20] using equation [5] has proposed that ^{13}C assignments can be made from the straight-line plot of $\Delta\nu$ against $J_r/(J_o^2-J_r^2)^{\frac{1}{2}}$, any wrong assignment being detected by its deviation from the line of gradient γB_2.

From the above discussion it can be seen that the application of equations [3] and [5] in the assignment of ^{13}C resonances is well documented. In contrast the use of these off-resonance equations for the assignment of complex proton spectra has not attracted such close attention. Although Emsley[24] (*vide supra*) assigned ^{13}C resonances in his experiment he did calculate the

proton chemical shifts of 1-nitronaphthalene to within ± 0.02 ppm of the observed values using equation [3]. Luzikov and co-workers[26] have used equation [5] to assign the proton spectrum of indene (4) by observing the collapse of residual splittings in the off-resonance decoupled spectra for a molecule in which the ^{13}C resonances have been assigned. This method of proton assignment adapted from the work of Freeman and Hill[13] in ^{13}C assignment has been reviewed by Gray[27].

In each of the above off-resonance equations the calculation of J_r and $\Delta\nu$ values requires that the true $^{13}C-^{1}H$ coupling constant (J_o) is known. Günther and Görlitz[28] have obtained some true $^{13}C-^{1}H$ spin-spin coupling constants by analysis of the ^{13}C satellites in the proton NMR spectra of cycloheptatrienes and then used them to identify some of the proton absorptions present. Nowadays values of J_o are usually obtained by recording gated decoupled ^{13}C NMR spectra which exhibit the true $^{13}C-^{1}H$ coupling constants while retaining the Overhauser enhancement present in noise decoupling. The first demonstration of this technique was reported by Feeney and co-workers[4] when they monitored the ^{13}C nuclei of 50% enriched ^{13}C methyl iodide in the CW mode after the proton decoupler had been switched off. On removal of the proton decoupler the axis of quantisation of the proton magnetic dipole returns to the Z-axis instantaneously (Fig.1) giving rise to the maximum spin-spin coupling constant possible i.e. J_o. An Overhauser enhancement of 24% was detected for a single scan experiment due to the slow relaxation of the excited proton nuclei. This method has the disadvantage that as the ^{13}C spectrum is swept in the CW mode the intensities decrease across the spectrum because the Overhauser increase in population relaxes on removal

of the decoupling field. Gated decoupled ^{13}C NMR spectra are therefore now recorded using a pulsed Fourier transform spectrometer allowing all ^{13}C resonances to be observed at the same time with larger Overhauser enhancements detected[4,29].

2. Proton Chemical Shifts derived from $^{13}C-\{^{1}H\}$ Decoupled ^{13}C NMR Spectra.

INTRODUCTION

During synthetic work (see Chapter 2) on the acid-catalysed acylations of 9-thiabicyclo [3,3,1] nonan-2,6-dione the structure elucidation of the tricyclic derivatives produced at high acid concentrations proved impossible using normal analytical techniques. The structural assignment of these products as 2-thiaadamantane derivatives was ultimately achieved by studying their chemical reactivity (see Chapter 2) and applying a new double resonance technique for the interpretation of their complex proton absorptions, which were broad, highly split, and overlapped.

The utility of heteronuclear off-resonance decoupling has been amply discussed (see preceding review) and attention has been drawn to the applicability and limitations of equations [3] [3,20,23,30] and [5] [20,30] in the assignment of ^{13}C resonances.

$$\Delta\nu = J_r \gamma B_2 / J_o \qquad [3]$$

$$\Delta\nu = J_r \gamma B_2 / (J_o^2 - J_r^2)^{\frac{1}{2}} \qquad [5]$$

In contrast the use of these equations for proton assignment in molecules whose ^{13}C resonances were already known had not been reported. Although the five 2-thiaadamantanes (5-9) exhibited complex proton NMR spectra which could not be simplified by spin-decoupling or by using a high resolution spectrometer, their ^{13}C spectra showed significant chemical shift differences and were readily assigned from comparison spectra [31]. A graphical method based on equation [5] has been developed for the assignment of proton absorptions in these 2-thiaadamantanes and is described in detail for diol (5). When the technique was

based on equation [3] the predicted proton chemical shifts were only accurate over the narrow frequency range for which the equation is linear [20](Table 2).

DISCUSSION

In this method [32] of proton assignment, proton chemical shifts are deduced from $\Delta\nu$ values (separations between individual proton resonance frequencies and the off-resonance decoupling frequency) calculated using equation [5]. Application of equation [5] for this purpose necessitates knowledge of the residual and true ^{13}C-^{1}H coupling constants (J_r and J_o) for each ^{13}C absorption and the factor γB_2. The values of J_r and J_o are derived from an off-resonance[3] and gated[4] decoupling ^{13}C spectra respectively. The factor γB_2 in which γ is the proton gyromagnetic ratio, is related to the decoupling power and is constant for a single off-resonance experiment. Thus from equation [5] $\Delta\nu$ is directly proportional to $J_r/(J_o^2-J_r^2)^{\frac{1}{2}}$ and γB_2 need not be known if a graphical method is to be employed.

The vinyl (δ4.80), hydroxyl (δ3.20), and C-4, C-8 protons (δ3.80) can be confidently assigned in the proton spectrum (Fig.3B) of diol (5). Although the remaining skeletal proton resonances are complex, the noise-decoupled ^{13}C spectrum (Fig.4A) is simple and shows only six distinct resonances of which the four to highest field each comprises two coincident absorptions as a result of C_2 symmetry. Assignment of the ^{13}C peaks (Table 2), made by spectral comparison with 9-thiabicyclo [3,3,1] nonanes and with documented spectra [31], is supported by the signal multiplicities observed in the off-resonance (Fig.4B) and gated (Fig.4C) decoupled spectra. The ratio $J_r/(J_o^2-J_r^2)^{\frac{1}{2}}$ is calculated

for each ^{13}C absorption using measured values of J_r and J_o (Fig.4B and C). For the vinylic methylene group the corresponding $\Delta\nu$ (in Hz) is found from the chemical shift difference between the vinyl proton singlet (δ 4.80; Fig. 3B) and the off-resonance double irradiation frequency. A straight-line plot (Fig.3A) is drawn using $J_r/(J_o^2-J_r^2)^{\frac{1}{2}}$ and $\Delta\nu$ (in ppm) values for the vinylic methylene group taken with a zero point, $J_r/(J_o^2-J_r^2)^{\frac{1}{2}} = 0$, $\Delta\nu = 0$, which applies at the decoupling frequency. For the remaining assigned ^{13}C signals the computed values of $J_r/(J_o^2-J_r^2)^{\frac{1}{2}}$ are plotted and the corresponding $\Delta\nu$ values read off. The latter (in ppm) are chemical shifts (Table 2) of the corresponding skeletal protons.

The predicted chemical shift of H-4 and H-8 corresponds exactly with the observed value (δ 3.80). The observed bridgehead multiplets are unambiguously located (Fig.3B) at δ 2.60 (H-1, H-3) and δ 2.71 (H-5, H-7). For the saturated methylene carbons, coincident by operation of the C_2 axis, the appearance of the ^{13}C signal as a double doublet (Fig.4B; five-fold scale expansion inset) shows that each of these carbon atoms is coupled to two non-equivalent protons. It is thus predicted that the corresponding proton spectrum should show two regions of absorption centred at δ 2.7 and 1.9 (Fig.3A). In the observed spectrum (Fig.3B) the former is partly obscured by the bridgehead signals while the latter (2H) appears as a pair of multiplets showing a larger (geminal) coupling of 13Hz and smaller vicinal coupling of ca.2Hz.

Application of the above method provides an acceptable proton assignment for 5 leaving ambiguity only between the two geminal protons on each of C-9 and C-10. To corroborate this interpretation, proton spectra (Fig.3C and D) of 5 were recorded with added $Eu(fod)_3$ shift reagent. The overlapping signals in the δ 2.6-2.8 region (Fig.3B)

became resolved into two two-proton multiplets, δ7.9 and 8.7 (Fig.3C), and a pair (2H overall) of multiplets centred at δ8.4, the latter having an appearance similar to the two-proton group at δ5.5 (Fig.3C). It is noteworthy that the shifted spectra do not allow a discrimination to be made between the two types of bridgehead signal.

The other four thiaadamantane derivatives similarly exhibit complex proton spectra but the gross appearance of the skeletal absorptions varies with the functional groups present. In all four cases the ^{13}C spectra were interpretable and a plot of $\Delta\nu$ against $J_r/(J_o^2-J_r^2)^{\frac{1}{2}}$ was obtained by assigning the proton and ^{13}C resonances of one structural unit viz. the vinyl methylene of 6, the acetate methyl group of 7, the tertiary methyl group of 8, and the $-CH_2Br$ group of 9. It is seen from Table 2 that the predicted chemical shifts of compounds (6-9) fall within 0.1 ppm of observed signals and again an appreciation is achieved of the components of the unresolved absorption envelopes.

In the ^{13}C NMR spectra of diketoalkene (6) the saturated methylene groups absorb in coincidence as a triplet rather than a double doublet. $\Delta\nu$, calculated from the observed values of J_r and J_o of this triplet, gives only an average chemical shift for the proton signal. Thus the predicted value (δ3.0) lies ca. midway between the two observed regions of absorption i.e. double multiplets centred at δ2.73 and 3.13. For acetate (7) and alcohol (8) the assigned methyl proton resonance lies close to the secondary irradiating frequency. Despite the reduced accuracy with which the graph of $\Delta\nu$ versus $J_r/(J_o^2-J_r^2)^{\frac{1}{2}}$ may be expected to be drawn, the predicted proton chemical shifts do indeed correspond closely with absorptions in the observed spectra.

In ratification of the above procedure, the method of proton

chemical shift prediction was applied to five 9-thiabicyclo[3,3,1]-nonanes (10-14) which bore certain structural similarities to the thiaadamantanes but showed a variety of functional group types and possessed proton absorptions over a wider spectral range. For these five compounds the ^{13}C spectra possessed well separated absorptions, many of which could be uniquely assigned. The remaining carbon resonances were assigned only in groups viz. certain aromatic carbons of 11, 12 and 14 and certain skeletal absorptions of 14. For the bicyclic compounds there was also little dubiety in the assignment of the proton spectra. However, application of the graphical method in an analogous fashion as for the thiaadamantanes gave close agreement between calculated and observed chemical shifts (Table 3). Figure 5A and B illustrate this close agreement for bis-enol acetate (13).

Because of the low solubility of 2-aminopyridine derivative (12) and pyridinium salt (14) in $CDCl_3$, their spectra were run respectively in D_6-DMSO and D_2O. This change of solvent offers no additional difficulty in the calculation of proton shifts provided a correction is made for the solvent-induced variation of the reference frequency. However, it should be noted that the method was inapplicable to the skeletal signals, C-3, C-7 and C-4, C-8 of amine (12). The broadening of these signals caused by long-range coupling rendered impossible the accurate measurement of residual couplings from the off-resonance spectrum.

CONCLUSION

The graphical method described allows the facile calculation of proton chemical shifts, irrespective of solvent, to within ca. 0.1 ppm using $^{13}C—^{1}H$ off-resonance and gated decoupled NMR spectra,

both of which can be acquired in a short time even on relatively small samples. As demonstrated above, the technique requires that only one ^{13}C signal and its corresponding proton absorption be assigned; but the accuracy of calculated values could be improved by using more than two correlated points to plot the graph of $\Delta\nu$ against $J_r \Big/ (J_o^2 - J_r^2)^{\frac{1}{2}}$. Accuracy of measurement is compromised by line broadening either in the assigned proton signal (as for 14) or in the ^{13}C resonances where long-range coupling may render major splittings indeterminate (as for 12) and increase spectrum accumulation time.

For the elucidation of complex proton spectra where high accuracy need not be important, the technique provides a speedy rationalisation of unresolved proton groups from the minimum number (two) of decoupled ^{13}C spectra. In contrast the method of proton assignment recently reported by Luzikov[26] and Gray[27] is based on the variation of J_r with changes in the off-resonance decoupling frequency and thus requires a larger number of graphical points and hence prolonged recording time.

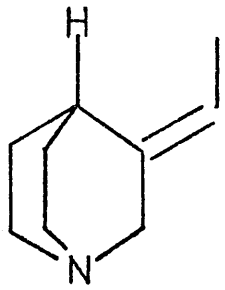
EXPERIMENTAL

^{13}C NMR spectra were recorded, on samples of 50-100 mg, at 25.2 MHz on a Varian XL-100-12 spectrometer using pulsed Fourier transform mode. Proton spectra were run on Varian T-60 and HA-100 instruments. The internal reference was tetramethylsilane for solutions in $CDCl_3$ and d_6-DMSO and sodium 2,2-dimethyl-2-silapentane sulphonate for solutions in D_2O. Noise decoupled, off-resonance decoupled, and gated decoupled ^{13}C spectra were obtained using a Gyrocode spin decoupler, the secondary irradiating frequency located

respectively at δ 5.0, 0.0 and 5.0 for solutions in $CDCl_3$. In d_6-DMSO and D_2O the off-resonance secondary irradiating frequency was located respectively at δ -4.3 and -2.6 as a result of the shift in the reference signal while the decoupler was maintained at the same frequency. Predicted proton chemical shifts are calculated with reference to 60MHz spectra and are corrected to the nearest 0.1 ppm.

PREPARATIONS

Preparations of thiaadamantanes (5-9) and bicyclic compounds (10,13) have been reported [33, 34, 35, 36]. The syntheses of 11, 12 and 14 are described in Chapter 4.



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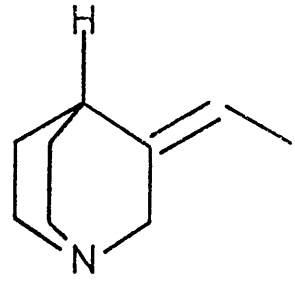

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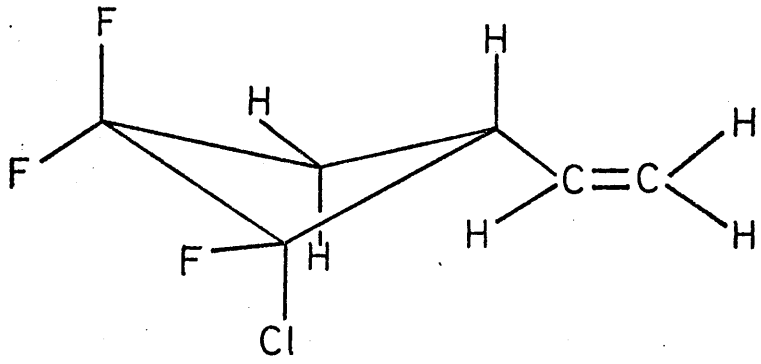

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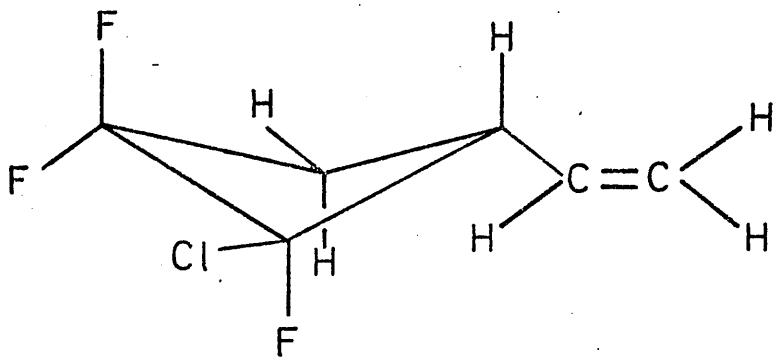

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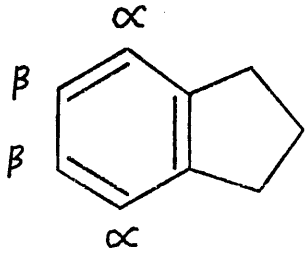

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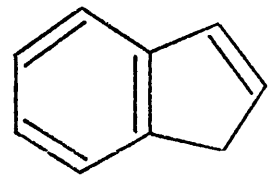

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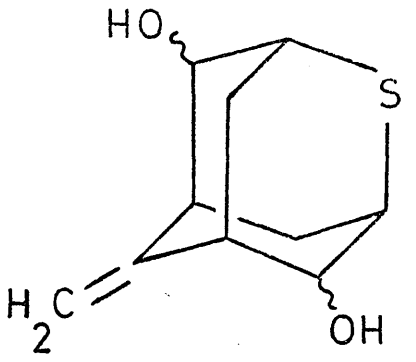

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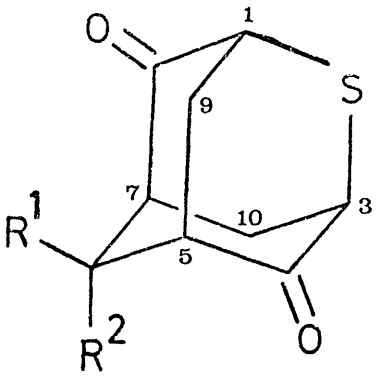
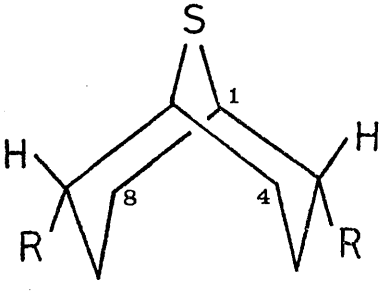


6 R^1, $R^2 = CH_2$

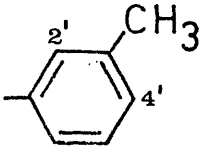
7 $R^1 = CH_3$; $R^2 = OAc$

8 $R^1 = CH_3$; $R^2 = OH$

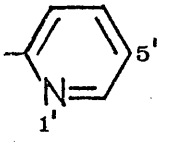
9 $R^1 = CH_2Br$; $R^2 = Br$



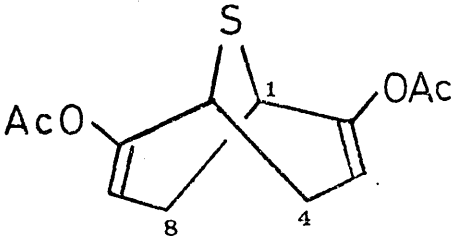
10 R = Cl



11 R = NH–



12 R = NH–



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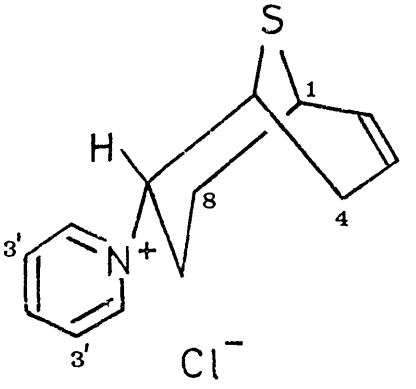


14

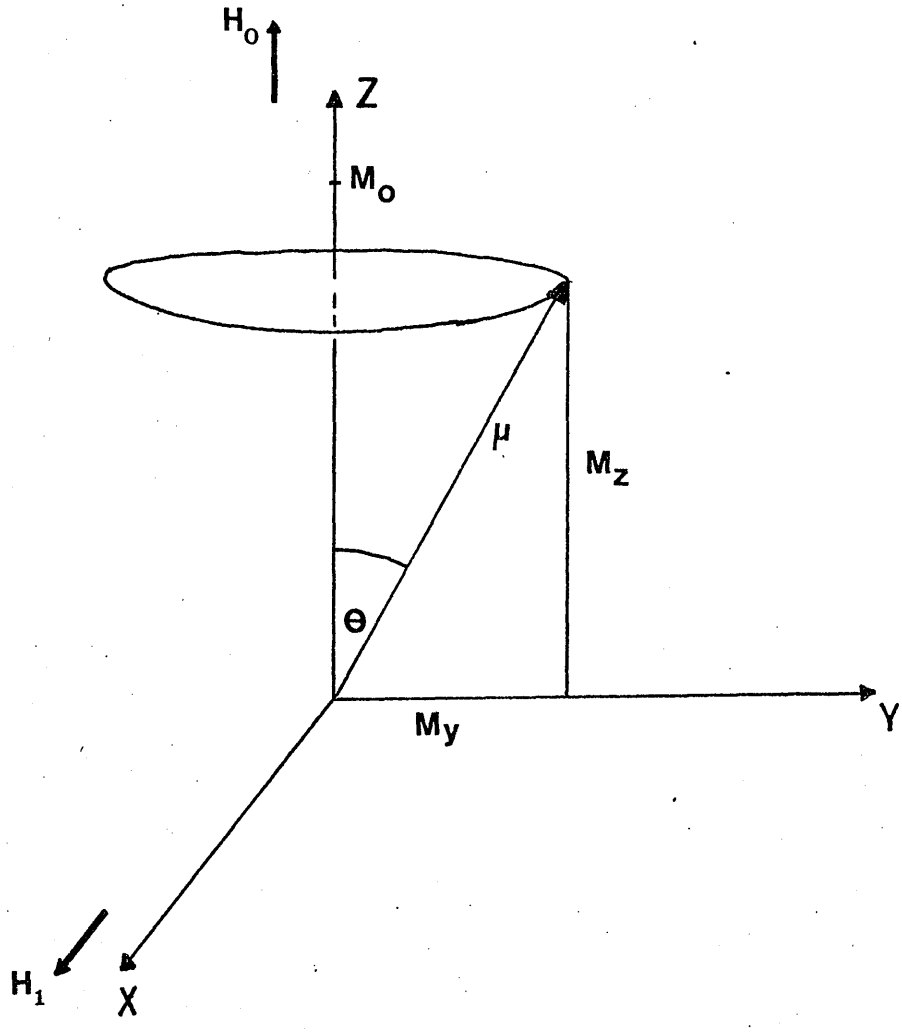
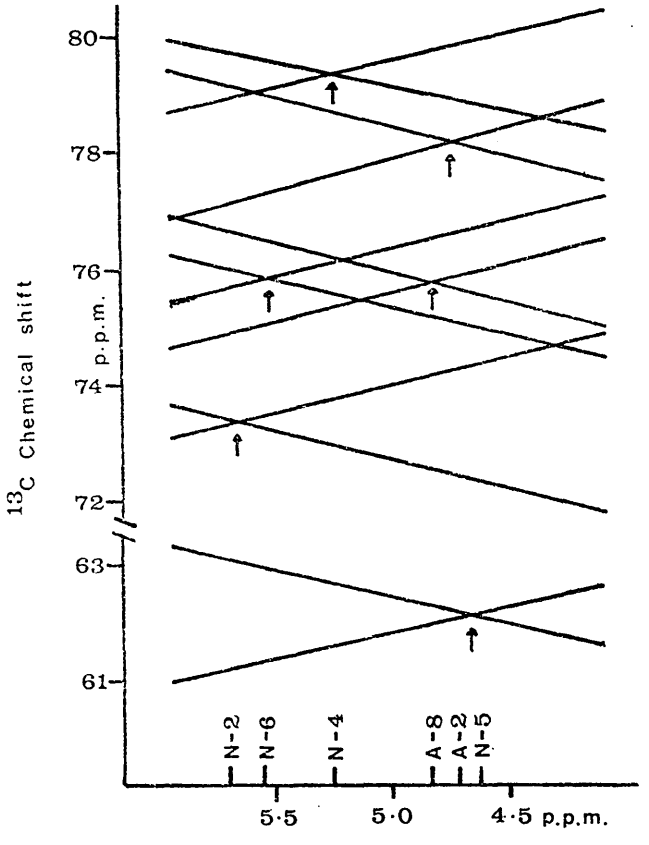


Fig.1.



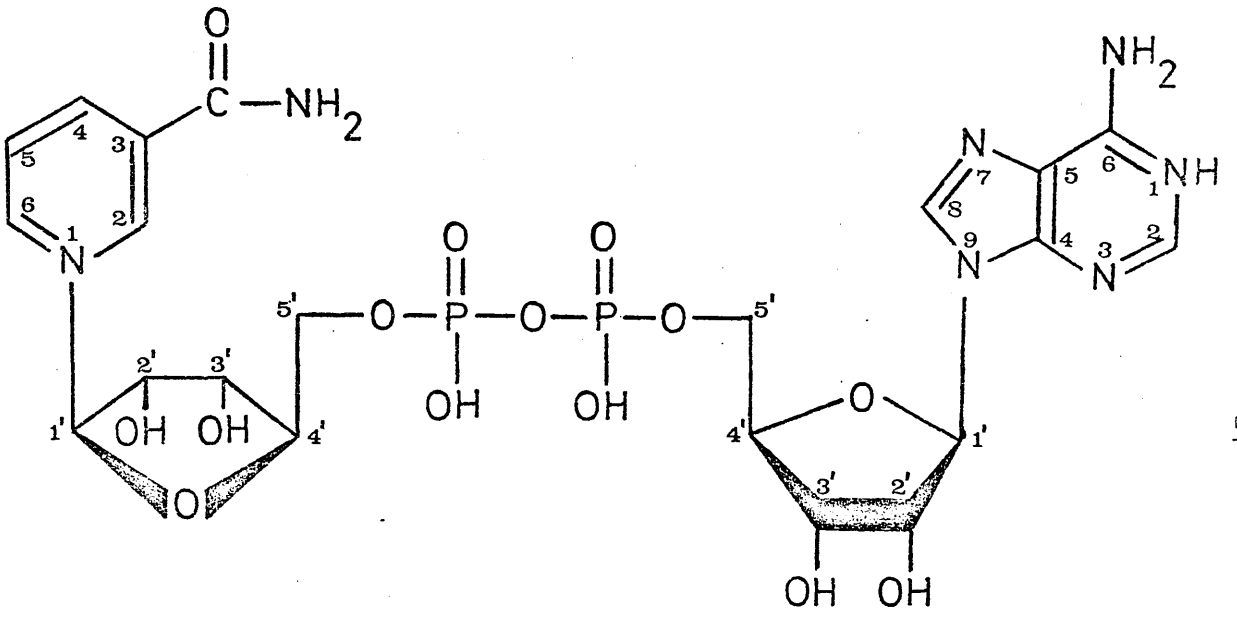


Fig.2. Plot of peak frequencies in the ^{1}H off-resonance selectively decoupled ^{13}C spectra of NAD^{+} as a function of position of irradiation in the ^{1}H spectrum, expressed in p.p.m. downfield from internal dioxan.

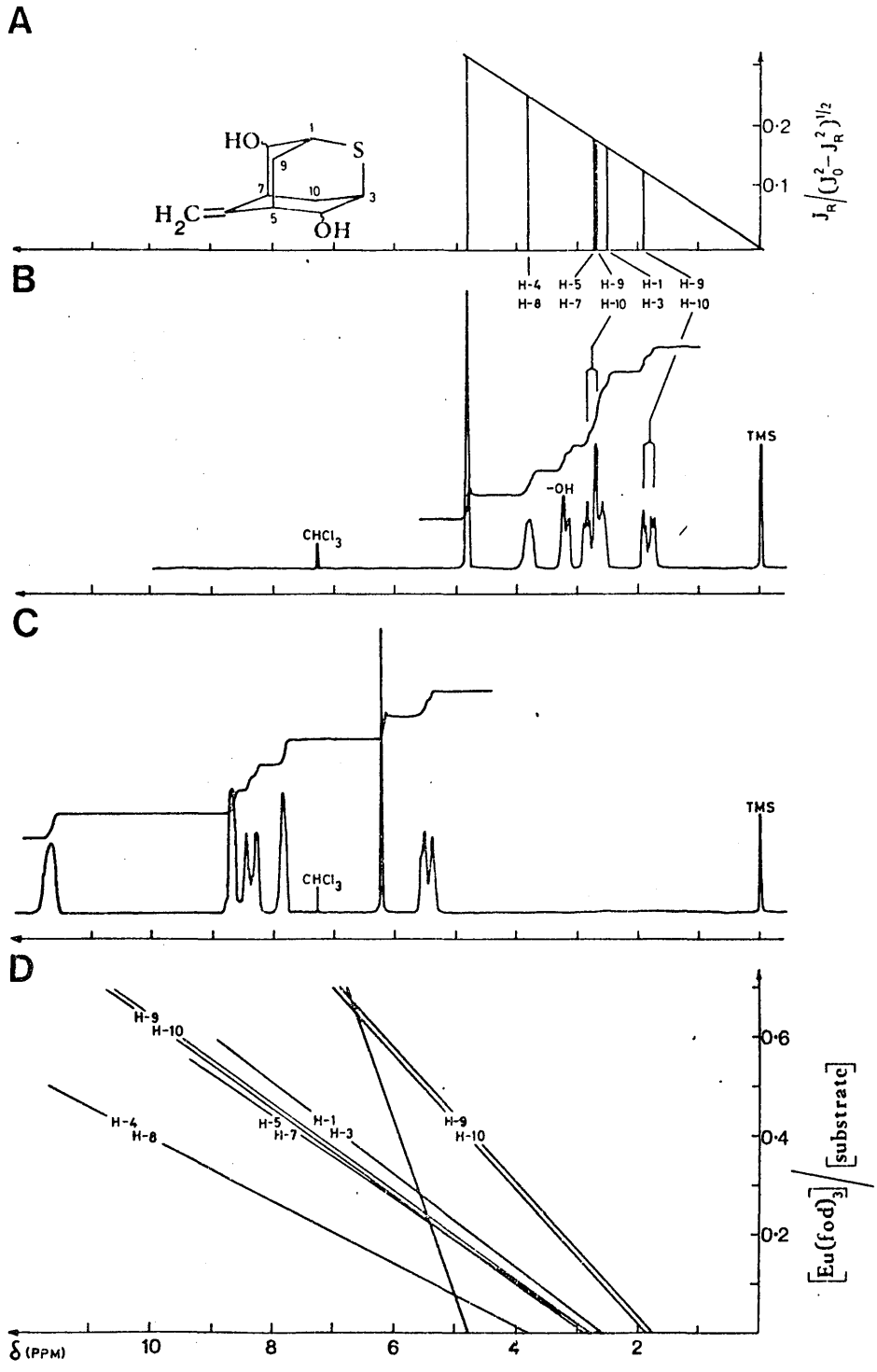


Fig. 3. Assignment of 100 MHz proton spectrum (B) of diol (5) based on calculated proton chemical shifts (A); C, proton spectrum of 5 recorded with molar ratio $[Eu(fod)_3]/[substrate]$ = 0.5; D, linear dependence of proton chemical shifts of 5 on this molar ratio.

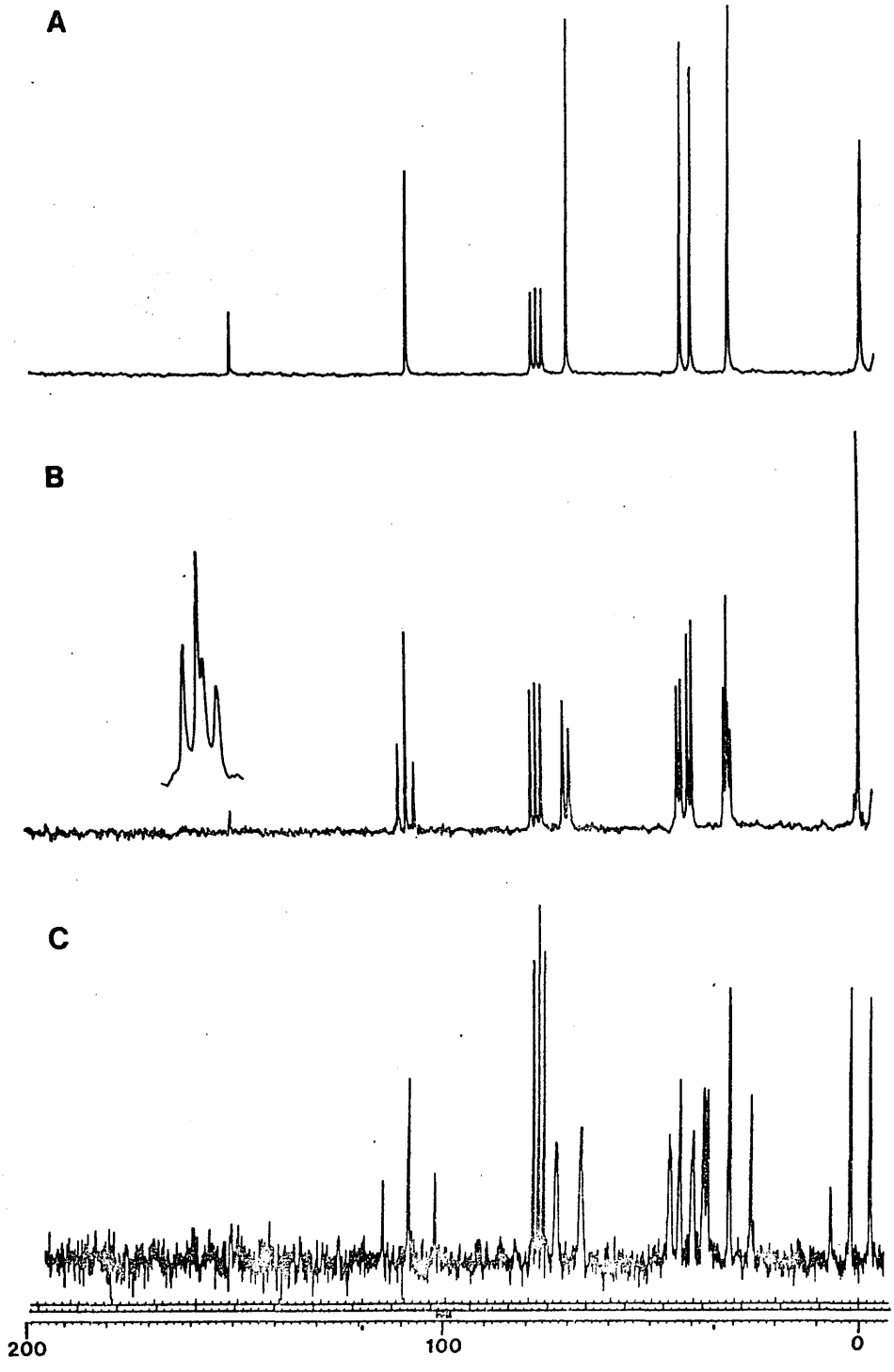


Fig. 4. ^{13}C-{^{1}H} decoupled NMR spectra of 5: A, noise; B, off-resonance; C, gated.

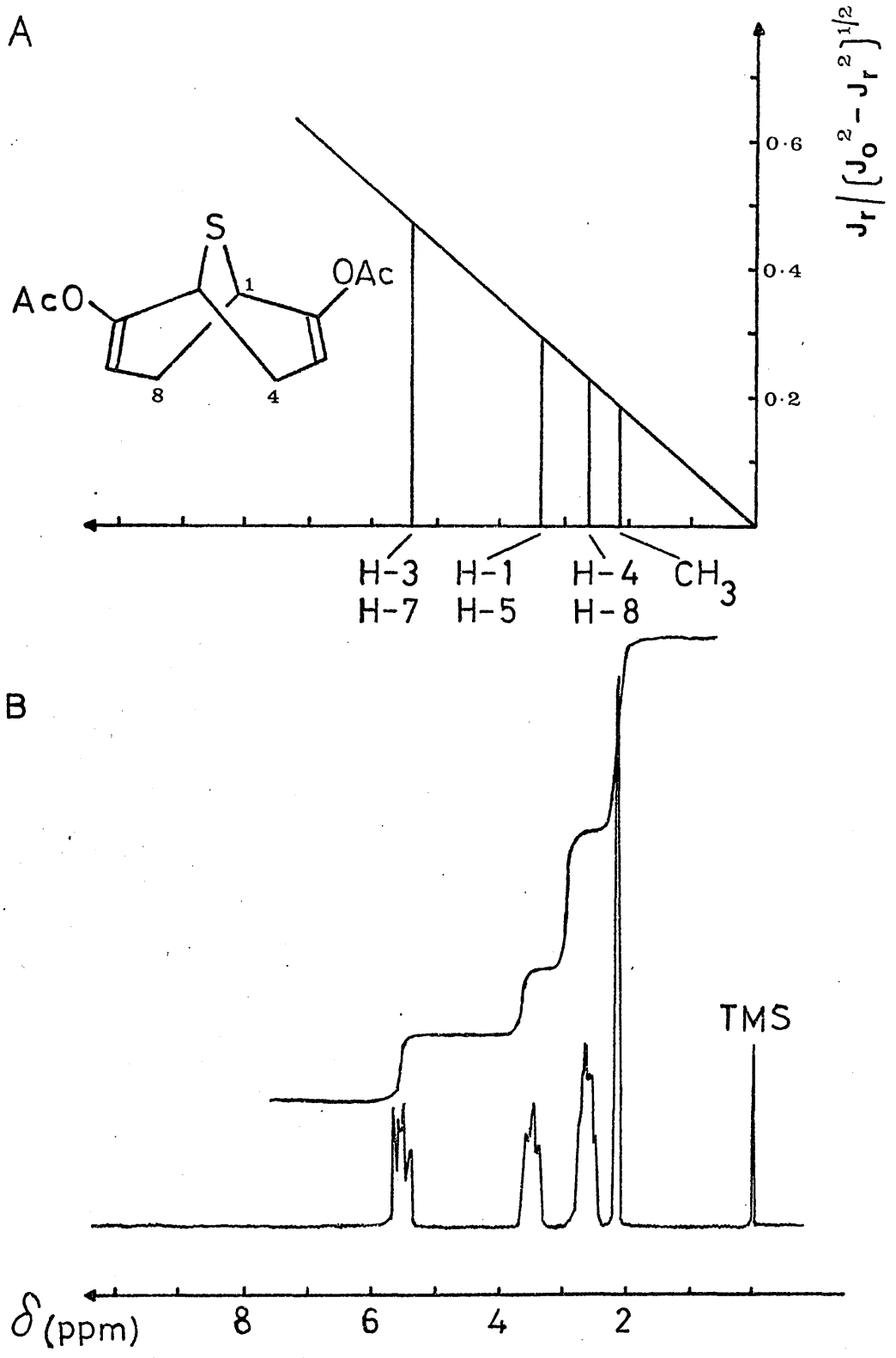


Fig.5. Assignment of 60 MHz proton spectrum (B) of bis-enol acetate (15) based on calculated proton chemical shifts (A).

TABLE 1.

ISOTOPE	SPIN	ABUNDANCE %	RELATIVE MAGNETIC SENSITIVITY
^{1}H	1/2	99.98	1000
^{2}H	1	0.015	9.65
^{13}C	1/2	1.11	15.9
^{14}N	1	99.63	1.01
^{15}N	1/2	0.37	1.04
^{17}O	5/2	0.04	29.1
^{19}F	1/2	100	833
^{31}P	1/2	100	66.3

T A B L E 2

Comparison of Calculated and Observed Proton Chemical Shifts (δ_H) for Thiaadamantanes (5 - 9).

	^{13}C Chem Shift (Hz)	J_O (Hz)	J_R (Hz)	δ_H Calc. from Equan. [3] (ppm)	δ_H Calc. from Equan. [5] (ppm)	δ_H Obs. (ppm)
5						
$H_2^aC{=}C$	2718.0	156.7	47.3	-	4.8	4.80 (2H, s)
C-4, C-8	1757.5	142.8	34.4	-	3.8	3.80 (2H, m)
C-1, C-3	1078.7	144.1	23.7	-	2.5	2.60 (2H, m)
C-5, C-7	1016.0	146.0	26.1	-	2.7	2.71 (2H, m)
			22.9	-	2.7	Multiplets (2H) ca.2.71,2.83
C-9, C-10	789.1	132.0	16.6	-	1.9	Multiplets (2H) at 1.77,1.89
6						
C-1, C-3	1131.2	153.0	43.5	3.4	3.2	3.26 (2H, m)
C-5, C-7	1397.6	142.2	42.3	3.6	3.4	3.46 (2H, m)
C-9, C-10	1170.2	136.5	35.9	3.1	3.0	Multiplets (2H) at 2.63,2.83 Multiplets (2H) at 3.03, ca.3.23
$H_2^aC{=}C$	2788.3	159.2	65.0	4.9	4.9	4.93 (2H, s)

T A B L E 2 (Continued)

	^{13}C Chem Shift (Hz)	J_O (Hz)	J_R (Hz)	δ_H Calc. from Equan. [3] (ppm)	δ_H Calc. from Equan. [5] (ppm)	δ_H Obs. (ppm)
7						
[a]CH_3COO	549.8	130.1	19.9	2.0	2.0	2.0 (3H, s)
CH_3	559.8	128.4	15.6	1.6	1.6	1.62 (3H, s)
C-1, C-3	1106.5	145.3	36.9	3.4	3.4	3.36 (ca. 2H, m)
C-5, C-7	1344.9	145.6	36.3	3.3	3.3	3.20 (ca. 2H, m)
	1370.4	142.5	35.4	3.2	3.3	
C-9, C-10	1034.1	136.3	31.4	3.0	3.0	2.90 (ca. 4H, m)
	1000.8	135.4	31.9	3.1	3.1	
8						
[a]CH_3	680.3	128.0	13.6	1.4	1.4	1.38 (3H, s)
C-1, C-3	1112.9	142.0	37.3	3.4	3.5	3.10-3.35 (ca. 3H, m)
	1098.8	150.0	37.9	3.3	3.4	
C-5, C-7	1425.1	140.0	31.0	2.9	2.9	2.70-3.10 (ca. 5H, m)
C-9, C-10	1039.2	134.0	32.9	3.2	3.3	
	1021.1	132.0	29.6	2.9	3.0	

T A B L E 2 (Continued)

	^{13}C Chem Shift (Hz)	J_0 (Hz)	J_R (Hz)	δ_H Calc. from Equan. [3] (ppm)	δ_H Calc. from Equan. [5] (ppm)	δ_H Obs. (ppm)
[a] CH_2Br	1017.0	151.5	40.5	-	3.8	3.8 (2H, m)
C-1, C-3	1103.1	150.2	35.5	-	3.3	
C-5, C-7	1425.0	142.6	33.7	-	3.3	Multiplets (ca. 6H) at
	1381.4	142.3	36.8	-	3.6	3.50, 3.26; (ca. 2H)
C-9, C-10	1134.8	137.8	32.8	-	3.3	at 2.93
	1017.0	136.4	28.6	-	2.9	

a Resonances on which plots of $\Delta\nu$ vs. $J_R/(J_0^2-J_R^2)^{\frac{1}{2}}$ are based.

T A B L E 3

Comparison of Calculated and Observed Proton Chemical Shifts (δ_H) for 9-Thiabicyclo [3,3,1] nonane Derivatives (10 - 14).

		^{13}C Chem Shift (Hz)	J_O (Hz)	J_R (Hz)	δ_H Calc. from Equan. [5] (ppm)	δ_H Obs. (ppm)
10	C-4, C-8	712.3	131.2	24.3	2.1	1.90-2.60 (8H, m)
	C-3, C-7	820.0	131.9	23.5	2.0	
	C-1, C-5	938.7	143.2	35.1	2.8	2.81 (2H, m)
	[a]C-2, C-6	1572.0	152.0	58.6	4.7	4.70 (2H, m)
11	[a]CH_3	544.1	126.3	23.2	2.3	2.26 (6H, s)
	C-4, C-8	673.4	129.8	22.4	2.1	1.53-2.50 (4H, m)
	C-3, C-7	751.1	126.2	15.7	1.5	
	C-1, C-5	839.3	140.0	32.1	2.9	2.96 (2H, m)
	C-2, C-6	1377.6	136.7	42.3	4.0	3.93-4.33 (2H, m)
	C-4', C-5', C-6'	2783.1	158.3	73.1	6.4	6.26-6.66 (6H, m)
		2984.6	164.8	74.7	6.2	
		2871.9	153.1	70.1	6.3	
	C-2'	3254.7	158.1	79.5	7.1	6.90-7.26 (2H, m)

T A B L E 3 (Continued)

		^{13}C Chem Shift (Hz)	J_O (Hz)	J_R (Hz)	δ_H Calc. from Equan. [5] (ppm)	δ_H Obs. (ppm)
12	C-4, C-8	671.1	127.9	-	-	1.70-2.50 (8H, m)
	C-3, C-7	697.3	128.7	-	-	
	[a]C-1, C-5	835.4	143.8	54.7	2.9	2.90 (2H, m)
	C-2, C-6	1306.0	143.1	62.6	4.3	4.10-4.66 (2H, m)
	C-3', C-5'	2736.5	160.0	82.9	6.5	6.20-6.80 (4H, m)
		2803.5	162.7	84.4	6.5	
	C-4'	3434.7	157.4	85.3	7.2	7.10-7.40 (2H, m)
	C-6'	3708.7	174.1	98.9	8.1	7.80-8.00 (2H, m)
13	[a]CH_3	526.6	129.9	24.1	2.2	2.16 (6H, s)
	C-4, C-8	794.7	130.8	28.9	2.6	2.62 (4H, m)
	C-1, C-5	833.7	142.4	41.0	3.4	3.40 (2H, m)
	C-3, C-7	2849.5	159.9	69.5	5.4	5.40 (2H, m)

T A B L E 3 (Continued)

	^{13}C Chem Shift (Hz)	J_O (Hz)	J_R (Hz)	δ_H Calc. from Equan. [5] (ppm)	δ_H Obs. (ppm)
	556.6	131.4	12.7	2.2	
C-4, C-7, C-8	655.7	127.3	11.1	2.0	1.66-2.60 (6H, m)
	838.8	133.4	14.4	2.4	
[a]C-1, C-5	810.8	149.6	22.7	3.2	3.16-3.43 (2H, m)
	971.9	143.8	22.6	3.3	
C-6	1898.7	147.1	38.5	5.3	5.10-5.50 (1H, m)
C-2, C-3	3250.6	171.8	51.5	6.1	5.90-6.00 (2H, m)
	3273.2	160.8	49.0	6.1	
C-3'	3250.6	186.1	70.7	7.7	7.80-8.20 (2H, t)
C-2'	3622.6	190.7	83.0	8.9	8.70-8.93 (2H, d)
C-4'	3701.0	173.6	73.2	8.6	8.30-8.60 (1H, t)

[a] Resonances on which plots of $\Delta\nu$ vs. $J_R/(J_O^2-J_R^2)^{\frac{1}{2}}$ are based.

Chapter 2

Acid-Catalysed Acylations of 9-Thiabicyclo[3,3,1]nonan-2,6-dione.

INTRODUCTION

Acylation of active methylene compounds is accomplished using an acid anhydride or chloride in presence of a catalytic quantity of acid (e.g. BF_3, $AlCl_3$, p-toluenesulphonic acid, H_2SO_4) or base (NaOAc, NaH, $NaNH_2$). Alternatively enol esters can be prepared by acid-catalysed acylation with 2-acetoxypropene. The proportions of O-and C-acylated derivatives formed are dependent on the reaction conditions[37] but are also influenced by electronic and steric effects of substituents present in the substrate[38]. Several authors have reported that O-acylation is favoured in reactions of an enolate anion with excess acid anhydride or chloride. In contrast, C-acylation is favoured where the ketone enolate is in excess. In the latter case the initially formed O-acylated product condenses with an additional equivalent of the enolate to yield the more stable anion of the C-acylated derivative.

The proportion of O-acylated products can be enhanced by reaction of the enolate anion in a polar solvent containing Na^+ or K^+ as counter cations which disfavour the formation of tightly associated ion pairs. An increase in the proportion of C-acylated products can be achieved by thermal, photolytic or acid-catalysed isomerisation of the initially formed O-acylated derivatives. In the acid-catalysed case it is believed that isomerisation occurs by electrophilic attack of either a Lewis acid-enol ester (15) [Scheme 1] or Lewis acid-anhydride complex (16) [Scheme 2] on a second molecule of the enol ester.

In 1922 Meerwein et al.[39] showed that the reaction of

bicyclo [3,3,1]nonan-2,6-dione (17) with acetic anhydride (Ac_2O) containing a catalytic quantity of conc.H_2SO_4 (one drop per 30 ml Ac_2O) furnished mainly bis-enol acetate (22), C-acetylated products being unreported. As part of a four-step synthesis[35] of 9-thiabicyclo [3,3,1]nona-3,7-diene-2,6-dione (26) from diol (27), acetylation of dione (18) (the 9-thia analogue of 17) using Meerwein's conditions gave 2,6-diacetoxy-9-thiabicyclo [3,3,1]nona-2,6-diene (13) in 59% yield accompanied by mono-enol acetate (28) and varying amounts of minor products. The fact that 13 is in equilibrium with its precursor, 28, accounts for the moderate yield obtained and introduces the additional difficulty of separating two chromatographically similar components of the tarry product mixture. Although a small increase in the proportion of 13 was achieved[35] through constant removal by distillation of the acetic acid formed during the reaction and prolonging reaction time a more substantial increase was sought by variation of the acetylating conditions.

DISCUSSION

Marshall et al.[40] have used Ac_2O in conjunction with p-TsOH for the formation of Δ17 (20) enol acetates of 20-ketosteriods. Acetylation (6 hr.) of 18 using this medium furnished mainly 13 free from the above minor products but only in 64% yield despite being a much cleaner reaction. Moffett and Weisblat[41] have shown that acetylation of 20-ketosteriods with 2-acetoxypropene and p-TsOH yields Δ20 (21) enol acetates. Application of this milder acetylation procedure to dione (18) gave a tar-free product mixture which was mainly 28 after 20 hr. and mainly 13 (60%) after 40 hr.

During a further investigation of the Ac_2O-H_2SO_4 treatment of 18 particular attention was paid to the changes effected by variation of the acid concentration. As might be expected an increase in acidity led to charring, but it was also found to disfavour O-acetylation with an increase in the proportion of the hitherto minor products[33]. Thus after 24 hr. at 150° using 21 drops of conc.H_2SO_4 per 30ml Ac_2O (Table 4) a tricyclic diketoacetate $C_{12}H_{14}O_4S$, m.p. 172-173° and a structurally similar diketoalkene $C_{10}H_{10}O_2S$, m.p. 169-170° were formed to the virtual exclusion of 13 (0.7%). At yet higher acidity (24 drops conc. H_2SO_4 per 30ml Ac_2O) the alkene was the sole product (Table 4).

The structures of these tricyclic compounds have been deduced by spectroscopic analysis[32,42] (see Chapter 1) and chemical interconversions [42] (vide infra) and are assigned respectively as 6-acetoxy-6-methyl-2-thiaadamantan-4,8-dione (7) and 6-methylene-2-thiaadamantan-4,8-dione (6). The formation of the 2-thiaadamantane skeleton must arise through two sequential condensations viz. a C-acetylation [Scheme 3] of enol (29) or more probably [43] its acetate (28) with the anhydride-acid complex (41) to form 19, followed by ring closure of this transient 1,3-dicarbonyl intermediate 19 in an acid-catalysed intramolecular aldol condensation involving the newly inserted 3-acetyl group which is endo in one tautomeric form (19b). This insertion of the carbonyl group of acetic anhydride between the closely spaced [36,44] C-3 and C-7 atoms of a bicyclo [3,3,1] nonane to form 7 is a novel method of creating the strain-free adamantane framework, the attainment of which is the driving force for ring closure.

The intermediacy of the C-acylated dione (19) remains experimentally unsupported, as it was not directly isolable and its

presence could not be inferred from NMR of aliquots of the reaction mixtures taken progressively throughout the reaction. In contrast the analogous acylation of 9-oxabicyclo [3,3,1] nonan-2,6-dione (20)[45] with Ac_2O-H_2SO_4 furnished [34,46] the doubly C-acylated bicyclic dione (21) as well as bis-enol acetate (23).

Dione (19) could also arise by thermal or acid-catalysed isomerisation of 28, a process discussed above. Additional support for the formation of 19 is gained from the isolation of a single tricylic product 32, m.p. 232-234°, bearing bridgehead acyl substituents, in the H_2SO_4-catalysed treatment of 18 with excess benzoic anhydride $(PhCO)_2O$. In this reaction, tricyclic benzoate (32) arises by the intramolecular aldol condensation of the triply C-acylated intermediate (33), C-acylation after ring closure being unlikely since enolisation in the tricyclic skeleton would place double bonds in unfavourable bridgehead locations. An attempt to generate a C-acyl precursor of 32 by reducing the ratio of anhydride to substrate to 2:1 furnished only mono-and bis-enol benzoates (30 and 24) in good yield.

The results shown in Table 4 indicate that this C-acetylation pathway is favoured at high acidity whereas only bicyclic enol esters (13 and 28) are formed at low acid concentration. By choosing an intermediate acidity (ca.5 drops conc.H_2SO_4 per 30ml Ac_2O, Table 4) it is possible to isolate both bicyclic (13 and 28) and tricyclic (7) products in proportions which are thermodynamically controlled[47] as is shown by the equilibration[46] of 13 to a mixture of 28, 7 and trace amounts of 6 on treatment with Ac_2O-H_2SO_4. The cyclisation 19 ⟶ 7 was shown to be irreversible since subjection of 7 to the acetylation conditions

(Table 5) afforded 6 but did not undergo a retro-aldol condensation to form any of the bicyclic products.

This latter observation also indicates that 6 does not arise directly from a bicyclic precursor but is the product of elimination of acetic acid from 7. The proposal that this conversion most probably proceeds via pyrolytic cis-elimination[33] has been discounted since pyrolysis of 7 at temperatures between 150° and 220° left 7 unchanged, apart from some minor charring. In addition, acetate (7) was slowly converted to alkene (6) when heated with a catalytic quantity of H_2SO_4 in an inert solvent (1,2-dimethoxyethane or 1,4-dioxan) (Table 5) while 6 itself was left unchanged by treatment with Ac_2O-H_2SO_4. Thus the elimination step, 7⟶6 [Scheme 3] , is an irreversible acid-catalysed process, most probably E-1[48] via the tertiary carbonium ion 42. The loss of a methyl proton from 42 to furnish 6 is favoured by its coplanarity with the vacant p-orbital and by the polar non-nucleophilic medium. Stabilisation of 42 is gained from the inductive effect of the alkyl substituents present.

The nature of the functional groups in these products was readily deduced from their NMR and IR spectra but the complexity of the skeletal proton NMR resonances prevented unambiguous assignment of skeletal structure. The structural assignment was achieved by the application of a new double resonance technique[32] (see Chapter 1) and by investigating the chemical reactivity of 6 and 7 as follows.

On base hydrolysis with sodium hydroxide acetate (7) (δ^{CH_3COO} 2.0; ν_{CO}(KBr) 1740cm^{-1}), which possessed a tertiary methyl group (δ 1.62), furnished a diketoalcohol $C_{10}H_{12}O_3S$(8),

m.p. 265-268° (ν(KBr)3399cm^{-1}) which on dehydration with phosphorous oxychloride-pyridine gave a diketoalkene (δ4.93,s,2H), identical in all respects to alkene (6). In contrast base hydrolysis with potassium hydroxide in aqueous methanol yielded[46] a mixture of dione (18) and alcohol (8) in the ratio 5:1. The formation of 18 confirms that the 9-thiabicyclo[3,3,1]nonan-2, 6-dione nucleus is contained in the skeletal framework of 7. Alkene (6) had also been formed by acid treatment of 7 (vide supra). The partial structure, $CH_3-\overset{|}{\underset{|}{C}}-OAc$ for 7 is therefore established, 6 differing from 7 only in the loss of acetic acid from this function.

The infra-red spectrum of 6 showed two coincident carbonyl absorptions at 1723cm^{-1} while the vinyl proton resonance appeared as a two-proton singlet at δ4.93. The presence of this exomethylene function of 6 was demonstrated by the formation of a crystalline dibromide (9), exhibiting a two-proton singlet at δ3.8 for $-CH_2Br$, in the reaction with Br_2/HOAc. In corroboration, the double bond of 6 was cleaved on ozonolysis forming trione (34) $C_9H_8O_4S$(ν_{CO}(KBr) 1705cm^{-1}) in which the nuclear thioether bridge had been oxidised to sulphoxide (ν_{SO} 1025cm^{-1}).

Desulphurisation of 6 using acetone-deactivated Raney nickel[49] furnished a sulphur free diketoalkene (38) which displayed two coincident carbonyl absorptions at 1720cm^{-1} and a two-proton singlet at δ4.96 for $>C=CH_2$.

The presence of two skeletal carbonyl groups in 6 was confirmed by the production of a diastereomeric mixture of diols (5) in the reduction with lithium aluminium hydride. Although the absolute stereochemistry of the racemic modification($[\alpha]_D$=0) isolated by preparative TLC has not been determined, the ^{1}H NMR

spectrum of this pair of enantiomers, which exhibit a two-proton multiplet at δ3.8 for the C-4 and C-8 methine resonances, has been fully assigned using the double resonance technique discussed in Chapter 1 and is consistent with the proposed 2-thiaadamantane nucleus.

Additional support for the skeletal functional groups was obtained in the reduction of 6 with undeactivated Raney nickel[49]. In contrast to the reduction with acetone — deactivated Raney nickel (vide supra), desulphurisation in this case was accompanied by reduction of the alkene and carbonyl groups yielding hydroxylic and ketonic products from which the enantiomeric dione mixture (39) ($\nu_{CO}(CCl_4)$ 1710cm^{-1}, ε^a703, $\Delta\nu_{\frac{1}{2}}{}^a$25cm^{-1}) was isolated after Jones oxidation. Alternatively reduction of the Raney nickel product by lithium aluminium hydride furnished a complex mixture of diols (40) which melted over the range 162-167°. The above chemical properties of the alkene and acetate isolated from acetylation of 18 confirm their assignment as 2-thiaadamantanes 6 and 7 respectively.

Since C-acylations as well as O-acylations have been encountered in reactions of 9-heterobicyclo[3,3,1]nonan-2,6-diones (18 and 20) with anhydrides, the absence of C-acyl or tricyclic products in the reported[39] acetylation of the 9-methano analogue (17) would seem incongruous. It was found[46] that a slight modification of the described[39] procedure, employing an increased amount of acid (15 drops conc.H_2SO_4 per 30ml Ac_2O) furnished three products i.e. bis-enol acetate (22), tricyclic alkene (35) and tricyclic acetate (36), in yields of 18, 31 and 20% respectively, arising by the C-acetylation-cyclisation process established above.

In an alternative approach, an increase in the yield of 13

was sought by changing the acetylating agent from Ac_2O to acetyl chloride, b.p.51°, retaining H_2SO_4 as the acid catalyst. Initially this reaction medium failed to yield either O-or C-acylated products. However, when the reaction mixture was distilled allowing the temperature to rise a trace amount of tricyclic alkene (6) was isolated from the tarry residue. The analogous reaction with chloroacetyl chloride-H_2SO_4 produced mono-and bis-enol acetates (31 and 25) which decomposed during preparative TLC. Similarly an unstable tricyclic dibromide (37) was formed by the C-acylation-cyclisation pathway in the reaction with bromoacetyl bromide-H_2SO_4. Reaction with benzoyl chloride-H_2SO_4 at 170° furnished in low yield enol benzoates (24 and 30), previously isolated from the benzoic anhydride treatment of 18. Thus in comparison with anhydride acylations discussed above, the sulphuric acid-catalysed acylations of 18 with acid halides give inferior yields of both O- and C-acylated products.

EXPERIMENTAL

Preparative TLC was performed on glass plates (20 x 20 cm^2 or 20cm x 1m) spread with Merck Kieselgel G or HF_{254} (1mm thick). Column chromatography was carried out on neutral Al_2O_3 (Weolm, Gd.1). Melting points were recorded on a Kofler hot-stage apparatus and are uncorrected. Petroleum spirit was of b.p. 60-80°. Dioxan was purified by percolation through Al_2O_3. PMR spectra were recorded on Varian T-60 or HA-100 instruments on solutions in $CDCl_3$ with TMS as internal reference. Mass spectra were measured on an AEI MS12 spectrometer. IR spectra were run on Perkin-Elmer 257 or 225 spectrometers on solutions in CCl_4 or on pressed discs (KBr). UV spectra were obtained on a Unicam SP800 instrument on solutions in AR MeOH. Pyrolyses and acid-catalysed equilibrations were carried out in thick-walled Pyrex tubes, flushed with N_2, sealed under vacuum and heated in Gallenkamp sublimation block.

Reaction of 18 with Ac_2O-H_2SO_4.

Details of reaction times, acidity and appropriate yields of O-acylated and C-acylated products are given in Table 4. In all cases the Ac_2O was replenished after 3 hr. and at later reaction times as required.

Specimen procedure. 18 (2.445g, 14.4mmol), Ac_2O (20ml) and conc. H_2SO_4 (AR, 14 drops) were heated at 150-160° (bath temp.) for 3 hr. allowing acetic acid to distil (stillhead temperature 115-116°). Further Ac_2O (20ml) was added and the reflux continued for 21 hr. The reaction mixture was concentrated and purged by azeotropic distillation with benzene. The dark residue was

extracted with boiling petroleum spirit and then with boiling Et_2O. The petroleum extract contained mainly 7 which recrystallised from $CHCl_3$-petroleum spirit as needles (261mg, 7%), m.p. 172-173°. (Found: C,56.62; H, 5.49. $C_{12}H_{14}O_4S$ requires: C, 56.69; H, 5.55%); ν max (KBr) 1740, 1712, 1238, 1102, 988 and 971 cm^{-1}; ν max (CCl_4) 1752 (ε^a 710, $\Delta\nu_{\frac{1}{2}}^a$ 13cm^{-1}), 1729 (ε^a560, $\Delta\nu_{\frac{1}{2}}^a20cm^{-1}$) and 1719$cm^{-1}$ (ε^a480, $\Delta\nu_{\frac{1}{2}}^a$ 13cm^{-1}); δ 1.62 (s, 3H; CH_3), 2.0 (s, 3H; CH_3CO_2-), 2.90 (m, ca.4H; C-9 and C-10 CH_2), 3.20 (m, ca.2H; C-5 and C-7 CH), 3.36 (m, ca.2H; C-1 and C-3 CH); mass spectral peaks at m/e 254 (M^+), 212, 194, 179, 166 and 133. The Et_2O extract furnished a mixture of 13, 7 and 6 which were separated by TLC using $CHCl_3$ as solvent. The most mobile component was 6 which crystallised from $CHCl_3$ - petroleum spirit as broad needles (254mg, 9.1%), m.p. 169-170°. (Found: C, 61.94; H, 5.32. $C_{10}H_{10}O_2S$ requires: C, 61.85; H, 5.19%); ν max (CCl_4) 1723, 905cm^{-1}; δ 2.63 and 2.83 (both m, 2H; C-9 and C-10 CH), 3.03 and 3.23 (both m, 2H; C-9 and C-10CH), 3.36 (m, 2H; C-1 and C-3 CH), 3.46 (m, 2H; C-5 and C-7 CH), 4.93 (s, 2H; olefinic); mass spectral peaks at m/e 194 (M^+), 166, 138, 123, 111, 105, 91 and 77.

The middle band contained 13 (28mg, 0.7%), m.p. 106-107° (lit.[35] m.p. 107-107.5°). The least mobile component was 7 (495 mg, 13.5%).

Reaction of dione 18 with Ac_2O-p-TsOH.

18 (2.14g,12.6 mmol), Ac_2O(25ml) and p-TsOH (10mg) were refluxed (oil bath temp. 150°) for 3 hr. During the following 3 hr. acetic acid was allowed to distil while the Ac_2O was replenished as required. Removal of Ac_2O as above and extraction with petroleum spirit gave a yellow gum (2.41g) which solidified on standing.

Recrystallisation from Et_2O-petroleum spirit gave 13 (1.46g,46%). The mother liquor (950mg) contained 13 and 28 in the ratio (byNMR) of 5:3.

Reaction of dione 18 with 2-acetoxypropene-p-TsOH.

(a) A solution of 18 (100.4mg, 0.59mmol) and p-TsOH (25mg) in 2-acetoxypropene (1.2ml, 11.5mmol) was refluxed (bath temp.115°) for 20 hr. , allowing acetone to distil. The reaction solution in EtOAc was washed with aq. $NaHCO_3$, brine, and dried ($MgSO_4$). Removal of solvent furnished a red-brown oil (145mg) which was fractionated into the two components by preparative TLC using Et_2O-petroleum spirit (7:3) as solvent. The more polar constituent (20mg) was unreacted 18. The more mobile component (82mg, 82% based on 18 consumed) was 28 which recrystallised from $CHCl_3$-petroleum spirit as needles, m.p. 88-90.5°. (Found: C, 56.67; H, 5.56. $C_{10}H_{12}O_3S$ requires: C,56.6; H, 5.7%); ν max (CCl_4) 1763, 1710, 1369, 1205, 1195 and 1100cm^{-1}; δ 2.16 (s, 3H; CH_3), 2.40-2.90 (m, 6H; CH_2), 3.20 (m, 1H; C-1CH), 3.46 (m,1H; C-5CH), 5.60 (t, 1H; J 4Hz; olefinic); mass spectral peaks at m/e 212 (M^+) and 170.

(b) Dione 18 (202mg, 1.19 mmol), p-TsOH (16mg) and 2-acetoxypropene (5.2ml) were refluxed as above for 15 hr. 2-acetoxypropene (5.2ml) and p-TsOH (16mg) were added and reflux continued for 25 hr. Volatiles were removed by raising the bath temperature and after cooling the reaction mixture was extracted as before. The residual brown oil, which solidified on standing, was purified by filtration through a column (9cm x 8mm) of Al_2O_3. Fractions eluted with $CHCl_3$-Et_2O 1:9 to 1:4 consisted of 13 (61mg,20%). Fractions eluted with $CHCl_3$-Et_2O 2:3 to 7:3 contained a mixture

of 13 and 28. Preparative TLC of this mixture using Et_2O - petroleum spirit (3:2) as solvent furnished a further portion of 13 (180mg, 59.6%).

In less efficacious reactions where 13 and 28 are produced in approximately equal quantities, closeness of TLC mobility prevents clean separation. The proportion of 13 may be increased by retreatment under the above conditions. Alternatively conc. H_2SO_4 may be used as catalyst as follows. A 13-28 mixture (972mg) in 2-acetoxypropene (25ml) containing 3 drops conc. H_2SO_4 was refluxed for 13 hr. Work-up as above followed by preparative TLC in Et_2O-petroleum spirit (1:1) yielded 13 (544mg).

Reaction of dione 18 with $(PhCO)_2O$-H_2SO_4.

(a) A magnetically stirred solution of 18 (250mg, 1.47mmol), $(PhCO)_2O$ (10ml) and conc. H_2SO_4 (5 drops) was heated at 160° (bath temp.) for 5 hr. , the benzoic acid formed being distilled out under reduced pressure (30mmHg). The solution was concentrated (155°, 1mmHg) and the red residue extracted with boiling petroleum spirit and then ether. The petroleum and ether extracts, identical on analytical TLC, were combined, evaporated and refluxed with aq.Na_2CO_3 (10% w/v) for 2 hr. The solution was extracted with $CHCl_3$ and the extract washed with water and dried ($MgSO_4$). The yellow semi-solid obtained on removal of solvent gave one major band on preparative TLC in $CHCl_3$. Recrystallisation from $CHCl_3$- petroleum spirit using decolourising charcoal furnished 32 as needles (100mg, 11.6%), m.p.232-234°. (Found: C, 73.64; H, 4.51. $C_{36}H_{26}O_6S$ requires: C, 73.71; H, 4.47%); ν_{max} (KBr) 1730, 1660, 1600 and 1260cm^{-1}; λ_{max} 242 (logε 4.63), 255 (4.45) and 279nm (4.17); δ 3.15 (d,4H; C-9 and C-10CH_2), 4.06

(t,2H; C-1 and C-3 CH), 7.30 and 7.88 (both m, 20H; aromatic); mass spectral peaks at m/e 586 (M^+), 558, 481, 464, 377, 360 and 343.

(b) A solution of 18 (250mg, 1.47mmol), $(PhCO)_2O$(0.6ml,3.15mmol) and conc.H_2SO_4 (0.3 drops) was heated at 165° for 5 hr , in an evacuated pyrolysis tube. Work-up as in (a) (10 min. reflux with aq. Na_2CO_3) followed by preparative TLC in $CHCl_3$ gave starting material and two products. Compound 18 (45mg) was contained in the band of lower Rf. The uppermost band furnished 24 which was decolourised with activated charcoal and crystallised from $CHCl_3$-petroleum spirit as plates (105mg, 18.9%), m.p. 189-190°. (Found: C,69.60; H, 4.87. $C_{22}H_{18}O_4S$ requires: C, 69.83; H, 4.80%); ν max (KBr) 1733, 1724, 1681, 1600, 1255, 1100 and 700cm^{-1}; ν max ($CHCl_3$) 1728cm^{-1}(ε^a186,$\Delta\nu_{\frac{1}{2}}^a30cm^{-1}$); λ max 233 (logε 4.35) and 281nm (3.21); δ 2.76 (t,4H; C-4 and C-8CH_2), 3.66 (t,2H;C-1 and C-5CH), 5.66 (t,2H; J4Hz; olefinic), 7.55 (m,6H; aromatic), 8.15 (dd, 4H;J 8 and 2Hz; aromatic); mass spectral peaks at m/e 378 (M^+), 257, 151, 105 and 77.

The middle band contained 30 which was decolourised and recrystallised from ether-petroleum spirit as needles (150mg, 54.7%), m.p. 75-76°. (Found: C, 65.39; H, 5.27. $C_{15}H_{14}O_3S$ requires: C,65.69; H, 5.15%); ν max (KBr) 1730, 1725, 1705, 1600, 1255, 1105 and 695cm^{-1}; ν max (CCl_4) 1738 (ε^a270,$\Delta\nu_{\frac{1}{2}}^a15cm^{-1}$) and 1709$cm^{-1}$ (ε^a307,$\Delta\nu_{\frac{1}{2}}^a15cm^{-1}$); λ max 232 (logε 4.26) and 282nm (3.47); δ 2.3-3.0(m,6H; C-3, C-4 and C-8 CH_2), 3.36 (m, 1H; C-1 CH), 3.53 (m,1H; C-5 CH), 5.8 (t,1H; J 4Hz; olefinic), 7.53 (m,3H; aromatic), 8.10 (dd, 2H; J7 and 2 Hz; aromatic); mass spectral peaks at m/e 274(M^+), 153, 105 and 77.

Reaction of 6 with Ac_2O-H_2SO_4.

6 (15mg, 0.077mmol) was heated in a pyrolysis tube at 160° for 5 hr. with 0.6ml of a solution of conc. H_2SO_4 (2 drops) in Ac_2O (5ml). The crystalline residue obtained on extraction with $CHCl_3$ and removal of Ac_2O as above was unconverted starting material.

Acid treatments of 7.

Treatment of 7 (20mg samples) with a solution (0.6ml) of conc. H_2SO_4 (12 drops) in solvent (30ml) at 155° in sealed tubes was carried out 3 times (see Table 5). The reaction in Ac_2O was worked-up as for 6 (vide supra). With $(CH_2OMe)_2$ and 1,4-dioxan as solvents the reaction mixtures were extracted with ether (2x25ml), the organic layer being washed with water (2x25ml), dried and evaporated. In all cases the product was a mixture of 7 and 6 in proportion estimated from NMR integration.

Pyrolyses of 7.

Samples of 7 were pyrolysed in sealed tubes at four different temperatures, viz. 150°, 165°, 180° and 220° for 2-4 hr. On cooling the tubes were washed out with hot $CHCl_3$. In all cases removal of solvent furnished unreacted 7.

6-Bromo-6-bromomethyl-2-thiaadamantan-4,8-dione(9).

A solution of bromine (84mg, 0.52mmol) in Me_2CO (AR, 3ml) was added dropwise to a magnetically stirred solution of 6 (100mg, 0.51mmol) in Me_2CO (2ml). Stirring was continued for 30 min., $CHCl_3$ was added and the solution washed with aq. Na_2CO_3, water, dried ($MgSO_4$) and evaporated to give crude dibromide 9 (160mg, 90%). Crystallisation from $CHCl_3$-petroleum spirit furnished plates, m.p. 189.5-190.5°. (Found: C, 34.20; H, 3.05. $C_{10}H_{10}O_2SBr_2$ requires: C, 33.92; H, 2.83%); ν_{max} (KBr) 3000, 2960, 2920, 1712, 1314, 1280, 1220, 979, 963, 923 and 670cm^{-1}; δ 2.93 (m, 2H; C-9 and C-10 CH),

3.26-3.5 (m,6H;C-1,C-3,C-5,C-7,C-9 and C-10 CH), 3.8 (m, 2H;CH_2Br); mass spectral peaks at m/e 354 (M^+), 274, 245, 218, 194 and 165.

2-Thiaadamantan-4,6,8-trione-2-oxide (34).

An oxygen-ozone mixture was bubbled for 2 hr. through a solution of 6 (45mg, 0.23mmol) in methylacetate (AR, 50ml) at -70°. The deep blue solution decolourised on standing. Zinc (20mg, 0.3mmol) and AcOH (AR, 1 drop) were added to the reaction solution at room temperature and the suspension magnetically stirred overnight. Filtration, concentration and preparative TLC in $CHCl_3$ gave 34 as cubes (10mg, 20%), decomp. ca.120°. (Found: 212.01434. $C_9H_8O_4S$ requires: 212.01432); ν_{max} (KBr) 2950, 2920, 2850, 1705, 1115, 1070, 1025 and 940cm^{-1}; δ (d_6-Me_2CO) 2.56, 2.83, 3.27 and 3.53 (all m, 4H; C-9 and C-10 CH_2), 3.3 (m, 2H; C-5 and C-7 CH), 3.96 (m, 2H; C-1 and C-3 CH); mass spectral peaks at m/e 212 (M^+), 186 and 164.

6-Methylene-2-thiaadamantan-4,8-diol (5).

A solution of 6 (133mg, 0.68mmol) in anhydrous Et_2O (10ml) was added dropwise to a magnetically stirred suspension of $LiAlH_4$ (52mg, 1.37mmol) in anhydrous Et_2O (20ml). Stirring was continued for 2 hr. Saturated aq.Na_2SO_4 was added dropwise and the suspension filtered. The filtrate on TLC in $CHCl_3$ gave two bands. The major band contained diol 5 which sublimed in vacuum (0.03mmHg) as plates (65mg, 48%), m.p. 218-220°. (Found: C,60.32; H, 7.14. $C_{10}H_{14}O_2S$ requires: C, 60.59; H, 7.12%); ν_{max} (KBr) 3360, 3080, 2945, 2920, 2895, 2850, 1655, 1432, 1348, 1271, 1073, 1050, 1030, 960, 950, 910, 890, 744 and 713cm^{-1}; δ1.77, 1.89, 2.71 and 2.83 (all m,4H; C-9 and C-10 CH_2), 2.6 (m, 2H; C-1 and C-3CH), 2.71 (m, 2H; C-5 and C-7CH), 3.13 (s, 2H; hydroxyl), 3.8 (m, 2H; C-4 and C-8CH), 4.8 (s, 2H; olefinic); mass spectral peaks at m/e 198 (M^+), 169 and 151.

This separated portion of the product represents only one of the three possible enantiomeric pairs of diols. This sharp melting product shows zero specific rotation in $CHCl_3$, gives a single sharp peak (ret. time 11.4 min.) on GLC (TMS ether, 1% OVI on Gaschrom Q, 4 ft column) and shows both PMR (vide supra) and ^{13}C spectra, characteristic of a single compound.

Treatment of 6 with undeactivated Raney nickel.

6 (70mg, 0.36mmol), excess Raney nickel and 95% ethanol (20ml) were refluxed for 15 min. After filtration the nickel was washed with hot EtOH and the combined extracts concentrated. The residue, a complex mixture of diols and hydroxyketones, remained unchanged after refluxing in EtOH with excess Raney nickel for a further hr. To simplify the product mixture reduction ($LiAlH_4$) and oxidation (Jones reagent) were carried out as in the two subsequent sections.

9-Methylbicyclo [3,3,1] nonan-2,6-diol (40).

Reduction of the above mixture (50mg) with $LiAlH_4$ (23mg,0.6mmol) followed the same procedure as used in the formation of 5 from 6 (vide supra). Sublimation (120°, 0.2mmHg) of the crude product gave 40 as plates (35mg, 57%), m.p. 162-167°. Analytical TLC in EtOAc showed 40 to be a mixture of diastereomers. (Found: C,70.77; H, 10.46. $C_{10}H_{18}O_2$ requires: C, 70.54; H, 10.66%); ν_{max} (KBr) 3280, 2930, 2875, 1455, 1084, 1060, 1032, 1022, 1005, 971 and 960cm^{-1}; δ 0.96-1.36 (m,4H; C-9CH and CH_3), 1.46(s,2H; hydroxyl), 1.4-1.9 (m,10H; C-3, C-4, C-7 and C-8CH_2, C-1 and C-5CH), 3.7-4.1 (m,2H; C-2 and C-6CH); mass spectral peaks at m/e 170 (M^+), 152, 134 and 119.

9-Methylbicyclo [3,3,1] nonan-2,6-dione (39).

Jones reagent (8N, 0.12ml) was added dropwise to a mechanically

stirred solution of the above mixture (35mg) in Me_2CO(AR,6ml). Stirring was continued for 30 min. The solution was concentrated, water added and extracted with EtOAc. The combined extracts, washed with water, brine, dried ($MgSO_4$) and evaporated furnished crude dione 39 (23mg,67%). Purification by TLC in $CHCl_3$, decolourisation with charcoal and sublimation (120°, 0.35mmHg) gave plates, m.p. 96-98°. (Found: C, 72.29; H, 8.50. $C_{10}H_{14}O_2$ requires: C, 72.26; H, 8.49%); ν_{max} (KBr) 2960, 2940, 2900, 2880, 1705, 1440, 1305, 1230, 770 and 740cm^{-1}; ν_{max} (CCl_4) 1710cm^{-1} (ε^a703, $\Delta\nu_{\frac{1}{2}}{}^a$ 25cm^{-1}); δ 1.05(d,3H; J 7Hz;CH_3), 0.9-1.3 (m, 1H; C-9CH), 1.95-2.2 (m, 4H; C-4 and C-8CH_2), 2.3-2.7 (m, 6H; C-3 and C-7CH_2, C-1 and C-5CH); mass spectral peaks at m/e 166 (M^+), 138, 123 and 112.

9-Methylenebicyclo [3,3,1] nonan-2,6-dione (38).

Raney nickel was deactivated by refluxing with Me_2CO for 1hr. The Me_2CO was decanted and the Raney nickel washed with 95% EtOH. 6 (70mg, 0.36mmol), 95% EtOH (20ml) and excess deactivated Raney nickel were refluxed for 15 min. Work-up (vide supra) furnished a solid which separated into two bands on TLC in EtOAc-petroleum spirit (1:1). The upper band was unreacted 6. The lower band on extraction and sublimation (0.3mmHg) furnished 38 as plates (20mg, 78%), m.p. 70-71°. (Found: C, 73.37; H, 7.46. $C_{10}H_{12}O_2$ requires: C, 73.14; H, 7.37%); ν_{max} (KBr) 3090, 2955, 2938, 2867, 1705, 1660, 1450, 1440, 1318, 1230, 1220 and 930cm^{-1}; ν_{max} (CCl_4) 1720cm^{-1} (ε^a800, $\Delta\nu_{\frac{1}{2}}{}^a$ 20cm^{-1}); δ 1.8-2.2 (m,4H; C-4 and C-8CH_2), 2.3-2.7 (m,4H; C-3 and C-7CH_2), 3.33 (t,2H; J 5Hz; C-1 and C-5CH), 4.96 (s, 2H; olefinic); mass spectral peaks at m/e 164 (M^+), 136, 122, 108, 94 and 79.

Reflux of 6 with Me_2CO deactivated Raney nickel for 45 min. gave a complex product mixture from which 38, 39 and 40 were isolated by TLC.

Reaction of dione 18 with acyl halides.

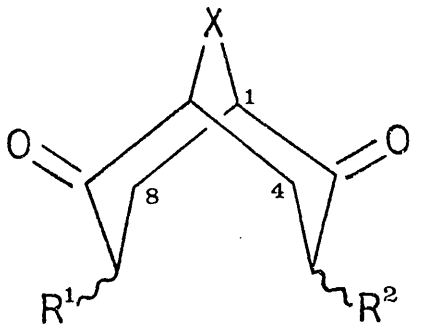
(a) A solution of 18 (200mg, 1.18mmol), AcCl (10ml) and conc. H_2SO_4 (4 drops) was refluxed for 6 hr. AcCl was distilled using a Bunsen burner. The resulting tar was extracted with ether and the extract washed with aq.$NaHCO_3$, water, dried ($MgSO_4$) and evaporated to give 6 (15mg, 6.6%).

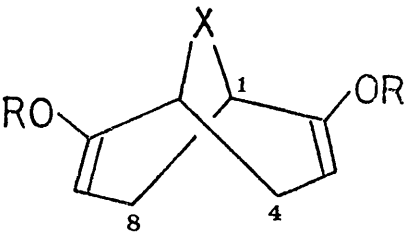
(b) A solution of 18 (160mg, 0.94mmol), PhCOCl (6ml) and conc. H_2SO_4 (4 drops) was heated at 170° (bath temp.) for 6 hr. PhCOCl was distilled (140°, 30mmHg) and the resulting tar extracted with petroleum spirit and with ether. The combined extracts after removal of solvent were refluxed with water for 1 hr. Extraction of the hydrolysate with $CHCl_3$ and washing of the extract as in (a) gave a mixture of 24 and 30 which were separated by TLC in Et_2O - petroleum spirit (1:1) (36mg, 10% and 20mg, 8% respectively).

(c) A solution of 18 (216mg, 1.27mmol), $BrCH_2COBr$ (5ml) and conc. H_2SO_4 (4 drops) was refluxed for 6 hr. $BrCH_2COBr$ was distilled (30mmHg) and the resulting tar extracted with petroleum spirit and with ether. Work-up of the combined extracts as in (a) gave 37, a yellow oily solid (310mg, 69%), δ2.7-3.9 (m, ca.8H; skeletal), 3.9-4.2 (m, ca4H; CH_2Br). This product decomposed on attempted purification by preparative TLC.

(d) A solution of 18 (200mg, 1.18mmol), $ClCH_2COCl$ (10ml) and conc. H_2SO_4 (8 drops) was refluxed for 9 hr. $ClCH_2COCl$ was distilled (30mmHg) and the resulting gum worked-up as in (a) yielding a 1:1 mixture of 25 and 31 as a yellow oil (150mg), δ2.60

(m, 10H; CH_2), 3.43 (m, 4H; CH), 4.16 (m, 6H; CH_2Cl), 5.55 (t,2H; J 4Hz; olefinic), 5.73 (t, 1H; J 4Hz; olefinic). Both products decomposed on attempted separation by preparative TLC.





17 X = CH_2 ; R^1= R^2= H

18 X = S ; R^1= R^2= H

19 X = S ; R^1= H ; R^2= Ac

20 X = O ; R^1= R^2= H

21 X = O ; R^1= R^2= Ac

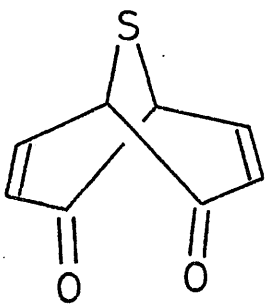
13 X = S ; R = Ac

22 X = CH_2 ; R = Ac

23 X = O ; R = Ac

24 X = S ; R = COPh

25 X = S ; R = $COCH_2Cl$



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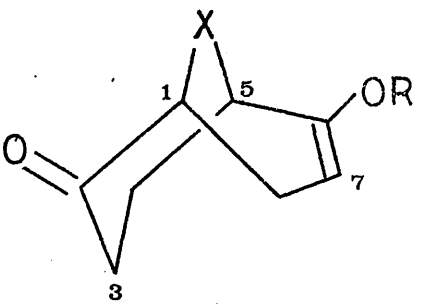
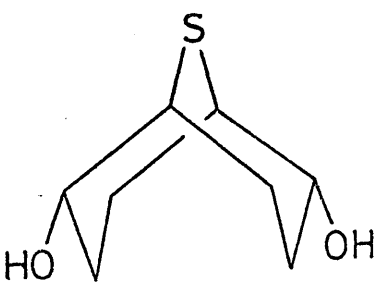




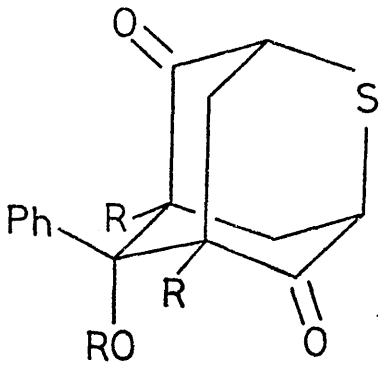
27

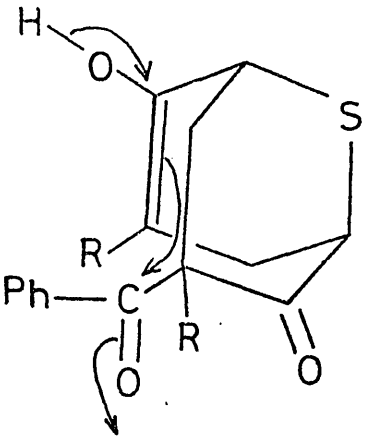
28 X = S ; R = Ac

29 X = S ; R = H

30 X = S ; R = COPh

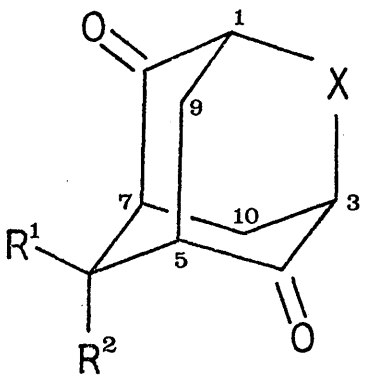
31 X = S ; R = $COCH_2Cl$

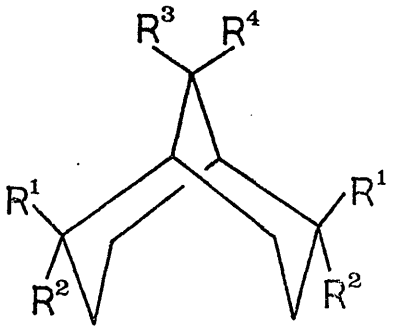




32 R = COPh

33 R = COPh





38 $R^1, R^2 = O$; $R^3, R^4 = CH_2$

39 $R^1, R^2 = O$; $R^3 = H$; $R^4 = CH_3$

40 $R^1, R^3 = H$; $R^2 = OH$; $R^4 = CH_3$

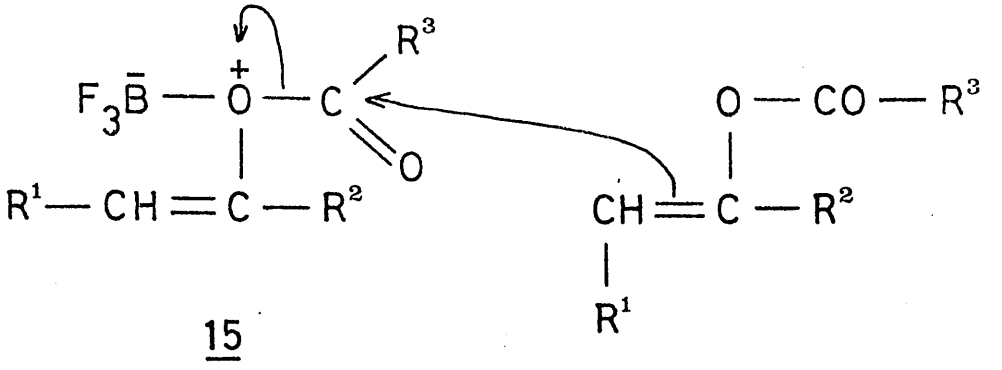
34 X = SO ; $R^1, R^2 = O$

35 X = CH_2 ; $R^1, R^2 = CH_2$

36 X = CH_2 ; $R^1 = CH_3$; $R^2 = OAc$

37 X = S ; $R^1 = CH_2Br$; $R^2 = OCOCH_2Br$

(Systematic numbering for 34 and 37 only)

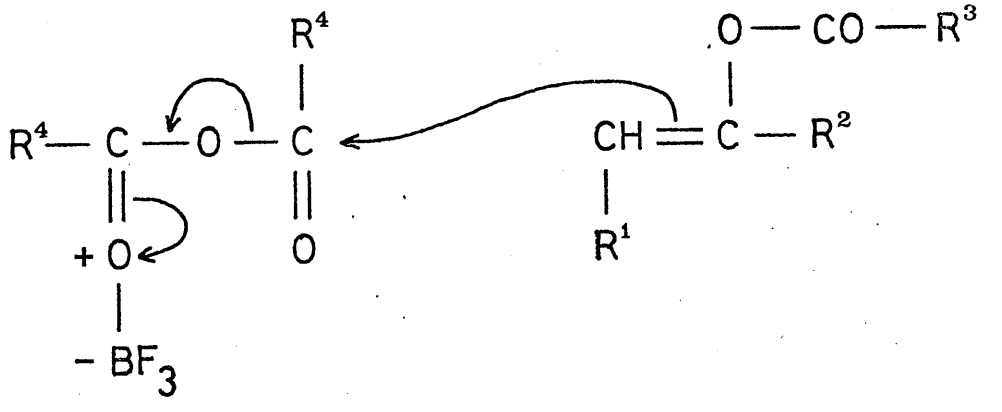


15

R^1 = H, Alkyl, Aryl

R^2, R^3 = Alkyl, Aryl

Scheme 1

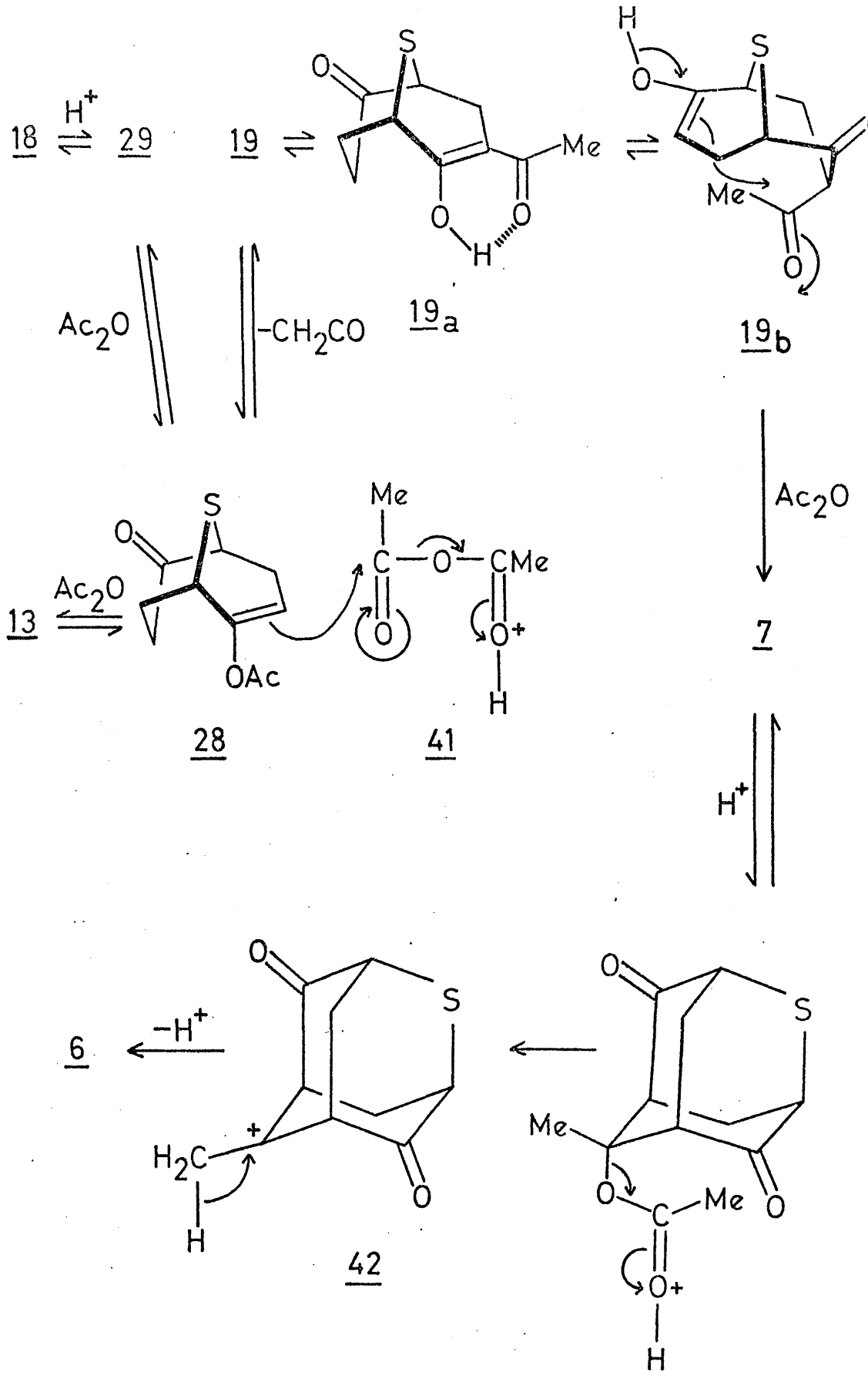


16

R^1 = H, Alkyl, Aryl

R^2, R^3, R^4 = Alkyl, Aryl

Scheme 2


18
H+
29
19
Me
19a
19b
Ac2O
-CH2CO
13
Ac2O
OAc
28
Me
CMe
41
7
H+
6
-H+
42
H2C
Me

Scheme 3

T A B L E 4.

Treatment of dione 18 with conc. H_2SO_4/Ac_2O

H_2SO_4 (drops/30ml Ac_2O)	Reaction Time (hr.)	O-Acylated Products	C-Acylated Products
0.5	10	28(60%);13(30%)	-
1.2	24	28(16%);13(64%)	-
5.0	6	28(18%);13(45%)	7(28%)
21.0	24	13(0.7%)	7(20.5%);6(9.1%)
24.0	24	-	6(26%)

Yields refer to purified material

T A B L E 5.

Treatment of 7 with conc. H_2SO_4

Solvent	Reaction Time (hr.)	Proportion 7 : 6
Ac_2O	4	1 : 4
$(CH_2OMe)_2$	2	9 : 1
1, 4 - Dioxan	4	4 : 1

Chapter 3

1. REVIEW - CYCLOOCTATETRAENOQUINONES.

Historically aromatic chemistry originated in Faraday's discovery of benzene in 1825. When Kekulé identified[50] its molecular structure forty years later he proposed that the unusual stability of all aromatic compounds was dependent on the properties of this ring system. As a result the term 'aromatic' became synonymous with 'benzenoid', a view which persisted for many years.

By 1925 the significance of the six π — electrons to the stability of benzene was well-known but chemists questioned whether aromaticity was only associated with molecules or ions having this sextet of electrons. This question was partly answered by Hückel[51] in the 1930's when he used simple molecular orbital theory to predict that conjugated monocyclic systems which exist in a planar conformation and contain $(4n + 2)$ π - electrons are aromatic while those which contain $(4n)$ π - electrons are non-aromatic. The main limitation of Hückel's rule was that it could not be used to predict the aromatic nature of polycyclic conjugated hydrocarbons. Assignments for these systems have been achieved using an empirical rule proposed by Craig[52] in 1959.

In the design of potentially aromatic systems, the inclusion of a carbonyl group has frequently been used to attain the requisite number of π - electrons while complete conjugation is maintained. For polyunsaturated cyclic ketones to exhibit pseudo-aromaticity their polarised canonical forms must make a significant contribution to the resonance hybrids. This will only occur if the stability achieved in becoming a $(4n + 2)$ π - electron system compensates for the increase in angle strain due to the assumption

of a planar conformation and the separation of charge.

The dicarbonyl systems (43) and (44) ("cyclooctatetraenoquinones") are of considerable interest because their canonical forms, 43a and 44a, embody the cyclooctatetraene dication (45), an eight-membered 6π – electron system (4n+2, n=1). Despite many attempts [53], neither 45 nor any of its substituted derivatives had been made before Olah et al. prepared dication (46) by two-electron oxidation [54] of 1,3,5,7-tetramethylcyclooctatetraene (47) with SbF_5 in SO_2ClF at -78°. Although 46 was shown by ^1H and ^{13}C NMR spectroscopy to be aromatic between -30° and -100° it irreversibly isomerised to cis - 2,3a,5,6a – tetramethyldihydropentalene dication (48) when the reaction solution was warmed to -20°. Thus it was not known whether 43 and 44 would exhibit pseudo-aromatic character or exist as non-planar and hence non-aromatic molecules.

Since 1962 several attempts have been made to prepare benzo-derivatives of 43 and 44. Although Cava and Ratts described [55] the formation of halodibenzo-1,4-cyclooctatetraenoquinones (49) and (50) from the sodium dichromate – acetic acid oxidation of the corresponding biphenylene derivatives (51) and (52), they were interested in the mechanism of this oxidation and did not discuss the possible aromatic nature of the quinone derivatives.

In 1966 Proctor and co-workers attempted [56] to synthesise the tetraketone (53) or (54) as a potential precursor of the quinone derivative (55). However, treatment of diketone (56) with selenium dioxide or sodium methoxide, with or without ethyl formate, resulted in transannular aldol condensation which furnished products of the type (57) instead of the proposed

oxidation yielding 53 or 54.

Yates, Lewars and McCabe have prepared [57] dibenzo(a,e) cyclooctene-5,6-dione (102) from hydrocarbon (100) via enone (101) [Scheme 4]. Pseudo-aromaticity in 102 requires a large resonance contribution by its canonical form (102_a) and this should cause the carbonyl stretching frequency to occur at appreciably longer wavelength than the corresponding bands in 101, 58 and 59. In addition the two protons on the eight-membered ring should exhibit NMR signals at lower field strength than the corresponding protons in either 101 or 60 due to the deshielding effect of the induced diamagnetic ring current, a characteristic property of aromatic systems in a magnetic field. The infra-red and NMR spectra of 102 did not confirm these relationships and hence it was concluded that 102 is non-aromatic.

Tropone (61) was known to have only a minor contribution from its canonical form (61_a) [58] presumably because of the high angle strain and charge separation involved in 61_a. Protonation on oxygen eliminated this charge separation and furnished the hydroxytropylium cation (61_b) which shows [59] appreciable aromatic character. Yates el al. therefore attempted to promote aromaticity in 102 by protonation with strong acid. However, the NMR spectrum of 102 recorded in trifluoroacetic acid is essentially the same as that obtained in deuteriochloroform and hence if they exist the mono-and di-protonated forms of 102 (analogous to structures 62, 63 and 64 for 44) are non-aromatic.

Ebine et al. have prepared [60] the benzocyclooctatetraenoquinones (65) and (66) as ring-expanded products from dichlorocarbene addition respectively to tetramethoxynaphthalene (67) and tetramethoxybenzotropone (68). The carbonyl stretching frequencies

($1702cm^{-1}$ for 65; $1723cm^{-1}$ for 66) and vinyl proton chemical shifts (δ6.39 for 65; 6.35 and 6.72 for 66) indicate that there is no aromatic stabilisation in the eight-membered rings of 65 and 66.

Several authors have made synthetic approaches to cyclooctatetraenoquinones (43) and (44) through their valence tautomers. Preparation of bicyclo [4,2,0] octa-3,7-diene-2, 5-dione (69) followed by tautomerisation should produce 43 while 44 may be formed by tautomerisation of bicyclo [4,2,0] octa-2, 4-diene-7,8-dione (70) or bicyclo [4,2,0] octa-4,7-diene-2,3-dione (71).

In an attempt to obtain a substituted derivative of 70 Pappas and co-workers [61] proposed that the photoaddition of an alkyne to methoxy-p-benzoquinone would furnish diene (103) [Scheme 5] which could be converted to a derivative (104) of 44 by a series of steps. However, this reaction sequence was found to be inapplicable as the photoaddition invariably took place at the methoxyl side of the quinone yielding 72 - 75. Although compounds (72)-(75) are formally derivatives of 69, the authors made no attempt to convert them to the corresponding derivatives of 43.

In 1973 Yates reported [62] that photoaddition of an alkyne to p-benzoquinone [63] and to 2,5-dimethyl-p-benzoquinone took place at the carbonyl group. In order to overcome this problem Yates reacted p-benzoquinone with anthracene to produce enedione (76) which underwent photoaddition at the ethylenic bond to form adducts (77), (78) and (79), in good yield, with but-2-yne, phenylacetylene and dimethylacetylenedicarboxylate respectively.

The stereochemical assignment of these molecules was based on the assumption that addition occurs at the less hindered side of the double bond. Adducts (77) and (78) fragmented thermally by a retro-Diels-Alder reaction to give 80 and 81 in good yield, but valence tautomerism of these products was not discussed.

Kitahara has described [64] the synthesis [Scheme 6] of 69 from cyclooctatetraene (105). Bromination of 105 gave trans-7, 8-dibromobicyclo[4,2,0]octa-2,4-diene [65] (106). Photooxygenation of 106 in acetone using hematoporphyrin as sensitizer furnished epidioxide (107) and diepoxide (108) in yields of 78% and 3.5% respectively. Lithium aluminium hydride reduction of 107 yielded diol (109). Debromination of the corresponding acetate (110) with zinc dust followed by reductive deacetylation afforded diene-diol (111) which was oxidised (Jones) to 69 in 41% overall yield from 105.

Thermolysis of 69 at 500° unexpectedly yielded [66] tropone (61). In rationalisation, the intermediacy [Scheme 7] of the all-cis quinone (43) or its cis, cis, trans isomer (112) was suggested, degradation taking place by extrusion of carbon monoxide from bis-cyclopropanone (113).

By analogy, thermolysis of 3,4-benzobicyclo[4,2,0]octa-3,7-diene-2,5-dione (82) was expected to produce 2,3-benzocyclo-octatriene-1,4-dione (83) which may be more resistant to decarbonylation than 69 due to the stabilising affect of the benzene ring. Dione (82) had previously been prepared in low yield by the photoaddition of acetylene to naphthoquinone [67]. However, Kitahara et al. prepared [68] 82 by a different route [Scheme 8] starting from 69. Diels-Alder addition of butadiene to 69 at 100° gave two cis 1:1 adducts (114, 53%) and (115, 7%) together with a small amount of a 1:2 adduct. The stereochemical

assignment of 114 and 115 to anti and syn respectively, was tentatively made from the steric viewpoint that the anti — side is more accessible to butadiene. Reaction of 69 with butadiene in presence of aluminium chloride at room temperature furnished trans-adduct (116), possibly by acid-catalysed isomerisation of the initially formed cis-adduct (114). Both 114 and 116 underwent allylic bromination with N-bromosuccinimide forming 117 from which 82 was obtained by dehydrobromination with triethylamine.

Thermolysis of 82 at 500° gave 5-hydroxyacenaphthenone (120) by an unexpected novel rearrangement [Scheme 9] presumably involving dione (83), the diradical (118) and ketene (119) as intermediates.

In an alternative approach to cyclooctatetraene-1,4-quinone (43) [Scheme 10], flash thermolysis (500°) of dione (121), formed by zinc reduction of 69, furnished diene (122)[69]. In strong acid a rapid equilibrium is set up between 122 and 1,6-dihydroxyhomotropylium ion (123). Bromination of 122 with N-bromosuccinimide in trifluoroacetic acid-methylene chloride (1 : 2) and treatment of the unstable 2-bromo-5,7-cyclooctadiene-1,4-dione (124) with triethylamine furnished 43.

The ^{1}H NMR signals of the vinyl protons of 43 and 122 are almost identical, indicating that the resonance contribution of its canonical form (43a) can be neglected and that 43 is non-aromatic. In corroboration 43 underwent ready catalytic hydrogenation with platinum dioxide to give cyclooctan-1,4-dione (84).

Protonation of 43 with trifluoroacetic acid failed to promote aromaticity and led to decomposition. Thermolysis at

500° left 43 unchanged, apart from some minor decomposition, which rules it out as a possible intermediate in the formation of tropone (61) by thermolysis of 69 (*vide supra*). However, the *cis, cis, trans* isomer (112) is expected to be the initial product of the thermal ring-opening of 69 in a conrotatory mode[70] and hence is still a possible intermediate.

Although 70 may be in equilibrium with 44 under normal conditions (thermal disrotatory ring-opening[70]), 71 may not (photochemical disrotatory ring-opening[70]) and hence this isomer should be an isolable compound. Oda and co-workers [71] have prepared 71 starting from epidioxide(107)[64] [Scheme 11]. Reaction of 107 with one equivalent of triphenylphosphine furnished a mixture of two diastereomeric 1,2-epoxides (125), stereoisomers differing in the configuration of the epoxy group and the bromines. Acetolysis of these epoxides followed by zinc debromination gave hydroxy-acetates (126) and (127) from which an epimeric mixture of enone-acetates (128) was obtained on low temperature Jones oxidation. Carbonyl protection, reduction of the ester function and oxidation of the resulting alcohol led to 129 which was deprotected with 12N H_2SO_4 to give 71 in high yield. Alternatively, 71 was formed in low yield from 127, acid hydrolysis of ketal (130) requiring 18N H_2SO_4 which led to appreciable decomposition.

Thermal rearrangement of 71 at 150° failed to produce 44 but furnished [72] bicyclo [3, 2, 1] octa-3, 6-diene-2, 8-dione (132) in low yield [Scheme 12]. Formation of 132 is thought to involve an electrocyclic ring-opening to give the *cis* unsaturated diketene (131) which undergoes an intramolecular Diels-Alder cyclisation. Raising the temperature from 150° to 200° caused rapid decarbonylation of 132 yielding tropone (61).

Several authors have investigated synthetic routes to 43 and 44 which do not involve their valence tautomers. In 1975 McKervey et al. prepared [73] cyclooctatriene-1,4-dione bisethyleneketal (85) as an immediate precursor of 43. Oxidation of hydroxy-ketone (86) afforded 84 which was converted to bisketal (87) under carefully controlled conditions. Bromination of 87 with bromine gave tribromide (88) which furnished 85 by dehydrobromination with potassium t-butoxide in t-butanol or with diazabicylo [5,4,0] undec-5-ene. The chemistry of 85 is now under active investigation by this group.

In an alternative approach[74] to 44, performic acid oxidation [Scheme 13] of cis, cis-1,5-cyclooctadiene (133) followed by hydrolysis gave the trans diol (134) which was oxidised to the corresponding dione (135). However, attempted allylic bromination of 135 failed to furnish dibromide (136), N-bromosuccinimide giving intractable tars while bromine in carbon tetrachloride produced bicyclic derivatives (138) and (139), possibly via bromonium ion (137). Ketalisation of 135 gave three products, optimisation of diketal (89) occurring in a two week reaction time. Treatment of (89) with bromine in pyridinium bromide perbromide yielded bicyclic derivatives (90) and (91) formed by the nucleophilic attack of the ketal oxygen on a bromonium ion analogous to 137. An allylic bromide (92) or (93) was produced in the small-scale reactions of 89 with N-bromosuccinimide and 1,3-dibromo-5,5-dimethylhydantoin but no further progress towards dione (44) was made.

In a related approach, LeGoff[75] has synthesised dione (135) from 133 via epoxy-olefin (140) and keto-alcohol (141) [Scheme 14]. Although dibromination of 135 in the presence of cupric acetate

furnished the key intermediate (142), all attempts to convert 142 to 44 by dehydrobromination failed. Monodehydrobromination of 142 by reaction with warm hexamethylphosphoric triamide[76] yielded 3-bromo-5,7-cyclooctadiene-1,2-dione (143) which was shown to exist predominately as the enol (143_a). In corroboration the isomeric bromocyclooctadienediones (94) and (95) have been reported [77, 78] to exist as their enol tautomers (94_a) and (95_a) respectively. Reaction of 143_a with N-bromosuccinimide produced [Scheme 15] dibromide (144) which failed to yield 1,2-quinone (145) on treatment with triethylamine. The intermediacy of 145 was inferred by the formation of benzocyclobutadienoquinone (147) produced by dehydrobromination of bicyclic tautomer (146). Although 145 had proved too labile for isolation, LeGoff succeeded in forming quinoxaline derivative (96) of 44 by dehydrobromination of quinoxaline (97). The small coupling constant between H-4 and H-5 indicated that the eight-membered ring in 96 was non-planar and hence non-aromatic.

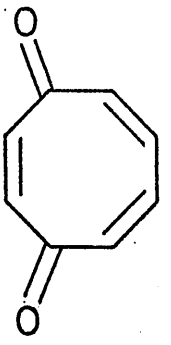
Oda el al. have recently synthesised [79] dione (44) and its 3-bromo analogue (145) by treatment of 7-bromo-3,5-cyclooctadiene-1,2-dione (148) [80] [Scheme 16] and dibromide (144) with triethylamine at -50°. Although the authors could find no evidence by ^{1}H NMR spectroscopy, for the equilibration of 44 with its valence tautomer (70) below -20°, the latter's presence at room temperature was inferred by the isolation of 147 and dione (149) which were proposed to arise by the redox reaction occurring between 44 and 70. In corroboration, Diels-Alder adduct (150) was formed by reaction of 70 with 4-phenyl-1,2,4-triazolin-3,5-dione.

In agreement with LeGoff's results, Oda also implied

equilibration of 145 and 146 at -20° as shown by the formation of 147.

Although some polar character was suggested by the low proton chemical shifts, δ6.2-7.2 for 44, and by the formation of hydroxy-ketone (98) in the nucleophilic addition of methanol to 44, Oda concluded that both 44 and 145 do not show appreciable aromaticity. In particular the small coupling constants between H-4 and H-5, and between H-6 and H-7 in 145 indicated that it was non-planar while electrophilic addition of bromine to 44 furnished an unstable dibromide (99).

An unsuccessful attempt was made to isolate a pure sample of 44 at low temperature; this reflects the high reactivity of these ring systems and their valence tautomers and corroborates the absence of aromatic stabilisation.



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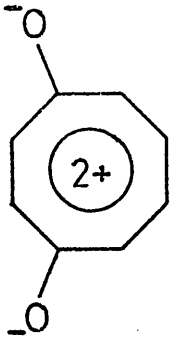
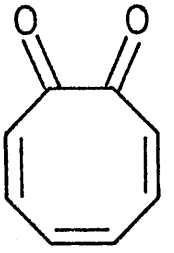


43a



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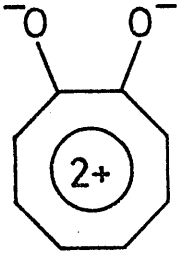
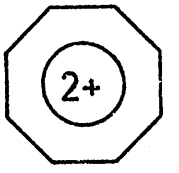


44a



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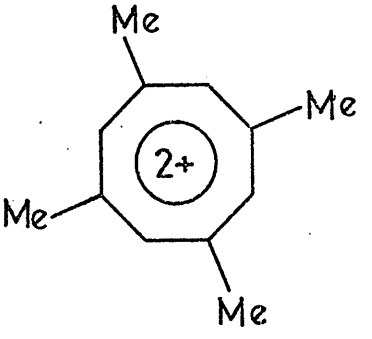

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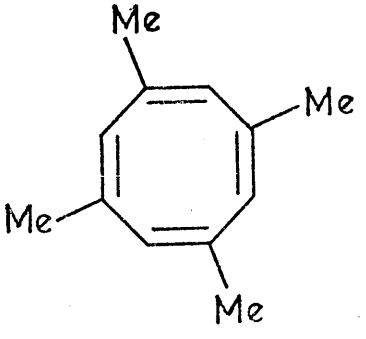

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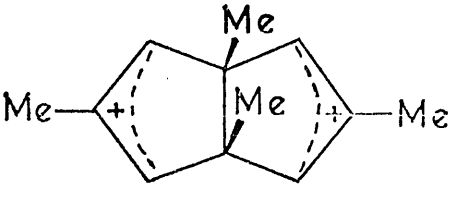

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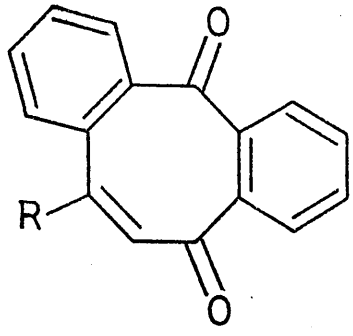
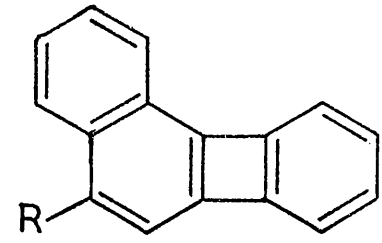


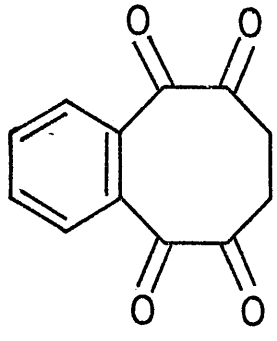
49 R = Br

50 R = I



51 R = Br

52 R = I



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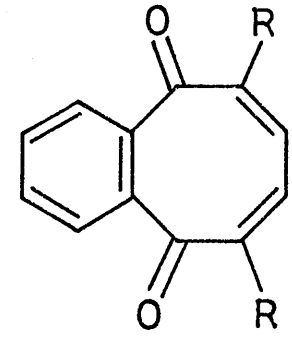
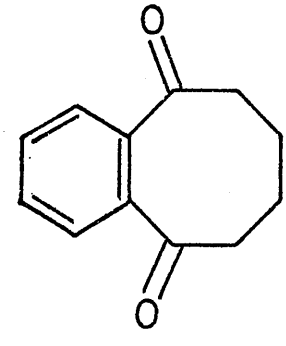


54 R = OH

55 R = H



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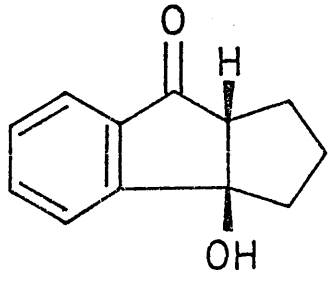

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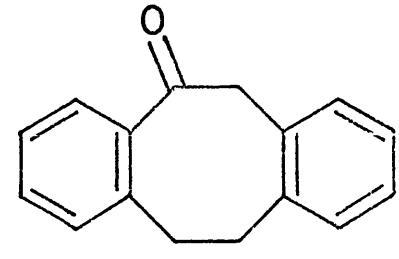

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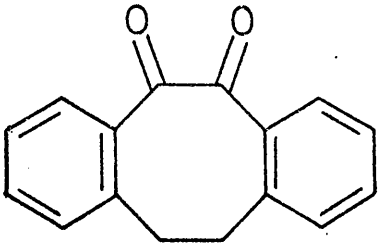

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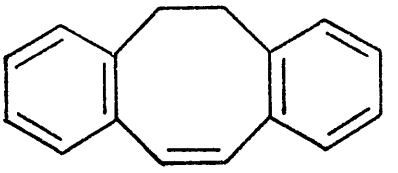

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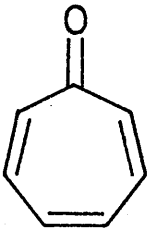

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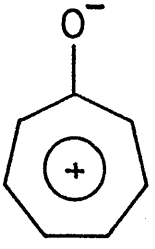

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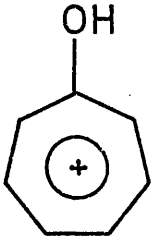

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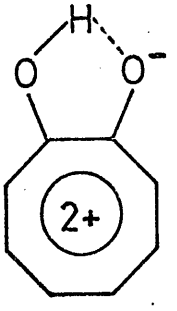

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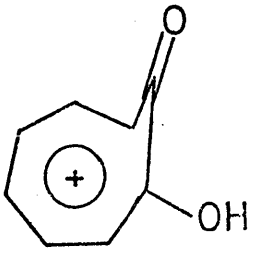

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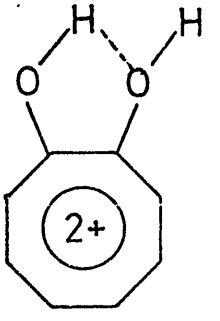

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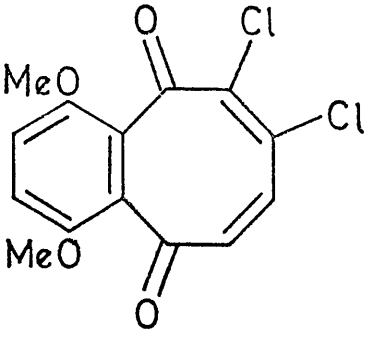

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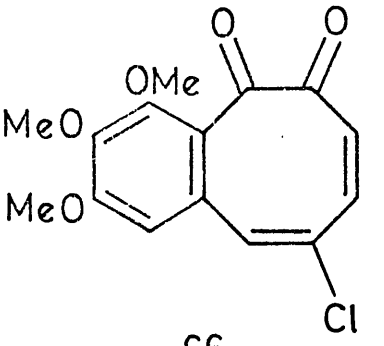

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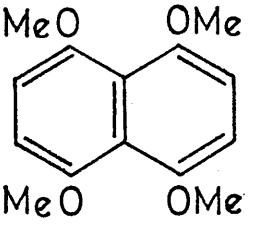

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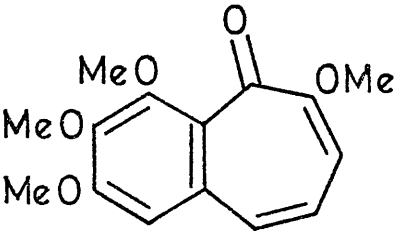

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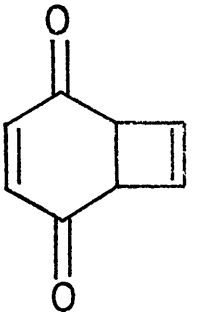

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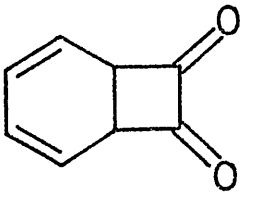

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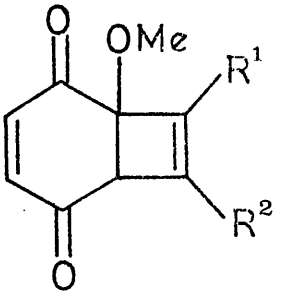
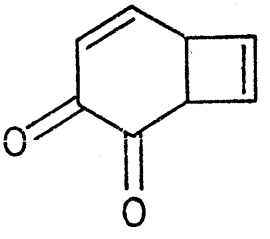




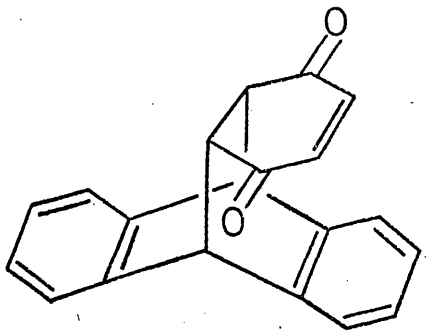
71

72 $R^1 = R^2 = Me$

73 $R^1 = R^2 = C_6H_5$

74 $R^1 = Me$; $R^2 = C_6H_5$

75 $R^1 = C_6H_5$; $R^2 = Me$



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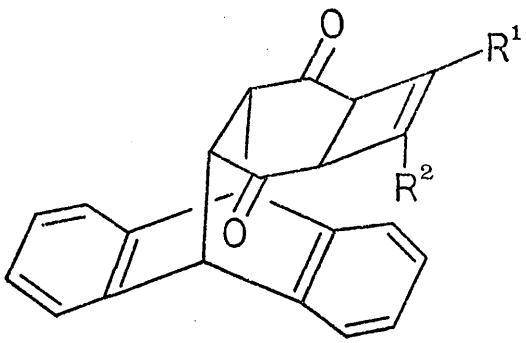
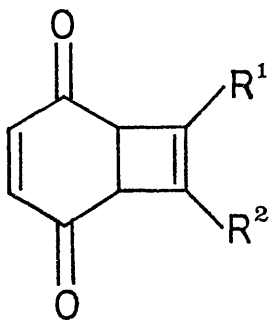


77 $R^1 = R^2 = Me$

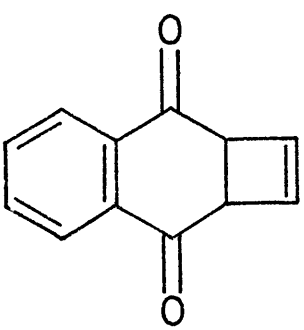
78 $R^1 = C_6H_5$; $R^2 = H$

79 $R^1 = R^2 = CO_2Me$



80 $R^1 = R^2 = Me$

81 $R^1 = C_6H_5$; $R^2 = H$



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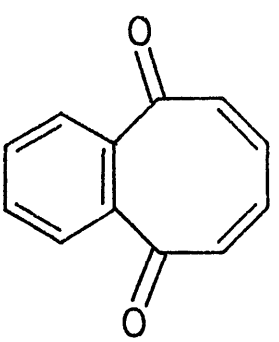

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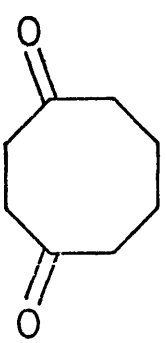

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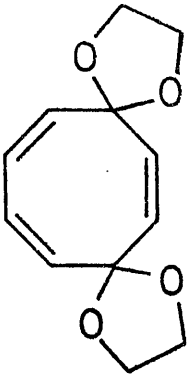

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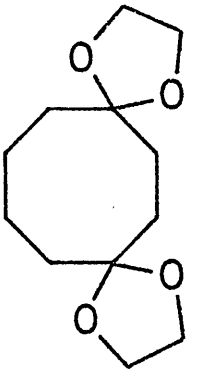

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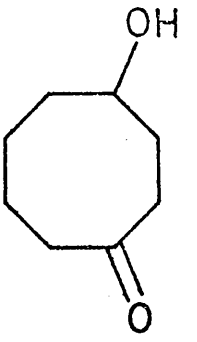

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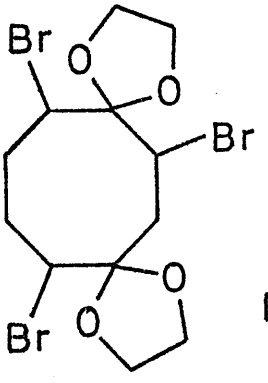

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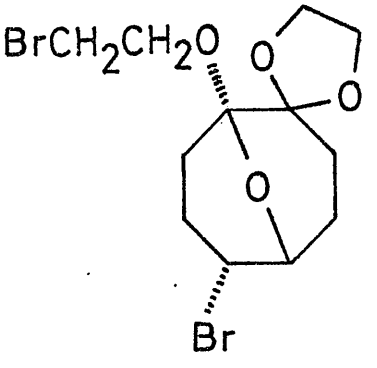

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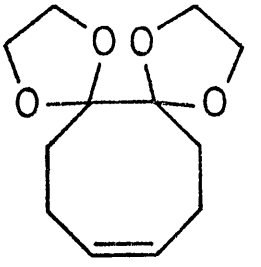

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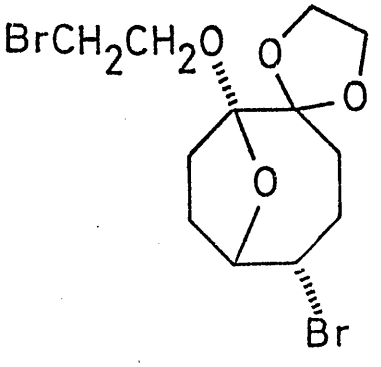

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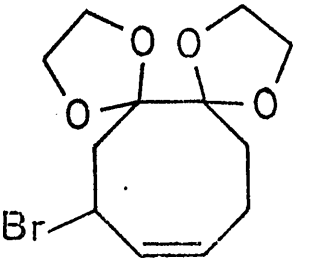

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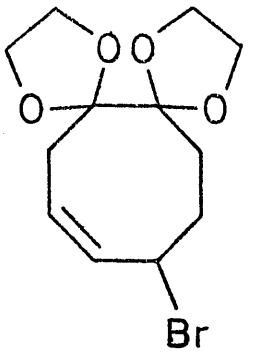

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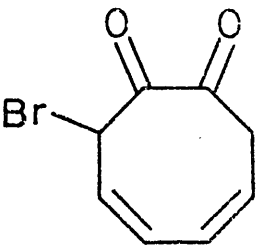

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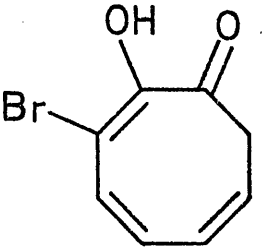

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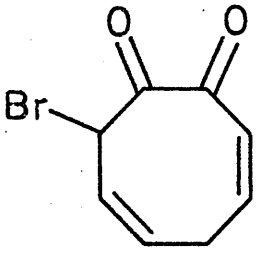

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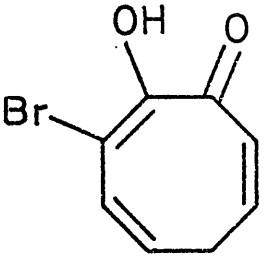

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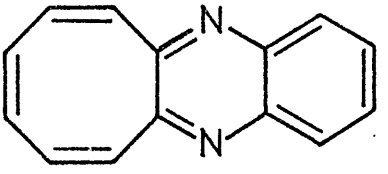

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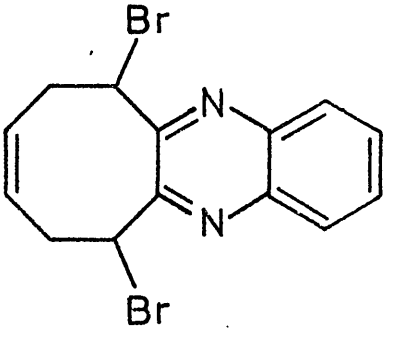

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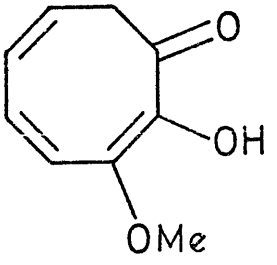

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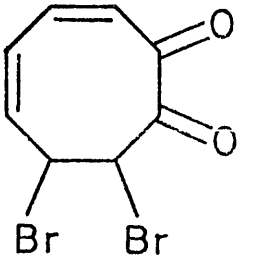

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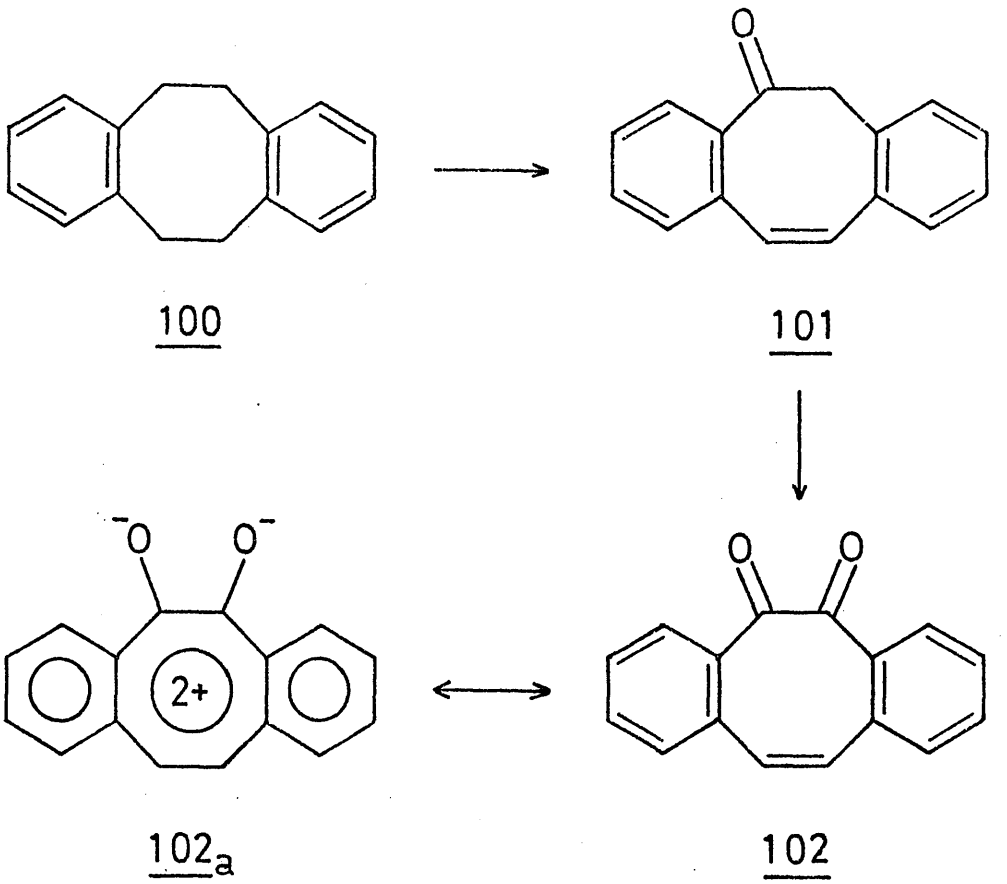
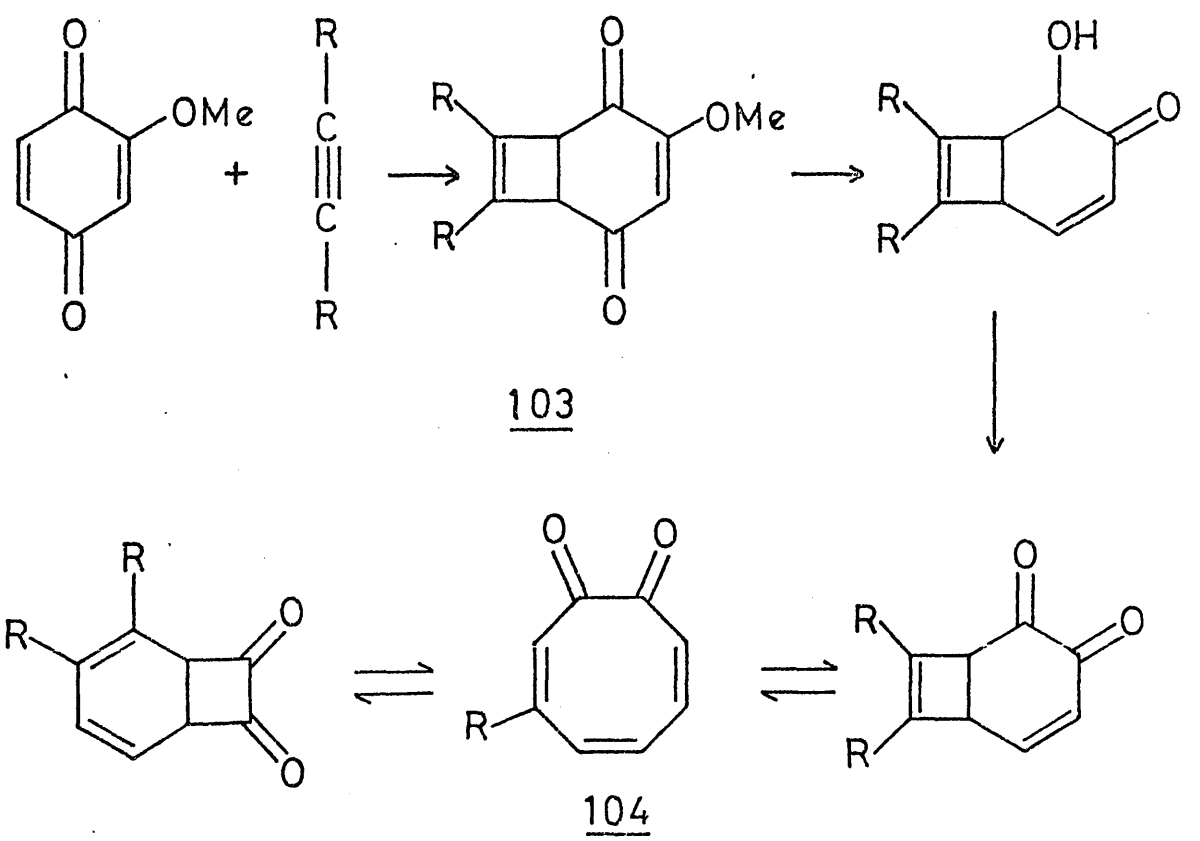
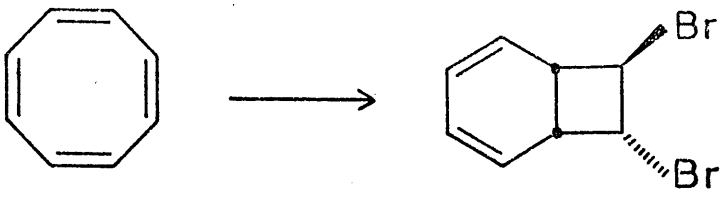


Scheme 4



Scheme 5



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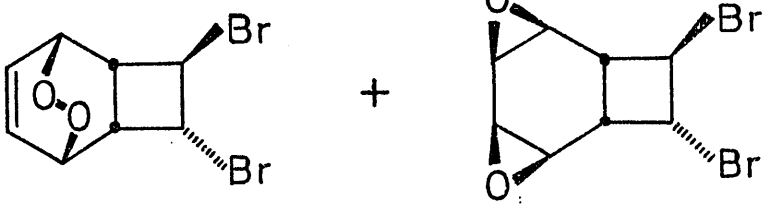
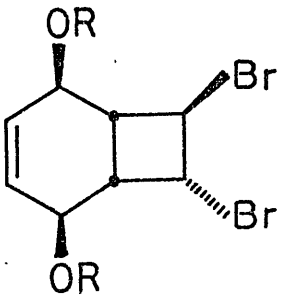
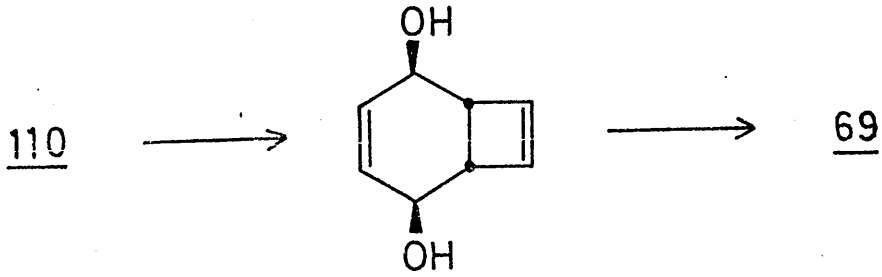


107 108



109 R = H

110 R = CO_2Me



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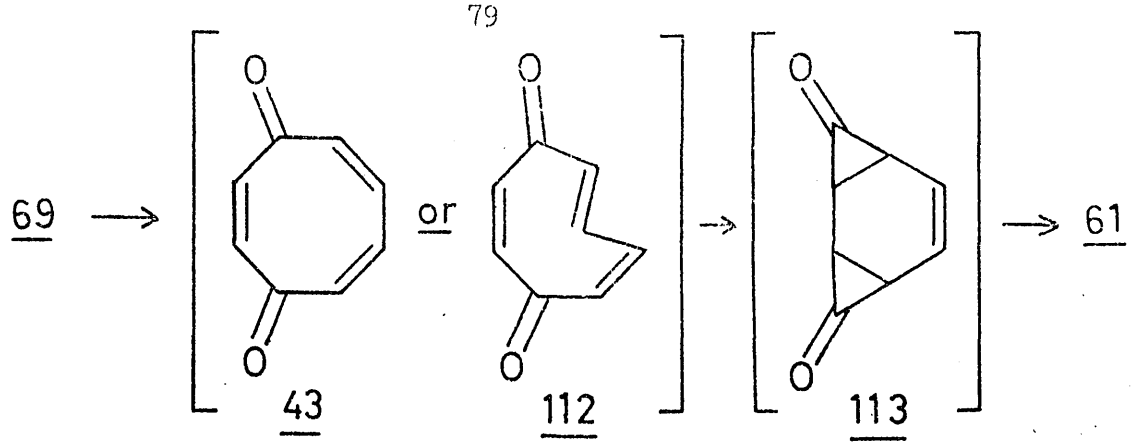
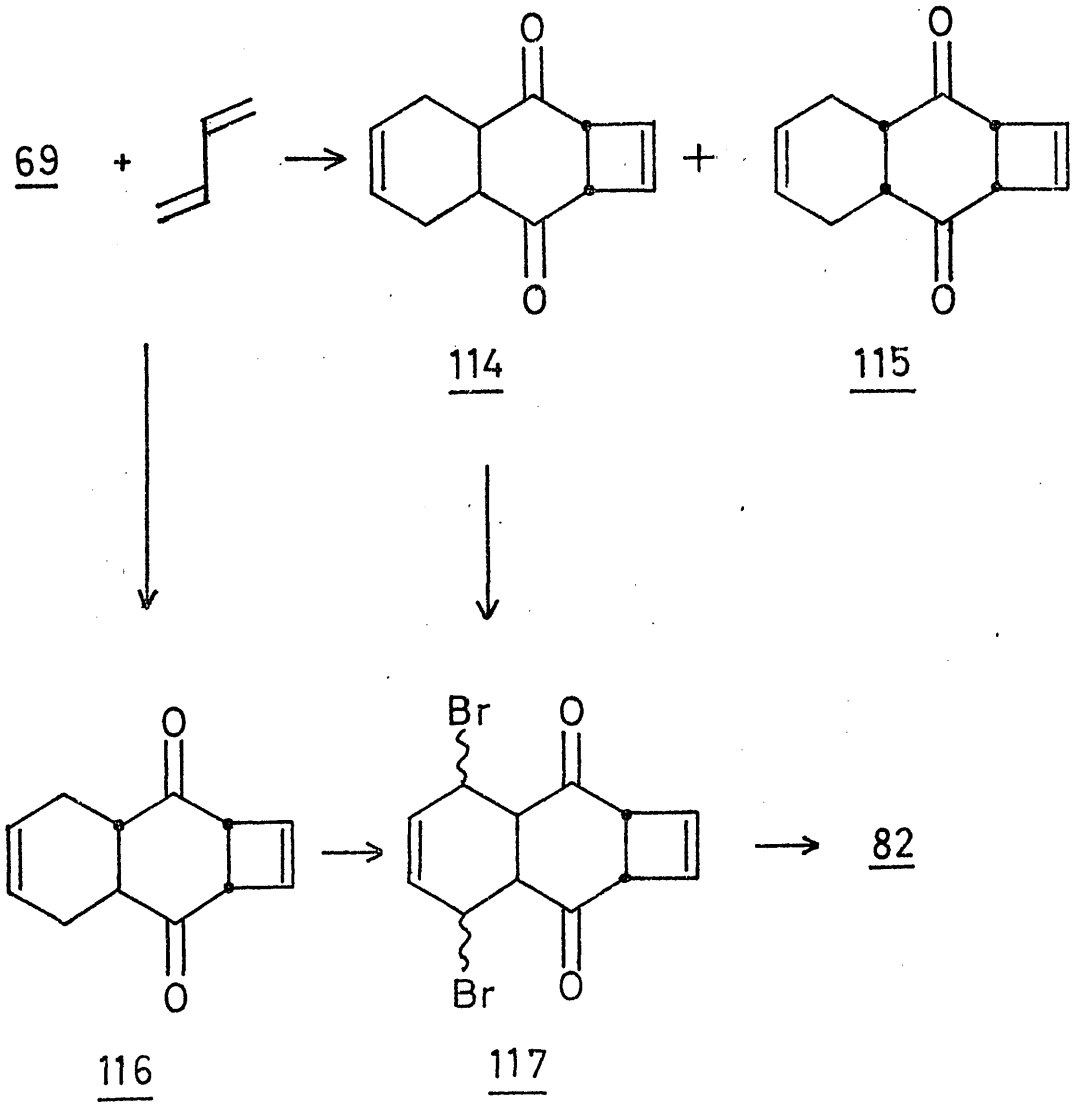
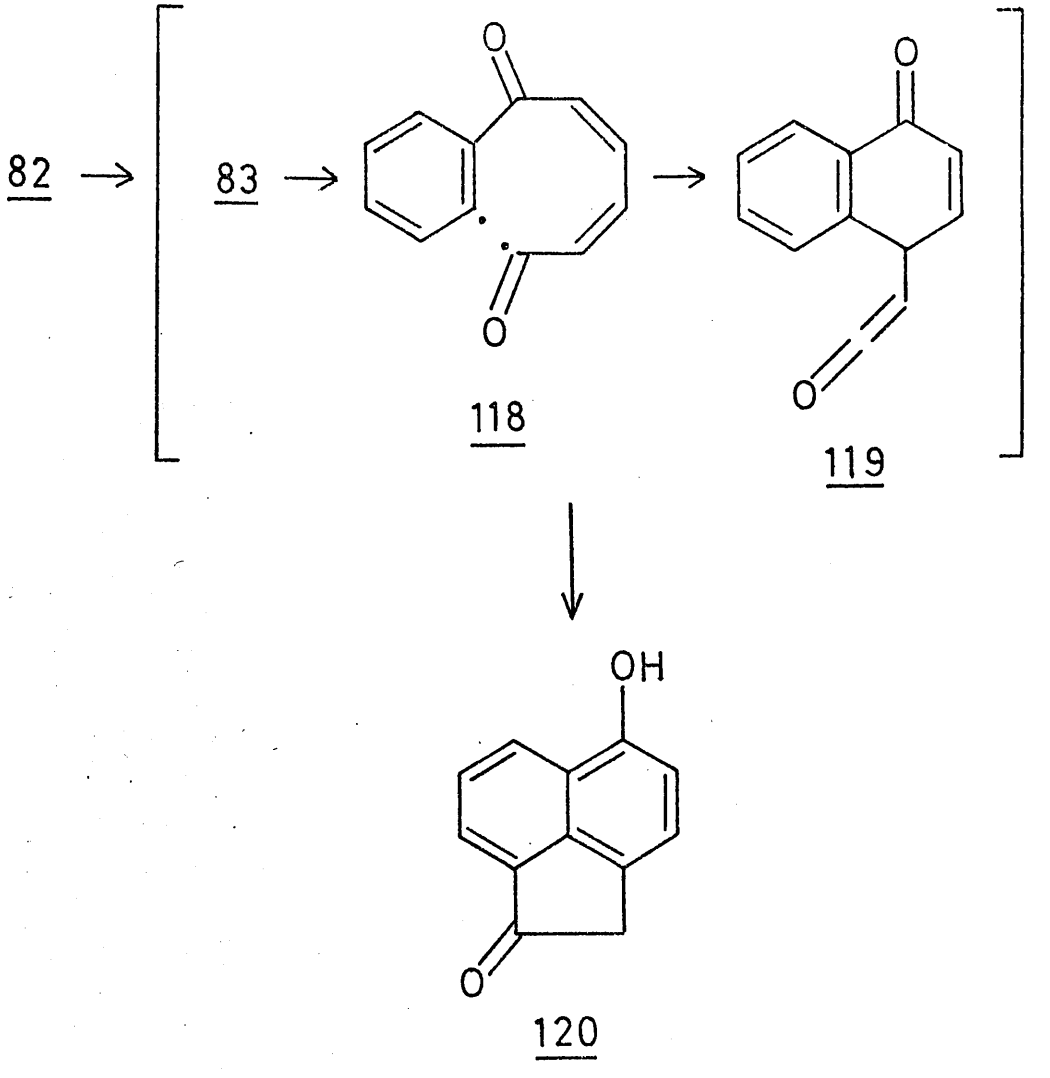
Scheme 6



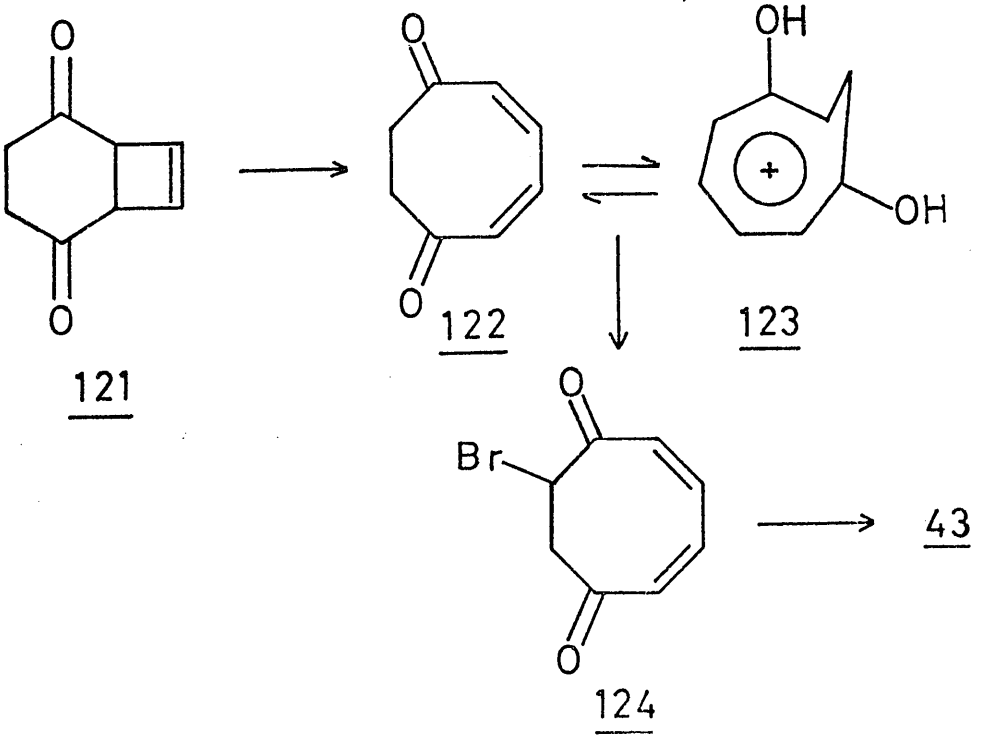
Scheme 7



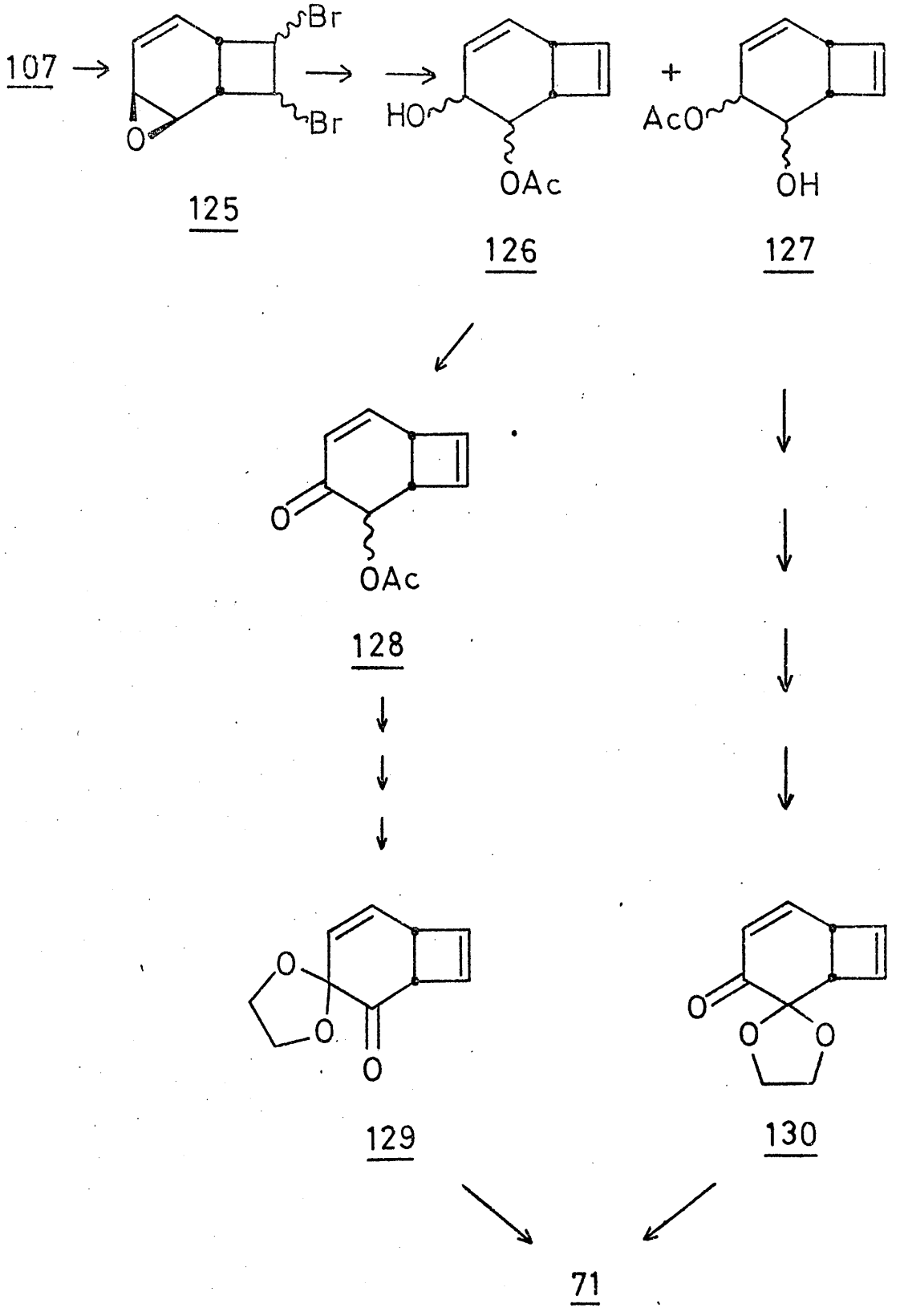
Scheme 8



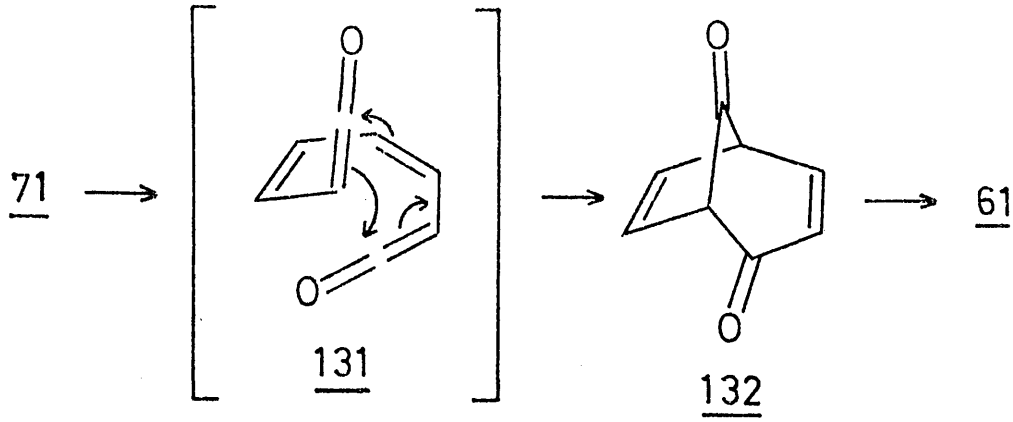
Scheme 9



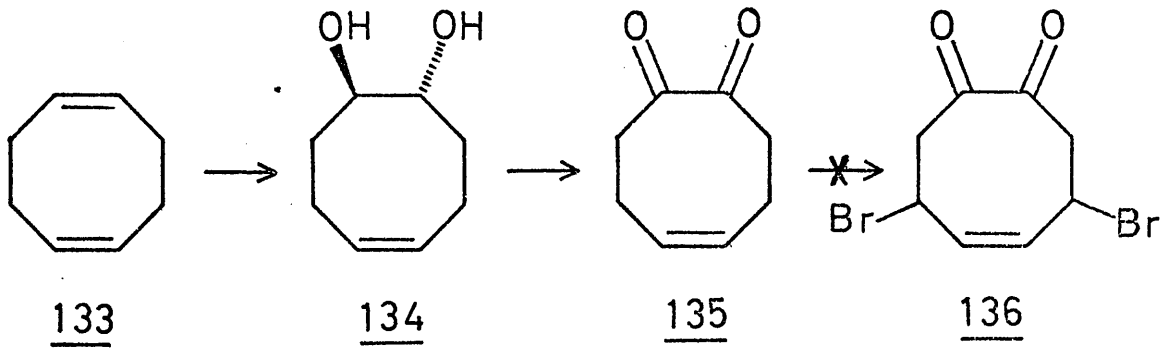
Scheme 10

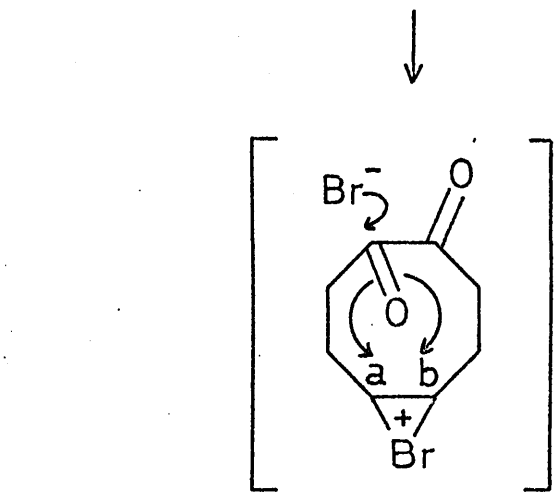


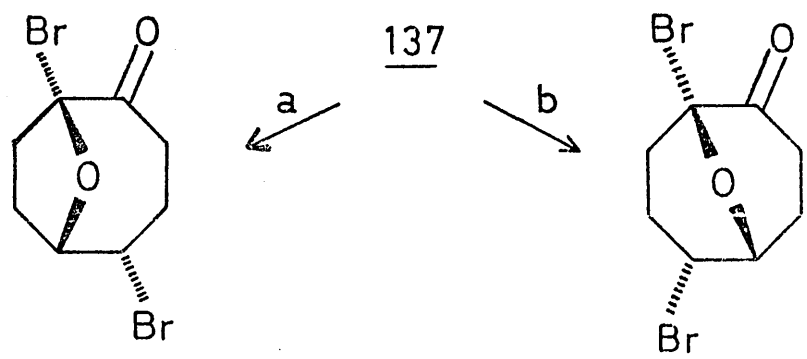
Scheme 11



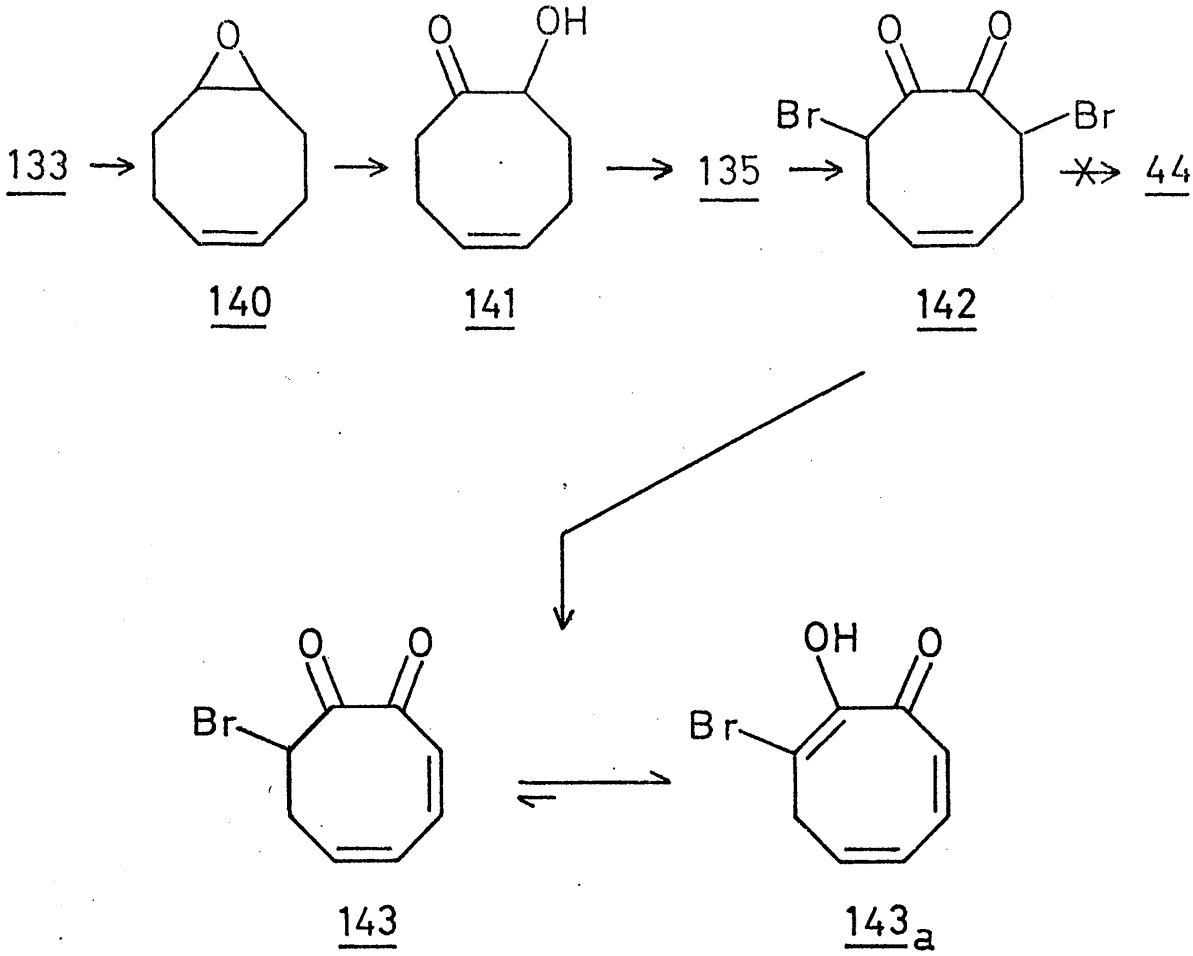
Scheme 12



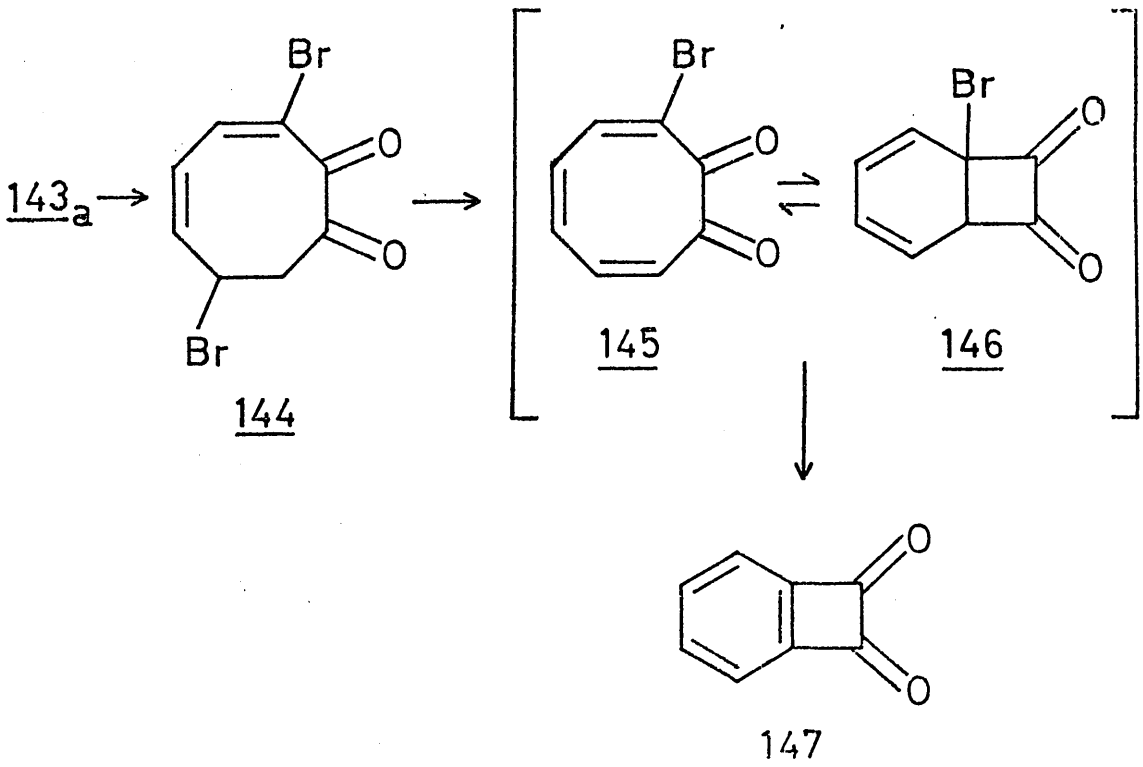




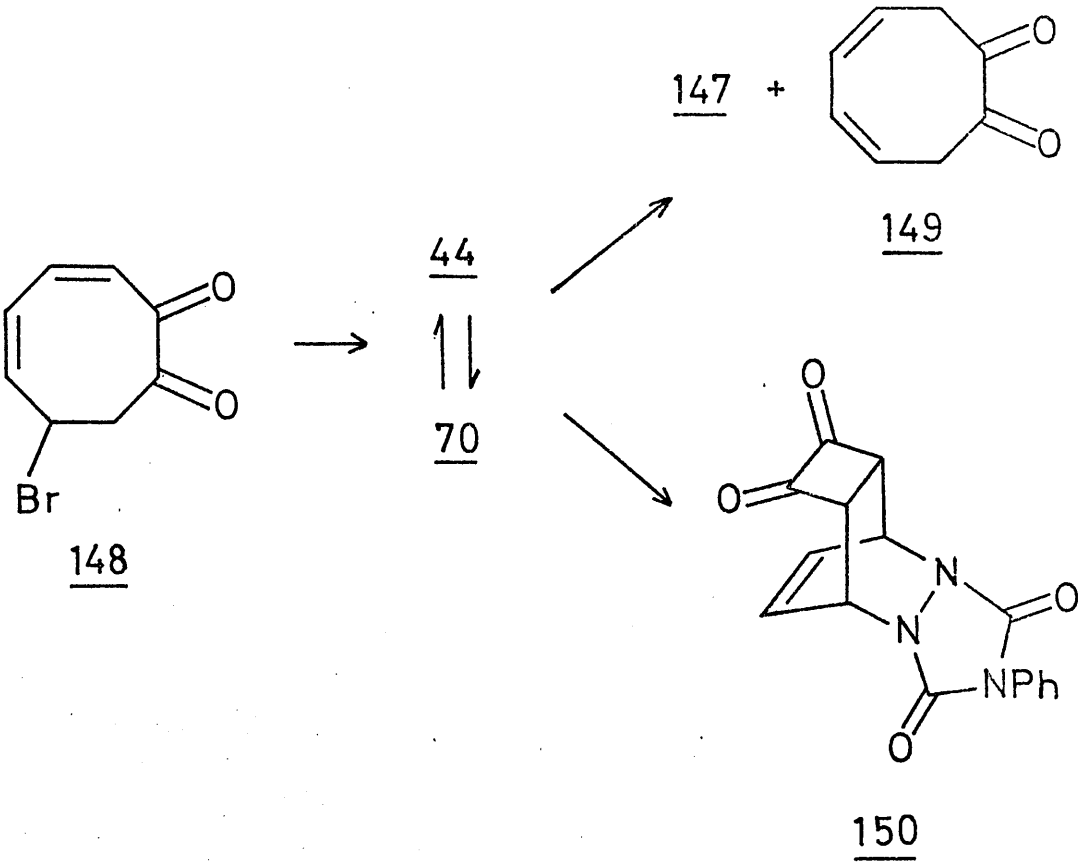
Scheme 13



Scheme 14



Scheme 15



Scheme 16

2. Synthesis and Photochemistry of Ketones of the 9-Thiabicyclo [3,3,1] nonane Series.

INTRODUCTION.

The ultraviolet absorption characteristics of cyclic keto-sulphides have been shown to be substantially different from those of saturated ketones. In particular, a bathochromic shift with an increase in intensity is observed for the n-π^* carbonyl frequency and a charge-transfer absorption band appears in the 240-270 mμ region. Paquette and Wise have attributed [81] these changes to the transannular interaction of a lone pair of electrons on sulphur with the carbonyl group, the coupling being strongly dependent on the orientation of the two groups. In addition, the interaction was shown [82] by photoelectron spectroscopy to affect the ground and excited state energy levels in these molecules and hence it should strongly influence the photochemistry exhibited by them. The photochemical reactivity of certain bicyclo [3,3,1]-nonanes containing a carbonyl group β to sulphur has been investigated by several groups [83, 84, 85] but as yet no unified relationship between chemical structure and reaction type has been developed on account of the limited number of examples studied.

Ganter and Moser have suggested [83] that irradiation of hydroxy-ketone (206) and its acetate (207) initially involves Norrish type I homolysis of the bond between the carbonyl carbon and the carbon α to sulphur (α-cleavage) [Scheme 17] . This cleavage of 206 furnished a diradical (208) which underwent internal hydrogen abstraction to produce ketene (210). The subsequent reactions of this ketene were dependent on the nucleophilicity of the irradiation solvent. Thus, intramolecular cyclisation of 210 gave bicyclic lactone (212) as the major product of the irradiation of 206 in benzene. In contrast,

when methanol was used as solvent, nucleophilic addition of methanol to 210 furnished the methyl ester (213). Irradiation of 206 also produced ester (215), formed by the intermolecular reaction of 206 and 210, and thiol (216) which was thought to arise through cleavage of the bond between the sulphur atom and the carbon α to the carbonyl group (C_α-S fission) followed by intramolecular hemiacetal formation.

Irradiation of 207 produced diester (214) presumably via the diradical (209) and ketene (211) [Scheme 17].

Padwa and Battisti have found [84] that irradiation of β-keto sulphide (151) in pentane gave α-keto sulphide (152) as the sole product whereas irradiation in methanol furnished a mixture of 153 and 152 in the ratio 8:1. Two different mechanisms were proposed for these rearrangements. The first involves α-cleavage by Norrish type I homolysis followed by diradical reorganisation analogous to that proposed by Ganter for 206 (vide supra). Alternatively a charge-transfer complex (156) may be formed which can then undergo bond reorganisation to the observed products via the ylide intermediate (157). This mechanism is analogous to that observed by Maheshwari and Berchtold in the ring expansion — contraction reaction of thiacyclohexan-3-one (158) in which ylide (159) is proposed as an intermediate [86].

The authors have distinguished between these mechanisms by carrying out the irradiation of 151 in MeOD. The formation of ketene (160) via Norrish type I cleavage followed by internal hydrogen abstraction would result in the deuterium atom being positioned α to the carbonyl group as in 154. Rearrangement via the charge-transfer complex (156) would place the deuterium atom α to sulphur on the six-membered ring as in 155. Analysis of the mass spectral fragmentation

pattern of the deuterated product showed that its molecular structure corresponded to that of 155 indicating that the charge-transfer mechanism was operative.

Photolysis of 9-thiabicyclo [3,3,1] nonan-2-one (161), the saturated analogue of 151, in methanol gave methyl ester (162) and 9-thiabicyclo [4,2,1] nonan-3-one (163). Deuteration studies revealed that the former is produced via a charge-transfer mechanism as above while the latter arises by C_{α}-S fission followed by internal hydrogen abstraction and intramolecular cyclisation of intermediate (164).

Irradiation of δ-thia-α,β-unsaturated ketone (26) in benzene, ether and methanol furnished only one monomeric product (165) along with polymeric material [85]. Berchtold and Lumma had previously observed the formation of thiochroman-3-one (166) in the photolysis of isothiochroman-4-one (167) [87]. The reaction mechanism postulated involved a 1,3-sulphur shift to form triene (168) which underwent C_{α}-S fission to give 166. Photolysis of the related 8-thiabicyclo [3,2,1] oct-3-en-2,6-dione (169) gave a 1,3-sulphur shift forming a labile dione (170) which was converted to methyl ester (171) by the addition of methanol [88]. Dione (165) is a product of a 1,3-carbon shift, probably proceeding by a concerted sigmatropic rearrangement as the reaction does not appear to be influenced by solvent. This unexpected result demonstrates the effect on reaction course of the orientation of the carbonyl group and the sulphur atom lone pairs.

Irradiation of the β-keto sulphoxides (172) and (172_a) results in an inversion of stereochemical configuration ("photostereomutation") at the sulphoxide sulphur through internal energy transfer from the excited carbonyl group to the sulphoxide group on direct irradiation [89].

In corroboration, irradiation of sulphoxide (173) and its epimer (173_a) did not cause stereochemical inversion.

Photostereomutation is invariably accompanied by polymer arising through C_α - S cleavage and intermolecular radical coupling. Hence epimerisation of sulphoxide sulphur may operate by recombination of such radical primary photoproducts. Alternatively the sulphoxide group may undergo simple pyramidal inversion on sulphur. For 172 and 172_a a reformation of the C_α - S bond should be highly favoured by the conformational stability of the bicyclic skeleton. Prolonged irradiation, however leads to a desulphurised ketone (174) through transannular hydrogen shift after C_α - S cleavage. The resulting sulphine (175) would be expected [90] to decompose by loss of sulphur to ketone (174).

DISCUSSION.

Although many attempts have been made to synthesise the 1,2-and 1,4-cyclooctatetraenoquinones (43) and (44) (see preceding review), preparation of the 1,5-dione diradical (176) has not been mentioned in the literature. Delocalisation allows 176 to be written as several resonance contributors viz. the two doubly degenerate 4π – electron systems (176 and 176_a [91]), the two four-fold degenerate 6π –electron systems (176_b and 176_c) and the cyclooctatetraene diradical (176_d). For dione (176) to exhibit pseudo-aromaticity the polarised canonical form (176_e) must make an appreciable contribution to the resonance hybrid and this will only occur if the stability of this planar molecule is greater than that of the non-planar bicyclic isomers (177) [92, 93] and (178) formed by radical pairing in 176 and 176_a respectively.

The possible intermediacy of either 9-thiabicyclo [3,3,1] nona-

3,7-diene-2,6-dione-9-oxide (179) or sulphone (180) in the preparation of 176 has been investigated. Both of these molecules contain the basic molecular structure of 176 and it was postulated that they might act as its immediate percursors , diradical formation occurring by the photochemically induced homolysis of the carbon-sulphur bonds. Mellor had previously examined the photochemistry of the corresponding sulphide (26) and found that it did not give 176 (vide supra). As the preparation of both 179 and 180 involved several reaction steps a preliminary investigation of the photochemical behaviour of the sulphide, sulphoxide and sulphone bridges in the more readily available diones (18, 181 and 182) was undertaken.

The products obtained by photolysis of β-keto sulphide (18) in methanol were found to be dependent on the length of irradiation time. Thus after 2 hr. the reaction mixture contained the β-keto sulphide (183), diester (186), disulphide (187), trimer (188) and unreacted starting material. After 16 hr. 186, 187 and 188 were accompanied by γ-keto sulphide (189), but 183 and 18 were not present. The formation of these products can be rationalised through an initial α-cleavage of 18 to produce 183 via the charge-transfer complex (190) and ylide (191). A second α-cleavage converts 183 to 186 while C_α- S fission followed by radical pairing with hydrogen and methoxyl abstraction from the solvent accounts for the formation of 187 and the trimer tentatively assigned as 188. The intermediacy of 183 is supported by its absence from the reaction mixture after 16 hr. and is corroborated by the formation of 186, 187 and 188 in the photolysis of 183 itself.

An alternative pathway involving α-cleavage of 9-thiabicyclo-

[4,2,1] nonan-3,7-dione (192) is envisaged for the formation of 189. Rearrangement of 18 to 192 is thought to occur by C_{α}-S fission followed by internal hydrogen abstraction and subsequent intramolecular cyclisation of thiol (193). The reaction time associated with this pathway is greater than that for the formation of 183 by α-cleavage (vide supra). This accounts for the absence of 189 at shorter irradiation times. By prolonging the irradiation, 183 is converted to 186, 187 and 188 whereas the γ-keto sulphide group in 189 is relatively inert and leads to the build up of 189 in the reaction mixture.

Irradiation of 18 in MeOD was shown by mass spectral analysis (Fig.6) to furnish 184 rather than 185, indicating that α-cleavage involves a charge-transfer mechanism. Irradiation of 18 in the presence of 1,3-cyclohexadiene, a triplet quencher (E_t 52-53 kcal/mole), did not affect the product distribution, hence all reactions proceed via singlet rather than triplet excited states.

Oxidation of 18 with meta-chloroperbenzoic acid and sodium metaperiodate furnished the corresponding β-keto sulphoxide (181) in yields of 53% and 79% respectively. Photolysis of 181 in methanol and in acetone furnished cyclooctan-1,5-dione (194) [94] as the sole product in low yield. NMR analysis of aliquots of the acetone reaction mixture, taken at selected time intervals, showed the emergence (after ca.10 hr.) of a deuterium exchangeable multiplet whose chemical shift depended on the concentration of the NMR solution. This multiplet is assigned as the S-OH absorption of sulphenic acid (195) arising through C_{α}-S fission followed by hydrogen abstraction from solvent. An attempt to trap 195 by its addition to methyl acrylate [95] failed to produce the expected sulphoxide. Instead base-catalysed condensation (Na_2CO_3 present) of 181 with two

molecules of methyl acrylate gave a single product assigned as diester (197). An attempt to trap the sulphonic acid by its addition to N-phenylmaleimide also proved unsuccessful.

Irradiation in methanol of β-keto sulphone (182), prepared by Jones oxidation of diol (27), furnished 194 and bicyclo [3,3,0]-octan-2,6-dione (198) [96] in low yield. The formation of these products involves sequential C_{α}- S fission via the intermediate sulphinic acid (196) followed by hydrogen abstraction from solvent to give 194 or radical pairing to produce 198. Although the presence of 196 in the reaction medium was inferred by the appearance of a deuterium exchangeable peak in the proton NMR spectrum at δ4.20, an attempt to trap it with N-phenylmaleimide [97] was unsuccessful. Alternatively 198 could be formed by homolysis of the carbon-sulphur bonds in a concerted manner.

Dione (18) was converted to 9-thiabicyclo [3,3,1] nona-3, 7-diene-2,6-dione-9,9-dioxide (180) in a four-step reaction sequence involving the formation [35] of 26, via bis-enol acetate (13) and dibromide (199), and its subsequent oxidation with meta-chloro-perbenzoic acid.

Irradiation of 180 in methanol for 2 hr. gave ester (200) in low yield. It is suggested that this product arises through an initial sulphur extrusion forming bicyclo [3,3,0] octa-3,7-diene-2, 6-dione (177) which undergoes double α-cleavage, cyclisation and addition of methanol. The photolysis of 180 was repeated in the ESR probe in an attempt to detect intermediate radical species. Although none were detected strong fluorescence at 530-540nm was observed indicating the initial formation of a triplet diradical, possibly 176_f by sequential C_{α}- S fission, followed by rapid spin inversion of an electron to produce singlet diradical (176_g) which

gives 177 through radical pairing. In support of this mechanism Farnum and Walker [98] have observed the formation of lactone (201) in the photolysis of 177 in ether. The authors postulate that this reaction proceeds by double α-cleavage to give bis-ketene (202), cyclisation to form the mono-ketene (203) and lactonisation of its tautomeric form 203_a.

The major product formed by irradiation of 180 in methanol for 10 sec. was tentatively assigned as 2,6-dihydroxypentalene (204). The ^{1}H NMR spectrum (Fig.7) of the reaction mixture contained doublets centred at δ7.75 and 6.35 with observed coupling constant of 15Hz and a deuterium enchangeable multiplet at δ3.60. These were attributed to the vinyl and hydroxyl absorptions of 204, the coincidence of the two AB systems resulting from the presence of a C_2 symmetry axis. Although the reported treatment [92] of 177 with sodium hydroxide had failed to produce 204, it was considered possible that 177 could undergo base-catalysed (Na_2CO_3 present) photochemically induced enolisation. In corroboration, 204 was not produced when the irradiation of 180 was performed in the absence of Na_2CO_3.

Pentalenes have been shown [99] to be thermally unstable, normally existing as dimers at room temperature. These dimers generally decompose on heating but can be converted to monomer by photolytic excitation at low temperature. Although the presence of the hydroxyl groups in 204 may allow it to exist as the monomer under the reaction conditions, the instability of 204 was demonstrated by its decomposition during preparative TLC and on heating in the mass spectrometer.

Irradiation of 177 [100] in methanol for 10 sec. failed to produce the same reaction mixture as in irradiation of 180. If 204

is the main product then it cannot be derived from 177 but it could be derived from the initially formed diradical (176) base-catalysed (Na_2CO_3 present) enolisation producing the 8-carbon-10 π-electron system (205) which gives 204 on radical pairing. Alternatively the major product may be 205 itself. The 8-carbon-10π-electron dianion [101] of cyclooctatetraene is known to be stable in the presence of a counter cation e.g. Na^+. Diradical 205 is a neutral species which may be stable due to its aromatic character (10 π-electrons i.e. 4n+2, n=2). A firm structural assignment for this photolysis product of 180 is currently being sought.

Photolysis of sulphoxide (179), prepared by oxidation of 26 with sodium metaperiodate or meta-chloroperbenzoic acid, gave a dark red oil which showed no vinyl resonances in the ^1H NMR spectrum. This reaction was not pursued.

EXPERIMENTAL

Nitrogen was bubbled through solutions in MeOH(AR) and Me_2CO(AR) for 10 min. prior to irradiation to remove dissolved oxygen. Solutions in MeOH for irradiation contained hydrated Na_2CO_3 (10 pellets (Hopkin and Williams Ltd.) per 60 ml) to prevent acid-catalysed [102] ketalisation [103] unless otherwise stated. The solutions were irradiated under nitrogen through a Pyrex filter with an internal water-cooled mercury arc lamp (Hanovia, 125W, medium pressure). For other general details see Chapter 2 experimental.

9-Thiabicyclo[3,3,1]nonan-2,6-dione (18).

(a) CrO_3(AR,157g,1.57 mmol) was added in small portions (2g) over 40 min. to a mechanically stirred solution of anhydrous pyridine (250ml) and CH_2Cl_2(1.5l). A solution of 27 (27g,0.157mol) in anhydrous pyridine (250ml) was added (5ml portions) over 30 min. and stirring continued for 2 hr. The supernatent liquor was decanted and the solid extracted with boiling EtOAc. The combined solutions were concentrated, EtOAc added and the solution washed with 2N HCl, 1N NaOH, water to neutrality, dried ($MgSO_4$) and concentrated to give a light yellow oil which recrystallised from $CHCl_3$ – hexane to give 18 (2.96g, 11.1%), m.p. 140-142° (lit.[35] m.p. 140-142°). The mother liquor was passed through a column of basic Al_2O_3(Woelm,Gd.1). Fractions eluted with $CHCl_3$-petroleum spirit 1:1 to 7:3 contained 18 (550mg, 2.1%).

(b) To a magnetically stirred solution of $Na_2Cr_2O_7.2H_2O$ [104] (28.73g, 9.54mmol) in DMSO (287.5g) was added 27 (5.0g,2.93mmol). Conc.H_2SO_4 (20.5ml, 38.23mmol) was added dropwise and the temperature maintained below 70°. Removal of solvent under reduced pressure gave a green tarry residue which was extracted with $CHCl_3$. The

combined extracts were washed with aq.Na_2CO_3, water, dried ($MgSO_4$) and concentrated to yield an oil (775mg) which contained 18 contaminated with 206. Attempts to increase the proportion of 18 were unsuccessful; consequently, this oxidation procedure was not further pursued.

(c) A solution of 18 (204mg,1.2mmol) in MeOH (60ml) was irradiated for 16 hr. The solvent was removed under reduced pressure, $CHCl_3$ added and the resulting solution washed with water, dried ($MgSO_4$) and concentrated to give a red oil. Preparative TLC of this oil using EtOAc/benzene (1:9) as solvent (four elutions) gave in order of decreasing mobility 186 (10mg,3.6%). (Found: 234.09283. $C_{10}H_{18}O_4S$ requires : 234.09256); ν_{max} (CCl_4) 1742,1436,1203,1170 and 1140cm^{-1}; δ1.85 (m,4H; C-3 and C-7 CH_2), 2.45 (broad m,8H; C-2,C-4,C-6 and C-8 CH_2), 3.68 (s,6H; OMe); mass spectral peaks at m/e 234(M^+), 203, 161, 160, 133, 129, 101 and 59.; 189, red stain with ceric sulphate, (60mg, 25.25%). (Found: C,53.33; H, 7.29. $C_9H_{14}O_3S$ requires: C,53.46; H,6.98%. Found: 202.06624. $C_9H_{14}O_3S$ requires: 202.06635); ν_{max} (CCl_4) 1740 (ε^a460, $\Delta\nu_{\frac{1}{2}}{}^a27cm^{-1}$) and 1712$cm^{-1}$ (ε^a390, $\Delta\nu_{\frac{1}{2}}{}^a21cm^{-1}$); δ2.10(m, 2H; C-6 CH_2), 2.75 (m,8H; C-3,C-5,C-7 and C-8 CH_2), 3.40(m, 1H; C-2 CH), 3.70(s, 3H; OMe); mass spectral peaks at m/e 202(M^+), 171, 142, 129, 110, 102, 101 and 59. ; 187, brown stain with ceric sulphate, (27mg,11.4%), m.p. ca.23°. (Found: 406.14852. $C_{18}H_{30}O_6S_2$ requires: 406.14836); ν_{max} (CCl_4) 1740 and 1718cm^{-1}; δ1.95 (m, 8H; C-3,C-7,C-12 and C-16 CH_2), 2.55 (broad m, 16H; CH_2-S and CH_2-CO), 3.68 (s, 6H; OMe); mass spectral peaks at m/e 406(M^+), 203 and 171. ; and 188, yellow stain with ceric sulphate, (20mg, 8%), m.p. 26-28°. ν_{max} (CCl_4) 1742 and 1720cm^{-1}; δ1.63-2.80(m, 32H; CH_2), 3.40 (s, 3H; OMe), 3.50 (t, 1H;

CH-S), 3.70 (s, 9H; OMe), 4.40 (t, 1H; CH-OMe); mass spectral peaks at m/e 540, 526, 408, 393, 305, 256, 200, 184, 169, 168, 138, 112 and 101.

(d) A solution of 18 (150mg, 0.88mmol) in MeOH(60ml) was irradiated for 2 hr. Work-up as in (c) gave 186; 183, orange stain with ceric sulphate, (25mg, 31% based on 18 consumed). (Found: 202.06619. $C_9H_{14}O_3S$ requires: 202.06635); ν_{max} (CCl_4) 1740 (ε^a560, $\Delta\nu_{\frac{1}{2}}{}^a$28cm^{-1}) and 1714cm^{-1} (ε^a540, $\Delta\nu_{\frac{1}{2}}{}^a$18cm^{-1}); δ1.95 (broad m,2H; C-7 CH_2), 2.50 (m, 6H; C-4, C-5 and C-8 CH_2), 2.80 (t, 2H; J 3Hz; C-6 CH_2), 3.53 (t, 1H; J 6Hz; C-2 CH), 3.70 (s, 3H; OMe); mass spectral peaks at m/e 202(M^+), 170, 143, 142, 128 and 100. ; 18 (82mg, 0.48mmol); 187 and 188.

(e) A solution of 18 (150mg, 0.89mmol), cyclohexa-1,3-diene (71mg, 0.89mmol) and MeOH (60ml) was irradiated for 2 hr. Work-up as in (c) gave 183, 186, 187, 188 and unreacted 18. Irradiation of an identical solution for 16 hr. furnished 186, 187, 188 and 189.

(f) A solution of 18 (150mg, 0.89mmol) in MeOD (60ml) without Na_2CO_3 was irradiated for 2 hr. Work-up as in (c) allowed the deuterated sample 184 to be isolated, m/e 203(M^+),144, 143, 129 and 101. Irradiation in the presence of Na_2CO_3caused polydeuteration of the carbonyl enolates but the product distribution was the same as in (d) indicating that the Na_2CO_3 is inessential for preventing possible ketalisation.

9-Thiabicyclo [3,3,1] nonan-2,6-dione-9-oxide(181).

(a) A solution of meta-chloroperbenzoic acid (m-CPBA) (112mg,0.65 mmol) in $CHCl_3$ (10ml) was added dropwise to a magnetically stirred solution of 18 (100mg, 0.59mmol) in $CHCl_3$(5ml) at -5°. Stirring was continued at room temperature for 16 hr., $CHCl_3$ added and the solution washed with 1N NaOH, water to neutrality, dried ($MgSO_4$)

and concentrated. Preparative TLC of the residue using EtOAc as solvent gave unreacted 18 (12mg) and crude 181 (51mg, 53% based on 18 consumed). Crystallisation from Me_2CO-hexane furnished 181, m.p. 189-193°. ν_{max} (KBr) 2941, 1695, 1442, 1210, 1059, 1035, 946 and 709cm^{-1} ; λ_{max} 230 (logε 2.78), 298(2.06) and 306nm(2.06); δ 2.60 (broad m, 8H; CH_2), 4.10 (m, 2H; C-1 and C-5 CH); mass spectral peaks at m/e 186(M^+), 158, 138, 110 and 82.

(b) A solution of sodium metaperiodate ($NaIO_4$) (830mg,3.88mmol) in water (6ml) was added dropwise to a magnetically stirred solution of 18 (600mg, 3.53mmol) in MeOH (18ml). Stirring was continued for 16 hr. After filtration the colourless precipitate was washed with hot EtOAc and the combined washings back extracted with water. The reaction solution was concentrated under reduced pressure and the EtOAc extracts added. The solution was dried ($MgSO_4$), concentrated and the resulting yellow oil washed with $CHCl_3$. Preparative TLC in EtOAc of the residue obtained by evaporation of these washings gave unreacted 18 (20mg) and 181 (500mg, 79% based on 18 consumed).

(c) A solution of 181 (200mg, 1.07mmol) in MeOH (60ml) was irradiated for 25 hr. Preparative TLC using EtOAc as solvent of the dark red residue obtained by work-up as in 18(c) gave 194 (7.5mg, 5%), m.p. ca.23° (lit.[94] m.p. 20-24°). (Found: 140.08379. $C_8H_{12}O_2$ requires: 140.08372) ; ν_{max} (CCl_4) 1714, 1320 and 1174cm^{-1}; δ 2.20 (m, 4H; C-3 and C-7 CH_2), 2.50 (m, 8H; C-2, C-4, C-6 and C-8 CH_2); mass spectral peaks at m/e 140(M^+), 112, 84, 70 and 55.

(d) A solution of 181 (200mg, 1.07mmol) in Me_2CO (60ml) was irradiated for 20 hr. Aliquots (5ml) were taken at 4 hr. intervals and worked-up as in 18(c). The ^1H NMR spectra recorded for the residues obtained from the 12, 16 and 20 hr. aliquots contained a

deuterium exchangeable multiplet at δ5.6, 5.9 and 4.7 respectively which is assigned as the S-OH absorption of 195.

(e) A solution of 181 (200mg, 1.07mmol) in MeOH (60ml) was irradiated for 25 hr. Redistilled methyl acrylate (10ml) was added and the solution magnetically stirred for 20 hr. Work-up as in 18(c) gave a dark red oil which was fractionated into three components by preparative TLC using EtOAc as solvent. The most mobile constituent was 194 (6mg, 4.4% based on 181 consumed). The middle band gave 197 (32mg, 9.2% based of 181 consumed), m.p. 157-159°. (Found: 358.10853. $C_{16}H_{22}O_7S$ requires: 358.10860); ν_{max} (KBr) 1735, 1720, 1700, 1438 and 1058cm^{-1}; δ2.20 (broad m, ca. 14H; CH_2, C-3 and C-7 CH), 3.70 (s, 6H; OMe), 4.03 (m, 2H; C-1 and C-5 CH); mass spectral peaks at m/e 358(M^+), 341, 327, 309, 227, 199, 167, 149, 139 and 121. The least mobile constituent was 181 (20mg).

(f) A solution of 181 (200mg, 1.07mmol) in Me_2CO(60ml) was irradiated for 20 hr. Redistilled methyl acrylate (10ml) was added and the solution magnetically stirred for 20 hr. Work-up as in (e) gave 194 in low yield and unreacted 181.

(g) A solution of 181 (200mg, 1.07mmol) in MeOH(60ml) without Na_2CO_3 was irradiated for 25 hr. After concentration to 10ml the reaction solution was stirred for 20 hr. with water (10ml) and N-phenylmaleimide (200mg, 1.15mmol). Evaporation furnished a yellow cake which was washed with hot $CHCl_3$. The combined washings were dried ($MgSO_4$) and concentrated to an oily residue which furnished 194 and unreacted 181 on preparative TLC using EtOAc as solvent.

9-Thiabicyclo[3.3.1]nonan-2,6-dione-9,9-dioxide(182).

(a) A solution of 27 (4g, 23mmol) and Jones reagent (90ml) in Me_2CO

(50ml) was magnetically stirred for 4 hr. Me_2CO was removed under reduced pressure and the aqueous solution continuously extracted with EtOAc. The combined extracts were washed with 0.5N NaOH, water, dried ($MgSO_4$) and concentrated to give crude 182 (480mg, 10.3%) which recrystallised from Me_2CO-hexane as colourless plates, m.p. 248-250°. (Found: C,47.17; H, 4.88. $C_8H_{10}O_4S$ requires: C, 47.53; H, 4.99%); $\nu_{max}(CCl_4)$ 1726 and 1724cm^{-1}(ε^a500, $\Delta\nu_{\frac{1}{2}}{}^a$30cm^{-1}); $\delta(d_6\text{-}Me_2CO)$ 2.40 (m, 4H; C-4 and C-8 CH_2), 2.80 (m, 4H; C-3 and C-7 CH_2), 4.10 (m, 2H; C-1 and C-5 CH); mass spectral peaks at m/e 202(M^+), 138, 110, 83 and 55.

(b) A solution of 182 (202mg, 1mmol) in MeOH(60ml) was irradiated for 4 hr. Work-up as in 18(c) gave a red oil which exhibited a deuterium exchangeable multiplet at δ4.2 in the ^{1}H NMR spectrum. Preparative TLC of this oil using $CHCl_3$ as solvent furnished 194 (5.5mg, 4%) and 198 (7mg, 5%). (Found: 138.06767. $C_8H_{10}O_2$ requires: 138.06807); $\nu_{max}(CCl_4)$ 1748cm^{-1}; δ2.23 (m, 8H; CH_2), 2.93 (m, 2H; CH); mass spectral peaks at m/e 138(M^+), 110, 109, 83 and 82.

(c) A solution of 182 (100mg, 0.5mmol) in MeOH(40ml) without Na_2CO_3 was irradiated for 6 hr. Treatment of the reaction mixture with N-phenylmaleimide followed the procedure described in 181(g). Preparative TLC of the residue using $CHCl_3$as solvent gave 194 and 198 but no adduct was obtained.

9-Thiabicyclo[3,3,1]nona-3,7-diene-2,6-dione-9,9-dioxide(180).

The preparation of 13 from 18 is given in Chapter 2.

(a) A solution of 13 (400mg, 2.74mmol), N-bromosuccinimide (1.138g, 6.4mmol) and azodiisobutyronitrile (8mg) in refluxing CCl_4(AR,20ml) was magnetically stirred for 40 min. The supernatent liquor was decanted and the residue washed with cold CCl_4. The combined CCl_4

solutions were washed with water, dried ($MgSO_4$) and evaporated to give crude 199 (594mg). A solution of this crude 199 in pyridine (AR,30ml) was maintained at 70° for 2 hr. The dark red solution was poured into brine, extracted with EtOAc and the organic layer washed with 1N HCl, saturated $NaHCO_3$, water to neutrality, dried ($MgSO_4$) and concentrated to give a yellow solid. Preparative TLC using Et_2O-petroleum spirit (2:3) as solvent gave 26 (170mg,65%), m.p. 96-98° (lit.[35] m.p. 96-97°).

(b) A solution of m-CPBA (98mg, 0.57mmol) in toluene (AR,1ml) was added dropwise to a solution of 26 (43mg, 0.26mmol) in toluene (AR,1ml). After standing (10 min.) the solution was refluxed (10 min.), filtered and the solid washed with cold CH_2Cl_2 to leave 180 (17mg, 17.6%). The combined washings were concentrated, EtOAc added and the solution washed with aq.$NaHCO_3$, brine, dried ($MgSO_4$) and concentrated to yield 180 as broad needles (18mg,18.7%), m.p. 231-235° decomp. (Found: C, 48.55; H, 3.06. $C_8H_6O_4S$ requires: C, 48.49; H, 3.05%); ν_{max}(KBr) 3061, 2963, 1686, 1331 and 1124cm^{-1}; λ_{max} 229(logε 3.90) and 375nm(2.94); δ(d_6-Me_2CO) 5.13 (d, 2H; J 8Hz; C-1 and C-5 CH), 6.36 (d, 2H; J 12Hz; C-3 and C-7 CH), 7.36 (dd, 2H; J 8 and 12Hz; C-4 and C-8 CH); mass spectral peaks at m/e 198(M^+), 149, 134, 115, 106 and 78.

(c) A solution of 180 (200mg, 1.01mmol) in MeOH(60ml) was irradiated for 2 hr. Removal of solvent gave a solid cake which was washed with $CHCl_3$. Prep. TLC($CHCl_3$) of the $CHCl_3$ washings gave 200 (3mg, 1.8%)[105]. (Found: 166.06298. $C_9H_{10}O_3$ requires: 166.06262); ν_{max} (CCl_4) 3610, 3020, 2950, 2920, 2855 and 1742cm^{-1} ; δ3.53(s, 2H; CH_2), 3.66(s, 3H; OMe), 6.93(m, 4H; aromatic CH); mass spectral peaks at m/e 166(M^+) and 107.

(d) A solution of 180 (200mg, 1.01mmol) in MeOH(60ml) was irradiated

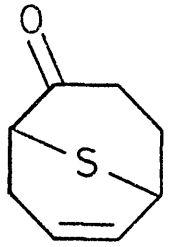
for 10 sec. Removal of solvent and extraction of the residue with Me_2CO gave a red oil which decomposed during preparative TLC in EtOAc/MeOH (9:1). ν_{max}(KBr)3450 (broad), 1650 (broad), 1595, 1480, 1410, 1310, 1250, 1155 and 1110cm^{-1}; δ 3.53 (m; OMe), 3.60 (m; OH), 5.90 - 6.30 (m), 6.35 (d; J 15Hz), 7.75 (d; J 15Hz); oil decomposed in mass spectrometer.

9-Thiabicyclo[3,3,1]nona-3,7-diene-2,6-dione-9-oxide(179).

(a) A solution of m-CPBA (384mg, 2.23mmol) in $CHCl_3$(AR,10ml) was added dropwise to a magnetically stirred solution of 26 (336mg, 2.02mmol) in $CHCl_3$ (AR, 25ml) at-5°. Stirring was continued for 2 hr., $CHCl_3$ added and the solution washed with 0.5N NaOH, brine, dried ($MgSO_4$) and concentrated to give crude 179 (70mg, 16.6%). Preparative TLC using EtOAc/$CHCl_3$ (1:9) as solvent and recrystallisation from Me_2CO-Et_2O furnished 179 as light yellow needles, m.p. 159-161°. (Found: 182.00363. $C_8H_6O_3S$ requires: 182.00375); ν_{max} (KBr) 1673, 1616, 1368, 1235, 1132 and 1065cm^{-1}; λ_{max} 263 (log ε 3.76) and 345nm (3.46) ; δ (d_6-Me_2CO) 4.76 (m, 2H; C-1 and C-5 CH), 6.25 (dd, 2H; C-3 and C-7 CH), 7.06 (m, 2H; C-4 and C-8 CH); mass spectral peaks at m/e 182(M^+), 134, 106 and 78.

(b) A solution of $NaIO_4$ (70.9mg, 0.33mmol) in water (2ml) was added dropwise to a magnetically stirred solution of 26 (50mg, 0.30mmol) in MeOH (AR,3ml). Stirring was continued for 24 hr. Work-up as in 181(b) with preparative TLC using Et_2O/petroleum spirit (4:1) (5 elutions) as solvent and sublimation (125°, 0.3mmHg) of the major TLC band gave 179 (15mg, 19.2%).

(c) A solution of 179 (150mg, 0.81mmol) in MeOH(60ml) was irradiated for 30 sec. Removal of solvent and extraction of the residue with Me_2CO gave a red oil showing no vinyl resonances in the ^{1}H NMR spectrum.



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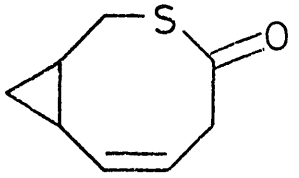

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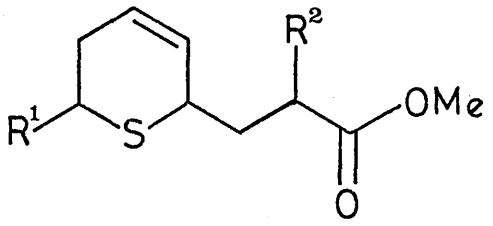
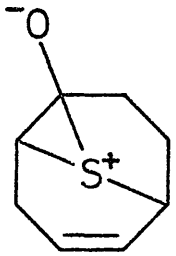


153 $R^1 = R^2 = H$

154 $R^1 = H$; $R^2 = D$

155 $R^1 = D$; $R^2 = H$



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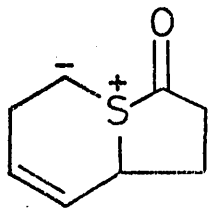

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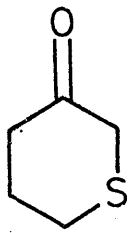

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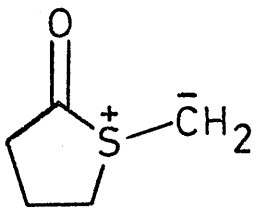

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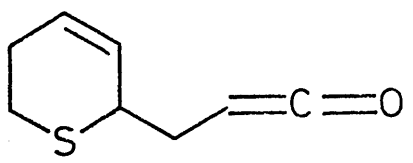

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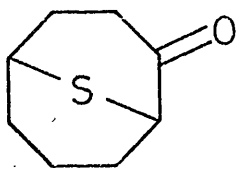

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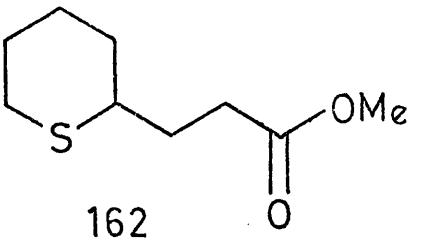

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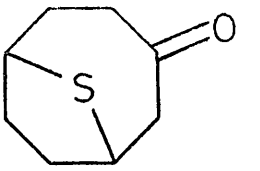

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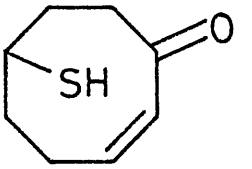

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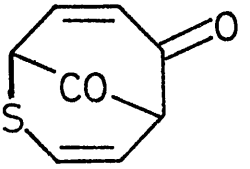

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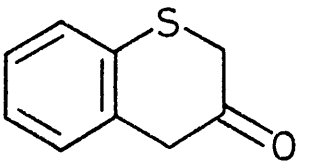

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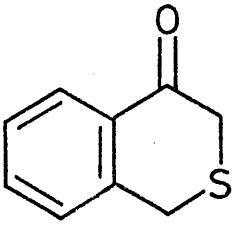

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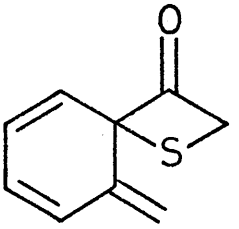

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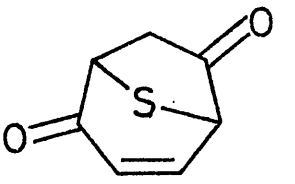

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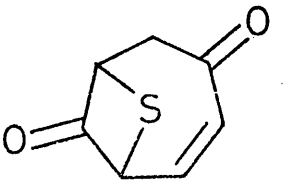

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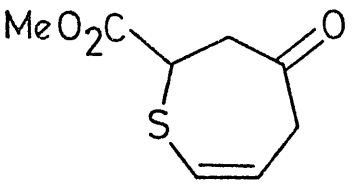

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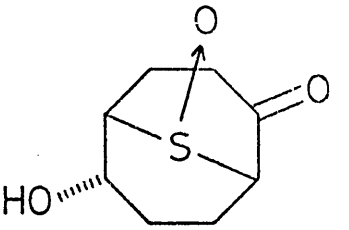

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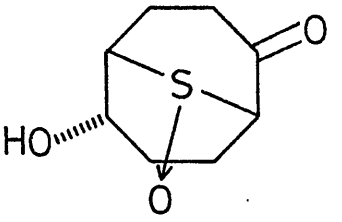

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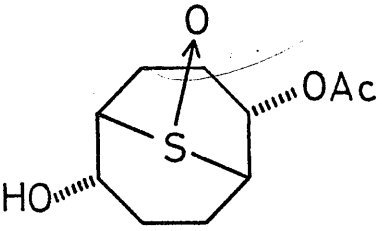

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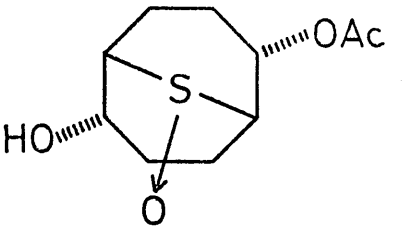

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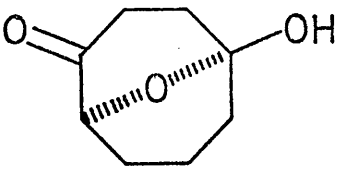

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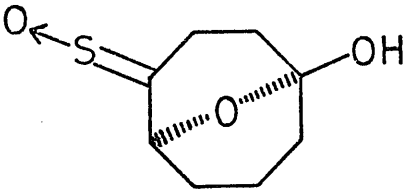

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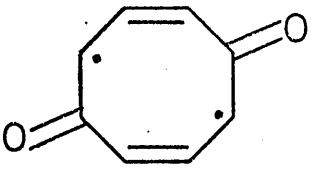

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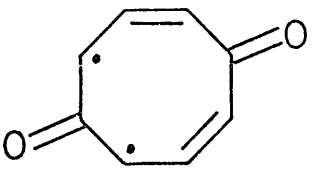

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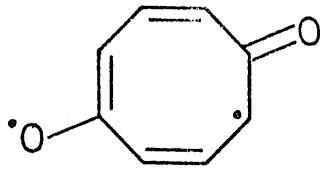

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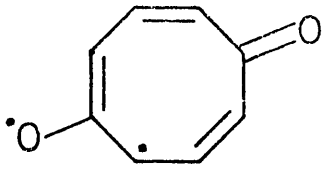

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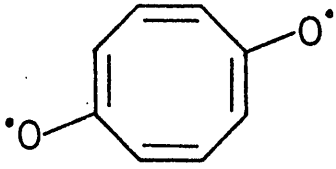

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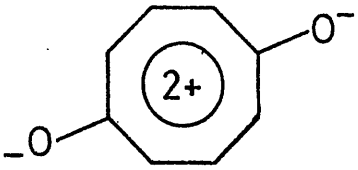

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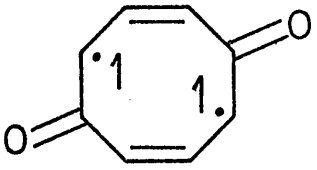

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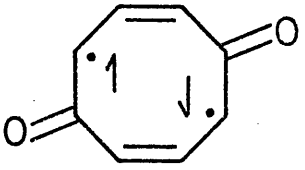

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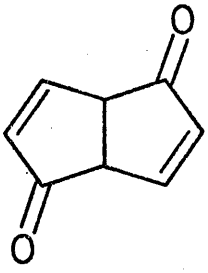

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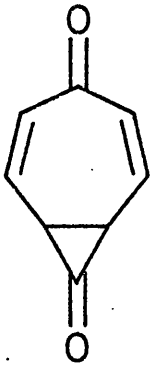

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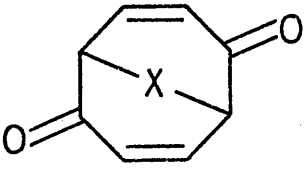

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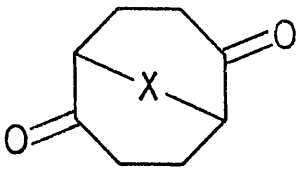
179 X = SO

180 X = SO_2



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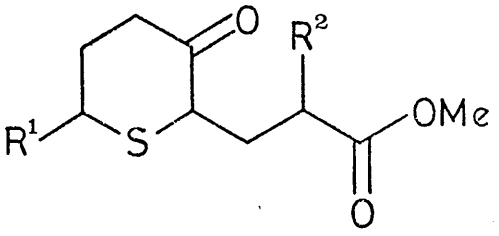
181 X = SO

182 $X = SO_2$



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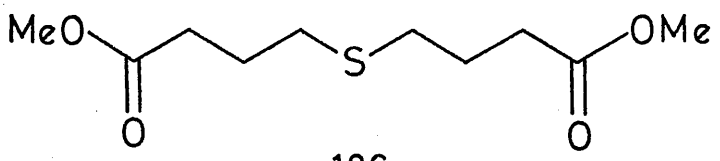
184 $R^1 = D$; $R^2 = H$

185 $R^1 = H$; $R^2 = D$



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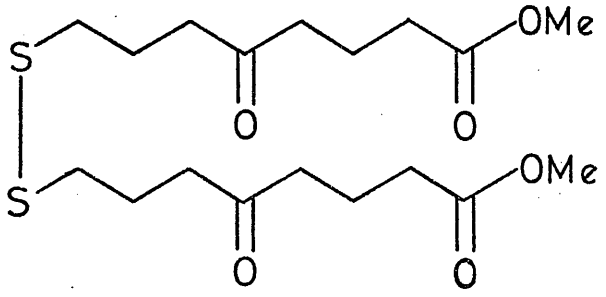

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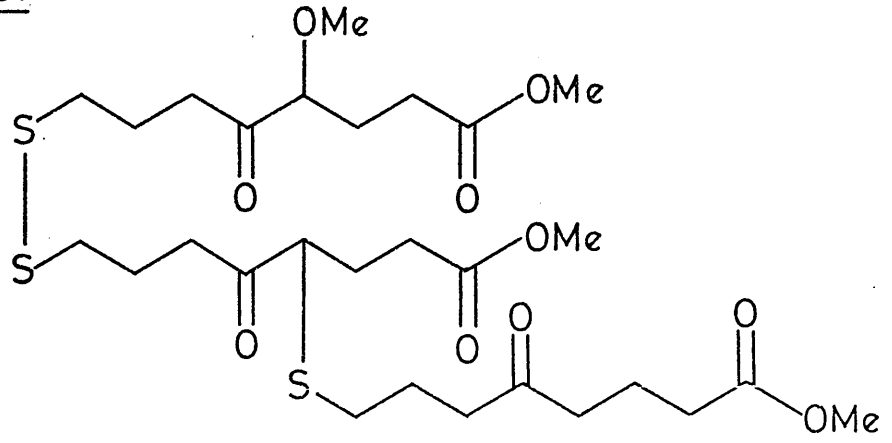

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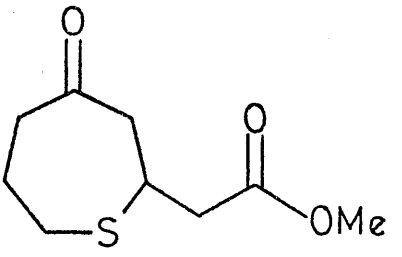

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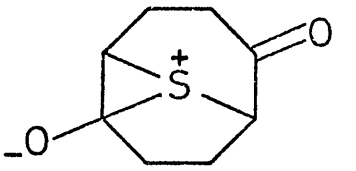

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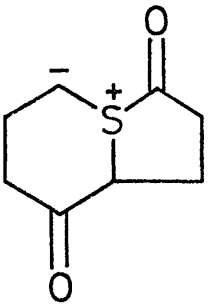

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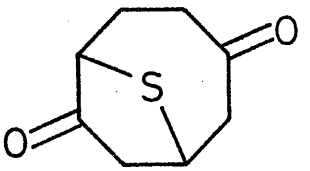

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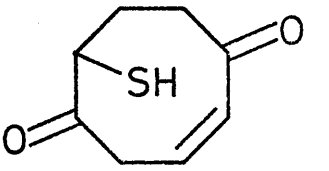

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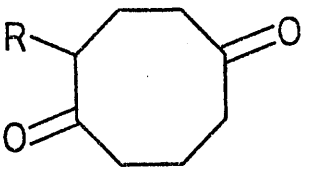
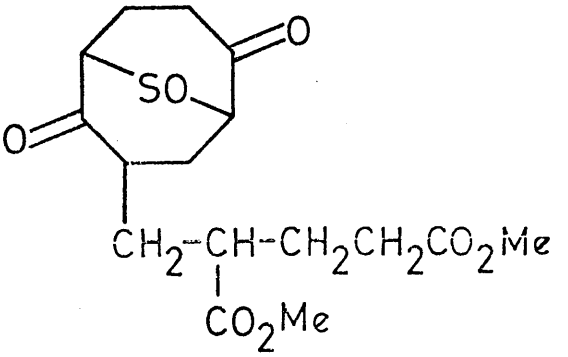


194 R = H

195 R = SOH

196 R = SO_2H



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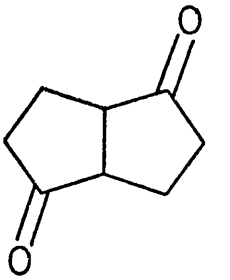

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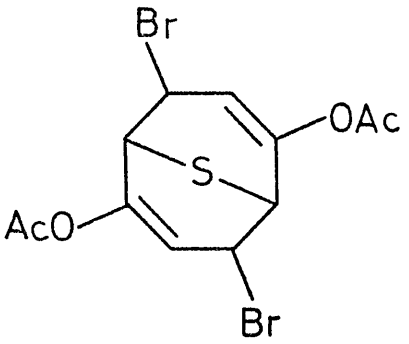

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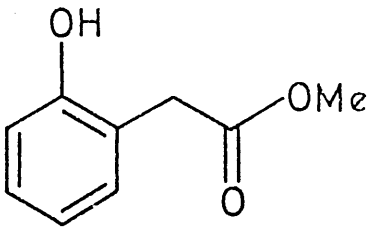

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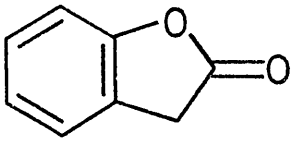

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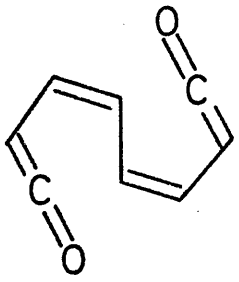

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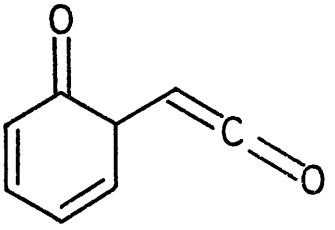

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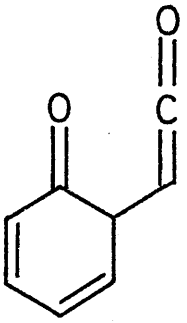

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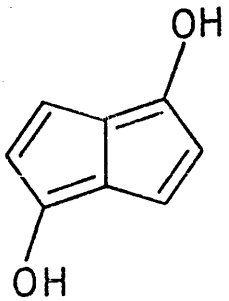

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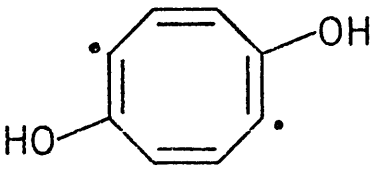

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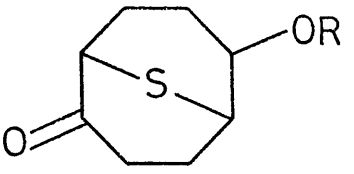
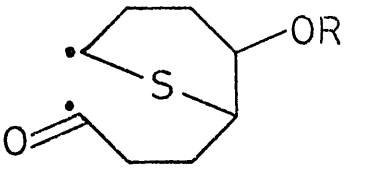


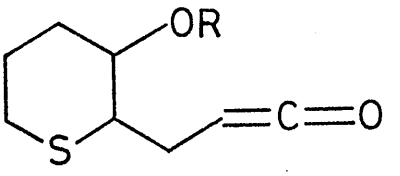
206 R = H

207 R = Ac



208 R = H

209 R = Ac



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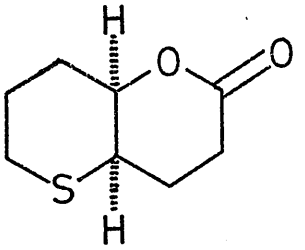
211 R = Ac



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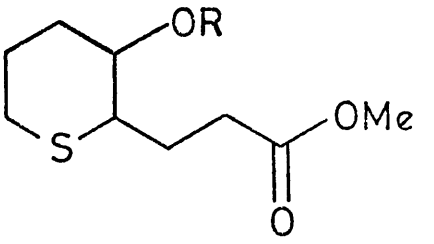
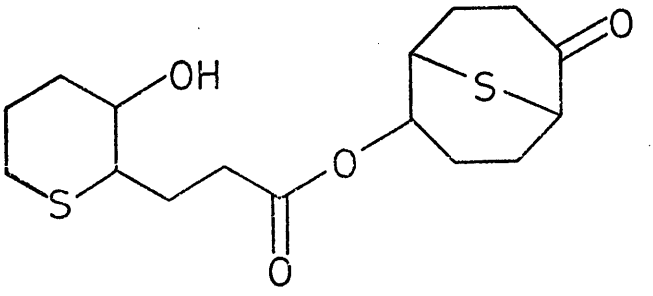


213 R = H

214 R = Ac

+



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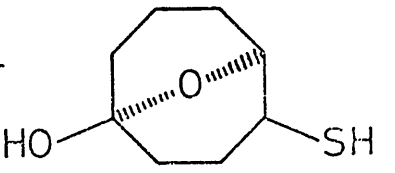


216

Scheme 17

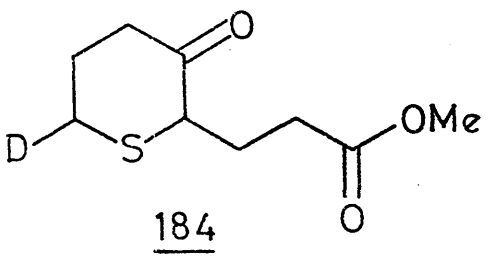
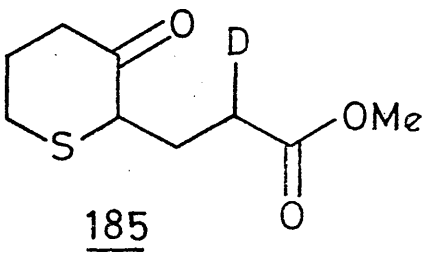
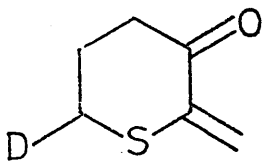
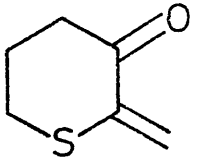
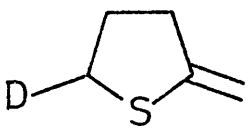
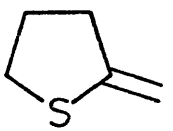
Charge-Transfer Mechanism	m/e	Observed m/e	m/e	Norrish Type I Mechanism
 184	203	203	203	 185
	129	129	128	
	101	101	100	

Fig.6. Comparison of the mass spectral fragmentation of 184 and 185 together with the observed spectrum (major peaks over m/e 100) of the deuterated sample isolated.

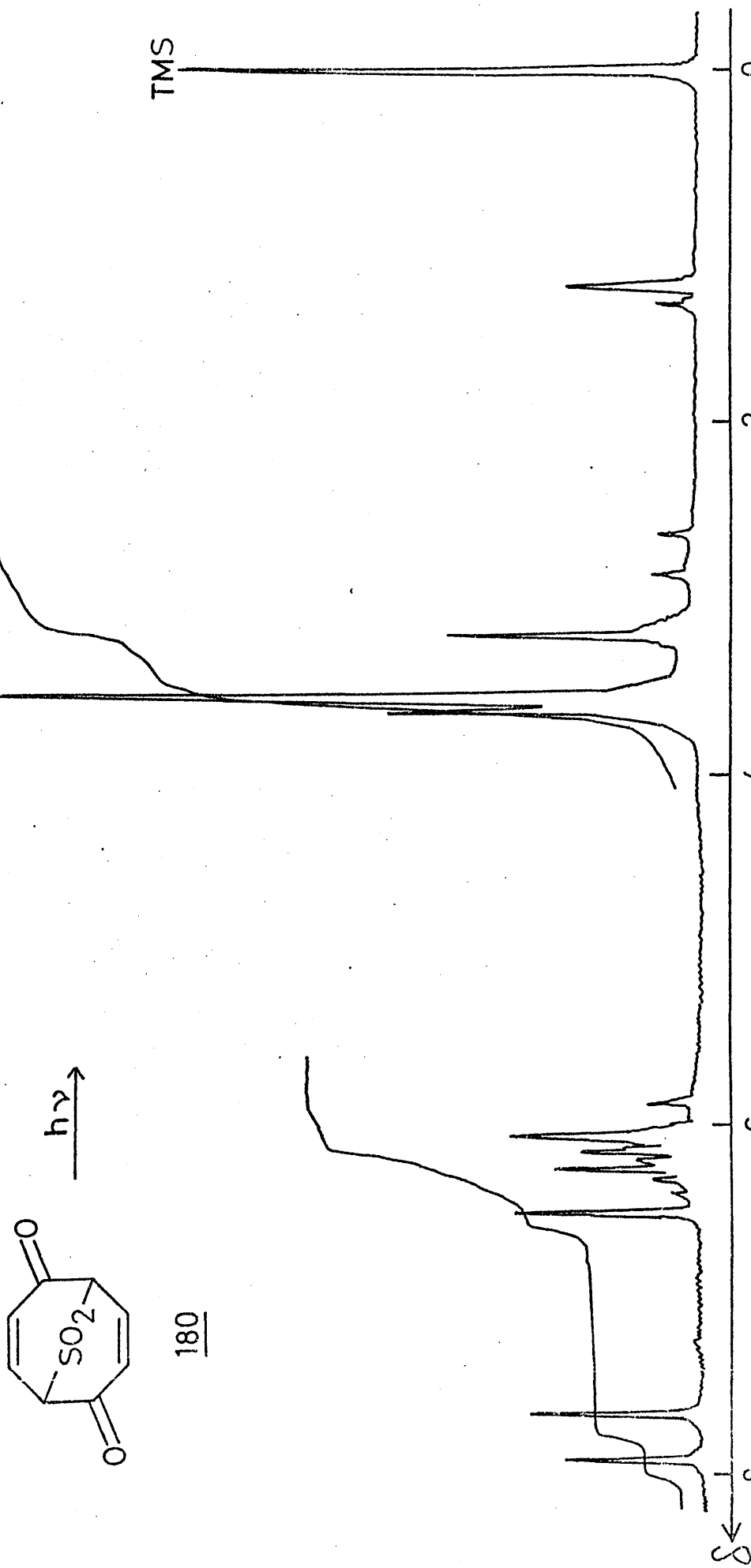


Fig.7. 60 MHz ^{1}H NMR spectrum of the reaction mixture produced by irradiation of 180 in MeOH for 10 sec.

Chapter 4

Synthesis and Biological Testing of 9-Thiabicyclo[3,3,1]nonane Derivatives.

INTRODUCTION

The synthesis of biologically active organic compounds for use as fungicides, insecticides and/or plant growth regulators is of considerable importance to efficient crop production and thus makes a major contribution to the alleviation of world food shortage. In most cases the activity exhibited by these compounds is associated with their electronic and stereochemical characteristics and their lipophilic or hydrophilic tendancy. In order to trace novel molecular systems which display significant activity random biological screening of diverse organic substances is undertaken. Once activity has been found a number of derivatives are prepared in which the substituents have been chosen to alter the fundamental biological action in predictable fashion [106, 107]. Activity is maximised on the basis of subsequent biological test results.

In an alternative approach, investigation of the important chemical processes occurring in a particular fungus, insect or plant may indicate the fundamental structural requirements for a molecule to produce a desired controlling influence. Once this structure-activity relationship is known a select number of compounds which satisfy these requirements are prepared and tested. Thereafter the best possible derivative is determined by variation of substituents as for the above method.

DISCUSSION

As part fulfilment of a Science Research Council C.A.S.E. Award a number of 9-thiabicyclo[3,3,1]nonanes were prepared and sent

to Imperial Chemical Industries Ltd. for biological testing (fungicides and insecticides) and Alderly Park (pharmaceuticals) Research Stations.

A primary objective was to append an N,N-dimethylethylene (or propylene) diamine substituent to the 9-thiabicyclo [3,3,1]nonane skeleton, these side chains having been associated with active compounds. Reaction of 10 with N,N-dimethylethylenediamine produced an unstable secondary diamino derivative (217), the hydrochloride of which proved too hygroscopic to purify in the open. The substituted phenylhydrazines (218) and(219) were similarly unstable but stable secondary aminobicyclics (11,12,220 and 221) were obtained through reaction of 10 with the appropriate aromatic amine. Quaternary ammonium salts (222)[108],(223)[109]and (224)[109] were formed as highly crystalline hydrates in reaction of bicyclic dihalides (10), (225) and (226) with pyridine or 2,4,6-collidine. Reaction of chloride (227) with pyridine produced pyridinium salt (14).

The oxime carbamates of certain α- and β-ketosulphides show potent insecticidal activity eg. 231 ("Lannate", Du Pont) and 232 ("Tennik", Union Carbide). An attempt to prepare the mono- and bis-oximes of 18 resulted in mixtures which were difficult to separate. Oxime (228) was synthesised in three steps from 227, a pyrolysis product of 10, by hydrolysis to 229, oxidation to 151 and oximation.

Pyridinium salts (14) and (222) have shown activity, 14 exhibited anthelmintic activity in a primary screening but was inactive in the secondary screen. This salt also showed antiviral activity against potato virus Y and bacterial blight of rice (XANTHOMONAS ORYZAE); 222 displayed mild anthelmintic activity (against tapeworm) in the secondary anthelmintic screen. Oxime carbamate (230) is currently

being tested.

A twelve week project was undertaken at Jealott's Hill Research Station during which the syntheses of 1-carboxy-5-methyl-bicyclo[3,3,1]nonane (233) and its des methyl analogue (234) were undertaken[110]. Preliminary testing of 233 had shown promising fungicidal activity on RHIZOCTONIA SOLANI (cotton) and PYTHIUM ULTIMUM (peas). The synthesis of 233 involved a zinc amalgam reduction of the 9-keto group of 1-carboxybicyclo [3,3,1]nonan-9-one (237) which proceeded in poor yield [Scheme 18]. Wolff-Kishner reduction of 237 gave 238, the pyrazolone ring being formed by internal cyclisation of the resulting hydrazone with the carboxyl function. Treatment of keto ester (236) with ethane dithiol in the presence of boron trifluoride etherate failed to produce 239. The alcohol (235) was oxidised by Jones reagent to dione (240) in 95% yield but the formation of bis-dithioketal (241) did not go to completion using ethane dithiol in refluxing toluene with either hydrogen chloride gas or p-toluenesulphonic acid as catalyst. However, Raney nickel reduction of the crude product mixture did give some bicyclic ester (242) which was hydrolysed to 234.

In an alternative synthesis [Scheme 19] Meerwein's tetraester (243)[111] was converted to 234 in 3.6% overall yield. Hydrolysis and decarboxylation of 243 followed by Wolff-Kishner reduction of 17 furnished hydrocarbon (244) the bridgehead position of which was carboxylated by reaction with formic acid-sulphuric acid (the Koch-Haaf reaction[112]).

The creation of bicyclic systems using a monocyclic enamine and acryloyl chloride is well documented[113] and involves the thermal rearrangement of the salt initially formed. Application of this annelation procedure to the syntheses of 233 and 234 [Scheme 20]

was otherwise satisfactory except that the Koch-Haaf carboxylation returned large amounts of unreacted hydrocarbons (244) and (245).

The test results obtained for both 233 and 234 were not as good as expected and as a result no application was made for a patent to cover their activity.

EXPERIMENTAL

Anhydrous pyridine was prepared by refluxing reagent grade pyridine over KOH pellets and distilling under reduced pressure. The distillate was stored over KOH pellets in amber bottles. Dimethylformamide (DMF) was prepared by refluxing over Linde type 4A molecular sieves and distilling under reduced pressure. The distillate was stored over Linde type 4A molecular sieves. Experimental detail of the twelve week project carried out at Jealott's Hill Research Station is confidential information of Imperial Chemical Industries Ltd. For other general details see Chapter 2 experimental.

Reaction of 10 with N,N-dimethylethylenediamine.

A solution of 10 (2.11g, 10mmol) in N,N-dimethylethylenediamine (3.87g, 44mmol) was magnetically stirred at 115° (bath temp.) for 2 hr. Unreacted diamine was removed by azeotropic distillation with benzene and the residue washed with Et_2O. The combined extracts were washed with water, dried ($MgSO_4$), concentrated and distilled (220°,1mmHg) to give crude 217 as a yellow oil which gradually turned brown on standing. ν_{max} (CCl_4) 3310, 3020, 2940, 2818, 1715, 1455, 1125, 1049 and 1039 cm^{-1}; δ 2.15(broad m, 20H; CH_2, CH and NH), 2.20 (s, 12H; Me); mass spectral peaks at m/e 314(M^+), 227, 226, 193, 167, 139, 138 and 88. An attempt was made to prepare a stable salt of 217 by passing excess HCl(g) through a solution of 217 in Et_2O. However, the product proved too hygroscopic to handle in the open.

Reaction of 10 with phenylhydrazine.

A magnetically stirred solution of 10 (4.22g, 20mmol), phenylhydrazine (9.5g, 88mmol) and DMF (20ml) was heated at 100-110° (bath temp.) for

1 hr. The precipitated solid was filtered off under suction and washed with $CHCl_3$. The combined extracts and reaction solution were washed with water, dried ($MgSO_4$) and concentrated to yield crude 218 which decomposed on standing.

Reaction of 10 with 2,4-dinitrophenylhydrazine.

A magnetically stirred solution of 10 (8.44g, 40mmol), 2,4-dinitrophenylhydrazine (29.2g, 176mmol) and DMF (100ml) was heated at 100-110° (bath temp.) for 18 hr. EtOAc was added and the solution washed with water, dried ($MgSO_4$) and concentrated to give 219 which decomposed during column chromatography on alumina.

Reaction of 10 with m-toluidine.

A magnetically stirred solution of 10 (4.22g, 20mmol), m-toluidine (9.42g, 88mmol) and DMF (15ml) was heated at 100° (bath temp.) for 18 hr. $CHCl_3$ was added and the solution washed with water, dried ($MgSO_4$) and concentrated to give crude 11 (4.2g, 59.5%) which recrystallised from $CHCl_3$-hexane as plates, m.p.188.5-189.5°. (Found: C, 74.80; H, 8.08. $C_{22}H_{28}N_2S$ requires: C, 74.96; H, 8.01%); ν_{max} (CCl_4) 3430, 1608 and 1590cm^{-1}; λ_{max} 253 (log ε 4.39) and 284nm (3.87); δ 2.00 (broad m, 8H; CH_2), 2.26 (s, 6H; Me), 2.96 (m, 2H; C-1 and C-5 CH), 3.56 (m, 2H; NH), 4.13 (m, 2H; C-2 and C-6 CH), 6.46 (m, 6H; C-4', C-5', and C-6' CH), 7.10 (m, 2H; C-2' CH); mass spectral peaks at m/e 352(M^+), 319, 246, 140, 139 and 107.

Reaction of 10 with 2-aminopyridine.

A magnetically stirred solution of 10 (4.22g, 20mmol), 2-aminopyridine (8.27g, 88mmol) and DMF (15ml) was refluxed for 40 hr. Work-up as for 11 gave 12 as a yellow solid (3.77g, 57.8%). The solid was decolourised with activated charcoal and crystallised from $CHCl_3$-petroleum spirit as plates, m.p.289-290°. (Found: C, 65.96; H, 6.64. $C_{18}H_{22}N_4S$ requires: C, 66.23; H, 6.79%); ν_{max} (KBr) 3370, 3060,

3020, 2930, 1605 and 1570cm^{-1}; λ_{max} 249 (log ε 4.52) and 299nm (3.90); δ 1.97 (m, 8H; CH_2), 2.90 (m, 2H; C-1 and C-5 CH), 4.38 (m, 2H; C-2 and C-6 CH), 6.50 (m, 6H; C-3' and C-5' CH, NH), 7.26 (m, 2H; C-4' CH), 7.86 (broad d, 2H; C-6' CH); mass spectral peaks at m/e 326(M^+), 293, 233, 232, 200 and 199.

Reaction of 10 with 2-amino-3-methylpyridine.

A solution of 10 (3.16g, 15mmol), 2-amino-3-methylpyridine (3.56g, 33mmol) and DMF (20ml) was heated at 120° (bath temp.) for 16 hr. $CHCl_3$ was added and the solution washed with aq.Na_2CO_3, water, dried ($MgSO_4$) and concentrated to give a dark red oil. Crystallisation from MeOH-petroleum spirit furnished 220 as plates (1.2g, 22%), m.p. 211-212°. (Found: C, 66.01; H, 7.58. $C_{20}H_{26}N_4S.\frac{1}{2}H_2O$ requires: C, 66.11; H, 7.44%); ν_{max} (KBr) 3620, 3440, 3360, 1600 and 1580cm^{-1}; λ_{max} 245 (log ε 4.50) and 301nm (3.99); δ (d_6-DMSO) 2.00 (broad m, 8H; CH_2), 2.10 (s, 6H; Me), 2.98 (m, 2H; C-1 and C-5 CH), 4.60 (broad m, 2H; C-2 and C-6 CH), 5.40 (d, 2H; NH), 6.43 (dd, 2H; C-5' CH), 7.20 (d, 2H; C-4' CH), 7.83 (d, 2H; C-6' CH); mass spectral peaks at m/e 354(M^+), 246, 213, 149, 133 and 108.

Reaction of 10 with 2-aminothiazole.

A magnetically stirred solution of 10 (6.33g, 30mmol), 2-aminothiazole (6.6g, 66mmol) and DMF (20ml) was heated at 110° (bath temp.) for 24 hr. Work-up as for 220 gave an orange solid. Column chromatography (silica gel) using MeOH as elutant gave crude 221 which recrystallised from $CHCl_3$-petroleum spirit as needles, m.p. 235-237°. ν_{max} (KBr) 3380, 3240, 3110, 1710, 1690, 1600 and 1570cm^{-1}; λ_{max} 241 (log ε 3.94) and 263nm (4.04); δ (d_6-DMSO) 2.00 (broad m, 8H; CH_2), 3.00 (m, 2H; C-1 and C-5 CH), 4.80 (m, 2H; C-2 and C-6 CH), 6.04 (d, 2H; J 5Hz; C-5' CH), 7.22 (d, 2H; J 5Hz; C-4' CH); mass spectral peaks at m/e 338(M^+), 239 and 139.

Reaction of 10 with pyridine.

Pyridinium salt (222) was prepared by A.Reid (Glasgow)[108].

Reaction of 225 and 226 with 2,4,6-trimethylcollidine.

Collidinium salts (223) and(224) were prepared by A.Stewart (Glasgow)[109].

6-Chloro-9-thiabicyclo[3,3,1]non-2-ene (227).

10 (24g, 113.7mmol) was sealed under vacuum in eight pyrolysis tubes (43cm x 22mm (Internal Diameter), wall thickness 4mm) and heated at 180° for 20 hr. The tubes were washed out with ether and the combined extracts concentrated to give a dark red liquid which distilled under reduced pressure to furnish 227 (11.4g, 57.4%), b.p. 66-70° at 0.3mmHg (lit.[36] b.p. 64-69°, 0.3mmHg). δ 2.06 (m, 4H; C-7 and C-8 CH_2), 2.60 (m, 2H; C-4 CH_2), 3.13 (m, 2H; C-1 and C-5 CH), 4.65 (m, 1H; C-6 CH), 5.96 (m, 2H; C-2 and C-3 CH); mass spectral peaks at m/e 174(M^+), 139, 97 and 79.

Reaction of 227 with pyridine.

A solution of 227 (2.2g, 12.62mmol) in pyridine (30ml) was magnetically stirred at room temperature for 4 days. The precipitated solid (14) was filtered off under suction and recrystallised from CH_2Cl_2-Et_2O as needles (1.16g, 32.8%), m.p. 111-113°. (Found: C, 55.60; H, 6.46. $C_{13}H_{16}NSCl.\frac{3}{2}H_2O$ requires: C, 55.63; H, 6.77%); ν_{max} (KBr) 3020, 1630, 1478, 1137 and 682cm^{-1}; λ_{max} 256 (logε 3.53), 262 (3.58), 268 (3.51) and 296nm (2.86); δ (D_2O) 2.40 (m, 6H; CH_2), 3.46 (m, 2H; C-1 and C-5 CH), 5.45 (m, 1H; C-6 CH), 6.09 (m, 2H; C-2 and C-3 CH), 8.12 (t, 2H; C-3' CH), 8.60 (t, 1H; C-4' CH), 9.01 (d, 2H; C-2' CH).

9-Thiabicyclo[3,3,1]non-2-en-6-ol (229).

10% w/v NaOH (41.4ml) was added dropwise over 20 min. to a magnetically stirred solution of 227 (17g, 97mmol) in glyme (35ml)

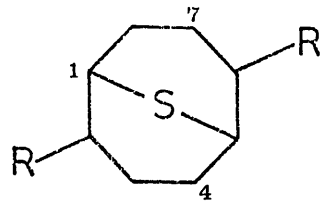
and the solution refluxed for 24 hr. The solvent was removed under reduced pressure and the residue extracted with $CHCl_3$. The combined extracts were washed with water, dried ($MgSO_4$) and concentrated to give 229 (12.7g, 83%) as plates, m.p. 261-262° (lit.[36] m.p. 176-177°). δ 1.95 (m, 5H; C-7 and C-8 CH_2, OH), 2.50 (m, 2H; C-4 CH_2), 3.05 (m, 2H; C-1 and C-5 CH), 4.20 (m, 1H; C-6 CH), 5.96 (d, 2H; J 4Hz; C-2 and C-3 CH); mass spectral peaks at m/e 156(M^+), 139, 122, 112, 99, 97 and 79.

9-Thiabicyclo [3,3,1] non-2-en-6-one (151).

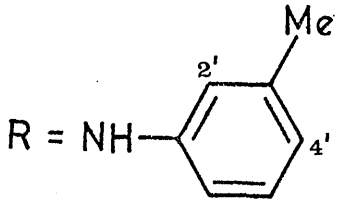
A solution of 229 (12.7g, 80.4mmol) in pyridine (50ml) was added dropwise over 15 min. to a stirred solution of CrO_3 (AR, 25.2g, 252mmol) in pyridine (370ml) at 0°. Stirring was continued for 1 hr. and the solution allowed to stand for 20 hr. at room temperature. The solution was extracted with ether and the combined extracts washed with 5% HCl, water, dried ($MgSO_4$) and concentrated to yield a viscous yellow oil. Column chromatography on alumina using Et_2O/petroleum spirit (3:2) as elutant furnished 151 as a colourless solid (4.0g, 31.8%), m.p. 80-82° (lit.[84] m.p. 79-81°).

6-Oximino-9-thiabicyclo [3,3,1] non-2-ene (228).

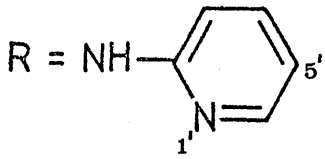
A solution of hydroxylamine hydrochloride (210mg, 3.02mmol), NaOH (400mg, 10mmol), water (4ml), 151 (308mg, 2mmol) and EtOH was refluxed for 30 min. The solvent was removed and the residue extracted with water, dried ($MgSO_4$) and concentrated to a yellow oil (358mg, 70%). Preparative TLC using Et_2O/petroleum spirit (1:4) and crystallisation from Et_2O-petroleum spirit gave 228 as cubes, m.p. 94-96°. (Found: 169.05626. $C_8H_{11}ONS$ requires: 169.05612); ν_{max} (CCl_4) 3600, 3250, 3020, 1650 and 670cm^{-1}; δ 2.30 (broad m, 7H; CH_2 and OH), 3.15 (broad m, 2H; C-1 and C-5 CH), 6.03 (m, 2H; C-2 and C-3 CH); mass spectral peaks at m/e 169(M^+), 152 and 97.



10 R = Cl

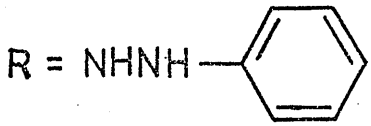


11 R = NH

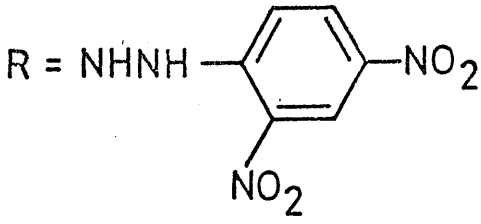


12 R = NH

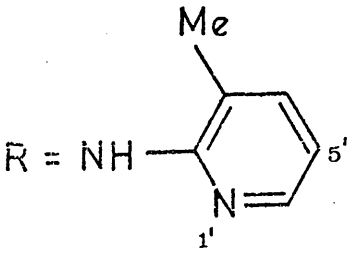
217 R = $NHCH_2CH_2NMe_2$



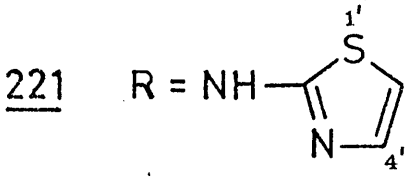
218 R = NHNH



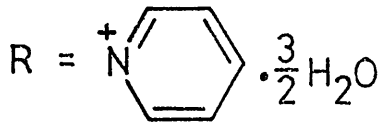
219 R = NHNH



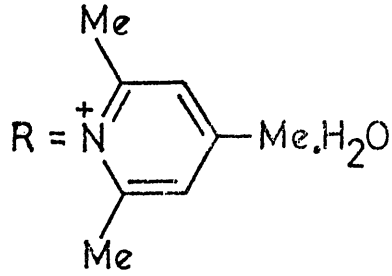
220 R = NH



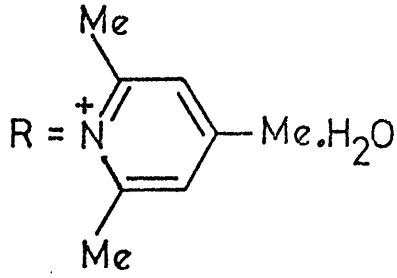
221 R = NH



222 R = $\cdot\frac{3}{2}H_2O$ Cl^-



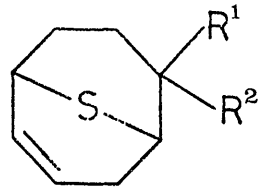
223 R = $Me.H_2O$ Br^-



224 R = $Me.H_2O$ I^-

225 R = Br

226 R = I



14 $R^1 = \overset{+}{N}(C_5H_5) \cdot \frac{3}{2}H_2O$; $R^2 = H$; Cl^-

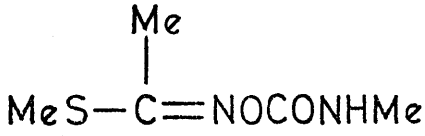
151 $R^1, R^2 = O$

227 $R^1 = H$; $R^2 = Cl$

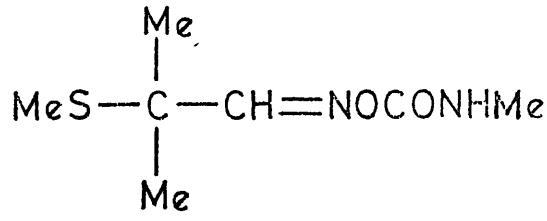
228 $R^1, R^2 = NOH$

229 $R^1 = H$; $R^2 = OH$

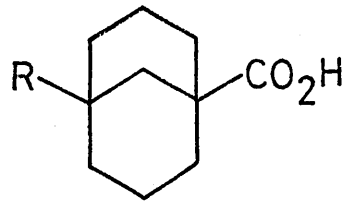
230 $R^1, R^2 = NOCONHMe$



231

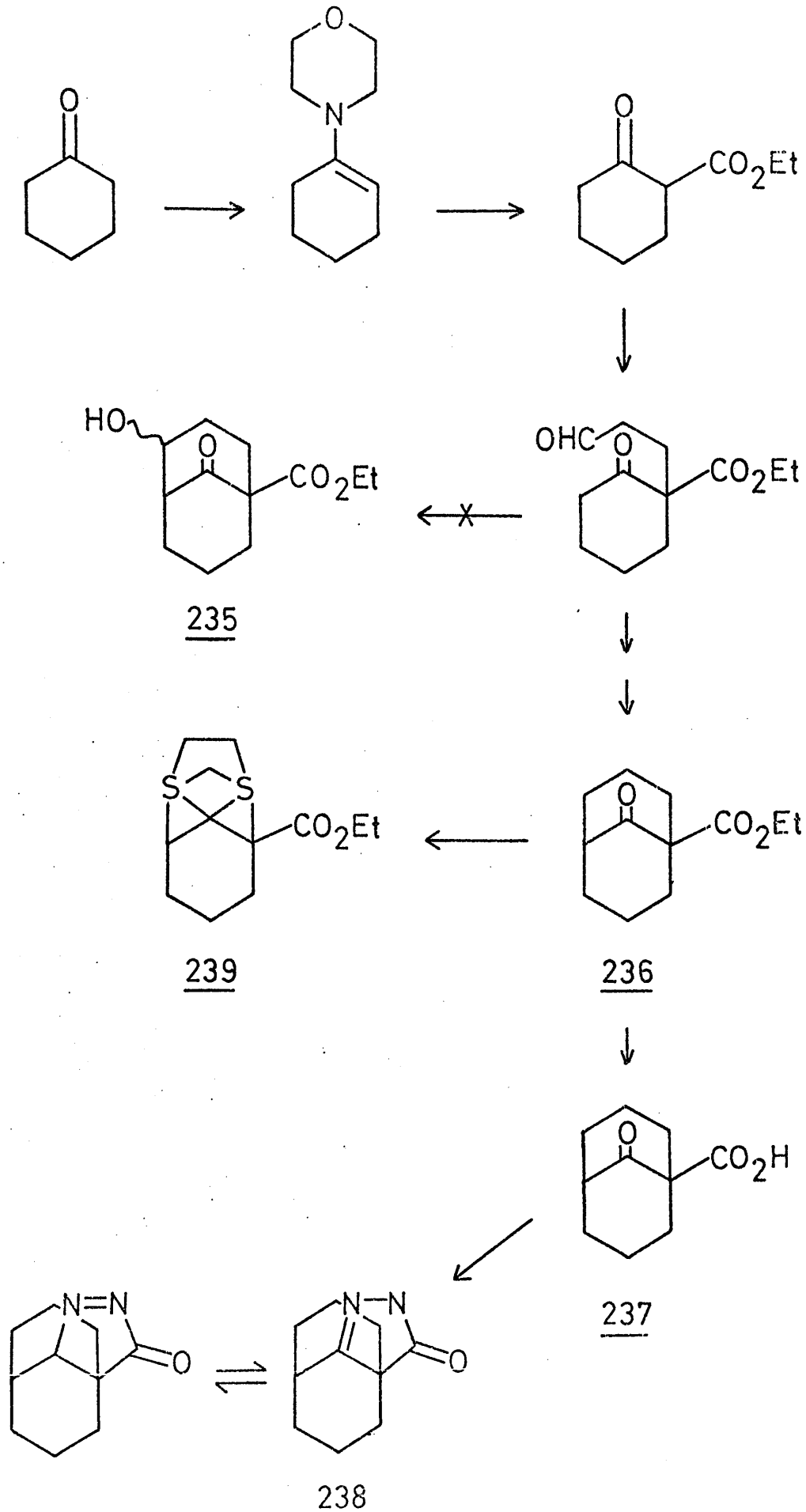


232



233 R = Me

234 R = H



235

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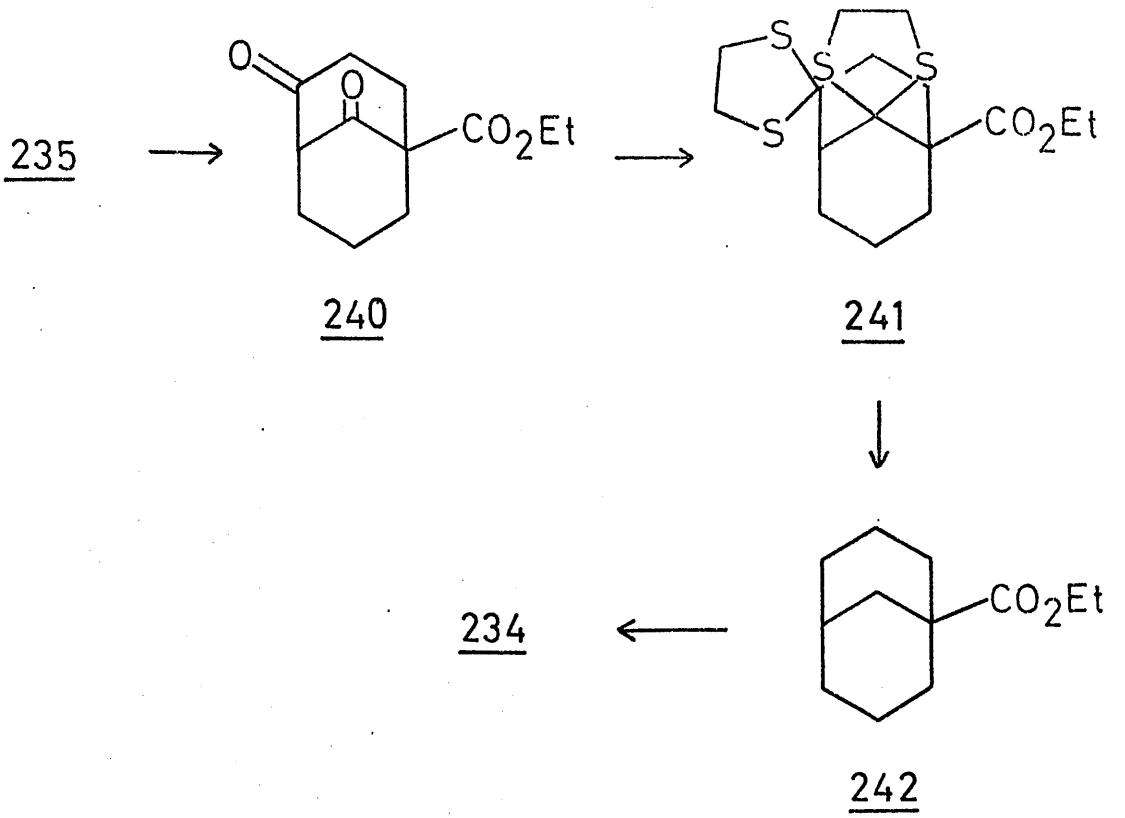
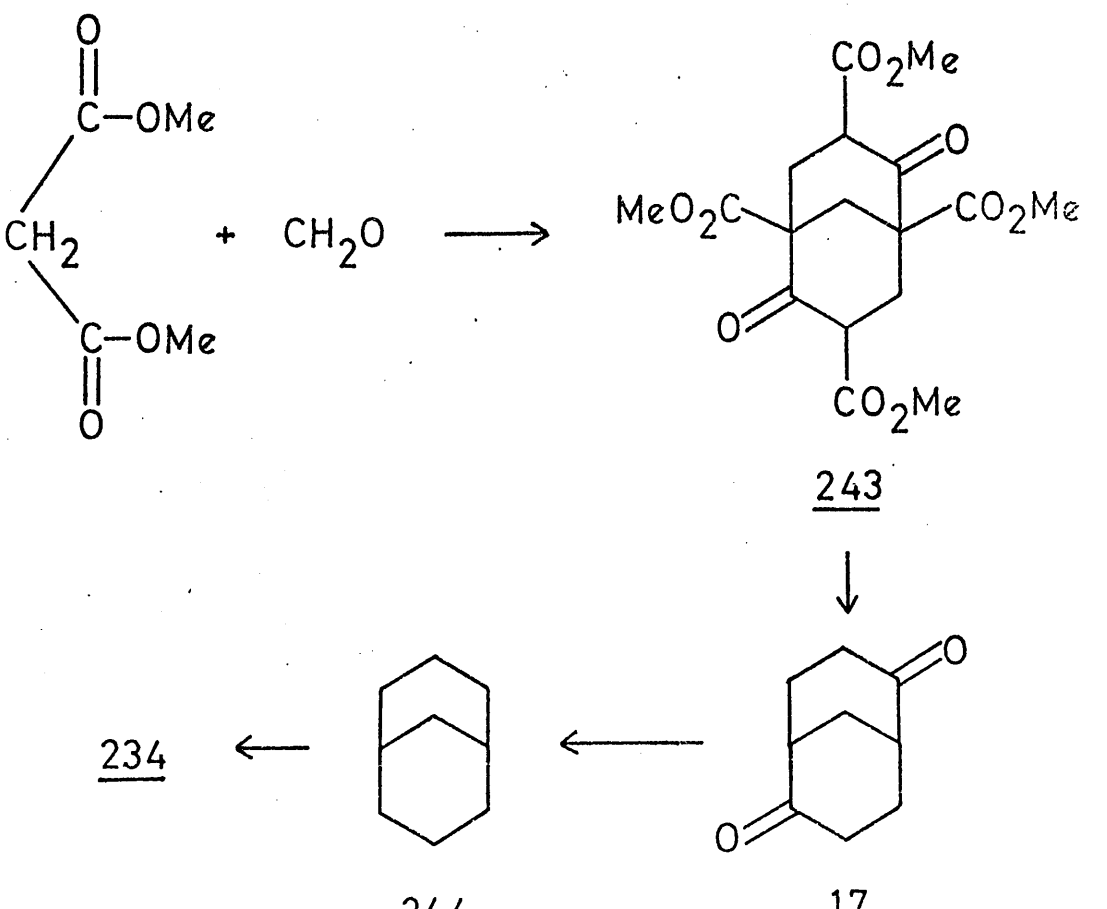
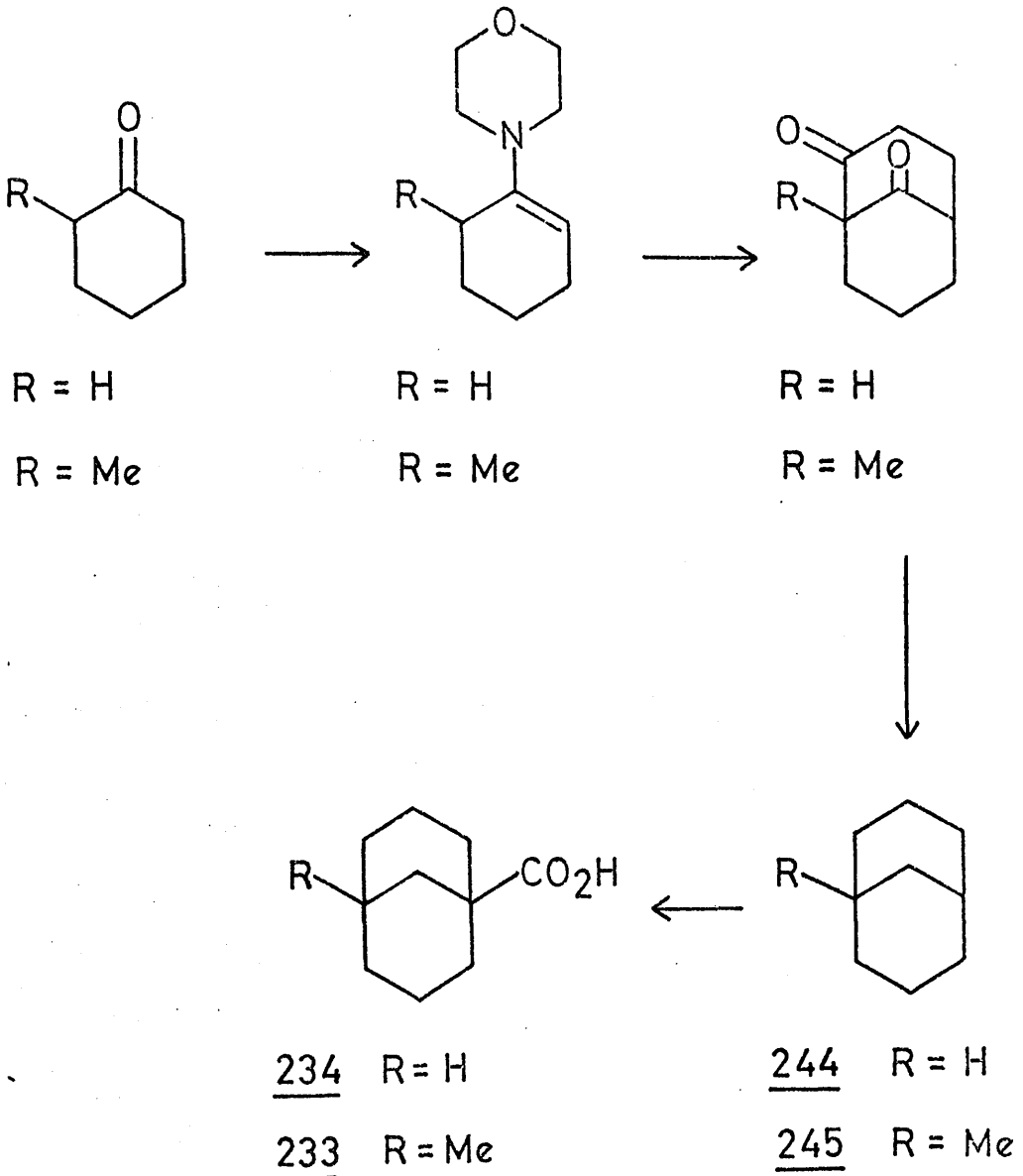


Scheme 18



Scheme 19


O
R
R = H
R = Me
O
N
R
R = H
R = Me
O
O
R
R = H
R = Me
R
CO2H
234 R = H
233 R = Me
R
244 R = H
245 R = Me

Scheme 20

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